Brain-charting autism and attention deficit/hyperactivity disorder reveals distinct and overlapping neurobiology

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Archival Report

Biological Psychiatry

Brain-Charting Autism and Attention-Deficit/Hyperactivity Disorder Reveals Distinct and Overlapping Neurobiology

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ABSTRACT

BACKGROUND: Autism and attention-deficit/hyperactivity disorder (ADHD) are heterogeneous neurodevelopmental conditions with complex underlying neurobiology that is still poorly understood. Despite overlapping presentation and sex-biased prevalence, autism and ADHD are rarely studied together and sex differences are often overlooked. Population modeling, often referred to as normative modeling, provides a unified framework for studying age-specific and sex-specific divergences in brain development.

METHODS: Here, we used population modeling and a large, multisite neuroimaging dataset (N = 4255 after quality control) to characterize cortical anatomy associated with autism and ADHD, benchmarked against models of average brain development based on a sample of more than 75,000 individuals. We also examined sex and age differences and relationship with autistic traits and explored the co-occurrence of autism and ADHD.

RESULTS: We observed robust neuroanatomical signatures of both autism and ADHD. Overall, autistic individuals showed greater cortical thickness and volume that was localized to the superior temporal cortex, whereas individuals with ADHD showed more global increases in cortical thickness but lower cortical volume and surface area across much of the cortex. The co-occurring autism+ADHD group showed a unique pattern of widespread increases in cortical thickness and certain decreases in surface area. We also found that sex modulated the neuroanatomy of autism but not ADHD, and there was an age-by-diagnosis interaction for ADHD only.

CONCLUSIONS: These results indicate distinct cortical differences in autism and ADHD that are differentially affected by age and sex as well as potentially unique patterns related to their co-occurrence.

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Neurodevelopmental conditions such as autism and attention-deficit/hyperactivity disorder (ADHD) are the products of altered neurodevelopmental trajectories (1), but their specific neurobiological underpinnings remain poorly understood. Both display significant variability in trajectory, associated traits, and neurobiology (2–8), which can hamper efforts to better understand these conditions. Sex and gender modulations of presentation, prevalence, and neuroanatomy (9–15) and clinical and etiological overlap (16–19) add complexity. Importantly, most studies have been based on male-dominant samples and may not be representative (15).

One of the most commonly reported findings is increased total brain volume in young autistic children (20–22), although evidence suggests that this may only hold true for a subset of autistic children (23–25) and for boys (26,27). Increased cortical thickness (CT) has often been associated with autism (28–31), although reductions have been reported (32,33), as well as alterations in cortical surface area (SA) and volume (34–36). Alterations, including both increases and decreases, have been reported in the superior temporal gyrus (STG), inferior and prefrontal cortex, sensory and motor regions (29–38), cerebellum, and subcortex (39–42) and seem to be moderated by age, sex, and co-occurring conditions or traits (31,43–48). Complementary work has suggested multiple subgroups with distinct patterns of neuroanatomical alterations and clinical characteristics (40,48–50). Sex differences in particular have been reported on multiple cortical measures and associations (31,44,51–57).

Recent meta-analyses have highlighted a similar lack of convergent findings in ADHD (58,59). Reduced total brain

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volume, gray matter volume (GMV), and cortical SA have been reported consistently (59–65). However, while earlier studies reported decreases in CT (66–70), more recent, larger studies have found no or very minimal differences (60–64,71–73). Cortical alterations have most commonly been reported in prefrontal and orbitofrontal, parietal, anterior cingulate, and occipital cortices (59,71). Volumetric reductions of subcortical structures and the cerebellum have also been reported (59,65,74), in particular the basal ganglia (75,76), likely related to atypicality in the frontostriatal network (77–79). Again, differences are highly dependent on age, sex, and co-occurring conditions (66,69,80–82).

The few studies that have examined structural and functional differences in autism and ADHD together have reported that they are largely distinct, with some overlapping, alterations (83–92). A recent review (93) highlighted the challenges of comparing these groups, including limited sample sizes, heterogeneity, often arbitrary clinical distinctions, and overlap in presentation. Even fewer studies have specifically examined the co-occurrence of autism and ADHD, with both similarities and differences being observed compared with individuals with only one diagnosis (47,88,94) and evidence that an ADHD diagnosis modulates the effect of autism on neuroanatomy (90).

While this variability in the literature is likely due in part to differences in methodology and sample size, another significant contributor is the heterogeneity within and overlap between the conditions. To identify average patterns of alterations, large datasets are needed along with techniques to harmonize multisite data. Critically, these alterations must be contextualized in light of typical brain development given the neurodevelopmental nature of autism and ADHD (95–97).

Population modeling, often referred to as normative modeling, has proven effective for characterizing age-dependent variation in brain development (98,99) and has recently been employed in studying autism and ADHD (48,54,89,100). Population modeling provides a framework for studying diverse conditions in reference to a common baseline, which allows us to better quantify individual differences and address heterogeneity and multisite datasets. Population modeling also provides a potential route toward clinical and translational applications of neuroimaging (101). Similar to the use of pediatric growth charts, by characterizing typical brain development, we can identify individually specific alterations from these trajectories that may be associated with neurodevelopmental conditions even before associated traits manifest clinically.

Here, we leveraged models of average brain development previously characterized by our group (98) to quantify alterations related to autism and ADHD. To our knowledge, this is the first study to use population modeling to investigate gray matter alterations related to these conditions in comparison to a common reference sample. We examined sources of variability related to sex, age, and measures of autistic and ADHD traits. Finally, we examined whether a subset of individuals with co-occurring autism and ADHD presented with distinct alterations.

