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Cortical Gyrfication Morphology in Individuals with ASD and ADHD across the Lifespan: A Systematic Review and Meta-Analysis

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Abstract

Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are common neurodevelopmental disorders (NDDs) that may impact brain maturation. A number of studies have examined cortical gyrfication morphology in both NDDs. Here we review and when possible pool their results to better understand the shared and potentially disorder-specific gyrfication features. We searched MEDLINE, PsycINFO, and EMBASE databases, and 24 and 10 studies met the criteria to be included in the systematic review and meta-analysis portions, respectively. Meta-analysis of local Gyrfication Index (IGI) findings across ASD studies was conducted with SDM software adapted for surface-based morphometry studies. Meta-regressions were used to explore effects of age, sex, and sample size on gyrfication differences. There were no significant differences in gyrfication across groups. Qualitative synthesis of remaining ASD studies highlighted heterogeneity in findings. Large-scale ADHD studies reported no differences in gyrfication between

cases and controls suggesting that, similar to ASD, there is currently no evidence of differences in gyrification morphology compared with controls. Larger, longitudinal studies are needed to further clarify the effects of age, sex, and IQ on cortical gyrification in these NDDs.

Key words: attention-deficit hyperactivity disorder, autism spectrum disorder, cortical gyrification, IGI, structural MRI

Introduction

Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are relatively common neurodevelopmental disorders (NDDs), with prevalence rates of 1.5% and 5.3%, respectively (Hoogman et al. 2017; Li et al. 2017). The core symptoms of ASD are social communication impairments and repetitive and restricted behaviors and interests, while ADHD is defined by age-inappropriate inattentiveness, impulsivity, and hyperactivity (American Psychiatric Association 2013). Both NDDs present with symptoms in early childhood (Lainhart 2015; Hoogman et al. 2017; Li et al. 2017), are more prevalent among males (M:F ratio of 3–4:1 (Willcutt 2012; Ofner et al. 2018), and are highly heritable (Folstein and Rutter 1977; Steffenburg et al. 1989; Faraone et al. 2005).

A shared etiological pathway in ASD and ADHD has been suggested given high comorbidity (Lim et al. 2015; Antshel et al. 2016) and phenotypic overlap (Van der Meer et al. 2012). Shared genetic susceptibility is suggested as later-born siblings of children with ASD and ADHD are more likely to have either NDD compared with siblings of non-diagnosed children (Miller et al. 2019). Shared genetic susceptibility is further supported by at least some shared risk genes affecting various early neuronal processes (Williams et al. 2012), including neuronal migration (Lionel et al. 2014), cell division, and response to medications (Martin et al. 2014), suggesting that early differences in brain development may confer risk for both disorders. In line with this possibility, neuroimaging studies have focused on characterizing aspects of cortical morphology across conditions. Gray matter alterations have been found across these disorders implicating both cortical thickness and subcortical volumes (Hoogman et al. 2017; van Rooij et al. 2018).

Possibly as a consequence of the growing surface area, the cortex begins to fold prenatally (Chi et al. 1977) and transforms from a lissencephalic state into a gyrencephalic structure mainly during the third trimester of fetal life, a period of remarkable brain growth (White et al. 2010). Specifically, primary and secondary sulci begin to appear at ontogenetic weeks 16 and 32 respectively, and tertiary sulci first appear from the 36th ontogenetic week but are found to mainly occur after birth (Armstrong et al. 1995). Cortical gyrification, which refers to the characteristic folds and grooves (sulci) on the surface of the cortex, reaches its peak development during toddlerhood, evident through both global and widespread local increases with larger growth rates in the first year of life compared with the second (Li et al. 2014), and gradually declines thereafter in typically developing (TD) children (Raznahan et al. 2011). Considering the timing of onset of ASD and ADHD symptoms in early childhood and peak gyrification expansion in early development, examination of gyrification in these NDDs may provide important insights into pathophysiology and/or contributing etiopathological factors. A recent finding implicating greater surface area expansion in infants at high risk of developing ASD compared with TD peers (Hazlett et al. 2017) highlights the importance of investigating

surface area development and its downstream effects, hence gyrification, in the pathophysiology of ASD and related conditions. Furthermore, surface-based morphometry (SBM) studies reporting atypicalities in individuals with ASD in gyrification, but not other SBM measures in children (Yang et al. 2016), adolescents (Kohli et al. 2018), and middle-aged (Kohli et al. 2019) cohorts, suggest that gyrification may be a sensitive measure of atypicalities in the cortical macrostructure of ASD.

Numerous theories regarding the formation of gyrification in brain development have been posed. Earlier theories postulated that folding of the cortex was due primarily to external constraints, specifically the limited space of the skull, placed upon the rapidly increasing surface area in early brain development (Le Gros Clark 1945). Alternatively, the tension-based hypothesis postulates that tension along axons, connecting neighboring neurons, in early development results in strongly interconnected regions being pulled towards one another and less interconnected regions being drawn apart, resulting in the emergence of gyri and sulci (Van Essen 1997). According to other theories, the differential surface expansion of the cortex is the primary mechanism driving gyrification either through radial or tangential non-uniform expansion. Specifically, the radial expansion hypothesis postulates that the formation of gyrification may be explained by the increased speed of tangential expansion of outer compared with inner cortical layers during brain development (Richman et al. 1975), while a more recent theory, the differential tangential expansion hypothesis, proposes that regional differences in tangential surface expansion of the cortex, driven primarily by underlying cytoarchitecture, results in pattern-specific folding (Ronan et al. 2014). Other theories have also been proposed based on variation of the themes described above but there is not yet consensus on which theory best accounts for gyrification in early development (for extensive reviews, please see Bayly et al. 2014; Ronan and Fletcher 2015; Striedter et al. 2015; Fernandez et al. 2016; Kroenke and Bayly 2018).

Cortical gyral and sulcal patterns are affected by both genetic and non-genetic factors, compared with cerebral volume which is almost entirely under genetic control (White et al. 2002; Kremen et al. 2010). In support of the genetic control model, a recent large-scale normative twin study reported high heritability in the degree of gyrification, measured through the Gyrification Index, or GI (Docherty et al. 2015). On the other hand, high correlations in brain volume but somewhat more modest correlations in gyral ($r=0.63$) and sulcal ($r=0.58$) curvature and surface complexity ($r=0.49$) (except for depth $r=0.84$) were reported among monozygotic (MZ) twins, compared with pairs of unrelated controls by White et al. (2002), Pearson's correlation coefficients for control group: gyral ($r=0.14$) and sulcal ($r=-0.05$) curvature, surface complexity ($r=-0.16$), and cortical depth ($r=0.21$). Interestingly, Lohmann et al. (1999) reported greater variability in twins in shallow and later-developing sulci

compared with deep and early-developing sulci, suggesting stronger genetic contributions on deep sulci as opposed to shallow folds, in which environmental factors may also play an important role. This finding has obvious implications for heritability estimates in studies measuring different gyrfication constructs. Studies exploring environmental factors suggest that nutritional status (Bernardoni et al. 2018), other drug exposures (e.g., cannabis in adolescence and early adulthood, Mata et al. 2010), and prenatal exposures (e.g., alcohol exposure, Kuhn et al. 2016) affect gyrfication. The impact of genetic and environmental factors also seem to be evident in individuals with ASD, as low concordance rates of gyrfication have been found between MZ twins, in which at least one twin has an ASD diagnosis (Kates et al. 2009), despite the presence of high rates of concordance in volume within the same cohort (Kates et al. 2004).

