Author/s:
Matthews, H;Muggli, E;Halliday, J;Claes, P

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DR. PETER CLAES (Orcid ID : 0000-0001-9489-9819)

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Mapping the spectrum of prenatal alcohol effects with dense surface models of the face and brain

Harold Matthews[1,2,3], Evelyne Muggli[1,2], Jane Halliday[1,2], Peter Claes[1,4,5,*]

[1]Murdoch Children's Research Institute, Parkville, Australia; [2]Department of Paediatrics, University of Melbourne, Australia; [3]Royal Children's Hospital, Melbourne, Australia; [4]Processing Speech and Images, Department of Electrical Engineering, KU Leuven, Leuven , Belgium; [5]Medical Imaging Research Center, UZ Leuven, Leuven, Belgium.

*Corresponding author:

Dr. Peter Claes
KU Leuven
ESAT PSI
University Hospital Gasthuisberg
Medical Imaging research center
Herestraat 49 bus 7003
Leuven
3000
Belgium
peter.claes@kuleuven.be

Fetal alcohol spectrum disorder (FASD) refers to the spectrum of teratogenic effects of prenatal alcohol exposure (PAE). Fetal alcohol syndrome (FAS) represents the extreme end of the spectrum and comprises somatic and neural growth deficiency, neurobehavioral impairment and a distinctive facial appearance (Hoyme et al., 2016). However, PAE affected individuals may have only some of these characteristics and many may go undiagnosed, particularly those without the characteristic facial appearance (Jones et al., 2010). The variability in presentation of FASD and outcome of PAE is likely the result of an interplay between maternal and infant risk factors and the timing and dose of PAE (Figure 1). An important component for our understanding of this variability lies in describing the full spectrum of fetal alcohol effects on the face and brain and the relationship between face and brain phenotype and outcomes, including cognition. Suttie et al. (2018) provides some important insights on this matter.

Suttie et al. analyse a sample of children of European and Latin American descent, comprising 47 controls, 22 diagnosed with FAS and 50 with confirmed heavy alcohol exposure (HE) who did not meet criteria for a diagnosis of FAS. The majority of individuals are aged from late childhood to early adolescence. An important strength of this study is the plethora of information available for each individual. These are 3D photographs, which record the outer surface of the facial soft-tissue

in high resolution; T3 magnetic resonance images (MRI); and two batteries of neurocognitive tests: the Differential Ability Scale, 2nd edition (DAS-2) and the California Verbal Learning Test for Children (CVLT-C).

The authors employ dense-surface modelling (DSM) to quantify the form of the face and brain regions. In contrast to more traditional approaches, which describe the form only as simple linear, angular or volumetric measurements, this approach represents the entire surface under study as a dense cloud of interconnected points, compressed into a smaller number of variables that explain almost all the shape variation (principal components). This allows many analyses not typically employed in FASD research including classification based on the shape of a structure itself, rather than derived measures; the synthesis of complete average forms of each group; the description of the phenotype of an individual, or the aggregate phenotype of a group as a 'signature', which codes the deviation of each dense point from an average as a z-score; and clustering of these signatures as a 'signature graph' to identify similarities among signatures of different individuals to identify phenotypic subgroups (right Figure 1). They also allow the authors to quantify individual asymmetry and systematic patterns of asymmetry within groups. The authors construct DSMs for different facial regions, the outline of a midline section of the corpus callosum, left and right caudate nuclei separately, and also DSMs combining information from the face and brain regions.

Variability in PAE phenotype

This study incorporates heavily exposed individuals who either did or did not meet criteria for FAS, allowing the authors to explore the variability in PAE effects for heavily exposed individuals. 'Signature graphs' of both caudate nuclei and of the face (in supplement) both identify a sub-group within the HE group with FAS-like morphology and a subgroup that does not cluster with the FAS group. In the analysis of asymmetry between the left and right caudate nuclei the control group shows left anterior dominance and the FAS group shows reduced left anterior dominance. In contrast the HE group shows no consistent pattern of asymmetry, although in general the amount of asymmetry of individuals in the HE group is comparable to controls. These two findings for the HE group indicate that the caudate nuclei are asymmetric, but that this asymmetry is heterogeneous among individuals within this group.

Relationships between the face, brain and neurocognitive measures

Exposure effects on the face and brain may emerge concurrently during embryogenesis. It is therefore possible that facial phenotype can be used as a proxy measure of brain phenotype and a predictor of cognitive outcomes. That face and brain phenotype are correlated is suggested by two

analyses here. In general, their classification analysis finds that combining information about the face and brain improves classification accuracy over the face alone, but these improvements are generally small suggesting the brain contains only minimal discriminative information over the information already present in the face. The second is that the FAS-like HE subgroup identified by signature graph analysis of the caudate nuclei contains mostly the same individuals as the subgroup identified by the same analysis of the face.