METHODS AND MATERIALS

Sample and Datasets

T1-weighted scans were combined from 49 sites across 7 datasets, including the ABIDE (Autism Brain Imaging Data Exchange) (102,103), the POND (Province of Ontario Neurodevelopmental) Network, the HBN (Healthy Brain Network) at the Child Mind Institute (104), the ADHD200 Consortium, the Multimodal Developmental Neurogenetics of Females with ASD dataset from the National Institute of Mental Health Data Archive, the UK MRC-AIMS (Medical Research Council Autism Imaging Multi-centre Study), and the University of California San Diego Biomarkers of Autism study. The final dataset after quality control (QC) included 4255 individuals (1869 typically developing control participants [687 female, 1182 male], 987 individuals with ADHD [270 female, 717 male], and 1399 autistic individuals [288 female, 1111 male], ages 2–64 years [mean 14.0, median 12.4]) (Figure 1). For details of each dataset, demographics before and after QC, and group differences, see Supplemental Methods Section 1. It is important to note the distinction between biological sex and gender identity, both of which may influence presentation (12). Here, we refer to sex assigned at birth, but we acknowledge the overlap with and influence of gender socialization and the lack of data available to examine gender identity effects. Individuals with magnetic resonance imaging data and a primary diagnosis of autism or ADHD or no diagnosis were included. Individuals were initially included in the group of their primary diagnosis. A subset of individuals with documented co-occurring autism and ADHD were examined in further analyses.

Ethical approval and informed consent were obtained for each primary study. The Cambridge Psychology Research Ethics Committee (PRE.2020.104) deemed that secondary analysis of deidentified data did not require ethical oversight.

Data Processing

FreeSurfer and Cortical Parcellations. T1 images from each dataset were processed using FreeSurfer, version 6.0.1 (105). Regional estimates of each cortical measure were extracted based on the Desikan-Killiany atlas (106). For computational efficiency and because BrainChart models for separate hemispheres were not available at the time of analysis, measures were averaged across hemispheres for each parcellation.

Quality Control. All scans underwent manual QC of raw image and FreeSurfer surface reconstructions using our FSQC tool (107), which allows for the evaluation of both surface reconstruction and raw scan quality, including motion artifacts (108). A cutoff of 2.5 was used for FSQC (107). Because even small variations in quality can bias downstream analyses (108,109), we also included the FreeSurfer-derived Euler number (110) as a covariate in all analyses.

Generation of Centile Scores Using Generalized Additive Models of Location Scale and Shape. Our previous work (98) generated reference models using generalized additive models of location scale and shape to map neuroanatomical developmental trajectories across the life span, using a sample of 75,241 TD individuals, for total GMV, subcortical GMV (sGMV), white matter volume (WMV), ventricular volume, total SA, mean CT, regional CT, regional cortical volume (CV), and regional SA, while accounting for

