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The Extreme Male Brain Theory of Autism: The Role of Fetal Androgens

Points of Interest

- There are sex differences in neuroanatomy, neural function, cognition, and behavior in the general population.
- People with ASD show an extreme of the typical male profile in terms of empathy and systemizing.
- Whether such hyper-masculinization is evident at the level of neuroanatomy and neural function in ASD remains to be tested.
- Fetal testosterone (fT) is known from animal research to play an organizing role in brain development.
- fT associated with individual differences in eye contact, vocabulary development, empathy, systemizing, attention to detail, and autistic traits in typically developing children.
- It remains to be tested whether fT is elevated in children who go on to develop an ASD.

Autism and Asperger Syndrome (AS) are autism spectrum disorders (ASDs). The diagnosis rests on the presence of difficulties in reciprocal social interaction and communication, along with strongly repetitive behavior and unusually narrow interests (A.P.A., 1994). The prevalence of ASD is currently estimated to be 1% (Scott et al., 2002). Autism spectrum disorder is biased toward males (Fombonne, 2005) with a 4:1 (male:female) ratio for classic autism (Chakrabarti & Fombonne, 2001) and 8:1 for AS (Scott et al., 2002). Classic autism and AS differ in terms of the presence of additional learning difficulties and language delay (in classic autism only). Autism spectrum disorders are neurobiological and genetic (Stodgell et al., 2001), but the specific factors responsible for the higher male incidence in ASDs remain unclear. One possible factor is that ASDs may be an extreme of the male brain (Baron-Cohen, 2002).

The Extreme Male Brain: Psychology

The extreme male brain (EMB) theory of autism is an extension of the empathizing-systemizing (E-S) theory of typical sex differences (Baron-Cohen, 2003). The latter theory proposes that females, on average, have a stronger drive to *empathize* (to identify another person's thoughts and feelings and to respond to these with an appropriate emotion), whereas males, on average, have a stronger drive to *systemize* (to analyze or construct rule-based systems) (Baron-Cohen, 2003). Evidence relevant to this is as follows: Individuals with ASD score higher on the systemizing quotient (SQ), an instrument on which typical males score higher than typical females (Baron-Cohen et al., 2003; Auyeung et al., 2006; Wheelwright et al., 2006). Individuals with ASDs have intact or superior functioning on tests of intuitive physics (Baron-Cohen et al., 2001; Lawson et al., 2004), a domain that shows a sex difference in favor of males (Lawson et al., 2004). Individuals with ASDs are faster and more accurate than controls on the Embedded Figures Task (EFT), a task on which typical males perform better than typical females (Shah & Frith, 1983; Jolliffe & Baron-Cohen, 1997). The EFT requires good attention to detail, a prerequisite for systemizing. All of these are relevant to systemizing.

On the empathizing quotient (EQ) (Baron-Cohen & Wheelwright, 2004), individuals with ASDs score lower than control groups, whereas typical females score higher than typical males (Baron-Cohen & Wheelwright, 2004). Individuals with ASDs score lower than typical males on the "Reading the Mind in the Eyes" task (Baron-Cohen et al., 1997), the Social Stories Questionnaire (Lawson et al., 2004), on tests of recognizing complex emotions from videos of facial expressions or audios of vocalizations (Golan et al., 2006), and on the Friendship and Relationship Questionnaire (which tests the importance of emotional intimacy and sharing in relationships)

(Baron-Cohen & Wheelwright, 2003). All of these are tests of empathy. On the Childhood Autism Spectrum Test (CAST) (Scott et al., 2002; Scott et al., 2002), boys score higher than girls (Williams et al., 2008), and children with ASDs score higher than controls (Williams et al., 2005). On the autism spectrum quotient (AQ) (Baron-Cohen et al., 2001a), individuals with ASDs score higher than those without a diagnosis (Baron-Cohen et al., 2001). Among controls, males score higher than females (Baron-Cohen et al., 2001; Baron-Cohen et al., 2006; Auyeung et al., 2008), a finding that has been reported cross-culturally (Wakabayashi et al., 2004; Wakabayashi et al., 2006; Wakabayashi et al., 2007; Hoekstra et al., 2008). Similar results have been found using the Social Responsiveness Scale (SRS), finding that individuals with an ASD diagnosis score higher than typical males, who in turn score higher than typical females (Constantino & Todd, 2005). All of these are measures of autistic traits.

