Alcohol, babies and the death penalty

Saving lives by analysing the shape of the brain

Alcohol can damage the brains of unborn babies. Shape analysis can assess the damage in fetal alcohol spectrum disorders. **Kanti Mardia**, **Fred Bookstein** and **John Kent** explain how it works, and how it can help babies and even murderers.

Babies in their mothers' wombs are vulnerable to chemical as well as physical challenges. One of the exposures that can particularly harm them is alcohol; and the organ that alcohol harms most seriously is the growing brain. Exposing otherwise normal human embryos to high levels of alcohol damages the brains of most of them in a wide variety of ways[1–3]. "Fetal alcohol spectrum disorder" (FASD) is an umbrella term that covers this range of abnormalities.

The alcohol, of course, reaches the baby through the mother. The mechanisms of damage are becoming increasingly well understood as consequences of defects of cell migration, of death of neurones, or of changes in the white matter that makes up the various structures of the brain itself. The very shape of the brain and its parts is changed; and the consequences last throughout the life of the baby, the child and the adult it becomes.

Statistics can identify damaged brains of babies who have just been born. Procedures based on likelihood mean that help can be delivered more accurately and more promptly

Our research was into those changes of shape in the brain – how to analyse the shapes statistically, how to distinguish affected brains from normal ones. Part of our motivation came from the US court system. Testimony based on brain imaging has been used in death-penalty court cases. The functional-imaging techniques remain controversial, but in recent years courts have become more willing to accept structural images like the ones we exploit here, and FASD provides an example where such testimony has become crucial. In particular, Fred Bookstein (one of the authors), using evidence based on the statistical shape methods we shall describe in this article, has acted as an expert witness for the defence in about 25 murder cases. In each case the guilt of the defendant was not in question, but evidence of FASD was used as a mitigating circumstance when sentencing. In more than half of those cases, the defendant was saved from the death penalty.

Another motivation was to "save life" in perhaps a more holistic sense, at the very beginning of that life: a severely affected baby diagnosed soon after birth is able to qualify for the extensive state support that in its area is available only to the most developmentally disabled of children. We shall return to these cases later in the piece.

The brain is a complicated organ, perhaps "the most complex structure in the known universe", and has many substructures within it. Exposure to alcohol while in the womb induces abnormalities of location, size, shape, or tissue structure in many of these[4]. K. L. Jones and D. W. Smith[5] noted in 1975 that the brain of one affected infant who died aged 5 days was quite small and was missing one particular structure, its corpus callosum, a component that sits between the two brain hemispheres and helps transfer information between them (see Figure 1). The same abnormality is often encountered in stillborn offspring of alcoholic mothers; it is also often found in brain images of patients who have been diagnosed much later in life[2, 6]. The callosum is easy to measure from a magnetic resonance (MR) image and yet is quite informative about the abnormalities that derive from prenatal alcohol exposure. So the size and shape of the callosum are the best current tools we have for the task

Figure 1. The corpus callosum of the brain. © Sebastian Kaulitzki/Shutterstock.com

that we set ourselves, which is detecting the traces of prenatal damage in medical images of adults. Other brain areas – the cerebellum, the basal ganglia – are also known to be affected by the alcohol exposure, but these effects have not yet been converted into detection tools. There are indications from the shape of the face as well – eyelid length, upper lip width, and the depth of the philtrum, the groove between the nose and the upper lip. Abnormal values of these measures can be noted in children but fade with adulthood; and even in children they seem to characterise, at most, fewer than half of the affected pool.

Corpus callosum

Stimulated by the pioneering report of Riley *et al.*[2], in 1997 a research team headed by Ann P. Streissguth launched a detailed study of the corpus callosum in MR images of the brains of 180 people living in or near Seattle, Washington. The images specifically highlighted the boundary between the corpus callosum and the fluid that surrounds it. The study[7] involved MR images and neuropsychological test scores for 90 adolescents (45 boys, 45 girls) and 90 adults (45 men, 45 women). Each group of 45 comprised 15 subjects with no prenatal alcohol exposure and 30 who already had an FASD diagnosis at the time of imaging.

From these 180 volunteers we learned how the form of a normal brain differs from an abnormal, alcohol-exposed form and what the features are that distinguish the two. Later, when we were presented with a new example, we could assess with some accuracy whether it was normal or abnormal – whether it had been affected by alcohol or not.