Understanding the differences between gyrfication modalities is important for gaining insight into biological constructs involved and factors that influence them. As such, [Supplementary Table 4](#) provides brief descriptions of several gyrfication modalities to facilitate interpretation. Gyrfication can be studied both qualitatively and quantitatively: qualitative visual comparisons of gyral and sulcal patterns allow the detection of differences in locations and patterns of gyrfication, while more recently reported metrics allow for the quantification of the degree of gyrfication at global or local scales. Both quantitative and qualitative measures are important as they provide complementary information in that it may be possible to have the same gyral and sulcal patterns but differing degrees of gyrfication, or vice versa. An example of a quantitative measure is the local Gyrfication Index (lGI), an extension of the 2D GI measure, which quantifies the degree of gyrfication locally, rather than globally, by estimating the amount of cortex hidden within sulci (Schaer et al. 2008, 2012) while taking into consideration the 3D nature of the brain; an lGI of 5 indicates five times more cortex buried within sulci relative to that which is exposed in a particular region, while an lGI of 1 represents a smooth cortex. Due to the similarity between these two measures (i.e., lGI and GI), and given the small number of studies that have examined other subtle sulcal characteristics in ASD (depth: 8; length: 2; pit: 1; curvature: 1) and ADHD (folding index: 1; curvature: 1; depth: 1; length: 1), in the current manuscript we synthesize the data from studies computing lGI (ASD: 13; ADHD: 2) and GI (ASD: 5; ADHD: 2) measures and provide results of the remaining studies in supplemental materials ([Supplementary Tables 9](#) and [10](#), also [Supplementary Tables 7](#) and [8](#) for participant demographics of these studies). We also discuss Sulcal Index (SI) findings ($n=2$ ASD) as this metric is also an area measurement, thus related to lGI and GI (Auzias et al. 2014).

There are well-known sex and age interactions with other metrics of brain structure in individuals with ASD (Sussman et al. 2015) and ADHD (Onnink et al. 2014; Hoogman et al. 2017). As such, these variables are important to consider when studying gyrfication as well.

As discussed above, age-related changes in gyrfication across the lifespan is well documented in TD. Similar to developmental trajectories of other metrics of cortical gray matter (volume, thickness, and surface area), cortical gyrfication follows an inverted-U developmental trajectory by reaching its peak development during toddlerhood and gradually decreasing thereafter (Raznahan et al. 2011). There are global, and widespread local, age-related increases in gyrfication during toddlerhood, with larger growth rates in the first year

of life compared with the second (Li et al. 2014). Modifications of gyrfication continue during adolescence with reports of reduced gyrfication (Klein et al. 2014). Studies of aging also report age-related decrease in gyrfication (Hogstrom et al. 2013). It is worth noting that increases or decreases detected by either GI or lGI reflect an increase or decrease in the amount of cortex buried within sulci compared with exposed on the gyral surface, rather than suggesting the emergence of new gyri or the disappearance of existing ones. Interestingly, Brun et al. (2016) report a stable number of sulcal pits within deep folds but an age-related increase in shallow folds, regardless of ASD diagnosis, suggesting that age-related increase in gyrfication observed in TD (Li et al. 2014) may be primarily driven by shallow folds.

Gyrfication development undergoes a sexually dimorphic course in TD with reports of greater degrees of gyrfication in males compared with females (Raznahan et al. 2011) in both children ($n=662$) and adults ($n=440$; Gregory et al. 2016), as well as greater age-related decrease in lGI in TD males relative to females (Mutlu et al. 2013).

In the current review we 1) quantitatively synthesize evidence related to local gyrfication (lGI) when it is feasible; 2) qualitatively synthesize findings of gyrfication in ASD and ADHD where quantitative synthesis is not feasible; and 3) quantitatively and qualitatively explore the effects of age, sex, and sample size on gyrfication in ASD and ADHD. Given the generally small sample sizes in the ASD and ADHD gyrfication literature, we conducted a meta-analysis to address the limitation of insufficient statistical power in the field.

Materials and Methods

Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were implemented. The systematic search for relevant studies was conducted on MEDLINE (Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), PsycINFO and EMBASE (Embase Classic + Embase) databases. The search words used are listed in [Supplementary Table 1](#). The original search was conducted in June 2017, and an additional search was conducted in March 2019 using the same search words to update our literature search prior to publication. All searches were conducted using OVID technologies, Wolters Kluwer Health.

The inclusion criteria were studies with human participants and published in the English language in scientific journals between years 2007 to 2019 with a minimum number of 10 participants per group. We excluded review papers, dissertations, conference papers, editorials, commentaries, and letters. We focused our meta-analytic efforts on studies that locally quantified the degree of gyrfication (lGI), either reported or provided in response to requests to authors, peak coordinates of clusters for between-group differences, and undertook a whole-brain approach (for a consistent thresholding across the brain, eliminating bias towards regions attributed liberal thresholds). We set the criteria for performing a quantitative synthesis as the availability of a minimum of 10 studies computing the lGI measure. As a result, lGI ADHD studies ($n=2$) did not meet this inclusion criteria and were thus only qualitatively synthesized. However, lGI ASD studies ($n=13$) did meet this inclusion criteria and thus were included in the meta-analysis and meta-regressions. The remaining ASD studies (computing the GI and SI measures) were qualitatively synthesized. The meta-analysis does not include results from replicate samples (Kohli et al.

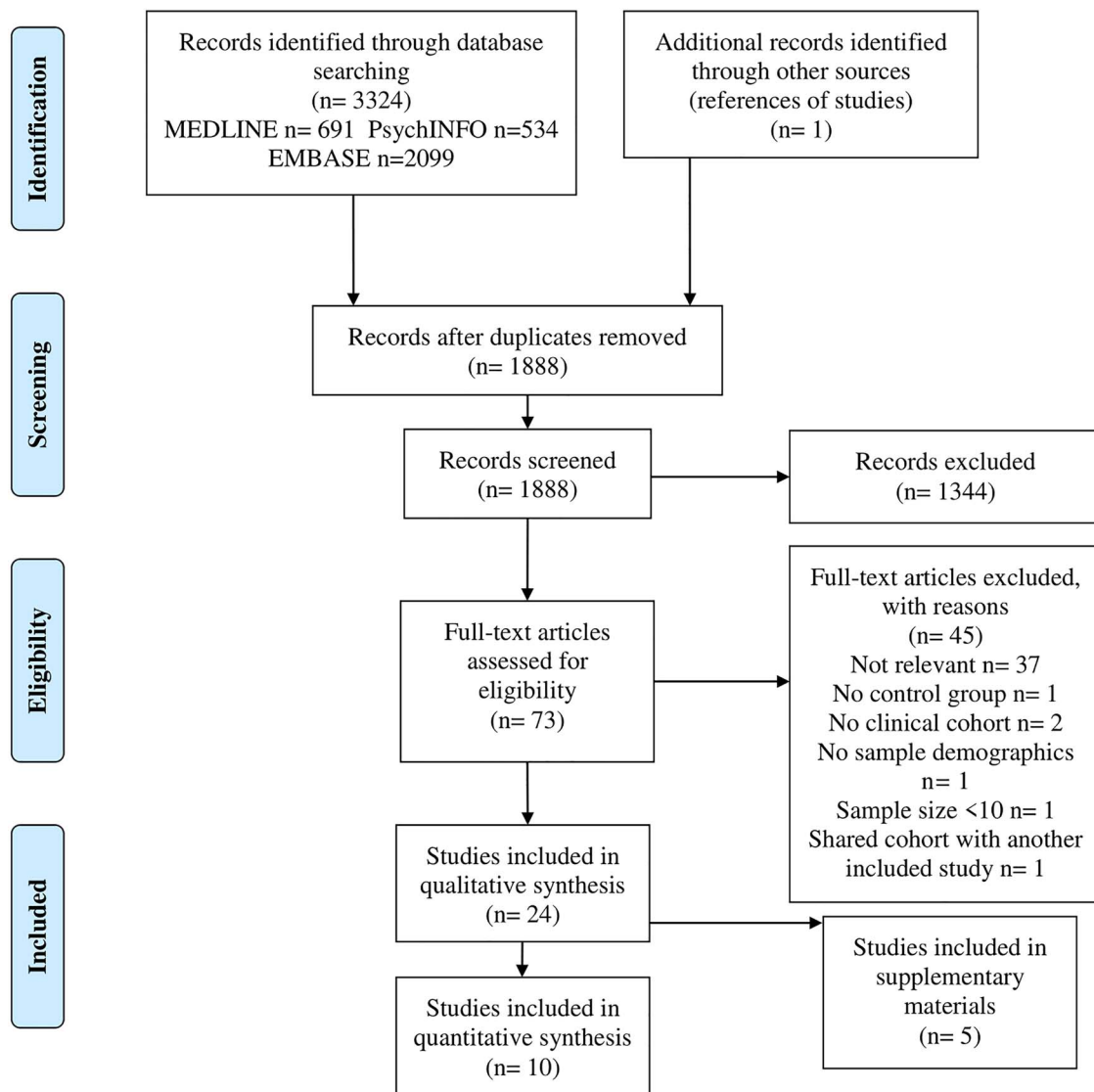


Figure 1. Procedure of screening papers for eligibility based on PRISMA 2009 Flow Diagram (from Moher et al. 2009).

