

Prenatal testosterone and gender-related behaviour

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Abstract

Testosterone plays an important role in mammalian brain development. In neural regions with appropriate receptors testosterone, or its metabolites, influences patterns of cell death and survival, neural connectivity and neurochemical characterization. Consequently, testosterone exposure during critical periods of early development produces permanent behavioural changes. In humans, affected behaviours include childhood play behaviour, sexual orientation, core gender identity and other characteristics that show sex differences (i.e. differ on average between males and females). These influences have been demonstrated primarily in individuals who experienced marked prenatal hormone abnormalities and associated ambiguities of genital development (e.g. congenital adrenal hyperplasia). However, there is also evidence that testosterone works within the normal range to make some individuals within each sex more sex-typical than others. The size of testosterone-related influences, and perhaps even their existence, varies from one sex-typed characteristic to another. For instance: prenatal exposure to high levels of testosterone has a substantial influence on sex-typical play behaviour, including sex-typed toy preferences, whereas influences on core gender identity and sexual orientation are less dramatic. In addition: there appears to be little or no influence of prenatal testosterone on mental rotations ability, although mental rotations ability shows a marked sex difference. These findings have implications for basic understanding of the role of testosterone in normative gender development, as well as for the clinical management of individuals with disorders of sex development (formerly called intersex syndromes).

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The hypothesis that levels of testosterone prenatally influence human behaviour derives from a large body of research on the neural and behavioural effects of early hormone manipulations in other mammals (1). Hundreds of studies on species ranging from rodents to non-human primates show that testosterone, and hormones produced from testosterone, play a primary role in neural and behavioural sexual differentiation, just as they do in sexual differentiation of the external genitalia. This article will begin by summarizing the findings from these experimental studies, and will then discuss evidence that hormones exert similar influences on the human brain and human behaviour. This evaluation of human relevance will focus largely on clinical studies. In addition, although any behaviour that shows a sex difference in humans might be hypothesized to be influenced by testosterone, limits on space allow

treatment of only a subset of sexually differentiated behaviours here. Therefore, this article focuses on the role of testosterone in the development of childhood play behaviour, sexual orientation, core gender identity and specific visuospatial ability, mental rotations ability.

Developmental influences of testosterone in non-human mammals

Studies examining the effects of testosterone on mammalian development typically involve manipulating hormone levels during critical periods of early life. These critical periods correspond to the periods when developing males of the species naturally produce testicular hormones, including testosterone, producing higher testosterone levels in males than in females (2). The exact periods when these critical periods occur differ from one species to the next. In the rat, for example, the primary critical period occurs neonatally, from about the first to the tenth day of postnatal life. In contrast, in the rhesus monkey, the corresponding critical period occurs prenatally. Therefore, the periods when hormonal manipulations influence neural and behavioural

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development are different for these two species, being prenatal in rhesus monkeys, but postnatal in rats.

Despite these differences in the periods when testosterone manipulations alter brain structure and function, the outcomes of the manipulations are largely consistent across species. In both rodents and non-human primates, exposing developing female animals to high levels of testosterone, for example, by injecting them or their pregnant mothers with the hormone, increases subsequent levels of male-typical behaviour (1). In rats, for instance, a single injection of testosterone on the day of birth produces female animals who show elevated levels of rough-and-tumble play, a behaviour that is normally more common in juvenile males than in juvenile females. Similarly, female rats treated with testosterone neonatally show increased capacity for male-typical sexual behaviour and reduced capacity for female-typical sexual behaviour in adulthood. Removing testosterone from developing male rats (e.g. by neonatal castration) has the opposite effects, reducing male-typical behaviour and increasing female-typical behaviour. Comparable effects, on both juvenile play behaviour and on sexual behaviour in adulthood are seen following prenatal testosterone manipulations in rhesus monkeys (3, 4).

Early manipulations of testosterone are thought to alter subsequent behaviour, because testosterone plays an important role in basic processes of neural development. Receptors for testosterone, or for hormones produced from testosterone, are found in a number of brain regions, including several hypothalamic nuclei, the medial amygdaloid nucleus and the cerebral cortex, and the location of these receptors is remarkably similar across mammalian species (4). Manipulating testosterone alters the development of these hormone-sensitive neural regions, influencing, for instance, patterns of programmed cell death, anatomical connections between brain regions and neurochemical characterization and usage (4). These neural changes are thought to underlie the behavioural changes seen following testosterone manipulations during early development.

