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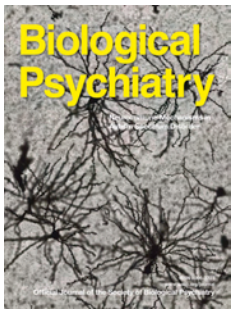

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Brain-charting autism and attention deficit hyperactivity disorder reveals distinct and overlapping neurobiology

Short title: "Brain-charting autism and ADHD"

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Key words: Neuroimaging; autism; ADHD; cortex; normative modelling; structural MRI

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 modelling, often referred to as normative modelling, provides a unified framework for studying age-specific and sex-specific divergences in brain development.

Methods

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

Results

We observed robust neuroanatomical signatures of both autism and ADHD. Overall, autistic individuals showed greater cortical thickness and volume, that was localised 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 autism+ADHD group displayed a unique pattern of widespread increases in cortical thickness, and certain decreases in surface area. We also found evidence that sex modulates the neuroanatomy of autism but not ADHD, and an age-by-diagnosis interaction for ADHD only.

Conclusions

These results indicate distinct cortical differences in autism and ADHD that are differentially impacted by age, sex, and potentially unique patterns related to their co-occurrence.

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For members of the Lifespan Brain Chart Consortium please refer to: https://docs.google.com/spreadsheets/d/1D8YNDcnhwlv2WcUDhreq3fwrkfpfGiFp0OGFVO5d-es/edit?usp=sharing

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Introduction

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 aetiological overlap (16–19), add complexity. Importantly, most studies have been based on male-dominant samples and might 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 this might only hold true for a subset (23–25), and for boys (26,27). Increased cortical thickness is often associated with autism (28–31), although reductions have been reported (32,33), as well as alterations in cortical surface area and volume (34–36). Alterations, including both increases and decreases, have been reported in the superior temporal gyrus, inferior and prefrontal cortex, sensory and motor regions (29–38), cerebellum, and subcortex (39–42), and appear to be moderated by age, sex, and co-occurring conditions or traits (31,43–48). Complementary work has suggested that multiple subgroups with distinct patterns of neuroanatomical alterations and clinical characteristics exist (40,48–50). Sex differences, in particular, have been reported in multiple cortical measures and associations (31,44, 51, 52, 53–57).

Recent meta-analyses have highlighted a similar lack of convergent findings in ADHD (58,59). Reduced total brain volume, grey matter volume and cortical surface area have been consistently reported (59–65). However, while earlier studies reported decreases in cortical thickness (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 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 largely distinct, with some overlapping alterations (90–99). A recent review (100) 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 observed compared to those with only one diagnosis (47,95,101), and evidence that ADHD diagnosis modulates the effect of autism on neuroanatomy (97).

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 harmonise multi-site data. Critically, these alterations must be contextualised in light of typical brain development given the neurodevelopmental nature of autism and ADHD (102–104).

Population modelling, often referred to as normative modelling, has proven effective for characterising age-dependent variation in brain development (105,106), and has recently been employed in studying autism or ADHD (48,54,96,107). Population modelling provides a framework for studying diverse conditions in reference to a common baseline, allowing us to better quantify individual differences and address heterogeneity and multi-site datasets. Population modelling also provides a potential route toward clinical and translational applications of neuroimaging (108). Similar to the use of paediatric growth charts, by characterising 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 characterised by our group (105) to quantify alterations related to autism and ADHD. This is, to our knowledge, the first study to use population modelling to investigate grey 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

Sample and datasets

T1-weighted scans were combined from 49 sites across 7 datasets, including the Autism Brain Imaging Data Exchange (ABIDE (109,110)), the Province of Ontario Neurodevelopmental (POND) Network, the Healthy Brain Network (HBN) at the Child Mind Institute (CMI) (111), the ADHD200 Consortium, the Multimodal Developmental Neurogenetics of Females with ASD (Female ASD) dataset from NIMH NDAR, the UK Medical Research Council Autism Imaging

Multi-centre Study (MRC-AIMS), and the University of California San Diego (UCSD) Biomarkers of Autism study. The final dataset after quality control (QC) included 4255 individuals, (1869 typically developing (TD) controls [1182 male, 687 female], 987 ADHD [717 male, 270 female] and 1399 autistic [1111 male, 288 female], age range 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 supplementary methods S1. It is important to note the distinction between biological sex and gender identity, which both might influence presentation (12). Here we refer to sex assigned at birth, but acknowledge the overlap with and influence of gender socialisation, and the lack of data available to examine gender identity effects. Individuals with MRI 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 recorded co-occurring autism and ADHD were examined in further analyses.

