Subcortical Brain Volume, Regional Cortical Thickness, and Cortical Surface Area Across Disorders: Findings From the ENIGMA ADHD, ASD, and OCD Working Groups

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Objective: Attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders that frequently co-occur. The authors sought to directly compare these disorders using structural brain imaging data from ENIGMA consortium data.

Methods: Structural T_1-weighted whole-brain MRI data from healthy control subjects (N=5,827) and from patients with ADHD (N=2,271), ASD (N=1,777), and OCD (N=2,323) from 151 cohorts worldwide were analyzed using standardized processing protocols. The authors examined subcortical volume, cortical thickness, and cortical surface area differences within a mega-analytical framework, pooling measures extracted from each cohort. Analyses were performed separately for children, adolescents, and adults, using linear mixed-effects models adjusting for age, sex, and site (and intracranial volume for subcortical and surface area measures).

Results: No shared differences were found among all three disorders, and shared differences between any two disorders did not survive correction for multiple comparisons. Children with ADHD compared with those with OCD had smaller hippocampal volumes, possibly influenced by IQ. Children and adolescents with ADHD also had smaller intracranial volume than control subjects and those with OCD or ASD. Adults with ASD showed thicker frontal cortices compared with adult control subjects and other clinical groups. No OCD-specific differences were observed across different age groups and surface area differences among all disorders in childhood and adulthood.

Conclusions: The study findings suggest robust but subtle differences across different age groups among ADHD, ASD, and OCD. ADHD-specific intracranial volume and hippocampal differences in children and adolescents, and ASD-specific cortical thickness differences in the frontal cortex in adults, support previous work emphasizing structural brain differences in these disorders.

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Attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders with lifetime prevalences of 2.5%−5%, ~1%, and 2.3%, respectively (1–3). Symptoms mostly develop early in life (ADHD, ASD) or later in childhood (OCD) and often persist into adulthood. Characteristic symptoms include inattentiveness, impulsivity, and hyperactivity for ADHD; impairments in social communication and restricted and stereotyped behaviors for ASD; and repetitive thoughts (obsessions) and behaviors or mental acts (compulsions) that cause distress or anxiety for OCD. Although each disorder is distinguished by its own core symptoms, the disorders frequently co-occur and overlap in phenomenology and pathophysiology (4, 5).

There are parallels between the uncontrollable impulsive behaviors of ADHD and the excessive and compulsive rituals of OCD and ASD. Impaired response inhibition and cognitive control processes may underlie the cross-disorder traits within the impulsive-compulsive spectrum (6), implicating cortico-striato-thalamo-cortical and fronto-parietal networks (7). It remains unclear whether—and if so, which—morphological brain abnormalities within these networks are shared (nonspecific) or distinct (specific to one disorder).

Imaging studies, including meta-analyses, have generally compared individuals with one of the three disorders to healthy control subjects (8–12). Large-scale studies have generally yielded small to moderate effect sizes, indicating that disorder-associated differences are subtle (13–17). Few structural imaging studies have directly compared these three disorders (18, 19), mostly in small numbers and with inconsistent results (20). A meta-analysis including 931 patients with ADHD and 928 with OCD reported shared smaller ventromedial prefrontal cortex gray matter volume, ADHD-specific smaller gray matter volume in the basal ganglia and insula, and OCD-specific smaller volume of the rostral and dorsal anterior cingulate and medial prefrontal cortex (21). Another meta-analysis comparing structural brain differences in 911 patients with ASD and 928 with OCD reported shared differences in the dorsal medial prefrontal cortex and OCD-specific differences in the basal ganglia (22). However, despite their clinical overlap, no structural gray matter study published to date has compared all three disorders.

The Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium (23) includes the largest samples for ADHD, ASD, and OCD worldwide (13–17). The consortium also improves on earlier meta-analyses by using harmonized protocols for brain segmentation and quality control procedures across ENIGMA working groups and by pooling extracted individual participant data. The ENIGMA consortium is therefore ideally positioned to investigate overlap and specificity of structural brain differences across disorders.

Here, we present the largest comparative study to date of subcortical and cortical differences across ADHD, ASD, and OCD. We extracted subcortical volumes, cortical thickness, and cortical surface area estimates of 12,198 individuals from 151 cohorts worldwide, using harmonized data processing protocols. Based on previous meta- and mega-analyses, we expected to find ADHD-specific differences in frontal and temporal surface areas and basal ganglia volumes in children (14, 15), ASD-specific differences in frontal and temporal cortical thickness (13), and OCD-specific differences in the thalamus of pediatric patients and the pallidum of adult patients (16). We expected that differences in the striatum and dorsomedial prefrontal cortex would be observed across disorders (21, 22).

