Shared and distinct alterations in brain structure of youth with internalizing or externalizing disorders: findings from the ENIGMA antisocial behavior, ADHD, major depressive disorder, and anxiety working groups

Townend, S.; Staginnus, M.; Gao, Y.; Alexander, N.; Arolt, V.; Banaschewski, T.; ... ; Fairchild, G.

Archival Report

Biological Psychiatry

Shared and Distinct Alterations in Brain Structure of Youth With Internalizing or Externalizing Disorders: Findings From the ENIGMA Antisocial Behavior, ADHD, Major Depressive Disorder, and Anxiety Working Groups

Sophie Townend, Marlene Staginnus, Yidian Gao, Nina Alexander, Volker Arolt, Tobias Banaschewski, Katja Beesdo-Baum, Mark A. Bellgrove, Vivek Benegal, Robert J. Blair, Laura Blanco-Hinojo, Ole Jonas Boeken, Joscha Böhnlein, Sven Bölte, Linda M. Bonnekoh, Daniel Brandeis, Rodrigo A. Bressan, Fabian Breuer, Willem B. Bruin, Jan K. Buitelaar, Katie L. Burkhouse, Monica E. Calkins, Marta Cano, Narcis Cardoner, Hui Chen, Xianliang Chen, David R. Coghill, Olivier F. Colins, Colm G. Connolly, Michael C. Craig, Kathryn R. Cullen, Udo Dannlowski, Christopher G. Davey, Andrea Dietrich, Daifeng Dong, Christine M. Freitag, Thomas Frodl, Liesbet Goossens, Dominik Grotegerd, Raquel E. Gur, Ruben C. Gur, Jan Haavik, Cindy C. Hagan, Tim Hahn, Alfons O. Hamm, Ben J. Harrison, Catharina A. Hartman, Martin J. Herrmann, Tiffany C. Ho, Pieter J. Hoekstra, Bharath Holla, Karim Ibrahim, Andrea Jackowski, Hamidreza Jamalabadi, Yali Jiang, Tilo Kircher, Kerstin Konrad, Anna Kraus, Jonna Kuntsi, Till Langhammer, Luisa Lazaro, Elisabeth J. Leehr, Ulrike Lueken, Ren Ma, Frank P. MacMaster, Gisele G. Manfro, Anne Martinelli, Hannah Meinert, Susanne Meinert, Jarosław M. Michałowski, Qingsen Ming, Robert Moeck, Markus Muehlhan, Lilianne R. Mujica-Parodi, Benson Mwangi, Janina Neufeld, Joel T. Nigg, Ruth L. O'Gorman Tuura, Hyuntaek Oh, Jaap Oosterlaan, Yannis Paloyelis, Pedro M. Pan, Luca Passamonti, Wenceslao Peñate, K. Luan Phan, Kerstin J. Plessen, Jesus Pujol, Karl Lundin Remnélius, Francisco Rivero, Katya Rubia, Ramiro Salas, Giovanni A. Salum, Theodore D. Satterthwaite, Anne Schienle, Elisabeth Schrammen, Koen R.J. Schruers, Gunter Schumann, Arjun Sethi, Tim Silk, Norbert Skokauskas, Jordan W. Smoller, Jair C. Soares, Lin Sørensen, Christina Stadler, Michael C. Stevens, Benjamin Straube, Thomas Straube, Andreas Ströhle, Gustavo Sudre, Denis G. Sukhodolsky, Kate Sully, Xiaoqiang Sun, Chad M. Sylvester, Nicola Toschi, Steven J.A. van der Werff, Alasdair Vance, Robert Vermeiren, Albert Wabnegger, Xiaoping Wang, Julia Wendt, Sarah Whittle, Julian Wiemer, Anderson M. Winkler, Hans U. Wittchen, Mon-Ju Wu, Qiong Wu, Tony T. Yang, Yunbo Yang, Shuqiao Yao, Jibiao Zhang, Jiansong Zhou, Andre Zugman, Giovana B. Zunta-Soares, Peter M. Zwanzger, Sophia I. Thomopoulos, Neda Jahanshad, Paul M. Thompson, Kevin Hilbert, Arielle Baskin-Sommers, Charlotte A.M. Cecil, Moji Aghajani, Daniel S. Pine, Nic J.A. van der Wee, Dan J. Stein, Nynke A. Groenewold, Janna Marie Bas-Hoogendam, Laura K.M. Han, Elena Pozzi, Lianne Schmaal, Barbara Franke, Martine Hoogman, Esther Walton, Stephane A. De Brito, and Graeme Fairchild, on behalf of the ENIGMA Antisocial Behavior, Anxiety, ADHD, and MDD Working Groups

ISSN: 0006-3223

ABSTRACT

BACKGROUND: Externalizing and internalizing disorders are common in youth but are often studied separately, preventing researchers from identifying shared (i.e., transdiagnostic) alterations in brain structure. Using data from the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Consortium, we conducted a mega-analysis to identify shared and distinct cortical and subcortical brain alterations across internalizing (anxiety disorders and depression) and externalizing (attention-deficit/hyperactivity disorder [ADHD] and conduct disorder [CD]) disorders in youth.

METHODS: 3D T1-weighted magnetic resonance imaging data from youths (age range 4–21 years) with anxiety disorders (n = 1044), depression (n = 504), ADHD (n = 1317), and CD (n = 1172) along with healthy control participants (n = 4743) were analyzed. We assessed group differences in regional cortical thickness, surface area (SA), and subcortical volume using linear models, adjusted for site, age, and sex, as well as total intracranial volume in the SA and subcortical volume models.

RESULTS: We observed transdiagnostic associations, with both internalizing and externalizing disorders characterized by lower SA in the insula, entorhinal cortex, and middle temporal gyrus and lower amygdala volume (Cohen's ds = −0.07 to −0.24) as well as total SA and intracranial volume (ds = −0.11 to −0.25). Externalizing-specific reductions in SA were observed in frontoparietal regions (ds = −0.08 to −0.13), but no internalizing-specific associations were identified. Disorder-specific alterations were identified for ADHD, CD, and anxiety disorders but not depression.

CONCLUSIONS: Both common and disorder-specific alterations were identified, with regions involved in salience attribution and emotion processing implicated across internalizing and externalizing disorders. These novel findings can guide future research targeting common biological processes across youth psychiatric disorders as well as features unique to individual disorders.

https://doi.org/10.1016/j.biopsych.2025.08.003

Psychiatric disorders often emerge during childhood and adolescence and lead to an increased risk of mental and physical health problems throughout the lifespan (1). While many studies have examined the correlates of individual disorders, there is increasing evidence that many disorders share common genetic underpinnings (2–4), environmental risk factors (5,6), and comorbidity patterns (1,7,8). An important question is whether this extends to brain structure.

Most neuroimaging studies have focused on single disorders in isolation, and even disorders with overlapping symptom profiles (e.g., anxiety and depression) have seldom been compared directly. Youth disorders have often been classified as either internalizing (reflecting internal distress, comprising depression and anxiety disorders) or externalizing (associated with externally focused distress or behaviors, including attention-deficit/hyperactivity disorder [ADHD] and conduct disorder [CD]) (9). Case-control studies of single disorders suggest neuroanatomical similarities within these diagnostic groupings, such as hippocampal volume reductions in internalizing disorders (10,11) and basal ganglia and frontotemporal alterations in externalizing disorders (12–14). Nevertheless, results are often inconsistent and based on small sample sizes, and overlapping alterations have been implicated across internalizing and externalizing disorders (e.g., altered amygdala volume) (11,13), raising questions about which alterations are transdiagnostic (shared across disorders) and which are disorder specific.

Meta-analytic work has attempted to identify common and distinct brain structure alterations across disorders (15–18). For example, when comparing across internalizing and externalizing disorders in adults, Goodkind *et al.* (19) observed transdiagnostic reductions in anterior cingulate and insula volumes. However, Goodkind *et al.* (19) studied adults only, included just one externalizing disorder (substance use disorder), and considered gray matter volume (GMV) rather than differentiating between cortical thickness (CT) and surface area (SA). Additionally, coordinate-based meta-analytic approaches can be affected by methodological heterogeneity (e.g., preprocessing and analysis approaches) and publication bias (20–22).

The advent of large-scale, international data-sharing collaborations in neuroimaging research has provided opportunities for systematic cross-disorder comparisons. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium facilitates team science through data-sharing and standardized analysis protocols (23). ENIGMA working groups focused on specific disorders have identified neuroanatomical alterations relative to control participants in individuals with ADHD (24,25), depression (26,27), anxiety disorders (28–30), and (most recently) CD (31). However, due to differences in methodology, it was not possible to directly compare these results, and it was unclear whether common (or distinct) structural alterations would be found when comparing individuals with each of these disorders to control participants within the same study. Previous meta-analytic studies have used ENIGMA data to study cross-disorder similarities (in adults) by comparing effect size estimates from published studies (32–35). However, conducting mega-analyses with individual participant-level data offers greater flexibility in statistical modeling and investigation of individual-

level characteristics (e.g., age and sex) (20,21). Only one mega-analysis has investigated shared and distinct brain alterations across disorders in youth. Leveraging ENIGMA data, Boedhoe *et al.* (36) compared youths with ADHD, autism, and obsessive-compulsive disorder to each other and healthy control (HC) participants, identifying lower total intracranial volume (TIV) as specific to the children and adolescents with ADHD relative to the obsessive-compulsive disorder, autism, and HC groups (36). Interestingly, no shared alterations were found across these 3 neurodevelopmental disorders.

We extended this work by investigating shared and distinct brain structural alterations across the most common and impairing mental health disorders of childhood and adolescence (37–39), guided by a well-established model of internalizing (e.g., anxiety disorders and depression) versus externalizing (ADHD and CD) groupings (1,4,40–42). Using newly generated ENIGMA Consortium data, we conducted a mega-analysis in which we examined CT and SA separately [given their distinct genetic and developmental profiles (43,44)] and subcortical volume. Based on previous findings (including disorder-specific ENIGMA studies), we hypothesized that we would find common alterations across disorders in frontostriatal and (para)limbic regions (19,24–29,31). Lower hippocampal volume was predicted in internalizing disorders, consistent with their links to emotion regulation and stress sensitivity, and lower CT or SA was predicted in frontotemporal regions in externalizing disorders, potentially related to disrupted impulse control and emotion processing (10–14).