Ethical approval and informed consent was obtained for each primary study. The Cambridge Psychology Research Ethics Committee (PRE.2020.104) deemed secondary analysis of de-identified data not to require ethical oversight.

Data processing

Freesurfer and cortical parcellations

T1 images from each dataset were processed using FreeSurfer (112), version 6.0.1. Regional estimates of each cortical measure were extracted based on the Desikan-Killiany (113) atlas. For computational efficiency, and because at the time of analysis BrainChart models for separate hemispheres were not available, 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 (114) which allows for the evaluation of both surface reconstruction and raw scan quality, including motion artefacts (115). A cut-off of 2.5 was used for FSQC (114). As even small variations in quality can bias downstream analyses (115,116), we also included the FreeSurfer-derived Euler number (117) as a covariate in all analyses.

Generation of centile scores using GAMLSS

Our previous work (105) generated reference models using generalised additive models of location scale and shape (GAMLSS) to map neuroanatomical developmental trajectories across the lifespan, based on a sample of 75,241 typically developing individuals, for total grey matter volume (GMV), subcortical grey matter volume (sGMV), white matter volume (WMV), ventricular volume, total surface area, mean cortical thickness, and regional cortical thickness (CT), volume (CV) and surface area (SA), accounting for 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 (supplementary methods section S2 (105)). Centile scores quantify variation in brain development, and range from 0-1, with 0.5 representing the average of the reference sample.

ComBat and accounting for site variability

GAMLSS has been demonstrated to adequately account for batch effects related to differences between site- and scanner-specific variables (105). However, we previously (105) 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 harmonised our data using ComBat (118), consistent with previous work (119). ComBat was applied to the whole

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-harmonised 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-harmonised centiles, and comparing in-sample and out-of-sample centiles (supplementary methods S2-3).

Statistical analysis

Group differences and sex modulation effects

Separate multiple linear regressions examined 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 (31,40,52,66,82,83,120,121), 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 (supplementary methods S4).

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 (FDR (122)), for each analysis and cortical measure separately. Cohen's d effect sizes were calculated using the "t_to_d" function in the "effectsize" package in R (123).

We also examined the amount of regional overlap in participants in each group with the greatest divergences from the average centile score (as in (124)). Other sensitivity analyses included controlling for global brain measures, using different QC methods, analysis of equal sex-matched

subsamples, 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 (supplementary methods S5-9).

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 included only TD individuals in the same age range, supported by a sensitivity analysis with the full sample (supplementary methods S11).

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 (126)) and overlap of brain maps between each pair of diagnostic groups (supplementary methods S10.2). We note that data on secondary diagnosis was not available for all datasets, and can be unreliable. While secondary diagnoses at some sites were confirmed by clinician consensus (e.g. HBN (111)), at other sites, they were community-based. 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 cut-off criteria on a measure of ADHD traits (N=118; see supplementary methods S10.2 for sensitivity analyses and demographics).

Results

Differences in global brain measures

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

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

Regional differences

Main effects

Significant group differences in regional centiles were much less widespread in autism than ADHD (Figure 2). In autistic individuals, CT and CV, but not SA, centiles, were increased in the superior temporal gyrus (STG; d = 0.13-0.15) only. Individuals with ADHD had significantly lower CV and SA centiles across most cortical regions (d = -0.07- -0.18), but higher CT centiles (d = 0.09-0.10). Effect sizes were relatively small. Results using in-sample and non-ComBat harmonised were highly similar. Autistic individuals showed the highest degree of both negative and positive “extreme” centiles (supplementary results S1-2). Controlling for global measures drastically

altered effects for ADHD but not autism, highlighting that the ADHD results are driven largely by global effects, but for autism are more localised. Increases in CT were particularly attenuated, and decreases in CV and SA disappeared, with some increases instead observed. Different QC methods had very little impact (supplementary results S4).

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, and appears to apply to autistic males only.

