An update on the hypothesis that one cause of autism is high intrauterine levels of testosterone of maternal origin

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ABSTRACT

Baron-Cohen’s hypothesis that autism is caused by exposure to high intrauterine testosterone levels is considered in the context of (1) my hormonal hypothesis of sex ratio and (2) the notion of multifactorial inheritance. This yields the suggestions that (1) female cases of autism may be the product of (high genetic loading + moderate environmental exposure) and male cases of (high environmental exposure + moderate genetic loading), (2) one environmental agent is intrauterine testosterone and (3) the mother is the major source of that testosterone. These suggestions may help to explain most of the major established epidemiological risk factors for autism. These include various forms of pathology associated with psychological and/or physical stress. Stress of many sorts promotes the secretion of adrenal androgens in women. The three suggestions above may also explain some recently described features of autism including the psychological, behavioural and neuroanatomical differences between male and female cases.

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1. Introduction

Baron-Cohen (2002) proposed that one cause of autism is in utero exposure to high levels of testosterone (T). This hypothesis was first tested indirectly by measuring finger-length ratios, (2D:4D) (Manning et al., 2001). This study will be treated at some length here because I think it may have given rise to misunderstandings. In conformity with those authors’ prediction, these ratios were reported to be significantly more masculinized in children with autism than in controls. However, though it will be accepted here that high intrauterine T levels are a major cause of autism, it is not clear (as will now be shown) to what degree these data of Manning et al. (2001) confirm that hypothesis. These data have been interpreted to confirm the two propositions that high foetal testosterone levels are the cause of both a. autism and b. low postnatal 2D:4D ratios. In contrast, it will be later suggested here that

(a) high levels of maternally derived testosterone are also a cause of autism and
(b) postnatal testosterone levels may also influence 2D:4D ratios and, perhaps, autistic symptoms.

The evidence that autism is associated with masculinized 2D:4D values has recently been reviewed and judged to be moderately well supported (Breedlove, 2010; Teatro and Netley, 2013). Moreover there are good grounds to suppose that 2D:4D is under hormonal control at the foetal stage (Honekopp et al., 2007). Indeed, Lutchmaya et al. (2004) assessed the foetal testosterone/ oestrogen ratio at amniocentesis; and reported significant negative correlations between that ratio and 2D:4D in both sexes. However, the proposition that masculinized childhood or adult 2D:4D ratios are primarily caused by high intrauterine T seems less well established (Berenbaum et al., 2009; Dressler and Voracek, 2011). The trouble is that postnatal 2D:4D has come to be regarded (by some) as a reliable guide to foetal testosterone levels. Yet as Cheema and Sharif (2011) wrote: “Digits continue to grow as the skeleton matures [presumably under the continuing partial control of testosterone and oestrogen]. In the absence of evidence that 2D:4D is preserved from neonates to adults, it is not possible to conclude that adult [finger length] proportions reflect prenatal hormone levels”. Furthermore (and consistent with this argument) there have been a number of reports that in large samples, 2D:4D correlates (weakly but significantly) negatively with adult male T levels (Auger and Eustache, 2011; Garcia-Cruz et al., 2012; Manning et al., 1998; Muller et al., 2011). These data are consistent with the possibility that 2D:4D is under the control, not only of prenatal T, but of postnatal T levels (as may also be suggested by the data of Voracek et al., 2010 on the feminized 2D:4D ratios of male firefighters).

So though the evidence from the above line of enquiry is consistent with the suggestion that autism is associated with (and indeed partially caused by) high levels of intrauterine T, that evidence does not exclude the possibility that high postnatal T
plays roles too (e.g. in activating autistic behaviour and masculinizing 2D:4D ratios). The evidence so far considered is not decisive either on the origin of the prenatal T (mother or foetus). It is known that male foetuses excrete higher quantities of T than female foetuses. So (to account for the otherwise unexplained high sex ratio of cases) there has been a consensus that the foetus was probably the source of the T (e.g. Manning et al., 2001). The basis for this consensus will now be questioned.

Gardener et al. (2009, 2011) published comprehensive meta-analyses of prenatal, perinatal and neonatal risk factors for autism. I have offered further evidence (James, 2008a) for the hypothesis of Baron-Cohen. But (in contrast with the consensus above) I suggested that most of the prenatal risk factors identified by Gardener et al. (2009) may be markers for, or causes of, high maternal (rather than foetal) T levels (James, 2012). There has also been some prenatal and postnatal confirmation that the mother is one source of the intrauterine T. Palomba et al. (2012) reported that children of women with polycystic ovary syndrome (a hyperandrogenized condition) have children with significantly higher Autism Quotient scores than controls: moreover, Xu et al. (2013) reported that in contrast with mothers of control children, mothers of autistic children had significantly higher T levels.