METHODS AND MATERIALS

Samples

We collated data from 4 ENIGMA working groups, including 1317 youths with ADHD from ENIGMA-ADHD, 1172 youths with CD from ENIGMA-Antisocial Behavior, 1044 youths with anxiety disorders (including generalized anxiety, social anxiety, panic disorders, and phobias) from ENIGMA-Anxiety (45), and 504 youths with depression from ENIGMA-Major Depressive Disorder (MDD). Finally, 4743 HC participants were included across the 4 working groups. We used all available youth data up to age 21 [consistent with (24–29,31)], with no minimum age cutoff. Groups were based on primary clinical/research diagnoses assessed using standardized clinical interviews or established questionnaire cutoffs (see Appendix 1 in the Supplement for further details, including inclusion/exclusion criteria). Demographic and clinical characteristics are presented in Table 1.

Informed consent was obtained from participants (and/or their parents/caregivers) at the contributing sites, and individual studies were approved by local institutional review boards/ethics committees. This project was preregistered on the OSF (https://osf.io/ar94t/) and approved by Bath University's Ethics Committee (21-278/22-149).

Image Acquisition and Processing

Structural T1-weighted brain magnetic resonance imaging (MRI) scans were acquired at each site and processed at the contributing or coordinating site using FreeSurfer 5.3/6.0. Standardized ENIGMA protocols for preprocessing and quality control were used (http://enigma.ini.usc.edu/protocols/imaging-protocols/), except in ENIGMA-Anxiety's Generalized Anxiety Disorder subgroup (see Appendix 2 in the Supplement) (30). Segmentations were based on the Desikan-Killiany and *aseg* atlases, yielding CT and SA measures for 34 cortical regions and volumes for 7 subcortical regions. Mean values across hemispheres were used in the analyses (see Appendix 16 in the Supplement for exploratory hemisphere-specific analyses). Additionally, average CT, total SA, and TIV were computed.

Statistical Analyses

Extracted values for CT, SA, and subcortical volume were pooled across sites to perform a mega-analysis using individual participant-level data. Statistical analyses were performed in R (version 4.2.2). Site and scanner effects were adjusted for using ComBat (Appendix 3 in the Supplement) (46). Differences between the diagnostic groups and the HC group were analyzed using general linear models, with each regional or global brain measure treated as an individual outcome and diagnostic group as the predictor (with 5 levels: control, ADHD, CD, anxiety, and depression) (see Appendix 4 in the Supplement). Because the 4 diagnostic groups had different mean ages and age distributions, we assessed the normal distribution and homoscedasticity of the residuals (see Appendix 17 in the Supplement).

Results were categorized as shared if ≥2 disorder groups differed from the HC group in the same region, measure, and direction and could be further categorized as transdiagnostic, partly shared, or internalizing- or externalizing-specific (Figure 1). Disorder-specific associations were defined by a significant difference between just one diagnostic group and the HC group. While this does not indicate exclusivity (e.g., a diagnostic group differs from the HC group and the other diagnostic groups), it is consistent with previous studies (36,47). Diagnostic groups were also directly compared to test for exclusive effects (see Appendix 7 in the Supplement). Age and sex were adjusted for in all analyses (plus TIV for SA and subcortical volumes). False discovery rate correction was applied separately to CT, SA, and subcortical outcomes (q = .05) (36).

Sensitivity analyses adjusted for IQ and psychotropic medication status, where available. To evaluate whether disorder-related alterations differed by sex or age, we modeled sex-by-diagnosis and age-by-diagnosis interactions. Supplementary analyses additionally adjusted for age^2 to account for potential nonlinear associations with age (see Appendix 9 in the Supplement). We also tested for sex-by-internalizing, sex-by-externalizing, age-by-internalizing, and age-by-externalizing interactions (see Appendices 12 and 14 in the Supplement).

RESULTS

Transdiagnostic associations (shared across all disorders) were identified, with lower SA in the insula, middle temporal gyrus, and entorhinal cortex (Figure 2A) and lower volume in the amygdala (Figure 3A). Additionally, all 4 disorder groups showed lower total SA (ds = −0.17 to −0.25) and TIV (ds = −0.11 to −0.21) relative to the HC group.

Table 1. Demographic and Clinical Characteristics of the Sample by Diagnostic Group

	Healthy Control, *n* = 4743		ADHD, *n* = 1317		CD, *n* = 1172		Anxiety, *n* = 1044		MDD, *n* = 504	
Characteristic	Data Available, *n*	Mean (SD) or *n* (%)	Data Available, *n*	Mean (SD) or *n* (%)	Data Available, *n*	Mean (SD) or *n* (%)	Data Available, *n*	Mean (SD) or *n* (%)	Data Available, *n*	Mean (SD) or *n* (%)
Age, Years	4743	13.62 (3.10)	1317	12.49 (3.45)	1172	13.69 (3.02)	1044	15.72 (4.20)	504	16.88 (2.45)
IQ	3135	106.69 (13.85)	1194	103.21 (14.62)	1054	96.69 (13.08)	489	102.38 (16.04)	289	104.78 (12.45)
Sex, Male	4743	2556 (53.89%)	1317	1023 (77.68%)	1172	837 (71.42%)	1044	322 (30.84%)	504	178 (35.32%)
Medication Status[a]	4158	59 (1.42%)	908	381 (41.96%)	1041	240 (23.05%)	979	107 (10.93%)	372	53 (14.25%)
Current Diagnoses										
ADHD	3143	0 (0%)	–	–	1134	461 (40.65%)	549	12 (2.19%)	302	25 (8.28%)
CD	1799	0 (0%)	NA	NA	–	–	549	1 (0.18%)	302	2 (0.66%)
Anxiety	4252	0 (0%)	859	36 (4.19%)	925	173 (18.70%)	–	–	383	216 (56.40%)
MDD	4409	0 (0%)	855	9 (1.05%)	925	88 (9.51%)	1003	100 (9.97%)	–	–
ODD	1463	0 (0%)	NA	NA	751	385 (51.26%)	549	3 (0.55%)	302	5 (1.66%)
OCD	3922	0 (0%)	859	2 (0.23%)	613	86 (14.03%)	974	7 (0.72%)	326	14 (4.29%)
PTSD	2649	0 (0%)	NA	NA	593	31 (5.23%)	991	25 (2.52%)	326	32 (9.82%)
AUD	987	0 (0%)	NA	NA	613	14 (2.28%)	NA	NA	355	43 (12.11%)
SUD	1640	0 (0%)	NA	NA	659	50 (7.59%)	514	10 (1.95%)	241	14 (5.81%)

Sex and age information was available for all participants, but IQ, medication status, and comorbidity information were not always available (see Appendices 8 and 10 in the Supplement). The age range was 4 to 21 years for the ADHD group, 7 to 21 years for the CD group, 6 to 21 years for the anxiety group, and 9 to 21 years for the MDD group. We note that the majority of participants in the overall sample (93.3%) were between ages 9 and 21 years. "–" represents not applicable.

ADHD, attention-deficit/hyperactivity disorder; AUD, alcohol use disorder; CD, conduct disorder; MDD, major depressive disorder; NA, not available; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder; SUD, substance use disorder.

[a]Psychotropic medication use status at the time of scan (binary coded as yes/no). *n* = number endorsed.

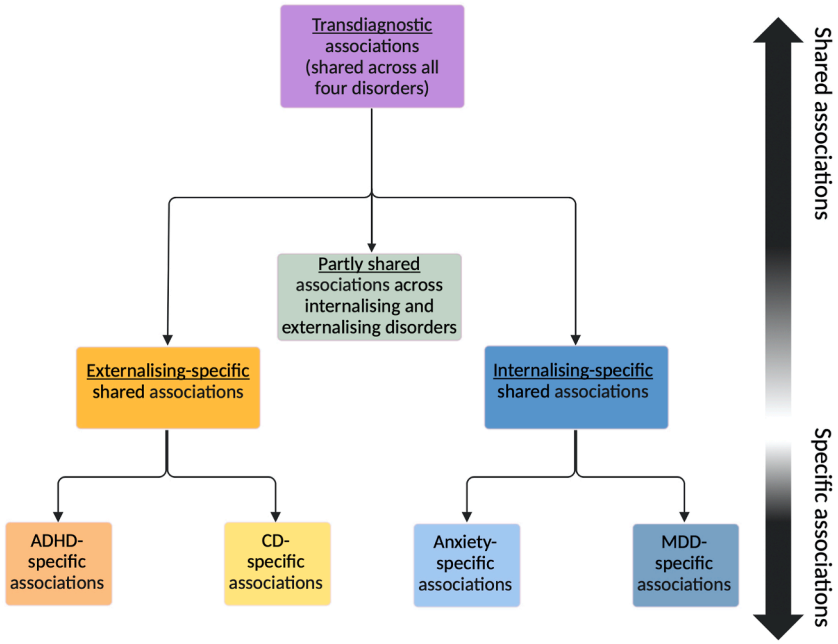

Figure 1. Definitions of transdiagnostic vs. shared vs. disorder-specific associations. Transdiagnostic associations were those where all 4 disorders showed the same case-control association. Partly shared associations were those where 2 or more disorders from different diagnostic groupings differed from the healthy control (HC) group in the same region and direction, but this association was not found across all 4 disorders. Internalizing-specific associations were those where both the anxiety and depression diagnostic groups showed the same association, and externalizing disorders did not display this association. Externalizing-specific associations were those where both the attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) diagnostic groups showed the same association, and internalizing disorders did not show this association. Finally, disorder-specific associations were defined by a significant difference at false discovery rate threshold between one disorder group and the HC group and nonsignificant differences between the other disorder groups and the HC group. (Figure created with BioRender.) MDD, major depressive disorder.

Shared associations across internalizing and externalizing disorders (i.e., ≥1 internalizing and ≥1 externalizing) included lower SA in the frontal pole and pars orbitalis (Figure 2A) and lower volume of the pallidum (Figure 3A) in CD, anxiety, and depression, while lower rostral middle frontal gyrus SA was shared by ADHD, CD, and anxiety disorders. Lower precentral gyrus CT was common to ADHD, anxiety, and depression (Figure 4A). Finally, the CD and anxiety groups both showed lower SA in the inferior temporal gyrus and lateral occipital cortex, while the CD and depression groups showed lower medial orbitofrontal cortex (OFC) and superior temporal gyrus SA.