Compared with same-sex controls, autistic males had significantly greater STG CV and CT centiles (d = 0.15-0.18), whereas autistic females had significantly lower cortical SA centiles in the fusiform gyrus (d = -0.18). Subthreshold effect size maps showed similar spatial patterning between males and females for CT (rho = 0.5, p_{spin} = 0.024), but were quite different for CV (rho = 0.24, p_{spin} = 0.13) and SA (rho = -0.06, p_{spin} = 0.40) (Figure 3B; Supplementary results S5). Males with ADHD had significantly lower CV and SA (d = -0.08 - -0.20) and higher CT centiles (d = 0.10-0.11) across much of the cortex relative to male controls. Unsurprisingly, given the lack of significant interaction, females with ADHD had very similar patterns of cortical alterations, though with fewer significant regions (CV and SA: d = -0.13- -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} = 0.0005-0.029).

Effect sizes and directions remained largely consistent in the sex-matched subsample analyses (supplementary results S6). Multimodal distributions of centiles were observed across most of the cortex for the autistic group, but not ADHD and controls (supplementary results S7). Dimensional

analyses of autistic and ADHD traits revealed limited significant but weak associations between some clinical and cortical measures (supplementary results S8).

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 slight 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 in primarily frontal and parietal regions, where there was a significant positive correlation with age in the ADHD group (partial r = 0.07-0.14), but minimal or no correlation in controls. In the insula there was a significant negative correlation in the ADHD group only (r = -0.14- -0.15; Figure 4). The ADHD analysis in the whole control sample yielded largely similar results (supplementary results S9).

Co-occurring autism and ADHD

The autism+ADHD group showed a distinct pattern of alterations, with some overlap, to those with only one diagnosis (Figure 5), with widespread significant increases in CT centiles relative to controls (*d* = 0.10-0.24) and decreased SA centiles in frontal and parietal regions (*d* = -0.11- -0.14). There was no significant interaction with sex. Male effects resembled those observed in the whole group, but there were no significant differences in the females (Figure 5A). Spin tests and overlap analysis revealed the greatest similarity between the autism+ADHD and ADHD groups, with minimal overlap between the autism and ADHD only groups (Figure 5B and S10.2). CT and SA both showed widespread homology in effect size direction across all groups, though with little overlap of significance, whereas CV primarily showed overlap between autism+ADHD

and ADHD. 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 cut-off yielded similar results, though with slightly fewer significant regions, and, notably, the male and female autism+ADHD effect sizes were more similar between sexes (Supplementary results S10).

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, localised to the 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 characterise these conditions (31,54,74,92,97,128), by also identifying sex-specific alterations in autism, and distinct alterations in individuals with co-occurring diagnoses, in this large, carefully manually QCed sample. Finally, we found evidence for age-specific effects which were overlapping but more widespread in ADHD, and limited significant associations between neuroanatomy and measures of autistic and ADHD traits.

Previous population modelling studies on a single diagnostic cohort have mainly observed divergence from typical brain development in individualised patterns (45,54,129), 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 previous studies, so, while

we also observed individualised patterns of centile scores, we may be better powered to detect average group differences that are consistent across datasets. However, it will be interesting to see in future work if a population modelling 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 (20–22,35,130,131), although we did not explicitly test the early age range that was the focus of most of these studies. We did, however, replicate findings of enlarged ventricular volume related to autism (128,130–135), and our findings of significantly greater localised regional CT and CV are at least partly consistent with recent, large-sample studies (30,31,128,136). Increases in the STG have been commonly reported in autism (31,54,136–145) which is known to be involved in cognitive functions often impacted in autistic individuals (25,146–150). We confirm previous reports of global GMV, WMV and SA reductions in ADHD, as well as widespread regional CV and SA decreases (59–63,65), which appear to be largely a global effect. We also confirm 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 (74,153–155).

It is interesting to note the divergent direction of diagnostic effects and cortical measures between autism and ADHD. CT, CV and SA are related to distinct neurodevelopmental processes and genetic underpinnings (25,156–164), with CV and SA more closely related than to CT (165). 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 appeared 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 might not be applicable to autistic females, though this was not the case for ADHD (as also observed in (169)). 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 (170). In contrast, in ADHD we did not observe evidence for sex modulation. An outstanding future question is to what extent sex effects in the cortical measures and clinical presentations are due to underlying differences in sex-related biology (e.g., so-called “female protective effect” and neuro-endocrine-immune theories) versus gender-related socialisation, identity or diagnostic-bias effects (171). For example, in the autism+ADHD analysis based on SWAN ADHD cut-offs (rather than diagnosis), the male and female effect size maps are more similar. It is possible that this analysis is less impacted 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 (45,54,172), in contrast to the lack of significant association observed here with the ADOS CSS, despite the large sample size. A significant caveat here is that due to the multi-site nature of the data, these analyses were conducted on a subset of participants only, which might partially explain the lack of robust associations.