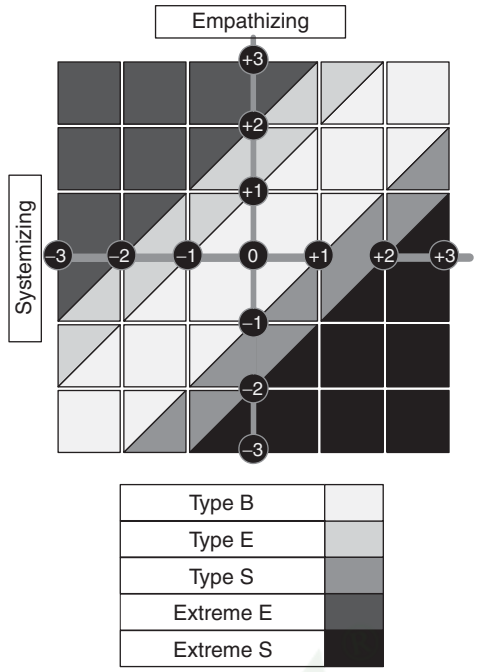

Figure 55–1. The Empathizing-Systemizing Model of Typical Sex Differences. The main brain types are illustrated on axes of Empathising (E) and Systemising (S) dimensions (numbers represent standard deviations from the mean). Balanced brain (Type B); female brain (Type E), male brain (Type S); the extreme Types E and S lie at the outer borders. According to the 'extreme male brain' theory of autism, people with ASD will generally fall in the darkest region. Modified with permission from Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Science, 6*, 248–254.

The Extreme Male Brain: Biology

Characteristics of neurodevelopment in autism may also represent an exaggeration of typical sex differences in brain development (Baron-Cohen et al., 2005). For example, there is larger overall brain volume in males during childhood (Giedd et al., 1996), and in ASDs, this may be even more extreme (Courchesne et al., 2004). There is greater growth of the amygdala in males during childhood (Merke et al., 2003), and in ASDs, this may be even more extreme (Sparks et al., 2002). The posterior section of the corpus callosum is thicker in females than males (Jancke et al., 1997) and in ASDs is even thinner than is typical (Herbert et al., 2004). These are all volumetric measures of the brain. Using fMRI, typical females show increased activity in the extrastriate cortex during the EFT and increased activity bilaterally in the inferior frontal cortex during the "Reading the Mind in the Eyes" Test compared to typical males (Baron-Cohen et al., 2006). People with ASDs show even less activity in each of these regions during these tasks (Baron-Cohen et al., 1999; Ring et al., 1999). Parents of children with ASDs also show hyper-masculinization of brain activity (Baron-Cohen et al., 2006), suggesting that this may be part of the broader autism phenotype. These are all functional neuroimaging measures of the brain. It remains important to identify the biological mechanisms that cause such sexual dimorphism. One possible biological mechanism is the effect of fetal testosterone (fT) (Geschwind & Galaburda, 1985), reviewed in the next section.

The Role of Fetal Testosterone in Brain Development

Fetal gonadal hormones (including the androgens [e.g., testosterone, dihydrotestosterone], estrogens [e.g., estradiol, estrone, estriol], and progestins [e.g., progesterone]) lead to the differentiation of the male and female phenotype (Fuchs & Klopper, 1983; Tulchinsky & Little, 1994; Kimura, 1999; Hines, 2004). If androgens and the androgen receptors are present, the male genital phenotype will develop. If not (as seen in Complete Androgen Insensitivity Syndrome), the female genital phenotype will develop (Jost, 1961; Jost, 1970, 1972; George et al., 1992). Fetal gonadal hormones are essential for sexual differentiation of both the body and the brain (Goy, 1980; Fitch & Denenberg, 1998). In what follows, we summarize some key points in this process. Three surges in testosterone levels are known to occur. The first surge is between weeks 8 and 24 of gestation (Collaer & Hines, 1995; Baron-Cohen et al., 2004; Hines, 2004). Most of the prenatal androgen effects occur between 7 and 12 weeks of gestation (Rommerts, 2001). Then, after birth, a second peak in circulating testosterone occurs in human male infants. Usually the levels remain in the pubertal range for a few months and then drop to the barely detectable levels observed in childhood by age 4 to 6 months (Smail et al., 1981). Finally, the third surge is associated with puberty. Individuals vary both in the levels of hormones to which they are exposed and in their sensitivity