Externalizing-specific associations (shared between ADHD and CD only) were found, with lower SA in the caudal middle frontal gyrus, superior frontal gyrus, lateral OFC, and inferior parietal cortex observed in CD and ADHD (Figure 2A). No internalizing-specific associations were identified.

Disorder-specific associations were identified for ADHD, CD, and anxiety but not depression. The ADHD group showed lower SA in the posterior cingulate cortex and lower CT in the fusiform gyrus and temporal pole (Figures 2A and 4A). The CD group showed unique reductions in SA in 7 frontal, parietal, and temporal regions (Figure 2A). Similarly, reductions in hippocampus, nucleus accumbens, and thalamus volume were specific to CD (Figure 3A). The anxiety group showed specific alterations in 2 fronto-occipital regions for SA, 3 frontocingulate regions for CT, and putamen volume (Figures 2A, 3A, and 4A). Only the anxiety group showed higher CT (in the isthmus cingulate cortex) and subcortical volume (in the putamen) compared with the HC group (Figures 3B and 4B; full results are provided in Appendix 6 in the Supplement).

Overall, disorder-related differences in SA and subcortical volume were more widespread and had larger effect sizes (*d*s between −0.33 and 0.11) relative to differences in CT (*d*s between −0.14 and 0.09) (Figures 2C and 4C).

Significant differences between diagnostic groups were also observed for SA and subcortical volume, with 2 types of effects emerging (Figures 2C and 3C). The first type were instances where all 4 diagnostic groups showed reduced SA/volume relative to the HC group, but to different extents (i.e., smaller vs. larger effects in the same region). This was true for the insula, frontal pole, and pallidum. A second pattern emerged in other regions wherein opposite effects were observed in ≥2 diagnostic groups. For example, the CD and anxiety groups differed from the HC group in opposite ways in the parahippocampal gyrus (lower vs. higher SA) and differed significantly from each other. Similar patterns were observed for fusiform gyrus, isthmus cingulate cortex, and postcentral gyrus SA and for hippocampal volume.

Effects of Sex and Age

Interactions With Sex. No significant sex-by-diagnosis interactions were observed (see Appendix 11 in the Supplement).

Interactions With Age. Age-by-diagnosis interactions were identified for ADHD in SA (lateral OFC), CT (cuneus cortex), and subcortical volume (nucleus accumbens), as well as total SA and TIV. Age-by-diagnosis interactions were also found for anxiety in SA (in the medial OFC, superior frontal cortex, and frontal pole). Finally, an age-by-diagnosis interaction was observed for depression in pallidum volume (see Appendix 13 in the Supplement). To explore these interactions further, we divided the sample into children (<12 years; $n = 2947$) and adolescents (≥12 years; $n = 5329$) (36). In these regions or global measures, effect sizes were consistently larger in children and smaller or nonsignificant in adolescents (Figure 5). However, only 8 depressed participants were <12 years of age, so the depression-by-age interaction is not displayed.

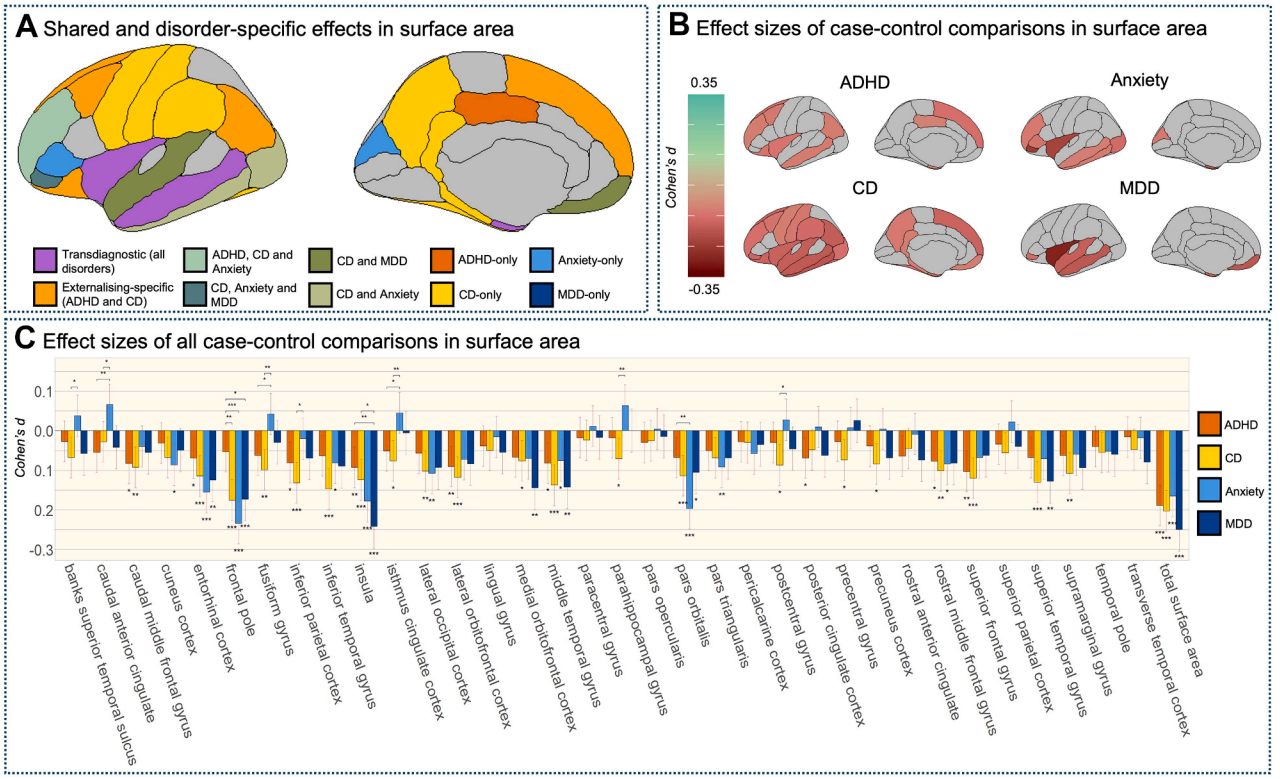

Figure 2. Transdiagnostic, shared, and disorder-specific effects on surface area. **(A)** Brain maps showing case-control effects in surface area that were shared across disorders or were disorder specific. Thirty-four cortical regions based on the Desikan-Killiany atlas were investigated, as illustrated in the maps. **(B)** Cohen's *d* maps indicating case-control differences in surface area for each disorder separately, where red represents a decrease and green represents an increase relative to control participants. **(C)** Effect sizes for all case-control comparisons in surface area, expressed as Cohen's *d*. Comparison lines in the top portion of the graph indicate significant differences between diagnostic groups. All analyses were adjusted for age, sex, and total intracranial volume (except for total surface area). Error bars represent 95% CIs. Significant results (false discovery rate [FDR] $q = .05$) are indicated by $^{*}p_{FDR} < .05$, $^{**}p_{FDR} < .005$, $^{***}p_{FDR} < .001$. ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; MDD, major depressive disorder.

Sensitivity Analyses

Most SA and CT results survived adjustment for IQ but were more affected by medication status, while the opposite was true for subcortical volume. For example, the transdiagnostic reductions in amygdala volume survived adjustment for medication status but not IQ. When we adjusted for IQ, all externalizing-specific associations survived, but when we adjusted for medication status, only CD youth showed differences in these regions (i.e., ADHD-related effects were nonsignificant). Ninety percent of the disorder-specific associations observed for SA, CT, and subcortical volume survived adjustment for IQ, while only 42% survived adjustment for medication status (see Appendix 8 in the Supplement). Results were largely unchanged when adjusting for age[2] (see Appendix 9 in the Supplement).

Comorbidity Analyses

Exploratory analyses examining comorbidity effects are reported in Appendix 10 in the Supplement. Notably, as comorbidity information was not consistently available across samples/working groups, we focused on CD only (where the most widespread structural alterations were observed and comorbidity information was largely available). Structural alterations were similar in pure and comorbid CD subgroups, suggesting a limited impact of comorbidity.

DISCUSSION

This study represents the largest mega-analysis to compare brain structure alterations in youths with the most common internalizing and externalizing disorders (combined $n = 4037$) versus HC participants ($n = 4743$). We identified several transdiagnostic associations. Compared with the HC group, all 4 diagnostic groups showed lower regional SA and amygdala volume and reductions in total SA and TIV. Additional shared associations were found across at least one internalizing and one externalizing disorder. An externalizing-specific signature was also identified, wherein youths with ADHD or CD showed common reductions in SA in fronto-parietal regions. Beyond shared associations, disorder-specific alterations were observed in ADHD, CD, and anxiety disorders. Finally, age-by-diagnosis interactions indicated more pronounced structural alterations in children with ADHD, anxiety disorders, and depression than in adolescents with the same disorders.

