Gender Development and the Human Brain

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Abstract

Convincing evidence indicates that prenatal exposure to the gonadal hormone, testosterone, influences the development of children's sex-typical toy and activity interests. In addition, growing evidence shows that testosterone exposure contributes similarly to the development of other human behaviors that show sex differences, including sexual orientation, core gender identity, and some, though not all, sex-related cognitive and personality characteristics. In addition to these prenatal hormonal influences, early infancy and puberty may provide additional critical periods when hormones influence human neurobehavioral organization. Sex-linked genes could also contribute to human gender development, and most sex-related characteristics are influenced by socialization and other aspects of postnatal experience, as well. Neural mechanisms underlying the influences of gonadal hormones on human behavior are beginning to be identified. Although the neural mechanisms underlying experiential influences remain largely uninvestigated, they could involve the same neural circuitry as that affected by hormones.

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influences on both gender-related behavior and the developing brain and because recent research provides convincing evidence that testosterone exerts similar influences on human development. The article critically reviews the evidence of prenatal hormonal influences on human neurobehavioral sexual differentiation and contextualizes these hormonal effects with genetic, social, and cognitive influences on gender development. It also critically reviews the evidence regarding possible neural changes underlying hormonal influences on human behavior and suggests that neural systems similar to those influenced by hormones underlie other types of influences on gendered behavior.

INTRODUCTION

Males and females differ both behaviorally and neurally. Indeed, the existence of behavioral sex differences implies the existence of neural sex differences, given that behavior depends on the nervous system. Contemporary research shows that gendered behavior results from a complex interplay of genes, gonadal hormones, socialization, and cognitive development related to gender identification. This article focuses on the role of gonadal hormones, particularly testosterone, during early development. This focus has been chosen because extensive experimental research in nonhuman mammals shows that testosterone exerts powerful

Gonadal hormones: gonads' products, including androgens, produced mainly by the testes, and estrogens and progesterone, produced mainly by the ovaries

Testosterone: the major androgenic hormone produced by the testes

GENERAL PRINCIPLES OF SEXUAL DIFFERENTIATION

Gender development begins at conception with the union of two X chromosomes (genetic female) or an X and a Y chromosome (genetic male). The main role of these sex chromosomes in human sexual differentiation is to determine whether the gonads become testes or ovaries (Arnold 2009). Genetic information on the Y chromosome leads to testicular differentiation (Wilson et al. 1981), whereas without the Y chromosome, ovaries develop instead of testes. The testes begin to produce testosterone prenatally, and the ovaries do not (Wilson et al. 1981). Consequently, male and female fetuses differ in the amount of testosterone to which they are exposed. This sex difference appears to be maximal between about weeks 8 and 24 of human gestation, with testosterone in males tapering off before birth (Carson et al. 1982, Reyes et al. 1973). In nonhuman mammals at comparable stages of early development, testosterone and hormones produced from testosterone influence neural survival, neuroanatomical connectivity, and neurochemical specification, producing sex differences in brain structure and function (McCarthy et al. 2009). These effects of testosterone on neural development provide powerful mechanisms for influencing behavior across the life span.

ANIMAL MODELS OF HORMONE EFFECTS

The influences of early testosterone exposure on neurobehavioral development were first documented in a landmark study by Phoenix et al. (1959). They showed that administering testosterone to pregnant guinea pigs produced female offspring who showed increased capacity for male-typical sexual behavior and decreased capacity for female-typical sexual behavior in adulthood (Phoenix et al. 1959). Phoenix et al. contrasted these early, and permanent, effects of hormones, which they called organizational because they were thought to reflect changes in the organization of neural systems, with the later, and transient, effects of hormones after puberty, which they called activational because they were thought to reflect transient activation of the previously organized systems. This organizational/activational distinction has stood up well in the subsequent 50 some years (Arnold 2009), and thousands of studies on numerous species, including not only guinea pigs, but also rats, mice, hamsters, gerbils, ferrets, dogs, sheep, and marmoset and rhesus monkeys, have documented the early organizing effects of testosterone on a wide variety of behaviors that show sex differences (Hines 2004, 2009; McCarthy et al. 2009). For instance, the female offspring of rhesus macaques treated with testosterone during pregnancy show increased male-typical, and reduced female-typical, sexual behavior in adulthood, and increased male-typical, rough-and-tumble play as juvenile animals.

