



Cortical gyrification in children with attention deficit-hyperactivity disorder and prenatal alcohol exposure

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ABSTRACT

Background: An improved understanding of the neurodevelopmental differences between attention deficit hyperactivity disorder with and without prenatal alcohol exposure (ADHD + PAE and ADHD-PAE, respectively) is needed. Herein, we evaluated gyrification (cortical folding) in children with ADHD + PAE compared to that in children with familial ADHD-PAE and typically developing (TD) children.

Methods: ADHD + PAE (n = 37), ADHD-PAE (n = 25), and TD children (n = 27), aged 8–13 years, were compared on facial morphological, neurobehavioral, and neuroimaging assessments. Local gyrification index (LGI) maps were compared between groups using general linear modelling. Relationships between LGI and clinicobehavioral parameters in children with ADHD ± PAE were evaluated using multivariate partial least squares.

Results: ADHD + PAE and ADHD-PAE groups showed significantly lower LGI (relative to TD) in numerous regions, overlapping in medial prefrontal, parietal, and temporo-occipital cortices (p < 0.001). However, LGI in left mid-dorsolateral prefrontal cortex was uniquely lower in the ADHD + PAE group (p < 0.001). Partial least squares analysis identified one significant latent variable (accounting for 59.3 % of the crossblock correlation, p < 0.001), reflecting a significant relationship between a profile of lower LGI in prefrontal (including left mid-dorsolateral), insular, cingulate, temporal, and parietal cortices and a clinicobehavioral profile of PAE, including a flat philtrum and upper vermilion border, lower IQ, poorer behavioral regulation scores, and greater hyperactivity/impulsivity.

Conclusions: Children with ADHD + PAE uniquely demonstrate lower mid-dorsolateral LGI, with widespread lower LGI related to more severe facial dysmorphism and neurobehavioral impairments. These findings add insight into the brain bases of PAE symptoms, potentially informing more targeted ADHD treatments based on an objective differential diagnosis of ADHD + PAE vs. ADHD-PAE.

1. Introduction

Prenatal alcohol exposure (PAE) can cause abnormal brain development, facial dysmorphism, deficient growth, and behavioral and neurocognitive deficits (O'Connor, 2014), as well as increased risk for preadolescent alcohol experimentation (Lees et al., 2020) and alcohol

use disorders in adulthood (Duko et al., 2020), resulting in a significant public health burden. While fetal alcohol spectrum disorders (FASD) affect up to 5% of children in the United States (May et al., 2018), it still remains greatly underdiagnosed in the general population. One issue is that children with PAE typically exhibit symptoms of attention deficit hyperactivity disorder (ADHD); thus, they are often diagnosed with

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ADHD and treated with stimulants despite limited evidence for their efficacy in children with ADHD + PAE (Doig et al., 2008; Frankel et al., 2006; Fryer et al., 2007; O'Connor, 2014; O'Malley and Nanson, 2002; Oesterheld et al., 1998; Peadar et al., 2009; Snyder et al., 1997). As ADHD + PAE is likely to be a distinct ADHD subtype, with an earlier onset, different clinical presentation, and different white-matter pathology than in non-PAE subtypes (ADHD-PAE) (Coles et al., 1997; Mattson et al., 2013; O'Neill et al., 2019), further research on the neurodevelopmental differences between ADHD + PAE and ADHD-PAE is imperative in order to refine future treatment approaches.

Neuroimaging studies have reported numerous PAE-related brain alterations, from infancy into adulthood (Wozniak et al., 2019). One important brain morphologic feature is gyrification (cortical folding), which enables more cortex to fit within the cranium and promotes the efficiency of neuronal connections (White et al., 2010). Greater gyrification, especially in frontal areas, is associated with better executive function performance and higher IQ (Gautam et al., 2015; Luders et al., 2008). The vast majority of the gyrification process occurs during gestation and, thus, may be especially susceptible to prenatal environmental stressors, such as PAE (Ishii and Hashimoto-Torii, 2015; Raznahan et al., 2011). After the first few months of life, gyrification generally shows a slight gradual decline lasting into early adulthood (Armstrong et al., 1995; Raznahan et al., 2011). Previous studies have shown widespread lower gyrification in children and adolescents with PAE compared to that in typically developing (TD) individuals (Hendrickson et al., 2018, 2017; Infante et al., 2015). However, potential differences between ADHD + PAE and ADHD-PAE in terms of gyrification remain unexplored.

Based on the above, we evaluated gyrification in children (aged 8–13 years) with ADHD + PAE compared to that in children with ADHD-PAE and TD children. To obtain a homogeneous ADHD-PAE comparison group with a well-defined ADHD etiology, this group only included children who met criteria for familial ADHD, verified by at least one first-degree relative with a similar diagnosis. To our knowledge, this is the first study to use this design to understand the differences between children with ADHD with and without PAE. We hypothesized that children with ADHD + PAE would have lower gyrification compared to both children with familial ADHD-PAE and TD children, especially in frontal regions, related to more impaired neurocognitive and behavioral functions.

