The Economist

Autism

Why it's not "Rain Woman"

Women have fewer cognitive disorders than men do because their bodies are better at ignoring the mutations which cause them

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AUTISM is a strange condition. Sometimes its symptoms of "social blindness" (an inability to read or comprehend the emotions of others) occur alone. This is dubbed high-functioning autism, or Asperger's syndrome. Though their fellow men and women may regard them as a bit odd, high-functioning autists are often successful (sometimes very successful) members of society. On other occasions, though, autism manifests as part of a range of cognitive problems. Then, the condition is debilitating. What is common to those on all parts of the so-called autistic spectrum is that they are more often men than women—so much more often that one school of thought suggests autism is an extreme manifestation of what it means, mentally, to be male. Boys are four times more likely to be diagnosed with autism than girls are. For high-functioning autism, the ratio is seven to one.

Moreover, what is true of autism is true, to a lesser extent, of a lot of other neurological and cognitive disorders. Attention deficit hyperactivity disorder (ADHD) is diagnosed around three times more often in boys than in girls. "Intellectual disability", a catch-all term for congenital low IQ, is 30-50% more common in boys, as is epilepsy. In fact, these disorders frequently show up in combination. For instance, children diagnosed with an autistic-spectrum disorder often also receive a diagnosis of ADHD.

Autism's precise causes are unclear, but genes are important. Though no mutation which, by itself, causes autism has yet been discovered, well over 100 are known that make someone with them more vulnerable to the condition.

Most of these mutations are as common in women as in men, so one explanation for the divergent incidence is that male brains are more vulnerable than female ones to equivalent levels of genetic disruption. This is called the female-protective model. The other broad explanation,

social-bias theory, is that the difference is illusory. Girls are being under-diagnosed because of differences either in the ways they are assessed, or in the ways they cope with the condition, rather than because they actually have it less. Some researchers claim, for example, that girls are better able to hide their symptoms.

The weaker sex

To investigate this question, Sebastien Jacquemont of the University Hospital of Lausanne and his colleagues analysed genetic data from two groups of children with cognitive abnormalities. Those in one group, 800 strong, were specifically autistic. Those in the other, 16,000 strong, had a range of problems.

Dr Jacquemont has just published his results in the *American Journal of Human Genetics*. His crucial finding was that girls in both groups more often had mutations of the sort associated with abnormal neural development than boys did. This was true both for copy-number variants (CNVs, which are variations in the number of copies in a chromosome of particular sections of DNA), and single-nucleotide variants (SNVs, which are alterations to single genetic letters in the DNA message).

On the face of it, this seems compelling evidence for the female-protective model. Since all the children whose data Dr Jacquemont examined had been diagnosed with problems, if the girls had more serious mutations than the boys did, that suggests other aspects of their physiology were covering up the consequences. Females are thus, if this interpretation is correct, better protected from developing symptoms than males are. And, as further confirmation, Dr Jacquemont's findings tally with a study published three years ago, which found that CNVs in autistic girls spanned more genes (and were thus, presumably, more damaging), than those in autistic boys.

The counter-argument is that if girls are better at hiding their symptoms, only the more extreme female cases might turn up in the diagnosed groups. If that were true, a greater degree of mutation might be expected in symptomatic girls as a consequence. However, Dr Jacquemont and his colleagues also found that damaging CNVs were more likely to be inherited from a child's mother than from his or her father. They interpret this as further evidence of female-protectedness. Autistic symptoms make people of either sex less likely to become parents. If mothers are the source of the majority of autism-inducing genes in children, it suggests they are less affected by them.

None of this, though, explains the exact mechanism that makes boys more susceptible than girls. On this question, too, there are two predominant theories. The first is that males are more sensitive because they have only one X-chromosome. This makes them vulnerable to mutations on that chromosome, because any damaged genes have no twin to cover for them. One cognitive disorder, fragile-X syndrome, is indeed much more common in men for this reason. Dr

Jacquemont's study, however, found only a limited role for X-chromosome mutations. That suggests the genetic basis of the difference is distributed across the whole genome.

The other kind of explanation is anatomical. It is based on brain-imaging studies which suggest differences between the patterns of internal connection in male and female brains. Male brains have stronger local connections, and weaker long-range ones, than do female brains. That is similar to a difference seen between the brains of autistic people and of those who are not. The suggestion here is that the male-type connection pattern is somehow more vulnerable to disruption by the factors which trigger autism and other cognitive problems. Why that should be, however, remains opaque.

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