The organizing influences of testosterone on behavioral development were originally thought to reflect subtle neural changes (Phoenix et al. 1959). Subsequent research, however, has shown that early hormone manipulations produce dramatic changes in the structure of neural regions with the relevant hormone receptors. The first dramatic neural sex difference described in the rodent brain was the sexually dimorphic nucleus of the preoptic area (SDN-POA). This region of the anterior hypothalamic/preoptic area (AH/POA) is several fold larger in the adult male rat than in the adult female rat, and its volume can be altered by manipulating testosterone during early development (Gorski et al. 1978, 1980). Administering testosterone to developing female animals increases the volume of the SDN-POA, and removing testosterone from developing males reduces its volume (Dohler et al. 1984, Jacobson et al. 1981). Other neural regions in addition to the SDN-POA show sex differences, and in these regions too, the size of the sex difference is influenced by the early hormone environment. For instance, a second region of the preoptic area, the anteroventral paraventricular nucleus, is larger and contains more neurons in female rats than in males, and these characteristics are reduced by early testosterone treatment (Ito et al. 1986, Sumida et al. 1993). Similar neural sex differences have been reported in other rodent species, including gerbils, hamsters, mice, and guinea pigs, as well as in ferrets, sheep, and rhesus monkeys, and studies investigating early hormone influences have found similar results to those seen in rats, in other rodent species, and in ferrets (Bleier et al. 1982, Byne 1998, Hines et al. 1987, Roselli et al. 2004, Simerly et al. 1997, Tobet et al. 1986, Ulibarri & Yahr 1988).

Some general principles can be derived from the extensive experimental work in nonhuman mammals, and these principles have informed hypotheses regarding possible hormonal influences on human brain and behavior (see Hines 2009, for a review). First, during early development, estrogens generally do not promote female-typical development. Instead, female-typical development occurs in the absence of testicular hormones. Thus, exposure to high levels of estrogen is not expected to femininize neurobehavioral development. Second, the effects of testosterone on development are graded and linear; the more hormone the animal is exposed to, the more male-typical its behavior and brain structure become. An implication of this principle is that gonadal hormones can contribute to individual differences within each sex, as well as to differences between the sexes. Third, neurobehavioral sexual differentiation is a multidimensional process. The many

Rough-and-tumble play: juvenile behavior characterized by overall body contact or playful aggression; more common in males than in females

SDN-POA: sexually dimorphic nucleus of the preoptic area

Critical period: programmed stage of development at which an influence is most likely (or only likely) to occur. Sometimes called sensitive period

Androgenic (anti-androgenic) progestins: synthetic hormones that mimic progesterone, but which can also mimic androgens (androgenic) or impair androgen action (antiandrogenic)

Congenital adrenal hyperplasia (CAH): genetic disorder causing increased adrenal androgen production, beginning prenatally

behaviors and neural systems that differ for males and females can be influenced by hormones during slightly different critical periods, or can be sensitive to different doses of hormone, or to different metabolites of testosterone, or can involve different downstream mechanisms such as cofactors. Implications of this principle include an expectation that the many human behaviors and brain structures that differ by sex may not relate in a uniform way to one another and that individuals can develop complicated patterns of sex-typed behavior, being masculine in some respects and feminine in others. Fourth, the effects of hormones can differ somewhat from one species to another. For instance, behaviors that are influenced in one species may not be influenced in all others. Similarly, brain regions that differ for males and females in one species may not show a sex difference in another. Thus the specific effects of gonadal steroids seen on the brain and behavior of nonhuman mammals cannot be automatically generalized to humans, as well. Instead, hypothesized neural and behavioral influences of testosterone during early development must be evaluated directly in humans. Fifth, the behaviors and neural features that are influenced by gonadal hormones are those that show sex differences, meaning that they differ on average for males and females. Therefore, the characteristics that are likely to be influenced in humans are also those that show sex differences.

HUMAN RESEARCH

Ethical considerations generally preclude experimental manipulations of gonadal hormones in humans during early development. However, information from genetic syndromes that produce fetal hormone abnormality, as well as from situations in which pregnant women have been prescribed hormones, and studies relating normal variability in hormones early in life to normal variability in subsequent behavior all suggest that hormones contribute to human gender development. The most convincing evidence of these influences has come from studies of childhood play.

Why Study Children's Play?

Girls and boys differ in their toy, playmate, and activity preferences (Hines, 2010a). For example, boys tend to prefer toy vehicles, whereas girls tend to prefer dolls. Girls and boys also generally prefer playmates of their own sex, and boys spend more time in rough-and-tumble play than girls do. Children's sex-typed play behavior is the aspect of human gender development that has been studied most extensively in relation to the early hormone environment. This focus on childhood play reflects several considerations. First, children spend most of their time playing, and play is thought to be essential for healthy cognitive and emotional development (Ginsburg et al. 2007, Piaget 1970, Vygotsky 1976). Second, children's sex-typed play behavior can be assessed readily and reliably. Third, large sex differences exist in children's play, larger than those in cognitive abilities or personality characteristics (Hines 2010b), providing scope for detecting hormonal influences. Fourth, sex differences in children's play are evident early in life and relate to other behaviors that show sex differences, including sexual orientation and gender identification (Bailey & Zucker 1995, Green 1985, Hines et al. 2004). Fifth, play can be assessed during a period of hormonal quiescence, allowing examination of the early and permanent organizational influences of hormones on brain development, prior to the addition of the transient, activational influences of hormones that occur after puberty.

Several types of studies provide convergent evidence that testosterone concentrations prenatally influence children's subsequent sex-typed toy, playmate, and activity preferences. Studies of girls exposed to unusually high levels of testosterone and other androgens before birth, because they have the genetic disorder known as classic congenital adrenal hyperplasia (CAH), consistently find that these girls show increased male-typical play and reduced female-typical play (Berenbaum & Hines 1992, Dittmann et al. 1990, Ehrhardt et al. 1968, Ehrhardt & Baker 1974, Hall et al.

