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## Opinion: Sex, Gender and the Diagnosis of Autism — A Biosocial View of the Male Preponderance

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Barbara, Virginia, and Elaine were the three girls among 11 children whom Leo Kanner described in his seminal paper published in 1943. Hans Asperger did not report any girls in his original 1944 paper. Today in the United States, 1 in 88 individuals will be diagnosed with an Autism Spectrum Disorder and 1 in 4 will be a boy. Seventy years later, this opinion paper outlines different attempts to explain the lower ratio of girls diagnosed with autism – from the role of sex hormones and genetic susceptibility to the biases inherent to clinical diagnosis.

Autism Spectrum Disorders – autism for short – are behaviorally-defined neurodevelopmental disorders of mostly polygenic etiologies influenced by environmental factors. The best known yet less understood characteristic of autism is prominent, unexplained prevalence in males. From a biosocial perspective that encompasses early gender-based socialization practices, I propose that this striking sex difference may be enhanced by clinical expectations and by the gender-biased standardized instruments used to support the diagnosis.

The hypothesis presented in this article rests on the assumption that both sex and gender contribute, but in distinct ways, to the male preponderance in autism (Cheslack-Postava & Jordan-Young, 2012). With rarest of exceptions, sex is dichotomous and genetically determined at conception. Biological sex is expressed in the individual's sexual dimorphisms, whereas gender emerges from early socialization processes. Whereas sex is biologically defined, gender is a psycho-social construct expressed through specific behaviors consistent with socio-cultural expectations derived from individuals' genetic sex. Unlike the sex ratio in clinically diagnosed autism which is established merely by determining the number of males and females, scores on diagnostic instrument like the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) or the parent report on the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), may

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be influenced by the child's expected behaviors in accordance with the prominent socialization gender attribute. So far the only widely used *screening* instrument using a differential gender cutoff is the Social Responsiveness Scale (SRS) (Constantino et al., 2003).

Let me raise the following two questions (1) what can be said about a child's biological sex and its effect on autism, and (2) how do universal, culture-specific gendered socialization practices affect the sex ratio in diagnosing autism? The first question ought to be addressed in the larger context of autism being but one among many other developmental disorders, such as dyslexia, Attention Deficit Hyperactivity Disorder (ADHD), or conduct disorders which affect more boys than girls. The reasons for the male preponderance in these conditions remain unclear and, thus far, it is being explained by tantalizing, but highly speculative mechanisms. Some studies suggest that boys are more vulnerable to a variety of prenatal insults (e.g., infection, malnutrition, stress) (Gardener, 2011) and, for uncertain reasons, might be more susceptible to genetic mutations relevant to autism (Goin-Kochel, Abbacchi, & Constantino, 2007; Szatmari et al., 2012). Other studies suggest that girls are more resilient to these prenatal potentially deleterious factors. A favored explanation for such a protective feature is higher exposure to female sex hormones and to oxytocin at critical periods of fetal development (Carter, 2007; Yamasue, Kuwabara, Kawakubo, & Kasai, 2009). Oxytocin (OT) is a sexually dimorphic neuropeptide associated with attachment, affiliative, and maternal behaviors. OT is known to foster pro-social behaviors, including social recognition, social learning, and reproductive behavior in both animals and humans (Feldman, Gordon, Influx, Gutbir, & Ebstein, 2013; Insel, 1997). Furthermore, in rodents estrogens acting in the amygdala together with OT reduce social anxiety — frequently elevated in autism — and foster higher levels of positive social interactions (Lee, Macbeth, Pagani, & Young, III, 2009; Ross & Young, 2009). In doing so these hormones — in animals — apparently oppose the influence of testosterone-dependent social arousal and anxiety (Lukas & Neumann, 2012). Several clinical trials are on their way testing the effect of daily nasal spray of OT on prosocial behaviors in ASD, however so far no results from longitudinal studies are available to assess the long term effects of these treatments in children (Miller, 2013).