2. Materials and methods

2.1. Participants

Three groups of children aged 8–13 years were included in the sample: 1) children with ADHD and PAE (ADHD + PAE; $n = 37$); 2) children with familial ADHD and without PAE (ADHD-PAE; $n = 25$); and 3) typically developing children with neither ADHD nor PAE (TD; $n = 27$). Children were recruited from community organizations, FASD parent organizations, national websites, other pediatric research studies, or physician referrals from local child psychiatry or pediatric clinics. This study was approved by the UCLA Institutional Review Board (IRB); written informed assent/consent was obtained from all participants.

Inclusion criteria for the ADHD + PAE group were as follows: ADHD by DSM-5 criteria for ADHD (any subtype) according to the clinician-administered computerized Schedule for Affective Disorders and Schizophrenia for School Aged Children, Parent Version (K-SADS) (Kaufman et al., 1997; Townsend et al., 2020) and the Conners-3 Parent Form (Conners, 2008); and diagnostic features of fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), or alcohol-related neurodevelopmental disorder (ARND) according to the Institute of Medicine (IOM) criteria proposed in updated guidelines (Hoyme et al., 2016; O'Connor et al., 2019). Four key diagnostic features of FAS were evaluated: 1) growth retardation; 2) the FAS facial phenotype, including short palpebral fissures, flat philtrum, and flat upper vermillion border

(see details below); 3) neurodevelopmental dysfunction; and 4) gestational alcohol exposure. Alcohol exposure was assessed using the Health Interview for Women (HIW) or the Health Interview for Adoptive and Foster Parents (HIAFP) (Quattlebaum and O'Connor, 2013). The HIW assesses frequency and quantity of typical and binge drinking and use of other teratogens prior to and following recognition of pregnancy. For adopted/fostered participants, information on prenatal exposure to alcohol and other teratogens was obtained via birth, medical, or adoption records or reports by reliable informants. Because many individuals with FASD are adopted or fostered, it is often necessary to use such records, and this is a method accepted in the scientific community for establishing PAE (CDC, 2004). No child in the ADHD + PAE group was accepted without a clear history of PAE. Criteria for alcohol exposure included >6 drinks/wk for ≥ 2 wk and/or ≥ 3 drinks on ≥ 2 occasions including the time periods prior to and following pregnancy recognition. These criteria are based on findings that 1 drink/day (or >6 drinks/wk) is an adequate measure of exposure for FASD, and on epidemiologic studies demonstrating adverse fetal effects of episodic drinking of ≥ 3 drinks per occasion (Hoyme et al., 2016). Although alcohol use was measured retrospectively, studies show that recall of drinking during pregnancy predicts neurodevelopmental outcomes as far back as 14 years past delivery (Hannigan et al., 2010).

Inclusion criteria for the ADHD-PAE group were as follows: ADHD (defined as above); at least one first-degree family member (i.e., biological parent or sibling) diagnosed with ADHD; and PAE < 2 standard drinks (1.20 oz absolute alcohol) during gestation. Inclusion criteria for the TD group were as follows: no current or lifetime history of an Axis I mental disorder by K-SADS interview; and PAE < 2 standard drinks during gestation.

The exclusion criteria for all participants were as follows: estimated Full-scale IQ < 70 on the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) (Wechsler, 2011); known genetic syndrome associated with ADHD, including fragile X, tuberous sclerosis, and generalized resistance to thyroid hormone; pervasive developmental disorder; serious medical or neurologic illness likely to influence cognition or brain function or brain anatomy (e.g. a seizure disorder or history of closed-head trauma); gestation < 34 weeks; history of claustrophobia; ferromagnetic metal implant, braces, or other contraindication to MRI; primary language at home was not English; unable to comply with study procedures; or poor MRI scan quality, resulting in inaccurate surface models despite manual editing.

2.2. Facial morphological assessments

The philtrum was rated from 1 to 5 based on the updated IOM guidelines for FAS, with a rating of 5 reflecting a flat philtrum and ratings of 4-5 meeting FAS criteria (Hoyme et al., 2016). The upper vermillion border was similarly rated from 1 to 5, with a rating of 5 reflecting a flat upper vermillion border and ratings of 4-5 meeting FAS criteria. In addition, the lengths of the right and left palpebral fissures were automatically calculated from digital photos of the participants' faces (with the exception of 4 participants who only had manual assessments of palpebral fissure length). The average of the right and left palpebral fissures was used for analysis.