2004, Nordenstrom et al. 2002, Pasterski et al. 2005). Similarly, children whose mothers took androgenic progestins during pregnancy have shown increased male-typical toy and activity preferences, whereas the opposite occurs in children whose mothers took antiandrogenic progestins (Ehrhardt et al. 1977, Ehrhardt & Money 1967).

Is the Behavioral Alteration Caused by Hormones Acting on the Developing Brain?

The external genitalia, as well as the brain, contain androgen receptors, and girls with CAH, as well as those whose mothers took androgenic progestins, are typically born with varying degrees of genital virilization (enlarged clitoris, fused labia). Those skeptical of gonadal hormone influences on human neurobehavioral development suggest that the abnormal genital appearance, rather than the neural influences of androgens, could cause behavioral masculinization (Fausto-Sterling 1992, Jordan-Young 2010). Specifically, they suggest that parents may treat their daughters differently because of the girls' external virilization at birth and that this difference in parental treatment could alter sex-typed behavior. In addition, they suggest that virilized genitalia could reduce self-identification as female, which could in turn cause increased male-typical behavior.

Some evidence suggests that parents can influence the development of children's gender-typical behavior. For instance, parents generally encourage sex-typical play (Fagot 1978, Langlois & Downs 1980, Pasterski et al. 2005), and the amount of such encouragement has been found to correlate with the amount of sex-typed toy play, at least among typically developing children (Pasterski et al. 2005). However, parents have been found to offer more, rather than less, encouragement of sex-typical play to their daughters with CAH than to their daughters who do not have the disorder (Pasterski et al. 2005), suggesting that parental encouragement is not responsible for cross-gendered toy choices in girls with CAH.

Similarly, although gender identification plays a role in children's acquisition of gender-related behavior, at least in typically developing children (Hines 2010a, Ruble et al. 2006), it is unlikely that the male-typical behavior in girls with CAH results solely from altered gender identity based on genital virilization at birth. Evidence arguing against this explanation comes from studies relating normal variability in prenatal testosterone exposure to normal variability in subsequent behavior. Testosterone concentrations in maternal blood samples taken during pregnancy or in amniotic fluid from normally developing fetuses relate positively to male-typical childhood behavior (Auyeung et al. 2009b, Hines et al. 2002). Because the children in these studies have normal appearing genitalia, it is unlikely that differential parental socialization or changes in gender identification based on genital appearance account for the observed relationships between prenatal testosterone and postnatal behavior.

Researchers have also looked at species in which children's toys are novel objects and therefore not subject to the socialization histories or processes of gender identification thought to explain sex-typed toy preferences in children. Two studies of nonhuman primates have reported sex-typed toy preferences similar to those seen in children. Male vervet monkeys (Alexander & Hines 2002) have been found to spend more time than females contacting toys that are typically preferred by boys (e.g., a car) and less time contacting toys that are typically preferred by girls (e.g., a doll) (**Figure 1**). Similarly, male rhesus monkeys have been found to prefer toys normally preferred by boys (wheeled toys) to plush toys (Hassett et al. 2008). These findings show that sex-typed toy preferences can arise independent of the social and cognitive processes involved in gender development.

Rethinking Children's Preferences for Sex-Typed Toys

Children's sex-typical toy preferences have been widely assumed to result from socialization and other postnatal factors and to

Androgens: substances, including testosterone, that promote masculinization. Produced by the testes, adrenal glands, and ovaries, with the testes the largest source

Virilized genitalia: masculinized genitalia, typically involving an enlarged clitoris and partially fused labia