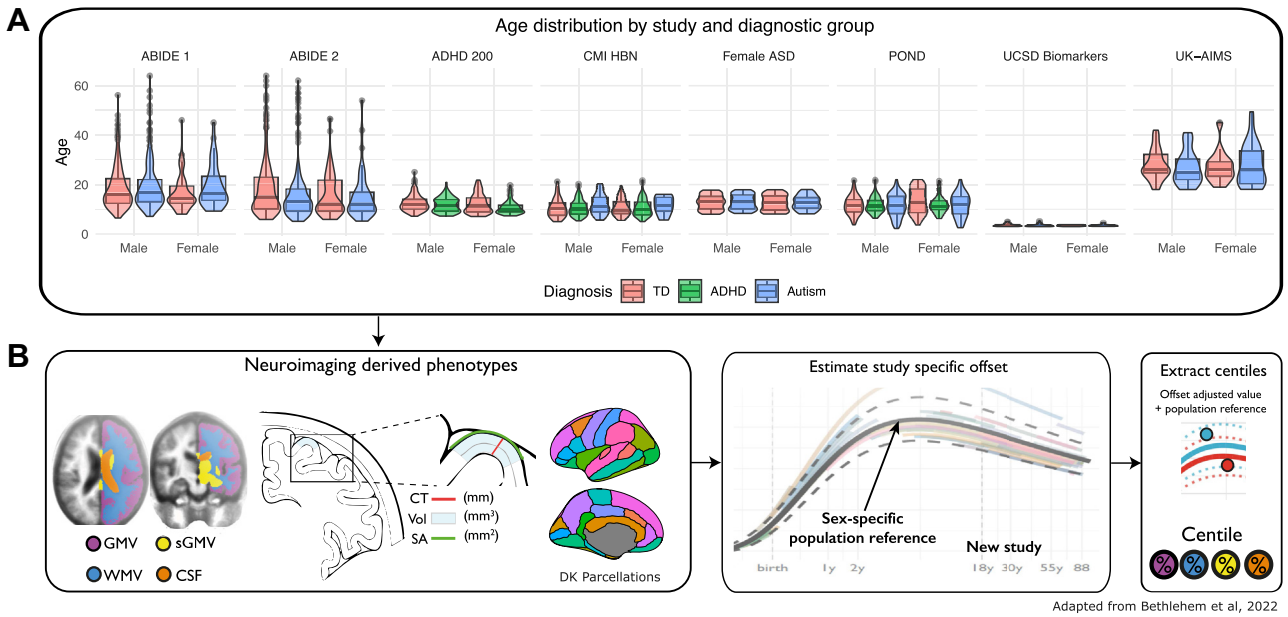

Figure 1. Study demographics and methods overview. **(A)** Box and violin plots representing the age distribution of each study by diagnostic group and sex. **(B)** Methods overview. Global cortical and subcortical gray matter volume (sGMV), white matter volume (WMV), and ventricular cerebrospinal fluid (CSF) volume and regional cortical thickness (CT), volume (Vol), and surface area (SA) based on the Desikan-Killiany (DK) parcellations were estimated for each participant. Sex-specific life span developmental trajectories for each neuroanatomical measure were estimated using generalized additive models of location scale and shape (GAMLSS) for a sample of 75,241 typically developing (TD) individuals, accounting for site- and scanner-specific variables (98). Out-of-sample estimates for the study sample used here were generated based on these reference models, resulting in a (per)centile score for each measure of each participant, indicating where they fall within the sample range (0–1). ABIDE, Autism Brain Imaging Data Exchange; ADHD, attention-deficit/hyperactivity disorder; CMI HBN, Child Mind Institute–Healthy Brain Network; POND, Province of Ontario Neurodevelopmental; UCSD, University of California San Diego; UK-AIMS, UK Medical Research Council Autism Imaging Multi-centre Study.

effects of age, sex, and site/scanner. Models for subcortical structures and the cerebellum were not available at the time of analysis. Out-of-sample centile scores for our study sample were generated based on these reference models using Brent's maximum likelihood estimation [Supplemental Methods Section 2 (98)]. Centile scores quantify variation in brain development and range from 0 to 1, with 0.5 representing the average of the reference sample.

ComBat and Accounting for Site Variability. Generalized additive models of location scale and shape has been shown to adequately account for batch effects related to differences between site- and scanner-specific variables (98). However, we previously (98) noted the relatively lower stability of the out-of-sample models for $n < 100$. Due to the smaller sample sizes of some sites in our dataset and higher variability in the clinical samples, we first harmonized our data using ComBat (111), consistent with previous work (112). ComBat was applied to the entire dataset across all global and regional measures, with each site treated as a batch and with covariates of age, sex, and diagnosis to preserve related biological variation. ComBat-harmonized data were used as inputs to the out-of-sample maximum likelihood estimation to generate centile scores. We also conducted sensitivity analyses on non–ComBat-harmonized centiles and compared in-sample and out-of-sample centiles (Supplemental Methods Sections 2 and 3).

Statistical Analysis

Group Differences and Sex Modulation Effects. Separate multiple linear regressions were used to examine diagnostic group differences in centile scores for all global volumes and regional measures. Sex-by-diagnosis interactions were examined, and given previous evidence of sex-specific neurobiological correlates in autism and ADHD (31,40,52,66,82,113–115), a priori sex-stratified analyses were also used to examine diagnostic differences in males and females separately and to compare sex-specific profiles of case-control differences. We assessed the similarity of sex-specific effect size maps by calculating Spearman correlations and using spin permutation testing to assess significance (Supplemental Methods Section 4).

All analyses included Euler number as a covariate, as well as age, to account for potential systematic age deviations in clinical groups. Multiple comparisons were controlled for using the false discovery rate correction (116), separately for each analysis and cortical measure. Cohen's *d* effect sizes were calculated using the "t_to_d" function in the "effectsize" package in R (117).

We also examined the amount of regional overlap in participants in each group with the greatest divergences from the average centile score [as in (118)]. Other sensitivity analyses included controlling for global brain measures, using different QC methods, analysis of equal sex-matched subsamples, and examining differences in the level of multimodality of the

distributions between groups, potentially suggesting the existence of subgroups and investigating dimensional associations between cortical measures and autistic and ADHD traits (Supplemental Methods Sections 5–9).

Age Modulation Effects. An age-by-diagnosis interaction was conducted for global and regional measures to assess age-dependent diagnostic differences. Due to the narrower age range of the ADHD sample (5–21 years), for ADHD, we only included typically developing individuals in the same age range, supported by a sensitivity analysis with the full sample (Supplemental Methods Section 11).

Co-occurring Autism and ADHD. We conducted an exploratory analysis to examine whether individuals with co-occurring autism and ADHD had unique neuroanatomical profiles. We compared a subgroup of 203 individuals with recorded clinical diagnoses of both conditions (autism+ADHD) to the control group and examined interactions with sex and sex-specific effects. We also compared the correlation [using spin tests (119)] and overlap of brain maps between each pair of diagnostic groups (Supplemental Methods Section 10.2). Data on secondary diagnosis were not available for all datasets and can be unreliable. While secondary diagnoses at some sites were confirmed by clinician consensus [e.g., Healthy Brain Network (104)], they were community based at other sites. There are likely individuals missed in this analysis; thus, this analysis was exploratory, and we attempted to replicate it in a subset of autistic individuals who also met the clinical cutoff criteria on a measure of ADHD traits (n = 118) (see Supplemental Methods Section 10.2 for sensitivity analyses and demographics).

RESULTS

Differences in Global Brain Measures

Impacted global brain features were largely distinct in autism and ADHD. Autistic individuals had significantly greater ventricular volume centiles than control participants (Figure 2). Individuals with ADHD had significantly lower total cortical and subcortical GMV, total WMV, and total cortical SA centile scores overall but greater mean CT centiles than control participants.

For autism, we observed trend-level significant interactions for total sGMV and ventricular volume (neither survived false discovery rate correction); autistic males had greater sGMV and ventricular volume than male control participants, but females showed no difference. There were no significant diagnosis-by-sex interactions for ADHD. There was a trend toward a significant interaction between autism diagnosis and age for total WMV, sGMV, and SA and for sGMV for ADHD, but none survived false discovery rate correction (Table 1).

