Abstract: Autism Spectrum Conditions (ASC) are much more common in males, a bias that may offer clues to the etiology of this condition. Although the cause of this bias remains a mystery, we argue that it occurs because ASC is an extreme manifestation of the male brain. The extreme male brain (EMB) theory, first proposed in 1997, is an extension of the Empathizing-Systemizing (E-S) theory of typical sex differences that proposes that females on average have a stronger drive to empathize while males on average have a stronger drive to systemize. In this first major update since 2005, we describe some of the evidence relating to the EMB theory of ASC and consider how typical sex differences in brain structure may be relevant to ASC. One possible biological mechanism to account for the male bias is the effect of fetal testosterone (fT). We also consider alternative biological theories, the X and Y chromosome theories, and the reduced autosomal penetrance theory. None of these theories has yet been fully confirmed or refuted, though the weight of evidence in favor of the fT theory is growing from converging sources (longitudinal amniocentesis studies from pregnancy to age 10 years old, current hormone studies, and genetic association studies of SNPs in the sex steroid pathways). Ultimately, as these theories are not mutually exclusive and ASC is multi-factorial, they may help explain the male prevalence of ASC.

Is There Really a Male Bias?

The diagnosis of classic autism and Asperger Syndrome (AS), known as Autism Spectrum Conditions (ASC), rests on difficulties in reciprocal social interaction and communication, alongside strong repetitive behavior and unusually narrow interests [1]. The prevalence of ASC is estimated to be 1% [2,3]. A diagnosis of classic autism, unlike AS, also requires the presence of additional learning difficulties and language delay. ASC is neurobiological, evidenced by atypical brain development in structure and function [4]. ASC is also genetic [5,6] though not without some interaction with environmental influences.

ASC is strongly biased towards males [7], with ratios of 4:1 (male:female) for classic autism [8] and as high as 11:1 in individuals with AS [9]. The specific factors responsible for the higher male prevalence in ASC remain unclear. ASC is not the only neurodevelopmental condition more common among males—a greater prevalence in males versus females is also seen in Attention Deficit and Hyperactivity Disorder (ADHD), dyslexia, conduct disorder (CD), specific language impairment, Tourette Syndrome, and Learning Difficulties (see Table 1) [10].

However, the male bias is much more pronounced in ASC, especially in the case of AS. This male bias could simply reflect the difficulty of diagnosing AS in females. Though classic autism would not be missed in females, AS could be if it presented as some other condition, such as anorexia [11] or borderline personality disorder [12], both of which involve the exercise of excessive control over the environment or other people, and a certain degree of a self-centeredness. Equally, AS in females could be under-diagnosed if females are more motivated to learn to conform socially or have better imitation skills that allow them to “pretend to be normal” [13]. Finally, this male bias might reflect the inability of the widely used diagnostic instruments (the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview-Revised (ADI-R)) to detect the more subtle ways in which AS may present in females.

While these explanations of mis- or under-diagnosis may explain part of the male bias, there may also be biological reasons for the male bias in ASC. We argue that the bias can be understood as an extreme expression of the psychological and physiological attributes of the male brain; that is, males need only slight psychological and physiological changes to exhibit ASC while females would require more, thus making ASC rarer in females. What factors might favor overdevelopment of male characteristics? One possible biological mechanism could be the masculinizing effect of fetal testosterone (fT). Two other possibilities include the X- and Y-linked theories and the reduced...
those relating to empathy and systemizing. All psychological sex differences will be exaggerated in ASC—only of the male profile. Note that the EMB theory does not state that direction of sex difference—people with autism show an extreme hyper-masculinization in ASC. A key finding supporting this EMB theory is defined at the psychological level, we should expect rule-based systems). Whilst sociologists still debate if there are any sex differences at all, and if so whether these are purely the result of cultural conditioning, biologists have long known from animal research that sex differences in behavior exist in primates and are influenced by biology as well as the environment.

On the Empathy Quotient (EQ) [15] typical females score higher than typical males who score higher than those with ASC [15]. On the Systemizing Quotient (SQ), individuals with ASC score higher than typical males who score higher than typical females [16–18]. Additional psychological evidence (summarized in Table 2 and in Text S1) shows that irrespective of the direction of sex difference—people with autism show an extreme of the male profile. Note that the EMB theory does not state that all psychological sex differences will be exaggerated in ASC—only those relating to empathy and systemizing.

Sexual Dimorphism in the Human Brain

Additional support for the EMB theory of ASC comes from evidence of neural sexual dimorphism across development. Some key examples of typical sexual dimorphism reveal an extreme of the typical male profile in the neurodevelopment of ASC [19]. However, one caveat to keep in mind is that just as all psychological sex differences do not constitute an exaggerated form of maleness in ASC, neither do all neural differences. Indeed, given that the EMB theory is defined at the psychological level, we should expect only a narrow set of neural sex differences will be involved in such hyper-masculinization in ASC. A key finding supporting this prediction is that infant males on average have a larger brain than females [20] and children with autism have even larger brains early in life right around the time they would typically receive a diagnosis (2–4 years) [21]. In addition, independent of global differences in brain size, the amygdala in typical males tends to be larger than in females [22], and early in development the amygdala in autism is even more enlarged than that observed in typical males [23–25]. In addition to such structural sexual dimorphism in the brain, exaggeration of neural sexual dimorphism extends to brain function and corroborates predictions from the EMB theory (see Table 3 and Text S1 for fuller discussion) [26–29].

The set of striking findings of hyper-masculinization in ASC at three simultaneous levels (cognitive, neuroanatomy, and neural function) raises the question as to which biological mechanism(s) are involved. Two plausible mechanisms that could give rise to sexual dimorphism, hyper-masculinization, and/or the absence of typical sexual dimorphism at the levels of brain, cognition, and behavior are the “organizing” effects of fetal testosterone (FT) [30–32] and X- or Y-linked genetic factors. We review these three interesting hypotheses, since these may also have relevance to the sex ratio in ASC. These are not proposed as complete explanations for ASC, since ASC is recognized to be multi-factorial, but they may form an important part of the explanation.

