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Subcortical brain volume, regional cortical thickness, and cortical surface area across disorders: findings from the ENIGMA ADHD, ASD, and OCD Working Groups

Article

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The American Journal of Psychiatry

Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) – findings from the ENIGMA-ADHD, -ASD, and -OCD working groups

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Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD)

– findings from the ENIGMA-ADHD, -ASD, and -OCD working groups

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders that frequently co-occur. We aimed to directly compare all three disorders. The ENIGMA consortium is ideally positioned to investigate structural brain differences across these disorders.

Methods: Structural T1-weighted whole-brain MRI of controls (*n*=5,827) and 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. We examined subcortical volume, cortical thickness and 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 intra-cranial volume (ICV) for subcortical and surface area measures).

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

Conclusion

Our findings suggest robust but subtle differences across different age-groups among ADHD, ASD, and OCD. ADHD-specific ICV 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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Introduction

Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders with a lifetime prevalence 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 share 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 which morphological brain abnormalities within these networks are shared (non-specific) versus distinct (specific to one disorder).

Imaging studies, including meta-analyses, have generally compared one of the three disorders to healthy controls (8-12). Large-scale studies 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 basal ganglia and insula, and OCD-specific smaller volume of 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 so far compared all three disorders.

The 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.

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Here, we present the largest comparative study investigating 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 controls. The ENIGMA-ASD working group includes 56 cohorts from 38 research institutes, with neuroimaging and clinical data from patients with ASD and healthy controls. The ENIGMA-OCD working group includes 47 cohorts from 34 research institutes, with neuroimaging and clinical data from patients with OCD and healthy controls..

All working groups included data from subjects across the lifespan. As prior results suggested differential effects between pediatric (<12 years), adolescent (12-18 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 controls. 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 Magnetic Resonance Spectroscopy (MRI) was acquired and processed locally. Image acquisition parameters for each cohort are listed in Supplementary Tables S1-S3. All cortical parcellations were performed with the fully automated segmentation program FreeSurfer, version 5.3, following standardized ENIGMA protocols to harmonize analyses and quality control (QC) 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 subsequenlty visually inspected for segmentation success. Individual volumes with poor segmentation were removed, as well as subjects with overall poor segmentation quality. All the quality control was performed locally on each site, and only data of sufficient quality was send for inclusion in the ENIGMA cohorts. All reported group sizes in this manuscript are after QC. Details on image exclusion criteria

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and quality control are presented in Supplementary Information SI1. 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 patients groups and controls using linear mixed-effects models in STATA; mixed models are used to take into account the differences between sites. The means of the left and right hemisphere of 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 diagnoses (ADHD, ASD, OCD, and HC) 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 HC 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*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, ICV was also added as a covariate, since these measures scale with head size (27). The standard formula with a putative random slope therefore looks as follows: ***MRI_feature_zscore ~ Dx1 + Dx2 + Dx3 + Age + Sex + (Dx*cohort), with Dx1-3 referring to 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 disorder differences. 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 supplementary table 3-13). 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, min and max p-value after all iterations), indicating how strongly the p-value of the comparison was influenced by single-site effects.

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Results

The demographic and clinical characteristics of participants are summarized per age category in Table 1a-c (entire sample Supplementary Table S4), these are also the final numbers of subjects used in each of the analyses. Results not surviving multiple comparison correction, but with p-values <0.05 were considered trends and are described for the main analyses in Supplemental Information SI2. Based on our statistical tests, indicating an effect is *specific* means we observe a significant difference between a diagnostic group and the control group but not necessarily between a diagnostic group, and each of the three other groups, but not the others. It should be noted this is distinct from diagnostic specificity based on a full interaction model as recommended in (43)"

Shared subcortical and cortical differences across clinical groups compared to healthy controls

Children with ADHD and those with ASD showed some overlap in *subcortical volume* and *cortical thickness* differences compared to controls (Supplementary Information SI2), however none of these results survived multiple comparison correction (Supplementary Tables S5-S6). In *adolescents*, we did not observe shared *subcortical and cortical* differences among any of the disorders (Supplementary Tables S7-S9). *Adult* patients with OCD and those with ASD showed smaller hippocampal volumes compared to adult controls, however this finding did not survive multiple comparison correction in adults with ASD (Supplementary Table S10). Adult patient groups showed no overlap in *cortical* differences (Supplementary Tables S11-S12). Details on differences compared to healthy controls per patient group can be found in Supplementary Tables S5-S13.