2.3. Neurobehavioral assessments

Participants completed the WASI-II (Wechsler, 2011) as a measure of IQ (Full-scale IQ); higher scores indicate higher IQ. Parents completed the Conners, Third Edition (Conners-3) (Conners, 2008) and the Behavioral Rating Inventory of Executive Functions (BRIEF2) (Gioia et al., 2015). The Conners-3 is used to assess the degree to which a child displays clinically significant symptoms of ADHD, with higher scores indicating greater symptom severity. In the present analysis, we utilized the scores of the Inattention and Hyperactivity/Impulsivity subscales. The BRIEF2 measures a child's executive functioning skills in everyday

settings as reported by the parent(s). The BRIEF2 comprises 9 scales that form 3 index scores (the Behavioral Regulation Index [BRI], comprising the Inhibit and Self Monitor scales; the Emotional Regulation Index [ERI], comprising the Shift and Emotional Control scales; and the Cognitive Regulation Index [CRI], comprising the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials scales). Higher scores indicate poorer executive function. All neurobehavioral parameters were converted into age-normed T-scores (mean = 50, standard deviation = 10).

2.4. Neuroimaging acquisition and pre-processing

Participants underwent extensive desensitization and training in keeping the head and other body parts still prior to MRI scanning. During scanning, participants watched a children's movie of their choice and were monitored via video feed from within the MRI unit; participants were reminded to hold still when motion was detected. A high-resolution T1-weighted MRI was acquired as a sagittal whole-brain multi-echo magnetization-prepared rapid gradient-echo (MPRAGE) scan with real-time motion correction (TR/TEs 2500/1.81, 3.6, 5.39, 7.18 ms; TI 1000 ms; flip angle 8°; voxel dimensions $0.8 \times 0.8 \times 0.8 \text{ mm}^3$) using a 3 T Siemens Prisma-Fit system (Siemens, Erlangen, Germany) with a 32-channel head coil. The four echoes were combined into one root mean squared image. Subsequently, a T2-weighted MRI was acquired (TR/TE 3200/564 ms). The T1- and T2-weighted pulse-sequences were from the Human Connectome Project (HCP; <http://protocols.humanconnectome.org/HCP/3T/imaging-protocols.html>).

Cortical reconstruction and volumetric segmentation were performed using updated HCP pipelines (Glasser et al., 2013), which utilize both the T1- and T2-weighted images to reconstruct the white and pial matter surfaces in FreeSurfer 6.0 (<http://surfer.nmr.harvard.edu>) (Dale et al., 1999). The resulting surfaces were visually inspected for accuracy and manually edited if necessary. Subsequently, local gyrification index (LGI) maps were calculated in FreeSurfer 6.0, using a 3-dimensional approach (Schaer et al., 2012, 2008). The LGI reflects the ratio of the amount of exposed cortical surface to the amount of cortical surface buried within the sulcal folds at each vertex. LGI values range from 1 to 5, with higher values representing greater gyrification and a value of 1 indicating a flat cortical surface. Individual LGI maps were normalized to a common template (fsaverage). As LGI maps are inherently smoothed, no additional smoothing was performed.

2.5. Statistical analysis

Group differences in demographic, morphological, and behavioral characteristics were evaluated in analyses of variance (ANOVAs) for continuous variables and in chi-square or Fisher's exact tests for categorical variables using SPSS v26 (IBM Corp., Armonk, NY).

Group differences in LGI were evaluated in a general linear model (GLM) using `mri_glmfit` in FreeSurfer, controlling for sex and age. Although an estimate of the total intracranial volume or total brain volume is often, but not always, entered as a nuisance variable in studies of gyrification, a smaller cranial size is an intrinsic feature of PAE and cannot be separated from PAE; thus, controlling for this variable could obscure and produce anomalous results (Miller and Chapman, 2001). Contrasts comprised simple pairwise comparisons. In addition, we performed conjunction analyses to identify differences from TD common to both ADHD + PAE and ADHD-PAE (overlap of ADHD + PAE vs TD and ADHD-PAE vs TD) and unique to ADHD + PAE (overlap of ADHD + PAE vs ADHD-PAE and ADHD + PAE vs TD). Cluster-wise correction for multiple comparisons with adjustment for two hemispheres was performed using Monte Carlo simulation by `mri_glmfit-sim` in FreeSurfer (10,000 iterations).

Partial least squares (PLS) analysis was applied to evaluate the relationship between LGI and clinical/behavioral parameters among children with ADHD ± PAE, using freely available code (<http://www.rotman-baycrest.on.ca/pls>) (McIntosh et al., 1996).

