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Original Article

ORIGINAL ARTICLE

Cortical Gyrification Morphology in ASD and ADHD: Implication for Further Similarities or Disorder-Specific Features?

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Abstract

Shared etiological pathways are suggested in ASD and ADHD given high rates of comorbidity, phenotypic overlap and shared genetic susceptibility. Given the peak of cortical gyrification expansion and emergence of ASD and ADHD symptomology in early development, we investigated gyrification morphology in 539 children and adolescents (6–17 years of age) with ASD (n=197) and ADHD (n=96) compared to typically developing controls (n=246) using the local Gyrification Index (lGI) to provide insight into contributing etiopathological factors in these two disorders. We also examined IQ effects and functional implications of gyrification by exploring the relation between lGI and ASD and ADHD symptomatology beyond diagnosis. General Linear Models yielded no group differences in lGI, and across groups, we identified an age-related decrease of lGI and greater lGI in females compared to males. No diagnosis-by-age interactions were found. Accounting for IQ variability in the model (n=484) yielded similar results. No significant associations were found between lGI and social communication deficits, repetitive and restricted behaviours, inattention or adaptive functioning. By examining both disorders and controls using shared methodology, we found no evidence of atypicality in gyrification as measured by the lGI in these conditions.

Key words: Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, cerebral cortex, cortical gyrification, lGI

Introducton

Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are relatively common (Li et al. 2017; Hoogman et al. 2017) and highly heritable (Ronald and Hoekstra 2011; Larsson et al. 2014) neurodevelopmental disorders (NDDs) with early childhood onsets, and are more prevalent among males (Willcut 2012; Ofner et al. 2018). Shared etiological pathways are suggested in these two NDDs given high rates of comorbidity (Antshel et al. 2016), phenotypic overlap (Van der Meer et al. 2012) and shared genetic susceptibility, evident through findings of shared genes affecting various neuronal processes (Lionel et al. 2014; Martin et al. 2014). This suggests that early disturbances in brain development may confer risk for both NDDs. In recent years, neuroimaging studies have begun to examine these two NDDs in the same cohort (Ameis et al. 2016; Aoki et al. 2017; Kushki et al. 2019) to better understand shared and possible disorder-specific brain mechanisms that may drive these conditions.

With advancements in neuroimaging techniques, subcomponents of cortical volume, surface area and cortical thickness, can be investigated, each reflecting different genetic and cellular processes (Rakic 1995; Panizzon et al. 2009). These surface-based morphometry (SBM) measures have been extensively studied using structural MRI in ASD (Van Rooij et al. 2018) and ADHD (Hoogman et al. 2017) literature. However, cortical gyrification, as a specific measure derived from MRI, has received less attention. Cortical gyrification refers to the convex (gyri, folds) and concave (sulci, grooves) patterns of the cerebral cortex which first appears prior to birth in the third trimester of fetal life marking the period in which the cortex transforms from a lissencephalic, smooth and unfolded, structure into a gyrencephalic, folded, one (Chi et al. 1977). Modifications in cortical gyrification continue after birth, peaking during toddlerhood (Raznahan et al. 2011) and gradually decreasing over time (Li et al. 2014; Klein et al. 2014) into old age (Hogstrom et al. 2013). Cortical gyrification is essential for the existing optimal arrangement of cortical areas which minimize the volume of interconnecting axons allowing for more efficient connectivity between regions (Klyachko and Stevens 2003). Thus, cortical gyrification is thought to facilitate efficient circuit wiring by expanding the surface area of the cortical sheet relative to its constrained cranium, thus impacting on underlying structural connectivity (Bos et al. 2015). Cortical gyrification is impacted by both genetic (Docherty et al. 2015) and non-genetic (Bernardoni et al. 2018) factors, compared to cerebral volume, which is almost entirely under genetic control (White et al. 2002; Kremen et al. 2010).

Cortical gyrification may be measured using various qualitative and quantitative approaches. Both approaches are valuable and provide complementary information with regards to understanding the cerebral cortex, however, understanding the differences between these modalities is crucial for gaining insight into biological constructs involved in shaping the cortex. Qualitative approaches refer to measures investigating gyral and sulcal *patterns*, while quantitative approaches refer to local (local Gyrification Index, lGI) or global (GI) measures *quantifying* the degree of gyrification. Moreover, qualitative features are found to be stable throughout development (sulcal patterns, Cachia et al. 2016), while quantitative features undergo developmental change (lGI, Klein et al. 2014). Environmental factors influence quantitative measures of cortical gyrification, as evident by findings of altered mean curvature (Luders et al. 2012) and lGI (Zhang et al. 2016) following postnatal experiences such as meditation and diving training, respectively.

Considering the peak of cortical gyrification expansion increase in early development and the timing of onset of ASD and ADHD symptomatology also in early childhood, investigating this brain metric in individuals with ASD and ADHD may provide important insights into contributing etiopathological factors and the nature of these two NDDs. In line with this, findings of atypical surface area in high-risk infants who later develop a diagnosis of ASD compared to typically-developing (TD) peers (Hazlett et al. 2017) suggested the importance of investigating surface area development and its downstream effects, hence gyrification, in the pathophysiology of ASD and related conditions. Thus, it is important to investigate cortical gyrification morphology during early developmental years in high-risk infants as well. Moreover, studying cortical gyrification among already diagnosed children and adolescents and investigating the changes of this brain metric across development in these individuals is crucial in providing important insights regarding the development of cortical gyrification in the pathophysiology of ASD. Also, findings of some studies reporting atypicalities in cortical gyrification and not in other SBM measures in ASD compared to TD (Yang et al. 2016; Kohli et al. 2019b), suggest that gyrification may be a more sensitive measure in detecting atypicalities in the cortical macrostructure of ASD.