What Might Cause an Extreme Male Brain?

The Fetal Testosterone (FT) Theory

Fetal androgens affect the brain: Evidence from animal and human studies. Animal studies, especially in rodents, confirm that early exposure to androgens (such as testosterone) acts on the brain to produce sex differences in behavior, cognition, brain structure, and function (see Text S1 for more discussion of work with animals) [31–33]. It is widely accepted that FT exposure also affects brain development and behavior in humans. Human males experience a surge in FT between weeks 8 to 24 of gestation [34–36], reaching almost pubertal levels. There is also a second surge soon after birth (here called “neonatal testosterone,” or nT). Usually the levels remain high and then drop to barely detectable levels by 4–6 months [37], until the third surge at puberty. Whilst the third surge is understood to be controlling the onset of puberty, the function of first surge (FT) is believed to play a major role in brain masculinization.

While direct manipulation of hormones as has been conducted in animal studies is unquestionably unethical in human fetuses and infants, alternative research strategies include relating individual variation in amniotic FT exposure to later development [38], or studying people in whom—for medical reasons—the sex hor-
mons are higher or lower than expected for a person’s sex [39], and using proxy measures of fT exposure. Here we review evidence from studies of cognitive traits relevant to ASC and their relationship with amniotic fT. (Evidence from disorders of sexual differentiation and from proxy measures of fT exposure is presented in the Text S1.)

Fetal androgens affect ASC traits: evidence from amniotic fluid testosterone. fT can be measured in amniotic fluid, obtained during routine amniocentesis. Because amniocentesis is typically performed during the second trimester of pregnancy (usually 14–20 weeks of gestation), when serum testosterone peaks in male fetuses, it offers a unique opportunity to compare fT with ASC traits. There is a well-documented large sex difference in amniotic androgen levels [40–44]. The origin of androgens in amniotic fluid appears to be the fetus itself, and testosterone obtained in amniotic fluid is thought to be a good reflection of the levels in the fetus [38]. In the Cambridge Fetal Testosterone Project, initiated by our group in 1998, children whose mothers had amniocentesis during pregnancy (but who were otherwise developing normally) have been followed up after birth every year or two and are now approximately 11 years of age [34].

Evidence that amniotic fT affects individual differences in cognitive development in typically developing children (but with clear relevance to ASC) includes the following: fT is inversely associated with frequency of eye contact at 12 months old [45] and with size of vocabulary development at 18 and 24 months [46]. fT is also inversely associated with quality of social relationships at 48 months [47] and with empathy at 48 and 96 months [48,49]. In contrast, amniotic fT is positively associated with narrow interests at 48 months [47], with “systemizing” at 96 months [18], and with performance on the Embedded Figures Test (EFT) as a measure of attention to detail at 96 months [50]. These are all behaviors that show sexual dimorphism, but critically, these fT effects are often found within one sex as well as when analyzing the sexes in 2003.

### Table 2

| Psychological Measure | Autism>Male>Female | Female>Male>Autism | Key References |
|-----------------------|--------------------|--------------------|----------------|
| Adolescent AQ         | ✓                  |                    | [120]          |
| Adult Autism Spectrum Quotient (AQ) | ✓                  |                    | [104,121–124] |
| Adult Systemizing Quotient (SQ) | ✓                  |                    | [16]           |
| Child AQ              | ✓                  |                    | [125]          |
| Child SQ              | ✓                  |                    | [126]          |
| Childhood Autism Spectrum Test (CAST) | ✓                  |                    | [127–130] |
| Embedded Figures Test | ✓                  |                    | [131,132] |
| Intuitive Physics Test | ✓                |                    | [133,134] |
| Social Responsiveness Scale | ✓                  |                    | [135,136] |
| Quantitative Checklist for Autism in Toddlers (Q-CHAT) | ✓                  |                    | [137]          |

### Table 3

| Brain Region            | Autism>Male>Female | Female>Male>Autism | Key References |
|-------------------------|--------------------|--------------------|----------------|
| Structure               |                    |                    |                |
| Total brain volume      | ✓                  |                    | [20,141–143]  |
| Amygdala                | ✓                  |                    | [22–25,144–150].|
| Corpus callosum         | ✓                  |                    | [151,152] |
| Perisylvian language areas (Heschl’s gyrus/planum temporale) | ✓                  |                    | [22,153–156] |
| L>R asymmetry in planum temporale | ✓                  |                    | [22,154,157–160] |
| Lateral fronto-parietal cortex | ✓                  |                    | [144,145,147,150,156,161–165] |
| Function                |                    |                    |                |
| Default Mode Network Connectivity | ✓                  |                    | [166,167] |
| Embedded Figures fMRI   | ✓                  |                    | [27–29,168] |
| Reading the Mind in the Eyes task fMRI | ✓                  |                    | [26,28] |

Table 2. A summary of the psychological evidence for the Extreme Male Brain (EMB) theory (see Text S1 for a fuller discussion).

Table 3. A summary of the evidence consistent with the EMB theory at the neural level (see Text S1 for a fuller discussion).
combined. The finding of a consistent inverse correlation between \( \Gamma \) and social domains, and a consistent positive correlation between \( t \Gamma \) and non-social domains, across development, is striking and suggests these are real effects which substantiate the notion that \( \Gamma \) plays an “organizational” role in development.

In the first study to directly assess if \( \Gamma \) affects not just human cognition but also human brain structure, we found that increasing levels of \( \Gamma \) are associated with increasing rightward asymmetry in the thickness of one subsection of the corpus callosum, the isthmus [51]. This is interesting since the isthmus projects to posterior parietal and superior temporal cortices, which are integral for language and visuospatial ability and are known to be sexually dimorphic in lateralization, structure, and function (see Text S1).