According to one hypothesis, the male preponderance in autism could be merely due to the fact that girls need a larger genetic load to become symptomatic. Yet a recent large epidemiological study reports lack of evidence for genetic loading among families with affected girls (Goin-Kochel et al., 2007). Clearly, there is no shortage of complex explanations to envision how sex, primarily through its endocrine influences on the developing brain, may modulate the propensity to develop a neuro-developmental disorder like autism (Bale et al., 2010; Connors et al., 2008; Marco, Macri, & Laviola, 2011). Fetal testosterone (fT) plays a central role in human neurobehavioral sexual differentiation and in later social behavior (Bergman, Glover, Sarkar, Abbott, & O'Connor, 2010; Constantinescu & Hines, 2012). Thus, elevated testosterone exposure during critical periods of early development might be responsible for permanent behavioral changes. These influences have been demonstrated primarily in individuals who experienced marked prenatal hormone abnormalities associated with ambiguous genital development (e.g. congenital adrenal hyperplasia). Recently, Auyeung and colleagues examined the link between autistic traits and fT levels measured in amniotic fluid during routine amniocentesis and suggested that the brain basis of autistic traits may reflect individual differences in prenatal androgens and androgen-related genes (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010; Knickmeyer, Baron-Cohen, Auyeung, & Ashwin, 2008).

In regard to epidemiological studies, it is worth remembering that the male prevalence of 4:1 in autism (Fombonne, 2009), is highly modulated by cognitive function. For instance, as

intellectual functioning, namely IQ, decreases, the skewness of the sex ratio decreases to the extent that in severely cognitively impaired children with autism the sex ratio approaches 1:1. In contrast, when IQ increases, skewness of the sex ratio increases as well, which is illustrated in the 8:1 sex ratio in Asperger Syndrome, a form of autism with near-average to high intellectual function (Scott, Baron-Cohen, Bolton, & Brayne, 2002).

Thus the relationship between IQ and sex ratio seems to be biologically based, but might a diagnosis of autism perhaps also be related to the qualitative aspects of the clinical behaviorally-based diagnosis? (Banach et al., 2009; McLennan, Lord, & Schopler, 1993; Pilowsky, Yirmiya, Shulman, & Dover, 1998). Severe cognitive deficits may override and attenuate other more subtle gendered behaviors and characteristics of communication that contribute to making a diagnosis of autism (Kopp & Gillberg, 2011). Autism is not a disease like diabetes or Parkinson disease which is diagnosed on the basis of well-recognized and validated biological criteria. Instead, autism is a developmentally defined *syndrome* characterized by a set of behavioral symptoms, not on validated biomarkers (Walsh, Elsabbagh, Bolton, & Singh, 2011). Therefore to arrive at the diagnosis of autism, clinicians rely on a series of observations, and scores on descriptive behavioral tests based on the magnitude of departures from the expected norms at specific ages, often supplemented by parent questionnaires.

What is the role of gender during this diagnosis? The process of socialization begins at birth and differs by sex. A mother attends to her baby boy or girl's emotions differently and her responses are moulded by to the baby's sex. Similar gender-based differences are observed toward the baby's motor behaviors. The same scenario will take place in the case of a child who only later will be diagnosed with autism, and the mother will naturally be influenced by the same psychological and cultural beliefs when interacting with that child. Children with autism do not come into the world with an "autism mark" on their forehead or with defining stigmata. Moreover, some children will not manifest clear symptoms until age 18 months or so when language deficits or highly routinized play become apparent. Thus, those children diagnosed in the second year of life are raised like any other children from the day they were born, *according to their sex*. They are perceived as girls or boys and are taught to play, talk, and interact in accordance with the particular gender-based rules of their families (Condry & Condry, 1976). Therefore, despite their symptomatic social impairment, most verbal children with autism presumably have sufficiently preserved sociability, especially in the language and play domains, to acquire many of the gender markers to conform to the main sex-based behavioral expectations of their culture. On the other hand, in non-verbal, severely cognitively impaired children with limited communication skills, the typical gender traits may be less noticeable and thus boys and girls may be identified at a more comparable rate. At the other extreme, usual female higher verbal communication skills and social empathy may help girls with high functioning autism to more easily camouflage their social deficits. In turn, in boys the same social communication issues may readily be more salient and thus reinforce male identification (Attwood, 2006; Lai et al., 2011). Another significant issue related to the effect of gender in autism is the later identification of high functioning girls with autism possibly due to specific presentation of social and verbal abilities as well as variations in the frequency of specific types of co-morbid disorders (Begeer et al., 2012). These factors may play a role in the longer delay between parental concern and diagnosis in girls.

