VIEWPOINT

Quashing sex bias in autism research calls for participant rainbow

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In 2010, a group of psychologists pointed out that behavioral researchers overwhelmingly rely on participants from Western, educated, industrialized, rich and democratic societies — what they termed a 'WEIRD' sample — to draw conclusions about human characteristics[1]. They

demonstrated that theories drawn from this subpopulation may not apply to the rest of the world. In fact, they contend that results from these samples often represent outliers.

In autism research, much of our knowledge is similarly drawn from a **WEIRD population**. But there is further 'weirdness': For far too long, autism researchers have assumed that what they've learned from males applies to people of other sexes and genders.

This is perhaps understandable given the history of the field. Initial reports of autism were primarily in boys, and researchers have long considered autism a male-dominant condition. In the past two decades, the consensus has been that the ratio is four or five boys for every girl diagnosed.

But work over the past 20 years points to a lower ratio for the condition. For example, a meta-analysis published in 2017 showed that in prevalence studies that rely on direct assessment in the general population instead of on clinical or educational databases, the ratio falls to 3.25-to-1 or so[2]. Studies of younger siblings of children with autism have similarly revealed that in this group, there is a 3.18-to-1 ratio[3].

These studies suggest that the male-to-female ratio is higher when clinicians do not recognize **autism in girls**. With increased awareness of the **unique experiences of autistic females**, this problem may be abating. But most studies in autism still do not include enough autistic girls and women. People with autism also show greater diversity in **gender** and **sexual identity** than is seen in the general population, but researchers rarely knowingly include sex- and gender-diverse individuals in their studies.

This blind spot impedes successful development of treatments and support strategies for people with autism across the spectrum of sex and gender.

Because of this, I'd like to call for sex and gender diversity in the design of autism studies as a rule rather than as an exception.

Mostly males:

The idea that autism disproportionately affects boys, along with the under-recognition of girls with the condition, has combined to create a male lens in the field. This contributes to results that create a self-fulfilling prophecy and an even more biased literature.

For example, the male-to-female ratio in a 2012 meta-analysis of brain-scan studies of cognition in autism was about 15-to-1 across all participants[4]. In 2016, a meta-analysis of studies of autistic people's brain organization reported a participant sex ratio of nine boys or men to every girl or woman[5]. Earlier this year, a 'mega-analysis' of brain anatomy data from 49 centers revealed that in the overall sample, the sex ratio was six boys or men to every girl or woman[6]. A study published in July on autism features across 18 European regions had a 4.8-to-1 male-to-female split in its

combined data[7].

All of these ratios are larger than 3-to-1, indicating that far fewer girls and women are being included in autism research than exist in the general population.

Researchers cite practical reasons for this bias in the literature. These may include difficulty recruiting females because there are ‘so few’ and the introduction of confounding factors that accompany inclusion of autistic girls and women, because they may be more likely than autistic boys and men to have epilepsy or a **low intelligence quotient**. These are real concerns, but they must not stop us from designing studies with autistic girls and women in mind.

Even when researchers include a substantial number of women, they sometimes do not analyze their results by sex or gender, missing an opportunity to fill key gaps in our knowledge. We need to know how findings hold up across different sexes and genders.

Sampling schemes:

Let us take a look at the principles of research sampling in three types of studies. The first, and most common, includes observational studies that describe the overarching features of autism, or clinical trials designed to test an intervention designed for people with autism in general. To generalize findings to everyone who has autism, a study sample needs to be randomly selected and representative of the population at large. With regard to sex and gender, a representative sample should have a male-to-female ratio of 3-to-1.

Here's the challenge: Without proper planning, studies are likely to lack the statistical power to further examine whether the results differ by sex or gender. Statistical power to detect a sex or gender dependency will be low when the sample has small numbers of girls and women relative to boys and men — even at a representative 3-to-1 ratio. Failure to include sufficient numbers of girls means that sex-dependent effects are likely to be overlooked or presumed absent. This scenario propagates a male-based understanding of autism, which further entrenches the status quo.

To investigate sex differences in autism, studies must be even more rigorous. This second type of study should include equal numbers of biological boys and girls — a 1-to-1, not a 3-to-1, ratio. The same applies to gender. This maximizes the statistical power to uncover any **qualitative sex and gender differences** within autism.

A third class of inquiry is aimed at uncovering developmental factors in autism that could explain sex and gender ratios. Biological or behavioral **shielding mechanisms** may protect girls from autism more so than they do boys with comparable risk factors.

For instance, some studies suggest that at-risk girls pay greater **attention to social cues** than do at-risk boys, which may be related to both their sex and gender. Other research indicates that

genes associated with the **brain's immune cells** or the **hormonal environment in the womb** play a role.

These studies obviously must include a broad spectrum of individuals — including various sexes and genders and people with and without autism to come to meaningful conclusions.

We should no longer ignore the elephant in the room. As researchers, we need to work hard to shun WEIRD science, whether sex-, gender- or culture-based. And we need to take a hard look at how biases surrounding sex and gender may influence science and clinical practice.

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