METHODS

Samples

The ENIGMA ADHD working group includes 48 cohorts from 34 research institutes, with neuroimaging and clinical data from patients with ADHD and healthy control subjects. The ENIGMA ASD working group includes 56 cohorts from 38 research institutes, with neuroimaging and clinical data from patients with ASD and healthy control subjects. The ENIGMA OCD working group includes 47 cohorts from 34 research institutes, with neuroimaging and clinical data from patients with OCD and healthy control subjects.

All working groups included data from subjects across the lifespan. Because previous results suggested differential effects between pediatric (<12 years), adolescent (≥12 years and <18 years), and adult (≥18 years) patients, we performed separate mega-analyses for these three age groups. In total, we analyzed data from 2,271 patients with ADHD, 1,777 with ASD, 2,323 with OCD, and 5,827 healthy control subjects. All local institutional review boards permitted the use of measures extracted from the coded data for mega-analyses.

Image Acquisition and Processing

Structural T_1-weighted whole-brain MRI was performed and processed locally. Image acquisition parameters for each cohort are listed in Tables S1–S3 in the online supplement. All cortical parcellations were performed with FreeSurfer, version 5.3, following standardized ENIGMA protocols to harmonize analyses and quality control procedures across multiple sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Segmentations of seven bilateral subcortical and 34 bilateral cortical regions of interest according to the Desikan-Killiany atlas were statistically evaluated for outliers and subsequently visually inspected for segmentation success. Individual volumes with poor segmentation were removed, as were data for subjects with overall poor segmentation quality. Quality control was performed locally at each site, and only data of sufficient quality were sent for inclusion in the ENIGMA cohorts. All reported group sizes in this study are after quality control. Details on image exclusion criteria and quality control are presented in Supplementary Information SI1 in the online supplement. Data for all cohorts of each working group underwent identical processing and quality control procedures.

Statistical Analysis

We pooled extracted subcortical volumes, cortical thickness, and cortical surface area measures from individual subjects across all cohorts from the different working groups into one database to perform a mega-analysis. We examined differences among patient groups and control subjects using linear mixed-effects models in STATA; mixed models are used to take into account the differences between sites. The mean values of the left and right hemisphere for 34 cortical regions (separately for cortical thickness and cortical surface area), whole-hemisphere measures (average thickness and total surface area), and seven subcortical regions were used in the mega-analyses. To obtain comparable standardized regression coefficients (effect sizes) for all comparisons, the z-scores for each of the cortical and subcortical regions of interest served as the outcome measures, and the diagnostic groups (ADHD, ASD, and OCD patients and healthy control subjects) were included as separate independent variables of interest, using three dummy variables. Disorder-specific differences were assessed by alternating the different diagnoses as reference category. Shared differences were assessed using the control subjects as a reference category. A random intercept for cohort was entered to account for clustering within cohorts; if necessary (i.e., when there was a significant improvement of the model fit), a random slope for diagnosis by cohort was included to account for different effect sizes between cohorts within the different working groups (24). Age and sex were included as covariates (25, 26); for the surface area and subcortical volume analyses, intracranial volume (ICV) was also added as a covariate, since these measures scale with head size (27). The standard formula with a putative random slope is therefore as follows: MRI_feature_zscore = Dx1 + Dx2 + Dx3 + Age + Sex + (Dx × cohort), where Dx1, Dx2, and Dx3 refer to the diagnostic groups.

To detect potentially different effects of disorder with age, we performed all analyses separately for pediatric, adolescent, and adult patients. Because only a limited number of cohorts had data on IQ and medication use, sensitivity analyses were performed to investigate how IQ and psychotropic medication use might have influenced the differences between disorders. For medication use (yes/no at time of scanning), stratified analyses according to medication status were performed. With respect to IQ, we included the variable as an additional covariate in the analyses. The Benjamini-Hochberg false discovery rate (FDR) was used to control for multiple comparisons within each model, with p values adjusted separately for each age group and for each modality (cortical thickness, surface area, and subcortical volume). Results were considered significant if the FDR-corrected p value (q) was ≤0.05.

To quantify the robustness of the main between-group comparisons, additional leave-one-site-out cross-validation was performed for each of the models (see Tables S3–S13 in the online supplement). For this cross-validation, the same model was repeatedly performed, each time removing one of the individual sites from the cohort. We report the distribution of the p values (mean, minimum, and maximum p values after all iterations), indicating how strongly the p value of the comparison was influenced by single-site effects.