All of the above behavioral domains (eye contact, language development, quality of social relationships, narrow interests, empathy, systemizing, and embedded figures/attention to detail) and brain structure show sexual dimorphism and appear hypermasculinized in ASC, raising the possibility that \( t \Gamma \) may play a role in the development of ASC itself. Three recent experiments have confirmed a positive correlation between \( t \Gamma \) levels and the number of autistic traits a child shows in toddlerhood [52] and in later childhood [53]. The Cambridge Fetal Testosterone Project has too few children (currently \( n = 635 \) are enrolled) to test whether \( \Gamma \) is elevated in those who later are diagnosed with ASC, but testing for a direct association between \( t \Gamma \) levels and diagnosed ASC will be possible in our ongoing collaboration with the Danish Biobank, which has tens of thousands of amniotic samples, with adequate power to test this hypothesis. Using a different line of evidence, a number of studies have found also current androgen dysregulation in ASC or in their relatives, and androgen-related genes being associated with ASC (see Table 4 for a summary of the evidence for the \( \Gamma \)/androgen theory).

Although some studies have failed to support a role for testosterone in ASC (and most of these have not been able to study \( t \Gamma \) specifically), the studies reported above suggest that \( t \Gamma \) is implicated in the biased sex ratio seen in ASC. However, alternative models exist which could also explain the excess of males with ASC. In the final part of this article we review the main contender, the X chromosome theory. For completeness, we also briefly review the Y chromosome theory and the reduced autosomal penetrance theory.

### The X Chromosome Theory

The X chromosome contains more genes expressed in the brain than the other chromosomes [54]. In addition, more than 10% of people with learning difficulties show an X-linked pattern of inheritance [55], involving mutations in over 90 different X-linked genes [56,57]. Individuals with X-linked learning difficulties may also have ASC, the best-known example being Fragile X Syndrome, where 46% of males and 16% of females carrying the full mutation also have ASC [58].

On the face of it, the biased sex ratio in ASC would therefore be parsimoniously explained by an X chromosome theory. A problem for this theory is that the majority of linkage and association studies of ASC have failed to find regions of interest on the X chromosome [59–72]. A related problem for this theory is that in the three recent genome-wide studies of copy number variation (CNV) in individuals with ASC that identified mutations affecting the X chromosome, this was only true in a very small minority of cases. This suggests X-linked mutations are only occasionally seen in ASC and therefore cannot account for the large majority of cases. A final problem for the X-linked theory is that other large CNV scans have reported no significant findings on the X chromosome [67,73–75]. While epigenetic effects on X chromo-

### Table 4. Evidence for the effect of sex steroids in autism (see Text S1 for a fuller discussion).

| Evidence | Key References |
|----------|----------------|
| **From typically developing children** | |
| Eye contact is inversely related to \( t \Gamma \) | [45] |
| Quality of social relationships are inversely related to \( t \Gamma \) | [47] |
| Vocabulary size is inversely related to \( t \Gamma \) | [46] |
| Empathy is inversely related to \( t \Gamma \) | [48,49] |
| Autistic traits are positively associated with \( t \Gamma \) | [52,53] |
| Restricted interests are positively associated with \( t \Gamma \) | [47] |
| Systemizing is positively associated with \( t \Gamma \) | [18] |
| Rightward asymmetry in the isthmus of the corpus callosum is positively associated with \( t \Gamma \) | [51] |
| **From people with ASC** | |
| 10 genes involved in sex steroid synthesis, transport, and/or metabolism associated with AS or AQ or empathy: \( \text{HSD11B1, LHCGR, CYP17A1, CYP19A1, SCP2, CYP11B1, ESR1, ESR2, HSD17B4, HSD17B2} \) | [169] |
| Timing of puberty: Boys with ASC enter puberty earlier. Girls with ASC enter puberty later | [170–172] |
| Testosterone related medical conditions in women with ASC and their mothers (e.g., PCOS, breast and ovarian cancers, acne) | [172] |
| Testosterone related characteristics in women with ASC and their mothers | [172,173] |
| Lower 2D:4D ratio in ASC, and parents | [174–176] |
| \( \text{SRD5A1 and A1T genes associated with ASC} \) | [177,178] |
| Decreased expression of \( \text{RORA gene} \) and aromatase in post-mortem frontal and cerebellar tissue | [179,180] |
| Females with Congenital Adrenal Hyperplasia (CAH) have elevated AQ | [181] |
| Testosterone levels are elevated in ASC | [182] |
| Androstenedione levels are elevated in ASC | [183] |

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some genes could affect risk for autism, this hypothesis has not yet been empirically tested. In summary, at present it appears that there are X-linked causes of ASC, but these represent a far smaller percentage of cases than is seen in learning difficulties. Girls with Turner Syndrome (TS) (characterized by the XO karyotype) [76] are at an increased risk for ASC, which could be the result of an X-linked recessive gene, but this is not clear-cut since XXY and XXXY males are also at increased risk [77]. One study [78] has also reported higher autistic traits scores (as measured on the Autism Spectrum Quotient [AQ]) in XXY males, though this is not always seen [77].

There are other possible versions of the X chromosome theory of ASC. Although females have two X chromosomes, only one of these is generally active. X chromosome inactivation (the process by which one X chromosome is suppressed while the other remains active) acts to negate the “dosage” difference in X chromosome genes between males and females. However, 10–15% of X chromosome genes may continue to be expressed from the supposedly inactive X. Creswell and colleagues [84] subsequently reported five cases of Turner Syndrome (TS) (characterized by the XO karyotype) in which one X chromosome was imprinted (the process by which genetic effects are influenced by whether the genes are transmitted through the father or the mother [81]) is also of interest. Ordinarily this would not result in sex differences in the rate of a condition, but could do so if the imprinting affects the X chromosome. Skuse [82,83] suggested that an imprinted X locus could explain sex differences in social and communication skills and the male vulnerability to learning difficulties are themselves a risk factor for ASC [80], so any evaluation of the X chromosome theory needs to consider these separately.