PLS is a multivariate statistical technique that identifies weighted patterns of variables in two blocks of variables (in this case, an LGI block and a clinicobehavioral block) that maximally covary with each other (Krishnan et al., 2011; McIntosh et al., 1996; McIntosh and Lobaugh, 2004). The clinicobehavioral block included the following measures: PAE; Full-scale IQ; the philtrum rating, upper vermillion border rating, and average length of the bilateral palpebral fissures, as facial parameters; BRI, ERI, and CRI scores, as neurobehavioral parameters; and Conners-3 Inattention and Hyperactivity/Impulsivity scores as ADHD severity parameters. In the present setting, PLS produced a set of latent variables (LVs), each comprising a spatial map (vertex loadings) paired with a clinicobehavioral profile (clinicobehavioral parameter loadings) and a singular value indicating the amount of the cross-block covariance accounted for by the LV. The statistical significance of the overall patterns identified by PLS was evaluated using permutation testing (1000 permutations); importance of each feature (LGI at each vertex, each clinicobehavioral measure) was assessed using bootstrap estimation (1000 samples); and stability of the patterns was assessed using split-half resampling (100 times).

3. Results

3.1. Participant characteristics

Demographic and clinicobehavioral data are summarized in Table 1. Groups did not differ on demographic characteristics. Significantly, the philtrum and upper vermillion border received higher ratings (indicating flatter philtrum and upper vermillion border) and the Full-scale IQ was significantly lower in the ADHD + PAE group than in the

Table 1
Demographic and clinical characteristics.

	ADHD + PAE 37	ADHD- PAE 25	TD 27	Overall p- value
N				
Male Sex, N (%)	24(64.9)	17(68.0)	15(55.6)	.62
Age, yrs	9.7 ± 0.2	10.3 ± 0.3	10.4 ± 0.3	.08
Race/ethnicity, N (%)				.15 [‡]
White	11(29.7)	16(64.0)	11(40.7)	
Black	6(16.2)	1(4.0)	0(0)	
Latino	7(18.9)	1(4.0)	8(29.6)	
Asian	2(5.4)	4(16)	3(11.1)	
Other	2(5.4)	0(0)	1(3.7)	
Mixed	9(18.0)	3(12.0)	4(14.8)	
Mother's education, yrs	15.9 ± 0.3	17.0 ± 0.7	17.6 ± 1.0	.15
Philtrum rating	3.6 ± 0.1 [†]	3.3 ± 0.1*	2.8 ± 0.1	<.001
Upper lip rating	3.6 ± 0.1 [†]	3.1 ± 0.1*	2.7 ± 0.1	<.001
Palpebral fissures	24.0 ± 0.3*	24.5 ± 0.4	25.6 ± 0.4	.006
Full-scale IQ	96.7 ± 2.3 [‡]	109.7 ± 2.7	113.4 ± 3.4	<.001
BRI	71.5 ± 1.3*	68.0 ± 2.0	43.3 ± 1.1	<.001
ERI	68.0 ± 1.5*	66.0 ± 1.8	44.9 ± 1.0	<.001
CRI	70.1 ± 1.1*	69.2 ± 1.6	45.1 ± 1.5	<.001
Inattention	82.8 ± 1.4*	81.8 ± 1.9	48.2 ± 1.9	<.001
Hyperactivity/ impulsivity	84.1 ± 1.4*	80.3 ± 2.5	49.3 ± 2.2	<.001

Mother's education is a proxy for socioeconomic status.

ADHD, attention deficit hyperactivity disorder; BRI, Behavioral Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotional Regulation Index; PAE, prenatal alcohol exposure; TD, typically developing.

* p < 0.05 ADHD+/-PAE vs TD.

† p < 0.05 ADHD + PAE vs ADHD-PAE.

‡ White vs non-White.

ADHD-PAE and the TD groups (p 's<0.01); and the BRI, ERI, and CRI on the BRIEF2, and Inattentive and Hyperactivity/Impulsivity scores on the Conners-3 were significantly higher in the ADHD + PAE and ADHD-PAE groups than in the TD group (p 's<0.001).

3.2. Group differences in LGI

Controlling for sex and age, the ADHD + PAE group had significantly lower LGI compared to that in both the ADHD-PAE and TD groups in the left prefrontal cortex (Fig. 1; Table 2). Additionally, the ADHD + PAE group had significantly lower LGI compared to that in the TD group in cingulate and parietal cortices (Fig. 1; Table 2). There were no areas of higher LGI in the ADHD + PAE group compared to that in ADHD-PAE and TD groups. The conjunction analysis of significance on both ADHD + PAE vs TD and ADHD-PAE vs TD revealed overlapping areas of lower LGI in children with ADHD regardless of PAE, including medial prefrontal, parietal, and temporo-occipital cortices. The conjunction analysis of significance on both ADHD + PAE vs ADHD-PAE and ADHD + PAE vs TD revealed that ADHD + PAE group had uniquely lower LGI in the left mid-dorsolateral prefrontal cortex (Fig. 1; Table 2). A conjunction analysis of significance on both ADHD + PAE vs ADHD-PAE and ADHD-PAE vs TD failed to show any areas of uniquely lower LGI in children with ADHD-PAE.