A limited number of studies have examined gyrification morphology in ASD and ADHD with contradictory results, possibly due to small sample sizes among other limitations (Gharehgazlou et al. 2020). To the best of our knowledge, no study has investigated cortical gyrification morphology in ASD and ADHD in the same cohort with shared methodology, and there is also limited knowledge of the relation of this measure to clinical symptoms. Here, we focus on addressing these gaps in the literature by first, through a categorical approach, investigating cortical gyrification morphology in a large sample of children and adolescents with ASD and ADHD compared to TD peers. Then we employ a dimensional approach to explore the potential functional implications of gyrification by investigating the relation between this brain construct and ASD and ADHD symptomology beyond diagnosis. Given known associations between cortical gyrification and intelligence levels in the normative literature (Gregory et al. 2016; Chung et al. 2017), we also explore the effect of IQ in our study.

Among the available modalities for studying cortical gyrification, we chose to focus our efforts on computing the local Gyrification Index (lGI), an extension of the Gyrification Index (GI) measure, which allows the detection of local, rather than global, atypicalities. lGI has been implemented to study cortical gyrification in NDDs (Gharehgazlou et al. 2020) and other psychiatric disorders (Depping et al. 2018; Molent et al. 2018). The lGI measure has excellent reliability (mean intraclass correlation coefficient, ICC = 0.85) in TD youth and youth with neuropsychiatric disorders including ADHD and anxiety (Drobinin et al. 2019) as well as TD adults (ICC = 0.94, Madan and Kensinger 2017). Considering the strong correlation between lGI and surface area (Forde et al. 2017b), we control for the effect of this brain metric in all our analyses to take into consideration brain size variation across individuals. By including both NDDs in the same study with shared methodology, we will further our understanding of shared and possible unique mechanisms in the neurodevelopmental alterations among ASD and ADHD.

Materials and Methods

Participants

A total of 762 participants were recruited from a CIHR-funded study (PI: Taylor) and the Province of Ontario (Canada) Neurodevelopmental Disorders (POND) network (PIs: Anagnostou, Lerch). POND is a research collaboration across 5 centres in Ontario (Holland Bloorview Kids Rehabilitation Hospital, Toronto; The Hospital for Sick Children, Toronto; Lawson Health Research Institute, London; McMaster Children's Hospital, Hamilton; and Queen's University, Kingston). This study includes POND recruitment between June 2012 and January 2020 and CIHR recruitment between October 2010 and April 2016. ASD and ADHD diagnoses were made by experienced clinicians based on criteria in the Diagnostic and Statistical Manual of Mental Disorders fourth/fifth edition (DSM IV, V) (American Psychiatric Association 2013). ASD was confirmed by the Autism Diagnostic Observation Schedule, Second Edition (ADOS-II; Lord et al. 2000) and the Autism Diagnostic Interview, Revised (ADI-R; Lord et al. 1994), while ADHD was confirmed by the Parent Interview for Child Symptoms (PICS; Ickowicz et al. 2016) assessments. Intelligence levels were assessed using either the Stanford-Binet, or the age appropriate version of a Wechsler scale (WASI-II; Wechsler 2011, WISC-IV; Wechsler 2003).

For the POND cohort, social communication deficits were also assessed using the Social Communication Questionnaire (SCQ; Rutter et al. 2003), restricted and repetitive behaviors using the Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al. 1998), inattention using the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN; Burton et al. 2019), and adaptive functioning using the Adaptive Behavior Assessment System- Second Edition (ABAS-II; Waisbren et al. 2015).

In an exploratory fashion we identify those participants with co-occurring ASD and ADHD based on dimensional measures by creating an ASD + ADHD group consisting of both 1) participants diagnosed with ASD who had a score within the clinical range on SWAN and 2) participants diagnosed with ADHD who had met the cut-off of 11 or higher on the total score on SCQ.

Imaging Parameters

Structural T_1-weighted images were obtained using Siemens 3 T scanner across an upgrade from Trio Tim to PrismaFit, with an MPRAGE sequence with grappa parallelization (Trio Tim: TE = 2.96 ms, TR = 2300 ms, 1 mm^3 isotropic voxels, 12 channel head coil; PrismaFit: TE = 3.14 ms, TR = 1870 ms, 0.8mm^3 isotropic voxels, 20 [16/4] channel head/neck coil). For participants with multiple scans available, the better quality scan (with fewer imaging artifacts, i.e., noise, ghosting or blurring) was selected; among acquisitions of equivalent quality, scans were selected that would best match groups based on age and sex.