In the present paper, I shall offer an update on the indirect evidence previously adduced in James (2008a, 2012) for the hypothesis that a major causal factor of autism is high intrauterine T of maternal origin. Let us call this the ‘Target Hypothesis’. The evidence will be divided into three categories viz.

1. The evidence from sex ratios (proportions male at birth),
2. Other evidence based on interpretation of the established risk factors, and
3. Evidence relating to the recently recognised differences between male and female probands.

1.1. The evidence from sex ratios

Evidence here is of three sorts viz

(a) that based on the inference that autism is subject to multifactorial threshold inheritance,
(b) that relating to the sex ratio of the unaffected sibs of autistic probands, and
(c) that relating to the variation of sex ratio of cases with (i) paternal age, (ii) incidence and time trend, and (iii) IQ.

All these types of evidence depend on my hormonal hypothesis of sex ratio, so that will now be described.

The hormonal hypothesis of sex ratio at birth.

I have suggested that the sexes of zygotes at the time of their formation (and thus of subsequent births) are partially controlled by the hormone levels of both parents around the time of conception (James, 1986, 1996, 2004, 2008b, 2010). Ex hypothesi, high testosterone levels (in either parent) are associated with the subsequent births of boys, and low levels with girls. The credibility of the hypothesis has recently been boosted by the demonstration James (2013) that levels of sex hormones (testosterone in men and oestrogen in women) fulfill the criteria of ‘condition’ proposed in the influential hypothesis of Trivers and Willard (1973). My hypothesis seems to explain the successes (and occasional failures) of theirs.

1.1.1. Autism and multifactorial threshold inheritance

Autism is diagnosed more commonly in males, but there is reportedly a higher proportion of secondary cases in the biological relatives of female than male probands (Wolpert et al., 2004; Sumi et al., 2006; Robinson et al., 2013). This finding suggests a multifactorial threshold (MFT) model of inheritance. It is important to note that since MFT is a model, it is arbitrary what features are initially assigned to it. However, any innovative features so assigned should be tested before the model is accepted as the basis for any subsequent explanation. The model to be used here will now be described.

The genetic contribution to autism is via some rare genes having large effects, and a large number of common variants exerting weak effects (Anney et al., 2012). These latter are largely sex-specific (Schwarz et al., 2011). The functions of these genes are mostly unknown: however, it seems likely that some of them partially control androgen levels and sensitivity. This might account for their sex-specificity because androgen functioning is controlled by different systems in the two sexes (Sarachana and Hu, 2013; for further references, see James, 2013). According to the MFT model proposed here, there is notionally an ‘additive’ effect of many weak genes to one or more environmental agents: when these are ‘summed’ and a threshold reached, cases occur.

As noted above, it has several times been reported that female probands have a higher proportion of affected relatives than male probands. One may draw one of two inferences from this observation viz

1. female probands have a higher genetic load than male probands or
2. female probands have had higher exposure to all (environmental + genetic) causes than male probands.

This second possibility is usually ignored, and since I can envisage no circumstances under which it might hold, I shall provisionally disregard it. (This is not logical legerdemain because, as mentioned above, the chosen model will have to be tested anyway before accepting any explanations derived from it). However, one may conclude from the first inference that female probands (as contrasted with male probands) require a lower environmental exposure (to reach the threshold). In short, it is proposed here that male cases are the consequence of (high gene loading + moderate environmental exposure) and male cases the consequence of (moderate gene loading + high environmental exposure). The question arises: to what prenatal environmental agent can males be more highly exposed than females? In conformity with my hypothesis, I suggest testosterone: for such variation ex hypothesi is partially a cause of their being males and females in the first place. Moreover, I can think of no other agent (except some other sex hormone profile) that might satisfy this criterion.

1.1.2. A prediction on the sex ratio of unaffected sibs of autistic probands

If Baron-Cohen’s and my hormonal hypothesis were both correct, the high sex ratio (proportion male) of autistic probands would be explained: ex hypothesi, high intrauterine T causes both the sex bias of probands and their pathology. (The point is important because otherwise the excess of males among autistic probands would still constitute a problem [see e.g. Baron-Cohen et al., 2011]). Moreover, since women’s T levels (vis-à-vis those of other women) are reportedly fairly stable throughout the reproductive life (Apter and Vihko, 1990), a further inference may be derived from jointly positing both hypotheses. It is that there would be an excess of brothers among the unaffected sibs of probands. There have been three significant reports of such a phenomenon (James, 2008b; Mouridsen et al., 2010; Mouridsen and Hauschild, 2010), and two failures to confirm in large samples (Parner et al., 2012; Mouridsen et al., in press). So the evidence from this line of enquiry is equivocal in regard to the Target
Hypothesis. One may offer an estimate of the probability that three (or more) out of five tests on independent data achieved significance at the 0.05 level by chance (about 0.0025). But interpretation of such a value is problematic. So it may be more profitable instead to speculate on the reasons for the inconsistency between the results of the above five studies. Here I offer a possible reason.