3.3. Relationships between LGI and clinicobehavioral parameters

The PLS analysis identified one significant LV (accounting for 59.3 % of the covariance between LGI and clinicobehavioral parameters; overall: $p = 0.001$, split-half: $p_{\text{brain}} = 0.03$, $p_{\text{behav}} = 0.04$), indicating

that among children with ADHD, a profile of lower LGI in large portions of the prefrontal, insular, cingulate, temporal, and parietal cortices was associated with a clinicobehavioral profile of PAE, including higher philtrum and vermilion border ratings (greater dysmorphia); lower Full-scale IQ; higher BRI scores on the BRIEF2 (poorer behavioral regulation); and higher Hyperactivity/Impulsivity scores on the Conners-3 (greater ADHD severity) (Fig. 2; Table 3). The relationship between the LGI and clinicobehavioral profiles remained significant when controlling for sex and age. Palpebral fissure length, ERI and CRI on the BRIEF2, and Inattention scores on the Conners-3 did not reach statistical significance.

4. Discussion

In the present study, we evaluated LGI in preadolescent children with ADHD + PAE compared to that in children with familial ADHD-PAE and TD children, using both a traditional univariate approach and a multivariate approach. The results supported our hypothesis that prefrontal LGI is particularly lower in children with ADHD + PAE, and that these lower values are related to facial dysmorphia and neurobehavioral impairments. Further, the results add to the accumulating evidence of differences between ADHD + PAE and ADHD-PAE.

Children with ADHD + PAE had lower LGI in the left mid-dorsolateral cortex than did children with ADHD-PAE, as well as lower LGI in frontal (including the left mid-dorsolateral cortex) and anterior cingulate cortices than did TD children. This latter result is consistent with previous studies that compared children with PAE to TD children, without regard to ADHD (Hendrickson et al., 2017; Infante et al., 2015). However, as we included a group of children with familial