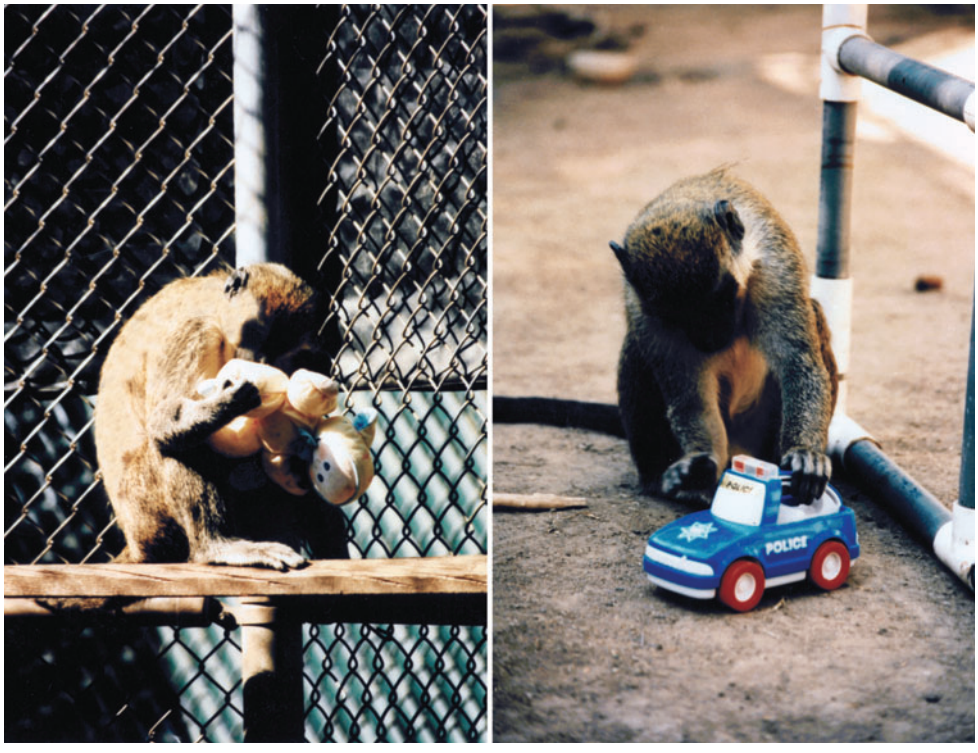

Figure 1

Examples of a male and a female vervet monkey contacting human children's sex-typed toys. The female animal (*left*) appears to be inspecting the doll in a manner similar to that in which vervet monkeys inspect infant vervets. The male animal (*right*) appears to be moving the car along the ground as a child might do. Reproduced by permission from Alexander & Hines (2002).

provide rehearsals for adult sex-typed social roles. Evidence of inborn influences has led researchers to reevaluate this perspective and to investigate the object features that make certain toys more or less interesting to brains exposed prenatally to different amounts of testosterone. Although boys' toys and girls' toys differ in shape and color (boys' toys tend to be angular and blue, whereas girls' toys tend to be rounded and pink), sex differences in toy preferences are present in very young infants (Alexander et al. 2009b, Campbell et al. 2000, Jadva et al. 2010, Serbin et al. 2001), before sex differences in color or shape preferences are seen (Jadva et al. 2010), suggesting that the object preferences do not result from the color or shape preferences. Another possibility is that boys like toys that can be moved in space, and prenatal androgen exposure may increase interest in watching things move in space (Alexander 2003, Alexander & Hines 2002, Hines 2004), perhaps by altering development of the visual system (Alexander 2003).

Early Hormone Influences on Sexual Orientation and Core Gender Identity

Adult behaviors that show sex differences, including sexual orientation and core gender identity, also appear to be influenced by prenatal testosterone exposure. Women with CAH not only recall more male-typical childhood behavior, but also show reduced heterosexual orientation as adults, and these two outcomes correlate (Hines et al. 2004; see Meyer-Bahlburg et al. 2008 for a review of additional

studies of CAH and sexual orientation). Normal variability in testosterone prenatally, e.g., from maternal blood or amniotic fluid, has not yet been related to sexual orientation, but a characteristic that is thought to provide an indirect measure of prenatal testosterone exposure, the ratio of the second to the fourth digit of the hand (2D:4D), which is greater in females than in males, has been linked. A study of more than 200,000 individuals, who measured their own 2D:4D and reported their sexual orientation online, found that 2D:4D related as predicted to sexual orientation in males, but not in females (Collaer et al. 2007). A meta-analysis that did not include this large study reached a somewhat different conclusion, however, finding that 2D:4D related as predicted to sexual orientation in females, but not in males (Grimbos et al. 2010). Finger ratios are probably a weak correlate of prenatal testosterone exposure, perhaps explaining the somewhat inconsistent results.

Women with CAH not only show reduced heterosexual interest, but also show diminished identification with the female gender, and this too correlates with their recalled childhood sex-typical behavior (Hines et al. 2004; see Hines 2010a for a review of studies of gender identity in females with CAH). About 3% of women with CAH express a desire to live as men in adulthood, despite having been reared as girls, in contrast with ~0.005% of all women (Dessens et al. 2005). Although 3% may seem small, it indicates that women with CAH are ~600 times more likely than women in general to experience severe gender dysphoria. Girls with other disorders involving exposure to unusually high levels of androgens prenatally also show increased gender dysphoria (Slijper et al. 1998). Additionally, even when not gender dysphoric, or wishing to change sex, girls and women with CAH show somewhat reduced satisfaction with the female sex assignment (Ehrhardt et al. 1968, Ehrhardt & Baker 1974, Hines et al. 2004). No evidence thus far has linked normal variability in the early hormone environment to gender dysphoria. In addition, research attempting to link 2D:4D to gender identification has produced inconsistent findings (Kraemer et al. 2009, Schneider et al. 2006, Wallien et al. 2008), again perhaps because of the weak relationship between 2D:4D and prenatal androgen exposure.

Early Hormone Influences on Personality and Cognition

Sex differences in personality characteristics and in cognitive ability are smaller than are sex differences in children's sex-typed activities, sexual orientation, or gender identity (Hines 2010b). Nevertheless, they also have been examined for evidence of early hormonal influence.