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 normalisation with age (130,173). 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 appeared to be a somewhat distinct subgroup, resembling ADHD more than autism, but with some overlapping features. It might be that these differences

in the autism+ADHD group represent a synthesised phenotype, but we caution against a simplified interpretation. Previous studies have not identified significant differences in CT between an autism+ADHD group and controls; however, the sample sizes were small (174,175). Notably, secondary diagnoses were not available for all datasets, and even when available, some are likely missed, based on known rates of co-occurrence (19,176). For this exploratory analysis we focused on individuals who had clearly recorded 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 avenue 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 was analysed consistently, in house, and data was harmonised in a two-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 (170,177,178); thus, these results should be interpreted in light of the potential limitation that they are based on a symmetric (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. Partly for this reason we also did not investigate relationships with IQ, though we note that controlling for IQ may also remove biological variation or confound results (179). Fourth, despite its size, the representativeness of the sample is still suboptimal. There is still a large imbalance in the number of diagnosed males and females, and 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 identifies distinct profiles of neuroanatomical divergence associated with autism and ADHD, that are 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 note that data on secondary diagnosis is not always reliable. Future work should further investigate individual variability and the existence of subgroups within and across diagnoses.

Table 1

	Main effect					
	Autism			ADHD		
	p value	q value	Cohen's d	p value	q value	Cohen's d
GMV	0.329	0.395	0.030	0.000 *	0.000 *	-0.139
WMV	0.216	0.395	-0.038	0.000 *	0.000 *	-0.156
sGMV	0.044	0.131	0.062	0.000 *	0.000 *	-0.132
Ventricles	0.000 *	0.000 *	0.150	0.412	0.412	0.025
Total SA	0.283	0.395	-0.033	0.000 *	0.000 *	-0.178
Mean CT	0.558	0.558	0.018	0.004 *	0.005 *	0.089
	Interaction					
	Autism interaction			ADHD interaction		
	p value	q value	Cohen's d	p value	q value	Cohen's d
GMV	0.057	0.113	-0.059	0.376	0.818	0.027
WMV	0.228	0.274	-0.037	0.514	0.818	0.020
sGMV	0.009 *	0.054	-0.080	0.961	0.961	0.002
Ventricles	0.020 *	0.060	-0.072	0.874	0.961	-0.005
Total SA	0.096	0.144	-0.051	0.200	0.818	0.039
Mean CT	0.927	0.927	-0.003	0.546	0.818	-0.019

Table 1. Cohen's d effect sizes, q values (FDR corrected p values) and P values for global brain measures for autism and ADHD main effects (top) and interaction effects (bottom). * denotes p<0.05, ** p<0.01, and *** p<0.001.

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Figure legends

Figure 1. Study demographics and methods overview. A. Box and violin plots representing age distribution of each study by diagnostic group and sex. **B.** Methods overview. Global cortical and subcortical grey matter volume (GMV, sGMV), white matter volume (WMV), and ventricular cerebrospinal fluid (CSF) volume, and regional cortical thickness, volume and surface area based on the Desikan-Killiany (DK) parcellations were estimated for each participant. Sex-specific lifespan developmental trajectories for each neuroanatomical measure were estimated using generalised additive models of location scale and shape (GAMLSS) for a sample of 75,241 typically developing individuals, accounting for site and scanner specific variables (105). 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).