Developmental influences of testosterone in humans

As is the case for non-human primates, the critical periods when testosterone is higher in developing males versus females, and thus the periods when testosterone would be hypothesized to influence human neural and behavioural sexual differentiation, appear to be largely prenatal. Although information is limited, there appears to be a dramatic sex difference in testosterone levels in human foetuses from about week 8 to 24 of gestation (5). Another, smaller sex difference in circulating testosterone occurs in the early postnatal period in humans as well as in rhesus monkeys, but studies to date have produced little evidence that it plays a role in

sexual differentiation of behaviour (5, 6), and research on the impact of testosterone on human development has focused largely on the prenatal period.

Prenatal treatment of developing humans with testosterone for experimental purposes is generally unethical. Consequently, researchers interested in the human relevance of research showing that testosterone influences neural and behavioural development in other mammals have used other approaches to gain information. These approaches have included studying: (i) individuals who have genetic disorders that cause abnormalities in the amount or activity of testosterone, beginning prenatally; (ii) individuals whose mothers were prescribed hormones during pregnancy for medical reasons; and (iii) individuals with no history of hormone abnormality, but for whom information on prenatal hormone levels is available and can be related to postnatal behaviour (2).

Studies of individuals with genetic disorders causing prenatal hormone abnormality

Perhaps the most extensive information on the human consequences of prenatal androgen abnormality has come from studies of girls and women with congenital adrenal hyperplasia (CAH), an autosomal recessive disorder that causes elevated adrenal androgens, particularly testosterone, beginning in the foetus. The underlying disorder typically involves deficiency in the enzyme, 21 hydroxylase (21-OH). Worldwide newborn screening suggests that classical CAH caused by 21-OH deficiency occurs in 1 in 14 500 live births (7). As a consequence of their prenatal androgen elevation, girls with CAH are typically born with partial to complete virilization of the external genitalia, resulting in their diagnosis soon after birth and postnatal treatment with corticosteroids to regulate the hormonal milieu (8). Despite this postnatal regulation of hormone levels, the prenatal exposure to elevated testosterone levels might be hypothesized to influence behavioural development. Specifically, the findings from studies of other mammals where testosterone was manipulated during critical periods of early development leads to the hypothesis that girls with CAH would show elevated levels of male-typical behaviour and reduced levels of female-typical behaviour.

Research on girls and women with CAH has provided some support for the hypothesized influence of testosterone on human behavioural development. Girls with CAH show increased male-typical play behaviour, including increased preferences for toys that are usually chosen by boys, such as vehicles and weapons, increased preferences for boys as playmates and increased interest in rough-and-tumble play. These findings of increased male-typical play behaviour have been seen using varied measures (interviews, standardized questionnaires, analyses of drawings and direct observation of behaviour in

playroom settings), and in samples of girls with CAH in several countries (the United States, Canada, The Netherlands, Sweden, Germany, Japan and the United Kingdom) (2). Like the CAH-related virilization of the external genitalia, CAH-related behavioural virilization is not complete. The toy, activity and playmate preferences of girls with CAH are more male-typical than those of their unaffected female relatives as well as of control girls matched for age and other aspects of demographic background, but they are not as male-typical as those of boys. For instance, in regard to playmates, 80–90% of the playmates of healthy boys and girls of elementary school age are children of the same sex, whereas girls with CAH do not appear to show a preference for playing with one sex over the other. They indicate that about 50% of their favourite playmates are girls and about 50% are boys (9).

As adults, women with CAH are less likely to be exclusively heterosexual than are their unaffected sisters, controls matched for age and demographic background, or women with other disorders that cause different hormone abnormalities or abnormalities of the external genitalia (10–12). The nature of this behavioural change is not necessarily to produce a homosexual orientation. In fact, bisexuality may be a similarly likely outcome. For instance, a study by Hines *et al.* (11), found that five out of 16 women with CAH reported that they were neither exclusively nor almost exclusively heterosexual. Of these five, one was exclusively homosexual, two were almost exclusively homosexual and two were equally homosexual and heterosexual in their behaviour. In addition, this study provided quantitative data, making it possible to compare the magnitude of the effect of CAH on sexual orientation with the magnitude of the effect on childhood play behaviour (see Fig. 1). For childhood play behaviour, females with CAH were moved about 60% of the distance toward mean male-typical behaviour, whereas for sexual orientation, females with CAH were moved only about 10% of the distance toward mean male-typical orientation.