Image Processing and Reconstruction

FreeSurfer software version 6.0 (https://surfer.nmr.mgh.harvard.edu) was utilized for image processing and reconstruction, the steps of which have been thoroughly described in previous work (Greve and Fischl 2018). Briefly, T_1-weighted images were registered to the MNI305 atlas prior to intensity normalization, skull stripping and white matter segmentation steps. A cortical surface mesh was computed for each individual scan. Pial (gray matter-cerebral spinal fluid boundary) and white matter (gray-white matter boundary) surfaces were then differentiated. Using spherical registration, individual scans were registered to FreeSurfer's fsaverage template space. Lastly, cortical segmentation based on the FreeSurfer default Desikan/Killany atlas (Desikan et al. 2006) was performed.

Quality Control

Quality control on FreeSurfer output was performed based on the ENIGMA Cortical Quality Control Protocol 2.9 (April 2017, http://enigma.ini.usc.edu) by visually inspecting data for accurate gray-white matter segmentation and cortical labelling. Quality control was performed by two independent raters (AG and JW) and discrepancies were solved by a third rater (JZ). Manual edits and troubleshooting were performed when needed by AG and JZ (i.e., to correct for inaccurate gray-white matter or gray matter-CSF boundary segmentation or improper skull stripping). 223 participants were excluded either due to scans failing quality control (n = 216) or participants having subthreshold ADHD (n = 7), and thus the final sample consisted of 539 (197 ASD; 96 ADHD; 246 TD) participants, 6.0–16.9 years of age (please refer to Tables 1 and S1 for demographic characteristics of included and excluded participants, respectively). The majority of the sample were males, with 167 females across all groups (35 ASD; 18 ADHD; 114 TD), and right-handed (n = 466) with the

Table 1 Participant demographics

	ASD	ADHD	TD	p-value
n (M:F)	197 (162:35)	96 (78:18)	246 (132:114)	
Mean age (years) ± SD [range]	11.59 ± 2.62 [6.2–16.9]	11.14 ± 2.59 [6.7–16.9]	11.59 ± 3.04 [6.1–16.7]	N.S
Mean IQ ± SD [range]¶	97.77 ± 18.41 [41–142]	103 ± 13.98 [72–133]	112.86 ± 13.05 [77–149]	$p < 0.001$
Mean SA (mm^2) ± SD [range]	236403.36 ± 20046.94 [181327–293 297]	230 187 ± 20092.4 [185594–286 285]	231160.37 ± 21117.92 [185401–298 487]	$p = 0.0107$
% meeting clinical concern cut-off on SCQ	74%	10%	0%	
% meeting clinical concern cut-off on SWAN	54%	71%	0%	

ADHD Attention deficit hyperactivity disorder. *ASD* Autism spectrum disorder. *N.S* Not significant. *SA* Surface area. *TD* Typically developing. ¶484 participants had IQ scores available (186 ASD; 76 ADHD; 222 TD).

rest being either left-handed (n = 42), ambidextrous (n = 6), or unknown (n = 8). Handedness information was not available for 17 participants (16 TD, 1 ASD). There are 80 participants with co-occurring ASD and ADHD as defined above (ASD + ADHD group).

local Gyrification Index (lGI)

lGI was computed using FreeSurfer by computing the degree of gyrification locally at approximately 150 000 vertices across each hemisphere (Schaer et al. 2012). The details of the lGI analysis have been thoroughly described in the validation paper (Schaer et al. 2008) and FreeSurfer's documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/LGI). Briefly, lGI is a measure of the ratio between the area of an estimated circular region of interest (ROI; 25 mm radius) on the pial surface and the area of the corresponding ROI on the outer surface (a smooth surface constructed by FreeSurfer which covers the cortex and does not follow the protuberances of the cortex). An lGI of 5 represents a highly folded cortex (indicating five times more cortex buried within sulci compared to the exposed cortex in this region) and an lGI of 1 represents a smooth cortex.

Due to a portion of our sample (n = 179 or 33%) being scanned on the upgraded MRI scanner, we used ComBat harmonization (Fortin et al. 2018) to remove the effects of the upgrade from vertex-wise measures of lGI. All subsequent analyses have been conducted on Combat-corrected data.

Statistical Analyses

To compare lGI differences between groups, we undertook a whole-brain vertex-wise approach and conducted General Linear Model (GLM) analyses using FreeSurfer. We tested for main effects and interaction terms in the same model utilizing FreeSurfer's "Different Offset, Different Slope" (DODS) design matrix creation utility. We first combined our ASD and ADHD participants into a single group called NDDs and examined lGI differences compared to the TD group. Then we looked at differences between each group and TD separately, as well as between ASD and ADHD groups. We controlled for the effects of sex, age and surface area (latter two demeaned). We did not apply smoothing to the lGI measure as the computation of the lGI construct makes it a relatively smooth measure (Schaer et al. 2012). We controlled for multiple comparisons using permutation testing with a cluster-forming threshold of $p < 0.05$ and a cluster-wise significance threshold of $p < 0.05$, two-tailed. Due to recent evidence of non-Gaussian patterns of spatial smoothness depicted by surface-based analyses (Greve and Fischl 2018), and the unexamined statistical distribution of the lGI measure across the cortex (Kohli et al. 2019a), we chose to use permutation testing rather than Monte-Carlo simulations to control for multiple comparisons. Using the same procedure, we then examined the effect of IQ by repeating our analyses on a subset of participants with available IQ scores (n = 484) to determine the effect of including IQ in the statistical model. For this analysis, we also controlled for IQ (demeaned) in addition to the other covariates. Next, within our POND (ASD, ADHD, TD) participants, we examined the effect of ASD/ADHD symptomatology and adaptive function (ABAS, SWAN-attention, SCQ, RBS-R) on lGI controlling for the effects of the same covariates as in the main analyses, and controlling for multiple comparisons using permutation testing ($p < 0.05$). Finally, in an exploratory fashion, we also investigated whether there are lGI differences between TD (n = 246), ASD only (n = 52), ADHD only (n = 71) or ASD + ADHD (n = 80) groups while controlling for the effects of sex, age and surface area (latter two demeaned). R software (v 3.4.2, https://www.r-project.org/) was used to investigate between-group differences in age and surface area.