Regional Differences

Main Effects. Significant group differences in regional centiles were much less widespread in autism than in ADHD (Figure 2). In autistic individuals, CT and CV, but not SA, centiles were increased in the STG (d = 0.13 to 0.15) only. Individuals with ADHD had significantly lower CV and SA centiles across most cortical regions (d = −0.07 to −0.18) but

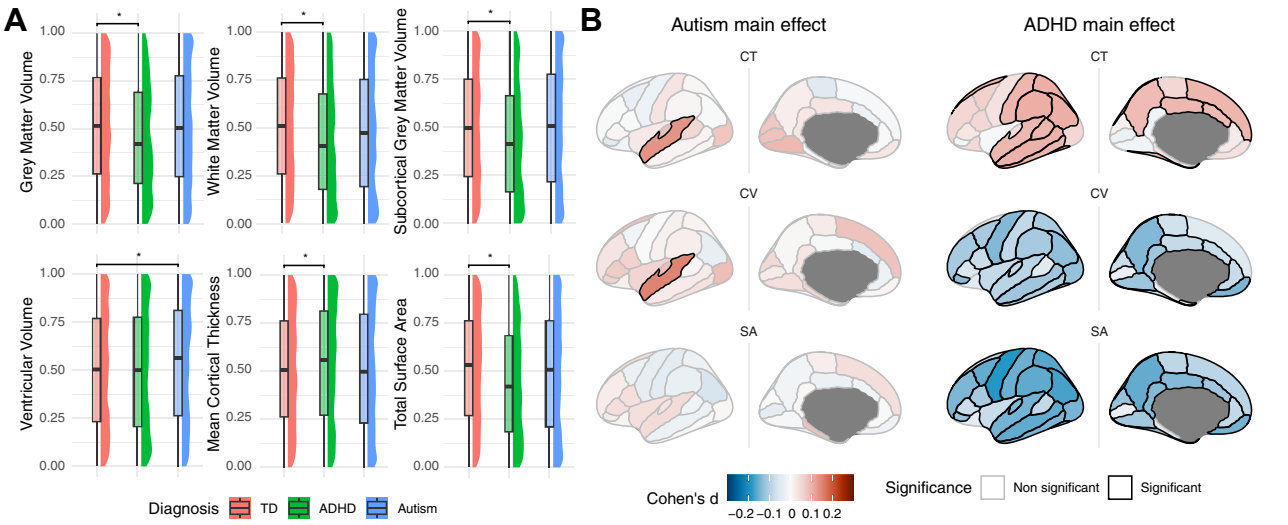

Figure 2. Case-control differences in global and regional centile scores of structural magnetic resonance imaging metrics. **(A)** Box and raincloud plots showing group differences in global neuroanatomical measures. Raincloud plots show the density distribution of centiles per group. Autistic individuals had significantly larger ventricles than typically developing (TD) individuals, but no differences were observed on any other measures. Individuals with attention-deficit/hyperactivity disorder (ADHD) had significantly lower cortical gray, white, and subcortical gray matter volume and total surface area (SA) centiles than control participants but greater mean cortical thickness (CT) centiles. **(B)** Regional group differences. Brain maps show Cohen's d effect sizes, with significant regions (passing 5% false discovery rate [FDR] applied to each analysis and cortical measure separately) outlined in black. Red represents positive effect sizes (autism or ADHD > control group), and blue represents negative effect sizes (autism or ADHD < control group). Overall, autistic individuals had significantly greater cortical volume (CV) and CT in the superior temporal gyrus, whereas individuals with ADHD had significant and widespread decreases in CV and SA and increases in CT. *p_{FDR} < .05.

Table 1. Analysis of Global Brain Measures for Autism and ADHD Main Effects and Interaction Effects

	Autism			ADHD		
	p Value	*q* Value	Cohen's *d*	*p* Value	*q* Value	Cohen's *d*
Main Effects						
GMV	.329	.395	0.030	<.0001[a]	<.0001[a]	−0.139
WMV	.216	.395	−0.038	<.0001[a]	<.0001[a]	−0.156
sGMV	.044	.131	0.062	<.0001[a]	<.0001[a]	−0.132
Ventricles	<.0001[a]	<.0001[a]	0.150	.412	.412	0.025
Total SA	.283	.395	−0.033	<.0001[a]	<.0001[a]	−0.178
Mean CT	.558	.558	0.018	.004[b]	.005[b]	0.089
Interaction Effects						
GMV	.057	.113	−0.059	.376	.818	0.027
WMV	.228	.274	−0.037	.514	.818	0.020
sGMV	.009[b]	.054	−0.080	.961	.961	0.002
Ventricles	.020[c]	.060	−0.072	.874	.961	−0.005
Total SA	.096	.144	−0.051	.200	.818	0.039
Mean CT	.927	.927	−0.003	.546	.818	−0.019

q Values are false discovery rate–corrected *p* values.

ADHD, attention-deficit/hyperactivity disorder; CT, cortical thickness; SA, surface area; sGMV, subcortical gray matter volume; WMV, white matter volume.

[a]$p < .001$.

[b]$p < .01$.

[c]$p < .05$.

higher CT centiles (d = 0.09 to 0.10). Effect sizes were relatively small. Results using in-sample and non-ComBat harmonized data were highly similar. Autistic individuals showed the highest degree of both negative and positive extreme centiles (Supplemental Results Sections 1 and 2). Controlling for global measures drastically altered effects for ADHD but not for autism, highlighting that the ADHD results were driven largely by global effects, but results were more localized for autism. Increases in CT were particularly attenuated, and decreases in CV and SA disappeared, with some increases being observed instead. Different QC methods had very little impact (Supplemental Results Section 4).

Interaction With Sex and Sex-Stratified Results. A sex-by-diagnosis interaction was observed for autism, but not ADHD, and sex-specific maps were far more similar for ADHD. For autism, there was a significant interaction for CV in the STG, insula, and temporal pole (Figure 3A). Importantly, the significant diagnostic main effect on STG CV must be interpreted in light of this interaction effect and seems to apply to autistic males only.

