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A preliminary investigation of the effects of prenatal alcohol exposure on facial morphology in
children with Autism Spectrum Disorder

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Scientific Abstract

Alcohol exposure during pregnancy has been associated with altered brain development and facial dysmorphology. While autism spectrum disorder (ASD) is not specifically related to distinct facial phenotypes, recent studies have suggested certain facial characteristics—increased facial masculinity and asymmetry—may be associated with ASD and its clinical presentations. In the present study, we conducted a preliminary investigation to examine the effects of prenatal alcohol exposure on facial morphology in autistic children with ($n = 37$; mean age = 8.21 years, $SD = 2.72$) and without ($n = 100$; mean age = 8.37 years, $SD = 2.47$) prenatal alcohol exposure. Using three-dimensional facial scans and principal component analysis, we identified a facial shape associated with prenatal alcohol exposure in autistic children. However, variations in the alcohol-related facial shape were generally not associated with behavioural and cognitive measures. These findings suggest that while early exposure to alcohol may influence the development of facial structures, it does not appear to be associated with ASD phenotypic variability. Importantly, although these findings do not implicate a role for prenatal alcohol exposure in the etiology of ASD, further research is warranted to investigate the link between prenatal alcohol exposure and facial morphology differences among neurodevelopmental conditions.

Keywords: Autism spectrum disorder; prenatal alcohol exposure, facial morphology, facial asymmetry

Lay Summary

Previous research has found alcohol use during pregnancy to be linked to altered brain development and changes to facial structures. In this study, we examined the impact of alcohol use during pregnancy on facial shapes of children diagnosed with ASD. We found that early alcohol exposure was associated with a distinct facial shape, however this was not related to clinical presentations in ASD.

Face and brain development occur in a dynamic and complex synchrony during embryonic development, with deviations in underlying brain development reflected in facial dysmorphology (DeMyer, Zeman, & Palmer, 1964). This is most clearly observed in neurodevelopmental conditions associated with syndromic facial changes, including Down syndrome (Starbuck, Cole, Reeves, & Richtsmeier, 2013) and Fetal Alcohol Spectrum Disorder (FASD; Suttie et al., 2013). While Autism Spectrum Disorder (ASD) is not considered to be a syndromic condition linked to a set of facial differences, subtle changes in facial morphology have been observed, providing clues to potential etiological pathways leading to a diagnosis of ASD in subsets of individuals. For instance, autistic children with more profound social difficulties presented increased facial masculinity (Tan et al., 2017) which has been linked to prenatal androgen exposure (Whitehouse et al., 2015). Of a range of facial differences examined in ASD to date (Boutrus et al., 2017), only facial asymmetry has been independently replicated (Boutrus et al., 2019; Hammond et al., 2008; Ozgen et al., 2011) which may be related to alcohol exposure during pregnancy (Klingenberg et al., 2010).

Prenatal alcohol exposure (PAE) is a known risk factor for fetal neurodevelopmental changes and in some cases may lead to FASD in offspring. While FASD has been linked to several facial phenotypes, including small palpebral fissures and smooth philtrums (Suttie et al., 2013), until recently measurement of these features has been limited to manual anthropometrics. Increasingly, three-dimensional (3D) photogrammetry has been adopted as a more precise tool to capture subtle variations in facial features. Using this method, a recent study found alcohol-linked changes to facial features in young children without FASD but who had been exposed to alcohol during pregnancy (Muggli et al., 2017). These subtle effects on facial development may reflect potential underlying changes in brain development.

While previous research has not shown an association between ASD and PAE (e.g., Singer et al., 2017), PAE has been linked to altered facial morphology (Klingenberg et al., 2010; Muggli et al., 2017). Therefore, the aim of the current study is to examine PAE as a possible mechanism underlying variability in neurodevelopment and concurrent facial morphology in ASD. Using a database of facial images collected on children with a diagnosis of ASD in Western Australia (WA), we investigated whether PAE was associated with facial morphology changes in

offspring. We hypothesised that PAE would be associated with changes in overall facial morphology and that these changes would be associated with variations in clinical phenotype.