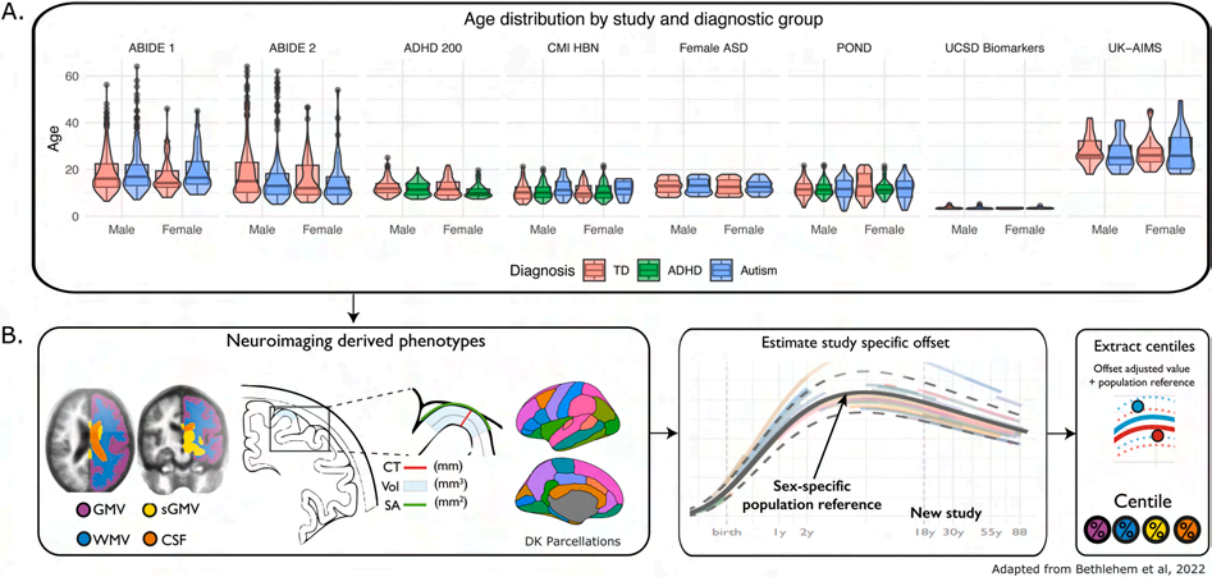
Figure 2. **Case-control differences in global and regional centile scores of structural MRI metrics. A**. Box and raincloud plots showing group differences in global neuroanatomical measures. Raincloud plots show the density distribution of centiles per group. Autistic individuals had significantly larger ventricles than TD individuals, but no differences were observed in any other measures. Individuals with ADHD had significantly lower cortical grey, white, and subcortical grey matter volume and total surface area centiles relative to controls, but greater mean cortical thickness centiles. **B**. Regional group differences. Brain maps show Cohen's d effect sizes, with significant regions (passing 5% FDR, applied to each analysis and cortical measure separately) outlined in black. Red represents positive effect sizes (autism or ADHD > controls), and blue represents negative effect sizes (autism or ADHD < controls). Overall, autistic individuals had significantly greater cortical volume and thickness in the superior temporal gyrus; whereas individuals with ADHD had significant and widespread decreases in cortical volume and surface area, and increases in cortical thickness.

Figure 3. **Interactions between sex and diagnostic group on centile scores of regional MRI metrics**. **A.** Brain maps showing effect sizes and significance of interaction per brain region, and box and violin plots showing comparison of values broken down by group for two significant regions. **B.** Sex-stratified regional association with diagnosis. All maps show Cohen's d effect sizes, with significant regions (passing 5% FDR) outlined in black. Red represents positive effect sizes (autism or ADHD > controls), and blue represents negative effect sizes (autism or ADHD < controls).

Figure 4. **Regional interactions between diagnosis and age**. Brain maps show interaction effect sizes and regional significance, and scatter plots show the relationship between CT and age in the autism/ADHD and TD groups in regions where a significant interaction was observed. For the superior frontal gyrus age-by-diagnosis interaction for autism, $r_{autism} = 0.11$ ($P < 0.001$); $r_{TD} = -0.008$ ($P = 0.8$). For the age-by-diagnosis interaction for ADHD, for the superior frontal gyrus

r_{ADHD} = 0.09 (P = 0.008); r_{TD} = -0.04 (P = 0.9); for the insula r_{ADHD} = -0.14 (P < 0.001); rTD = -0.05 (P = 0.48).

Figure 5. **Cortical alterations (relative to controls) in individuals with co-occurring autism and ADHD and overlap of effect size significance and direction. A.** Main effects of diagnosis relative to controls; 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% FDR) outlined in black. Red represents positive effect sizes (autism+ADHD > controls), and blue represents negative effect sizes (autism+ADHD < controls). **B.** Brain maps showing the pairwise overlap of effect size direction and significance for the autism, ADHD and autism+ADHD groups. Regions which had a positive effect size in both groups' analysis (in comparison to controls) are shown in red; regions which had a negative effect size in both groups are shown in blue. Regions in white were in discordant directions between groups. Regions which were significantly different from controls in both groups are outlined in black. Note that the superior temporal gyrus showed a significant effect in both autism and ADHD for cortical volume, but in opposite directions.