to those hormones. Variations in androgen responsivity (caused by mutations in the human androgen receptor gene) can result in complete insensitivity to androgens (and thus female differentiation) or to infertility and minor undervirilization (Casella et al., 2001). The timing of hormonal effects influences whether effects are organizational or activational (Goy, 1980). Organizational effects produce *permanent* changes in the brain (Phoenix et al., 1959) and are most likely to occur during early development when most neural structures are becoming established. The discovery of such organizational effects of fT came from animal research (mostly rodents), and to date, these have only looked at neuroanatomy or limited aspects of behavior (spatial ability and mating). Activational effects occur later and are associated with concurrent changes in circulating hormone levels (Kimura & Hampson, 1994; Cooke et al., 1999).

Fetal Androgens Affect Brain and Behavior: Evidence from Rare Medical Conditions

Although animal research provides strong evidence for the effect of hormones in development, the direct manipulation of hormones in human fetuses is unethical. Instead, researchers have studied people, in whom for medical reasons the sex hormones are higher or lower than expected for a person's sex (Money & Ehrhardt, 1972). Two examples are *Congenital Adrenal Hyperplasia (CAH)* and *Complete Androgen Insensitivity Syndrome (CAIS)*. Congenital Adrenal Hyperplasia is a condition in which an enzymatic defect (usually caused by mutations in the gene coding for 21-hydroxylase) results in high levels of adrenal androgens, beginning very early in gestation. It has an incidence of 1 in 10,000 to 1 in 15,000 live births (Grumbach et al., 2003). Females with CAH differ from unaffected females (their siblings or age- and sex-matched controls) in spatial orienting, visualization, and targeting (Resnick et al., 1986; Hampson et al., 1998; Hines et al., 2003b). Females with CAH are also more likely than controls to be left-handed (Nass et al., 1987), although the difference is small and inconsistent. Females with CAH are more interested in male-typical activities and less interested in female-typical activities (Ehrhardt & Baker, 1974; Berenbaum & Hines, 1992; Berenbaum & Snyder, 1995; Berenbaum, 1999; Hines et al., 2004). Girls with CAH score lower than sex-matched controls on measures assessing empathy, intimacy, and the need for close social relationships (Mathews et al., 2009; Helleday et al., 1993; Resnick, 1982; Kuhnle & Bullinger, 1997). Individuals with CAH showed higher levels of language and learning difficulties than unaffected family members (Resnick et al., 1986). All these changes can be interpreted as masculinization.

Complete Androgen Insensitivity Syndrome is a second example of a rare medical condition affecting prenatal endocrine responses. It occurs when there is a complete deficiency of working androgen receptors. It is an X-linked recessive disorder and hence occurs more often in genetic males. Prevalence is between 1 in 20,000 and 1 in 60,000 live male births. At birth, genetic male infants with CAIS are phenotypically female, despite an XY complement, and are usually raised as girls. At puberty, breasts develop under the influence of estrogen derived from testicular androgens. Diagnosis usually takes place when menarche fails to occur (Nordenstrom et al., 2002; Grumbach et al., 2003). In studies, gender identity has not differed between genetic males with CAIS and control women (Quadagno et al., 1977; Hines et al., 2003a). Individuals with CAIS perform in a female-typical fashion on tests of visuo-spatial ability (Money et al., 1984).

These findings suggest that two X chromosomes or functioning ovaries are not required for feminine-typical psychological development in humans and highlight the role of androgen receptors in influencing masculine-typical psychological development. However, existing studies have not examined all sexually dimorphic aspects of neurobiology and cognition in these populations. Therefore, one cannot rule out an effect of X-chromosome genes or ovarian hormones on some aspects of sex-typical neurodevelopment.