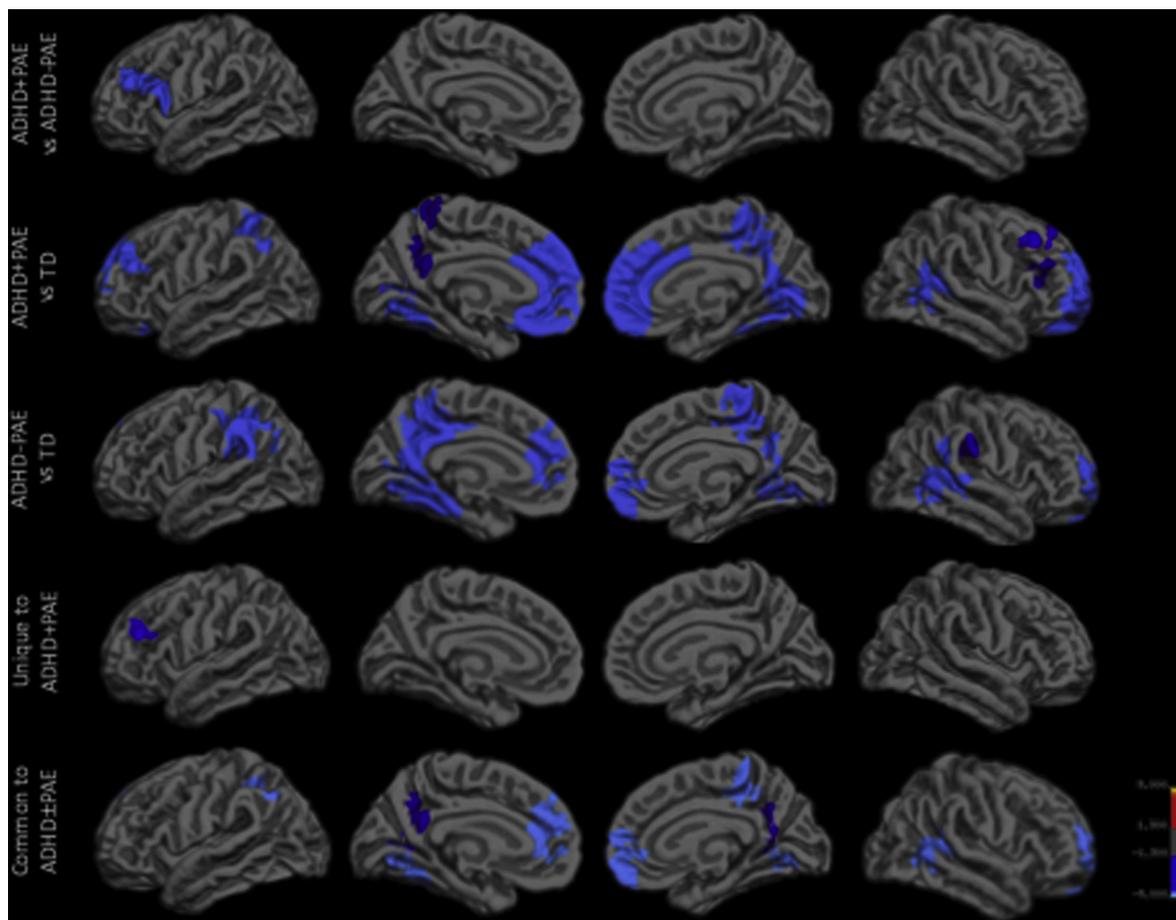


Fig. 1. Group differences in LGI, controlling for sex and age, are shown for each pairwise contrast and conjunction analysis. ADHD, attention deficit hyperactivity disorder; LGI, local gyrification index; PAE, prenatal alcohol exposure; TD, typically developing.

Table 2
Group differences in LGI.

Contrast	Peak Region	MNI coordinates	Peak Value	Size (mm ²)	Corrected p-value
<i>ADHD + PAE vs ADHD-PAE</i>					
	Left 46	-28 32 30	-4.4	2342	<.001
<i>ADHD + PAE vs TD</i>					
	Left 9p	-17 48 35	-4.8	5757	<.001
	Left 7PC	-33 -53 62	-3.8	2314	<.001
	Left V3	-18 -75 -10	-2.7	1428	<.001
	Left V1	-14 -82 5	-2.3	982	<.001
	Left d23ab	-5 -48 26	-2.4	552	.03
	Left 5L	-16 -45 58	-2.4	543	.03
	Right a10p	28 58 -10	-4.5	6938	<.001
	Right V2	15 -72 -5	-3.8	6375	<.001
	Right TPOJ2	58 -56 6	-3.3	2321	<.001
	Right 46	25 28 35	-3.1	765	.003
	Right IFSp	41 25 21	-3.1	587	.02
<i>ADHD-PAE vs TD</i>					
	Left 31pd	-9 -54 38	-3.5	7058	<.001
	Left PF	-55 -45 30	-4.3	3879	<.001
	Left 9 m	-9 46 22	-3.1	1371	<.001
	Right TPOJ1	49 -35 5	-3.8	3263	<.001
	Right V2	14 -72 -4	-2.7	2578	<.001
	Right p32	12 48 0	-2.6	2013	<.001
	Right 5 m	7 -35 54	-2.8	1577	<.001
	Right PF	50 -32 31	-3.8	651	.009
<i>ADHD ± PAE vs TD^a</i>					
	Left 9 m	-9 46 22	-3.1	1370	<.001
	Left IP2	-32 -52 34	-2.3	1240	<.001
	Left V2	-13 -64 -3	-2.3	1028	<.001
	Left V1	-17 -75 10	-1.9	702	.001
	Left d23ab	-5 -48 26	-2.4	544	.02
	Right p32	12 48 -1	-2.6	2001	<.001
	Right TPOJ2	58 -56 6	-3.1	1864	<.001
	Right V2	14 -72 -4	-2.9	1451	<.001
	Right 5 m	7 -35 54	-2.7	1073	<.001
	Right 7m	9 -57 35	-2.0	540	.02
<i>ADHD + PAE vs ADHD-PAE/CON^a</i>					
	Left 46	-41 40 325	-2.9	734	<.001

ADHD, attention deficit hyperactivity disorder; LGI, local gyrification index; MNI, Montreal Neurological Institute; PAE, prenatal alcohol exposure; TD, typically developing; TPOJ, temporo-parieto-occipital junction.

^a Conjunction analysis performed to determine regions common to both pairwise contrasts (areas of overlap).

ADHD without PAE, the present study more clearly shows an association between lower LGI in the frontal cortex and PAE, localized to the left mid-dorsolateral cortex. The left mid-dorsolateral cluster comprised portions of areas 46, p9-46v, 9-46d, and 9p (Baker et al., 2018b). These areas play a role in the conscious, active control of planned behavior (Petrides, 2005). Furthermore, dissociable contributions of the left and right mid-dorsolateral prefrontal cortex to planning have been demonstrated. For example, activity in the left mid-dorsolateral prefrontal cortex seems to be more strongly impacted by goal hierarchy (clear or ambiguous sequence for attaining the overall goal) than by search depth (degree of interdependence between consecutive steps), and vice-versa for the activity in the right mid-dorsolateral prefrontal cortex (Kaller et al., 2011). However, controversies remain, as a neuroimaging meta-analysis published in 2017 failed to find strong evidence of lateralized involvement of the mid-dorsolateral prefrontal cortex in planning-related processes (Nitschke et al., 2017). In contrast, transcranial direct current stimulation studies show clear dissociations between the right and left prefrontal cortex in self-regulation, with differential effects of lateralized stimulation/inhibition protocols on a