2018) and only includes results from the first time point in longitudinal data (Libero et al. 2018).

Initially, papers were screened for eligibility based on inclusion criteria. After removing duplicates, two independent reviewers (AG and CF) examined titles and abstracts for each paper and any discrepancies for eligibility determination were resolved by EA. Full papers were reviewed by AG and EA (Fig. 1).

Meta-Analysis

Seed-based d Mapping with Permutation of Subject Images (SDM-PSI: www.sdmproject.com) version 6.12 neuroimaging software was used. Due to lack of availability of a meta-analytic software for use with SBM data, here, we use a voxel-based morphometry (VBM) meta-analytic software with the incorporation of an appropriate gray matter mask (FreeSurfer mask) created for meta-analyzing surface-based studies. Unlike the gray matter mask in SDM, the FreeSurfer mask restricts the meta-analysis to cortical regions as opposed to all gray matter

(i.e., subcortical and cortical regions; details regarding the creation of this mask are explained in Li et al. 2019). We further rationalize the use of SDM with our SBM data by considering that meta-analyses utilize information regarding peak coordinates in a standard space, regardless of how these coordinates have been obtained in the original manuscripts (i.e., through VBM or SBM data). The majority of IGI studies in this review (8 out of 13) reported peak coordinates. Three studies reported no significant group differences in IGI (Schaer et al. 2015; Hirjak et al. 2016; Koolschijn and Geurts 2016), and 2 studies reported no coordinates despite finding group differences (Libero et al. 2014; Kohli et al. 2019).

From clusters of significant between-group differences in IGI in each study, we extracted peak coordinates (and converted to MNI152 space) and P -values (and converted to t -statistics when none were already reported).

SDM methodology has been described previously (Albajes-Eizagirre et al. 2019a) and we followed the standard pipeline (Albajes-Eizagirre et al. 2019b) with the only exception of the use

of the FreeSurfer mask. Briefly, pre-processing was performed to generate lowest and highest possible effect size values for each study using peak coordinate information. Then, we imputed multiple maps of the effect size of each study using maximum likelihood and multiple imputation techniques. A mean analysis was conducted to estimate the mean difference of IGI between ASD and TD across studies by computing the meta-analytic mean of all studies of each imputation set and then applying Rubin's rules to obtain a single mean map (note that the mean map represents both negative and positive differences). The mean map was corrected by family-wise error (FWE) through permutation tests, generating a distribution of maximum statistic and using it to threshold results of the main analysis ($P < 0.05$, extent threshold of 10 voxels, as recommended by Radua et al. 2012). In the event of no statistically significant group differences, we further explored more liberal thresholds ($P < 0.1$) to enhance our understanding of possible trend-level group differences in IGI as this is the first meta-analysis of ASD studies focusing on gyrfication morphology. The heterogeneity of significant voxels was explored by extracting I^2 statistics ($I^2 > 50$ is evidence of high heterogeneity).

Meta-Regression

We also explored the potential effects of age, sex, and sample size of the ASD group on gyrfication differences in separate meta-regressions, to further understand the heterogeneity of findings. Correction was implemented (FWE) with the same threshold as the main analysis ($P < 0.05$). We explored more liberal thresholds ($P < 0.1$) if no statistically significant results were found as this is the first attempt in the ASD literature to quantitatively explore the potential effects of age, sex, and sample size on gyrfication differences.

Results

The current review includes 24 final papers (Fig 1): 20 ASD (Table 1) and 4 ADHD (Table 2) studies. Results of ASD studies not included in the meta-analysis are qualitatively reviewed (including IGI studies excluded from the meta-analysis due to not taking a whole-brain approach, Duret et al. 2018, or not reporting or responding to our request for peak coordinates, Libero et al. 2014 and Kohli et al. 2019). All ADHD results and effects of variables of interest are qualitatively presented, given the small numbers of studies and variable measures. Results are presented for each NDD in relation to TD and only significant findings are presented unless stated otherwise. No single study included both ASD and ADHD participants, thus we attempted no direct comparisons between NDD groups.

Quantitative Review of ASD Studies

Ten studies, drawn from the broader sample of the 20 ASD studies in Table 1, utilized the IGI measure, reported peak coordinates and undertook whole-brain approach and as such are included in the meta-analysis (please refer to Supplementary Table 2 for imaging parameters of all ASD studies). Three studies reported no main effect of group (Schaer et al. 2015; Hirjak et al. 2016; Koolschijn and Geurts 2016). The overall sample of the meta-analysis consisted of 977 individuals (ASD = 527; TD = 450). The results of the meta-analysis demonstrate no statistically significant differences between ASD and TD in IGI after multiple

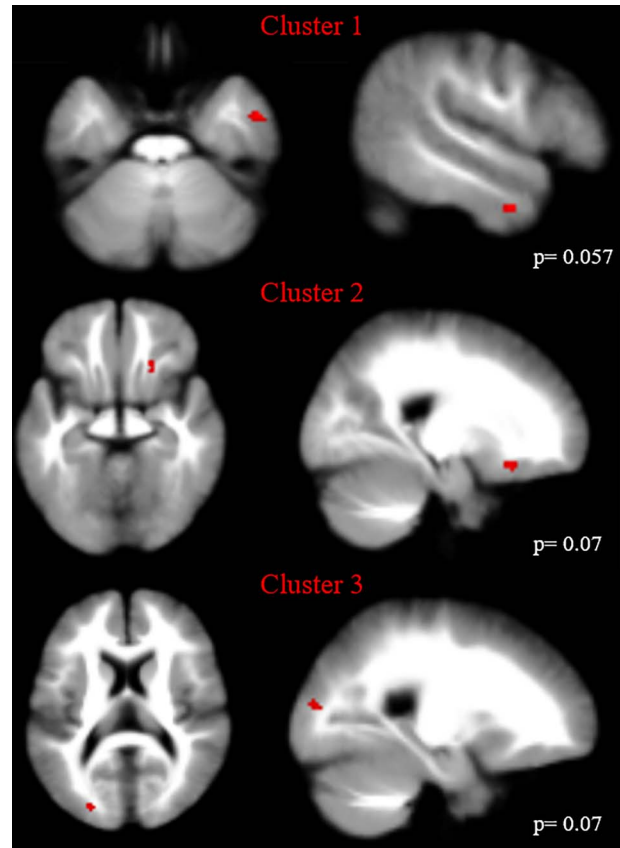


Figure 2. Results of the meta-analysis demonstrating greater IGI in ASD relative to TD in three clusters shown in axial and sagittal views. These clusters only appeared with a liberal threshold ($P < 0.1$) and on the map of uncorrected P values.

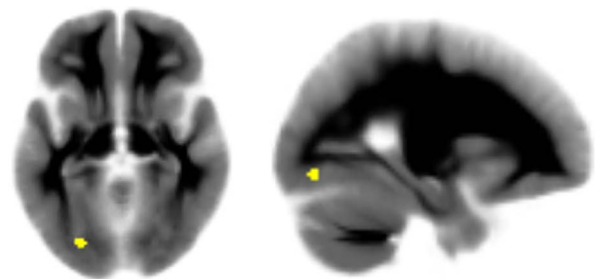


Figure 3. Results of the meta-regression demonstrating a trend-level effect of sex ($P = 0.083$) on gyrfication in a cluster, on the map of uncorrected P values.

comparison correction. However, with a more liberal threshold ($P < 0.1$) and only on the map of uncorrected P -values, trends were observed: specifically greater IGI in ASD relative to TD in clusters located in the right temporal ($P = 0.06$, $I^2 = 0.56$; cluster 1 in Fig. 2), right frontal ($P = 0.07$, $I^2 = 25.56$; cluster 2 in Fig. 2) and left occipital ($P = 0.07$; $I^2 = 3.06$; cluster 3 in Fig. 2) lobes (Supplementary Table 5). Heterogeneity of these voxels, as expressed with I^2 statistics, represents low to moderate heterogeneity. The meta-regressions ($n = 10$ studies included) yielded no statistically significant effects of age, sex, or sample size. With a more liberal threshold ($P < 0.1$) trends were observed

Table 1 Participant demographics (ASD studies).