Supporting our hypotheses, transdiagnostic reductions in insula, middle temporal gyrus, and entorhinal cortex SA and

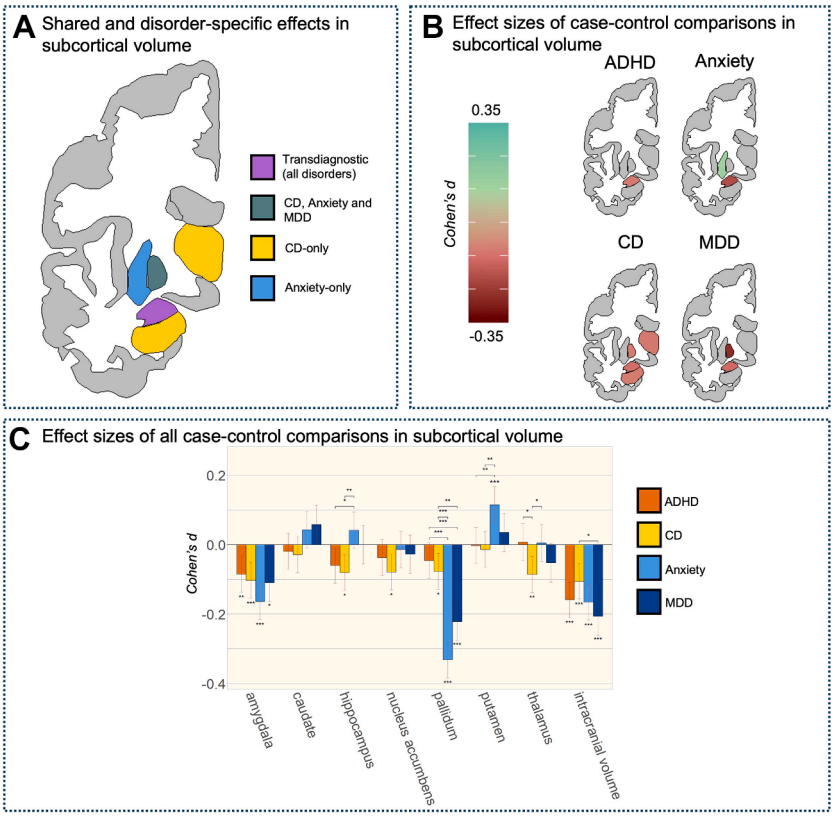

Figure 3. Transdiagnostic, shared, and disorder-specific effects on subcortical volume. **(A)** Brain maps showing case-control effects in subcortical volume that were shared across disorders or were disorder specific. **(B)** Cohen's *d* maps indicating case-control differences in subcortical volume for each disorder separately, where red represents a decrease and green represents an increase relative to control participants. Note that the lower nucleus accumbens volume found in the conduct disorder (CD) group is not visible. **(C)** Cohen's *d* effect sizes for all case-control comparisons in subcortical volume. Comparison lines in the top portion of the graph indicate significant differences between diagnostic groups. All analyses were adjusted for age, sex, and intracranial volume (except for intracranial volume itself). Error bars represent 95% CIs. Significant results (false discovery rate [FDR] $q = .05$) are indicated by $^{*}p_{FDR} < .05$, $^{**}p_{FDR} < .005$, $^{***}p_{FDR} < .001$. ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder.

amygdala volume were observed across all 4 disorders, spanning internalizing and externalizing groupings. This fits with previous cross-disorder studies of brain structure and function in adults (19,32,48), including a recent meta-analysis that confirmed that common GMV alterations (including in the insula) were not due to comorbidity (16). Cortico-amygdala network alterations are implicated in both internalizing and externalizing disorders (49) and may relate to shared emotion-processing deficits (50). The insula and amygdala are key nodes within the salience network, which is involved in the detection of salient stimuli (51). Salience network dysfunction may be present across psychiatric disorders, contributing to misattributions of salience and subsequent maladaptive behavior (e.g., threat-based responses and biases) (52). Together with previous work (19,32,48,53,54), our results suggest that the salience network may be implicated in general psychopathological processes shared across diagnostic categories, consistent with theories of the latent structure of psychopathology (40,41). These common alterations could represent targets for intervention, using neurofeedback or neuromodulation to enhance cognitive control and salience attribution with potential transdiagnostic applicability (19,48,54,55), particularly during youth when these regions are still developing (56).

We identified additional alterations common to at least one internalizing and one externalizing disorder, with several regions implicated in 3 disorders. Many identified alterations replicate findings from ENIGMA working groups focusing on specific disorders (24,26) but highlight cross-disorder similarities, such as lower SA in prefrontal regions. Prefrontal cortex alterations have been identified across psychiatric disorders in youth (10,12,14,47), consistent with evidence that executive dysfunction is shared across internalizing and externalizing disorders (49,52). Previously, such common alterations were difficult to identify due to methodological differences between single-disorder studies. Thus, our results demonstrate the potential of mega-analyses to allow formal statistical comparisons of each diagnostic group against control participants and to one another within the same study.

Consistent with predictions, some brain alterations were observed only in externalizing disorders (lower SA in frontoparietal regions). These regions support higher-order cognition and emotional appraisal (48,51), and therefore structural alterations in these regions may contribute to attention, working memory, and cognitive control deficits observed in externalizing disorders and underlying common symptoms (e.g., impulsivity) (57,58). ADHD and CD frequently co-occur (59), and while we evaluated the impact of comorbidity in CD (these analyses showed that effect sizes were similar in pure and comorbid forms of CD), this was not possible in ADHD. As rates of comorbid CD in the ADHD group are unknown, these results should be interpreted with caution. Nevertheless, previous studies have reported that frontoparietal structural alterations in ADHD or CD were independent of comorbidity (14,24,31).

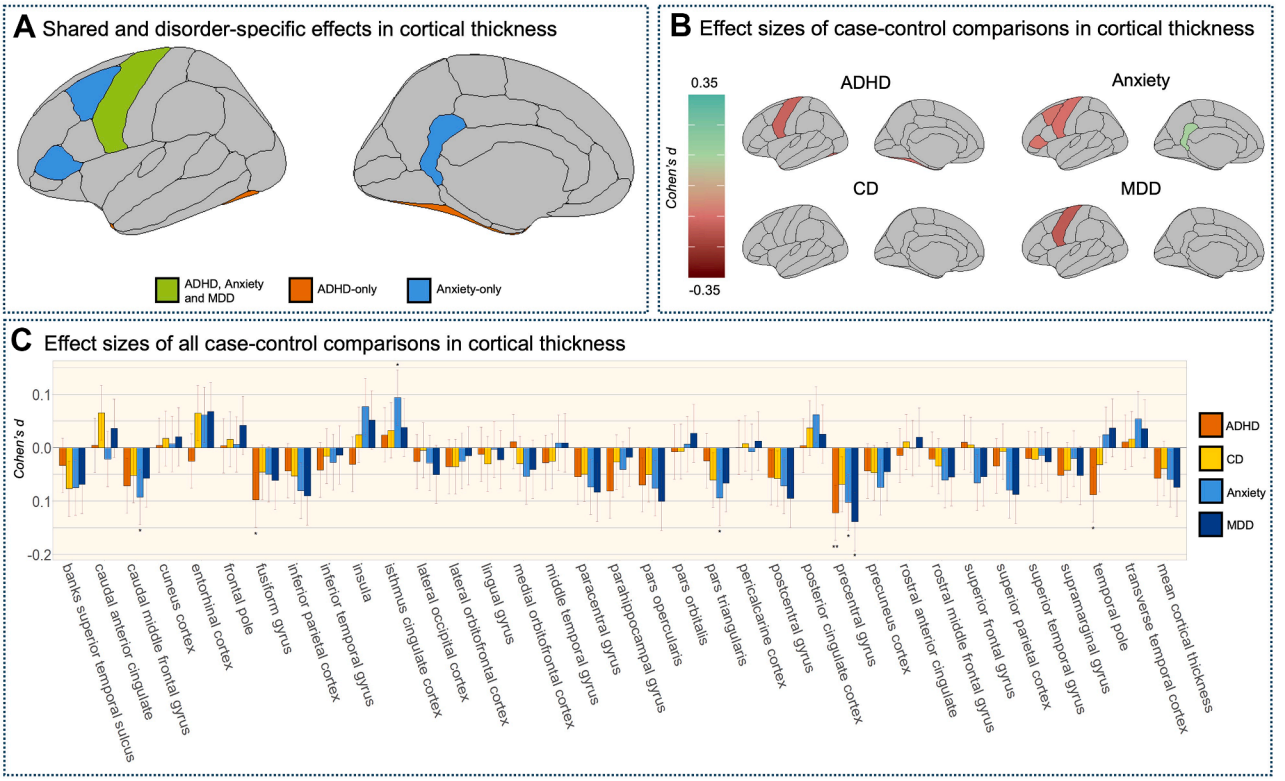

Figure 4. Transdiagnostic, shared, and disorder-specific effects on cortical thickness. **(A)** Brain maps showing case-control effects in cortical thickness that were shared across disorders or were disorder specific, again presented showing the 34 regions investigated from the Desikan-Killiany atlas. **(B)** Cohen's *d* maps indicating case-control differences in cortical thickness for each disorder separately, where red represents a decrease and green represents an increase relative to control participants. **(C)** Effect sizes for all case-control comparisons in cortical thickness, expressed as Cohen's *d*. All analyses were adjusted for age and sex. Error bars represent 95% CIs. Significant results (false discovery rate [FDR] $q = .05$) are indicated by $^{*}p_{FDR} < .05$, $^{**}p_{FDR} < .005$. ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; MDD, major depressive disorder.

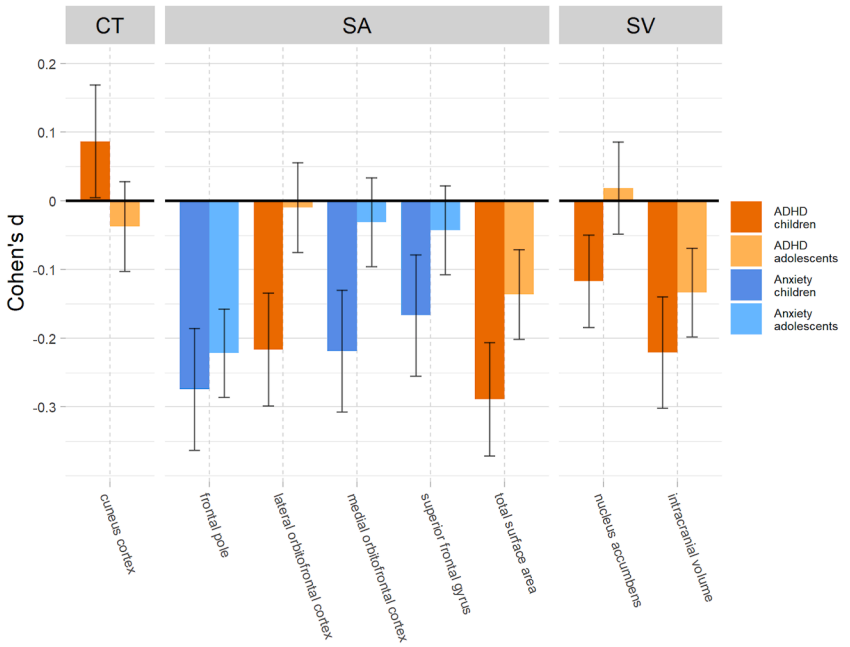

Figure 5. Case-control effect sizes displayed for age-stratified subsamples for regions and disorders where significant age-by-diagnosis interactions were identified. Cohen's *d* effect sizes for false discovery rate–corrected case-control comparisons are presented separately in child (<12 years) and adolescent (12–21 years) subgroups for the anxiety and ADHD groups. Error bars represent 95% CIs. ADHD, attention-deficit/hyperactivity disorder; CT, cortical thickness; SA, surface area; SV, subcortical volume.