Fetal Androgens Affect Brain and Behavior: Evidence from Amniotic Fluid Testosterone

Another approach to testing if fetal androgens affect brain and behavior is to measure fT in amniotic fluid obtained during routine diagnostic amniocentesis. An advantage of this approach is its timing. It is typically performed during the second trimester of pregnancy (usually 14–20 weeks of gestation) that coincides with the serum testosterone peak period in male fetuses. Several studies have documented a large sex difference in amniotic androgen levels (Judd et al., 1976; Dawood, 1977; Robinson et al., 1977; Nagami et al., 1979; Finegan et al., 1989). The origin of androgens in amniotic fluid is the fetus itself. Hormones enter the amniotic fluid via diffusion through the fetal skin in early pregnancy and via fetal urine in later pregnancy (Judd et al., 1976; Schindler, 1982). Testosterone obtained in amniotic fluid is thought to be a good reflection of the levels in the fetus (van de Beek et al., 2004) and represents an alternative to direct assay of fetal serum that would be unnecessarily invasive. In the Cambridge Fetal Androgen Project, children whose mothers had amniocentesis during pregnancy (but who were otherwise typically developing children) were followed-up after birth at ages 12, 18, 24, 48, and 96 months (Baron-Cohen et al., 2004). Evidence that amniotic testosterone affects cognitive development includes the following. Fetal testosterone is inversely associated with eye contact in males at age 12 months (Lutchmaya et al., 2002). Fetal testosterone is inversely associated with size of vocabulary development at ages 18 and 24 months (Lutchmaya et al., 2002). Fetal testosterone is inversely associated with quality of social relationships, and positively associated with narrow interests, at age 48 months (Knickmeyer et al., 2005). Fetal testosterone is inversely

associated with empathy at ages 48 and 96 months (Chapman et al., 2006; Knickmeyer et al., 2006). Fetal testosterone is positively associated with "systemizing" at age 96 months (Auyeung et al., 2006). Fetal testosterone is positively associated with performance on the EFT, as a measure of attention to detail, at age 96 months (Auyeung et al., submitted). The effect sizes in these studies range from 0.2 to 0.4. Because all of these domains of behavior (eye contact, language development, quality of social relationships, narrow interests, empathy, systemizing, and embedded figures/attention to detail) show sexual dimorphism and may be hyper-masculinized in ASDs, it raises the question as to whether fetal testosterone plays a role in the development of autism. In the final section, we review evidence that androgens—especially fetal testosterone—may play a role in autism or autistic traits.

The Role of Sex Steroid Hormones in Autism Spectrum Disorders or Autistic Traits

Evidence that supports a role for hormones in the development of ASDs is preliminary and includes the following: Androgen-related medical conditions such as polycystic ovary syndrome (PCOS), ovarian growths, and hirsutism occur with elevated rates in women with AS and in mothers of children with autism (Ingudomnukul et al., 2007). Girls with CAH have a higher AQ score than their unaffected sisters (Knickmeyer et al., 2006c). Children with AS and children with classic autism have lower 2D:4D ratios than typical developing children (Manning et al., 2001; Milne et al., 2006). The ratio of the second digit to the fourth digit (2D:4D ratio) is lower in men than in women. The 2D:4D ratio is fixed by week 14 of fetal life (Garn et al., 1975) and is influenced by testosterone (Manning et al., 2002). This suggests children with ASD have been exposed to higher amounts of androgens. A subset of male adolescents with autism show hyper-androgeny, or elevated levels of androgens, and precocious puberty (Tordjman et al., 1997). Delayed menarche has also been found in females with AS (Knickmeyer et al., 2006; Ingudomnukul et al., 2007). Puberty timing reflects hormonal programming of the hypothalamic-pituitary-gonadal axis during gestation (Grumbach & Shaw, 1998).

