

Sex/Gender Differences and Autism: Setting the Scene for Future Research

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Objective: The relationship between sex/gender differences and autism has attracted a variety of research ranging from clinical and neurobiological to etiological, stimulated by the male bias in autism prevalence. Findings are complex and do not always relate to each other in a straightforward manner. Distinct but interlinked questions on the relationship between sex/gender differences and autism remain underaddressed. To better understand the implications from existing research and to help design future studies, we propose a 4-level conceptual framework to clarify the embedded themes.

Method: We searched PubMed for publications before September 2014 using search terms “sex OR gender OR females’ AND autism.” A total of 1,906 articles were screened for relevance, along with publications identified via additional literature reviews, resulting in 329 articles that were reviewed.

Results: Level 1, “Nosological and diagnostic challenges,” concerns the question, “How should autism be defined and diagnosed in males and females?” Level 2,

“Sex/gender-independent and sex/gender-dependent characteristics,” addresses the question, “What are the similarities and differences between males and females with autism?” Level 3, “General models of etiology: liability and threshold,” asks the question, “How is the liability for developing autism linked to sex/gender?” Level 4, “Specific etiological–developmental mechanisms,” focuses on the question, “What etiological–developmental mechanisms of autism are implicated by sex/gender and/or sexual/gender differentiation?”

Conclusions: Using this conceptual framework, findings can be more clearly summarized, and the implications of the links between findings from different levels can become clearer. Based on this 4-level framework, we suggest future research directions, methodology, and specific topics in sex/gender differences and autism.

Key Words: autism, sex, gender, nosology, etiology

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The autism spectrum (henceforth “autism”), a constellation of neurodevelopmental conditions with heterogeneous etiologies,¹ has been reported as more prevalent in males since the initial case series.^{2,3} This reported sex/gender bias in prevalence has had various impacts on both research and clinical practice. (Note: we adopted the definition from the World Health Organization [http://www.who.int/gender/whatisgender/en/] that “sex” refers to “the biological and physiological characteristics that define men and women,” and that “gender” refers to “the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women.” Because most human studies of autism focus on children, adolescents, and adults, it is difficult to separate the effect of sex and gender, as gendered socialization begins at birth. For this reason, unless we specifically refer to “sex” or “gender” as defined above, we use the term “sex/gender” to acknowledge the inevitable overlap between them).⁴ How this male bias relates to the etiologies of and liability to develop autism has been widely discussed,

both recently⁵ and 3 decades ago.^{6–9} The downside is that the longstanding underrepresentation of females in research and clinical practice may have generated a male-biased understanding of autism.

Recently, an increasing number of studies from different perspectives and methodologies have revisited how sex/gender differences are related to autism. Some have attempted to clarify how males and females with autism are similar or different in behavioral features via meta-analyses,¹⁰ multi-site large datasets,^{11,12} and by means of a male/female-balanced design.^{13,14} This has been extended to proteomics,¹⁵ anthropometrics,¹⁶ brain structure,¹⁷ and neural/somatic growth patterns,^{18–20} to name a few levels. On the other hand, studies of population genetics²¹ and genomics^{22–26} have revisited the sex/gender-differential liability hypotheses using well-powered datasets and advanced technology. The use of adequately powered datasets and statistical design as well as multi-level approaches offer promising avenues for advancing our understanding.

However, findings from different studies are complex and do not always relate to each other in a straightforward manner. This is because there are several different (but interlinked) questions embedded in the broad theme



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of the relationships between sex/gender differences and autism. For instance, asking “Do females with autism have different behavioral characteristics from males with autism?” is different from “Why are there more males diagnosed with autism?” or “Why are males more susceptible to developing autism?” These questions may be interlinked but require different methodologies to address them. Although it is often stimulating to discuss findings from 1 question to address others (e.g., from finding a behavioral difference between males and females with autism, “jumping” to implications for sex/gender-differential liability and etiology), it can be conceptually challenging.

Therefore, we propose a conceptual framework that we hope will help clarify distinct research questions and their interrelationships, aid interpretation of findings to date, and design future research. We first briefly revisit epidemiological evidence for the sex/gender bias in prevalence. We then illustrate 4 different but interlinked levels of research themes, review key findings, and discuss how they may be mutually informative. We conclude by suggesting potential research directions, methodology, and specific topics.