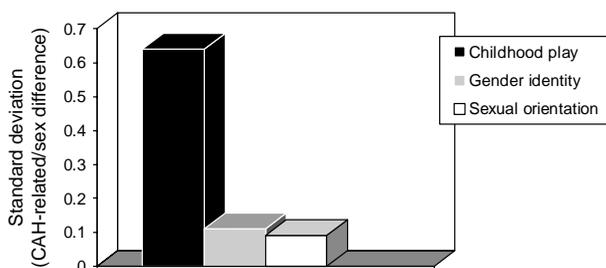


Figure 1 The size of the difference between females with congenital adrenal hyperplasia (CAH) and those without CAH relative to the size of the sex difference in three characteristics: childhood play behaviour (sex-typed toy, activity, temperamental and playmate preferences); sexual orientation (preferences for erotic partners of the same or the other sex); and core gender identity (sense of self as male or female). Group differences (CAH versus control; male versus female) are expressed in standard deviation units.

Studies of core gender identity, or sense of self as male or female, in females with CAH also suggest an influence of testosterone on human psychosexual development. Although the vast majority of women with CAH are content with their female identity, a small minority, perhaps about 3–5%, indicate a desire to live as males (10, 11, 13, 14). Once again, quantitative data (11) suggest that this effect of CAH on gender identity is markedly smaller than the effect on sex-typed childhood play behaviour, and similar in magnitude to the effect on sexual orientation (see Fig. 1).

Studies of children born following maternal treatment with hormones during pregnancy

Other situations where hormone levels or responses are altered prenatally provide additional support for the conclusion that prenatal levels of testosterone influence human psychosexual development. For instance, genetic males with complete androgen insensitivity syndrome (CAIS), an X-linked disorder in which the cells of XY individuals lack functional androgen receptors, and so cannot respond to the testosterone and other androgenic hormones produced by their gonads, are almost always female-typical not only in physical appearance, but also in terms of behaviour, including core gender identity, sexual orientation and childhood play behaviour (15, 16). This suggests that their functional lack of androgen exposure has produced female-typical psychosexual development, despite the presence of a Y chromosome. Similarly, girls whose mothers were prescribed hormones that stimulate androgen receptors prenatally, like girls with CAH, show more male-typical childhood play behaviour and interests (17).

Studies of normal variability in prenatal testosterone

Studies of the relationships between normal variability in testosterone prenatally and behaviour postnatally are challenging, because differences between one healthy male or female foetus and another in hormone levels are smaller than those between healthy individuals and those with a genetic disorder, such as CAH or CAIS, or than pregnancies treated with hormone versus those left untreated. Nevertheless, some studies relating normal variability in hormones prenatally to postnatal behaviour support the hypothesis that prenatal levels of testosterone predict male-typical behaviour.

Maternal testosterone during pregnancy shows a substantial correlation with foetal testosterone (18) and testosterone production is highly heritable (19, 20). Therefore, measures of maternal testosterone during pregnancy provide indirect measures of testosterone levels in the foetus. Using this approach, one study

(21) found that maternal testosterone during pregnancy predicted male-typical versus female-typical interests in adult female offspring, and another (22) found that maternal testosterone during pregnancy predicted the amount of male-typical behaviour in female offspring at the age of 3.5 years. This last study used the same measure of childhood sex-typed behaviour as has also been used in studies of females with CAH, thus providing directly comparable evidence of similar, though less marked, influences of testosterone on the development of children's behaviour.