The callosum itself, as seen in a cut of the brain up the middle, can be described as a shallow upside-down letter "C" or cap, with varying curvatures and thicknesses. A shape of that sort can vary in all kinds of ways. Some method of defining the important qualities of the shape is needed. Shape analysis is a branch of statistics that helps define how similar, or how different, shapes may be to one another, and where it is (and at what scale) that the similarities and the differences lie. From each three-dimensional MR image of a callosum we extracted the "callosal midcurve" (the locus of greatest bilateral symmetry) and projected it onto a plane curve as in Figure 2. This is something like a cross-section down the middle. Then we represented the curve as a polygon of 40 points – this is one good way of analysing data from curves in biomedical scenes like this one. A first point was easy to identify: we used the rostrum, a clear anatomical feature, the sharp point at the front in Figure 2. This was our main landmark. Choosing the other 39 points – 'semi-landmarks' – was less obvious. (How, after all, do you establish corresponding points on a gentle curve?) The solution is to choose points that "slide" from case to case in accordance with the principle of minimum bending energy[8]. In effect, these points optimize the match between the curves.

For each subject the end result is a polygon as in Figures 2 and 3. Altogether we had 180 of them. They had different sizes and orientations as well as different shapes. To handle that, each polygon was translated, rotated, and scaled so that they lined up and matched as closely as possible. Technically, the resulting set of all 180

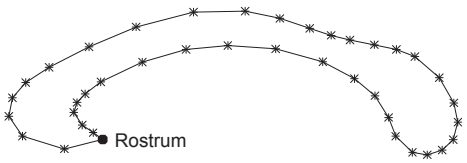

Figure 2. Average callosal midcurve of one landmark point (rostrum: closed circle) and 39 sliding landmarks (stars) for the 15 Seattle adult males of Bookstein *et al.*[7]

outlines now has the smallest possible sum of variances of all coordinates, subject to a constraint on the net second moment of the entire stack of outlines. The procedure is known as a generalized Procrustes analysis, and each polygon was represented by its Procrustes tangent coordinates[9]. (Procrustes, for those unsure of their Greek legends, was a giant who invited travellers to sleep on his iron bed. If they were too short, he stretched them to fit it; if too long, he cut their legs off to the appropriate length. One way or another, everyone on a Procrustean bed ended up the same size.)

Now that the shape of each callosum had been brought to a common standard for comparison, the usual statistical tools could be applied to tease out principal components, regression predictors, and other statistical characteristics of the set[10, 11].

In light of the findings of earlier investigators, we determined to concentrate our attention on the isthmus region in Figure 4 – the relatively narrow neck before the bulge at the right-hand end. In particular, its cross-sectional thickness turned out to be important. Our analyses of the 180 polygons showed that one summary statistic, the thickness at one particular section of the isthmus, was a particularly useful discriminator. (The identification of it builds on the multiscale methodology described by Mardia *et al.*[12]) If the thickness was average, in the middle of the distribution, it was a sign that the brain in question might not have been exposed to much prenatal alcohol; if the thickness was at the extremes – either much thicker than average or much thinner – it was a very good indicator of brain damage owing to fetal alcohol exposure. Useful though this finding was, it is not a stand-alone indicator. Statistical work incorporated isthmus thickness but also used the whole curve, via the 40-point representation, to identify the patients who were more likely to have FASD.

Useful practice – saving lives

We now had a tool to discriminate between those adults or adolescents who had suffered from alcohol in the womb and those who were not exposed. How does this finding translate into useful practice? How can we use it? Fred Bookstein's courtroom experiences can provide an example.

In one particular case the subject is actually a felon – we shall call him XX – who has been convicted of murder with special circumstances that make him eligible for the death penalty in the American state in which he resides. Analysis of his MRI scan was part of the court proceedings at the penalty phase of this trial. If a jury could be convinced that he had been born with brain damage, the death penalty might not be applied. Put crudely, whether or not he was to be executed could depend on the shape of his corpus callosum.