Results

Participant Characteristics

One-way ANOVAs showed no significant differences among our three groups in age but significant differences in surface area ($p = 0.0107$) and IQ ($p < 0.001$, Table 1) were found. Thus, we examined surface area differences between groups through independent t-tests and found: significant differences between TD and ASD ($p = 0.007849$) with higher mean surface area values in ASD; significant differences between ASD and ADHD ($p = 0.01374$) with higher mean values in ASD; and no significant differences between TD and ADHD. We accounted for significant IQ differences between groups in our secondary analyses.

ComBat Harmonization

Across all participants and vertices, ComBat harmonization resulted in an average percentage difference in lGI of 0.23% ± 0.30 compared to the non-harmonized data. Prior to ComBat harmonization, 366 of the 327 684 bilateral vertices in the brain showed significant effect of scanner upgrade (t-tests, $p_{corr} < 0.05$ FDR-corrected (Benjamini and Hochberg 1995)). After

ComBat harmonization, there were no longer any significant effects of the scanner upgrade.

Between-group Differences in lGI

We found no significant between-group differences in lGI, accounting for surface area, sex and age, when comparing across the three groups: TD versus NDDs (n = 539), TDs versus ASD (n = 443), TD versus ADHD (n = 342) or ASD versus ADHD (n = 293) groups. In an exploratory fashion we also found no significant lGI differences between ASD only, ADHD only, ASD + ADHD or TD groups on either hemisphere.

Effect of Age

No significant diagnosis-by-age interaction effects were found. We found a decrease of lGI with age across all groups in clusters located in all lobes of the brain bilaterally (peak of clusters: postcentral, $p = 0.002$, Fig. 1). Moreover, no significant age-by-diagnosis interaction effects were found while controlling for the effects of SWAN and SCQ in addition to the other variables (sex and surface area).

Effect of Sex

No significant diagnosis-by-sex, age-by-sex or diagnosis-by-sex-by-age interaction effects were observed. We found greater lGI in females compared to males across groups (Fig. 2). Specifically, we found a significant main effect of sex depicting greater lGI in females in 2 clusters on the left hemisphere, covering all lobes except the occipital (peak of cluster 1: middle temporal, $p = 0.002$; peak of cluster 2: lateral orbitofrontal, $p = 0.009$) and 2 clusters extending to all lobes except the temporal on the right hemisphere (peak of cluster 1: pericalcarine, $p = 0.006$; peak of cluster 2: lateral orbitofrontal, $p = 0.018$).

Effect of IQ

A total of 484 participants (186 ASD, 76 ADHD, 222 TD) had IQ scores available and thus are included in these analyses. Including IQ in the statistical model yielded similar results as the main analyses: i.e., no significant group differences in lGI, an age-related decrease of lGI across groups (Fig. S1), and no significant diagnosis-by-age, diagnosis-by-sex, age-by-sex or diagnosis-by-sex-by-age interaction effects. When IQ was added in the model, although the direction of sex effects remained the same, some clusters that were significant in the main analyses were no longer significant; significantly greater lGI in females compared to males was now observed in the frontal and parietal lobes bilaterally (Across TD and NDDs) (Fig. S2). We found no significant main effect of IQ or age-by-IQ interaction effect across groups.

Effect of ASD/ADHD Symptomatology

238 participants (111 ASD, 86 ADHD, 41 TD) had ABAS-II scores, 252 participants (117 ASD, 91 ADHD, 44 TD) had SCQ scores, 251 participants (119 ASD, 90 ADHD, 42 TD) had RBS-R scores and 247 participants (112 ASD, 93 ADHD, 42 TD) completed the SWAN assessment (please refer to Tables S2S5 for demographic characteristics of participants included in brain-behavioral analyses). In all analyses, we found no significant association between ASD/ADHD symptomatology and lGI in either hemisphere at $p < 0.05$ (permutation correction). To provide some confidence that this was not due to the smaller sample size, we re-ran the analysis for $p < 0.10$ and the results did not change.