Compared with same-sex control participants, autistic males had significantly greater STG CV and CT centiles (d = 0.15 to 0.18), whereas autistic females had significantly lower cortical SA centiles in the fusiform gyrus (d = −0.18). Subthreshold effect size maps showed similar spatial patterning in males and females for CT (rho = 0.5, p_{spin} = .024), but they were quite different for CV (rho = 0.24, p_{spin} = .13) and SA (rho = −0.06, p_{spin} = .40) (Figure 3B; Supplemental Results Section 5). Males with ADHD had significantly lower CV and SA (d = −0.08 to −0.20) and higher CT centiles (d = 0.10 to 0.11) across much of the cortex than male control participants. Unsurprisingly, given the lack of a significant interaction, females with ADHD had very similar patterns of cortical alterations, although with fewer significant regions (CV and SA: d = −0.13 to −0.22; CT: d = 0.18). Male and female ADHD subthreshold effect size maps were visually similar, with high spatial overlap for all measures (rho = 0.34–0.59; p_{spin} = .0005–.029).

Effect sizes and directions remained largely consistent in the sex-matched subsample analyses (Supplemental Results Section 6). Multimodal distributions of centiles were observed across most of the cortex for the autistic group but not for the ADHD and the control group (Supplemental Results Section 7). Dimensional analyses of autistic and ADHD traits revealed limited significant but weak associations between some clinical and cortical measures (Supplemental Results Section 8).

Interactions With Age. Limited age-by-diagnosis interactions were observed for autism and ADHD. A significant age-by-diagnosis interaction for autism was observed only in the superior frontal gyrus for CT centiles. There was a small positive significant correlation between age and CT centile for the autism group only (partial r = 0.11).

For ADHD, there was a significant interaction for CT centiles primarily in frontal and parietal regions, whereas there was a significant positive correlation with age in the ADHD group (partial r = 0.07 to 0.14) but minimal or no correlation in the control group. In the insula, there was a significant negative correlation in the ADHD group only (r = −0.14 to −0.15) (Figure 4). The ADHD analysis in the whole control sample yielded largely similar results (Supplemental Results Section 9).

Co-occurring Autism and ADHD. The autism+ADHD group showed a distinct pattern of alterations, with some overlap, compared with individuals with only one diagnosis (Figure 5), with widespread significant increases in CT centiles compared with control participants (d = 0.10 to 0.24) and decreased SA centiles in frontal and parietal regions (d = −0.11 to −0.14). There was no significant interaction with sex. Effects for males resembled those observed in the whole group, but there were no significant differences in females (Figure 5A). Spin tests and overlap analysis revealed the greatest similarity between the autism+ADHD and ADHD-only groups, with minimal overlap between the autism and ADHD-only groups (Figure 5B; Supplemental Results Section 10.2). CT and SA both showed widespread homology in effect size direction across all groups, although with little overlap of significance, whereas CV primarily showed overlap between autism+ADHD and ADHD only. The STG overlapped in significance between autism and ADHD, but in opposite directions.

Most results were no longer significant after controlling for global measures. The replication analysis based on the ADHD trait cutoff yielded similar results, although with slightly fewer significant regions, and, notably, the male and female autism+ADHD effect sizes were more similar between sexes (Supplemental Results Section 10).

DISCUSSION

Using an aggregated dataset and existing models of brain development, we observed largely distinct, robust neuroanatomical signatures of autism and ADHD, with some overlap. Both conditions presented with greater CT, localized to the

