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Letter to Editor

The sex ratio of the sibs of probands diagnosed with autism

HIGHLIGHTS

- It has been proposed that a. Testosterone causes autism, and b. The mother is its source.
- So I suggested that probands' sib sex ratio would test these two hypotheses jointly.
- Data on this test are indecisive.
- Ex post facto evidence suggests that there is a weakness in the test.
- It is concluded that this evidence leaves both hypotheses unimpaired.

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1. Introduction

It is established that the causes of autism are both environmental and genetic. This paper focuses on one suspected environmental cause, viz. intrauterine exposure to high levels of testosterone (T).

Baron-Cohen (2002) proposed this hypothesis. And in confirmation of it, he and his colleagues reported elevated steroidogenic (including T) activity in the amniotic fluid of individuals who were later diagnosed with autism (Baron-Cohen et al., 2015). The source of this hypothesized additional T has been the subject of discussion. Autism is more frequently diagnosed in males; moreover male fetuses excrete more T than females, and lastly there is a robust sex difference in amniotic T fluid levels (Van de Beek et al., 2004). So it was suggested that the fetus is a source of the additional T (e.g. Baron-Cohen et al., 2011, 2015).

I have adduced evidence to suggest that the sexes of zygotes at the time of their formation are partially controlled by the hormone levels of both parents around the time of conception (James, 1996, 2004, 2008a, 2010). Ex hypothesi, high levels of T (in either parent) and of estrogen (in women) are associated with subsequent male births. The credibility of the hypothesis has recently been boosted by the demonstration (James, 2013) that the sex hormones (testosterone in men and estrogen in women) fulfill the two criteria of 'condition' proposed in the influential evolutionary hypothesis of Trivers and Willard (1973) viz. these hormones are a. heritable and b. positively associated with fertility. Furthermore, my hypothesis has been described as the 'most coherent' available explanation of the variation of human sex ratio at birth (Spiegelhalter, 2015, p. 295).

Since it is not established why autism is diagnosed more frequently in males, I suggested, in accordance with my hypothesis and with Baron-Cohen's, that the mother's high T levels partially cause both the sex and the pathology. In other words, I proposed that the mother is another source of the additional intrauterine T hypothesized to cause autism. There is strong external evidence for this in the sense that many of the risk factors for autism are stressors which are causes (or markers) of high levels of maternal adrenal androgens (including T). For instance, it is known that high levels of maternal adrenal androgens are caused by exposure to chronic physical or psychological stress e.g. illness, surgery, anxiety, depression and fear (Kemper, 1990; Powell et al., 2002; Goldberg, 1995; Baischer et al., 1995; Roos et al., 2011). The stressors reportedly associated with autism include chronic pathological conditions such as obesity (Gardner et al., 2015) and diabetes (Xu et al., 2014) which are both known to be associated with high levels of T. Other maternal risk factors for infant autism include autoimmune diseases (Chen et al., 2016), and atopic dermatitis (also known to be associated with high T and male offspring) (Billeci et al., 2015). Moreover, maternal psychological stressors which are reportedly associated with infant autism include bereavement (Class et al., 2014), severe mental illness (McCoy et al., 2014), exposure to hurricanes (Kinney et al., 2008) and the Quebec Ice Storm of 1998 (Walder et al., 2014), deprivation (Campbell et al., 2013) and intimate partner abuse (Roberts et al., 2016).

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The present note concerns an inference that may be drawn given the joint truth of the two hypotheses viz Baron-Cohen's that one cause of autism is exposure to high intrauterine T levels, and mine that the mother is a source of that T. This is that autistic probands should have an excess of brothers among their unaffected sibs, as I proposed (James, 2008b). This prediction has had a checkered history, which will now be briefly summarized. The purpose of the present note is twofold viz.

1. To cite a number of studies that support the prediction (at conventional levels of statistical significance) and a number of larger studies that fail to support it, and
2. To suggest reasons why the prediction failed (at least in some cases).

1.1. The supporting evidence for the prediction

Statistically significant evidence for the inference (that autistic probands have an excess of brothers) was presented in James (2008b), Mouridsen et al. (2010) and Mouridsen and Hauschild (2010).