Discussion

Our study is the first to investigate cortical gyrification in ASD and ADHD in the same cohort using shared methodology. Our sample consists of the largest number of ASD participants in relation to studies in the ASD gyrification literature, the largest TD cohort, and the largest number of TD females compared to studies in both ASD and ADHD gyrification literature. Importantly, we found no significant between-group differences in lGI in school-aged children and adolescent youth. This is in agreement with the results of our recent systematic review and meta-analysis of previous ASD and ADHD gyrification studies (Gharehgazlou et al. 2020) suggesting that the null findings were not the result of identified limitations. The ten studies included in the previous meta-analysis consisted of an overall sample of 977 individuals (527 ASD; 450 TD) yielding no significant group differences in lGI between ASD and TD. Interestingly, qualitative synthesis of the ASD literature also showed that large-scale ASD studies with a large number of female participants ($n > 30$, Schaer et al. 2015; Koolschijn and Geurts (2016)) also reported no atypicalities in lGI. The most suggestive evidence for potential alterations in gyrification in ASD may be the findings of altered surface area expansion in toddlerhood (Hazlett et al. 2017), which could have downstream effects on gyrification. We don't see any evidence of such alterations using this metric in a large sample of children and youth but our sample does not include toddlers. No significant between-group differences in gyrification among large ADHD studies ($n > 200$) were also found. The addition of our study, that specifically examines ASD and ADHD in the same cohort, confirms that both conditions are generally associated with typical gyrification using a local gyrification construct in this age range. Although we cannot rule out the possibility of the presence of weak atypicalities, higher individual variability compared to between-group differences, the existence of atypicalities merely in a small subgroup of individuals with ASD and ADHD, or atypical gyrification before age 6, our current work, provides further evidence of shared neurodevelopmental processes in these two NDDs and TD controls, during childhood and adolescence. Importantly, our study highly contributes to the literature by being among the very few ASD (merely Ecker et al. 2016) and ADHD (merely Forde et al. 2017a) lGI studies that have accounted for surface area variation across individuals. This is crucial given the strong correlation between lGI and surface area specifically (Forde et al. 2017b) as well as the significant differences observed in surface area between groups in the present work.

In the normative literature, similar to the developmental trajectories of other metrics of cortical gray matter (cortical volume and its two subcomponents), cortical gyrification also undergoes an inverted-U developmental trajectory, reaching its peak development during toddlerhood and gradually decreasing thereafter (Raznahan et al. 2011). We found age-related decrease of gyrification across all groups, in agreement with normative (Klein et al. 2014; Forde et al. 2017b), ASD (Wallace et al. 2013; Libero et al. 2014; Bos et al. 2015; Kohli et al. 2019a) and ADHD (Forde et al. 2017a; Ambrosino et al. 2017) literature depicting a decrease of gyrification with age during adolescence. Our study's age effects, affecting clusters extending to all lobes of the brain, is in agreement with results from normative lGI studies during