Genomic imprinting (the process by which genetic effects are influenced by whether the genes are transmitted through the father or the mother [81]) is also of interest. Ordinarily this would not result in sex differences in the rate of a condition, but could do so if the imprinting affects the X chromosome. Skuse [82,83] suggested that an imprinted X locus could explain sex differences in social and communication skills and the male vulnerability to learning difficulties and low verbal IQ scores, despite the fact that intelligence is usually in the average range in TS. This raises the possibility that the kind of ASC observed was related to learning difficulties (i.e., applicable only to classic autism rather than the full autistic spectrum, which includes AS). Also, given that 77% of TS females are XpO, while only 23% are XoO [85], this means that by chance one would expect to find ASC more often associated with XpO than with XoO.

No specific X-linked genes have yet been identified which explain these findings, but there is evidence that whichever genes are involved may modulate amygdala circuits which are disrupted in ASC [86]. Whilst the amygdala has not been directly examined, a study of the whole brain in a mouse model of TS did not identify any paternally expressed X-linked genes, but did identify a maternally expressed gene, xshb, which was implicated in cognitive flexibility [87]. However, it is unclear if a functioning human orthologue of this gene exists.

A recent study searched for imprinted genes in the preoptic area (POA) and medial prefrontal cortex (mPFC) in mouse. No X-linked imprinted genes were identified when using a cut-off of \( p<0.05 \), but using a less stringent cut-off of 0.1, a small set of putative X-linked imprinted genes were identified including three paternally expressed genes in the POA and three different paternally expressed genes in the mPFC [88]. Three of these genes (aok, acbd4, and id4) have human orthologues whose disruption can cause MR. Another intriguing finding from this study was that total levels of expression from XoO were increased relative to those of XoO in females. This could reflect preferential inactivation of the \( X_o \) and would act to minimize dosage differences between the sexes. If a screen of females with ASC identified rare mutations or CNVs on the \( X_p \), this would provide important evidence for the theory.

The Y Chromosome Theory

Since the XYY and XXXY syndromes have an increased incidence of ASC [89–91], it is important to consider if the male bias in ASC could also result from the male-limited expression of genes on the Y chromosome. This possibility has attracted very little research attention. Such genes should be located in the non-recombining region of the Y. SRY (the sex determining gene) is expressed in the medial rostral hypothalamus, as well as the frontal and temporal regions of the human brain [92]. In vitro assays suggest that SRY can increase transcription of tyrosine hydroxylase (the rate-limiting enzyme in dopamine biosynthesis) by binding at a promoter site [93]. In addition, the knockdown of SRY expression in the substantia nigra of the rat decreases tyrosine hydroxylase expression [94]. This could implicate SRY in the male bias for disorders involving deregulated catecholamines such as ADHD. SRY may also regulate the monoamine oxidase A (MAOA-4) gene [95]. Other Y-linked genes known to be expressed in human brain include \( ZFY \) and \( PCDH11Y \) [92,96].

A small candidate gene study failed to find associations between variants in \( PCDH11Y \) and autism [96], while \( ZFY \) has not been specifically investigated. One study has reported a missense variant in \( MLGN4 \) in a single patient with autism and his father with learning difficulties [97]. Comparison of Y chromosome haplotype groups between cases and controls represents an alternative strategy to identifying Y chromosome effects. Two such studies have been conducted in regard to ASC— one was positive [98] and one was negative [99]. Y chromosome effects certainly merit additional research attention, but current evidence is too sparse to evaluate to what extent this mechanism could explain the sex bias in ASC.

Reduced Autosomal Penetrance in Females? A Final Theory

For completeness we briefly mention a final theory, arising from studies of rare CNVs with ASC [67,74,100,101]. As mentioned earlier, these scans have not routinely implicated the X chromosome, but this final model proposes that a significant proportion of ASC cases are the result of dominant de novo mutations (on the autosomes) which have reduced penetrance in females. Statistical analysis of ASC family data has provided supporting evidence [102]. A problem for this theory, however, is that the majority of studies report that the sex ratio in children with ASC and de novo CNVs is 1:1. This clearly does not fit with...
in females. However, we agree that it is critical that large-scale
research into understanding the relationship between empathy and systemizing will require
further research because presenting them as independent ignores the
fact that both are related to $\textit{fT}$. Nor can we yet extrapolate the $\textit{fT}$
results to individuals with an ASC diagnosis since this will require
much larger collections of amniotic samples than has been possible
to date. Strengthening a role for $\textit{fT}$ in ASC is the recent genetic
evidence in which SNPs in key sex steroid genes are associated
with either diagnosed AS and/or autistic traits.

### Not Mutually Exclusive Theories

The X and Y chromosome theories and the $\textit{fT}$ model offer
potential explanations for the biased sex ratio in ASC and warrant
further research. While often conceived as competing theories,
they need not be mutually exclusive. This is because we cannot
rule out the possibility that genes on the X and Y chromosomes
may be regulated by $\textit{fT}$ or have products that affect the production
or sensitivity of an individual to $\textit{fT}$. X chromosome genes may also
regulate Y chromosome genes and vice versa. In addition, it is
possible that X or Y chromosome genes and $\textit{fT}$ exposure are
independent risk factors for ASC.

The theories do, however, make contrasting predictions for
individuals with certain intersex conditions, in particular those
with Complete Androgen Insensitivity Syndrome (CAIS), where
there is a complete deficiency of working androgen receptors,
in the presence of a typical male genetic complement (XY). Given the
rarity of this condition, studies using measures of autistic traits
(such as the AQ [104]) may be more feasible than studies of
diagnosed cases of ASC in CAIS per se. (These contrasting
predictions are summarized in Table 5.)

Finally, whilst it may be that the psychiatric classification system
is “carving nature at its joints,” it is also possible that some of the
underlying hormonal and genetic mechanisms are involved not
just in ASC but are relevant to a broader category of
neurodevelopmental conditions (see Box 1).

### Looking Ahead: Toward a Unified Theory?

For as long as ASC has been recognized, a higher prevalence
has been observed in males, yet until 1997, when our group
proposed the extreme male brain theory, this potential clue to the
etiologic of the condition went unexplored [105]. In the early years
following the publication of the EMB theory, the majority of the
evidence relevant to the theory came from psychological studies,
but since 2001 supporting evidence has also come from biology.