Interestingly, internalizing-specific alterations were not observed. Although youths with anxiety disorders and depression did show common alterations in SA, CT, and subcortical volume, these alterations were also observed in externalizing disorders. These findings could be due to comorbidity between internalizing and externalizing disorders. Although the hippocampus has been implicated in internalizing disorders in adults (10,19), no changes were observed here. Previous ENIGMA investigations suggest that these effects may be associated with longer illness duration, as smaller volume was observed in recurrent depression and in adults (but not youths) with early-onset social anxiety (27,28). Future research should investigate the impact of comorbidity and examine how alterations change with disorder course across the lifespan.

Beyond shared associations, disorder-specific alterations were identified in ADHD, anxiety disorders, and CD. For example, only youths with ADHD displayed lower fusiform gyrus and temporal pole CT and posterior cingulate cortex SA. These findings highlight the potential importance of these regions to the pathophysiology of ADHD, given that they are implicated in ADHD-related processes, such as socioemotional processing and cognition-motivation interactions (60,61).

Youths with anxiety disorders showed disorder-specific alterations in frontal, occipital, and cingulate regions, largely consistent with previous ENIGMA-Anxiety studies (28–30). Interestingly, while we found lower pallidum and higher putamen volume in youths with anxiety disorders, previous ENIGMA studies of social anxiety disorder and specific phobia identified higher pallidum and lower putamen volume in adults (28,29). The basal ganglia's role in reward processing has been linked to anxiety and social avoidance during adolescence (28,62). Further discrepancies between previous ENIGMA findings and our results may be explained by methodological differences (e.g., surface-based vs. voxel-based morphometry and combining vs. separating several anxiety disorders).

No depression-specific alterations were identified, possibly due to high rates of co-occurring anxiety in the MDD group (56%) and insufficient power to detect subtle structural alterations, as the depression group was considerably smaller than the other groups (504 vs. >1000). Indeed, when considering nominally significant associations with effect sizes comparable to other diagnostic groups, there was suggestive evidence for depression-specific associations (e.g., transverse temporal cortex SA).

Interestingly, the CD group showed the most extensive alterations relative to the HC group, with lower SA in 21 of 34 cortical regions, 7 of which were CD specific, and lower volume in 5 subcortical regions, 3 of which were disorder specific. These results are broadly consistent with previous meta-analyses (13,14) and support recent findings on CD from ENIGMA-Antisocial Behavior (31). Notably, CD is underrecognized and understudied relative to the other disorders included here (57), despite being associated with the greatest burden of all mental disorders in 0- to 14-year-old individuals (39).

We also observed differences between diagnostic groups when we compared them directly. Some reflected differences in effect magnitude only. For example, while all 4 disorder groups exhibited lower SA in the insula relative to the HC group, the depression group also showed significantly lower SA than the ADHD and CD groups. In other regions, the diagnostic groups showed opposing associations relative to the HC group. This was most evident when we compared the CD and anxiety groups, which differed from the HC group in opposite ways and differed significantly from each other in parahippocampal gyrus, fusiform gyrus, isthmus cingulate cortex, and postcentral gyrus SA, as well as hippocampal volume. These regions are broadly related to sensory processing, memory, and emotion regulation. Direct comparisons of youth with these disorders are rare in the literature, and our findings provide novel insight into their differing neuroanatomical profiles. While this could provide targets for precision medicine, we note that the lack of exclusive effects and extent of shared alterations instead suggest that these diagnostic groups may have more in common than was previously thought. This is consistent with 2 recent network-level meta-analyses, also suggesting a lack of specificity across diagnostic groups (and identifying transdiagnostic overlap within the salience network) (53,63).

Across the 4 disorders studied here, widespread alterations were observed for SA and subcortical volume but not for CT. Moreover, effect sizes were smaller for CT. These findings are consistent with previous ENIGMA disorder-specific studies of youths (24,26,31). In contrast, large-scale studies of psychiatric disorders in adults have reported CT reductions, with less clear evidence of SA alterations (26,64). In healthy development, SA tends to peak during preadolescence before plateauing and gradually decreasing during adolescence, while CT peaks during early childhood before decreasing in late childhood/adolescence (44). Our findings fit with the hypothesis that youth psychopathology is associated with disrupted maturation of SA, potentially normalizing by adulthood. Transdiagnostic causes or mechanisms may underlie these findings. For example, there are reports of significant negative genetic correlations between SA and certain psychiatric disorders (e.g., ADHD, MDD), indicating that genetic influences that result in smaller SA may overlap with those that increase risk for psychopathology (43). Our results also suggest that many previous findings of altered CT in single disorders in youth samples might have been false positives, which may explain challenges with replication in this area (65–68).

Notably, we did not examine the range of established subtypes within each of the included diagnostic groups. For example, the class of anxiety disorders groups together several subtypes, including generalized anxiety disorder, social anxiety disorder, specific phobias, and panic disorders, while subtype specifiers for CD include age of onset (childhood vs. adolescent onset) and with versus without limited prosocial emotions. These sources of heterogeneity within each of the disorders might have contributed to the small effect sizes observed here (maximum Cohen's $d = -0.33$). As only a subset of those with a given disorder may show brain alterations (69–71), averaging across them may yield small effect sizes.

No sex-by-diagnosis interactions were identified, consistent with limited evidence for sex differences in the ENIGMA studies of these disorders (24–28,30,31). However, a small number of age-by-diagnosis interactions were observed for

ADHD, anxiety disorders, and depression: Associations were more pronounced in children versus adolescents, consistent with findings from ENIGMA-ADHD (24,25). Notably, these interactions were mainly found in later-developing frontal regions, which may explain why they are more vulnerable to disrupted maturation (56). Although our results are suggestive of altered developmental trajectories, we note that our results were based on cross-sectional data, and longitudinal designs are needed to investigate hypotheses regarding altered brain development.

Most findings survived adjustment for IQ but were more affected by adjusting for medication status, suggesting that some structural alterations were more related to medication use than to disorder status. Alternatively, medication status may serve as a proxy for disorder severity (e.g., children with severe ADHD are more likely to be prescribed psychostimulants). Missing information on disorder severity prevented us from exploring this aspect here. Moreover, the sensitivity analyses should be interpreted cautiously as medication (and IQ) data were unavailable for many sites/participants, reducing sample sizes for these analyses.

A key strength of this study is the sample size, representing the largest cross-disorder analysis of brain structure in youths performed to date, and the broad age range (4–21 years). Our comparison of common internalizing and externalizing disorders builds on a leading model of the latent structure of psychopathology and earlier studies on genetic and environmental risk factors (4,40–42). Standardized protocols reduced site-related heterogeneity, while using individual participant-level data enabled us to explore individual-level characteristics (e.g., age and sex).

However, comorbidity effects could not be systematically investigated due to a lack of consistent data across samples and working groups. Comorbidity might have impacted our identification of transdiagnostic and disorder-specific associations. While we conducted exploratory analyses of comorbidity effects in youths with CD, these were based on small subgroups and are presented only for completeness, highlighting the need for future research. The diagnostic groups differed in age, with youths with depression being older on average. Although we adjusted for age, these differences might have impacted our findings. Our definition of disorder-specific associations depended on false discovery rate–corrected case-control differences and did not indicate exclusivity (i.e., a diagnostic group differing from the HC group and the other 3 disorder groups). We note that there were instances where similar effect sizes were found for 2 groups, but only 1 was significant (potentially due to differing sample sizes). While no examples of true exclusivity were identified, the strongest evidence for a specific association was for parahippocampal gyrus SA, where the CD and anxiety groups differed from the HC group in opposite ways and differed significantly from each other, with no differences observed in ADHD or depression. Finally, we only studied 4 disorders, and although these are the most common [and impairing (39)] internalizing and externalizing disorders in youth (37,38), the terms transdiagnostic, internalizing-specific, and externalizing-specific should be interpreted with this in mind.

Although this mega-analysis included community- and population-based cohorts, most of the included studies used case-control designs with clinical samples (in common with most neuroimaging research). This represents a limitation of the current study, as the biases associated with case-control designs may limit generalizability to the wider population (72). However, we note similarities between our findings and those obtained in more representative community- and population-based samples. For example, 3 studies based on the ABCD (Adolescent Brain Cognitive Development) sample suggest that general psychopathology (a measure of shared variance across internalizing and externalizing dimensions) in youth is associated with lower global SA rather than CT (73–75), consistent with our results. Nevertheless, while community-based samples are more representative of the general population, case-control designs are more generalizable to help-seeking individuals (76). Arguably, this is the (sub)population that will benefit most from advances in clinical neuroimaging.

Conclusions

In this first mega-analysis of structural brain alterations across internalizing and externalizing disorders in youth, we demonstrated that youths with different diagnoses showed common reductions in cortical SA and subcortical volume relative to HC participants. Beyond transdiagnostic alterations, additional shared and disorder-specific associations were identified, with youths with CD showing the most widespread associations overall. These results extend our understanding of the neurobiological basis of youth psychopathology and have the potential to guide research targeting common biological processes across psychiatric disorders and examining how and why shared alterations in the salience network (e.g., the insula and amygdala) may give rise to different forms of psychopathology. We also observed some evidence for more pronounced brain structural alterations during childhood than adolescence for certain disorders, highlighting the need to study psychopathology during childhood [when many psychiatric disorders emerge (77)] to reduce the global disease burden.

ACKNOWLEDGMENTS AND DISCLOSURES

ST was supported by a Ph.D. studentship from the Economic and Social Research Council (Grant No. ES/P000630/1). See the Supplement for all relevant funding sources. The funders had no role in the study design; collection, management, analysis, or interpretation of data; or writing, reviewing, or the decision to submit the article.