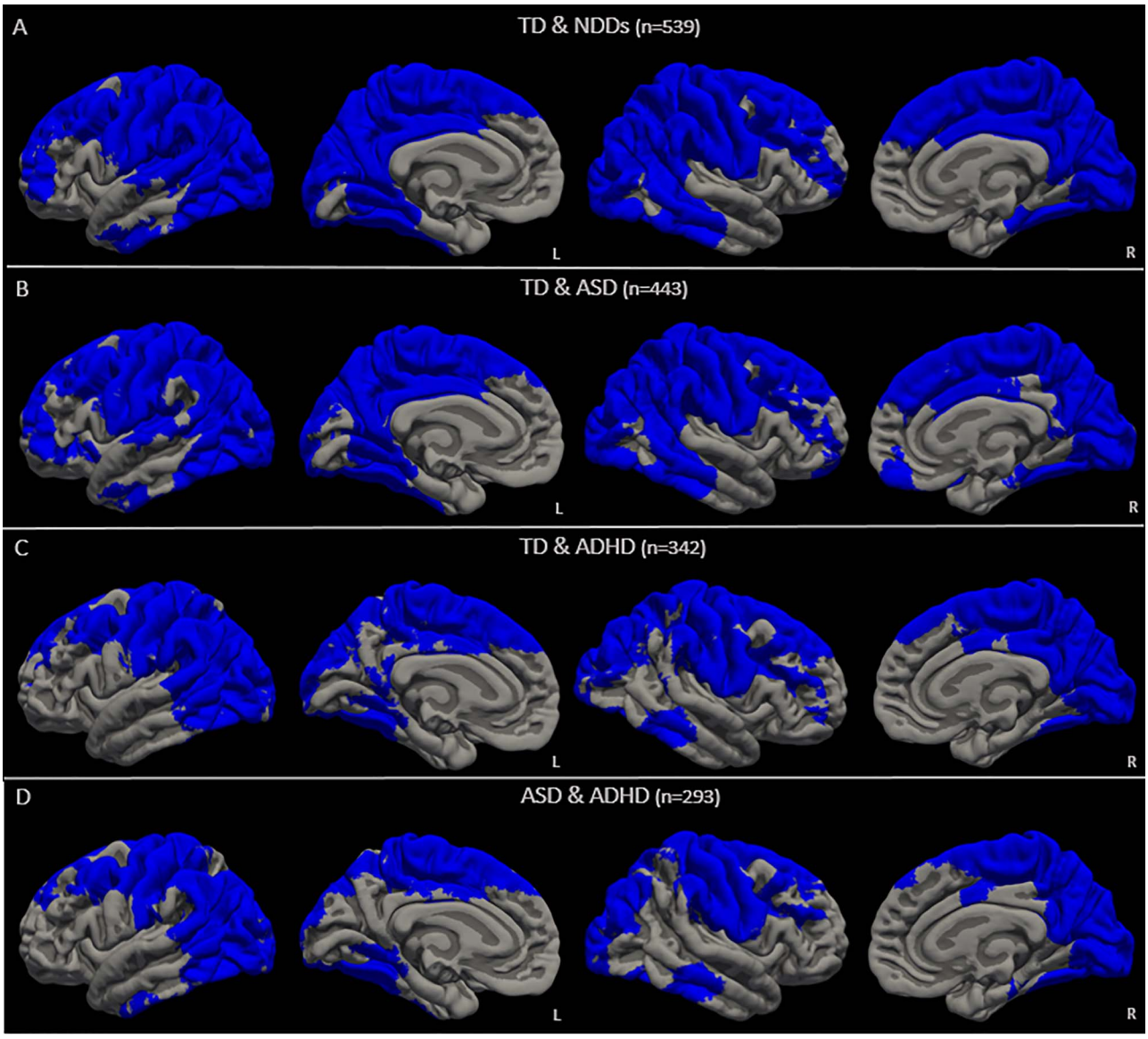

Figure 1. Main effect of age across different group combinations. All significant clusters depict a decrease of lGI with age. *A*) **TD and NDDs (n = 539):** L & R peaks: postcentral, $p = 0.002$. *B*) **TD and ASD (n = 443):** L & R peaks: postcentral, $p = 0.002$. *C) TD and ADHD (n = 342):* L peak: precentral; R peak: superior frontal, $p = 0.002$. *D*) **ASD and ADHD (n = 293):** L & R peaks: postcentral, $p = 0.002$.

adolescents (Mutlu et al. 2013; Klein et al. 2014; Forde et al. 2017b). Interestingly, medial prefrontal regions which are spared in our study are consistent with findings of a previous large-scale (n = 209) longitudinal normative lGI study showing no age-related changes in these regions among males and females 6–30 years of age (Mutlu et al. 2013). Lastly, we found no significant diagnosis-by-age interaction effects, suggesting similar developmental trajectories of lGI across ASD, ADHD and TD in the age range of 6–17 years.

Gyrification development has been shown to undergo a sexually dimorphic course in the normative literature, with reports of greater gyrification in males compared to females (Raznahan et al. 2011; Gregory et al. 2016). In contrast to this, we found greater gyrification in females compared to males across all groups. This discrepancy may be due to methodological differences between our study and previous work, including the choice of covariates when controlling for the effect of brain size variation across individuals. Previous studies accounted for brain size variation by controlling for various cortical indices including total brain volume (Gregory et al. 2016). However, we chose to control for surface area due to the consistent and widely reported association between lGI and surface area in a recent large-scale normative study showing a strong positive correlation between lGI and surface area in all brain regions (Forde et al. 2017b). This study found that while males had significantly greater lGI compared to females, after including surface area in their model, surface area accounted entirely for these differences. This finding, together with our results of greater lGI in females when accounting for surface area, highlight the importance for future studies to investigate the effect of controlling for different metrics of brain size variation on lGI findings.