Methods

Participants

Children were recruited to the Telethon Kids Institute, Perth, WA with a clinical diagnosis of ASD (DSM-IV or DSM-5). In WA, an ASD diagnosis is made following consensus by a paediatrician, clinical psychologist, and speech pathologist (Glasson et al., 2008). To reduce confounding influences on facial morphology, pubescent children >12 years old, who were non-Caucasian, had a history of facial trauma, or known genetic syndromes, were excluded from facial analysis. Ethical approval was granted by the Human Research Ethics Committee at the University of Western Australia (RA/4/1/5657) and informed written consent was provided by a parent or legal guardian.

Prenatal alcohol exposure (PAE)

A family history questionnaire was completed for each child by the primary caregiver with a section of the questionnaire related to prenatal and perinatal development. PAE was assessed using the question: "During pregnancy, did the biological mother drink alcohol?" with the response options 'Never' or 'Yes, during the first/second/third trimester'. As reports of alcohol use during the last two trimesters of pregnancy were infrequent (7.3%), we combined any endorsement of alcohol exposure during pregnancy and created a binary variable of 'no PAE' and 'any PAE'.

Cognitive and behavioural assessments

Cognitive assessments were available for 72% of children, as part of their participation in other research projects at the Telethon Kids Institute, measured using the Mullen Scales of Early Learning (MSEL; Mullen Scales of Early Learning, 1995) for those <6 years of age or the Wechsler Intelligence Scale for Children-IV (WISC-IV; Wechsler, 2003) for children >6 years old.

Quantitative behavioural measures of autistic phenotype were assessed using the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012). The ADOS is a semi-structured and standardised assessment of communication and social interaction, designed to elicit behaviours relevant for an ASD diagnosis. Total scores on items related to social interaction,

communication, and repetitive behaviours or restricted interests are combined to a calibrated severity score that is less sensitive to differences in age, verbal abilities, and IQ (Gotham, Pickles, & Lord, 2009). 37.5% of children were administered the older ADOS-G; these were re-scored to ADOS-2 algorithms and severity scores.

Parents/caregivers also completed the Social Responsiveness Scale-2 (SRS-2; Constantino, 2012) and Children's Communication Checklist-2 (CCC-2; Bishop, 2003), which assess difficulties in social interaction and communication, respectively. Analyses included standardised total raw scores on the SRS and two DSM-5 indices, social communication and interaction (SCI) and restricted interests and repetitive behaviors (RRB), and the two composite scores generated by CCC-2, General Communication Composite (GCC) and Social Interaction Deviance Composite (SIDC).

3D photogrammetry

The 3dMDface system (3dMD, Atlanta, GA) uses two sets of synchronized stereo cameras to capture a 3D ear-to-ear facial image, resulting from the combination of multiple colour, texture, and infrared images. Anthropometric data acquired using the 3dMDface system have been shown to be highly precise and replicable (Aldridge, Boyadjiev, Capone, DeLeon, & Richtsmeier, 2005). Children sat in front of the 3dMDface system with their gaze fixed on a spot behind the camera. For those who could understand verbal instructions, children were asked to maintain a neutral expression (or, not to smile) and keep their lips closed. For younger children or those with receptive language difficulties, multiple images were taken, and the image that most fitted these criteria was used.

Image pre-processing

MeshLab (Cignoni et al., 2008) was used to remove extraneous parts of each facial scan. Then, facial scans were annotated with 65 landmarks (see Figure 1) in MorphAnalyser 2.4 (Tiddeman, Duffy, & Rabey, 2000) which were aligned in orientation, rotation, and scale using Procrustes superimposition. Additionally, MorphAnalyser resampled the surface map of each face according to a standard model annotated with the same set of landmarks. This process aligned the surface map of each model to those of the standard model, thus achieving homology

for the entire facial surface of each model, and allowing the analyses and visualisation of whole surfaces (Holzleitner et al., 2014).