In the present article we have considered studies that suggest
that fetal testosterone is involved in sex differences in key areas of
behavior and cognition in the general population (in social
development, language development, empathy, systemizing, and
attention to detail), as well as in influencing brain structure, and
the number of autistic traits an individual possesses. Understand-
ing the relationship between empathy and systemizing will require
more research because presenting them as independent ignores the
fact that both are related to $\textit{fT}$. Nor can we yet extrapolate the $\textit{fT}$
results to individuals with an ASC diagnosis since this will require
much larger collections of amniotic samples than has been possible
to date. Strengthening a role for $\textit{fT}$ in ASC is the recent genetic
evidence in which SNPs in key sex steroid genes are associated
with either diagnosed AS and/or autistic traits.

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**Box 1.** $\textit{fT}$ and X-linked factors in other neurodevelopmental conditions.

**ADHD:** $\textit{fT}$ has been implicated by several studies using
the proxy measure of 2D:4D (finger) ratio [176,184,185]
and one study of genetic variation at the androgen
receptor [186]. An animal model of ADHD suggests that
early androgen exposure affects catecholamine innerva-
tion of the frontal cortex and cognitive function [187].
ADHD has also been associated with X-linked genes, in
particular monoamine oxidase-B [188,189] and steroid
sulfatase [190]. The latter has also been implicated in
attention deficits in a mouse model of Turner Syndrome
[191]. However, genome-wide scans have not implicated
the X chromosome in ADHD [192,193].

**Conduct Disorder (CD):** Activational effects of gonadal
steroids have shown relationships with CD [194–196], but
there is not a simple one-to-one correspondence. In
addition, the X-linked gene coding for monoamine oxidase
A has been linked to aggression and neural hyperactivity
to threat [197].

**Reading Disorder/Dyslexia:** Two studies have failed to
find a relation between 2D:4D (digit) ratio (as a proxy for
$\textit{fT}$) and dyslexia [115,198]. One genome-wide linkage
analysis suggested a locus on Xq26 [199]. A nearby
susceptibility locus in a single extended family has also
been reported [198].

**Specific Language Impairment:** The correlation be-
tween amniotic $\textit{fT}$ levels and early vocabulary [46,200]
could indicate a role for $\textit{fT}$ in SLI. Genome-wide linkage
studies have not implicated the X chromosome [201–203].

**Tourette Syndrome:** Tics in individuals with TS increase
in intensity during puberty, suggesting an activational
testosterone effect. A role for $\textit{fT}$ has also been proposed
based on a study of gender dysphoria, play preferences,
and spatial skills in individuals with TS [204]. Genome-wide
linkage studies have not implicated the X chromosome
[205], but Lawson-Yuen [206] have reported a pedigree
with a NLGN4X deletion which was associated with TS in
one family-member.

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**Table 5.** Rates of ASC/autistic traits in different medical conditions, as predicted by the X and Y chromosome theories, and the $\textit{fT}$
theory.

| Medical Condition                          | Prediction from X-Dosage or X-Linked Recessive Model | Prediction from Imprinted X Model | Prediction from Y-Chromosome Model | Prediction from $\textit{fT}$ Theory |
|-------------------------------------------|-----------------------------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Complete Androgen Insensitivity Syndrome (CAIS) in males | Similar to typical males | Similar to typical males | Similar to typical males | Similar to typical females |
| Congenital Adrenal Hyperplasia (CAH) in females | Similar to typical females | Similar to typical females | Similar to typical females | Similar to typical males |
| Turner Syndrome (with a maternal X; XpO) | Similar to typical males | Similar to typical males | Similar to typical females | Similar to typical females |
| Turner Syndrome (with a paternal X; XpO) | Similar to typical males | Similar to typical males | Similar to typical females | Similar to typical females |

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The main alternatives to the GT theory are the X and Y chromosome theories. Future research could usefully test these theories against each other, or test if all are valid, either independently or because of gene-hormone interactions. Whilst it remains a possibility that the male bias in ASC simply reflects diachronic difficulties in recognizing ASC in females, the link between ASC and maleness has generated a novel framework for exploring the link between sex and ASC, and a wealth of data relating prenatal hormones to masculinization of the mind and the brain.