RESULTS

The participants' demographic and clinical characteristics are summarized, by age category, in Tables 1, 2, and 3 (for the entire sample, see Table S4 in the online supplement); these are also the final numbers of subjects used in each of the analyses. Results that did not survive correction for multiple

TABLE 1. Demographic and clinical characteristics for pediatric patient groups and control subjects in a study of subcortical brain volume, regional cortical thickness, and cortical surface[a]

Measure	Patients									Control Subjects (N= 1,590, from 69 sites)		
	OCD Patients (N=140, from 14 sites)			ADHD Patients (N=709, from 26 sites)			ASD Patients (N=723, from 35 sites)					
	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD
Age (years)	140	10.28	1.22	709	9.41	1.33	723	8.64	2.46	1,590	9.35	1.72
IQ	70	108.75	16.50	648	106.09	15.20	526	100.02	21.49	1,302	111.23	15.37
	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%
Male	140	76	54.29	709	530	74.75	723	588	81.33	1,590	997	62.70
Medication	140	38	27.14	438	126	28.77	413	97	23.49			
Comorbid disorders												
OCD				408	0	0.00	73	0	0.00			
ADHD	126	14	11.11				73	8	10.96			
ASD	126	3	2.38	271	0	0.00						
Tourette's syndrome	119	12	10.08	240	1	0.42	73	0	0.00			
Anxiety disorder	129	41	31.78	408	21	5.15	73	4	5.48			
Major depression	129	7	5.43	404	0	0.00	73	1	1.37			

[a] ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; OCD=obsessive-compulsive disorder.

comparisons but had uncorrected p values <0.05 are described for the main analyses in Supplemental Information SI2 in the online supplement. Based on our statistical tests, indicating that an effect is *specific* means that we observed a significant difference between a diagnostic group and the control group but not necessarily between a diagnostic group and the other two patient groups. It should be noted that this is distinct from diagnostic specificity based on a full interaction model as recommended by Nieuwenhuis et al. (28).

Shared Subcortical and Cortical Differences Across Clinical Groups Compared With Healthy Control Subjects

Children with ADHD and those with ASD showed some overlap in subcortical volume and cortical thickness differences compared with control subjects (see Supplementary Information SI2 in the online supplement), although none of these results survived correction for multiple comparisons (see Tables S5 and S6 in the online supplement). In adolescents, we did not observe shared subcortical and cortical differences among any of the disorders (see Tables S7–S9 in the online supplement). Adult patients with OCD and those with ASD showed smaller hippocampal volumes compared with adult control subjects, although this finding did not survive correction for multiple comparisons in adults with ASD (see Table S10 in the online supplement). Adult patient groups showed no overlap in cortical differences (see Tables S11 and S12 in the online supplement). Details on differences compared with healthy control subjects, by patient group, are provided in Tables S5–S13 in the online supplement.

Disease-Specific Subcortical and Cortical Differences

Children. Figure 1A depicts the pattern of subcortical volume differences in children. Children with ADHD showed significantly smaller ICV compared with those with ASD (effect size=−0.23) or OCD (effect size=−0.28). Children with ADHD also showed smaller hippocampal volumes compared with children with OCD (effect size=−0.22). No significant cortical differences among disorders survived correction for multiple comparisons (see Tables S15 and S16 and Supplementary Information SI2 in the online supplement).

Adolescents. Adolescents with ADHD had significantly smaller ICV compared with those with ASD (effect size=−0.22) or OCD (effect size=−0.19) (Figure 1B; see also Table S17 in the online supplement); however, the latter did not survive correction for multiple comparisons. Group differences in cortical thickness did not survive correction for multiple comparisons (see Table S18 and Supplementary Information SI2 in the online supplement). Surface area analysis revealed significantly lower surface area of the medial orbitofrontal cortex in patients with OCD compared with patients with ADHD (effect size=−0.22) (see Table S19 in the online supplement).

Adults. None of the subcortical volumes differed significantly among adult patient groups (Figure 1C; see also Table S20 in the online supplement). Cortical thickness analysis revealed significantly thicker cortical gray matter in several frontal regions in adults with ASD compared with adults with OCD or ADHD (Figure 2), with effect sizes varying between 0.17 and 0.30. Adults with OCD did not differ significantly from

TABLE 2. Demographic and clinical characteristics for adolescent patient groups and control subjects in a study of subcortical brain volume, regional cortical thickness, and cortical surface[a]