METHOD

We searched PubMed for all articles published before September 2014 using search terms “sex OR gender OR females’ AND autism.” A total of 1,906 articles were screened for relevance, along with publications identified via additional literature reviews, resulting in 329 articles that were extensively reviewed.

RESULTS

Why Link Sex/Gender Differences to Autism? Epidemiology Revisited

The most widely reported male–female ratio for autism prevalence is 4–5:1, lower in individuals with intellectual disability and higher at the high-functioning end.²⁷ The association with IQ (a higher proportion of females have concurrent intellectual disabilities) has long been taken as having etiological implications, such as a higher liability threshold for females to develop autism.^{6,8} Most autism studies tend to include participants based on this ratio, or opt to include only males; hence our understanding of autism may have been substantially biased toward males. This problem is evident from the male bias in research samples summarized by meta-analyses: ~8:1 in brain volumetric studies²⁸ and ~15:1 in task-functional magnetic resonance imaging (fMRI) studies.²⁹

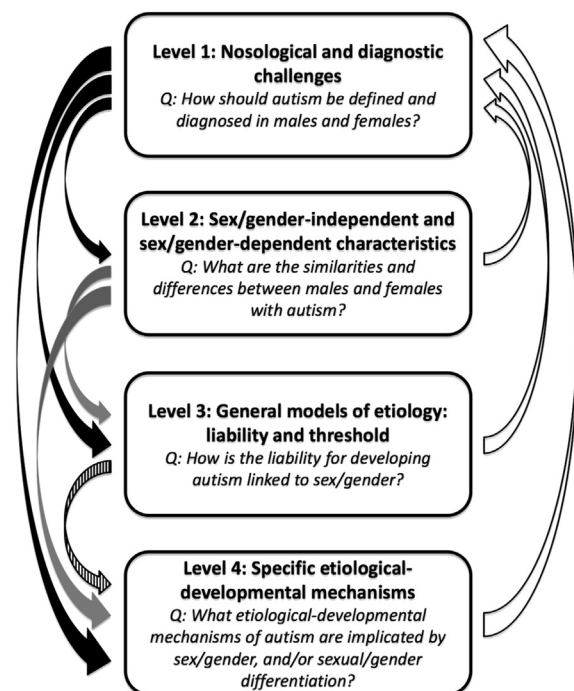
Recent large-scale (nationwide), population-based epidemiological studies suggest that the ratio in prevalence/incidence may in fact be lower, in the range of 2–5:1 male:female.^{30–39} Some studies have shown that the sex/gender ratio is not associated with intellectual disability,^{31,32} contrary to previous reports. The trend of lower sex/gender ratio and dissociation from intellectual disability may mean that recent studies have been more successful in identifying higher-functioning females, who may have been missed previously, particularly in clinic- or school-based samplings that are susceptible to ascertainment bias.⁴⁰ This trend may also reflect the broadening of the diagnostic concept that

enables more high-functioning females to be categorized on the spectrum.

To confirm the biased sex/gender ratio, it is critical to ensure that the estimation is derived from representative general population samples so as to minimize clinical ascertainment bias, and that the diagnostic criteria and assessment tools are not themselves sex/gender biased.⁴¹ The relatively smaller male bias in recent large-scale studies is therefore important: the samples are from general population or nationwide cohorts, and some use screening instruments that may be better at capturing subtle presentations in higher-functioning individuals.⁴² It is therefore likely that the male bias, although it exists, is less pronounced than was previously believed.

In brief, the 4–5:1 male bias may be partly due to the underrecognition of females (particularly higher-functioning), ascertainment bias, and issues of diagnostic instruments. Nevertheless, even studies that better account for these issues still show a 2–5:1 male predominance, which has important etiological and developmental implications.

FIGURE 1 The 4-level framework. Note: This conceptual framework comprises 4 levels of research themes (in bold) and main research questions (in italics). They are distinct but interlinked and mutually informative. Level 1 affects the discovery and interpretation of findings at all other levels (black arrows). Level 2 findings can contribute to the formulation, testing, and revision of etiological models and mechanisms (gray arrows). General etiological models from level 3 can enlighten investigation into specific mechanisms at level 4 (striped arrow). Finally, all findings from levels 2 to 4 can feed back to level 1 reflection (white arrows) for the process of epistemic iteration.⁶⁴



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