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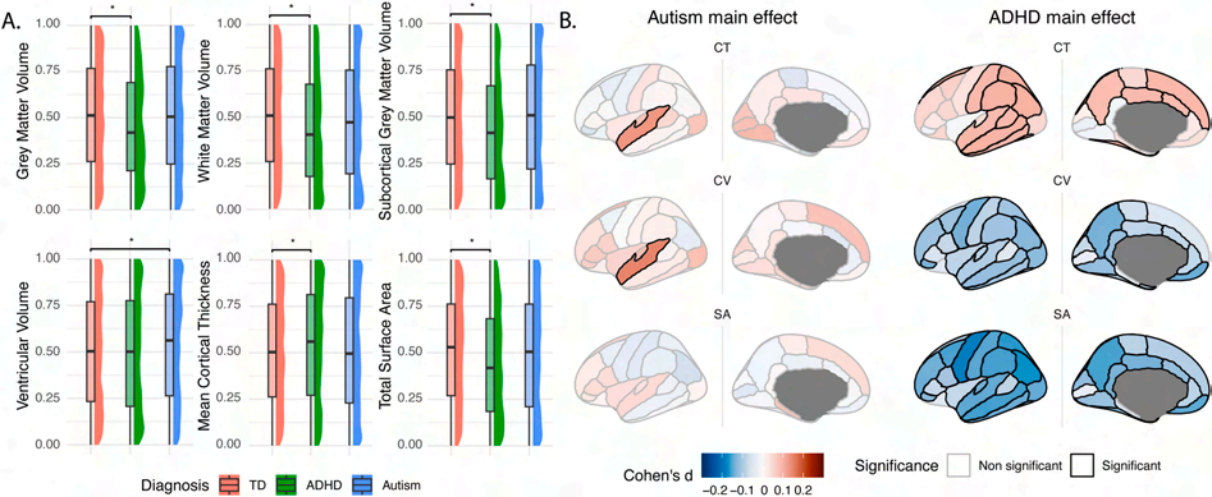
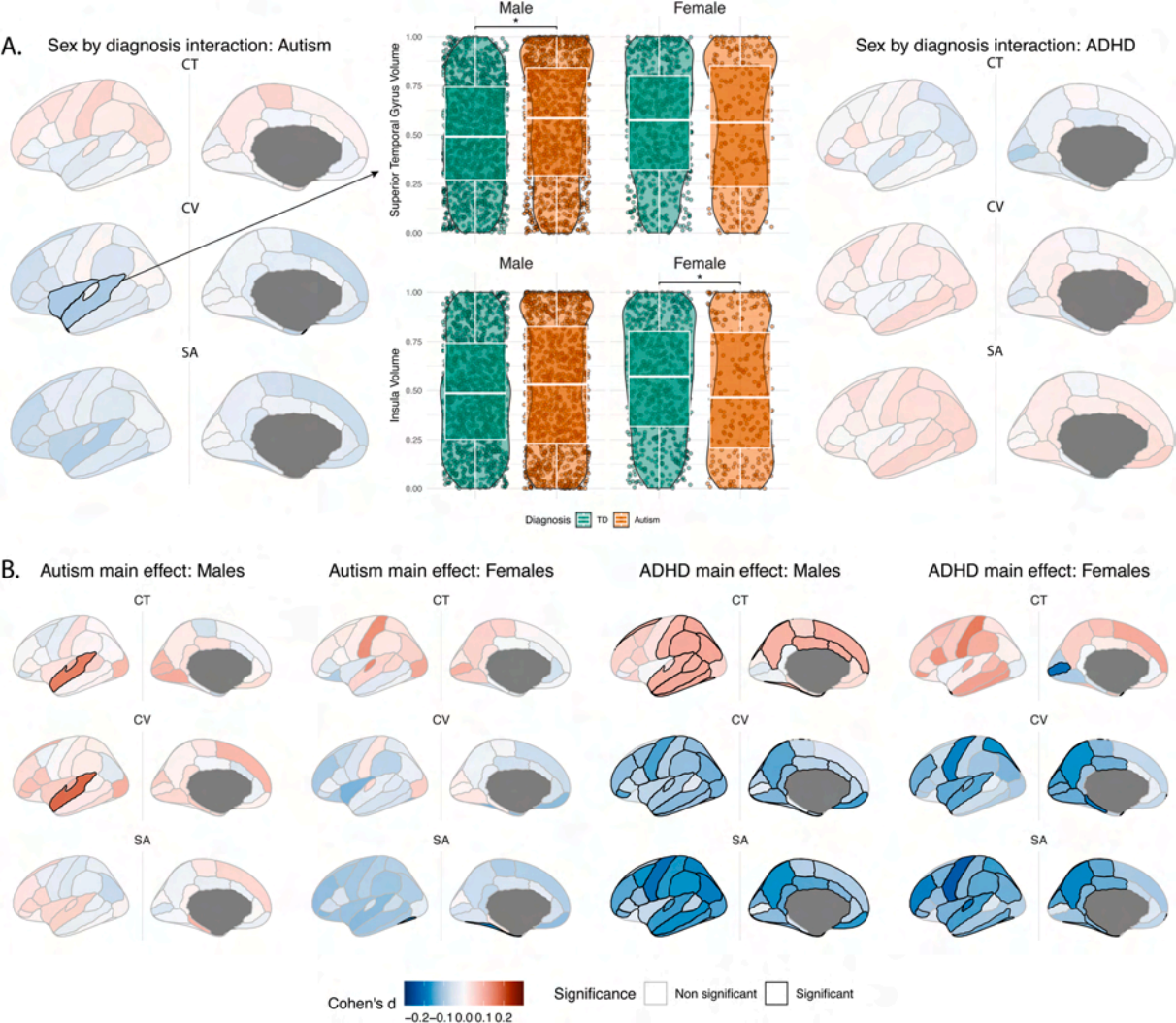