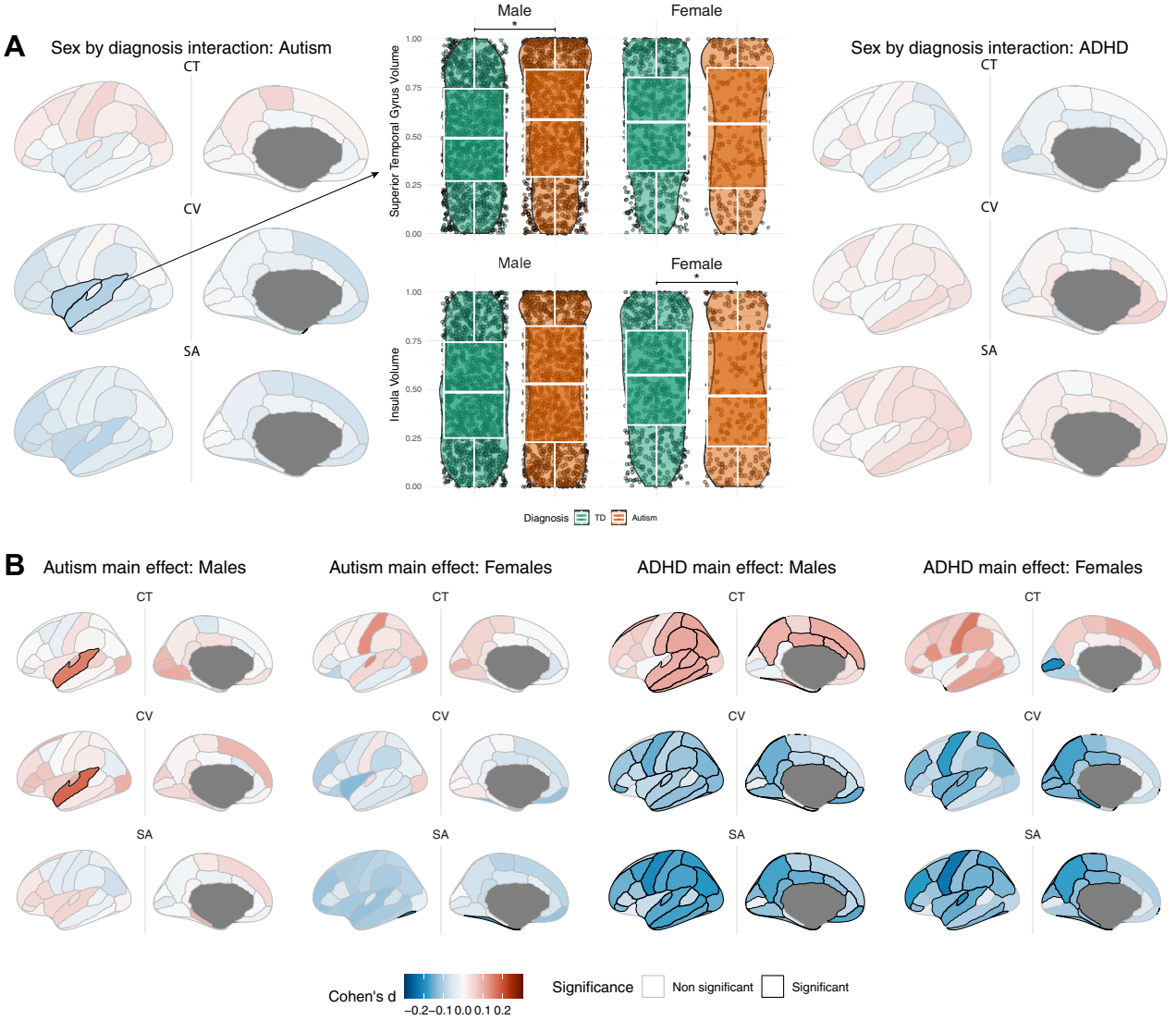

Figure 3. The effect of interactions between sex and diagnostic group on centile scores of regional magnetic resonance imaging metrics. **(A)** Brain maps showing effect sizes and significance of interaction per brain region, and box and violin plots showing comparison of values separately by group for 2 significant regions. **(B)** Sex-stratified regional association with diagnosis. All maps show Cohen's *d* effect sizes, with significant regions (passing 5% false discovery rate [FDR] correction) outlined in black. Red represents positive effect sizes (autism or attention-deficit/hyperactivity disorder [ADHD] > control group), and blue represents negative effect sizes (autism or ADHD < control group). *$p_{FDR} < .05$. CT, cortical thickness; CV, cortical volume; SA, surface area; TD, typically developing.

STG in autism but widespread in ADHD. In contrast, while autistic individuals also showed STG increases in CV, ADHD was associated with globally decreased CV and SA. This work confirms and extends previous large-scale and consortium efforts to characterize these conditions (31,54,74,85,90,120), by also identifying sex-specific alterations in autism and distinct alterations in individuals with co-occurring diagnoses in this large, carefully and manually QCed sample. Finally, we found evidence for age-specific effects that were overlapping but more widespread in ADHD and limited significant associations between neuroanatomy and measures of autistic and ADHD traits.

Previous population modeling studies on a single diagnostic cohort have mainly observed divergence from typical brain development in individualized patterns (45,54,121) or multiple subgroups with distinct patterns of divergence and clinical profiles (48,50) rather than group differences. We note that our sample size is considerably larger than that of previous studies, so while we also observed individualized patterns of centile scores, we may have had more power to detect average group differences that are consistent across datasets. However, it will be interesting to see in future work whether a population modeling approach is more adept at detecting data-driven subtypes and better parsing the complexities of the underlying neuroanatomy.

We did not observe the greater total GMV or SA in autistic individuals that have been reported previously