First author (year)	ASD [other]				Controls			
	n	M/F	Age range	Mean age (SD)	n	M/F	Age range	Mean age (SD)
Kohli et al. (2019)	20	16/4	41.1–60.6	50.2 (5.9)	21	20/1	40.4–60.9	50.8 (6.9)
Duret et al. (2018)	[SOD 28] [nSOD 27]	[SOD 25/3] [nSOD 24/3]	14–30	[SOD 20.4 (0.78)] [nSOD 19.8(0.79)]	37	32/5	14–30	20.4 (0.68)
*Kohli et al. (2018)	64 [+31]	52/12 [+31/0]	7–19 [+7–18]	13.32 (2.65) [+11.44 (2.84)]	64 [+31]	55/9 [+31/0]	7–19 [+7–18]	13.53 (2.95) [+11.78 (2.57)]
***Libero et al. (2018)	[ASD-N 88] [ASD-M17]	105/0	2.13–3.67	3.0 (5.28)	49	49/0	2.27–3.67	2.98 (4.77)
Maier et al. (2018)	30	19/11	21–52	35.4 (9.1)	30	19/11	22–53	35.5 (8.3)
Pappaianni et al. (2018)	39	39/0	8–11	10.10 (0.98)	42	42/0	8–11	10.39 (1.08)
*Pereira et al. (2018)	+++22	18/4	14–25	17.45 (3.29)	29	19/10	14–25	18.48 (2.82)
*Ecker et al. (2016)	51	51/0	18–43	26 (±7)	48	48/0	18–43	28 (±6)
*Hirjak et al. (2016)	16	9/7	18–35	23.56 (±4.45)	16	9/7	18–35	23.06 (±4.2)
*Koolschijn and Geurts (2016)	51	35/16	30.04–73.98	51.46 (12.61)	49	32/17	30.62–73.77	50.14 (11.9)
*Yang et al. (2016)	60	60/0	4.49–11.99	8.35 (2.07)	41	41/0	4.75–12.16	8.83 (2.30)
Bos et al. (2015)	30 [+39]	29/1 [+34/5]	8–18 [+9–18]	12.7 (2.5) [+12.0 (2.6)]	29 [+65]	28/1 [+48/17]	7–18 [+8–18]	12.5 (2.8) [+12.8(2.8)]
*Schaer et al. (2015)	106	53/53	8.1–46.0	17.2 (±8.4)(M) 17.1 (±8.3)(F)	104	53/51	8.1–46.0	17.1 (±8.2) (M) 17.2 (±7.6) (F)
Auzias et al. (2014)	59	59/0	1.5–9	57.4 m (19.2)	14	14/0	1.5–9	57 m (19.8)
Libero et al. (2014)	55	49/6	8–40	18.5 (0.89)	60	55/5	8–36	18.2 (0.91)
*Schaer et al. (2013)	11	8/3	9.3–17.4	12.9 (±2.7)	11	8/3	8.7–16.8	12.7 (±2.7)
*Wallace et al. (2013)	41	41/0	12–24	16.75 (2.84)	39	39/0	12–23	16.95 (2.71)
Shokouhi et al. (2012)	15	15/0	12–20	15.4 (2.2)	16	16/0	12–20	15.5 (1.6)
Casanova et al. (2009)	14	14/0	8–38	22.5 (9.9)	27	28/0	8–38	22.6 (9.9)
Kates et al. (2009)	28 (MZ)	24/4	5.6–13.8	8.8 (2.6)	14 (S)	12/2	5.4–13.9	8.6 (2.4)

Note: All ages are reported in years. ASD, autism spectrum disorder; ASD-N, ASD with typical brain range; ASD-M, ASD with disproportionate megalencephaly; F, females; M, males; MZ, monozygotic twins; nSOD, ASD without speech onset delay; S, singleton; SOD, ASD with speech onset delay; TD, typically developing; +, Replication sample from Autism Brain Imaging Data Exchange (ABIDE); ++, Longitudinal study and information correspond to scan time 1; +++, Some individuals in the ASD group used psychoactive medications, but participants were asked not to take medication a day prior to study visit; *, Included in meta-analysis.

Table 2 Participant demographics (ADHD studies).

First author (year)	ADHD [other]				Controls			
	n	M/F	Age range	Mean age (SD)	n	M/F	Age range	Mean age (SD)
+Ambrosino et al. (2017)	94	78/16	6–28	11.4 (2.9)	94	80/14	6–28	11.2 (4.0)
Forde et al. (2017a)	306 [Sib 148]	208/98 [Sib 62/86]	6–18 [Sib 6–18]	17.2 (3.4) [Sib 17.7 (3.8)]	164	87/77	6–18	16.8 (3.2)
Mous et al. (2014)	19	16/3	12–19	15.4	23	12/11	9–19	14.8
Shaw et al. (2012)	234	151/83	5.1–18.4	*10.2 (3.3)	231	148/83	4.5–19.0	*10.6 (3.6)

Note: All ages are reported in years. ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation; Sib, siblings of individuals with ADHD; +, Longitudinal study and information correspond to scan time 1.

for the interaction of sex and diagnosis, on the map of uncorrected P-values, in a region close to the occipital region in the main analysis ($x: -24, y: -80, z: -12$; SDM-Z: -1.39 ; $P=0.083$, Fig. 3, Supplementary Table 6), suggesting that between-group

differences may be smaller the higher the percentage of males included in the ASD group.

Although all studies used a whole-brain approach, Pereira et al. (2018) computed lGI based on ROIs rather than per vertex.

Table 3a Findings of reduced IGI in ASD; Results are significant following correction and presented as ASD versus TD.

Study	Contrast	Covariates	Results (ASD vs. TD)	P (correction)
+Libero et al. (2018)	Dx	Age, TBV	Sample: N.S. differences in age. Lower ++DQ, greater brain volume: in ASD groups (combined) and in ASD-M versus ASD-N ASD versus TD: Reduced IGI in caudal fusiform gyrus (bil). ASD-N versus TD: Reduced IGI in fusiform (bil). ASD-M versus TD: Greater IGI in dmPFC (R), cingulate cortex (L). ASD-M versus ASD-N: Greater IGI in paracentral, parahippocampal (R), precentral gyri (L). N.S. DQ-IGI relation in regions of sig. Differences in IGI Change in IGI from Time 1–3: ASD-N versus TD: Decrease in/stable IGI in TD in inferior frontal and inferior temporal cortices, inferior parietal lobule (R) and lingual gyrus (L) but increased in ASD-N (except lingual gyrus). ASD-M versus ASD-N/TD: N.S.	P < 0.05 (MCS)
Libero et al. (2014)	Dx	Age Age AgexDx AgexDx xICV	Sample: N.S. differences in age, ¶IQ Reduced IGI in supramarginal gyrus (L) Reduced IGI with age in precentral gyri (bil) Reduced IGI with age in supramarginal (L) N.S.	P < 0.05 (FDR)
Duret et al. (2018)	Dx	Age Age AgexDx	Sample: Matched on age, ¶IQ, sex. N.S. differences in TICV, age, FSIQ, PIQ ASD-SOD versus TD and ASD-nSOD: Reduced IGI in fusiform (L). ASD-nSOD versus TD and ASD-SOD: Greater IGI in middle temporal gyrus (R). N.S. group-by-difference score interaction on IGI with cognitive strength (ASD-SOD: block design and AS-nSOD: information) in fusiform (L)/temporal (R) Reduced IGI with age in precentral, supramarginal, middle temporal (L), caudal and rostral middle frontal, superior frontal, precuneus, superior parietal, paracentral (R) N.S. Exploring IGI maturation in middle temporal (R) and fusiform (L) clusters: Interaction in temporal cluster driven by difference in ASD-nSOD versus other groups (increase of IGI in TD but decrease in AS-nSOD) and fusiform area (L) driven by difference in ASD-SOD and TD (decrease of IGI in TD and ASD-nSOD only)	P < 0.01 (vertex-wise) P < 0.05 (cluster-wise) (MCS)
Kohli et al. (2019)	Dx	NVIQ, TBV Age AgexDx	Sample: Matched on age, sex, race, ethnicity. Reduced TBV and IQ Reduced IGI in perisylvian, ACC (bil), postcentral, middle frontal gyri (L), OFC and supramarginal (R) Reduced IGI with age in supramarginal (R), precentral (bil) gyri N.S.	§P < 0.01; §§P < 0.05 (MCS)
Schaer et al. (2013)	Dx	Age, sex	Sample: N.S. differences in CV. Matched on sex and age Reduced IGI in precentral, inferior parietal lobe, IFG, medial parieto-occipital (R)	P < 0.05 (MCS)