Some personality characteristics that show sex differences relate to prenatal testosterone exposure. For instance, empathy, which is higher on average in females than in males, appears to be reduced by testosterone exposure before birth. Females with CAH show reduced empathy (Mathews et al. 2009), and testosterone measured in amniotic fluid relates negatively to empathy in both boys and girls (Chapman et al. 2006). Tendencies toward physical aggression, which are higher on average in males than in females, also relate to prenatal testosterone exposure, with prenatal testosterone exposure increasing aggression. Girls and women with CAH show increased physical aggression (Mathews et al. 2009, Pasterski et al. 2007), as do children exposed prenatally to androgenic progestins (Reinisch 1981). Not all personality dimensions that show average sex differences relate to prenatal testosterone exposure, however. For instance, the study that reported increased aggression and reduced empathy in females with CAH also considered the personality dimension of dominance/assertiveness, which is higher on average in males than in females. Despite seeing the expected sex difference in healthy controls, no difference in dominance/assertiveness was seen between females with and without CAH.

Cognitive and motor abilities that show sex differences also have been examined for influences of prenatal testosterone exposure (reviewed in Hines 2010a). One study found that

females with CAH showed more male-typical behavior in the form of increased accuracy in throwing balls and darts at targets (Hines et al. 2003), a result that was not accounted for by increased muscle strength (Collaer et al. 2009). Some studies have also found that females with CAH resemble males in showing enhanced mental rotations performance, but other studies have not corroborated these results (Hines et al. 2003). Two studies found that males with CAH show reduced performance on mental rotations or other visuo-spatial tasks (Hampson et al. 1998, Hines et al. 2003), results that had not been predicted. Several studies have also found that both males and females with CAH show impaired performance on arithmetic and mathematical tests (Baker & Ehrhardt 1974, Perlman 1973, Sinforiani et al. 1994), despite males generally being viewed as better than females at mathematics. Studies relating amniotic fluid testosterone to spatial and mathematical performance have also produced inconsistent and largely negative results (Finegan et al. 1992, Grimshaw et al. 1995). Most studies have found no alterations in individuals with CAH on tasks at which females excel, such as verbal fluency or perceptual speed, although one study suggests reduced female-typical behavior in females with CAH in the form of impaired fine motor performance (Collaer et al. 2009). Perhaps prenatal testosterone exposure has a clearer impact on motor abilities that show sex differences (e.g., targeting and fine motor performance) than on cognitive abilities assessed with paper-and-pencil tests.

Socialization and Sex Differences in Cognitive Performance

Substantial evidence supports social and cultural influences on some cognitive sex differences (see Hines 2010a for a review). For instance, sex differences on certain measures of cognitive abilities appear to have declined over time (Feingold 1988). For the SAT Mathematics, in particular, the sex ratio among those scoring at the upper extreme has declined from 13 boys to one girl in 1982 to 2.8 boys to 1 girl more recently (Halpern et al. 2007). There are also large national differences in mathematical and science performance, differences that are many fold larger than the sex difference within any nation (Mullis et al. 2008). Additionally, the magnitude of the sex difference in mathematics performance within a nation relates to the role of women. Nations where women and men are similar in regard to variables such as representation in the legislature show more equal mathematics performance (Guiso et al. 2008).

Sex-Related Psychiatric Disorders

Some psychiatric disorders are more common in one sex or the other, and testosterone could contribute here, as well. For example, prenatal testosterone exposure has been suggested to contribute to autistic spectrum conditions (ASC) (Baron-Cohen 2002) and to obsessive compulsive disorder (OCD) and Tourette Syndrome (Alexander & Peterson 2004), and to be protective against eating disorders (Culbert et al. 2008, Klump et al. 2006). For OCD and Tourette syndrome, evidence that individuals with these disorders are more male-typical in other respects, such as childhood play behavior, has been interpreted to support a link to testosterone (Alexander & Peterson 2004). For ASC (Auyeung et al. 2009a, Chapman et al. 2006, Knickmeyer et al. 2006) and for eating disorders (Culbert et al. 2008, Klump et al. 2006), behaviors in the normal range that are similar to those seen in the disorders (e.g., empathy for ASC, disordered eating for eating disorders) have been linked to prenatal androgens, although for disordered eating, some studies have failed to replicate these results (Raevuori et al. 2008). In addition, for ASC and for eating disorders, studies have not shown that variability in the early hormone environment leads to the disorder itself, as opposed to behaviors in the normal range that resemble those that characterize the disorder. For instance, although a study of females exposed to high levels of androgens prenatally, because of CAH, found increased scores on an inventory

of traits related to ASC, none of the women with CAH scored high enough to suggest a clinical diagnosis (Knickmeyer et al. 2006). The proposed link between prenatal testosterone and ASC has also been questioned by evidence indicating that both males and females with gender identity disorder, rather than females only, are at increased risk of ASC (de Vries et al. 2010) and by the larger male predominance for the less severe ASC, Asperger syndrome, than for the more severe ASC, classical autism. One possibility is that prenatal androgen exposure contributes to individual differences within the normal range in behaviors that show sex differences and that some of these resemble behaviors associated with developmental disorders, such as ASC. As a consequence, exposure to testosterone before birth, when added to other risk factors, could contribute to some individuals crossing a threshold for diagnosis. However, developmental disorders are one area in which direct genetic effects (Skuse 2006), particularly those of genes encoded in the X and Y chromosomes (Reinius et al. 2008, Reinius & Jazin 2009, Skuse 2006), may play an important role.