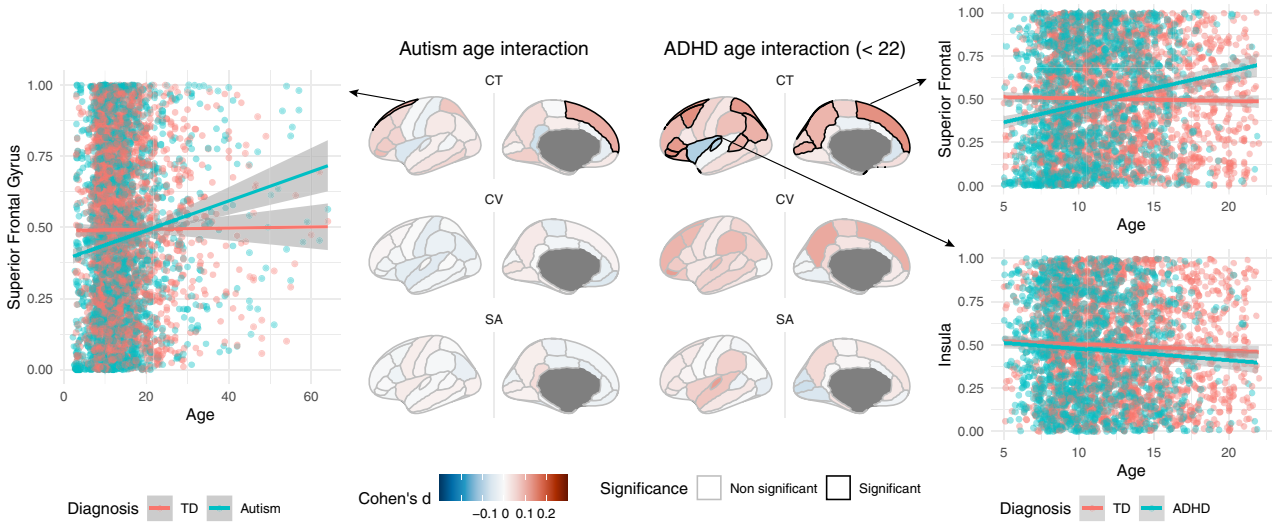

Figure 4. Regional interactions between diagnosis and age. Brain maps show interaction between effect sizes and regional significance, and scatter plots show the relationship between cortical thickness (CT) and age in the autism/attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) groups in regions where a significant interaction was observed. For the superior frontal gyrus age-by-diagnosis interaction for autism, $r_{autism} = 0.11$ ($p < .001$); $r_{TD} = -0.008$ ($p = .8$). For the age-by-diagnosis interaction for ADHD, for the superior frontal gyrus $r_{ADHD} = 0.09$ ($p = .008$), $r_{TD} = -0.04$ ($p = .9$); for the insula $r_{ADHD} = -0.14$ ($p < .001$); $r_{TD} = -0.05$ ($p = .48$). CV, cortical volume; SA, surface area.

(20–22,35,122,123), although we did not explicitly test the early age range that was the focus of most of these studies. However, we did replicate findings of enlarged ventricular volume related to autism (120,122–127), and our findings of significantly greater localized regional CT and CV are at least partially consistent with the results of recent large-sample studies (30,31,120,128). Increases in the STG, which is known to be involved in cognitive functions often affected in autistic individuals, have been commonly reported in autism (25,31,54,128–142). We confirmed previous reports of global GMV, WMV, and SA reductions in ADHD, as well as widespread regional CV and SA decreases (59–63,65), which seem to be largely a global effect. We also confirmed recent reports of greater CT, which contradict some earlier studies of ADHD (60–64,72,73). It will also be important in future work to extend these investigations to the subcortex and cerebellum (74,143–145).

It is interesting to note the divergent direction of diagnostic effects and cortical measures in autism and ADHD. CT, CV, and SA are related to distinct neurodevelopmental processes and genetic underpinnings (25,146–154), with CV and SA being more closely related than to CT (155). Thus, these different measures could point to distinct underlying neurobiological mechanisms or processes related to the emergence of each condition.

The overall main effect of autism seemed to be driven by males, who comprise the majority of the sample, with distinct alterations observed for females. Critically, this suggests that inferences drawn from mixed-sex samples may not be applicable to autistic females, although this was not true for ADHD [as was also observed in (156)]. Autistic females differed from neurotypical females only in fusiform gyrus SA, a region in which alterations in asymmetry in autistic females have also been reported (157). In contrast, we did not observe evidence for sex modulation in ADHD. An unanswered question for future research is to what extent sex effects on the cortical measures and clinical presentations are due to underlying differences in sex-related biology (e.g., the so-called female protective effect and neuro-endocrine-immune theories) rather than to gender-related socialization, identity, or diagnostic bias effects (158). For example, in the autism+ADHD analysis based on Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale ADHD cutoffs (rather than diagnosis), the male and female effect size maps are more similar. It is possible that this analysis was less affected by sex biases in clinical diagnosis, leading to higher similarity between the sexes.

Significant associations between neuroanatomical alterations and autistic traits have also often been reported previously (45,54,159), in contrast to the lack of significant association observed here with the Autism Diagnostic Observation Schedule calibrated severity score despite the large sample size. A significant caveat here is that due to the multisite nature of the data, these analyses were conducted only on a subset of participants, which may partially explain the lack of robust associations in the current study.

The absence of an age-by-diagnosis interaction across global measures and most cortical regions in autism offers limited support for the hypothesis of early brain overgrowth and normalization with age (122,160). However, longitudinal data are needed to properly investigate these relationships. The regional age interaction for ADHD suggests that the nature of these deviations in ADHD is not static across development, at least in some cortical measures.

Finally, the autism+ADHD group seemed to be a somewhat distinct subgroup, resembling ADHD more than autism, but with some overlapping features. It may be that these differences in the autism+ADHD group represent a synthesized