<Insert Figure 1 here>

Facial and statistical analyses

All 3D facial models were subjected to Principal Component Analysis (PCA) using MorphAnalyser. The resulting principal components were compared between children in the 'no PAE' and 'any PAE' groups. Factor loadings of the components that differed between the two groups were used in computing an 'alcohol-related facial score' for each face. Potential confounding effects in the sex distribution, age, BMI, head circumference and presence of intellectual disability/global developmental delay (ID/GDD) were examined and controlled for in the (a) between-subject ANOVAs comparing the two groups on ADOS, SRS-2 and CCC-2 scores; and (b) correlation analyses examining the relationship between the alcohol-related facial scores and behavioural measures.

Results

PAE data were not recorded for 12.7% ($n=20$) of the participants and were excluded from the analysis. The final sample consisted of 137 children, comprising two groups with 'no PAE' ($n=100$) and 'any PAE' ($n=37$; Table 1). Both groups were similar for sex distribution, age, BMI, and head circumferences (all p -values $>.05$). There was a higher proportion of children with ID/GDD (MSEL/WISC-IV standard score of <70) in the 'no PAE' group than the 'any PAE' group (22.0% vs 8.1%; $p=.02$). Therefore, ID/GDD was controlled for in the subsequent analyses.

<Insert Table 1 here>

The PCA identified 24 principal components accounting for 88.6% of the variations in facial shapes. One principal component significantly differed between children with and without PAE, $t(77.6)=2.66$, $p=.009$, $d=.47$ (2,000 bootstrap samples, 95%CI $[-220.3, -36.8]$). The scores under this principal component were therefore interpreted as 'alcohol-related facial scores', where higher positive scores were associated with more alcohol-related facial changes. Using MorphAnalyser, average faces representing children from the 'no PAE' and 'any PAE' groups were generated. Differences between the two averages were analysed using Hotelling's T^2 test at each vertex. The heatmap in Figure 2 shows facial regions (highlighted in green) that were

statistically significantly different between the two groups. Upon visual examination, a greater degree of facial asymmetry was associated with PAE particularly in the forehead and nose areas.

<Insert Figure 2 here>

Between-subject ANOVAs were conducted to compare cognitive and behavioural scores derived from WISC-IV, MSEL, SRS-2 and CCC-2. None of the scores differed between children with and without PAE (see Table 3). Partial correlation analyses examined the relationships between alcohol-related facial scores and behavioural scores while controlling for WISC/MSEL standard scores. Facial scores were not correlated with any clinical scores except the SRS SCI subscale, where a positive correlation was found, $r = .29$, $p < .001$, suggesting that children with greater social communication difficulties presented more alcohol-related facial variations.

<Insert Table 2 here>

Discussion

In this preliminary study we observed changes in facial morphology that were associated with PAE in children diagnosed with ASD. This replicates previous findings of distinct facial structure differences in children from the general population with PAE, but without FASD (Muggli et al., 2017). By comparing face models averaged across children with PAE and those of children without PAE, this overall difference in facial shape appeared to reflect asymmetry which is consistent with previous observations of greater facial asymmetry among children with FASD relative to neurotypical children (Klingenberg et al., 2010). Given that facial development begins during the earliest stage of embryonic development, these results combined suggest that early exposure to alcohol influences facial morphology in both children of typical neurodevelopment and those with diagnosed neurodevelopmental conditions.

The alcohol-related facial score was not associated with most aspects of clinical phenotype except social and communication difficulties measured by SRS-2 which were somewhat associated with greater alcohol-related facial changes. These results contrasted previous reports of increased facial masculinity linking to social difficulties (Tan et al., 2017) and greater facial asymmetry linking to repetitive behaviours in ASD (Boutrus et al., 2019). Similar to other population-based studies (Eliassen et al., 2010; Singer et al., 2017), behavioural and cognitive measures did not differ between autistic children with and without PAE in the current

study. The current findings suggest that alcohol-related changes in facial structures may not be indicative of clinical variability in ASD. Nevertheless, there is compelling evidence for the detrimental effects of PAE on executive functioning (Eichler et al., 2018; Khoury, Milligan, & Girard, 2015) which was not measured in the current study.