1.2. The countervailing evidence against the prediction

However, subsequent large studies failed to support this prediction (Parner et al., 2012; Mouridsen et al., 2014; Cheslack-Postava et al., 2015). The data of the first two of these papers apparently overlap, and were extracted from the Danish nationwide registry system. They were based on 1.3 million births, including 10,297 autistic probands and 17,380 sibs. Their failure to find a significantly biased sex ratio among the sibs of probands was repeated in the findings of Cheslack-Postava et al. (2015) on the sex ratio of the sibs of cases diagnosed with autism spectrum syndrome among 1.1 million births in California.

The discrepant results cited above dictate caution in interpretation. Accordingly, I shall consider new external evidence that casts doubt on the grounds for making the prediction in the first place.

2. Re-appraisal of the grounds for predicting a bias in the sex ratio of unaffected sibs of probands with autism

As noted above, the ground for the prediction was the assumption that both of two hypotheses are correct viz.

1. Baron-Cohen's hypothesis that one cause of autism is intrauterine exposure to high levels of T, and
2. My hypothesis that high maternal levels of T around the time of conception are causally associated with the subsequent births of sons.

I suggested that my hypothesis would explain the male excess in autism, and I predicted further that the unaffected sibs of probands with autism should contain an excess of brothers (James, 2008b). I am grateful to a reviewer for pointing out that to the extent that the fetus itself contributes to the testosterone that causes the autism (as proposed by Baron-Cohen in papers cited above) my prediction will be weakened. Moreover, at the time that my prediction was made, I was not aware of several circumstances which will now be outlined.

2.1. The sources of the maternal testosterone hypothesized to be causally associated with autism and with sex determination

The major source of T in healthy women is the ovaries. In contrast, the major source of T in stressed women is the adrenals (Kemper, 1990; James, 2014). All the types of relevant stress are severe, and some have been specified above. (It may be admitted that the levels of stress required to shift the source of T from ovaries to adrenals would presumably vary from woman to woman). However, as suggested above, there are strong grounds for supposing that the major source of the maternal T hypothesized to cause autism is the adrenals. The justification for this claim is that most (if not all) of the major epidemiological environmental risk factors for autism may be classified as stressors severe enough to cause increases in maternal adrenal androgens. (The term 'stress' is used here in the broad endocrinological sense viz. of causing severe physical and/or mental distress).

In contrast, the source of the maternal T hypothesized to influence offspring sex at conception is presumably the ovaries. This is so because, at the time of initiating a live-birth conception, most women may be assumed to be healthy and unstressed. There are evolutionary grounds for this assumption. Most products of human conception die early in pregnancy (Boklage, 1990). And it has been plausibly proposed that these deaths serve an evolutionary (adaptive) function (Catalano et al., 2014). These latter authors suggest that: "natural selection conserved well-regulated, though non-conscious decisional biology that protects the reproductive fitness of women by spontaneously aborting gestations that would otherwise yield frail infants, particularly small males". This claim is supported by evidence that males born in cohorts with low sex ratios outreproduce males born in cohorts with high sex ratios (Bruckner et al., 2015a). In short, there are grounds for supposing that the high overall rate of human fetal loss facilitates a selection process such that mothers of live-birth conceptions are healthy at that time. Thus one would infer that the main source of the maternal T that partially controls the sex of live births is the ovaries. So if the sources of maternal T do usually differ vis-à-vis autism and sex determination, then my prediction depends on there being a positive correlation between these two sources of maternal T at two different specifiable times viz.

1. Adrenal androgens at the time that the proband's autism is initiated (here presumed to be some time during pregnancy) and
2. Ovarian androgens at the time of formation of the zygote of the sib.

I know little evidence on the correlation between levels of maternal adrenal and ovarian androgens. It may be positive (Rodriguez-Gutierrez et al., 2014), but I know no grounds to infer its magnitude. I had misguidedly relied on the evidence of Apter and Vihko (1990) who reported a substantial positive correlation between the levels of serum androgens (including testosterone) within young women across a time period of 12 years. However, their sample was of healthy, unstressed women.

3. The deleterious effects of maternal adrenal androgens on pregnancy

Over recent years, evidence has accumulated that high maternal androgen levels also have a deleterious effect on ongoing pregnancies (James, 2015). In that paper I cited evidence that

1. High pregnancy androgens in women are associated with suboptimal reproduction viz. fetal growth restriction, spontaneous abortion, short gestation, stillbirth and infant death.