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 to those with ASD (effect size=-0.23) or OCD (effect size=-0.28). Children with ADHD (effect size=-0.22) also showed smaller hippocampal volumes compared to children with OCD. No significant *cortical* differences among disorders survived multiple comparison correction (Supplementary Tables S15-S16 & Supplementary Information SI2).

Adolescents: Adolescents with ADHD had significantly smaller ICV compared to those with ASD (effect size=-0.22) or OCD (effect size=-0.19), shown in Figure 1b (Supplementary Table S17). However, the latter did not survive multiple comparison correction. Group differences in *cortical thickness* did not survive multiple comparison correction (Supplementary Table S18 & Supplementary Information SI2). *Surface area* analysis revealed significantly lower surface area of the medial orbitofrontal cortex (effect size=-0.22) in patients with OCD compared to patients with ADHD (Supplementary Table S19).

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Adults: None of the *subcortical* volumes differed significantly among adult patient groups (Figure 1c & Supplementary Table S20). *Cortical thickness* analysis revealed significantly thicker cortical gray matter in several frontal regions in adults with ASD compared to 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 those with ADHD (Supplementary Table S21). *Surface area* analysis revealed that none of the regions differed significantly among patient groups (Supplementary Table S22).

Influence of medication on cross-disorder effects

Medication status information was incomplete. Table 1a-c lists 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 (Supplementary Table S23) since ICV did not significantly differed among disorders when comparing the medicated children (Supplementary Tables S24). No *cortical* differences survived multiple comparison correction when comparing unmedicated children among disorders (Supplementary Tables S25 and S26).

Medicated children with OCD had larger amygdala volumes than medicated children with ADHD (effect size=0.43) (Supplementary Table S24). Medicated children with ASD showed a thicker cuneus cortex (effect size=0.60) compared to medicated children with OCD and a thinner middle temporal gyrus (effect size=-0.44) compared to medicated children with ADHD (Supplementary Table S27). No differences in *surface area* differences survived multiple comparison correction when comparing medicated children among disorders (Supplementary Tables S28).

Adolescents & Adults: Except for significantly larger *surface area* of the parahippocampal gyrus in unmedicated adults with ASD (effect size=0.33) compared to unmedicated adults with ADHD (Supplementary Table S29), no significant *subcortical* and *cortical* differences survived multiple comparison correction when comparing unmedicated (Supplementary Tables S30–S34) or medicated (Supplementary Tables S35–S40) adults and adolescents among disorders. Details on disease-specific differences for unmedicated or medicated patients compared to controls can be found in Supplementary Tables S41-S58.

Adjusting for Individual Differences in IQ

Information about IQ was incomplete. Table 1a-c shows the number of patients for whom IQ scores were available. We did not have sufficient IQ data to include *adult* patients with OCD into the analysis (Table 1a). Therefore, results for *adults* are based on ASD, ADHD, and HC only.

Adjusting for IQ resulted in similar findings as the main results across all age-groups (Supplementary Tables S59-S67). However, *subcortical volume* analysis did not show smaller hippocampal volumes in children with ADHD and children with ASD compared to those with OCD (Supplementary Table S59). *Cortical thickness* analysis additionally revealed significant thicker cortices

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of pars orbitalis (effect size=0.20), superior frontal gyrus (effect size=0.22), and frontal pole (effect size=0.23) in adults with ASD compared to adults with ADHD (Supplementary Table S67). Details on disease-specific differences compared to healthy controls adjusted for IQ can be found in Supplementary Tables S65-S73.

Supplementary robustness analyses

The leave-one-site-out cross-validation analyses (supplementary table 3-13) indicated that the main effects of diagnostic group in all age-bins was not influenced by single outlying site effects. Further scatterplots with polynomial age-fits for several selected key MRI features can be viewed in SI3, demonstrating the full distribution of data points over the lifespan for each diagnostic group.

SI4 shows for several key MRI features the Estimated Marginal Means for each diagnostic group after the main group comparisons model has been 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.