Note: Studies are ordered based on sample size from largest to smallest. ACC, anterior cingulate cortex; ASD-M, ASD with megalencephaly; ASD-N, ASD with typical brain range; ASD-nSOD, ASD without speech onset delay; ASD-SOD, ASD with speech onset delay; Bil, bilateral; CV, cerebral volume; dmPFC, dorsal medial prefrontal cortex; DQ, developmental quotient; Dx, diagnosis; FDR, false discovery rate; FSIQ, full-scale IQ; IFG, inferior frontal gyrus; L, left hemisphere; MCS, Monte Carlo simulations; NVIQ, nonverbal IQ; N.S., no(t) significant; OFC, orbitofrontal cortex; PIQ, performance IQ; R, right hemisphere; Sig, significant; TBV, total brain volume; TICV, total intracranial volume; VIQ, verbal IQ; +, Longitudinal study, results correspond to Time 1; ++, Measured by Mullen Scales of Early Learning (MSEL); §, Cluster-forming threshold; §§, Cluster-wise significance threshold; ¶, Full-scale, verbal, and performance IQ.

Table 3b Findings of greater gyrification in ASD.

Study	Contrast	Covariates	Results (ASD vs. TD)	P (Correction)
Kohli et al. (2018)	Dx	+++TBV, age	Sample: N.S. differences in age, TBV, NVIQ (in-house and ABIDE), N.S. differences in VIQ, FSIQ in former) In-house: Greater lGI in precentral, STG, SPL(L), frontal pole, perisylvian/precentral, lateral OFC, SFG (R), and reduced lGI in lingual (L). Same results when excluding F. Few clusters not sig. After correction in analyses without TBV as covariate. ABIDE: Greater lGI in insula, STG (L)	++P < 0.01; P < 0.05 (MCS)
	AgexDx	TBV	In-house: Greater “-” slope in CS, lateral occipital cortex, caudal middle frontal gyrus (R). ABIDE: Greater “-” effect in rostral middle frontal gyri (bil), precuneus (L), cuneus (R)	
	Age		In-house: Reduced lGI with age in dorsal and medial frontal, parietal, occipital lobes (bil). Secondary analyses (permutation testing): Only detected main effect of age ABIDE: Reduced lGI with age in superior frontal, parietal to lateral occipital lobes (L) and most of frontal, parietal, occipital lobes (R). Secondary analyses (permutation testing): Only detected main effect of age	
Yang et al. (2016)	Dx	Age	Sample: Matched on TGMV, TWMV, SGMV, ICV, IQ Greater lGI in inferior parietal, inferior temporal, lingual (R), isthmus cingulate (L)	¶P < 0.05 (MCS)
	AgexDx		Increase of lGI in precentral, superior parietal (L), rostral middle frontal, gyrus, STG, pars opercularis (R)	
Ecker et al. (2016)	Dx	Age, TSA, center, FSIQ, TBV	Sample: N.S. differences in age, FSIQ, TSA, TGMV, TWMV, TBV Greater lGI in CS, pre/postcentral, posterior middle frontal, supramarginal gyri (L) N.S. differences in depth/curvature in clusters of sig. lGI difference	¶P < 0.05 (RFT)
Wallace et al. (2013)	Dx		Sample: N.S. differences in ICV Greater lGI in occipital (bil), precuneus (L) Greater depth in occipital lobe (L) (in clusters of sig. lGI difference) Exploring within clusters of sig. lGI differences: Greater SA in precuneus, greater depth in lateral occipital (L) in ASD. Across both groups, sig. SA-lGI relation in all clusters, but sig. depth-lGI relation only in lateral occipital cortex (L) + vocabulary-lGI relation in TD. Whole-brain analyses within TD: vocabulary-lGI relation in inferior parietal (L). In clusters of sig. lGI differences: vocabulary-lGI relation in occipital (bil) in TD N.S. differences in relation between lGI and FSIQ/Matrix reasoning	P < 0.01 (MCS)
	AgexDx		N.S. [age-group (<17 vs. >17 years) by Dx. N.S. differences in IQ in age groups]	
	Age		“-” relation between lGI and age in frontal, posterior temporal and parietal cortices (bil)	
Pereira et al. (2018)	Dx	Age, total IQ (TIV in ROI analyses)	Sample: N.S. differences in age, FSIQ, PIQ, TBV, TSA. Lower VIQ Vertex-wise: Greater lGI in lingual, precuneus, STS, superior parietal (R), pre/paracentral areas (L). ROI-based: Greater lGI in pre/postcentral, superior parietal, supramarginal (bil), frontopolar, middle frontal (R), paracentral regions (L)	P < 0.01; Bonferroni (ROI analyses)

Continued

Table 3b Continued

Study	Contrast	Covariates	Results (ASD vs. TD)	P (Correction)
Kates et al. (2009)	Dx	Age	<p>Sample: Sig. different in IQ</p> <p>ASD and co-twins versus TD: Greater GI in parietal lobe (R) [N.S. differences in twin pairs; Sig. contribution of age]. Same results when excluding F (but findings of co-twins not sig.). Sig. contribution of parietal WMV (R), not GMV, to parietal GI</p> <p>“+” age-GI relation in cerebral (bil), parietal (L) in ASD (magnitude not different from TD). Analyses on subsample of discordant and concordant co-twins: “+” age-GI association in temporal lobe (R) in discordant & “-” age-GI association in frontal lobe (R) in concordant co-twins</p> <p>“+” IQ-GI association in TD in cerebrum, parietal, temporal (bil), occipital (L) lobes. “+” IQ-GI association in frontal (R) lobe in discordant unaffected co-twins</p>	+P = 0.002; 0.043 Bonferroni/Dunn statistic

Note: Results are significant following correction and presented as ASD versus TD. Studies ordered based on sample size from largest to smallest. ASD, autism spectrum disorder; bil, bilateral; CS, central sulcus; Dx, diagnosis; F, female; FSIQ, full-scale IQ; GI, gyrfication index; GMV, gray matter volume; ICV, intracranial volume; IGI, local gyrfication index; L, left hemisphere; MCS, Monte Carlo simulations; NVIQ, nonverbal IQ; N.S., no(t) significant; OFC, orbitofrontal cortex; PIQ, performance IQ; RFT, random field theory; R, right hemisphere; ROI, region of interest; SA, surface area; SGMV, subcortical gray matter volume; Sig, significant; SFG, superior frontal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; SPL, superior parietal lobule; TBV, total brain volume; TD, typically developing; TGMV, total gray matter volume; TSA, total surface area; TWMV, total white matter volume; VIQ, verbal IQ; TIV, total intracranial volume; WMV, white matter volume; +, Effect sizes for children with autism and their co-twins, respectively; ++, Cluster-forming threshold of $P < 0.01$ and cluster-wise significance threshold of $P < 0.05$; +++, IGI analyses also performed without TBV as covariate, please refer to the original article for results; †, Two-sided.

To eliminate possible effects on our results, we repeated our mean analysis without this study and found similar results. Specifically, with a liberal threshold ($P < 0.1$) and only on the map of uncorrected P values, the right temporal lobe now reached significance ($P < 0.05$, $I^2 = 0.78$), the left occipital lobe cluster remained ($P < 0.08$, $I^2 = 4.82$) but not the frontal lobe cluster. Heterogeneity of these voxels was low.

Qualitative Review of ASD Studies

Group Effects

IGI, GI, and SI. The remaining studies that could not be included in the meta-analysis (3 IGI, 5 GI, and 2 SI studies), present contradictory results of greater (Kates et al. 2009; Duret et al. 2018, Table 3a), reduced (Liberio et al. 2014; Duret et al. 2018; Kohli et al. 2019, Table 3b), or no difference in gyrfication (Casanova et al. 2009; Bos et al. 2015; Maier et al. 2018; Pappaianni et al. 2018, Table 3c) in ASD, in parietal (Kates et al. 2009; Liberio et al. 2014; Kohli et al. 2019), temporal (Duret et al. 2018) and frontal (Kohli et al. 2019) lobes. Neither SI study reported group differences (Shokouhi et al. 2012; Auzias et al. 2014, Table 3c). Please note that results of the 10 studies included in the meta-analysis are also included in Tables 3a, b and c for the reader's reference.

