VIEWPOINT

Mind the gender gap

BY **MENG-CHUAN LAI**

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Autism has long been perceived as a condition that is predominantly seen in males. This probably comes from its initial description: **Leo Kanner reported** seeing eight boys and three girls with it in 1943, and Hans Asperger's four initial case reports in 1944 were all of boys. Research since then has been biased toward understanding males with the condition, and there is an urgent need to understand more about females.

For example, in a report published 8 August in *Brain*, my colleagues and I showed that among high-functioning adults with autism, males and females show substantial differences in the characteristics of their brain structures[1].

However, what the initial 'male bias' in prevalence reflects is **something quite complex**.

First, it may mean that the definition of autism commonly used nowadays, which is based on behaviors, is by design **better at identifying males** with the condition[2, 3]. If females with autism, despite having the same core cognitive-behavioral characteristics as males with the condition, present differently in their behavioral repertoire, the current **diagnostic criteria may miss them**.

Second, it may also mean that on top of the potentially male-biased criteria, in real-world clinical settings practitioners are also biased toward diagnosing males more readily than females[4]. **Girls tend to receive their clinical diagnoses later**[5], for example, and compared with boys who have similar levels of autism traits, girls are **less likely to be diagnosed** unless they have other behavioral or intellectual issues[6, 7].

Finally, in the long process of growing up and interacting with peers, and in the larger social context, females tend to learn to mask or camouflage their difficulties[8, 9]. This, on the other hand, may also be due to better compensatory strategies developed through years of rehearsal.

So what do these all add up to? We should critically reflect on what defines autism and revisit the male predominance in prevalence. Even if there is indeed a gender bias in prevalence, this should

not mean that research should also be biased toward males. In neuroimaging studies, for example, **male participants outnumber females** 8 to 1 in studies of brain volume[10] and 15 to 1 in cognitive task-evoked functional magnetic resonance imaging studies[11].

What we understand about autism to date might be fairly male-biased. Especially when it comes to research, we are probably quite agnostic about the similarities and differences in how autism presents in different sexes/genders.

Mixed messages:

There have been increasing efforts over the years to understand the similarities and differences between males and females with autism. One heuristic, but perhaps not entirely accurate, thought is that similarities imply shared underlying processes resulting in the emergence of autism, and differences imply sex/gender-distinct factors that substantially contribute to heterogeneity in the spectrum.

Behaviorally, girls with autism seem to have less repetitive and stereotyped behaviors than boys[12]. Biologically, **early brain growth trajectories**[13-16], **genetic profiles**[17, 18] and serum biomarkers[19] might all be different in some aspects between males and females.

In our new study, my colleagues and I scanned the brains of 60 adults with autism, half of them males and half females, along with the same number of controls. To confirm some analyses, we also analyzed data from a larger male sample from the U.K. Medical Research Council's Autism Imaging Multicentre Study consortium (84 males with autism and 84 male controls).

We compared the volume of distinct brain structures in the participants with and without autism. If autism manifests in the same way in males and females, the patterns in males and females would be quite alike. If it manifests differently by sex/gender, on the other hand, the two patterns would be quite distinct.

We found it to be the latter — that is, we found minimal similarity between the patterns in men and women. The data suggest that autism manifests differently in males and females in terms of brain volume changes.

We also found that in terms of regional volume differences, the brains of females with autism have a shift toward looking like typically developing males rather than typically developing females. Interestingly, males with autism also show a shift, but in another direction (though with less strong evidence): They shift toward typically developing females rather than typically developing males.

These findings link autism to the so-called 'typical sexual dimorphism' (that is, average characteristic differences between neurotypical males and females) at the level of neuroanatomy. Admittedly, similarities in how brains look do not necessarily indicate shared underlying

mechanisms in action.

But if such a correspondence is partly valid, our findings may imply that mechanisms contributing to the emergence of autism are somehow related to how typically developing males and females differ, including factors related to sexual differentiation (such as sex chromosome genes and prenatal sex hormones) as well as social-environmental effects related to gendered experiences (such as rearing experiences related to gender stereotypes).

As in most empirical studies, what we found may be limited to the characteristics of the participants involved in the study — here they are all adults without intellectual disability and major comorbidities of autism such as **epilepsy**.

Piece by piece, subgroup by subgroup, hopefully one day the jigsaw of understanding the whole autism spectrum can be completed. During this process, we should constantly remind ourselves that all subgroups within the broad and diverse spectrum must be equally attended to and understood. As such, autism may be male-biased in prevalence, but our understanding and appreciation of it should not be.

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