Sex Differences in Brain Structure and Function

There are numerous reports of sex differences in human brain structure or function (reviewed by Cahill 2009, Hines 2009). For instance, total brain volume, like body size, is larger in males than females. In addition, the amygdala is larger in males, whereas the hippocampus is larger in females (Goldstein et al. 2001). Women also show greater cortical thickness than men do in many regions (Luders et al. 2006). Perhaps in compensation for the smaller brain, women also show greater gyrification in parts of frontal and parietal cortex and perhaps more efficient use of white matter (Gur et al. 1999). There are many reports of sex differences in the human brain, particularly in its function, and many of these are as yet unreplicated. Because males and females are routinely compared in studies, and positive results are more readily published than negative results, some findings of neural sex differences may prove to be spurious.

In addition, although many neural sex differences have been described, few have been linked to behavioral sex differences. In fact, many differences in brain function have been noted during equivalent performance by the sexes. For instance, men and women show different patterns of asymmetry of function when performing certain phonological tasks, despite showing no sex difference in task performance (Shaywitz et al. 1995). Similarly, for men and women matched for mathematical ability, mathematical performance correlates with temporal lobe activation in men but not in women (Haier & Benbow 1995), and for women, performance on intelligence tests that do not differ by sex correlates with gray and white matter in frontal regions, whereas for men the correlation is with parietal regions (Haier et al. 2005). Indeed, neural sex differences may sometimes, or even commonly, exist to produce similar behavior in males and females, rather than to produce differences (De Vries & Sodersten 2009, McCarthy et al. 2009). Additionally, it appears that during performance of many tasks, male and female brains function similarly (Frost et al. 1999, Halari et al. 2005, Mansour et al. 1996).

Despite the many neural sex similarities and the many neural sex differences that do not relate to any behavioral sex difference, neural and behavioral sex differences have been linked in some instances. Much research in this area has focused on neural differences related to sexual orientation, particularly in men. The only finding in this area that has been independently replicated, at least as of yet, involves the third interstitial nucleus of the anterior hypothalamus (INAH-3). INAH-3 is thought to be the human homolog of the rodent SDN-POA, and four different research groups have reported that INAH-3, like the SDN-POA, is larger in males than in females (Allen et al. 1989, Byne et al. 2001, Garcia-Falgueras & Swaab, 2008, LeVay 1991). INAH-3 is also smaller (i.e., more female-typical) in homosexual than heterosexual men (Byne et al. 2001, LeVay 1991), although the number of neurons in the nucleus

INAH 1 to 4: interstitial nuclei of the anterior hypothalamus, numbers 1 to 4

appears similar for these two groups (Byne et al. 2001). The volumetric sex difference does not appear to relate to disease processes (e.g., HIV status) or to hormone use in adulthood (see Hines 2009 for discussion). Because the sex difference in SDN-POA volume in other mammals results from early testosterone exposure, differences in INAH-3 volume in humans may relate to the early hormone environment, as well. This possibility has not yet been directly investigated, however.

Heterosexual and homosexual men also differ in corpus callosum anatomy; the isthmus, in particular, is significantly larger in right-handed homosexual compared with right-handed heterosexual men (Witelson et al. 2008). Patterns of cerebral asymmetry and functional cortical connectivity have also been linked to sexual orientation in both men and women (Savic & Lindstrom 2008).

Researchers have also searched for neural correlates of gender identity disorder. One group has reported that the central subregion of the BNST (BNSTc) is smaller in women and in male-to-female transsexuals than in non-transsexual men (Zhou et al. 1995). Interpretation of this finding is complicated, however, because the sex difference in BNSTc does not appear until after puberty (Chung et al. 2002), whereas most transsexual individuals recall feeling strongly cross-gendered from early childhood. Thus, the difference in BNSTc may be the result of experience (Hines, 2009) or of the adult hormone treatment associated with changing sex (Lawrence 2009). This same research group also reported that INAH-3 is smaller and contains fewer neurons in male-to-female transsexuals than in control males (Garcia-Falgueras & Swaab 2008).

In the realm of cognitive and motor sex differences, the midsagittal area of posterior callosal regions, particularly the splenium, relates negatively to language lateralization and positively to verbal fluency in women (Hines et al. 1992b). These findings suggest a correspondence between female-typical brain structure and female-typical cognitive function, given that language lateralization is reduced in women compared to men (McGlone, 1980, Voyer, 1996), whereas verbal fluency is greater in women than in men (Hyde & Linn 1988, Kolb & Wishaw 1985, Spreen & Strauss 1991) and posterior callosal regions tend to be larger in women than in men as well (de LaCoste-Utamsing & Holloway 1982, Witelson 1985).