Age Effects

IGI, GI, and SI. The age and sex effects presented here represent findings of all ASD studies including those in the meta-analysis. All ASD studies, except Liberio et al. (2018), included cross-sectional cohorts. All studies except two (Wallace et al. 2013; Koolschijn and Geurts 2016) used age as a continuous variable. Results of the effect of age were inconsistent across studies, although the mean age in these cohorts may be informative to understand the heterogeneity in findings. Specifically, in toddlers, the only ASD longitudinal study reported an increase

of IGI in ASD, but a decrease or no change (depending on the brain region) in TD boys aged 3–5 years old (Liberio et al. 2018). Of note, the 9 boys with megalencephaly, showed no differences in the developmental trajectory of IGI compared with TD boys, although this analysis was underpowered. In children, gyrfication was found to mostly decrease with age in TD (Auzias et al. 2014; Yang et al. 2016), but either not change (Auzias et al. 2014) or increase (Yang et al. 2016) in ASD. Discordant is the study by Kates et al. (2009), which reported an increase in gyrfication with age across both groups, although this is one of the smallest included studies ($n=42$). In adolescents, gyrfication was reported to either not change (Shokouhi et al. 2012; Bos et al. 2015) or decrease (Wallace et al. 2013; Liberio et al. 2014; Kohli et al. 2018) in TD. In all but one study (Shokouhi et al. 2012), there was a negative effect of age on gyrfication in ASD (Wallace et al. 2013; Liberio et al. 2014; Bos et al. 2015; Kohli et al. 2018). In younger adults, studies report no age-by-diagnosis interaction effects (Duret et al. 2018; Maier et al. 2018), but a negative main effect of age (Duret et al. 2018). The same pattern continues with older adults with both available studies in aging also reporting negative main effects of age with no interaction effects (Koolschijn and Geurts 2016; Kohli et al. 2019). Of note, in an exploratory analysis, Koolschijn and colleagues (2016) reported that when each adult group was separated by median ages into younger ($n=26$ ASD, mean age: 40.99 and $n=24$ TD, mean age: 39.99 years old) and older ($n=25$ ASD, mean age: 62.35 and $n=17$ TD, mean age: 59.88 years old) subgroups, there was an interaction effect in the right insular cortex among the older groups, with an age-related decrease of gyrfication in ASD (Koolschijn and Geurts 2016).

Sex Effects

IGI and GI. Most studies had too few females to explore sex effects adequately (only Schaer et al. 2015 had more than 20

Table 3c Findings of no significant differences in gyrification in ASD versus TD.

Study	Contrast	Covariates	Results (ASD vs. TD)	P (Correction)
Schaer et al. (2015)	Dx	Age, CV, sex	Sample: Matched on age, site. N.S. differences in VIQ, PIQ. Greater FSIQ in TD F versus ASD M. Sig. main effect of sex on supratentorial and CV (smaller in F)	P < 0.01 (MCS)
	Sex Sex x Dx		N.S. N.S. ASD M had the lowest, ASD F the highest, IGI in vmPFC and OFC (R) versus TD M and F (same results with site and FSIQ as covariates). Exploring sex effects within ASD: lower IGI in this cluster and homologous OFC (L) in M. Dx effects within the sexes: lower IGI in vmPFC/OFC in ASD versus TD M (N.S. differences in F)	
Koolschijn and Geurts (2016)	Dx	[†] Age, ICV, sex	Sample: N.S. differences in IQ, age, sex	[§] P < 0.05
	Age		N.S. differences in IGI (same results when repeating analyses with ⁺⁺ ADOS-group/M). N.S. differences in lateralization indices	FDR; ^{§§} Holm–Bonferroni
	AgexDx		Vertex-wise: N.S. Lobar-based: Decline of IGI with age in frontal lobe (same results when repeating analyses with ⁺⁺ ADOS group/without ICV covariate)	
Pappaianni et al. (2018)	Dx	Age	N.S. [decrease of IGI in ASD in insular cortex (R) in ⁺ older group]	P < 0.05 (FWE) (cluster-level)
Auzias et al. (2014)	Dx	Age	Sample: Matched on age, sex. N.S. differences in FSIQ, PIQ, TIV. Differences in VIQ	P < 0.0023 (Bonferroni)
	AgexDx		N.S. [but, greater GI in middle frontal gyrus (R) with VIQ as covariate]. N.S. differences in depth	
Maier et al. (2018)	Dx	Age	Sample: Matched on age, TBT. N.S. differences in WMV, GMV	P < 0.05 (FDR)
	AgexDx Dx x sex	Sex	N.S. differences in GSI, GSL, GMD. Greater mean depth in IPS (R), reduced max depth in medial frontal sulcus (L). Reduced length in CS, medial frontal sulcus (L)	
Bos et al. (2015)	Dx	Age	N.S. interaction in GSI, GSL, GMD. “+” relation between age & mean depth in medial frontal sulcus (L), length of STS (L), max depth of internal frontal sulcus (R) in TD. “-“relation between age and length of IPS (R), SI of postcentral sulcus and inferior temporal sulcus (R), length of calcarine fissure (R) in TD	None
	AgexDx		Sample: Matched on IQ, age, sex N.S. (for GI or depth) N.S. N.S.	
			Sample: Matched on age, sex. Differences in total IQ, VIQ (vocabulary subset), PIQ (block design) (Madrid). Differences in VIQ, not total IQ, PIQ (replication)	
			N.S. Reduced GI with age in PFC, parietal lobe (L) (same results when excluding F) Replication sample: Similar results. Similar results when repeating analyses with VIQ-matched subsample. Age-related decrease in parietal lobe (L) sig. when including sex as a covariate	

Continued

Table 3c Continued

Study	Contrast	Covariates	Results (ASD vs. TD)	P (Correction)
Casanova et al. (2009)	Dx	+++Age	Sample: Matched on age, sex, cerebral volume N.S.	None
Shokouhi et al. (2012)	Dx	Age, hem. Volume	Sample: Matched on age, sex, IQ Greater length in IPS (R), N.S. differences in depth/GSI N.S. correlation with any measure N.S.	$P < 0.05$ (Tukey's method, 0.95 CI)
Hirjak et al. (2016)	Dx	Age, sex	Sample: Matched on age, sex, not IQ. N.S. differences in cortical area N.S.	$P < 0.0041$ (Bonferroni)

Note: Results are significant following correction and presented as ASD versus TD. Studies are ordered based on sample size from largest to smallest. ASD, autism spectrum disorder; CI, confidence interval; CS, central sulcus; CV, cortical volume; Dx, diagnosis; F, female; FDR, false discovery rate; FWE, family-wise error; GI, gyrification index; GMD, global mean depth; GMV, gray matter volume; GSL, global sulcal length; GSI, global sulcal index; Hem, hemisphere; IPS, intraparietal sulcus; L, left hemisphere; M, male; Max, maximum; MCS, Monte Carlo simulations; N.S., no(t) significant; OFC, orbitofrontal cortex; PFC, prefrontal cortex; R, right hemisphere; SI, sulcal index; Sig, significant; STS, superior temporal sulcus; TBTv, total brain tissue volume; TD, typically developing; TIV, total intracranial volume; VIQ, verbal IQ; vmPFC, ventromedial prefrontal cortex; WMV, white matter volume; +, When each group divided into "younger" (ASD mean age: 40.99, TD: 39.99 years) and "older" (ASD: 62.35, TD: 59.88 years) subgroups; ++, Individuals with ADOS scores > 7; +++, Logarithm of ages; ||, Also added age-squared (and group-by-age-squared interactions) as covariate; §, Vertex-wise analyses; §§, Lobar analyses.

female ASD participants). The largest study by Schaer et al. (2015) ($n = 53$ ASD males, 53 ASD females, 53 TD males, 51 TD females) reported lower lGI in ASD males compared with females (when examining differences within ASD) and lower lGI in ASD versus TD males (when examining differences within the sexes; no differences found in females). They reported no main effect of sex.