Measure	Patients									Control Subjects (N=1,368, from 79 sites)		
	OCD (N=359, from 16 sites)			ADHD (N=633, from 27 sites)			ASD (N=565, from 39 sites)					
	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD
Age (years)	359	14.91	1.72	633	14.00	1.65	565	14.40	1.66	1,368	14.37	1.71
IQ	136	106.75	14.31	608	102.41	14.63	467	103.02	18.26	1,085	110.07	12.79
	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%
Male	359	195	54.32	633	514	81.20	565	492	87.08	1,368	937	68.49
Medication	357	172	48.18	487	212	43.53	227	74	32.60			
Comorbid disorders												
OCD				452	0	0.00	68	0	0.00			
ADHD	314	27	8.60				68	13	19.12			
ASD	299	10	3.34	316	7	2.22						
Tourette's syndrome	314	17	5.41	272	1	0.37	68	1	1.47			
Anxiety disorder	316	109	34.49	452	8	1.77	68	3	4.41			
Major depression	317	24	7.57	452	5	1.11	68	2	2.94			

[a] ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; OCD=obsessive-compulsive disorder.

those with ADHD (see Table S21 in the online supplement). Surface area analysis revealed that none of the regions differed significantly among patient groups (see Table S22 in the online supplement).

Influence of Medication on Cross-Disorder Effects

Medication status information was incomplete. Tables 1–3 list the numbers of patients for whom information about medication status at the time of scanning was available.

Children. The smaller ICV between children with ADHD and those with OCD (effect size=−0.32) or those with ASD (effect size=−0.19) may be driven by the unmedicated children (see Table S23 in the online supplement), since ICV did not differ significantly among disorders when the medicated children were compared (see Table S24 in the online supplement). No cortical differences survived correction for multiple comparisons when unmedicated children were compared among disorders (see Tables S25 and S26 in the online supplement).

Medicated children with OCD had larger amygdala volumes than medicated children with ADHD (effect size=0.43) (see Table S24 in the online supplement). Medicated children with ASD showed a thicker cuneus cortex compared with medicated children with OCD (effect size=0.60) and a thinner middle temporal gyrus compared with medicated children with ADHD (effect size=−0.44) (see Table S27 in the online supplement). No differences in surface area differences survived correction for multiple comparisons when medicated children were compared among disorders (see Table S28 in the online supplement).

Adolescents and adults. Except for significantly larger surface area of the parahippocampal gyrus in unmedicated adults with ASD compared with unmedicated adults with ADHD (effect size=0.33) (see Table S29 in the online supplement), no significant subcortical and cortical differences survived correction for multiple comparisons when unmedicated (see Tables S30–S34 in the online supplement) or medicated (see Tables S35–S40 in the online supplement) adults and adolescents were compared among disorders. Details on disease-specific differences for unmedicated or medicated patients compared with control subjects are provided in Tables S41–S58 in the online supplement.

Adjusting for Individual Differences in IQ

Information about IQ was incomplete. The numbers of patients for whom IQ scores were available are listed in Tables 1–3. Because we did not have sufficient IQ data to include adult patients with OCD in the analysis (Table 3), results for adults are based on ASD, ADHD, and control subjects only.

Adjusting for IQ resulted in findings similar to the main results across all age groups (see Tables S59–S67 in the online supplement). However, subcortical volume analysis did not show smaller hippocampal volumes in children with ADHD and children with ASD compared with those with OCD (see Table S59). Cortical thickness analysis additionally revealed significantly thicker cortices of the pars orbitalis (effect size=0.20), the superior frontal gyrus (effect size=0.22), and the frontal pole (effect size=0.23) in adults with ASD compared with adults with ADHD (see Table S67). Details on disease-specific differences compared with healthy control

TABLE 3. Demographic and clinical characteristics for adult patient groups and control subjects in a study of subcortical brain volume, regional cortical thickness, and cortical surface[a]

Measure	Patients									Control Subjects (N=2,869, from 91 sites)		
	OCD (N=1,824, from 33 sites)			ADHD (N=929, from 28 sites)			ASD (N=489, from 36 sites)					
	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD	N (data available)	Mean	SD
Age (years)	1,824	31.69	9.66	929	29.82	10.19	489	26.03	9.00	2,869	29.74	9.88
IQ	408	105.99	13.22	765	106.91	14.52	439	108.96	16.01	1,449	112.20	13.36
	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%	N (data available)	N	%
Male	1,824	923	50.60	929	622	66.95	489	432	88.34	2,869	1,634	56.95
Medication	1,803	829	45.98	650	119	18.31	226	46	20.35			
Comorbid disorders												
OCD				787	3	0.38	116	3	2.59			
ADHD	1,142	51	4.47				116	3	2.59			
ASD	1,079	1	0.09	343	0	0.00						
Tourette's syndrome	1,182	22	1.86	389	4	1.03	116	0	0.00			
Anxiety disorder	1,491	276	18.51	768	13	1.69	116	0	0.00			
Major depression	1,513	193	12.76	731	7	0.96	116	6	5.17			

[a] ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; OCD=obsessive-compulsive disorder.

subjects adjusted for IQ are provided in Tables S65–S73 in the online supplement.