The authors demonstrate that caudate nucleus asymmetry predicts cognitive performance on several measures within exposed individuals. In previous work from this group they have also shown that those with FAS-like facial features, among heavily exposed individuals without a diagnosis, show lower cognitive performance than those with more control like features (Suttie et al., 2013, Suttie et al., 2017). Given the unique dataset available to the authors we suggest that they explore this relationship between (particularly facial) phenotype, and cognitive outcomes in more detail in future. This raises the interesting statistical problem of relating multiple phenotypic measures (point co-ordinates or principal component scores) to multiple cognitive outcomes. One solution would be to use two-block partial least-squares analysis to explore how broad patterns of phenotypic variation predict broad patterns of variation in cognitive outcomes within exposed individuals (Bookstein et al., 2002). Another approach is to condense multivariate phenotypic variation onto a single meaningful dimension that can then be analysed with cognitive outcomes in separate bivariate correlations. In fact, the authors create an appropriate compression of shape variation into a single score in their supplementary analyses (Figure S5). Here they express different individuals' positions relative to the FAS and control means along each x-axis. Position along this axis could be interpreted as a continuous measure of phenotype severity, quite amenable to bivariate correlation.

Looking beyond heavy PAE and the cardinal facial phenotype

An important strength of the DSM approach is that it allows analysis of the entire geometry of an anatomical structure, not only those aspects able to be measured or graded by standard techniques. Diagnosis of FAS in this study follows typical criteria (Hoyme et al., 2016), and requires the presence of two or more out of three cardinal facial features (smooth philtrum, thin vermillion line and short palpebral fissure). DSM analysis in this and previous studies demonstrates that additional characteristics distinguish FAS from controls and are present in some exposed individuals without a diagnosis. These include malar flattening or midfacial hypoplasia, retrognathia, shortening of the nose (although this was not documented in the FAS group in this study). We detected a similar effect on the nose and a general retrusion of the midface of 12-month old Caucasian children even

with low to moderate PAE (Muggli et al., 2017). Together, these studies highlight the need to look beyond the cardinal facial features in order to characterise the full spectrum of fetal alcohol effects.

We expect ordination of individuals according to their position along the phenotypic spectrum may be particularly valuable moving forward. This will allow future studies to investigate the factors that drive heterogeneity in FASDs including PAE timing and dose and environmental, genetic and epigenetic risk factors that could modify the effect of PAE. Further, diagnosis of a FASD is frequently not possible because PAE cannot be confirmed, yet the importance of this diagnosis is paramount for appropriate management of the child and family. If an ordination based on facial morphology can sensitively and specifically detect the effects of PAE, this may reduce the need to confirm PAE by other means, thereby allowing targeted clinical and social support for affected families.

The authors have no conflict of interest to declare.

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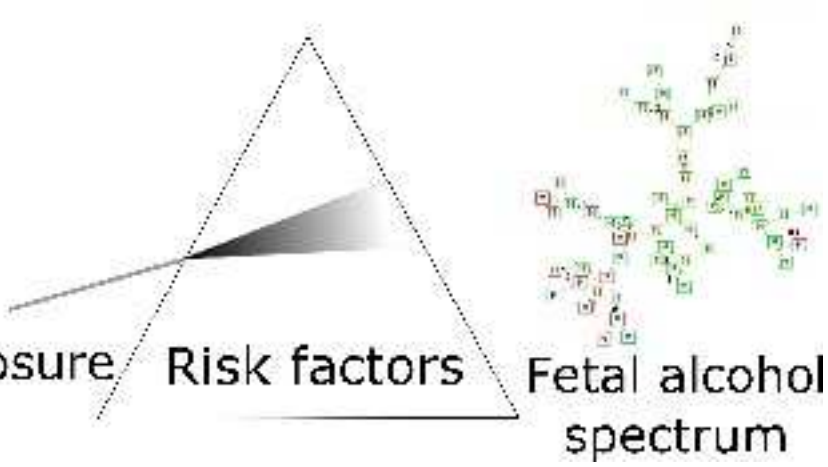
Figure Legend

Figure 1. The fetal alcohol spectrum. The spectrum of fetal alcohol effects likely arises from the interplay of prenatal alcohol exposure, and maternal and infant risk factors. Far right shows a ‘signature graph’ of the caudate nucleus from Suttie et al (2018) illustrating the heterogeneity within heavily exposed indivduals.



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