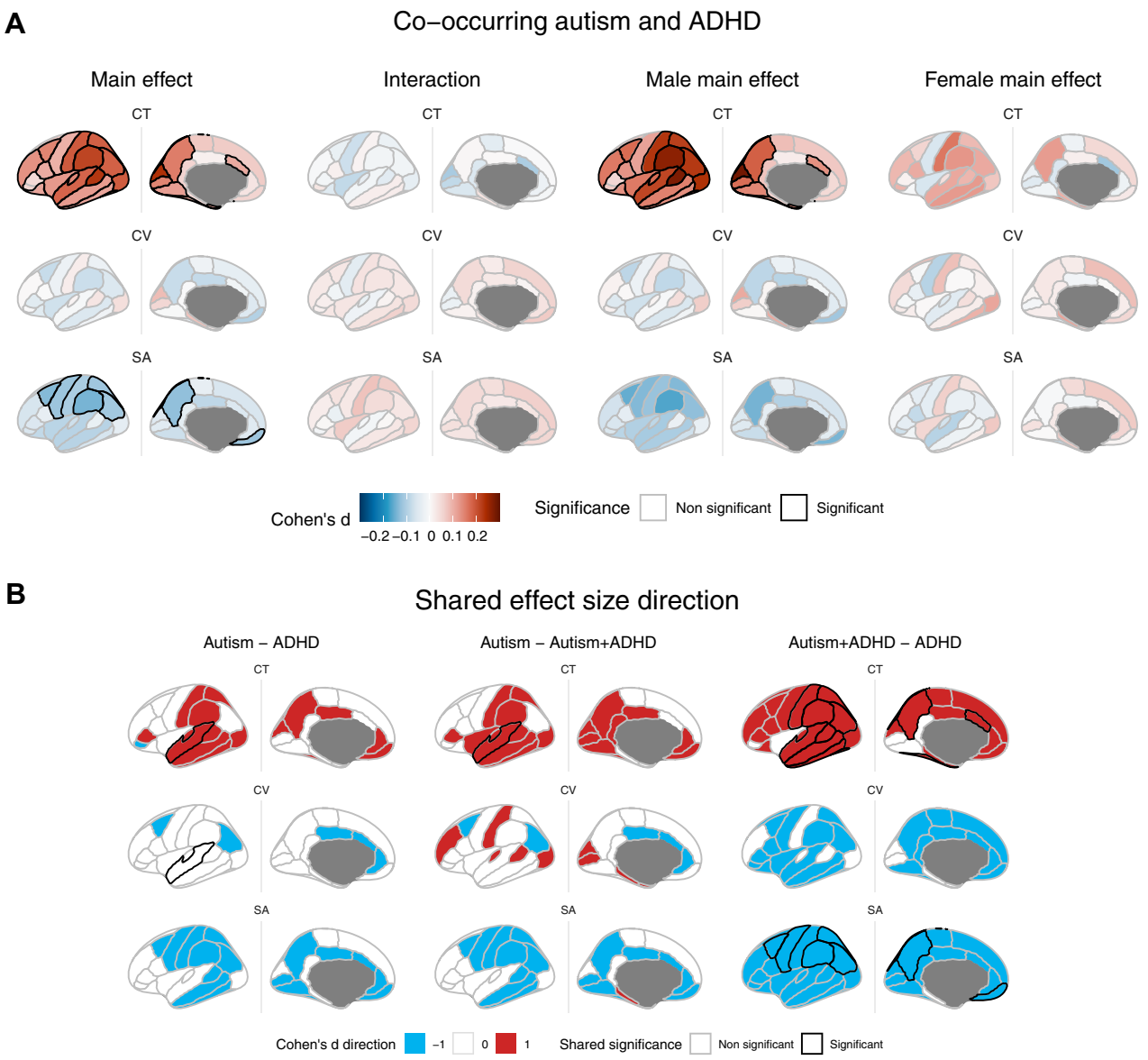

Figure 5. Cortical alterations (compared with control group) in individuals with co-occurring autism and attention-deficit/hyperactivity disorder (ADHD) and overlap of effect size significance and direction. **(A)** Main effects of diagnosis compared with control group; interaction with sex; main effects in males, and main effects in females. All maps show Cohen's *d* effect sizes, with significant regions (passing 5% false discovery rate correction) outlined in black. Red represents positive effect sizes (autism+ADHD > control group), and blue represents negative effect sizes (autism+ADHD < control group). **(B)** Brain maps showing the pairwise overlap of effect size direction and significance for the autism, ADHD, and autism+ADHD groups. Regions that had a positive effect size in both groups' analysis (in comparison to control group) are shown in red; regions that had a negative effect size in both groups are shown in blue. Regions in white were in different directions in different groups. Regions that were significantly different in both groups from the control group are outlined in black. Note that the superior temporal gyrus showed a significant effect in both autism and ADHD for cortical volume (CV), but in opposite directions. CT, cortical thickness; SA, surface area.

phenotype, but we caution against a simplified interpretation. Previous studies have not identified significant differences in CT between an autism+ADHD group and control group; however, the sample sizes have been small (161,162). Notably, secondary diagnoses were not available for all datasets, and even when available, some are likely missed based on known rates of co-occurrence (19,163). For this exploratory analysis, we focused on individuals who had clearly documented secondary diagnoses. Future research could be improved if co-occurring diagnoses and dimensional clinical data were reported consistently across studies. However, these preliminary findings provide an interesting direction for future research.

Our results should be interpreted in light of some limitations. First, as is increasingly common, the data come from multiple

sources, with different scanners, protocols, recruitment procedures, and demographic characteristics. We have attempted to address this variability as rigorously as possible: all data were analyzed consistently in house, and data were harmonized in a 2-step process. While it is impossible to fully eliminate site effects, we believe that the size of this dataset and, in particular, the large female sample and availability of both autism and ADHD data, mitigate these issues. However, we note that the effect sizes observed in most analyses were very small and thus may have limited clinical or practical significance. Additionally, out-of-sample centiles were generated for our dataset, despite some of these being included in the original BrainCharts models, to properly account for site differences. Sensitivity analyses demonstrate the stability of the models; however, we caution that doing so in smaller sites could lead to overestimation of effects. Second, due to the availability of the models, cortical measures were averaged across hemispheres. Both autism and ADHD have been associated with atypical asymmetry (157,164,165); thus, these results should be interpreted in light of the potential limitation that they are based on a symmetrical (unihemispheric average) model of the cerebral hemispheres. Third, the lack of consistent phenotypic and diagnostic information led to limited data in the analyses of clinical measures and co-occurring diagnoses. Partially for this reason, we also did not investigate relationships with IQ, although we note that controlling for IQ may also remove biological variation or confound results (166). Fourth, despite its large size, the representativeness of the sample is still suboptimal. There is still a large imbalance in the number of diagnosed males and females, a substantial lack of participants with lower IQ and/or high support needs, and insufficient diversity across racial-ethnic groups. Finally, the lack of longitudinal data limits our ability to draw conclusions about developmental trajectories over time and should be a priority of future studies.

Conclusions

This study identified distinct profiles of neuroanatomical divergence associated with autism and ADHD that were differentially modulated by age and sex. These observations offer valuable insights into associated developmental processes and could potentially serve as indicators of biomarkers. We also identified potential differential impacts of co-occurring diagnoses of autism and ADHD, but we note that data on secondary diagnosis are not always reliable. Future work should further investigate individual variability and the existence of subgroups within and across diagnoses.

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