SI5-7 show meta-analytic results for several key MRI features for each age-bin, containing both forest plots per site as well as the average meta-analytic results. These plots demonstrate considerable heterogeneity in the effect size between site, as well as overall smaller effect sizes in the mean meta-analysis result per MRI feature than those reported in our main mega-analysis.

As previous studies have shown field-strength may influence FreeSurfer segmentations (42), we have repeated the main between-group comparisons, split by sites employing either 1.5T or 3T scanner. As demonstrated in supplementary table 75, we mostly have a much larger sample of 3T scans. The results of these comparisons (see supplementary tables 75-84) indicate that the between-group results are mostly stable across field-strengths.

Discussion

This study comprised the largest neuroimaging investigation to date of structural brain alterations across ADHD, ASD and OCD. 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 controls, were mostly replicated, albeit not always using an FDR-corrected threshold. The current study included more patients and considerably more controls than the previously published working group studies (13-17). Accordingly, the present investigation 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 amongst controls from

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different cohorts (24).

Overall, results were subtle with small to moderate effect sizes. These effect sizes emerge even after combining 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 in- 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 (Supplementary Information SI2). 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 (18,29). Smaller hippocampus volume might be a shared alteration in adults with ASD and OCD (Supplementary Information SI2). Hippocampal differences are also described in other psychiatric disorders, such as major depressive disorder, schizophrenia and bipolar disorder (30,31). Decreased hippocampal volume may reflect a disorder non-specific effect, potentially related to chronic stressors (32).

Deficits in social communication and interaction are hypothesized to be related to a thinner temporal cortex (33). Our results fit with the involvement of the temporal cortex in ASD compared to controls, but we did not detect temporal cortex differences in patients with ASD compared to 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 (13,34). 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 (35). Although executive dysfunction is present in all three patient groups (4,5), diagnostic categories might differ in executive functioning profiles. Future studies, such as the COMPULS study (36), that focus on neural correlates of executive functioning in all three patient groups will give more insight in this.

Inattention, hyperactivity and impulsivity are the main symptoms of ADHD, presumably modulated by abnormal fronto-striatal circuits (37). Our study confirms frontal surface area and striatal volume differences in children with ADHD compared to controls, but we did not detect these fronto-striatal differences in patients with ADHD compared to those with ASD or OCD. Smaller ICV did appear 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 (29), which possibly normalizes in adulthood. These results are also in line with the genetic correlation between risk for ADHD and smaller ICV (38).

Children with ASD (Supplementary Info SI2) and ADHD seemed to have smaller hippocampal

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volumes compared to 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 (39). Further cross-disorder analyses adjusted for IQ revealed similar results as the main analyses across all age-groups.

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

Two studies performed VBM meta-analyses and reported shared differences and disease specific differences between patients with ASD and OCD, and patients with ADHD and OCD, respectively (21,22). Our findings do not corroborate with these findings. This inconsistency might reflect reporting bias in these meta-analyses of published studies and/or differences in analytical methods. FreeSurfer segments brain regions based on probabilistic information from a predefined atlas compared to VBM's 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 (40).

Strengths and Limitations of the study

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. QC procedures were also harmonized across site, however, given the large datasets involved, QC 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 vs 3 Tesla field strength in the supplement (see SI2), indicating that our main group effects are largely unaffected by field strength. However, other acquisition parameters like RF coil or imaging sequence were not available from sufficient sites to run sensitivity analyses, which must be considered a limitation of the current study, as these factors may influence segmentation results (41).

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 confounds at the level of individual patients and specific studies are significant advantages. Mega-analyses are also

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recommended as they avoid the assumptions of within-study normality and known within-study variances, which are especially problematic when including small samples. Within supplementary materials 5-7 we demonstrate forest plots of the main group effects split by site, together with overall meta-analysis effects and I2 heterogeneity statistics. These results indicate substantial heterogeneity in the effect sizes between individual sites. Indeed our recent study comparing meta- and mega-analytical methods showed that the mega-analytical framework appears to be the better approach for investigating structural neuroimaging data in multi-center studies (24).

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 observed sex specific effects in their patient groups (13-17).

We chose to differentiate children**,** adolescents, and adults; cut-offs might not have been optimal, given different disorder onsets. 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 might also differ among groups. The primary focus of this manuscript 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 e.g., 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 might 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 to what extent 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.