Supporting Information

Text S1 Supplementary material. (DOC)
52. Anyang B, Taylor K, Hackett G, Baron-Cohen S (2010) Fetal testosterone and autistic traits in 18 to 24-month-old children. Mol Autism 1: 1–11.
53. Anyang B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, et al. (2009) Fetal testosterone and autistic traits. Brit J Psychiatry 100: 1–22.
54. Nguyen DK, Dutech CM (2006) High expression of the mammalian X chromosome in brain. Brain Res 1126: 46–49.
55. Laumonnier F, Cuthbert PC, Grant SG (2007) The role of neuronal complexes in human X-linked brain diseases. Am J Hum Genet 80: 205–220.
56. Green J, Skolet RA, Corbett M (2009) The genetic landscape of X-linked intellectual disability arising from X chromosome. Trends Genet 25: 308–316.
57. Ropers HH, Hame1 BC (2005) X-linked mental retardation. Nat Rev Genet 6: 86–97.
58. Bailey DB, Jr, Koppe M, Olmedo M, Holiday DB (2008) Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. Am J Med Genet Part A 146A: 2060–2069.
59. Consortium IMGSoA (1998) A full genome screen for autism with evidence for a multilocus etiology. Am J Hum Genet 65: 493–507.
60. Schutz CK, Polley D, Robinson PD, Chalfius M, Maciarello F, et al. (2002) Autism and the X chromosome: no linkage to microsatellite loci detected using the affected sibling pair method. Am J Hum Genet 109: 36–41.
61. Schellenberg GE, Dawson G, Sung YJ, Estes A, Munson J, et al. (2006) Evidence for multiple loci from a genome scan of autism kindreds. Mol Psychiatry 11: 1049–1060, 1979.
62. Duvall JA, Lu A, Cantor RM, Todd RD, Constantin JN, et al. (2007) A quantitative trait locus analysis of social responsiveness in multiplex autism families. Am J Hum Genet 164: 656–662.
63. Kilpinen H, Yliuako-oja T, Rehastrom K, Gaal E, Turunen JA, et al. (2009) Linkage and linkage disequilibrium scan for autism loci in an extended pedigree from Finland. Hum Mol Genet 18: 2912–2921.
64. Nazarian P, Patterson AD, Zwaaghaanen L, Roberts W, Brian J, et al. (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet 39: 319–326.
65. Philippe A, Martinez M, Guilloud-Bataille M, Gillberg C, Rastam M, et al. (1999) Genomewide scan for autism susceptibility genes. Part I: Autism Research International Sibpair Study. Hum Mol Genet 8: 805–812.
66. Wang K, Zhang H, Ma D, Bucan M, Glessner JT, et al. (2009) Common genetic variants on 5q14.1 associate with autism spectrum disorders. Nature 459: 328–333.
67. Weiss LA, Arking DE, Daly MJ, Chakravarti A (2009) A genomewide linkage and association scan reveals novel loci associated with autism. Nat 461: 802–808.
68. Anzenen M, Vanhala R, Varilo T, Ayers K, Kemppainen A, et al. (2009) Linkage and linkage disequilibrium scan for autism loci and genes in a multiplex Finnish autism pedigree. Hum Mol Genet 18: 2912–2921.
69. van Rijn S, Swaab DH, Almeran A, Karlen RD, et al. (2006) Social behavior and autism traits in a sex chromosomal disorder. Klinefelter (47XXY) syndrome. J Autism Dev Disord 36: 1643–1649.
70. Gong X, Bacchiello E, Blasi F, Toma C, Betancur C, et al. (2006) Analysis of X chromosome in autism spectrum disorders. Am J Med Genet Part B: Neuropsychiatric Genetics 147: 830–835.
71. Tartaglia N, Davis S, Hinchliff S, Beauregard R, et al. (2006) A new look at XXY syndrome: medical and psychological features. Am J Med Genet Part A 146A: 1509–1522.
72. Auyeung B, Taylor K, Hackett G, Baron-Cohen S (2010) Foetal testosterone explaining sex differences in the liability to autism. Ped Res 47: 9–16.
73. Creswell CS, Skuse DH (1999) Autism in association with Turner Syndrome: genetic implications for male vulnerability to pervasive developmental disorders. Neurocase 5: 511–518.
74. Grumbach MM, Hughes IA, Conte FA (2003) Williams textbook of endocrinology. In: Larsen PR, ed. Williams textbook of endocrinology. Philadelphia: Saunders.
75. Skuse D (2006) Genetic influences on the neural basis of social cognition. Philos T Roy Soc B 361: 2129–2141.
76. Elsas W, Ismail R, Kamenska J, Burmanna D, et al. (2005) Xlrb1 is a new imprinted candidate for X-linked parent-of-origin effects on cognitive function in mice. Nat Genet 37: 623–629.
77. Gregg C, Zhang J, Butler JE, Haig D, Dulec C. (2010) Sex-specific parent-of-origin allelic expression in the mouse brain. Science.
78. Brainh E, Swaab DH, van Engeland H (2009) Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. Pediatrics 123: e565–e570.
79. Geerts M, Steyaert J, Froy J (2003) The XXY syndrome: a follow-up study on 103 affected males. J Med Genet 40: 267–270.
114. Shaywitz SE, Shaywitz BA, Fletcher JM, Escobar MD (1990) Prevalence of reading disability in boys and girls. Results of the Connecticut Longitudinal Study. JAMA Am Med Assoc 264: 998–1002.

115. Liederman J, Kantrowitz L, Flannery K (2005) Male vulnerability to reading disability is not likely to be a myth: a call for new data. J Learn Disabil 38: 109–129.

116. Bishop DVM (1997) Uncommon understanding: development and disorders of language comprehension in children. Hove: Psychology Press.

117. Tomblin JB, Records NL, Buckwalter P, Zhang X, Smith E, et al. (1997) Prevalence of specific language impairment in kindergarten children. J Speech Lang Hear Res 40: 1245–1260.

118. Law J, Rush R, Schoon I, Parsons S (2009) Modeling developmental language difficulties from school entry into adulthood: literacy, mental health, and employment outcomes. J Speech Lang Hear Res 52: 1425–1446.

119. Kadesjö B, Gillberg C (2000) Tourette’s disorder: epidemiology and comorbidity in primary school children. J Am Acad Child Psy 39: 540–555.

120. Baron-Cohen S, Happe F, Wadsworth S, Wheelwright S (2006) The Autism-Spectrum Quotient (AQ): Adolescent version. J Autism Dev Disord 36: 343–350.

121. Wakabayashi A, Baron-Cohen S, Wheelwright S (2004) The Autism Spectrum Quotient (AQ) in Japan: a cross-cultural comparison. J Autism Dev Disord 34: 263–270.

122. Wakabayashi A, Baron-Cohen S, Uchiyama T, Yoshida Y, Tojo Y, et al. (2007) The Autism-Spectrum Quotient (AQ): Children’s Version in Japan: a cross-cultural comparison. J Autism Dev Disord 37: 491–500.

123. Happe F, Barchels M, Cathy DC, Boomsma DI (2008) Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in a large population and autistic groups. J Autism Dev Disord 38: 1533–1566.

124. Anoye S, Baron-Cohen S, Wheelwright S, Allison C (2008) The Autism Spectrum Quotient: Children’s Version (AQ-Child). J Autism Dev Disord 38: 1230–1240.

125. Anoye S, Wheelwright S, Allison C, Atkinson M, Samarawickrema N, et al. (2009) The children’s Empathy Quotient and Systemizing Quotient: sex differences in typical development and in autism spectrum conditions. J Autism Dev Disord 39: 1509–1521.

126. Scott F, Baron-Cohen S, Bolton P, Brayne C (2002) Prevalence of autism spectrum conditions in children aged 5–11 years in Cambridge, UK. Autism 6: 231–237.

127. Scott F, Baron-Cohen S, Bolton P, Brayne C (2002) The CAST (Childhood Asperger Syndrome Test) preliminary development of UK screen for mainstream primary-school children. Autism 6: 9–31.