variety of self-regulation activities such as delay discounting, emotional regulation, and risk-taking (Kelley et al., 2018). Other stimulation studies support the greater involvement of the left prefrontal cortex in the initial planning and the right prefrontal cortex in monitoring/updating the planning process (Basso and Saracini, 2020). Thus, the lower LGI in the mid-dorsolateral cortex may underlie symptoms such as poor behavioral regulation (as supported by the PLS analysis discussed below) and sensitivity to initiating planning under ambiguous conditions as described in individuals with PAE (Schonfeld et al., 2009).

The PLS analysis showed that, among children with ADHD, a profile of lower LGI in prefrontal (including left dorsolateral cortex), insular, cingulate, and parietal cortices was significantly associated with a clinicobehavioral profile of features central to the diagnosis of ADHD + PAE, including PAE, facial dysmorphia in terms of philtrum and the upper vermilion border of the lip, lower Full-scale IQ, poorer behavioral regulation, and greater hyperactivity/impulsivity. Although smaller palpebral fissure length, another facial morphology feature central to PAE, was also associated with lower LGI, the reliability of its correlation failed to reach significance, as did that for the neurobehavioral parameters of ERI and CRI on the BRIEF2 and the Conners-3 inattention score. To our knowledge, this is the first analysis to relate facial dysmorphia to brain morphology in these well-defined etiologies, and suggests that some facial features may be more robustly associated with brain alterations impacting developmental dysfunction.

Two previous large-scale studies found no significant differences in gyrification between children (Shaw et al., 2012) and adolescents/young adults (Forde et al., 2017) with and without ADHD. However, two smaller studies found some significant differences, with lower gyrification in the left medial temporal lobe in adolescents with ADHD than in TD adolescents (Mous et al., 2014), and lower gyrification overall and in the right frontal lobe, as well as a tendency toward lower gyrification in the right parietal lobe, in preadolescents with ADHD than in TD preadolescents (Wolosin et al., 2009). The present study included a group of children with ADHD with a more homogenous etiology (familial and not due to PAE) than that in previous studies, and some significant differences between children with ADHD-PAE and TD children were observed. Compared to that in TD children, children with ADHD-PAE had lower LGI extending into the left medial temporal cortex, similar to the findings of Mous et al. (2014), as well as in additional regions, overlapping those reported in Wolosin et al. (2009). These additional regions comprised areas of somatosensory and visuomotor integration (5 m; mirror system, PF) and default mode network regions (lateral, TPOJ, IP2; posterior, 31pd; and anterior, 32, 9 m) (Baker et al., 2018a, c, d). Most of these regions also showed altered LGI in the ADHD + PAE group. The results of the present study, as well as our previous study, generally suggest that future ADHD-related neuroimaging studies would benefit from greater consideration of the diagnostic etiology (O'Neill et al., 2019), particularly PAE.

The present study has some limitations. First, the sample size was relatively small, but was comparable to some prior gyrification studies of ADHD (Mous et al., 2014; Palaniyappan et al., 2019) and PAE (De Guio et al., 2014; Infante et al., 2015) in children. Second, the Full-scale IQ was lower in the ADHD + PAE group; however, all participants had IQ > 70. This differs from some research samples of children meeting criteria for an intellectual disability, which often include results from extreme cases. Furthermore, lower IQ is a common symptom of PAE and it is not conventional to correct for it as there are valid arguments against such practice in groups with this inherent disability (Dennis et al., 2009). Third, although there is some evidence that the effects of PAE vary with the sex of the offspring (Fontaine et al., 2016; May et al., 2017; Weinberg et al., 2008), this is an underexplored area. A previous study showed no sex differences in the rate of decline in LGI during preadolescence in children with PAE (Hendrickson et al., 2018). Similarly, the current study failed to find notable sex differences; however, larger sample sizes may be necessary to determine an impact of sex. Fourth, only LGI was evaluated; the inclusion of cortical thickness and

