Commentary

Is autism really a coherent syndrome in boys, or girls?

David H. Skuse*
Behavioural and Brain Sciences Unit, Institute of Child Health, London, UK

This article is a commentary on ‘Fetal testosterone and autistic traits’ (Auyeung et al., 2009).

Autism is much more common among males than females; this is a well-established fact, yet the mechanisms that underlie that universal observation are as yet obscure. There has been remarkably little discussion to date as to whether understanding the difference in prevalence between the sexes could shed light on the fundamental causes of the condition.

Ultimately, whatever pathology is responsible for male vulnerability to autistic disorders (as currently defined) it must be linked to the fact that males and females differ in terms of their sex-chromosome constitution. Bear in mind that biological risk factors for a specific disorder may differ from risk factors for differences in rates or manifestations of disorder between the sexes. This caveat is of particular relevance to the theory proposed by Baron-Cohen in the Auyeung et al. (2009) study, in which it is not clear whether exposure of the fetus to testosterone increases risk of autism specifically, or whether it reduces the threshold at which autistic symptoms manifest in ways that are measurable by conventional means. Although autism is almost certainly a complex genetically heterogeneous condition (Skuse, 2007), in biological terms the explanation for the difference in prevalence by gender could be relatively simple. Amongst the outstanding questions arising from the observation of gender prevalence is the need to understand why the magnitude of the sex-ratio differs with IQ. In autistic samples with mental retardation the sex ratio is low (about 2:1) but among those with above average intelligence it is at least 10:1 (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Volkmar, Szatmari, & Sparrow, 1993). Recent research has suggested that among children with high verbal IQ, boys are substantially more vulnerable than girls to deficits in social-communicative competence (Skuse et al., in press).

* Correspondence should be addressed to Professor David H. Skuse, Behavioural and Brain Sciences Unit, Institute of Child Health, London WC1N 1EH, UK (e-mail: dskuse@ich.ucl.ac.uk).

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There are two main theories to account for sex differences in autism prevalence. First, Skuse (Skuse et al., 1997; Skuse, 2005) proposed an explanation for male vulnerability based on the fact that males have a single X-chromosome. By a variety of potential mechanisms, this could reduce the threshold at which autistic symptoms express themselves in a clinical phenotype (Skuse, Morris, & Dolan, 2005). Possession of a second X-chromosome is hypothesized to protect females from the impact of (autosomally-mediated) genetic vulnerability by its influence on the development, structure and function of the social brain. The theory proposes that autistic symptoms as such largely result from genetic or environmental influences that are independent of the sex-chromosomes. Second, Baron-Cohen (Auyeung et al., 2009) has proposed that exposure to fetal testosterone (fT) is ‘related to the development of autistic traits’. It is unclear whether the risk is direct or indirect in his model, although he suggests one mediating variable might be atypical lateralization of brain function which Geschwind & Galaburda (1985) proposed occurs as a consequence of fetal exposure to androgens. He appears to consider that exposure to high levels of androgen in utero is associated with an increased severity of some ‘autistic traits’ measured on a continuum, irrespective of sex-chromosome constitution. Supporting data are available from his study of females with congenital adrenal hyperplasia (CAH) who score similarly to males on the AQ-child (total, imagination and social skills scales; Knickmeyer, Baron-Cohen, Fane et al., 2006). It is important to note that they did not score higher than normal males, and that males with CAH did not have significantly different scores to normal males.

It is a component part of both theories that autistic vulnerability is not confined to the small proportion of the population that expresses clinically significant autistic traits (a figure amounting to 1% or more). Rather, it is a general feature of sex differences that can be found in the population at large. One crucial distinction between the theories is that, in Skuse’s conceptualisation, the sex difference is attributable to female compensatory mechanisms in the domains of social perception and language, relating to their possession of two X-chromosomes. In Baron-Cohen’s work, the difference is primarily a male vulnerability associated with a cognitive predisposition to be higher on a dimension he refers to as ‘systemizing’ (Baron-Cohen, 2002). His ideas have recently been expanded into the ‘EMB theory’ discussed in the paper under review, as he now takes the view that not only does testosterone predispose to a male tendency to systemize but it also reduces the capacity to empathize (Knickmeyer, Baron-Cohen, Raggatt, Taylor, & Hackett, 2006).

Baron-Cohen’s theory proposes that the level of fetal testosterone (which may itself be influenced by unspecified genetic mechanisms) has an impact that is negative upon males’ social interest during early development (including reduced eye-contact and attention to faces) and upon language development (in terms of vocabulary). On the other hand, it enhances attention to detail, and promotes intense but narrow interests. The key evidence supporting the theory is that there is a negative correlation between amniotic fluid measures thought to reflect fetal testosterone, and his measure of ‘empathising’, and a positive correlation with measures of what he defines as ‘systematizing’. It is not clear whether the theory predicts fT is sufficient to cause autism, or how it interacts with other markers of genetic vulnerability (for example, a family history of autistic traits).