Supplementary Robustness Analyses

The leave-one-site-out cross-validation analyses (see Tables S3–S13 in the online supplement) indicated that the main effects of diagnostic group in all age bins were not influenced by single outlying site effects. Further scatterplots with polynomial age fits for several selected key MRI features are provided in Supplementary Information SI3 in the online supplement, demonstrating the full distribution of data points over the lifespan for each diagnostic group.

Supplementary Information SI4 in the online supplement shows, for several key MRI features, the estimated marginal means for each diagnostic group after the main group comparison model was run, as well as full distributions of the residuals (with and without correction for site). These figures demonstrate that the inclusion of random slopes per site leads to more normally distributed residuals.

Supplementary Information SI5–SI7 in the online supplement show meta-analytic results for several key MRI features for each age bin, containing both forest plots per site and the average meta-analytic results. These plots demonstrate considerable heterogeneity in effect sizes between sites, as well as overall smaller effect sizes in the mean meta-analysis result per MRI feature than those reported in our main mega-analysis.

Given that previous studies have shown that field strength may influence FreeSurfer segmentations (29), we repeated the main between-group comparisons, split by sites employing either 1.5-T or 3-T scanners. As demonstrated in Table S75 in the online supplement, we mostly have a much larger sample of 3-T scans. The results of these comparisons (see Tables S75–S84 in the online supplement) indicate that the between-group results are mostly stable across field strengths.