The present study has several strengths, including the use of fine-grained 3D facial photogrammetry and analyses, well-matched samples, and detailed information on clinical presentations and potential confounds. However, information on PAE collected in this study were based on retrospective self-reports which may be subject to recall bias (average recall period of eight years) and social desirability responding, where caregivers with knowledge about the effects of PAE on fetal development may be less likely to report alcohol use during pregnancy. A further limitation is that the majority of the parents/caregivers in the 'any PAE' group reported alcohol use in the first trimester of the pregnancy, we were unable to examine whether the relationships between PAE, changes in facial morphology, and behavioural outcomes occur in a temporally- (Lipinski et al., 2012) or dose-dependent (Coles et al., 2015) manner. Further work using prospective study designs is warranted to advance our understanding of the effects of PAE on facial morphology.

This is, to our best knowledge, the first study to examine the effects of PAE on facial morphology in children with ASD. While morphological changes in facial structures observed in the current study suggest a link between early alcohol exposure and developmental changes in facial, and possibly neural structures (Lebel et al., 2012), they were unrelated to behavioural and cognitive features of ASD. The outcomes of the current study add to the increasing evidence that facial structures may reflect developmental deviations during pregnancy.

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Table 1

Descriptive statistics of the study sample.

Characteristics	No PAE (<i>n</i> = 100)			Any PAE (<i>n</i> = 37)			<i>p</i> value
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	
Male (%)	84 (84.0%)			29 (78.4%)			.44
Age, in years	100	8.37	2.47	37	8.21	2.72	.75
BMI	85	17.6	3.19	33	17.1	2.70	.41
Head circumference (cm)	43	53.6	2.49	13	53.1	3.33	.66
ID/GDD (%)	22 (22.0%)			3 (8.1%)			.02*
WISC-IV Composite FSIQ	59	89.1	23.7	16	89.5	19.1	.93
MSEL Standard Scores	5	73.0	15.8	19	69.5	19.8	.49
ADOS-2: Total †	100	5.76	1.80	36	5.97	2.35	.57
ADOS-2: Social Affect †	100	6.21	1.81	36	6.33	2.33	.74
ADOS-2: RRB †	100	5.57	2.49	36	5.92	2.43	.46
SRS-2: Total †	87	101.1	27.1	33	92.2	23.9	.09
SRS-2: SCI †	87	91.9	26.3	33	94.2	26.6	.64
SRS-2: RRB †	87	20.8	6.21	33	19.2	6.24	.20
CCC-2: GCC †	76	32.9	13.5	25	35.2	11.7	.44
CCC-2: SIDC †	76	−4.23	9.21	25	−5.68	9.87	.47
PAE (%)							
<i>Never</i>	100 (84.0%)			—			—
Yes, during first trimester	—			27 (19.7%)			—
Yes, during second trimester	—			3 (2.2%)			—
Yes, during third trimester	—			7 (5.1%)			—
Alcohol-related facial scores †‡	100	−29.9	282.4	37	96.6	232.4	.009**

† Comparisons were adjusted for the presence of probable ID/GDD

‡ Higher positive scores indicate more alcohol-related facial changes relative to an averaged face

p* < .05; *p* < .01

Table 2

Partial correlations between alcohol-related facial scores and behavioural measures while controlling for WISC-IV and MSEL standard scores.

Behavioural measures	Facial scores	
	<i>r</i>	<i>p</i> value
ADOS-2: Total	.08	.36
ADOS-2: Social Affect	.10	.26
ADOS-2: RRB	-.03	.70
SRS-2: Total	.09	.30
SRS-2: SCI	.29	<.001
SRS-2: RRB	.11	.20
CCC-2: GCC	-.12	.17
CCC-2: SIDC	-.11	.19

Figure 1

A three-dimensional 'average' face with 65 landmarks.

Figure 2

Heat map comparing differences in facial shapes between 'any PAE' and 'no PAE' groups.

Note. Regions coloured in green are areas that are significantly different between the two groups.