IQ Effects

lGI and GI. Meta-regressions were not conducted on intelligence quotient (IQ) given that only 2 lGI studies in ASD explored the role of IQ. However, given known association between IQ and gyrification in the normative literature (Luders et al. 2008; Gregory et al. 2016), we qualitatively explored the effect of IQ on gyrification in ASD. All studies ($n = 4$) reported no association between gyrification and intelligence level in ASD among toddlers (Libero et al. 2018), children (Kates et al. 2009), and adolescents (Wallace et al. 2013; Bos et al. 2015). Specifically, Libero et al. (2018) found no relation in either ASD or TD groups, while Kates et al. (2009) and Wallace et al. (2013) reported positive associations in their TD groups (and in group of discordant unaffected co-twins of individuals with ASD in Kates et al. 2009). The only hint that IQ may have some impact on gyrification is the Pappaianni et al. (2018) study in which they repeated their main analysis controlling for verbal IQ and found changed results for the main effect of group, specifically greater gyrification in ASD, whereas no group differences were observed previously in this study when not using IQ as a covariate.

Qualitative Review of ADHD Studies

Group Effects

lGI and GI. Most ADHD studies (Table 2, please refer to Supplementary Table 3 for imaging parameters of all ADHD studies) report no between-group differences (Shaw et al. 2012; Ambrosino et al. 2017; Forde et al. 2017a Table 4), except the smallest study (Mous et al. 2014) which reported greater gyrification in ADHD compared with TD in the medial temporal lobe. Forde et al. (2017a), the largest available study, included TD siblings of individuals with ADHD in their cohort and reported

no differences in gyrification between individuals with ADHD, their siblings, or TD.

Age Effects

lGI and GI. Two ADHD studies included longitudinal data (Shaw et al. 2012; Ambrosino et al. 2017) while the rest consisted of cross-sectional cohorts. Among studies that examined the effect of age, all reported a significant negative effect of age, such that as age increased lGI decreased. Only Ambrosino et al. (2017) reported an age-by-diagnosis interaction effect as well, where a less steep decline of lGI with age was observed in ADHD in left cuneus and right pars opercularis (only in local, not total, lGI). Mean age of the cohorts did not explain these differences.

Sex and Intelligence Effects

lGI and GI. Forde et al. (2017a), including a relatively large number of female participants, reported no sex-by-diagnosis interaction effects, nor an effect of IQ.

Discussion

Our findings summarize a burgeoning, yet still small, literature focused on gyrification in ASD and ADHD. Our quantitative synthesis presents findings of no significant differences in lGI between ASD and TD individuals, although trend-level evidence of possible greater lGI in ASD relative to TD was observed as well as trend evidence of possible effects of sex but not age or sample size on gyrification differences. However, the number of studies available renders the analyses underpowered. Our qualitative synthesis of the remaining ASD studies presents highly heterogeneous findings, with gyrification atypicalities, when found, widespread in all lobes and in differing directions of effect. Across ADHD studies no significant between-group differences in gyrification were reported, despite the availability of two large ($n > 200$) studies.

The finding of no differences in gyrification between groups in both the meta-analysis in ASD as well as the majority of studies in ADHD is interesting and may point to an additional potential shared etiological factor between these two NDDs.

Table 4 Gyrfication findings in ADHD; results are significant following correction and presented as ADHD versus TD.

Study	Contrast	Covariates	Results (ADHD vs. TD)	P (correction)
Forde et al. (2017b)	Dx	TCSA, sex, IQ	Sample: Differences in sex, IQ, not age N.S. [N.S. effect of IQ]. Exploring a subset matched on sex, scanner, age (those with comorbid diagnoses excluded): N.S.	P < 0.05 (alpha level adjusted to 0.004)
	Age		Decline of lGI, increase of curvature, with age in frontal, parietal, temporal, occipital, cingulate and insula regions	
	Sex		Greater curvature in F in frontal region	
Shaw et al. (2012)	AgexDx Sex x Dx		N.S. (lGI or curvature)	P < 0.05 (log-rank Mantel-Cox)
	Dx	Age	Sample: Matched on sex, IQ, number of scans N.S. [Similar developmental trajectories between groups]	
Ambrosino et al. (2017)	Dx	Age, sex, average lGI, slice thickness (1.5 vs 1.2 mm)	Sample: Matched on sex, number of scans. N.S. differences in age, but differences in total IQ at baseline	P = 0.00008 (Bonferroni)
	Age		Total: N.S. Local: Reduced lGI in rostral middle frontal (L), pars opercularis (R) (N.S. after correction or including average lGI as covariate)	
	AgexDx		Decline of total lGI with age Total: N.S. Local: Less steep decline of lGI in cuneus (L) & pars opercularis (R)	
Mous et al. (2014)	Dx	Age, sex	Greater GI in medial temporal lobe (L)	P < 0.05 (Sidak)

Note: Studies ordered based on sample size from largest to smallest. bil, Bilateral; Dx, Diagnosis; F, Female; M, Male; N.S., No(t) significant; OFC, Orbitofrontal cortex; Sig, Significant; TCSA, Total cortical surface area; TD, Typically developing.

However, at this point it is challenging to present any conclusions regarding the gyrfication morphology of these two NDDs in a cohesive manner given the small number of studies available in the ASD and ADHD literature focused on this brain metric, as well as the lack of any study directly examining gyrfication morphology in ASD and ADHD in the same cohort, using the same scanner and protocol. Thus, as mentioned earlier and following the style in which the results have been presented (i.e., results for each NDD in relation to TD separately), in the discussion section as well we attempt no direct comparisons between the NDD groups.

The null findings in our meta-analysis and large ADHD studies may be explained by both biological and methodological factors. It is possible that no systematic differences actually exist in gyrfication between these NDDs and TD. Other explanations may include that 1) atypicalities are present but weak,

2) the degree of individual variability is high and may be larger than between-group differences, or 3) atypicalities may only be present in a subgroup of individuals with ASD or ADHD or detectable at certain stages of development. To take an example from another morphometric characteristic, [Liberio et al. \(2016\)](#) reported that only in the subgroup of megalencephalic children (referring to participants with ratio of total cerebral volume to height that is 1.5 standard deviations higher than that of TD) was there greater cortical volume in ASD compared with TD peers, suggesting that the widely reported findings of greater cortical volume in ASD ([Hazlett et al. 2006, 2011, 2017](#); [Schumann et al. 2010](#)) may be driven by a subgroup of ASD individuals with megalencephaly. Alternatively, there may be high heterogeneity across studies due to yet unknown features that were not systematically studied. Lack of detecting atypicalities in these two NDDs may also be due to insufficient

statistical power resulting from the limited number of studies included.

A factor possibly contributing to heterogeneity of results in this field may be the nature of the gyrfication construct itself. Gyrfication is a variable construct as evident by high variability of this measure across MZ twins in both ASD and TD studies (White et al. 2002; Kates et al. 2009), despite high rates of concordance in cortical volume. Such findings highlight the importance of both genetic and non-genetic factors in gyrfication and suggest that discrepant findings in this review may partially be due to the variable nature of gyrfication as a construct.

Although no effect of age was observed in the meta-analysis, our qualitative synthesis of all available data suggests that gyrfication findings in NDDs relative to TD may vary across different developmental stages. In the current review, although the rate of gyrfication change differed between ASD and TD in toddlerhood and childhood (and less so in adolescence), developmental trajectories did not significantly differ among adult or old age cohorts. This is in line with other morphometric results (cortical thickness) of the recent ENIGMA mega-analysis which showed greatest structural differences in ASD in childhood and adolescence (van Rooij et al. 2018). It is important to note that very little is actually known about brain changes in aging across NDDs (mean age = 50 years old, only two ASD studies available, Koolschijn and Geurts 2016; Kohli et al. 2019). In ADHD, all studies report a decrease of gyrfication with age and most studies did not find differences from TD. Although there are fewer ADHD papers, two relatively large studies in ADHD (Shaw et al. 2012; Forde et al. 2017a), including cohorts of 4.5–19 years of age, found no differences from typical development, so even though we could not do a meta-analysis, these provide fairly good preliminary evidence that there is no difference in gyrfication in ADHD when examining this brain construct in earlier developmental years.