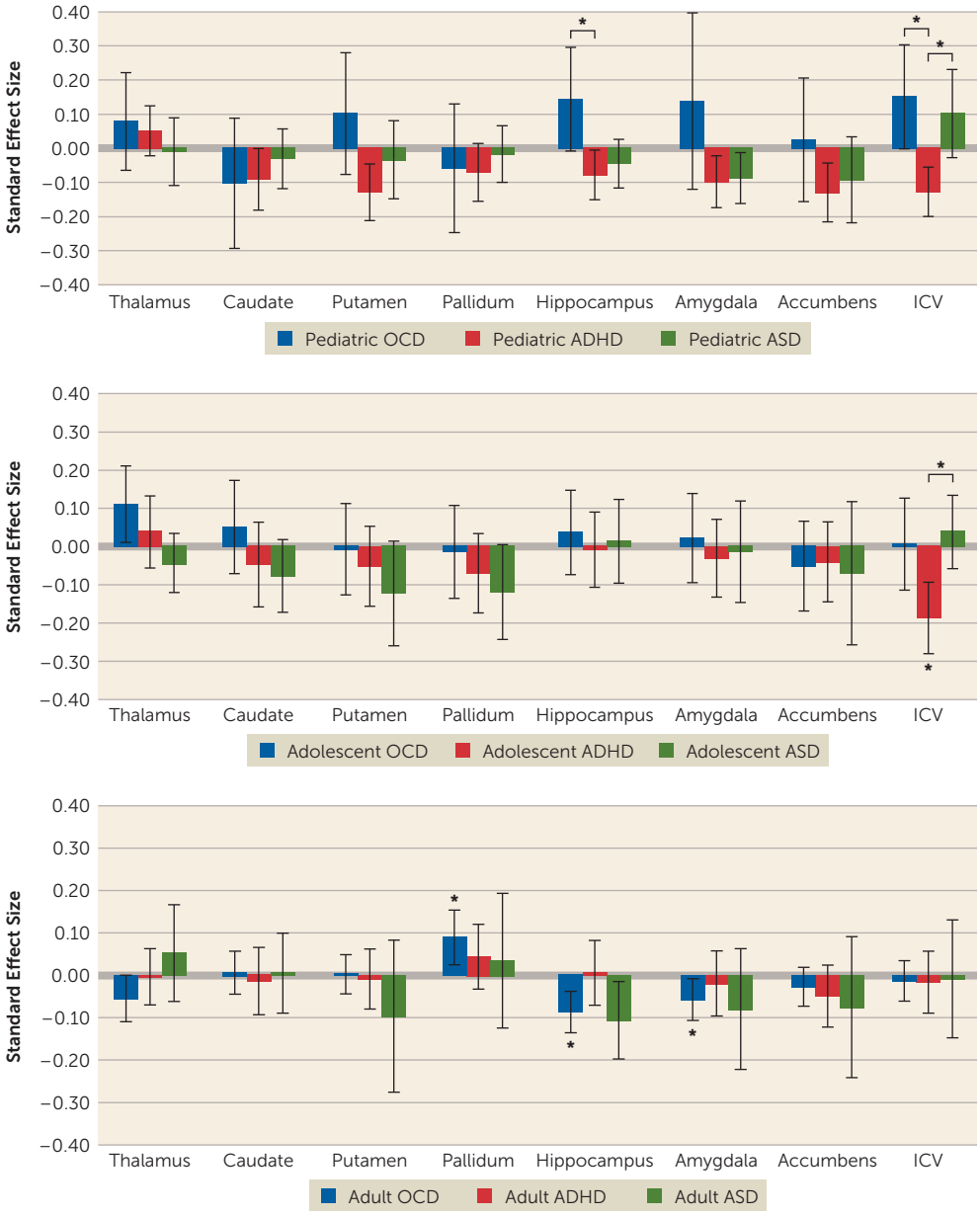
DISCUSSION

This study constitutes the largest neuroimaging investigation to date of structural brain alterations across ADHD, ASD, and OCD. The results revealed differing patterns of subcortical and cortical differences among the disorders across childhood, adolescence, and adulthood. We found ADHD-specific smaller ICV in children and adolescents and ASD-specific thicker frontal cortices in adults. We did not find OCD-specific differences across the different age groups. No brain differences were shared among all three disorders.

Previous ENIGMA disease working group results, comparing patients with distinct disorders to control subjects, were mostly replicated, albeit not always using an FDR-corrected threshold. The present study included more patients and considerably more control subjects than the previously published working group studies (13–17). Accordingly, the present results may more accurately represent the normal heterogeneity in the control population. Importantly, our method allowed different mean control group outcomes per cohort, meaning that it statistically accounted for the heterogeneity among control subjects from different cohorts (24).

Overall, the results were subtle, with small to moderate effect sizes. These effect sizes emerge even after combining

FIGURE 1. Subcortical volume differences in children, adolescents, and adults with ADHD, ASD, or OCD compared with control subjects[a]



[a] Significant results (false discovery rate q≤0.05) are indicated by an asterisk; see Tables S5, S7, and S10 in the online supplement. For effect size values across disorders, see Tables S14, S17, and S20 in the online supplement. ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; ICV=intracranial volume; OCD=obsessive-compulsive disorder. Error bars indicate 95% confidence interval.
*p<0.05.

dozens of different scanner types and rise above the noise. Large-scale studies like those of the ENIGMA consortium convey another important message, mainly by not replicating the extremely large effect sizes that have been found in previous research with smaller samples. Small clinical samples are often rather homogeneous samples carefully selected on the basis of a specific set of inclusion and exclusion criteria. Homogeneous samples can increase statistical power to discover larger effect sizes, but are typically not representative of the broader population, and such effect sizes are less likely to generalize to the population, where patient groups are highly heterogeneous.

Smaller amygdala volume and thinner frontal and temporal cortices might be shared differences in children with ASD and ADHD (see Supplementary Information SI2 in the online supplement). We did not observe similar shared differences in the adolescents and adults with ASD and ADHD. These findings may be indicative of a more general delayed brain development (18, 30). Smaller hippocampus volume might be a shared alteration in adults with ASD and OCD (see Supplementary Information SI2). Hippocampal differences are also described in other psychiatric disorders, such as major depressive disorder, schizophrenia, and bipolar disorder (31, 32). Decreased hippocampal volume may reflect a disorder-nonspecific effect, potentially related to chronic stressors (33).

Deficits in social communication and interaction are hypothesized to be related to a thinner temporal cortex (34). Our results fit with the involvement of the temporal cortex in ASD compared with control subjects, but we did not detect temporal cortex differences in patients with ASD compared with those with ADHD or OCD. A thicker cortex of several frontal regions was specific to patients with ASD and has been linked to impaired cognitive control and executive dysfunction (13, 35). The pattern of thinner temporal and thicker frontal cortices in patients with ASD has been reported in longitudinal studies and suggests accelerated expansion in early childhood, accelerated thinning in later childhood and adolescence, and decelerated thinning in adulthood (36). Although executive dysfunction is present in all three patient groups (4, 5), diagnostic categories may differ in executive functioning profiles. Future studies, such

as the COMPULS study (37), that focus on neural correlates of executive functioning in all three patient groups will give more insight on this issue.

Inattention, hyperactivity, and impulsivity are the main symptoms of ADHD, presumably modulated by abnormal fronto-striatal circuits (38). Our study confirms frontal surface area and striatal volume differences in children with ADHD compared with control subjects, but we did not detect these fronto-striatal differences in patients with ADHD compared with those with ASD or OCD. Smaller ICV did appear to be specific to children and adolescents with ADHD. These results support the hypothesis that differences in ADHD may be due to a delay in brain maturation (30), which possibly normalizes in adulthood. These results are also in line with the genetic correlation between risk for ADHD and smaller ICV (39).