Left-handedness and ambidexterity are more common in typical males (Peters, 1991) and individuals with autism (Gillberg, 1983). Body asymmetries are related to prenatal sex hormones and breast or testis size on the left versus right sides of the body are related to cognition (Kimura, 1999). Fetal testosterone is implicated in left-handedness and asymmetric lateralization (Fein et al., 1985; Satz et al., 1985; Soper et al., 1986; McManus et al., 1992). The typical male brain is heavier than the female brain, a difference that partly results from fT exposure (Hines, 2004). Individuals with autism have even heavier brains than typical males (Hardan et al., 2001). Amniotic fT levels are positively associated with higher scores (indicating greater number of autistic traits) on the CAST and on the child autism spectrum quotient (AQ-C) (Auyeung et al., 2008). These findings are consistent with the fetal androgen theory of autism, although the ultimate test of this theory will require testing between fetal testosterone and clinically diagnosed ASDs. The latter will require much larger samples than have previously been tested.

It is important in a review chapter such as this to summarize criticisms of the fetal androgen theory of ASDs. First, if autism is an extreme of the typical male behavioral profile, why do people with ASD not show high levels of aggression or a strong interest in competitive sports? We suspect this criticism reflects a misunderstanding of the different roles that fetal as opposed to current (circulating) testosterone play. The latter may well affect aggression and competitiveness, but fetal androgens may selectively affect very different aspects of cognition such as attention to detail and empathy. This remains to be tested. Second, given that testosterone interacts with multiple systems in the body, why single it out for a special role? We acknowledge that if fT plays a role in ASDs, it is likely to do this in complex ways, as testosterone modulates neurotransmitters (such as GABA) as well as peptide hormones (such as oxytocin), to name just two examples. Understanding such relationships will require testing of multiple systems within the same experiment. Third, given that amniotic testosterone is currently only studied in humans via amniocentesis and only 6% of pregnant women undergo amniocentesis, does this not lead to potentially biased samples? We acknowledge this bias but would note that currently this is the only ethical way to study fT because amniocentesis itself carries a risk of inducing miscarriage (in 2% of cases) and so cannot be justified purely for research on a randomly selected, and therefore representative, sample of pregnant women. The main risk of bias comes from higher maternal age because this is one reason why women are referred for an amniocentesis (being older than 35 years old). For this reason, maternal age is entered as a variable in the regression analysis. All fT effects that have been found remain significant after removing any variance because of maternal age.

A further criticism is that if sex differences in the population are only found when one compares equal numbers of males and females, and if studies of ASDs tend to be biased toward males, is the extreme male brain theory really just a reflection that ASDs affect more males than females? This is a valid concern, but it is interesting that where it is possible to compare equal numbers of males and females with ASDs, typical sex differences are absent, which argues against any risk of circularity. Also, when fT effects are found on behavior, these are seen *within* sex, not just when the sexes are combined. This suggests these are hormone effects rather than a redescription of sex differences. Finally, Skuse and others have pointed out that sex-linked neural and behavioral phenotypes could emerge not just because of hormone effects but genetic effects. We agree that fT is only one of many mechanisms that are likely candidates for giving rise to such sex differences, and indeed our recent candidate gene study identified 10 genes

involved in the sex steroid hormone pathway that were nominally associated with either autistic traits, empathy, or an ASD (Chakrabarti et al., 2009).

Conclusions

The higher incidence of autism in male individuals might provide important clues to the etiology of the condition, which has been described as an "extreme of the male brain" (Baron-Cohen, 2002). The studies reviewed here suggest that prenatal testosterone could be involved in the sex differences in key areas of behavior in the general population (social development, language development, empathy, systemizing, and attention to detail) and to the male vulnerability to autism. These studies suggest that variations in fetal testosterone are related to individual differences in cognition and behavior in typically developing children, but caution needs to be taken when extrapolating these results to individuals with autism. Our ongoing collaboration with the biobank in Denmark that has thousands of amniotic samples will enable a test of the fetal testosterone theory in clinically diagnosed cases of ASD.

Challenges and Future Directions

- Testing the fetal testosterone theory in relation to diagnosed ASD will require tens of thousands of amniotic samples because only 1 in 100 of these are expected to go on to develop an ASD.
- It is an assumption that amniotic testosterone reflects testosterone levels in the brain, but this remains untested.
- Ethically, if it were established that in ASD there are elevated fetal testosterone levels, this does not mean a treatment implication is to block fT, as fT is likely to be involved in many systems, not just the development of autistic traits.

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