In the paper under review, the results are presented from a longitudinal study of children born during a period some years ago in Cambridge, UK, whose mothers had ‘fetal testosterone’ measured in utero. The amniocentesis usually occurred in the second trimester. Data are from a subset of 235 mothers who completed one or other of two...
autism-screening questionnaires (25% of the total sample contributed to the study). Concern about the psychometric properties of one of the autism screening instruments (CAST) has been expressed by Mandy and Skuse (2008), and it is not possible fully to evaluate the the psychometric properties of the other instrument (AQ-Child) because it is as yet unpublished (Au yeung, Baron-Cohen, Wheelwright, & Allison, 2008). It is unclear how many of the children in the survey sample were ever seen personally by the research team in order to validate the questionnaire data; less than a third were brought for cognitive assessment. We must bear in mind the information on which these analyses are constructed are entirely based upon the children’s behaviour filtered through their mothers’ perceptions. This filtering is of particular importance when any measurements of culturally influenced gender-appropriate social traits are made, whether by parental report or by self-report (as in the adult Autism Questionnaire: (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001).

The initial set of analyses chosen for presentation concern the newly developed instrument, the AQ-child. A regression is presented that showed there was a significant impact upon the AQ-child score of having an older sibling, suggesting there may have been some contrast effect (parents tending to rate the behaviour of children with autistic traits as more abnormal if they had already had a ‘normal’ child). Fetal testosterone levels apparently predicted AQ-child scores independent of the child’s sex (the interaction term was specifically excluded as a predictor). The data in Figure 2 imply the relationship between AQ score and sex is largely driven by males with fetal testosterone levels above 0.8 nmol/L. When the subscales of the AQ-child are considered, males in general score higher than females (i.e. in the direction of being more ‘autistic’) and there is a positive correlation between fT levels and subscale scores as shown on Table 5. As Figure 2 shows clearly that a substantial proportion of males are associated with much higher fT levels than any female, the data on Table 5 are to be expected. Recall that the AQ scales were constructed in such a way that males would generally obtain higher scores than females. Data on the correlations in Table 5 broken down by sex would be more interesting; if fT were to predict more ‘autistic’ behaviours irrespective of sex then we ought to see a positive correlation for females alone.

A separate analysis was performed for the CAST. Mean scores for girls and boys are only marginally different from one another, in a general population sample. There was a weak relationship between fT levels and scores on this instrument in boys, but no correlation was found between fT levels and CAST scores for girls alone.

Finally, the study examined the relationship between components of IQ and fetal testosterone levels, but found no significant correlations. There is considerable debate, and no consensus, about whether androgenisation of the brain could be responsible for male superiority in certain visuospatial skills (Malouf, Migeon, Carson, Petrucci, & Wisniewski, 2006; Mueller et al., 2008).

The key questions for the interpretation of the research presented here concern: (i) the nature of the phenotype being measured; (ii) its relationship to autism; (iii) the relevance of fetal testosterone measures to risk. First, what is the nature of the phenotype being measured by the AQ-child and the CAST? We know that males tend to score more ‘abnormally’ than females on the subscales of the AQ-child. Presumably, the scale was developed with this objective in mind. The standard deviations of subscales are similar in boys and girls, which suggests the sex difference in mean scores is not driven by a few extreme cases. Very high scores on the instrument indicate risk of autism and, because of the way the scale has been constructed, males will tend to be overrepresented among those with very high scores. The CAST has been developed in...
much the same way, but it is not so discriminating between males and females (compare the gender-specific distributions in Figures 1 and 3).

Second, is the phenotype being measured relevant to autism? Examining the distributions of the AQ-child, we find approximately 9% of boys and 1% of girls score over the cut-off for ‘significant autistic traits’ - the equivalent figure for the CAST is about 5% of boys and 1% of girls. We don’t know if any of these children had an autistic disorder, but the contrasting proportions of high scorers do reflect current views on the probable difference in autism prevalence among children with normal-range IQ. These data raise fundamental questions about the nature of autistic spectrum disorders, in particular about whether they should be regarded as ‘the extreme of male behaviour’ or as a collection of complex neurodevelopmental conditions that is more likely to manifest as a recognizable phenotype among males than females.

Third, comes the issue of attributable risk. Let us assume that Baron-Cohen’s data on fetal testosterone (whatever that is measuring) are correct; in general the levels measured in amniotic fluid among women pregnant with males will be higher than for women pregnant with females. My main concern with the thesis presented here is in the degree of circularity in the argument that ‘male sex hormones and, in particular, prenatal exposure to testosterone (are) related to the development of autistic traits’ because of: (i) the lack of specificity of the argument; (ii) the lack of predictive validity independent of the truism that testosterone renders the fetus more masculine and males are more likely to have autistic characteristics as conventionally specified. Data indicating that there is an impact on ‘autistic traits’ in females are, in my interpretation, ambiguous at best.

Finally, there is a conceptual point relevant to the definition of autism as a coherent syndrome. As conventionally measured, autistic traits are more common in boys than girls; Baron-Cohen and his colleagues have attributed this to the fact that the male brain is more ‘systematizing’ and the female brain is more ‘empathizing’ (Baron-Cohen et al., 2005). They conceptualize autistic features as dimensional in quality, but as presented in this article vulnerability appears to be unidimensional. We do not learn from the discussion in this paper how this unidimensional model of risk is reconciled with the multidimensional construct of autistic traits presented by Ronald et al. (2006) – which used the CAST as a measure of the phenotype. Is exposure to fetal testosterone associated with increased risk in terms of social reciprocity, and language-communication skills and stereotyped behaviours and restricted interests? These are supposedly under separable genetic influences according to Ronald, Happe et al. (2006), and the implication of the finding is that we should ‘give up’ on the concept of autism as a unitary construct (Happe, Ronald, & Plomin, 2006; Skuse, 2007). Discovering what mechanisms are responsible for the apparent association between fetal testosterone and autistic traits could be facilitated by a more critical evaluation of the autistic phenotype.

References


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