Studies relating testosterone measured in amniotic fluid to sex-typed behaviour have generally not found the hypothesized relationships with postnatal behaviour, particularly in girls. This may be because the studies have relied on small samples, thus limiting experimental power. In addition, a single measure from amniotic fluid may be a poor estimate of the prenatal hormone environment. For instance, one study found no relation between amniotic fluid testosterone and sex typed play behaviour in childhood (23). However, this study included only 22 girls, limiting the study's power to detect existing effects. In addition, the measure of play behaviour used in the study may have been insensitive to within-sex variability. In contrast, the study reporting a positive relationship between maternal testosterone during pregnancy and subsequent sex-typed behaviour used extreme gender-typed groups from a sample of over 3500 girls, and a measure of sex-typed behaviour that was designed specifically to assess behavioural variability within each sex. Similarly, the study reporting a relationship between maternal testosterone and sex-typed behaviour in adult female offspring used a sample of over 100 pregnant women and their daughters, and targeted sex-typed behaviour with multiple measures, thereby increasing the reliability of behavioural measurement. Therefore, a single measure of testosterone from amniotic fluid may not be a sufficiently powerful measure of foetal testosterone, particularly in small samples of females, and unless efforts are made to maximize the reliability of behavioural measurement.

Despite the lack of a significant relationship between testosterone measured in amniotic fluid and sex-typed play behaviour (23), a relationship has been reported between testosterone measured in amniotic fluid and other psychological characteristics, including eye contact and vocabulary development (24). The focus on eye contact and vocabulary reflected an interest in the possibility that testosterone plays a role in the development of autistic spectrum conditions. Interestingly, the relationships reported involved primarily males rather than females, as is also the case for autistic spectrum conditions. Approximately four males are diagnosed with classic autism for every one female diagnosed, and about nine males for every one female receives the less severe diagnosis of Asperger Syndrome (25, 26). In contrast, most other research studying the role of testosterone in human psychosexual development has

produced more supportive evidence in females than in males. For instance, behavioural alterations related to CAH have been seen primarily in females, even when males are also studied (2, 27), as have relationships to maternal testosterone (22). A study of psychological characteristics related to autism in individuals with CAH has also found some, but not all, predicted alterations, and where predicted alterations were seen, they occurred in females but not in males (28). One possible explanation of significant relationships between amniotic fluid measures of testosterone and behaviours related to autism in males but not in females is that testosterone in amniotic fluid shows less variability in females than in males, thus making detection of relationships in females less likely. Alternatively, relationships between testosterone and behaviours related to autism may differ from relationships in other areas, such as childhood play behaviour, sexual orientation and core gender identity, in being applicable to males rather than females, although the recent data on characteristics related to autism in individuals with CAH argue against this explanation (28).

Prenatal testosterone and cognitive abilities that show sex differences

Despite the influences of prenatal testosterone on some behaviours that show sex differences, not all behaviours that show sex differences appear to be similarly influenced by testosterone. For instance, much research has been devoted to trying to establish a link between prenatal testosterone levels and postnatal visuospatial and mathematical abilities as reflected in performance on standardized tests. It is widely believed that men and boys are better at spatial and mathematical abilities than women and girls. However, the validity of this generalization depends on the age of the individuals being studied, as well as on the type of task. Specifically, although men perform better than women on tests of mental rotations ability (that is, the ability to rotate two- or three-dimensional figures in the mind and compare them to other figures), these differences are larger in adults than in children (29, 30). In addition, sex differences in performance on other spatial tasks are smaller than the sex differences in mental rotations performance (29, 30). Indeed, for some tasks, such as those requiring spatial visualization skills, or the ability to take spatial manipulations through several steps, sex differences are virtually non-existent (29). Similarly, sex differences in mathematics performance vary with age and the type of task. Among children, girls perform better on measures of computational ability, although there are no sex differences on computational tasks in adults (31). For mathematical concepts, there are no sex differences in children or adults, however, some standardized measures used to screen for admission to University in the United States (the Scholastic Aptitude

Test and the Graduate Record Exam) show a sex difference in favour of males (31).

Despite these sex differences in the population at large, girls and women with CAH do not show consistent alterations in performance on spatial abilities at which males typically excel (32) (Table 1). Although studies occasionally report that females with CAH show enhanced spatial ability, this result is not the norm. In addition, if the effects were reliable, they would be expected to be most marked for measures of mental rotations, since mental rotations measures show the largest sex differences. In contrast, the results are similar for a variety of measures, including measures of spatial visualization, although these measures show essentially no sex differences in the population at large. Similarly, if the findings were reliable, they would be expected to be seen more frequently in larger, rather than smaller, samples. On the contrary, two of the three studies reporting a relationship between CAH and spatial performance have used the smallest and second smallest samples of studies published to date. Both the lack of specificity for measures that show sex differences and the appearance of significant differences in smaller, rather than larger, samples suggest that the effects are spurious. With regard to mathematical performance, instead of showing enhanced mathematical abilities, as would be predicted if androgen exposure prenatally promoted mathematical performance, some aspects of mathematical performance in individuals with CAH appear to be impaired (2, 33–35).