128. Williams J, Allison C, Scott F, Bolton P, Baron-Cohen S, et al. (2008) The Childhood Autism Spectrum Test (CAST): sex differences. J Autism Dev Disord 38.

129. Williams J, Scott D, Allison C, Bolton G, Polatajko H, Baron-Cohen S, et al. (2005) The CAST Childhood Asperger Syndrome Test: test accuracy. Autism 9: 45–68.

130. Shah A, Frith U (1983) An inedit of ability in autism: a research note. J Child Psychol Psyschiatry 24: 613–620.

131. Jolliffe T, Baron-Cohen S (1997) Are people with autism or Asperger’s Syndrome faster than normal on the Embedded Figures Task? J Child Psychol Psyschiatry 38: 527–534.

132. Lawson J, Baron-Cohen S, Wheelwright S (2004) Empathising and systemising in adults with and without Asperger Syndrome. J Autism Dev Disord 34: 301–310.

133. Baron-Cohen S, Wheelwright S, Scambler V, Lawson J, Spong A (2001) Are atypical neural substrates of Embedded Figures Task performance in children and adolescents with autism. J Autism Dev Disord 35: 479–486.

134. Wiersema SF, Glezer II, Kigar DL (1995) Women have greater density of neurons in posterior temporal cortex. J Neurosci 15: 3431–3438.

135. Sowell ER, Petousis H, Kan E, Woods RP, Yotshi J, et al. (2007) Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex 17: 1500–1506.

136. Wiersema SF, Kigar DL (1992) Sylvain fissure morphology and asymmetry in men and women: bilateral differences in relation to handedness in men. J Comp Neurol 323: 326–340.

137. Herbst MR, Ziegler DA, Deutsch CK, O’Brien LM, Kennedy DN, et al. (2005) Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. Brain 128: 213–226.

138. Wada JA, Clarke R, Hamm A (1973) Cerebral hemispheric asymmetry in humans: Cortical speech zones in 100 adults and 100 infant brains. Arch Neurol-Chicago 32: 239–246.

139. Gage NM, Juranek J, Filippek PA, Osann K, Rodman P, et al. (2009) Rightward hemispheric asymmetries in auditory language cortex in children with autism spectrum disorders: a MRSI investigation. J Neuro Dev Disord 1: 203–214.

140. In K, Lee JM, Lee J, Shin YW, Kim Y, et al. (2006) Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. Neuroimage 31: 31–38.

141. Linder G, Nair NL, Thompson PM, Rex DE, Woods RP, et al. (2006) Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp 37: 314–324.

142. Bregan C, Lepore N, Luders E, Chou YY, Madsen SK, et al. (2009) Sex differences in brain structure in auditory and circulatory regions. Neuroreport 20: 930–935.

143. Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. Cereb Cortex 16: 1276–1292.

144. McAlonan GM, Cheung V, Suckling J, Lam GY, Tai KS, et al. (2005) Mapping the brain in autism: a voxel based MRSI study of volumetric differences and intercorrelations in autism. Brain 128: 268–276.

145. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, et al. (2010) Toward discovery science of human brain function. P Natl Acad Sci U S A 107: 4734–4739.

146. Kennedy DP, Courchesne E (2006) The intrinsic functional organization of the brain is altered in autism. Neuroimage 39: 1877–1885.

147. Lee JG, Pess-Frig F, Henning J, Kaur S, Thoburn C, et al. (2007) Atypical neural substrates of Embredered Figures Task performance in children with Autism Spectrum Disorder. Neuroimage 38: 184–193.

148. Chakrabarti B, Dudbridge F, Kent L, Wheelwright S, Hill-Cawthorne G, et al. (2009) Genes related to sex steroids, neural growth, and social-emotional behavior are associated with autistic traits, empathy, and Asperger syndrome. Autism Res 2: 157–177.

149. Tordjman A, Ferrari P, Silvamont V, Dyme M, Roubertoux P (1997) Atypical neural activity in autism spectrum disorder. Biol Psychiatry 42: 156–167.

150. Knickmeyer R, Baron-Cohen S (2006) Foetal testosterone and sex differences in typical social development and in autism. J Child Neuro 21: 823–845–845.
181. Knickmeyer R, Baron-Cohen S, Fane BA, Wheelwright S (2008) Masculinized model of ADHD. Behav Brain Res 107: 35–43.

182. Martel MM, Gobrogge KL, Breedlove SM, Nigg JT (2008) Right-handedness of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is altered pathways in neuronal development and steroid biosynthesis. PLoS ONE 4: e5775. doi:10.1371/journal.pone.0005775.

183. Knickmeyer R, Baron-Cohen S, Fane BA, Wheelwright S, Mathews GA, et al. (2006) Androgens and estrogens differentially and reciprocally regulate RORA, whose protein product is reduced in autistic brain. FASEB J 20: 3036–3051.

184. Schindrova E, Kelemenova S, Cizek P, Ficek A, Ostatnikova D (2010) Forced-feeding and form coherence detection in Autistic Spectrum Disorder: relationship to motor control and 2:4 digit ratio. J Autism Dev Disord 36: 1–13.

185. de Bruin EI, Verheij F, Wiegman T, Ferdinand RF (2006) Differences in finger length ratio between males with autism, pervasive developmental disorder-not otherwise specified, ADHD, and anxiety disorders. Dev Med Child Neurol 48: 962–963.

186. Henningsson S, Jonsson L, Ljunggren E, Westberg L, Gillberg C, et al. (2009) A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. Psychol Med 39: 962–965.

187. Murphy E, White S, Campbell R, Swettenham J, Hansen P, et al. (2006) Motion and form coherence detection in Autistic Spectrum Disorder: relationship to motor control and 2:4 digit ratio. J Autism Dev Disord 36: 1–13.

188. Jiang S, Xin R, Wu X, Lin S, Qian Y, et al. (2000) Association between attention deficit hyperactivity disorder and the DXS7 locus. Am J Medical Genet 96: 289–292.