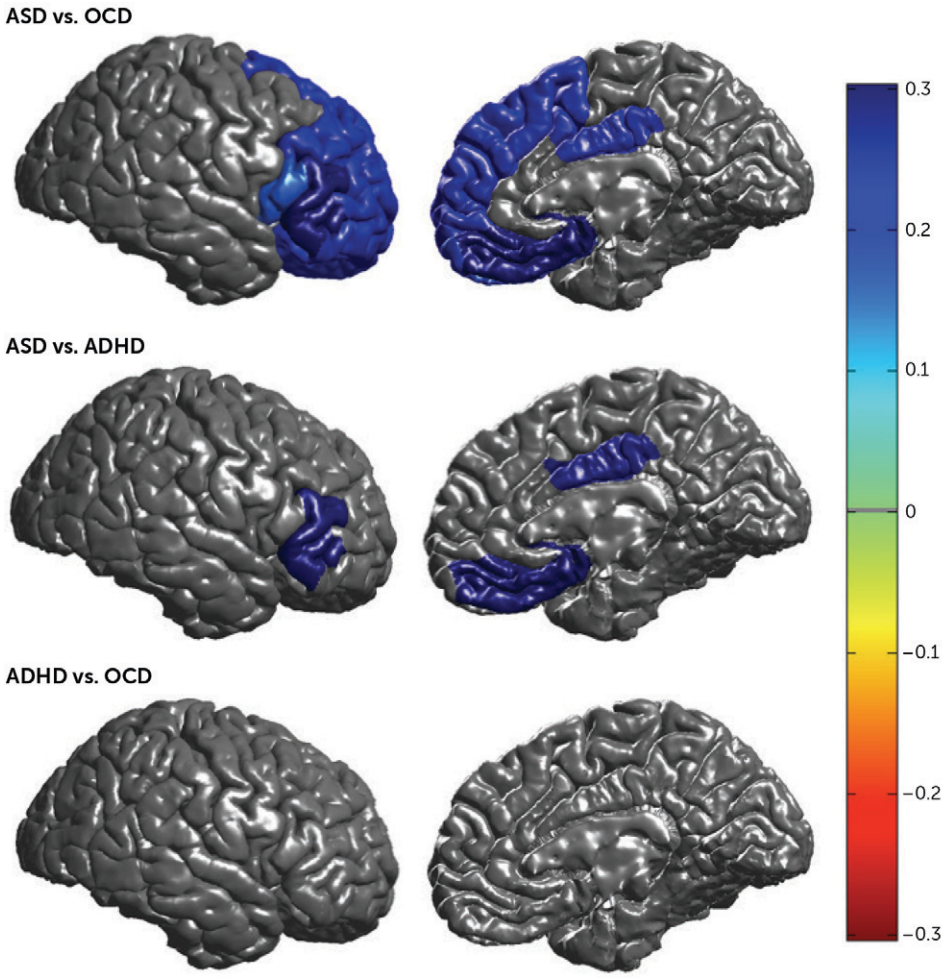
Children with ASD (see Supplementary Information SI2 in the online supplement) and ADHD seemed to have smaller hippocampal volumes compared with children with OCD. This effect was not detected when adjusting for IQ. Although the sensitivity analysis adjusting for IQ was performed in a smaller subgroup, these findings indicate that the hippocampal volume differences may be driven by IQ differences among patient groups. Indeed, previous studies have shown an association between IQ and hippocampal volume (40). Further cross-disorder analyses adjusted for IQ revealed results similar to those of the main analyses across all age groups.

Cross-disorder main effects were not detected when medicated patients and unmedicated patients were compared separately. However, these analyses may have been underpowered to detect the small effect sizes we observed in the larger combined group because of smaller sample sizes when patients were stratified by medication status.

Two studies performed voxel-based morphometry (VBM) meta-analyses and reported shared differences and disease-specific differences between patients with ASD and OCD and between patients with ADHD and OCD (21, 22). Our findings do not corroborate these previous findings. This inconsistency may reflect reporting bias in these meta-analyses of published studies and/or differences in analytical methods. FreeSurfer segments brain regions on the basis of probabilistic information from a predefined atlas, whereas VBM uses voxel-wise registration. The differences in these methodological approaches may lead to diverging results. Mainly global or regional differences in structure can be inferred from atlas-based FreeSurfer analyses, as opposed to voxel-level morphology with VBM. Thus, local morphological differences may not be detected when averaging across regions (41).