Data supporting the findings of this study are not publicly available due to privacy or ethical considerations but can be requested from the corresponding authors or the ENIGMA working group in question (contact details can be found on the ENIGMA Consortium website: https://enigma.ini.usc.edu). Requested data can only be shared if approved by the working group in question and the principal investigators of the individual cohorts. Some of the included datasets (e.g., ABCD Study, The Neurobiology and Treatment of Adolescent Female Conduct Disorder [FemNAT-CD] study, IMAGEN, and Consortium on Vulnerability to Externalizing Disorders and Addictions [cVEDA]) have additional data-sharing requirements.

BF received educational speaking fees and travel support from Medice. MH has received a speaker fee from Medice. DJS has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oréal, Lundbeck, Orion, Sanofi, Servier, Takeda (Roche), and Vistagen. DGS receives royalties from Wolters Kluwer and Guilford Press for a treatment manual on cognitive behavioral therapy for anger and aggression in children. LS received research funding for speaking and conference support from Medice in 2023. SB discloses that he has acted as an author,

consultant, or lecturer for Medice and LinusBio during the last 3 years. He receives royalties for textbooks and diagnostic tools from Hogrefe, UTB, Ernst Reinhardt Verlag, Kohlhammer, and Liber. SB is also a partner in NeuroSupportSolutions International AB. PMP received payment or honoraria for lectures and presentations in educational events for Daiichi Sankyo, Abbot, and Instituto Israelita de Pesquisa e Ensino Albert Einstein. JKB has been a consultant to, member of the advisory board of, and/or speaker for Takeda, Roche, Medice, Angelini, Neuraxpharm, and Servier. He is not an employee of any of these companies and is not a stock shareholder of any of these companies. JK has received speaking honoraria and advisory panel payments for participation at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. JWS is a member of the Scientific Advisory Board of Sensorium Therapeutics (with options), has received a consulting fee from Tempus, Inc., and has received grant support from Biogen, Inc. He is the principal investigator of a collaborative study of the genetics of depression and bipolar disorder sponsored by 23andMe, for which 23andMe provides analysis time as in-kind support but no payments. DRC reports receiving royalties from Oxford University Press and Cambridge University Press and honoraria from Takeda, Novartis, Medice, and Servier. KR has received a grant from Takeda for another project. TB has served in an advisory or consultancy role for AGB Pharma eye level, Infectopharm, Medice, Neurim Pharmaceuticals, Oberberg GmbH, and Takeda. He received conference support or speaker's fees from AGB Pharma, Janssen-Cilag, Medice, and Takeda and received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. The current work is unrelated to these relationships. KH is a scientific advisor and received virtual stock options of Mental Tech GmbH, which develops an artificial intelligence–based chatbot that provides mental health support. CMF receives royalties for books on ASD, ADHD, and MDD. She has received speaker fees for talks at different public institutions and hospitals, and served as consultant to the German Institute for Quality and Efficiency in Health Care (IQWiG) and the IGES Institute GmbH, Berlin. PMZ has received speaker fees or honoraria for advisory board participation from Janssen Cilag/Johnson & Johnson, Schwabe, Sympatient, GAJA, MagVenture, Boehringer, Idorsia, and Neuraxpharm. He is board member of the German Society of Psychiatry (DGPPN), Speaker of the DGPPN-Committee Digital Psychiatry, and President of the German Society of Anxiety Research (GAF). None of these affiliations are relevant to the work covered in this article. JH has received educational speaking fees from Medice. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychology, University of Bath, Bath, United Kingdom (ST, MS, EW, GF); Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, United Kingdom (YG, SADB); Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany (NA, HJ, TK, BS); Center for Mind, Brain and Behavior, University of Marburg, Marburg, Germany (NA); Institute for Translational Psychiatry, University of Münster, Münster, Germany (VA, JB, LMB, FB, UD, DG, TH, AK, EJL, HM, SM, ES); Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, German Center for Mental Health, partner site Mannheim-Heidelberg-Ulm, Mannheim, Germany (TB, DB); Behavioral Epidemiology, Institute of Clinical Psychology and Psychotherapy, Dresden University of Technology, Dresden, Germany (KB-B); School of Psychological Sciences, Monash University, Melbourne, Victoria, Australia (MAB); Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, India (VB); Child and Adolescent Mental Health Center, Copenhagen University Hospital – Mental Health Services, Copenhagen, Denmark (RJB); Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark (RJB); MRI Research Unit, Department of Radiology, Hospital del Mar, Barcelona, Spain (LB-H, JP); Barcelona Institute for Global Health, Barcelona, Spain (LB-H); Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany (OJB); Center of Neurodevelopmental Disorders, Centre for Psychiatry Research, Department of Women's and Children's Health, Karolinska Institutet and Region Stockholm, Stockholm, Sweden (SB, JN, KLR); Child and Adolescent Psychiatry, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden (SB); Curtin Autism Research Group, Curtin School of Allied Health, Curtin University, Perth, Western Australia, Australia (SB); Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Münster, Münster, Germany (LMB); Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zürich, University of Zürich, Zürich, Switzerland (DB); Department of Psychiatry, Laboratory of Integrative Neurosciences, Universidade Federal de São Paulo, São Paulo, Brazil (RAB, PMP); Section Forensic Family and Youth Care, Institute of Education and Child Studies, Leiden University, Leiden, the Netherlands (WBB, MA); Department of Medical Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands (JKB, BF, MH); Department of Psychology, Penn State University, University Park, Pennsylvania (KLB); Neurodevelopment and Psychosis Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (MEC); Sant Pau Mental Health Research Group, Institut de Recerca Sant Pau, Barcelona, Spain (MC, NC); Centre for Biomedical Research in the Mental Health Network, Instituto de Salud Carlos III, Madrid, Spain (MC, NC); Department of Psychiatry, National Clinical Research Center for Mental Disorders, and National Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, China (HC, XC, XW, JZho); Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria, Australia (DRC); Department of Special Needs Education, Faculty of Psychology and Educational Sciences, Ghent University, Gent, Belgium (OFC); Department of Biomedical Sciences, Florida State University, Tallahassee, Florida (CGC); Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (MCC, ASe); Department of Psychiatry and Behavioural Sciences, University of Minnesota Medical School, Minneapolis, Minnesota (KRC); Department of Psychiatry, Medical School and University Medical Center OWL, Protestant Hospital of the Bethel Foundation, Bielefeld University, Bielefeld, Germany (UD); Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia (CGD, BJH); Department of Child and Adolescent Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (AD, PJH); Accare Child Study Center, Groningen, the Netherlands (AD, PJH); Medical Psychological Center, The Second Xiangya Hospital of Central South University, Changsha, China (DD, RMa, QM, XS, SY, JZha); National Clinical Research Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, China (DD); Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt am Main, Goethe University, Frankfurt am Main, Germany (CMF, AM); Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Rhineland-Westphalian Technical University, Aachen, Germany (TF); Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands (LG); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (REG); Lifespan Brain Institute, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (REG); Brain Behavior Laboratory, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania (RCG); Department of Biomedicine, University of Bergen, Bergen, Norway (JH); Division of Psychiatry, Haukeland University Hospital, Bergen, Norway (JH); California Institute of Technology, Pasadena, California (CCH); Department of Biological and Clinical Psychology/Psychotherapy, University of Greifswald, Greifswald, Germany (AOH); Department of Psychology, University of Greifswald, Greifswald, Germany (AOH); Interdisciplinary Center Psychopathology and Emotion Regulation, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (CAH); Center for Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital Würzburg, Würzburg, Germany (MJH); Department of Psychology, University of California Los Angeles, Los Angeles, California (TCH); Department of Integrative Medicine, National Institute of Mental Health and Neurosciences, Bengaluru, India (BH); Child Study Center, Yale University School of Medicine, New Haven, Connecticut (KI, DGS); Department of Psychiatry, Universidade