189. Rommelse NN, Ahink ME, Arias-Vasquez A, Bouchez CJ, Fliers E, et al. (2006) Differential association between MAOA, ADHD and neuropsychological functioning in boys and girls. Am J Medical Genet Part B Neuropsychiatric Genetics 147B: 1524–1530.

190. Brooks-Kuslanski G, Kuslanski R, Winer B, Barry E, Gill M, et al. (2008) Association of the steroid sulfatase (STS) gene with attention deficit hyperactivity disorder. Am J Medical Genet Part B Neuropsychiatric Genetics 147B: 1531–1535.

191. Davies W, Hymby T, Isles AR, Burgoyne PS, Wilkinson LS (2007) X-linked microdeletions in Down syndrome. J Med Genet 44: 399–403.

192. Fisher SE, Francks C, McCracken JT, McGough JJ, Marlow AJ, et al. (2002) A genomewide scan identifies a chromosome 18 quantitative-trait locus influencing dyslexia. Am J Human Genet 71: 399–407.

193. Rowe R, Maughan B, Worthman CM, Costello EJ, Angold A (2004) Testosterone, antisocial behaviour and social dominance in boys: pubertal development and biocultural interaction. Psychol Med 35: 545–552.

194. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, R, HA, Pezawas L, et al. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. P Natl Acad Sci U S A 103: 6269–6274.

195. van Gelder M, Tijms J, Hoeks J (2005) Second to fourth digit ratio and dyslexia: no evidence for an association between reading disabilities and the 2:4D ratio. Dev Med Child Neurol 47: 710; author reply 719.

196. Dorn LD, Kellof DJ, Susman EJ, Huang B, Stein H, et al. (2009) Salivary gonadal and adrenal hormone differences in boys and girls with and without disruptive behavior disorders: contextual variants. Biol Psychi 81: 31–39.

197. Brookes K, Tabbah R, Gardiner W, Rubin RT, Cambell KL, et al. (2009) Adrenal androgen and gonadal hormone levels in adolescent boys with conduct disorder. Psychoneuroendocrinol 34: 1245–1256.

198. Rowe R, Maughan B, Worthman CM, Costello EJ, Angold A (2004) Testosterone, antisocial behaviour and social dominance in boys: pubertal development and biocultural interaction. Psychol Med 35: 545–552.

199. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, R, HA, Pezawas L, et al. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. P Natl Acad Sci U S A 103: 6269–6274.

200. van Gelder M, Tijms J, Hoeks J (2005) Second to fourth digit ratio and dyslexia: no evidence for an association between reading disabilities and the 2:4D ratio. Dev Med Child Neurol 47: 710; author reply 719.

201. Fisher SE, Francks C, Marlow AJ, MacPhie IL, Newbury DF, et al. (2002) A genomewide scan identifies a chromosome 18 quantitative-trait locus influencing dyslexia. Am J Human Genet 70: 86–91.

202. Finegan JK, Nichols GA, Staremanos G (1992) Relations between prenatal testosterone levels and cognitive abilities at 4 years. Dev Psychol 28: 1075–1089.

203. Bartlett CW, Flax JF, Logue MW, Veldman J, Bassett AS, et al. (2002) A major susceptibility locus for specific language impairment is located on 15p21. Am J Human Genet 71: 45–53.

204. Villanueve P, Newbury DF, Jara I, De Barbieri Z, Mirza G, et al. (2011) Genomewide analysis of genetic susceptibility to language impairment in an isolated Chilean population. Eur J Human Genet Jan 19: [Epub ahead of print].

205. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, R, HA, Pezawas L, et al. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. P Natl Acad Sci U S A 103: 6269–6274.

206. Ruta L, Ingudomnukul E, McRae KJ, Haidasz P, Newbury DF, et al. (2010) A genomewide scan identifies two novel loci involved in specific language impairment. Am J Human Genet 70: 384–398.

207. Alexander GM, Peterson BS (2004) Testing the prenatal hormone hypothesis of ADHD. Behav Brain Res 155: 70–76.

208. Dorn LD, Kellof DJ, Susman EJ, Huang B, Stein H, et al. (2009) Salivary gonadal and adrenal hormone differences in boys and girls with and without disruptive behavior disorders: contextual variants. Biol Psychi 81: 31–39.

209. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, R, HA, Pezawas L, et al. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. P Natl Acad Sci U S A 103: 6269–6274.

210. van Gelder M, Tijms J, Hoeks J (2005) Second to fourth digit ratio and dyslexia: no evidence for an association between reading disabilities and the 2:4D ratio. Dev Med Child Neurol 47: 710; author reply 719.

211. Fisher SE, Francks C, Marlow AJ, MacPhie IL, Newbury DF, et al. (2002) A genomewide scan identifies a chromosome 18 quantitative-trait locus influencing dyslexia. Am J Human Genet 70: 86–91.

212. Finegan JK, Nichols GA, Staremanos G (1992) Relations between prenatal testosterone levels and cognitive abilities at 4 years. Dev Psychol 28: 1075–1089.

213. Bartlett CW, Flax JF, Logue MW, Veldman J, Bassett AS, et al. (2002) A major susceptibility locus for specific language impairment is located on 15p21. Am J Human Genet 71: 45–53.

214. Villanueve P, Newbury DF, Jara I, De Barbieri Z, Mirza G, et al. (2011) Genomewide analysis of genetic susceptibility to language impairment in an isolated Chilean population. Eur J Human Genet Jan 19: [Epub ahead of print].

215. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, R, HA, Pezawas L, et al. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. P Natl Acad Sci U S A 103: 6269–6274.

216. van Gelder M, Tijms J, Hoeks J (2005) Second to fourth digit ratio and dyslexia: no evidence for an association between reading disabilities and the 2:4D ratio. Dev Med Child Neurol 47: 710; author reply 719.

217. Fisher SE, Francks C, Marlow AJ, MacPhie IL, Newbury DF, et al. (2002) A genomewide scan identifies a chromosome 18 quantitative-trait locus influencing dyslexia. Am J Human Genet 70: 86–91.