It is noted above that the prediction (that the sex ratio of unaffected sibs of probands is high) would be expected to hold if three conditions were met viz that both hypotheses were correct, and that women’s T levels (vis-à-vis those of other women) remain roughly stable through the reproductive life as observed by Apter and Vihko (1990). However, there may be grounds for questioning this latter conclusion where autism is a pregnancy outcome. This is so because, as will be noted, the established risk factors for autism may mostly be interpreted as causes of (or markers for) high levels of maternal androgens of adrenal origin (James, 2012). These are caused by exposure to psychological and physical stress e.g. illness, anxiety, depression and fear (Kemper, 1990; Powell et al., 2002; Goldberg, 1995; Baischer et al., 1995; Roos et al., 2011).

As such, they may mark unusual or temporary circumstances that are not often experienced by healthy women such as may be presumed to have been sampled by Apter and Vihko (1990). In short I suggest that the maternal hormonal antecedents of autism are usually associated with relatively unusual physical or psychological pathology, rather than with normal health. Women in good mental and physical health may have relatively stable T values with a wide range – but autism, I suggest, is not frequently associated with these women – even those with high T levels within the normal range. (Only about 1 woman in 100 bears an autistic child.) If this interpretation were correct, the high adrenal androgens expected higher environmental component (testosterone) and hence lower risk (Gronborg et al., 2013). So the secular increase in incidence of maternal obesity and diabetes are both associated with high testosterone levels in women (for reference, see James, 2012). If the so-called ‘epidemic’ of autism were partially caused by increases in environmental factors, and if one of these were testosterone (which is associated with the production of males), then (given that the increase was largely caused by environmental factors), there should have been a secular increase in the sex ratio of cases. Keyes et al. (2012) found that the reported increase in autism 1992–2003 in California exhibited a robust and linear positive cohort effect that was stronger among high-functioning cases. And as noted in the next section, the sex ratio of high-functioning cases (e.g. those diagnosed with Asperger’s syndrome) is higher (of the order of 4–8 males per female) as contrasted with 2–4 in respect of low-functioning cases. So the Target Hypothesis is also indirectly supported by the data of Keyes et al. (2012).

1.1.3. Evidence from risk factors

1.1.3.1. Paternal age. Anello et al. (2009) reported that the sex ratio (proportion male) of autistic probands decreases with paternal age but not maternal age. They inferred (correctly, it will be assumed here) an increasing paternal genetic contribution with age. It is true that in the general population of births, high paternal age is (very weakly) associated with a diminution of offspring sex ratio (proportion male) (James, 1987). However, the magnitude of the reported variation of sex ratio of autistic probands with paternal age is far greater than occurs in the general population. So I suggest that the explanation lies in the threshold described above. I suggest (in conformity with the threshold) that when the genetic contribution to autism increases (as is proposed in elderly fathers), the environmental contribution (of testosterone) is less, with the effect, ex hypothesi, that the sex ratio of cases is less. Thus, these data support the Target Hypothesis.

1.1.3.2. Incidence and time trend. In recent decades there have been many reports of a secular increase in rates of autism. It seems unlikely that this has been entirely due to increased recognition or to changes in definition (Rutter, 2009). Moreover it has been reported that there has been no secular increase in recurrence risk (Gronborg et al., 2013). So the secular increase in incidence seems unlikely to have arisen primarily through genetic changes (especially as the reported increase has been relatively rapid). Accordingly, following Howard (2006), I suggest that the secular increase is due mainly to environmental factors. I strongly suggest that these include the widespread epidemics of maternal obesity and diabetes, both of which have tripled in the U.S. in the last three decades (Hill et al., 2013). These authors estimated that worldwide, 2 billion people are overweight or obese, and that in 2011, about 366 million people had diabetes. The point is that obesity and diabetes are both associated with high testosterone levels in women (for reference, see James, 2012). If the so-called ‘epidemic’ of autism were partially caused by increases in environmental factors, and if one of these were testosterone (which is associated with the production of males), then (given that the increase was largely caused by environmental factors), there should have been a secular increase in the sex ratio of cases.