Biologic sex almost certainly bears the major responsibility for the male preponderance in autism, yet the issue of the sensitivity of the clinical diagnostic instruments needs to be raised. Germane to this discussion is the fact that the majority of the behavioral instruments used to diagnose autism have been standardized using male cohorts and very few studies have tested their sensitivity for identifying girls with autism (Kopp & Gillberg, 2011;

Rinehart, Cornish, & Tonge, 2011). Also, the number of studies that examine common and sex-specific core symptoms of autism across age remain limited (Kozlowski, Matson, & Rieske, 2012; Rivet & Matson, 2011; Sipes, Matson, Worley.J.A, & Kozlowski, 2011). Lastly, although externalizing (e.g., aggressiveness, destructiveness) and internalizing behaviors (e.g., depression, anxiety) are known to be differentially distributed across the sexes, diagnostic instruments remain mostly sensitive to the presentation of the syndrome in males.

## Conclusion

Clinical diagnosis is in the eyes of the beholder. Overall, girls are expected to be social, caring and empathic, therefore they must show greater positive symptoms like externalizing behaviors (e.g., aggressiveness, hyperactivity, severe lack of reciprocity) to be referred and diagnosed with autism (Bauminger, Solomon, & Rogers, 2010; Constantino & Charman, 2012; Dworzynski, Ronald, Bolton, & Happe, 2012). Stronger examiner bias toward male expectations may inflate the prevalence of autism in males, along with the fact that so far, the science of autism has been dominated by a male view of the disorder (e.g., test standardization, MRI samples, Baron-Cohen's "extreme male theory" (Baron-Cohen, 2002)).

It is now undisputable that both male and female brain development requires interactions with the environment and that these interactions shape the expression of behaviors, in particular language and communication (Hines, 2011). In turn, continuous cross-talk between sex and gender contributes to differences in the autism phenotype and its variable outcome. The potential effect of gendered social environment on the expression of symptoms may be quite different for a boy and a girl with autism, to the point where, despite the same social deficit, a girl may be perceived as shy and a boy as unresponsive. These gendered perceptions of symptoms may contribute to the diagnostic bias toward increased identification of social psychopathology in boys (Giarelli et al., 2010; Lai et al., 2011; Worley.J.A & Matson.J.L., 2011). Furthermore, socialization being an ongoing developmental process, the outcome of autism in terms of symptom severity and success of remediation is no doubt influenced in part by hormonal changes during puberty, but also by reinforcement of behaviors shaped by perceived gender.

As long as we have such imperfect understanding of the pathophysiology and etiologies of autism explanations for the striking male preponderance, both the biological and psychosocial contributions to the imbalance need to be explored. More studies should examine the expression of symptoms as a function of IQ and of both sex and gendered social factors in autism and other developmental disorders (Rinehart et al., 2011). Cognitive functioning being negatively associated with severity of autistic features, sex discrepancy in IQ in some studies may have obscured true differences in autistic symptoms between boys and girls (Lai et al., 2012). As an example, it would be relevant to identify verbal and non-verbal gender markers from ADOS videos and in unidentified gender written protocols or standardized testing reports, and to develop a coding system to rate gender magnitude across IQ levels and autism severity. Together, basic scientists and clinicians ought to design longitudinal studies using instruments standardized for each sex to test the hypothesis that girls are less likely to be diagnosed with autism but when they are, girls are often more severely affected or may display a distinctive presentation.

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**Highlights**

1. Biosocial perspective of the male preponderance in ASD
2. Effects of biological sex and gendered socialization practices on ASD diagnosis
3. Gender normed standardized clinical instruments
4. Differential expression of autism symptoms in girls and boys e