Federal de São Paulo, São Paulo, Brazil (AJ); Department of Health and Wellness Design, School of Public Health, Indiana University, Bloomington, Indiana (AJ); School of Psychology, South China Normal University, Guangzhou, China (YJ); Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Rhineland-Westphalian Technical University, Aachen, Germany (KK); JARA-BRAIN Institute II, Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH, and RWTH Aachen, Jülich, Germany (KK); Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (JK); Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany (TL, UL); Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, August Pi i Sunyer, Biomedical Research Institute, Centre for Biomedical Research in the Mental Health Network, Barcelona, Spain (LL); Department of Medicine, Institute of Neuroscience, University of Barcelona, Barcelona, Spain (LL); German Center for Mental Health, partner site Berlin/Potsdam, Germany (UL); IWK Health, Halifax, Nova Scotia, Canada (FPM); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (FPM); Department of Psychiatry, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (GGM, GAS); Psychiatry Services, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (GGM, GAS); Psychology School, Fresenius University of Applied Sciences, Frankfurt am Main, Germany (AM); Institute for Translational Neuroscience, University of Münster, Münster, Germany (SM); Poznań Laboratory of Affective Neuroscience, University SWPS, Poznań, Poland (JMM); Department of Psychiatry, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China (QM); Institute of Medical Psychology and Systems Neuroscience, University Hospital Münster, Münster, Germany (RMo, TSt); Department of Psychology, Faculty of Human Sciences, Medical School Hamburg, Hamburg, Germany (MM); Biomedical Engineering, Laufer Center for Physical and Quantitative Biology, State University of New York at Stony Brook, Stony Brook, New York (LRM-P); Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (LRM-P); Center of Excellence on Mood Disorders, Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, UTHealth Houston, Houston, Texas (BM, JCS, M-JW, GBZ-S); Swedish Collegium for Advanced Study, Uppsala, Sweden (JN); Department of Psychiatry, Oregon Health and Science University, Portland, Oregon (JTN); University Children's Hospital Zurich, Zurich, Switzerland (RLOT); University of Zurich, Zurich, Switzerland (RLOT); Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas (HO); Menninger Clinic, Houston, Texas (HO, RS); Clinical Neuropsychology Section, Vrije Universiteit, Amsterdam, the Netherlands (JO); Emma Children's Hospital, Amsterdam University Medical Center location University of Amsterdam, Department of Pediatrics, Emma Children's Hospital Amsterdam University Medical Center Follow-Me program & Emma Neuroscience Group, Amsterdam, the Netherlands (JO); Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands (JO); Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (YP); Clinical Neuroscience Department, University of Cambridge, Cambridge, United Kingdom (LP); Department of Clinical Psychology, Psychobiology and Methodology, University of La Laguna, La Laguna, Tenerife, Spain (WP); University Institute of Neuroscience, La Laguna, Tenerife, Spain (WP); Department of Psychiatry and Behavioral Health, The Ohio State University, Columbus, Ohio (KLP); Division of Child and Adolescent Psychiatry, Department of Psychiatry, University Hospital Lausanne and University of Lausanne, Lausanne, Switzerland (KJP); Facultad de Ciencias de la Salud, Universidad Europea de Canarias, La Orotava, Tenerife, Spain (FR); Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (KR, GSu); Department of Neuroscience, Baylor College of Medicine, Houston, Texas (RS); Center for Translational Research on Inflammatory Diseases, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (RS); Child Mind Institute, New York, New York (GAS); Penn Lifespan Informatics and Neuroimaging Center, Philadelphia, Pennsylvania (TDS); Penn-CHOP Lifespan Brain Institute, Philadelphia, Pennsylvania (TDS); Clinical Psychology, University of Graz, Graz, Austria (ASc, AW); Research Institute for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands (KRJS); Mondriaan Mental Health Center, Maastricht, the Netherlands (KRJS); Centre for Population Neuroscience and Stratified Medicine, The Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, China (GSc); Centre for Population Neuroscience and Precision Medicine, Department of Psychiatry and Neuroscience, Charité Universitätsmedizin Berlin, Berlin, Germany (GSc); School of Psychology and the Centre for Social and Early Emotional Development, Deakin University, Geelong, Victoria, Australia (TSi); Regional Centre for Child and Youth Mental Health and Child Welfare, Norwegian University of Science and Technology, Trondheim, Norway (NS); Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts (JWS); Center for Precision Psychiatry, Massachusetts General Hospital, Boston, Massachusetts (JWS); Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway (LS); Child and Adolescent Psychiatric Research Department, Universitäre Psychiatrische Kliniken Basel, Basel, Switzerland (CS); Olin Neuropsychiatry Research Center, Hartford, Connecticut (MCS); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (MCS); Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany (AS); School of Psychology, University of Southampton, Southampton, United Kingdom (KS); Department of Psychiatry, Washington University in St. Louis, St. Louis, Missouri (CMS); Department of Radiology, Washington University in St. Louis, St. Louis, Missouri (CMS); Taylor Family Institute for Innovative Psychiatric Research, Washington University in St. Louis, St. Louis, Missouri (CMS); Department of Biomedicine and Prevention, University of Rome "Tor Vergata," Rome, Italy (NT); Martinos Center for Biomedical Imaging, Boston, Massachusetts (NT); Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands (SJAvdW, NJAvW, JMB-H); Leiden Institute for Brain and Cognition, Leiden, the Netherlands (SJAvdW, NJAvW, JMB-H); Academic Child Psychiatry Unit, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Victoria, Australia (AV); Leiden University Medical Center Curium, Child and Adolescent Psychiatry, Leiden University Medical Center, Leiden, the Netherlands (RV); Biological Psychology and Affective Science, University of Potsdam, Potsdam, Germany (JWe); Oberberg Clinic Potsdam, Potsdam, Germany (JWe); Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Victoria, Australia (SW, EP, LS); Centre for Youth Mental Health, University of Melbourne, Parkville, Victoria, Australia (SW, LKMH, EP, LS); Institute of Psychology (Biological Psychology, Clinical Psychology, and Psychotherapy), University of Würzburg, Würzburg, Germany (JWi); Division of Human Genetics, The University of Texas Rio Grande Valley, Browsville, Texas (AMW); Department Psychiatry and Psychotherapy, Ludwig Maximilians University, München, Germany (HUW, PMZ); Department of Neurology, Max-Planck-Institute for Human Cognitive and Brain Sciences, Leipzig, Germany (QW); Clinic for Neurology, University of Leipzig Medical Center, Leipzig, Germany (QW); Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, California (TTY); Institut for Psychology, University of Hildesheim, Hildesheim, Germany (YY); National Institute of Mental Health Intramural Research Program, Bethesda, Maryland (AZ, DSP); kbo-Inn-Salzach-Hospital Clinical Center for Psychiatry, Psychotherapy and Psychosomatics, Wasserburg am Inn, Germany (PMZ); Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina del Rey, California (SIT, NJ, PMT); Department of Psychology, Health and Medical University Erfurt, Erfurt, Germany (KH); Department of Psychology, Yale University, New Haven, Connecticut (AB-S); Department of Child and Adolescent Psychiatry and Psychology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands (CAMC); Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands (CAMC); South African Medical Research Council Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa (DJS); Department of Psychiatry, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa (DJS); Department of Psychiatry and Mental Health, Neuroscience Institute, University of Cape Town, Cape Town, South Africa (NAG); Institute of

Psychology, Leiden University, Leiden, the Netherlands (JMB-H); Department of Psychiatry, Amsterdam University Medical Center location Vrije Universiteit, Amsterdam Neuroscience, Amsterdam, the Netherlands (LKMH); Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands (BF); Department of Psychiatry, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands (MH); Institute for Mental Health, School of Psychology, University of Birmingham, Birmingham, United Kingdom (SADB); Centre for Developmental Science, School of Psychology, University of Birmingham, Birmingham, United Kingdom (SADB); Birmingham Centre for Neurogenetics, School of Psychology, University of Birmingham, Birmingham, United Kingdom (SADB).

Address correspondence to Sophie Townend, Ph.D., at st2325@bath.ac.uk.

Received Jan 21, 2025; revised Jul 11, 2025; accepted Aug 4, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2025.08.003.

REFERENCES

1. Caspi A, Houts RM, Ambler A, Danese A, Elliott ML, Hariri A, *et al.* (2020): Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin birth cohort study. JAMA Netw Open 3:e203221.
2. Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, *et al.* (2018): Analysis of shared heritability in common disorders of the brain. Science 360:eaap8757.
3. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, Cross-Disorder Group of the Psychiatric Genomics Consortium (2019): Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179:1469–1482.e11.
4. Kendler KS, Prescott CA, Myers J, Neale MC (2003): The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 60:929–937.
5. Arango C, Dragioti E, Solmi M, Cortese S, Domschke K, Murray RM, *et al.* (2021): Risk and protective factors for mental disorders beyond genetics: An evidence-based atlas. World Psychiatry 20:417–436.
6. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC (2010): Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 67:113–123.
7. Krueger RF, Caspi A, Moffitt TE, Silva PA (1998): The structure and stability of common mental disorders (DSM-III-R): A longitudinal-epidemiological study. J Abnorm Psychol 107:216–227.
8. Plana-Ripoll O, Pedersen CB, Holtz Y, Benros ME, Dalsgaard S, De Jonge P, *et al.* (2019): Exploring comorbidity within mental disorders among a Danish national population. JAMA Psychiatry 76:259–270.
9. Cicchetti D, Toth SL (1991): A developmental perspective on internalizing and externalizing disorders. Internalizing and externalizing expression of dysfunction. In: , 2. Rochester Symposium on Developmental Psychopathology: Internalizing and Externalizing Expressions of Dysfunction. Rochester: University of Rochester Press.
10. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM (2012): Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. Eur Neuropsychopharmacol 22:1–16.
11. Kolesar TA, Bilevicius E, Wilson AD, Kornelsen J (2019): Systematic review and meta-analyses of neural structural and functional differences in generalized anxiety disorder and healthy controls using magnetic resonance imaging. NeuroImage Clin 24:102016.
12. Nakao T, Radua J, Rubia K, Mataix-Cols D (2011): Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 168:1154–1163.
13. Rogers JC, De Brito SA (2016): Cortical and subcortical gray matter volume in youths with conduct problems: A meta-analysis. JAMA Psychiatry 73:64–72.
14. Noordermeer SDS, Luman M, Oosterlaan J (2016): A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (ODD) and conduct disorder (CD) taking attention-deficit hyperactivity disorder (ADHD) into account. Neuropsychol Rev 26:44–72.
15. Brandl F, Weise B, Mulej Bratec S, Jassim N, Hoffmann Ayala D, Bertram T, *et al.* (2022): Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: A transdiagnostic multimodal meta-analysis of structural and functional MRI studies. Neuropsychopharmacology 47:1071–1080.
16. Fortea L, Ortuño M, De Prisco M, Oliva V, Albajes-Eizagirre A, Fortea A, *et al.* (2025): Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders. Biol Psychiatry 98:76–90.
17. Matsumoto J, Fukunaga M, Miura K, Nemoto K, Okada N, Hashimoto N, *et al.* (2023): Cerebral cortical structural alteration patterns across four major psychiatric disorders in 5549 individuals. Mol Psychiatry 28:4915–4923.
18. Taylor JJ, Lin C, Talmasov D, Ferguson MA, Schaper FLWVJ, Jiang J, *et al.* (2023): A transdiagnostic network for psychiatric illness derived from atrophy and lesions. Nat Hum Behav 7:420–429.
19. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, *et al.* (2015): Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72:305–315.
20. Boedhoe PS, Heymans MW, Schmaal L, Abe Y, Alonso P, Ameis SH, *et al.* (2018): An empirical comparison of meta- and mega-analysis with data from the ENIGMA obsessive–compulsive disorder working group. Front Neuroinform 12:102.
21. Zugman A, Harrewijn A, Cardinale EM, Zwiebel H, Freitag GF, Werwath KE, *et al.* (2022): Mega-analysis methods in ENIGMA: The experience of the generalized anxiety disorder working group. Hum Brain Mapp 43:255–277.
22. Müller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, *et al.* (2018): Ten simple rules for neuroimaging meta-analysis. Neurosci Biobehav Rev 84:151–161.
23. Thompson PM, Jahanshad N, Ching CRK, Salminen LE, Thomopoulos SI, Bright J, *et al.* (2020): ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. Transl Psychiatry 10:100.
24. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, *et al.* (2019): Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples. Am J Psychiatry 176:531–542.
25. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, *et al.* (2017): Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. Lancet Psychiatry 4:310–319.
26. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, *et al.* (2017): Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol Psychiatry 22:900–909.
27. Schmaal L, Veltman DJ, van Erp TG, Sämann PG, Frodl T, Jahanshad N, *et al.* (2016): Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry 21:806–812.
28. Groenewold NA, Bas-Hoogendam JM, Amod AR, Laansma MA, Van Velzen LS, Aghajani M, *et al.* (2023): Volume of subcortical brain regions in social anxiety disorder: Mega-analytic results from 37 samples in the ENIGMA-Anxiety Working Group. Mol Psychiatry 28:1079–1089.
29. Hilbert K, Boeken OJ, Langhammer T, Groenewold NA, Bas-Hoogendam JM, Aghajani M, *et al.* (2024): Cortical and subcortical brain alterations in specific phobia and its animal and blood-injection-injury subtypes: A mega-analysis from the ENIGMA anxiety working group. Am J Psychiatry 181:728–740.
30. Harrewijn A, Cardinale EM, Groenewold NA, Bas-Hoogendam JM, Aghajani M, Hilbert K, *et al.* (2021): Cortical and subcortical brain