1.2. Evidence from risk factors

Here the prenatal risk factors will be treated separately from the perinatal and neonatal risk factors.

1.2.1. Prenatal risk factors for autism

Gardener et al. (2009) identified three prenatal risk factors which (as documented in James, 2012) are unquestionably associated with high maternal testosterone levels viz gestational diabetes, obstetric suboptimality and primiparity. These give strong evidence that one associated factor (possibly causal) of autism is high maternal T. They will not be further mentioned here. Four other risk factors will be considered here, two of which were identified by Gardener et al. (2009) as reliable risk factors for autism (high parental age and migration), and two which were not (smoking during pregnancy, and short interpregnancy interval).

1.2.1.1. Advanced parental age. In James (2012) I speculated that advanced parental age might be associated with high intrauterine T via maternal stress. However, though that speculation may partially account for the association, it now seems (as suggested above) that advanced parental age might simply be associated with autism via the increased probability of de novo genetic or genomic anomalies arising more frequently as men age and then sire children. This latter interpretation is supported by the finding that the sex ratio of cases decreases with increasing paternal age (Anello, 2009). [As described above, the higher suspected genetic component being associated – because of the threshold – with a lower environmental component (testosterone) and hence lower sex ratio.]

1.2.1.2. Migration. Gardener et al. (2009) identified maternal migration as a reliable risk factor for infant autism, and I suggested that the relationship might be mediated by high levels of maternal adrenal androgens occasioned by stressful condition in countries of
origin, and by the stress of attempting to cope with a new and different society (James, 2012). My explanation may be correct where those stresses occur, but now requires qualification. In an earlier study, Fombonne (1999) had questioned whether migration is reliably related to autism. And it has subsequently become clear that (contrary to the suggestion of Gardner et al. (2009), the offspring of immigrant mothers are not always at higher risk of autism than the offspring of their new country. A recent Dutch study reports that children born to migrants from developing countries were at significantly lower risk than those of Dutch-born parents (van der Ven et al. 2013). Similarly, Haglund and Kallen (2011) reported that children of immigrant mothers were at significantly lower risk of Asperger's syndrome than native-born Swedish children. Lastly, Schieve et al. (2012) reported that in the U.S., Hispanic children with two U.S.-born parents had a significantly higher risk of ASD than Hispanic children with two foreign-born parents. So it would seem wise to defer explanations of the relationship between autism and migration until more order is discerned in the relationship between them. It may be acknowledged that migrants experience varying degrees of anxiety: I suggest that only highly stressed migrant women are at risk of producing autistic children.

1.2.1.3. Maternal smoking during pregnancy. In recent years, it has been repeatedly reported that maternal smoking during pregnancy is associated with autism and related disorders, especially ADHD. As far as I know, this has not been studied in a systematic meta-analysis. So the point will now be documented more thoroughly than would otherwise seem necessary (Ellis, 2012; Hultman et al., 2002; Indredavik et al., 2007; Kalkbrenner et al., 2012; Langley et al., 2007, 2012; Larsson et al., 2009; Linnet et al., 2003, 2005; Mozrek-Budzyń et al., 2013; D’Onofrio et al., 2008; St. Pourcain et al., 2011; Tran et al., 2013; Visser et al., 2013—but see Lee et al., 2012). The relevant point here is that high androgen levels have been reported in women who smoke (Kaergaard et al., 2000; Polkki and Rantala, 2009; Sowers et al., 2001) and this has specifically been reported in pregnant women (Toriola et al., 2011). I suggest that the association between maternal smoking during pregnancy and offspring autism is mediated by high levels of maternal testosterone. The evidence is very strong and would explain the particularly high sex ratio in ADHD, thus, giving further support to the Target Hypothesis. However, more research is required to establish whether the additional maternal androgens associated with maternal smoking otherwise affect foetuses of the two sexes equally (Fowler, 2011).

1.2.1.4. Interpregnancy interval. Following earlier suspicion that short interpregnancy intervals were associated with autism (Grether, 2006), two very large studies have reported that when the interpregnancy interval is less than 1 year, the second sib is substantially and significantly more likely to suffer autism (Cheslack-Postava et al., 2011; Gunnes et al., 2013). In the data of Cheslack-Postava et al. (2011) the association was not mediated by high levels of maternal testosterone. The evidence is strongly shown to cause foetal growth retardation in the sheep (a common model for human pregnancy) (Manikamm et al., 2004; Steckler et al., 2005). If the current argument were substantially correct, then many of the above postnatal risk factors for autism would be interpretable as markers for, rather than causes of, high intrauterine T and thus, as markers for, rather than causes of, autism. These data also are consistent with (indeed would be predicted on the basis of) the Target Hypothesis.