Gron et al. (2000) have also described links between sex differences in brain function and navigational performance (Gron et al. 2000). In both men and women, navigating through a virtual maze, on which males perform better on average than do females, is accompanied by neural activity in the medial occipital gyri, medial and lateral superior parietal lobules, posterior cingulate and parahippocampal gyri, and the right hippocampus proper. However, women show more activity than men do in the right prefrontal cortex at Brodmann's areas 46/9, the right inferior parietal lobule, and the right superior parietal lobule, whereas men show significantly more activity than women do in the left hippocampus proper, the right parahippocampal gyrus, and the left posterior cingulate. Women with CAH have been found to perform better than healthy women on a different virtual maze task (Mueller et al. 2008), but there is, as yet, no evidence regarding neural activation in women with and without CAH while performing navigational tasks.

Effects of Experience on the Brain

Sex differences in brain structure or even function are often interpreted to imply inborn differences between males and females. This leap is inappropriate, however. Behavioral differences must be accompanied by neural differences, so the observation of a neural sex difference on its own tells us little to nothing about how the difference developed. This is true not only for differences in brain function, but also, at least in some cases, for differences in brain structure. For instance, experience can change the mammalian brain throughout the life span, and even neurogenesis in some brain regions can continue in adulthood (Juraska 1998, Maguire et al. 2006, Ming & Song 2005).

Hence, the existence of a neural sex difference, even one that relates to a behavior known to be influenced by early androgen exposure, does not prove that the hormone exposure caused the neural difference. A more direct strategy for identifying links between early hormones and the brain could be to look at neural structure or function in individuals with early hormone abnormality or in individuals for whom the early hormone environment has been measured. Although very little information of this type is available, some neural differences have been described in individuals with CAH (Hines 2009). Most notably, both males and females with CAH show decreased amygdala volume (Merke et al. 2003), and females with CAH show increased amygdala activation to negative facial emotions and, in this respect, resemble healthy males (Ernst et al. 2007). These findings fit well with expectations based on experimental work in other species because the amygdala, or some of its subregions, is larger in males than in females, contains receptors for androgen, is influenced by early manipulations of testosterone, and is involved in behaviors that show sex differences, including rough-and-tumble play and aggression (Cooke et al. 2007, Hines et al. 1992a).

Other Potential Critical Periods for Hormone Influences on Gender Development

In addition to the difference in testosterone in male and female fetuses, males and females differ in gonadal hormone levels neonatally. Shortly after birth, testosterone surges in boys (Forest et al. 1974), and estrogen surges in girls (Bidlingmaier et al. 1974, 1987). The testosterone surge has been called "mini-puberty" and may play a role in development of the gonads and external genitalia in infant boys (Quigley 2002). Human brain development, particularly cortical development, continues rapidly for the first two years after birth and reacts to experience (de Graaf-Peters & Hadders-Algra 2005, Huttenlocher 2002). Thus, this early postnatal period could provide a time when gonadal hormones and experience interact to shape the brain and behavioral propensities.

The early postnatal hormone surges, particularly the testosterone surge in boys, are a focus of current research activity. Men with anorchia (missing testes) but with normal penile development, who apparently experience normal testosterone levels prenatally, but who lack testosterone after birth, resemble controls in terms of sexual orientation, core gender identity, and questionnaire measures of personality characteristics viewed as masculine or feminine (Poomthavorn et al. 2009). Other characteristics may be influenced by the postnatal hormone surge, however. For example, men who lack the postnatal testosterone surge because they have idiopathic hypogonadotropic hypogonadism show reduced spatial abilities, and this condition is not reversed by subsequent testosterone replacement (Hier & Crowley 1982). In addition, females who do not experience the early postnatal surge of gonadal steroids because they have Turner syndrome show evidence of reduced performance on tasks at which males excel, as well as on tasks at which females excel, but not on sex-neutral tasks (Collaer et al. 2002). Evidence from healthy infants also suggests that the postnatal testosterone surge may play a role in gender development. Initial evidence suggests that testosterone during early infancy relates to infants' visual preferences for social stimuli (Alexander et al. 2009a), to neural organization for language processing (Friederici et al. 2008), and to sex-related development of the visual system (Held et al. 1996). Although these initial reports are somewhat inconsistent and require replication, they provide intriguing glimpses through a potential new window on early gonadal hormone contributions to human gender development.

Contemporary research is also focusing on possible hormonal influences on neurobehavioral sexual differentiation at puberty. The hormonal changes of puberty produce dramatic changes in the human body, and experimental research in rodents suggests that they produce

Idiopathic hypogonadotropic hypogonadism: involves gonadotropin deficiency and impaired gonadal steroid production after birth in affected males

Turner syndrome: absent or imperfect second X chromosome causes ovarian regression, typically before birth, impairing or eliminating ovarian hormone production

an additional wave of neural and behavioral organization as well (Schulz et al. 2009).