A.
Grey Matter Volume
White Matter Volume
Subcortical Grey Matter Volume
Ventricular Volume
Mean Cortical Thickness
Total Surface Area
1.00
0.75
0.50
0.25
0.00
*
Diagnosis
TD
ADHD
Autism
B.
Autism main effect
ADHD main effect
CT
CV
SA
Cohen's d
−0.2 −0.1 0 0.1 0.2
Significance
Non significant
Significant


A.
Sex by diagnosis interaction: Autism
CT
CV
SA
Male
Female
*
Superior Temporal Gyrus Volume
1.00
0.75
0.50
0.25
0.00
Male
Female
*
Insula Volume
1.00
0.75
0.50
0.25
0.00
Diagnosis
TD
Autism
Sex by diagnosis interaction: ADHD
CT
CV
SA
B.
Autism main effect: Males
Autism main effect: Females
ADHD main effect: Males
ADHD main effect: Females
CT
CV
SA
Cohen's d
−0.2
−0.1
0.0
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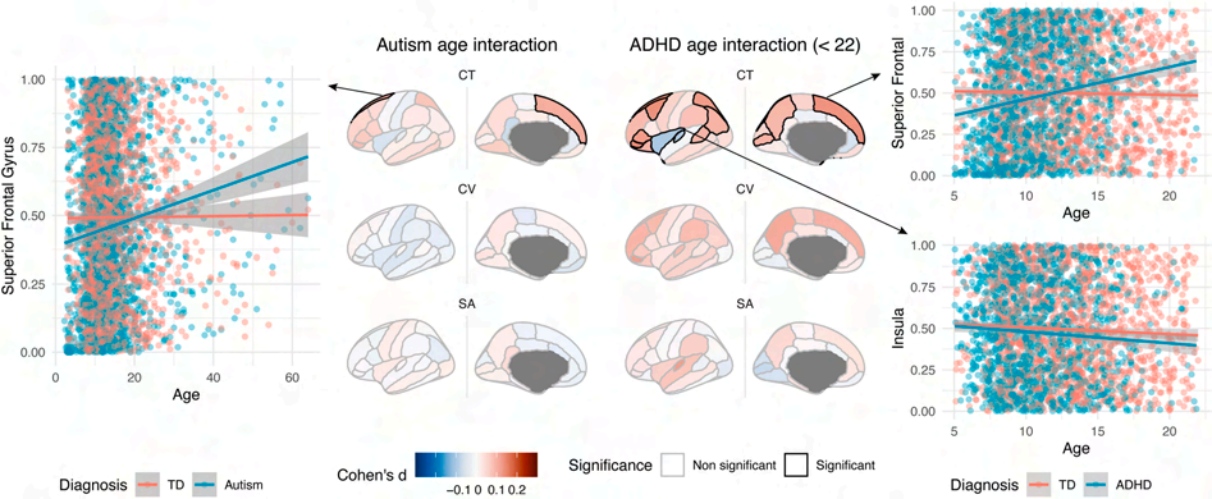
Significance
Non significant
Significant