This study has several strengths and limitations. As the largest mega-analysis to date, sample size is an obvious strength. Another strength is harmonization of segmentation protocols across all participating sites, reducing variation caused by differences in methods. Quality control procedures were also harmonized across site, although given the large

FIGURE 2. Thicker cortices of several frontal regions in adults with ASD compared with those with OCD or ADHD[a]



[a] The figure presents regions that showed a significant difference (false discovery rate q≤0.05) in cortical thickness among adults with ASD, ADHD, or OCD. Positive effect sizes (in blue) indicate thicker cortices in adults with ASD compared with those with ADHD or OCD. ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; OCD=obsessive-compulsive disorder.

data sets involved, quality control was largely based on automated outlier detection before visual inspection. This means that more subtle biases (for instance, limited head motion) may have remained unnoticed.

Another key limitation is the variation attributable to different scanners and acquisition protocols across cohorts. This issue was mitigated by the formal consideration of potential site differences in all statistical analyses. We have included comparisons of 1.5-T and 3-T field strength in the supplement (see Supplementary Information SI2 in the online supplement), which indicate that our main group effects are largely unaffected by field strength. However, other acquisition parameters, such as radiofrequency coil and imaging sequence, were not available from enough sites to run sensitivity analyses, which must be considered a limitation of this study, as these factors may influence segmentation results (42).

Another strength of the study was the use of mega- as opposed to meta-analysis. The comprehensive evaluation of missing data and greater flexibility in control of confounders at the level of individual patients and specific studies are significant advantages. Mega-analyses are also recommended because they avoid the assumptions of within-study normality and known within-study variances, which are especially problematic when including small samples. In Tables S5–S7 in the online supplement, we provide forest plots of the main group effects split by site, together with overall meta-analysis effects and I^2 heterogeneity statistics. These results indicate substantial heterogeneity in the effect sizes between individual sites. Indeed, our recent study comparing meta- and mega-analytical methods (24) showed that the mega-analytical framework appears to be the better approach for investigating structural neuroimaging data in multicenter studies.

We did not perform stratified analyses for reported sex, even though ADHD and ASD have a strong sex bias. This issue was mitigated by adjusting for sex in all statistical analyses. Moreover, the independent working groups did not observe sex-specific effects in their patient groups (13–17).

We chose to differentiate children, adolescents, and adults, and the age cut-offs we used may not have been optimal, given different onset ages for the disorders. Our rationale was to minimize differences in average age among disorders—in addition to age as a nuisance covariate—and thus to minimize the detection of age effects rather than disease effects. Separate analysis by age group also avoids the difficulties in modeling possibly complex—yet unknown, a priori—nonlinear age effects that may also differ among groups. The primary focus of this study was cross-disorder comparisons. Yet, such analyses of age effects are of great interest and should be addressed in future research using multivariate pattern recognition, for example, the support vector machine that can detect informative patterns in the data that may not be identified by traditional linear analyses.

Structural differences among disorders did not show any significant association with medication use and IQ. Nonetheless, we did not have data on medication use and IQ for all patients, indicating insufficient statistical power to address this issue with confidence. We also lacked detailed information on psychotropic treatment. Further efforts are required to draw valid conclusions on the impact of psychotropic medication use on brain structure.

Effects of comorbidity or general phenotypic overlap among ADHD, ASD, and OCD could not be analyzed, because this was not systematically addressed across the cohorts of the different working groups. Presence of comorbidities may have reduced disorder-specific findings. However, excluding comorbid conditions would have ignored complex interactions that are often integral to the disorder. Future studies should test the extent to which the comorbid cases differ from the "pure" disorders. Greater consideration of how data may be used in international collaborations such as ENIGMA may influence the collection of data in future studies, which may increase their impact beyond their primary focus.

CONCLUSIONS

We found subcortical and cortical differences across different age categories among ADHD, ASD, and OCD. We found ASD-specific cortical thickness differences in the frontal cortex of adult patients and ADHD-specific subcortical differences in children and adolescents. We did not find shared differences among the three disorders, and shared differences across any two disorders did not survive correction for multiple comparisons. Further work, such as multivariate pattern recognition analyses and normative modeling incorporating neural correlates and cognitive and genetic variables, will be useful in understanding the mechanisms underlying distinct and shared deficits in these neurodevelopmental disorders.

AUTHOR AND ARTICLE INFORMATION

The full list of authors in the ENIGMA working groups, author affiliations, author disclosures, and acknowledgments are provided in online supplements.

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Correction to Boedhoe et al.

When the article "Subcortical Brain Volume, Regional Cortical Thickness, and Cortical Surface Area Across Disorders: Findings From the ENIGMA ADHD, ASD, and OCD Working Groups," by Premika S.W. Boedhoe, Ph.D., et al. (doi: 10.1176/appi.ajp.2020.19030331), was published online on June 16, 2020, the name of author Kerstin Konrad, Ph.D., was presented incorrectly. The name was corrected and the article was reposted on June 24, 2020.