Puberty is also a time of great change in human behavior, characterized by increased sexual interest and activity and the emergence of some types of behavioral problems, including higher rates of depression in females than in males (Halpern et al. 1993, Hyde et al. 2008). Evidence supports the existence of sex differences in the timing of some neural changes that accompany puberty, and these seem to parallel the earlier puberty experienced by girls compared with boys. Total cerebral volume peaks earlier in girls than in boys (at about age 10.5 years versus 14.5 years), and although both adolescent girls and adolescent boys show an inverted-U-shaped pattern of change in cortical and subcortical gray matter, the peak occurs one to two years earlier in girls than in boys (Lenroot et al. 2007). Studies have also proposed links to hormones at this time. One study found that among girls global gray matter volume related negatively to estradiol levels, but among boys the same variable related positively to testosterone levels (Peper et al. 2009). Similarly, neural sex differences in adolescent girls and boys have been found to relate to circulating testosterone levels (Neufang et al. 2009). These data are correlational, so investigators do not know if hormones, or other associated developmental processes, are the causal factors. Another study, however, suggests that testosterone may play a role in the growth of white matter in the adolescent brain. In this study, white matter increased at different rates in girls and boys, and testosterone levels and androgen receptor type interacted in relation to this sex difference. The association between male-typical brain development and testosterone levels was significantly stronger in boys with the more efficient type of androgen receptor than in boys with the less efficient type (Perrin et al. 2008). Like the investigations of possible organizational influences of hormones during neonatal development, research on puberty as an additional time of brain organization in relation to gender-linked behavior is in its early stages, but it offers promise for understanding the dramatic behavioral changes that occur at this time of adolescent development.

CONCLUDING REMARKS

The prenatal hormone environment clearly contributes to the development of sex-related variation in human behavior and plays a role in the development of individual differences in behavior within each sex, as well as differences between the sexes. Thus, early hormone differences appear to be part of the answer to questions such as why males and females differ behaviorally and neurally, as well as why some of us are more sex-typical than others. In other species, the early hormone environment exerts its enduring effects on behavior by altering neural development. Similar neural changes are thought to underlie associations between the early hormone environment and human behavior, but the specific neural changes involved are just beginning to be identified. Many sex differences have been described in the human brain, but only a subset of these has been related to behavioral sex differences and still fewer have been linked to the early hormone environment. Steroid-sensitive regions, including regions of the hypothalamus and the amygdala, are implicated, as are interhemispheric connections, but establishing firm links between early hormones, brain development, and behavior is a primary area for future research.

Although this review has focused on hormonal influences on gender-related brain development and behavior, it has also discussed direct genetic influences that may contribute, in particular, to developmental disabilities, such as autistic spectrum conditions. In addition, the role of socialization, culture, and cognitive developmental processes in the development of behavioral differences between males and females has been noted. Although hormones contribute to behavioral sex differences, other factors contribute, as well. In addition, gender development is multidimensional, and developmental processes involved in each dimension are likely to differ somewhat. A good

example of the numerous types of factors that can influence human gender development comes from research on children's play. Here, evidence clearly shows that prenatal testosterone exposure plays a role in sex differences and individual differences, promoting male-typical toy, playmate, and activity interests. After birth, the early surges of testosterone or estrogen may be important, too, but socialization factors also gain in importance, as parents and then peers and eventually teachers encourage children to engage in gender-typed play (Fagot 1978, Langlois & Downs 1980, Pasterski et al. 2005). The child also begins to develop the understanding that he or she is male or female, and this knowledge produces motivation to imitate the behavior of others of the same sex and to respond to information that things, such as toys or activities, are for girls or for boys by choosing the things that they have been told are for their own sex (Bussey & Bandura 1999, Martin et al. 2002, Masters et al. 1979, Perry & Bussey 1979). These social and cognitive developmental influences on children's activities could engage the same neural circuitry as underlies the effects of the early hormone environment. Thus, identifying the brain systems influenced by early androgen exposure could help elucidate systems involved in other types of influences on the same behavioral outcomes, as well.

SUMMARY POINTS

1. Human gender development begins before birth and is influenced by levels of testosterone prenatally, and perhaps neonatally. Sex-typed play in childhood relates to levels of testosterone before birth, and evidence indicates that the prenatal hormone environment also contributes to variability in sexual orientation, gender identity, and some, but not all, personality traits that differ on average for males and females.
2. Other types of influences on neurobehavioral gender development include direct genetic effects of the sex chromosomes and postnatal socialization and cognitive understanding of gender.
3. Gender development is multidimensional, and the combinations of factors that influence the many different dimensions of gender appear to differ. Early hormonal influences appear to play a larger role, for example, in children's toy preferences than they do in cognitive abilities that show sex differences, where social and cultural influences appear to be more important.

FUTURE ISSUES

1. Which neural changes can be associated with the early hormone environment, either in individuals with disorders that cause hormone abnormality or in healthy individuals for whom measures of the early hormone environment are available?
2. Does the early hormone environment contribute to the development of psychological disorders that are more common in one sex or the other?
3. Will early infancy and puberty prove to be critical periods when hormones exert permanent influences on human gendered behavior, as has been shown for prenatal development?
4. Are the neural systems associated with hormone-induced changes in behaviors that show sex differences also the systems that respond to experiential effects on the same behavioral outcomes?

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