1.3. Evidence from differences between male and female cases of autism

In recent years, it has become clear that there are differences between males and females diagnosed as autistic. Such differences have been reported in regard to behaviour (Werling and Geschwind, 2013); neuroanatomy (Lai et al., 2013) and physical habitus and gender coherence (Bejerot et al., 2012). What can be the causes of these differences?

Baron-Cohen et al. (2005) suggested that specific aspects of autistic neuroanatomy may be extremes of typical male neuroanatomy. More recently it has become clear that androgen levels of male humans are associated with brain neuroanatomy (Bryant et al., 2011; Chao et al., 2013) and brain activity (Mascaro et al., 2013; Kuo et al., 2012). Such androgenic effects have been reversed by estradiol administration to reeler mice (a putative model of neuroanatomical and behavioural endophenotypes in autism spectrum disorders, Macri et al., 2010). So there are good grounds to suppose that androgens and neuroanatomy are causally associated with autism. However, it is not clear why there should be these sex differences between male and female cases.

Grounds have been given above to suggest that male cases of autism have been exposed to higher levels of intrauterine T than female cases. So they may potentially explain some of these observed differences. However, there is a further difference between the sexes. It is that pathologically high intrauterine T may be associated with low postnatal T in male (Recabarren et al., 2008, 2013) but apparently not female, offspring (Padmanabhan et al., 2006). These conclusions were based on observations following experimental injection of T into pregnant sheep (as noted above, a common model for human pregnancy). I shall try to indicate how these studies may be relevant here.

1. They may explain the report of Bejerot et al. (2012) that autism correlates with androgynous facial features in both sexes. The assumption here is that postnatal T levels and/or sensitivity to T are partially responsible for the degree of masculinity of facial features and body habitus in both sexes. There is evidence that men with low fluctuating asymmetry (viz who inter alia have symmetrical faces), as contrasted with other men, are perceived by women as more handsome, socially dominant, muscular, vigorous and attractive (Thornhill and Gangestad,

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1. The evidence is overwhelming for Baron-Cohen’s hypothesis that one cause of autism is exposure to high levels of intrauterine testosterone.

2. There is strong evidence for my hypothesis that the mother is a major source of that intrauterine testosterone.

3. The suggestion that male cases, on the average, have been exposed to higher levels of intrauterine T than female cases seems attractive. But it nevertheless crucially depends on the properties assigned above to the model of ‘multifactorial threshold old inheritance’ (from which it was derived). That model needs to be tested. Does the threshold exist? If there are genetic and environmental causes, do female cases have higher genetic loading than male cases? And have male cases been exposed to higher doses of environmental causes? It is shown above that such a model is remarkably successful at explaining sex ratios of cases – but even successful models still needs testing.

4. The question of the sex ratios of unaffected sibs of autistic probands also needs further investigation. We need to know if these sex ratios are high, and if so, whether such bias occurs in the unaffected sibs of all the various diagnostic categories. If the high sex ratios only occur in the sibs of some categories of autistic proband, that may provide a guide to causes that differentiate the disorders.

5. It remains to be seen whether the studies of Recabarren et al. (2008, 2013) and Padmanabhan et al. (2006) throw any light on the reported masculinization of female, but not male, autistic brains. More needs to be known about the organizational and activational functions of testosterone in regard to autism, and on the direct effects of testosterone on brain anatomy. It is hoped that the present study may prompt such research.

4. Further research

There is a proliferation of male-biased neurodevelopmental diagnoses e.g. Asperger’s syndrome, attention deficit hyperactivity disorder, autism, autism spectrum disorder, developmental reading disorder, dyslexia, oppositional defiant disorder, and Tourette’s syndrome. Subject to the constraints of initial factual observations, it is arbitrary how each of these is defined. But in the past, estimates of their co-morbidities have emphasised the separateness as well as the similarities of these conditions. I suggest here that the similarities of these conditions indicate that they may share common causes, one of which is exposure to testosterone (perhaps at different times and in different doses). It would seem that establishing any common cause is a logical precursor to establishing other causes. And if that were so, then there may be a need for a term to denote this whole class of male-biased neurodevelopmental disorders. I suggest the (admittedly clumsy) acronym MBNDD’s. The Target Hypothesis needs to be separately tested on each of the MBNDD’s. One way of doing so would be to examine the sex ratios of unaffected sibs of probands with each of the MBNDD’s. It may be suspected from material cited above that these sex ratios are high only in respect of some diagnoses. That may prove useful in elucidating the aetiology of these conditions.

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