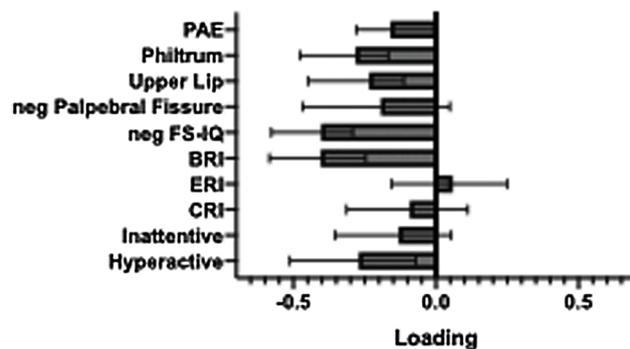


Fig. 2. Significant relationship between LGI and clinicobehavioral profiles as identified partial least squares analysis. The left panel indicates the importance of individual clinicobehavioral features to the overall pattern, with error bars indicating bootstrap-estimated confidence intervals. The negative of the palpebral fissure length and Full-scale IQ are plotted so that the worse/more severe endpoint of all clinicobehavioral features is toward the left. The right panel indicates the importance of individual vertices to the overall pattern according to the bootstrap ratio (approximately equivalent to a z-score). The results are shown on both pial (upper) and inflated surfaces (lower). ADHD, attention deficit hyperactivity disorder; BRI, behavioral regulation index; CRI, cognitive regulation index; ERI, emotional regulation index; FS-IQ, Full-scale IQ; LGI, local gyrification index.

Table 3

Location of peak vertices from the partial least squares analyses, depicted in Fig. 2.

Peak Region	MNI coordinates	Peak Value	Size (mm ²)
Left anterior ventral insula	-28 27 -6	5.67	20547
Left 7A (lateral parietal)	-20 -52 59	3.6	1298
Left PH (temporo-occipital)	-43 -53 -9	3.5	1043
Left V2	-10 -71 -2	3.2	760
Left TPOJ2	-46 -64 10	2.7	595
Right anterior ventral insula	31 29 -4	6.3	20468
Right V1	5 -73 4	4.2	5642
Right LIPd	30 -59 46	3.5	1169
Right frontal eye field	35 -2 44	2.8	772

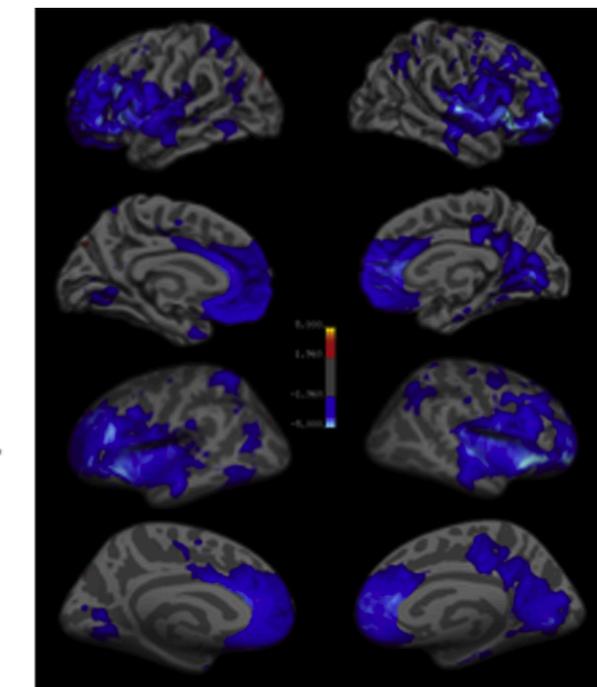
All p 's < 0.001 by bootstrap resampling.

LIPd, dorsal lateral intraparietal; MNI, Montreal Neurological Institute; TPOJ, temporo-parieto-occipital junction.

surface area could have added to the characterization of the cortical morphology and potentially compliment the LGI results. Finally, various epidemiological epiphenomena may co-occur alongside PAE (e.g. neglect, maternal stress, etc.) and contribute to the observed neurodevelopmental disruptions. Thus, the current study design should be reapplied to a larger number of children to enable the evaluation of interactions between PAE and these epiphenomena in terms of LGI in the context of ADHD.

4.1. Conclusions

The present study used a novel design, in which preadolescent children with ADHD and PAE were compared not only to TD children, but also to children with a well-defined ADHD etiology (familial) without PAE. The results demonstrated uniquely lower gyrification in the left mid-dorsolateral cortex, in children with ADHD due to PAE than in children with familial ADHD or TD children. These findings add



insight into the brain bases of PAE symptoms. Moreover, our findings support the notion that ADHD in the presence of PAE represents a distinct subtype with specific neurodevelopmental abnormalities that may inform the development of more targeted ADHD treatments based on an objective differential diagnosis of ADHD + PAE vs. ADHD-PAE.

Contributors

All authors participated in the research or article preparation. MJO and JGL received the funding. MJO, JGL, KLN, JRA, and JO designed the study. AD, KMB, and GK contributed to data acquisition and interpretation. LAK, SHJ, MJO, JGL, KLN, JRA, and JO contributed to data analysis and interpretation. All authors contributed to the writing of the manuscript.

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Declaration of Competing Interest

The authors report no declarations of interest.

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