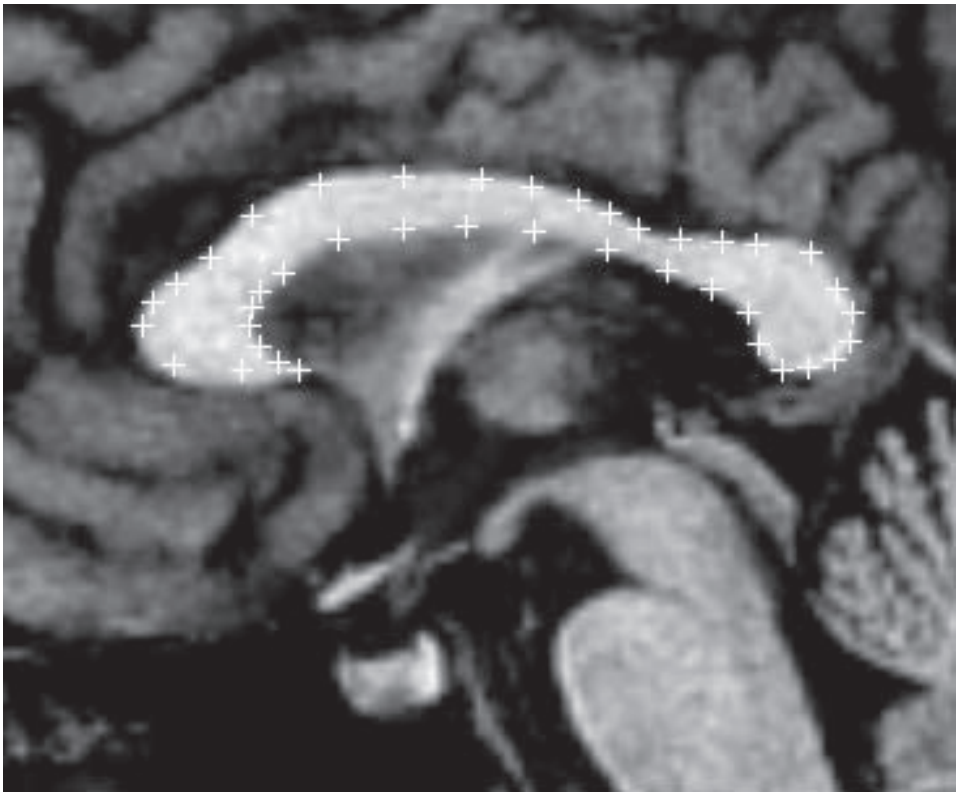

Figure 3. The callosal midcurve of defendant XX as visualized over a nearby plane of his MRI scan[3]

Figure 3 shows his callosal midcurve superimposed over a nearby plane section of his MRI scan. Figure 4 shows the same polygon now Procrustes-superimposed over the average for the 15 unexposed Seattle adult males of our training group. He clearly differs. The isthmus of his corpus callosum (labelled in Figure 4) looks too narrow, exactly at the location that has been found to be most informative for the effect of prenatal alcohol. This gives a particularly powerful signal of the prenatal alcohol effect.

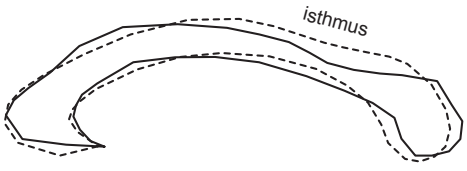

Figure 4. The average curve from Figure 2 (dashed lines) compared to the polygon in Figure 3 (solid lines) of XX. Note the narrowing of XX's callosum in the isthmus region[3]

Figure 5a repeats the curve for the normal Seattle average and marks the narrowest width of XX's isthmus. The variability of this vector between patients and normals is, as we have seen, a clear way that FASD presents itself. The courtroom aim is to assess the likelihood of a hypothesis of detectable damage at the isthmus. Figure 5b plots the likelihood ratio in support of the hypothesis of prenatal alcohol damage versus normality. The conventional log-odds ratio reporting the extent to which the data support the one hypothesis (damage of the sort seen in FASD) over the other hypothesis (a normal isthmus outline) is about 800 to 1. In open courtroom testimony, Fred Bookstein pointed to this strong evidence for congenital brain damage. As a consequence of that argument, together with observations by other experts, the American jury found the defendant not to be sufficiently culpable to deserve execution. Instead he is serving a life sentence in an American prison.

FASD in infants

Here is another example, this time a more uplifting one. It comes from the other end of life,

the beginning[13]. The life 'saved' – in the sense of at least made considerably better – was of an infant whom we shall call Baby S.

It is difficult to produce an MR image of a normal infant, as the child cannot be induced to lie still without sedation, which is an intervention that cannot be justified ethically. Typically, therefore, FASD is not diagnosed in children's brains until developmental or behavioural problems become apparent, at age 7 years or later. Almost none of the children who lack the facial signs mentioned above are identified while they are still young babies. To diagnose these children earlier would benefit both them and their caregivers.