structure in generalized anxiety disorder: Findings from 28 research sites in the ENIGMA-Anxiety Working Group. Transl Psychiatry 11:502.
31. Gao Y, Staginnus M, ENIGMA-Antisocial Behavior Working Group (2024): Cortical structure and subcortical volumes in conduct disorder: A coordinated analysis of 15 international cohorts from the ENIGMA-Antisocial Behavior Working Group. Lancet Psychiatry 11:620–632.
32. Opel N, Goltermann J, Hermesdorf M, Berger K, Baune BT, Dannlowski U (2020): Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: A secondary analysis of mega- and meta-analytical findings from the ENIGMA Consortium. Biol Psychiatry 88:678–686.
33. Hettwer MD, Larivière S, Park BY, van den Heuvel OA, Schmaal L, Andreassen OA, *et al.* (2022): Coordinated cortical thickness alterations across six neurodevelopmental and psychiatric disorders. Nat Commun 13:6851.
34. Hansen JY, Shafiei G, Vogel JW, Smart K, Bearden CE, Hoogman M, *et al.* (2022): Local molecular and global connectomic contributions to cross-disorder cortical abnormalities. Nat Commun 13:4682.
35. Patel Y, Parker N, Shin J, Howard D, French L, Thomopoulos SI, *et al.* (2020): Virtual histology of cortical thickness reveals shared neurobiology across six psychiatric disorders. Biol Psychiatry 87:S239–S240.
36. Boedhoe PSW, van Rooij D, Hoogman M, Twisk JWR, Schmaal L, Abe Y, *et al.* (2020): Subcortical brain volume, regional cortical thickness, and cortical surface area across disorders: Findings from the ENIGMA ADHD, ASD, and OCD working groups. Am J Psychiatry 177:834–843.
37. Kieling C, Buchweitz C, Caye A, Silvani J, Ameis SH, Brunoni AR, *et al.* (2024): Worldwide prevalence and disability from mental disorders across childhood and adolescence: Evidence from the global burden of disease study. JAMA Psychiatry 81:347–356.
38. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA (2015): Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 56:345–365.
39. GBD 2019 Mental Disorders Collaborators (2022): Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9:137–150.
40. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, *et al.* (2014): The p factor: One general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2:119–137.
41. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, *et al.* (2017): The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol 126:454–477.
42. Lahey BB, Van Hulle CA, Singh AL, Waldman ID, Rathouz PJ (2011): Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. Arch Gen Psychiatry 68:181–189.
43. Grasby KL, Jahanshad N, Painter JN, Colodro-Conde L, Bralten J, Hibar DP, *et al.* (2020): The genetic architecture of the human cerebral cortex. Science 367:eaay6690.
44. Bethlehem RAI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C, *et al.* (2022): Brain charts for the human lifespan. Nature 604:525–533.
45. Bas-Hoogendam JM, Groenewold NA, Aghajani M, Freitag GF, Harrewijn A, Hilbert K, *et al.* (2022): ENIGMA-Anxiety Working Group: Rationale for and organization of large-scale neuroimaging studies of anxiety disorders. Hum Brain Mapp 43:83–112.
46. Radua J, Vieta E, Shinohara R, Kochunov P, Quidé Y, Green MJ, *et al.* (2020): Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. NeuroImage 218:116956.
47. Yu G, Liu Z, Wu X, Becker B, Zhang K, Fan H, *et al.* (2023): Common and disorder-specific cortical thickness alterations in internalizing, externalizing and thought disorders during early adolescence: An Adolescent Brain and Cognitive Development study. J Psychiatry Neurosci 48:E345–E356.
48. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A (2017): Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am J Psychiatry 174:676–685.
49. Buckholtz JW, Meyer-Lindenberg A (2012): Psychopathology and the human connectome: Toward a transdiagnostic model of risk for mental illness. Neuron 74:990–1004.
50. Zald DH (2003): The human amygdala and the emotional evaluation of sensory stimuli. Brain Res Brain Res Rev 41:88–123.
51. Bressler SL, Menon V (2010): Large-scale brain networks in cognition: Emerging methods and principles. Trends Cogn Sci 14:277–290.
52. Sha Z, Wager TD, Mechelli A, He Y (2019): Common dysfunction of large-scale neurocognitive networks across psychiatric disorders. Biol Psychiatry 85:379–388.
53. Segal A, Parkes L, Aquino K, Kia SM, Wolfers T, Franke B, *et al.* (2023): Regional, circuit and network heterogeneity of brain abnormalities in psychiatric disorders. Nat Neurosci 26:1613–1629.
54. Shanmugan S, Wolf DH, Calkins ME, Moore TM, Ruparel K, Hopson RD, *et al.* (2016): Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. Am J Psychiatry 173:517–526.
55. Peters SK, Dunlop K, Downar J (2016): Cortico-striatal-thalamic loop circuits of the salience network: A central pathway in psychiatric disease and treatment. Front Syst Neurosci 10:104.
56. Sydnor VJ, Larsen B, Bassett DS, Alexander-Bloch A, Fair DA, Liston C, *et al.* (2021): Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. Neuron 109:2820–2846.
57. Fairchild G, Hawes DJ, Frick PJ, Copeland WE, Odgers CL, Franke B, *et al.* (2019): Conduct disorder. Nat Rev Dis Primers 5:43.
58. Castellanos FX, Proal E (2012): Large-scale brain systems in ADHD: Beyond the prefrontal–striatal model. Trends Cogn Sci 16:17–26.
59. Angold A, Costello EJ, Erkanli A (1999): Comorbidity. J Child Psychol Psychiatry 40:57–87.
60. Wong C, Gallate J (2012): The function of the anterior temporal lobe: A review of the empirical evidence. Brain Res 1449:94–116.
61. Rubia K, Smith AB, Brammer MJ, Toone B, Taylor E (2005): Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry 162:1067–1075.
62. Caouette JD, Guyer AE (2014): Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. Dev Cogn Neurosci 8:65–76.
63. Wall J, Miller GN, Taylor JJ, Stubbs JL, Warfield SK, Cohen AL (2025): Coordinate network mapping of focal brain volume differences in ADHD reveals common patterns that lack specificity: A systematic review. Annals of the Child Neurology Society 3:91–104.
64. Hoy N, Lynch SJ, Waszczuk MA, Reppermund S, Mewton L (2023): Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population. Neurosci Biobehav Rev 155:105431.
65. Fairchild G, Sully K, Passamonti L, Staginnus M, Darekar A, Sonuga-Barke EJS, Toschi N (2023): Neuroanatomical markers of familial risk in adolescents with conduct disorder and their unaffected relatives. Psychol Med 53:1721–1731.
66. Sarkar S, Daly E, Feng Y, Ecker C, Craig MC, Harding D, *et al.* (2015): Reduced cortical surface area in adolescents with conduct disorder. Eur Child Adolesc Psychiatry 24:909–917.
67. Smaragdi A, Cornwell H, Toschi N, Riccelli R, Gonzalez-Madruga K, Wells A, *et al.* (2017): Sex differences in the relationship between conduct disorder and cortical structure in adolescents. J Am Acad Child Adolesc Psychiatry 56:703–712.
68. Stevens MC, Haney-Caron E (2012): Comparison of brain volume abnormalities between ADHD and conduct disorder in adolescence. J Psychiatry Neurosci 37:389–398.
69. ENIGMA Clinical High Risk for Psychosis Working Group, Haas SS, Ge R, Agartz I, Amminger GP, Andreassen OA, *et al.* (2024): Normative modeling of brain morphometry in clinical high risk for psychosis. JAMA Psychiatry 81:77–88.

70. Li T, van Rooij D, Roth Mota N, Buitelaar JK, ENIGMA ADHD Working Group, Hoogman M, *et al.* (2021): Characterizing neuroanatomic heterogeneity in people with and without ADHD based on subcortical brain volumes. J Child Psychol Psychiatry 62:1140–1149.
71. Wolfers T, Beckmann CF, Hoogman M, Buitelaar JK, Franke B, Marquand AF (2020): Individual differences v. the average patient: Mapping the heterogeneity in ADHD using normative models. Psychol Med 50:314–323.
72. Horga G, Kaur T, Peterson BS (2014): Annual research review: Current limitations and future directions in MRI studies of child- and adult-onset developmental psychopathologies. J Child Psychol Psychiatry 55:659–680.
73. Mewton L, Lees B, Squeglia LM, Forbes MK, Sunderland M, Krueger R, *et al.* (2022): The relationship between brain structure and general psychopathology in preadolescents. J Child Psychol Psychiatry 63:734–744.
74. Modabbernia A, Michelini G, Reichenberg A, Kotov R, Barch D, Frangou S (2022): Neural signatures of data-driven psychopathology dimensions at the transition to adolescence. Eur Psychiatry 65:e12.
75. Romer AL, Ren B, Pizzagalli DA (2023): Brain structure relations with psychopathology trajectories in the ABCD study. J Am Acad Child Adolesc Psychiatry 62:895–907.
76. Rutter M, Pine DS (2015): Diagnosis, diagnostic formulations, and classification. In: Thapar A, Pine DS, Leckman JF, Scott S, Snowling MJ, Taylor EA, editors. Rutter's Child and Adolescent Psychiatry, 6th ed. Chichester, UK: John Wiley & Sons Limited, 17–30.
77. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, *et al.* (2022): Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry 27:281–295.