Conclusion

To conclude, 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

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survive multiple comparison corrections. Further work, e.g., multivariate pattern recognition analyses and normative modeling incorporating neural correlates, cognitive and genetic variables will be useful in understanding the mechanisms underlying distinct and shared deficits in these neurodevelopmental disorders.

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ADHD working group

Disclosures

David Coghill served in an advisory or consultancy role for Lilly, Medice, Novartis, Oxford outcomes, Shire and Viforpharma. He received conference support or speaker's fee by Janssen McNeil, Lilly, Medice, Novartis, Shire and Sunovian. He is/has been involved in clinical trials conducted by Lilly & Shire. The present work is unrelated to the above grants and relationships. *Jonna Kuntsi* has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. *Anders Dale* is a Founder of CorTechs Labs, Inc. He serves on the Scientific Advisory Boards of CorTechs Labs and Human Longevity, Inc., and receives research funding through a Research Agreement with General Electric Healthcare. *Paulo Mattos* was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, and Shire in the previous five years; he also received travel awards to participate in scientific meetings from those companies. The ADHD outpatient program (Grupo de Estudos do Déficit de Atenção/Institute of Psychiatry) chaired by Dr. Mattos has also received research support from Novartis and Shire. The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. *Tobias Banaschewski* served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Neurim Pharmaceuticals, Novartis and Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. 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With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. *Joseph Biederman* is currently receiving research support from the following sources: AACAP, Feinstein Institute for Medical Research, Food & Drug Administration, Genentech, Headspace Inc., Lundbeck AS, Neurocentria Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Shire Pharmaceuticals Inc., Sunovion Pharmaceuticals Inc., and NIH. Dr. Biederman has a financial interest in Avekshan LLC, a company that develops treatments for attention deficit hyperactivity disorder (ADHD). His interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. 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ASD working group

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OCD working group

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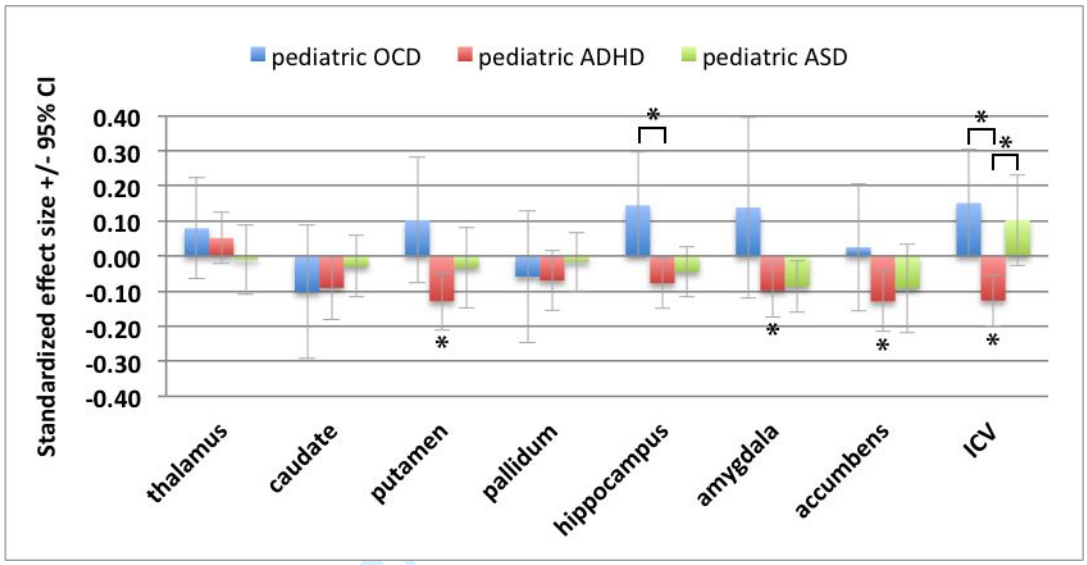
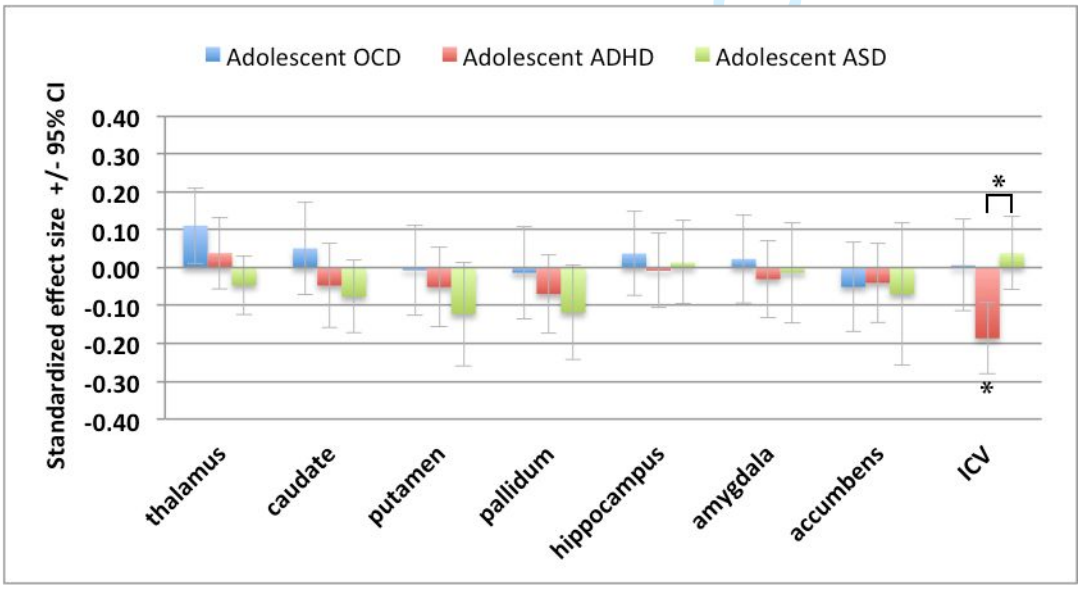
Figure 1a: Subcortical volume differences in children with ADHD, ASD, or OCD compared to controls



Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S5). For Effect size values across disorders see Supplementary Table S14. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

Figure 1b: Subcortical volume differences in adolescents with ADHD, ASD, or OCD compared to controls



Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S7). For Effect size values across disorders see Supplementary Table S17. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

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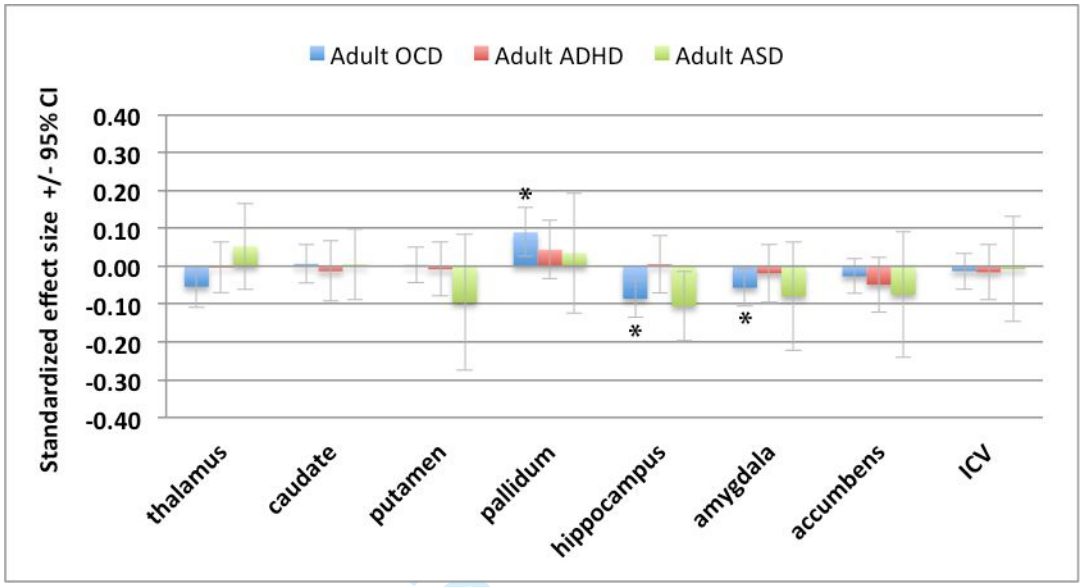
Figure 1c: Subcortical volume differences in adults with ADHD, ASD, or OCD compared to controls



Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S10). For Effect size values across disorders see Supplementary Table S20. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