Autism age interaction
ADHD age interaction (< 22)
CT
CV
SA
Superior Frontal Gyrus
Superior Frontal
Insula
Age
Diagnosis
TD
Autism
ADHD
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−0.1 0 0.1 0.2
Significance
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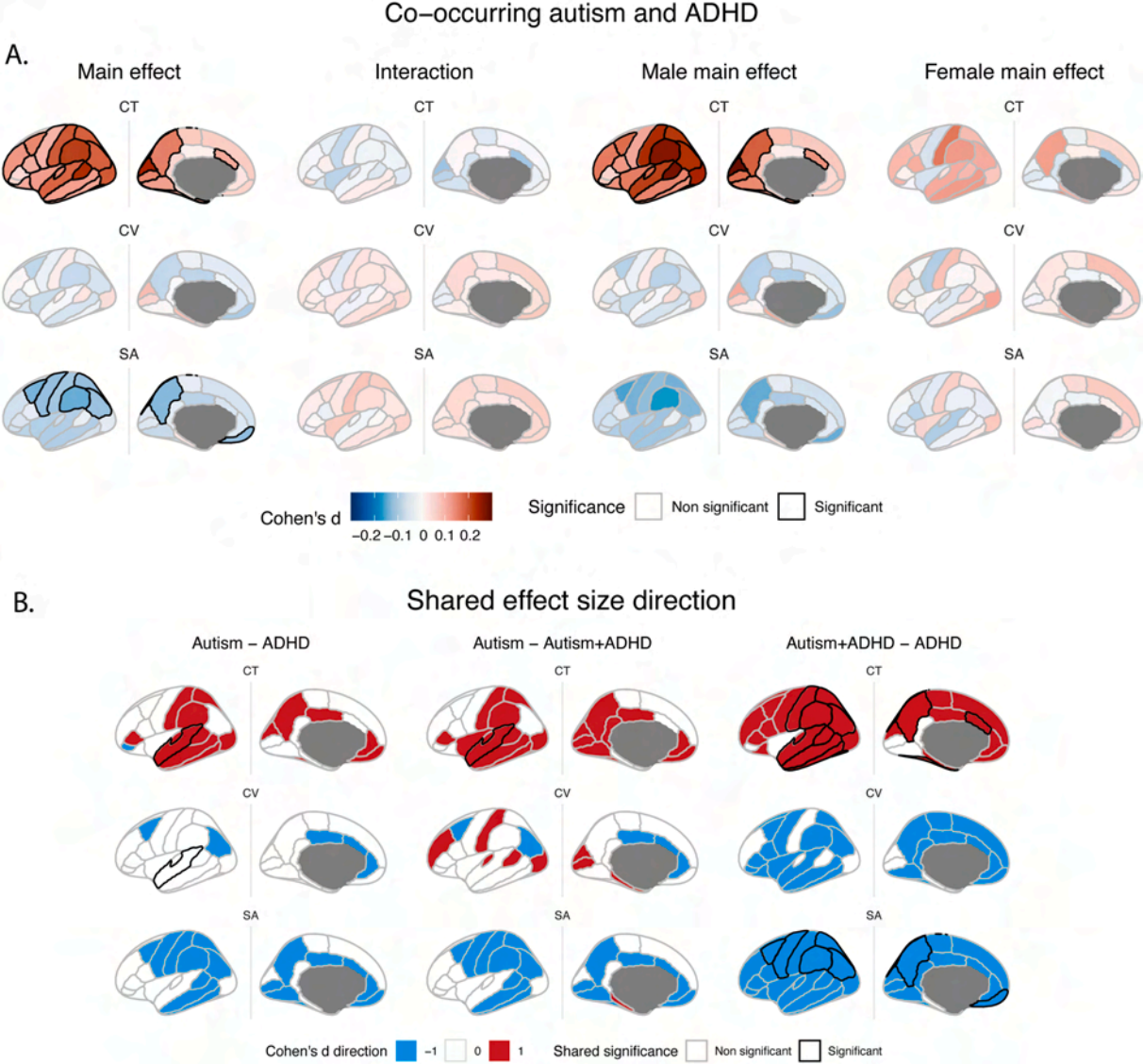
Co−occurring autism and ADHD
A.
Main effect
Interaction
Male main effect
Female main effect
CT
CV
SA
Cohen's d
−0.2 −0.1 0 0.1 0.2
Significance
Non significant
Significant
B.
Shared effect size direction
Autism − ADHD
Autism − Autism+ADHD
Autism+ADHD − ADHD
Cohen's d direction
−1
0
1
Shared significance
Non significant
Significant