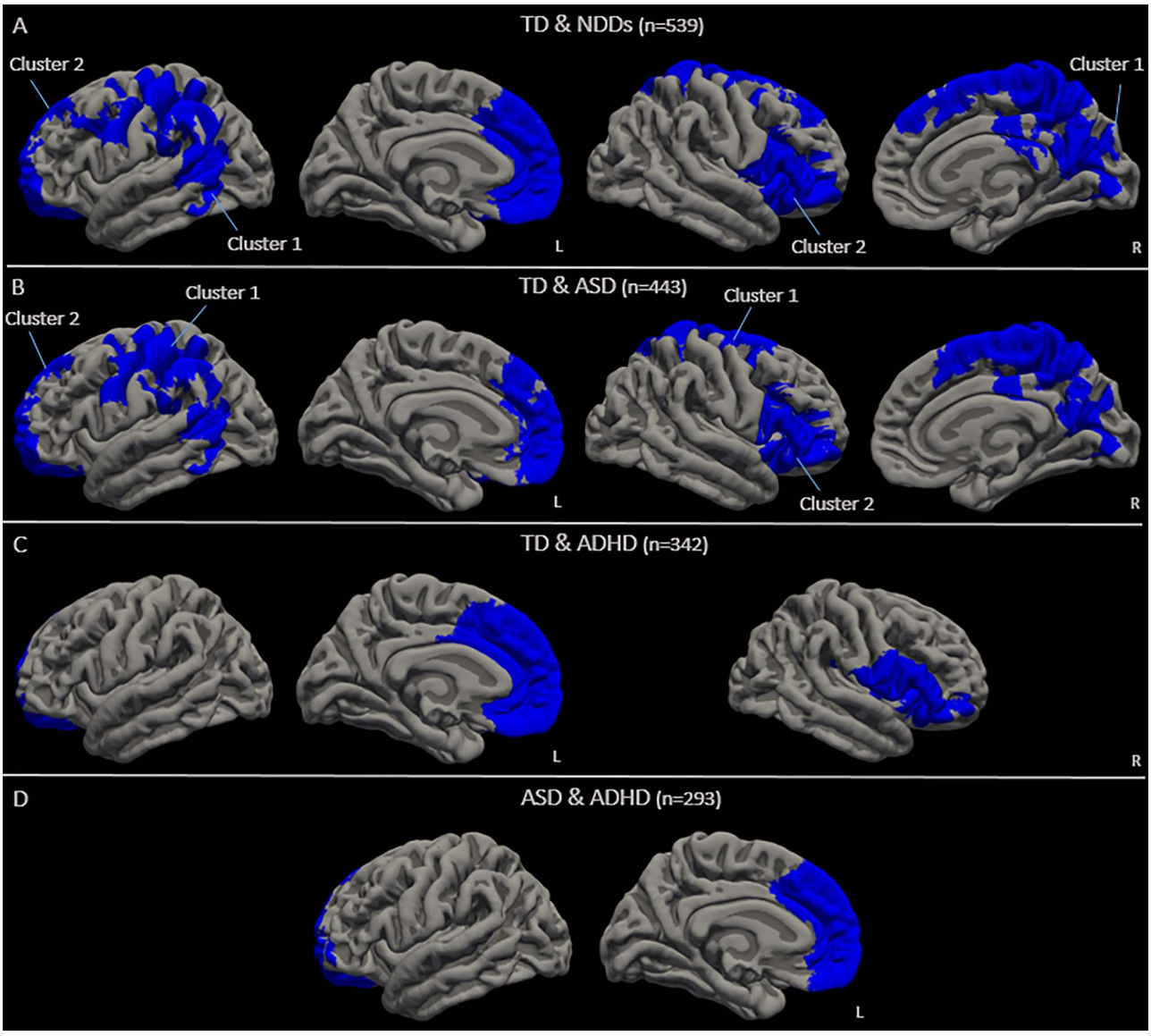

Figure 2. Main effect of sex across different group combinations. All significant clusters depict greater lGI in females compared to males. *A*) **TD and NDDs (n = 539):** *L* cluster 1 peak: middle temporal, $p = 0.002$, cluster 2 peak: lateral orbitofrontal, $p = 0.009$; *R* cluster 1 peak: pericalcarine, $p = 0.006$, cluster 2 peak: lateral orbitofrontal, $p = 0.018$. *B*) **TD and ASD (n = 443):** *L* cluster 1 peak: postcentral, $p = 0.004$, cluster 2 peak: lateral orbitofrontal, $p = 0.028$; *R* cluster 1 peak: precentral, $p = 0.002$, cluster 2 peak: lateral orbitofrontal, $p = 0.032$. *C*) **TD and ADHD (n = 342):** *L* cluster 1 peak: rostral anterior cingulate, $p = 0.024$; *R* peak: parsopercularis, $p = 0.034$. *D*) **ASD and ADHD (n = 293):** *L* peak: lateral orbitofrontal, $p = 0.036$.

Including IQ in our statistical model in the subset of participants with available scores yielded similar results to the main analyses. Although the direction of sex effects across TD and NDDs remained the same, only clusters in the frontal and parietal lobes, bilaterally, reached statistical significance showing greater lGI in females compared to males. There was no main effect of IQ on local gyrification, which is in agreement with the few ASD (Wallace et al. 2013; Libero et al. 2018) and ADHD (Forde et al. 2017a) gyrification studies that have explored the role of IQ. In normative literature, only two studies have been conducted with children (mean age: 14.7 years, Gregory et al. 2016) and adolescents (mean age: 17.38 years, Chung et al. 2017), both reporting positive relations between lGI and cognitive abilities. Chung et al. (2017) however reported different strengths of this brain-behavior association during adolescence, with mid-adolescence (15–17 years) portraying the strongest relation between lGI and cognitive abilities compared to early adolescence (12–14 years). This highlights the complexity of investigating the relation between lGI and cognitive ability among younger cohorts. However, we did not find any age-by-IQ interaction effects across our TD and NDD groups among children and adolescents 6–17 years of age in the current study. The lack of a significant diagnosis-by-IQ interaction effect in our study reflects also a lack of an effect of IQ in our TD participants. In addition, our choice to adjust for brain surface area across participants may have impacted this result, as two studies, albeit in adults, that controlled for the effects of surface area reported weaker relations of IQ and lGI after adjusting for

this brain metric (Green et al. 2018; Mathias et al. 2020). Lastly, given the wide range of IQs in the neurodevelopmental groups in our cohort, that extend beyond normative range, future ASD and ADHD studies need to further explore the effect of the full range of IQ on gyrification.

Functional implications of gyrification have only been explored by a few ASD studies, all using different assessment scales from our study except two (Schaer et al. 2013; Libero et al. 2018). In agreement with these results, we also found no significant associations between social communication deficits (SCQ, Schaer et al. 2013) or repetitive and restricted behaviors (RBS-R, Libero et al. 2018) and lGI. We also add to the literature by further presenting no significant effects of adaptive functioning or inattention.