We turned therefore to a different form of imaging, paediatric ultrasound. In a pilot study along these lines[14], we were able to locate four 'semi-landmarks' around the (quite differently shaped) infant callosal outline, and found an analogous discriminator – this time not isthmus length, but one particular angle in a quadrilateral of the semi-landmarks. Again, if the quadrilateral differs greatly from the average, it is a clear sign of fetal alcohol damage.

In the course of our pilot study we came across one baby brain that was damaged

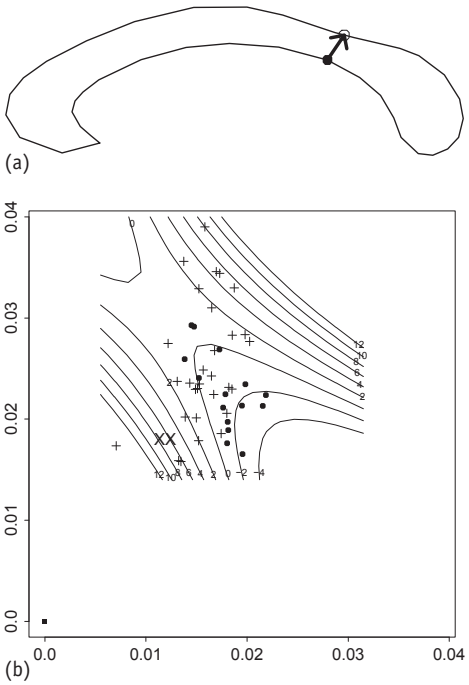

Figure 5. (a) Narrowness of isthmus with the shortest width shown by a vector of the outline (inset bottom). (b) The likelihood ratio contours (equispaced) for the hypothesis of prenatal alcohol damage versus normality by the quadratic discrimination discussed in the text. (+ = FASD; filled circles = normal; Seattle data, XX = the new candidate). The likelihood isolines are log likelihoods base e

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more extensively than anything we had expected[13]. His mother was an alcoholic who reported drinking an average of 1500 cc of wine – around two bottles – daily during the first and second trimesters of pregnancy. At birth, Baby S had facial features of fetal alcohol syndrome but these were not noted at the time.

Soon after delivery Baby S went to a special care centre to treat, among other things, feeding problems due to difficulty in swallowing. At the same time his mother enrolled in a case management intervention designed for pregnant and postpartum women who abuse alcohol and drugs, and entered residential treatment for her alcoholism. We carried out intracranial ultrasound on Baby S, with the consent of his mother, at 3 months of age. We found that his corpus callosum had only partially developed.

We reported this to the baby's mother and paediatrician. When Baby S was 8 months old and back in the care of his mother, this same ultrasound image (now serving as a primary indicator of central nervous system problems), along with his observable growth deficiency and "classic face" of fetal alcohol syndrome, supported an official diagnosis. By this time Baby S was showing moderate delays in speech and language and increasingly apparent behaviour problems. At 10 months of age he was approved for Developmental Disabilities services and enrolled in an infant and toddler early intervention programme, with a package of supports including therapeutic childcare, nutrition services and physical, occupational, and speech therapy (which taught Baby S to use sign language). His mother was coached on techniques for the developmentally disabled toddler, including helping the baby respond to frustration and accommodate to transitions.

Although Baby S was recognised as having developmental delay it took nearly a year and a half, until he was 29 months old, for the mother to obtain Social Security benefits for him. The initial petition was denied because, in the official wording, there was "no evidence of long term disability found". This was appealed; and the appeal was won on the basis of his fetal alcohol diagnosis. None of this would have happened without the fetal alcohol diagnosis based on the ultrasound scan. It was the brain damage, not the "face of fetal alcohol syndrome", that entitled this baby to the treatment he needed.

Conclusion

Shape analysis can now encompass the sort of individual-level decisions that are familiar from other branches of statistics. In our examples, evidence of damage to the brain has been revealed by mostly standard statistical methods. In the courtroom they are expressed with

A baby (not Baby S) in sign language asks for more. © iStockphoto.com/DSGpro

particular force in the language of likelihood ratios; the beneficiaries are the defendants and the legal system. In the welfare system science and statistics again overlap with society: the same likelihood-based procedures make it possible to deliver help more accurately, more efficiently, and more promptly, in accord with the criteria that society has decided upon.

It was not physical appearance but statistical analysis that enabled Baby S to receive the treatment he needed and was entitled to

Statistical shape analysis has been developed partly through various workshops of Leeds Annual Statistical Research whose mission has been to promote holistic statistics with Mardia's paradigm:

> **statistics without science is incomplete, science without statistics is imperfect.**

This principle embraces many of the ways that science and statistics together serve society today.

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