Studies relating normal variability in hormones measured in amniotic fluid to postnatal behaviour also provide no support for an association between high levels of androgen and enhanced spatial or mathematical abilities (36, 37). In fact, although many cognitive measures show no relationship to amniotic fluid testosterone, some significant relationships have been reported in the opposite direction (i.e. higher testosterone or other androgens associated with poorer performance on mathematics or spatial tasks (36, 37)). The only possibly supportive data that have been

published involved a relationship between the speed of rotating figures on a mental rotations task and testosterone in amniotic fluid (37). However, in the same study, the number of correct answers on the mental rotations test, the usual dependent variable and the one known to show a sex difference and predicted to relate to prenatal testosterone, did not relate to testosterone from amniotic fluid. Thus, there is little or no evidence, either from studies of individuals with CAH or studies relating normal variability in prenatal hormones to postnatal behaviour, that prenatal testosterone influences performance on measures of spatial or mathematical ability.

Summary and conclusions

Convergent data from studies of individuals with genetic disorders, such as CAH or CAIS, offspring of pregnancies where women were treated with medications that influence testosterone, and studies relating normal variability in prenatal testosterone to postnatal behaviour, all suggest that levels of prenatal testosterone predict levels of sex-typed postnatal childhood play behaviour. Although there are fewer studies relating prenatal testosterone levels to postnatal sexual orientation and core gender identity, there is also some evidence, particularly from women with CAH or CAIS, that testosterone influences these psychosexual outcomes as well. However, these influences are substantially smaller than those on childhood play behaviour. Despite the influences of testosterone on childhood play behaviour, and to a lesser extent on sexual orientation and core gender identity in adulthood, prenatal levels of testosterone do not appear to influence mathematical abilities or visuospatial abilities that normally show sex differences. These findings imply that sexual differentiation of human behaviour is a complicated process, and that aetiological factors differ between different psychosexual outcomes. An important clinical implication of these findings is that

Table 1 Studies of spatial abilities in individuals with congenital adrenal hyperplasia (CAH).

Source	Participants		Age (in years)	Findings and type of task
	CAH	Control		
Perlman (34)	11F	11 (MT)	3–15	CAH F better (a)
Baker & Ehrhardt (33)	13F, 8M	11F, 14M (RL)	4–26	No differences M or F (a and c)
McGuire <i>et al.</i> (38)	15F, 16M	31 (MT)	5–30	No differences M or F (a)
Resnick <i>et al.</i> (39)	17F, 8M	13F, 14M (RL)	11–31	CAH F better on 3 (a, c and c), but no different on 2 (a and a). CAH M no differences
Helleday <i>et al.</i> (40)	22F	22 (MT)	17–34	CAH F worse on 1 (b), but no different on 3 (a, a and c)*
Hampson <i>et al.</i> (41)	7F, 5M	5F, 4M (RL)	8–12	CAH F better, CAH M worse on 1 (a)
Hines <i>et al.</i> (32)	40F, 29M	29F, 30M (RL)	12–45	CAH F no different CAH M worse on 1 (c)

M, males; F, females; MT, matched; RL, relative. (a) Spatial visualization tasks. (b) Spatial perception task. (c) Mental rotations task.

*For example, CAH F worse on 1 (b), but no different on 3 (a, a and c) means that CAH females performed worse than controls on a spatial perception task (b), but no different from controls on three other tasks, two of which were spatial visualization tasks (a and a) and one of which was a mental rotations task (c). (Reprinted from Hines M. *Brain Gender* New York: Oxford University Press, 2004. Copyright Melissa Hines).

cross-gendered behaviour in childhood does not imply a disorder of gender development, since, for instance, many girls with CAH will show increased male-typical behaviour in childhood, but will not show alterations in their core gender identity.

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