Figure 2: Thicker cortices of several frontal regions in adults with ASD compared to those with OCD or ADHD

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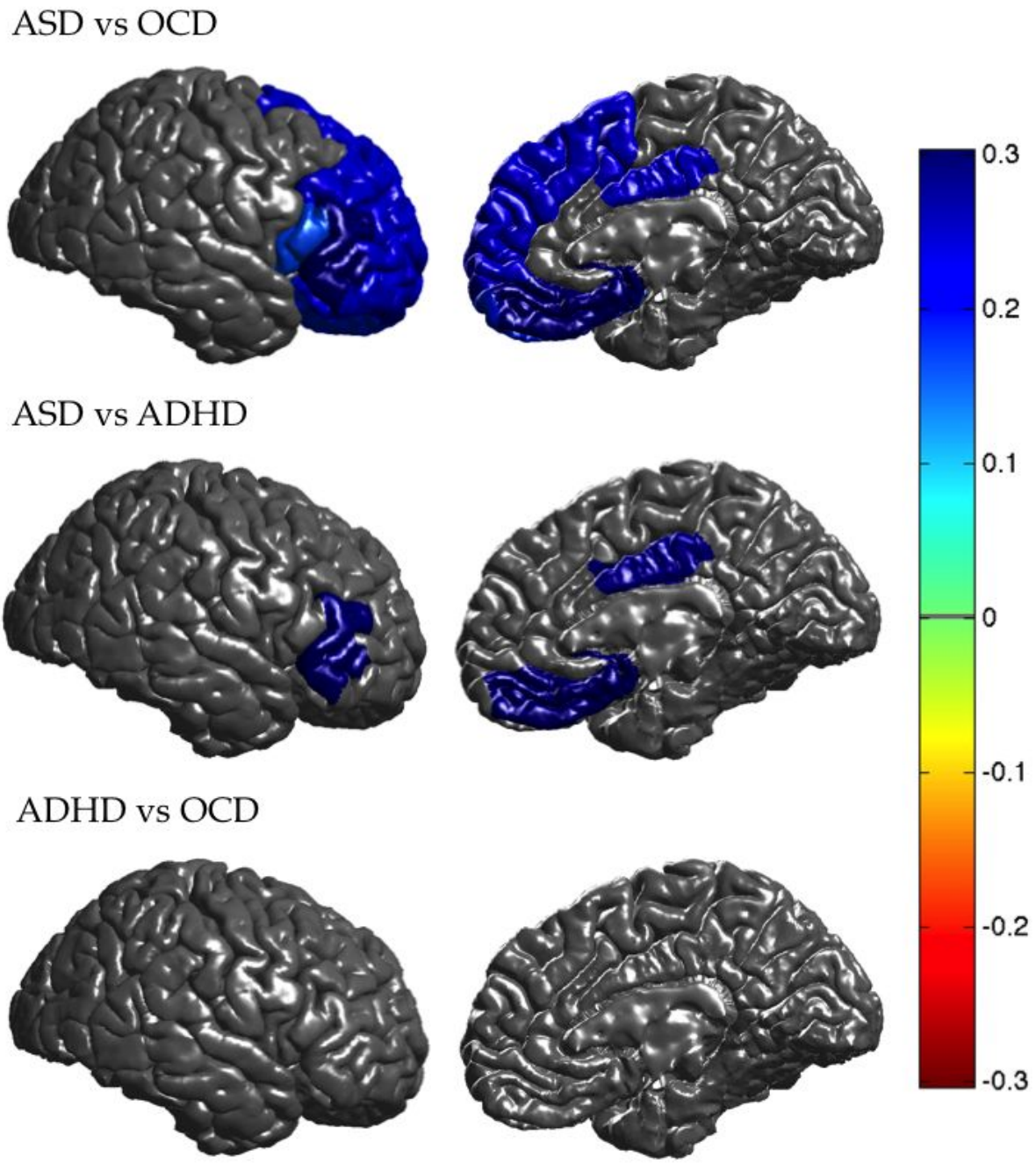

Regions that showed a significant (FDR q ≤ 0.05) difference in cortical thickness among adults with ASD, ADHD or OCD. Positive effect sizes *d* (blue) indicate thicker cortices in adults with ASD patients compared to those with ADHD or OCD.