Considering that gyrfication begins prior to birth (Chi et al. 1977) and peaks during toddlerhood (Raznahan et al. 2011), the potential effects of environmental factors (Mata et al. 2010; Kuhn et al. 2016; Bernardoni et al. 2018) and timing of onset of ASD and ADHD symptoms in early development, it is important to study gyrfication at younger ages. On this point, the study by Libero et al. (2018), which consists of a very young cohort, is of particular interest. The age-related increase of gyrfication found in toddlers with ASD compared with TD (Libero et al. 2018) suggests a greater rate of gyrfication increase in ASD during a period when the cortex is at its peak folding level in TD (Raznahan et al. 2011). This greater rate of gyrfication expansion in ASD may reflect the greater surface area expansion found in infants at high risk for ASD that later go on to manifest the disorder (Hazlett et al. 2017). As surface area may expand more rapidly in a subgroup of children with ASD, it is plausible that gyrfication levels also expand at a greater rate to fit the growing surface area in the limited space of the cranium (Le Gros Clark 1945). It is important for future studies to investigate gyrfication at early ages in ADHD as well to better understand gyrfication morphology in this cohort during toddlerhood also (Raznahan et al. 2011), while further studies on young cohorts in ASD are needed for replicability of results. Following the discussion earlier regarding only the subgroup of megalencephalic children with ASD presenting differing morphometric characteristics compared with TD (Libero et al. 2016), it may be important for future studies to also track subtypes of ASD and ADHD cohorts and include large sample sizes to better understand gyrfication morphology in these highly heterogeneous NDDs.

An understanding of the effect of sex on neural development, especially given the higher prevalence rates of both NDDs among boys, is crucial for understanding the biological underpinnings of cortical development in these two NDDs. Gyrfication development undergoes a sexually dimorphic course in TD (Raznahan et al. 2011; Mutlu et al. 2013), and to this end, some studies in this review investigated the effect of sex as well. Our quantitative synthesis suggests trend-level evidence of the effect of sex on gyrfication, specifically, the smaller between-group differences (ASD > TD) in IGI, the higher the percentage of males included in the ASD group. As only one study included sufficient number of ASD female participants (Schaer et al. 2015) and thus could examine sex effects, our knowledge regarding the effect of this variable on gyrfication in ASD literature is very limited. Effect of sex on gyrfication in ADHD is understudied as only one study (Forde et al. 2017a) analyzed sex. When focusing only on ADHD studies that included a large number of female participants ($n > 30$, Shaw et al. 2012; Ambrosino et al. 2017; Forde et al. 2017a), we found reports of no significant group differences in IGI between ADHD and TD, which suggests a potential effect of sex on IGI atypicalities in ADHD.

It is also important to consider sample demographics across included studies due to their potential impact on findings. For instance, the presence of co-occurring intellectual disabilities (ID) may have an effect, given known findings of gyrfication atypicalities in individuals with ID (Zhang et al. 2010). Most participants in the studies included had no ID. The inclusion criteria of many of these studies included only ASD participants with FSIQs above 70. Two studies included individuals with a broader range of IQ (i.e., Kates et al. 2009; Schaer et al. 2013), but neither study examined the effect of ID on gyrfication. The higher prevalence rate of ASD individuals with average or above average intelligence levels in the studies included in this manuscript is common in the field of neuroimaging research, partly due to considerations of feasibility, including maintaining scan quality. However, this limits the ability to generalize the reported neuroimaging results to those on the autism spectrum and intellectual disability (and limits knowledge of cortical macrostructure in this group).

Other important sample demographics to consider across studies include comorbidities and medication use. The majority of ASD studies in this manuscript excluded participants with neurologic, genetic, and psychiatric disorders or did not provide any information on comorbidity. Of the four that reported comorbidity, one study included ASD participants with and without speech onset delay (Duret et al. 2018), another included ASD participants with and without megalencephaly, another study (Maier et al. 2018), allowed for presence of anxiety and depression and the Casanova et al. (2009) study included ASD participants with comorbid disorders such as OCD, epilepsy, and bipolar disorder. Given the variability of diagnoses included and the small number of participants disclosed to have comorbid conditions, it is not possible at this stage to explore the effect of specific comorbidities on gyrfication. Only a few studies allowed medication use (Casanova et al. 2009; Wallace et al. 2013; Bos et al. 2015; Koolschijn and Geurts 2016; Pereira et al. 2018). Two of these studies specifically examined the effect of medication on gyrfication (Wallace et al. 2013; Bos et al. 2015), and both reported no significant effects of medication use on this construct. Considering the limited number of studies in this review that have examined medication use effects on gyrfication morphology, it would

be beneficial for future studies to examine this matter further.

The development and expansion of the cerebral cortex involves numerous sequential prenatal processes including neurogenesis, gliogenesis, and migration. In humans, the subventricular zone can be subdivided into an inner and outer layer with recent postulations regarding the involvement of the increase of the outer subventricular zone in the expansion of the cortex and ultimately gyrification (Rash et al. 2019). In line with this, it has been found that gliogenesis is a principal function of the outer subventricular zone at a prenatal period which overlaps with the start of gyrification (Rash et al. 2019). An in-depth understanding of these mechanical and cellular processes in early development is essential for understanding atypicalities in cortical gyrification and the underlying brain mechanisms involved in neurodevelopmental disorders such as ASD and ADHD.

In this work, we chose to focus on synthesizing results from three measures of cortical gyrification that we believe capture similar aspects of cortical morphology. IGI, GI, and SI are considered related brain constructs as all three are area measurements of inner sulcal and outer exposed cortical areas (Auzias et al. 2014). It is important to consider the methodological differences between gyrification constructs as their specific computation may capture different aspects of cortical morphology and cortical geometry. For instance, another measure of cortical gyrification, mean or extrinsic curvature (computed as the average of the two principal curvatures: maximal curvature, K_1 , and minimal curvature, K_2), captures the extrinsic qualities of a surface (Pienaar et al. 2007) and thus distinct properties of cortical geometry when compared with the IGI measure (Schaer et al. 2008). IGI is considered similar to intrinsic or Gaussian curvature (computed as the product of the two principal curvatures), with the difference that it captures a wider area (50-mm diameter, Schaer et al. 2008). Although mean curvature and IGI/SI are related measures of the gyrification of the cortex, they capture separate aspects of cortical geometry which need to be fully understood and taken into consideration prior to interpreting results from these two brain constructs. For this reason, we chose to focus our current work on the synthesis of results only from three measures of cortical gyrification which we believe are most appropriate to compare, considering their methodological and computational similarities which capture similar aspects of cortical morphology and geometry.

There are several limitations to this study, many of which are related to the characteristics of studies included, including variability in samples sizes, small number of females included, a focus on younger populations and methodological differences across studies such as differences in field strength of MRI scanners, lack of longitudinal cohorts, variability in gyrification constructs, and possible inconsistent implementation of quality control. As IGI is found to correlate strongly with surface area (Forde et al. 2017b), part of the observed heterogeneity may be due to the lack of the majority of included studies controlling for the effect of this variable on IGI (except Ecker et al. 2016; Forde et al. 2017a). Another limitation may be the use of a VBM meta-analytic software on SBM data, due to the lack of availability of a meta-analytic software for use. However, we rationalized the use of this software by incorporating an appropriate gray matter mask and taking into consideration that meta-analyses utilize information regarding peak coordinates in a standard space, regardless of how these coordinates have been obtained. Lastly, the limited number of studies included in our quantitative

synthesis (meta-analysis and meta-regressions) result in insufficient statistical power to detect small effects.

To address the gaps in the existing literature, large-scale longitudinal studies with a large number of female participants are needed, as well as a particular focus on aging as data from available studies is limited towards younger populations. In terms of methodology, it would be optimal for studies to employ whole-brain approaches and utilize local measures of gyrification (in addition to global scales) to better localize atypicalities. Considering the strong correlation between IGI and surface area (Forde et al. 2017b), future studies should control for the effect of this brain metric. Lastly, considering the high comorbidity and rate of co-occurring symptoms in ASD and ADHD, investigating gyrification in both NDDs in a single study with shared methodology will contribute to our understanding of further shared and possible unique mechanisms.

Supplementary Material

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

Notes

A.G. and E.A. decided eligibility for, and reviewed, the included studies and developed the structure of this manuscript. A.G. wrote the manuscript. A.G. conducted the meta-analysis and meta-regression. C.F. was the second reviewer in deciding eligibility for studies. S.A., M.T., J.L., and J.R. reviewed and revised the manuscript. This manuscript has been read and approved by all authors. A special thank you to Pui Ying Wong, for her guidance in the literature search. The opinions, results, and conclusions are those of the authors, and no endorsement by the Ontario Brain Institute is intended or should be inferred.

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