The emergence of cortical gyrification has been a mystifying process with many proposed theories suggesting the predominance of either extrinsic or intrinsic forces to the cerebral cortex as responsible for explaining this process in early brain development. On the microscopic level, experimental studies of mechanisms involved in the expansion of surface area in early brain development provide important insights regarding the forces that may also be important for the emergence of cortical gyrification. In particular, the subventricular zone, an embryonic layer adjacent to the ventricular zone, has been suggested as important in the formation of cortical gyrification. Empirical evidence in support of this include results of cross-species studies reporting larger subventricular zones in ferret (gyrencephalic species) compared to rat (lissencephalic species) embryos (Martinez-Cerdeno et al. 2006) as well as reports of a positive association between outer subventricular zone progenitors and Gyrification Index (GI) values of adult cortices of gyrencephalic species (Reillo et al. 2011). Moreover, the first attempt of inducing cortical gyrification in a lissencephalic species (mice) suggested the importance of radial glial cells in the formation of gyri and sulci. More recent studies also suggest the predominance of outer subventricular zone expansion and gliogenesis in this embryonic layer, which overlaps with the onset of the appearance of gyri and sulci, in the formation of cortical gyrification (Rash et al. 2019). Given these findings of prenatal mechanisms possibly involved in the emergence of cortical gyrification, the null results of the current study may shed light on the underlying neural mechanisms that may be preserved in the pathogenesis of ASD and ADHD.

Contradictory findings observed in ASD and ADHD structural neuroimaging studies with small sample sizes reflect the high heterogenous natures of both NDDs and highlight the need and predominance of large-scale investigations with high statistical power, such as our current work, to better understand the neurobiological bases of these complex conditions. In line with this, recent large-scale mega-analyses from the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium, which have reported on other surface-based morphometry measures in ASD (n = 3222, van Rooij et al. 2018) and ADHD (n = 4180, Hoogman et al. 2019), are of great value. The null surface area results in ASD (van Rooij et al. 2018) and the small effect sizes in the significant findings in ADHD (Hoogman et al. 2019) among these studies are consistent with our null lGI results given the strong association between lGI and surface area (Forde et al. 2017b). Conversely, given findings of cortical thickness atypicalities in both ASD (van Rooij et al. 2018) and ADHD (Hoogman et al. 2019), the neural mechanisms involved in, or affected by, this brain metric may instead be disrupted in the pathogenesis of both NDDs. Together, these findings suggest disruptions in biological mechanisms or timing of neural processes that are involved in cortical thickness rather than surface area or lGI. Surface area and cortical thickness are known to reflect distinct cellular (Rakic et al. 1988) and genetic mechanisms (Panizzon et al. 2009). According to the radial unit hypothesis (Rakic 1988), surface area is determined by the rate of symmetrical division during embryonic mitosis, specifically prior to the 6th week of gestation, and the number of proliferative units in the ventricular zone or ontogenetic columns in the cortical plate. However, cortical thickness is determined by the rate of asymmetrical division, after the 6th week of gestation, and the number of cells in each proliferative unit. Thus, atypicalities in one brain metric but not the other is highly informative of the involvement of specific underlying biological processes and the potential timing of neural insults. As such, studying the subcomponents of cortical volume (cortical thickness and surface area) and surface area (lGI) individually highly contributes to our understanding of the different mechanisms that may be involved in various conditions.

Considering the limited number of studies that have investigated cortical gyrification morphology in the ASD and ADHD literature, as well as the majority of ASD studies consisting of small and male-only samples, our large-scale study contributes significantly to our understanding of cortical gyrification morphology in these two NDDs. Although our sample includes the largest number of TD females in relation to previous ASD and ADHD gyrification literature, our study is still limited due to its low number of ASD and ADHD female participants. Future large-scale studies powered to explore sex effects are likely needed. How to most appropriately control for brain size variation (i.e., surface area versus total brain volume) on lGI findings still remains an area of active thought. Lastly, and most importantly, our study was cross-sectional, and cannot rule out developmental trajectory differences; longitudinal studies would shed light on gyrification morphology in ASD and ADHD at different developmental stages and on causal implications on any atypicalities found.

In conclusion, this work supports the emerging literature suggesting similarities in brain development between ASD and ADHD and, most importantly, also demonstrates no widespread atypicalities in gyrification as measured by lGI in these conditions.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

AG: Formal analysis, methodology, software, quality control (first rater), visualization, writing—original draft. **MV:** Analysis, methodology and software planning, technical expertise and support, Combat analysis. **JZ:** Quality control (third rater). **JW:** Quality control (second rater). **SHA:** manuscript editing and consultation support. **CH:** Data curation, technical expertise and support, manuscript editing and consultation support. **MJT and JPL:** Data curation, analysis planning and technical expertise, manuscript review and editing, funding acquisition. **EA:** Participant recruitment data curation, analysis planning and expertise, manuscript writing, review and editing, funding acquisition, supervision. **JC, RS, RN, SG, EK and MA:** Participant recruitment, manuscript review and editing. This manuscript has been read and approved by all authors. *Conflicts of Interest:*

Dr Anagnostou has received consultation fees from Roche and Quadrant, grant funding from Roche and In kind support from Amo Pharma. She holds a patent for the device, "Anxiety Meter". She has received royalties from APPI and Springer, and editorial honorarium from Wiley. Dr Schachar has consultant and holder of equity Ironshore Pharmaceuticals Advisory Board. Other authors do not declare any conflicts of interest.

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