Human gender development begins before birth. Sex chromosomes and sex hormones are the two major sources of prenatal influence on lifelong neurobehavioral gender phenotypes. Differential expression of genes during the embryonic stage of life begins the processes by which sex differences develop. Variation in exposure to prenatal hormones, particularly testosterone, is an important contributor to behavioral and cognitive differences between the sexes, as well as an important explanatory factor for why certain individuals are more sex typical than others. In addition, males and females adjust their neurobehavioral developmental trajectories differentially in response to the same signals.

Biology of Sex

In all mammals, including humans, the first stage of gender development is conception, which in nonpathological conditions results in a genome that includes two X chromosomes (genetic female) or one X and one Y chromosome (genetic male). During the early embryonic phase of life, the genital ridges have the potential to develop into either ovaries or testes depending on certain genes that are differentially expressed in XX and XY embryos. Testes development is initiated by expression of the sex-determining region Y (SRY) gene. Subsequently, many other genes and their transcription factors, as well as hormones and their receptors, are involved in the complex developmental process of sex differentiation. Across the life course, males and females differ in physiological (the concept of sexual dimorphism) and neurobehavioral phenotypes. These range from conspicuous differences such as gonadal organs to subtle differences such as the likelihood of preferring certain activities.

The placenta, the organ at the interface between the mother and the fetus, plays a central role in synthesizing hormones and regulating developmental processes. It is therefore worth noting that not only are fetuses sexually dimorphic but the placenta itself contains primarily fetal (XX or XY) tissue and functions differently based on the sex of the fetus.

Fetal Programming

While some of our traits are determined directly by DNA sequence, many of our traits, especially those involved in cognition and behavior, exhibit a wide degree of flexibility (the concept of phenotypic plasticity). Evidence suggests that the genes related to neurobehavioral traits often allow for a wide range of possible outcomes (the concept of reaction norms). Environmental conditions determine which particular phenotype will be expressed among the wide array of potential phenotypes (the concept of developmental programming). In this context, the intrauterine phase of life represents a particularly important period because during this time, phenotypic plasticity is the greatest in the life span and critical developmental processes occur with lifelong, often irreversible consequences (e.g., cellular proliferation, tissue differentiation, and organ development). In the process of prenatal development, an embryo or fetus detects and responds to biochemical cues in the intrauterine environment, altering developmental trajectories that shape the phenotype. Many traits involved in neurobehavioral sex differences and sex-typical cognition and behavior exhibit high degrees of phenotypic plasticity, with hormonal cues exerting programming effects during prenatal development.

Programming of Sex Differences

In 1959, in a landmark study of guinea pigs, it was recognized that prenatal androgen
exposure can produce masculinized behavior in females. Charles Phoenix’s prescient prediction that prenatal testosterone (the primary androgenic hormone) exerts organizational effects on the neural systems involved in sex-typical behavior has been supported by thousands of subsequent studies in a variety of mammalian species. Female fetuses are only exposed to extremely low levels of testosterone that derive from the fetal and maternal adrenal glands and the maternal ovaries and fat tissue, whereas male fetuses are additionally exposed to much higher levels of testosterone that derive from the fetal testes. Animal models involving the manipulation of prenatal hormones confirm that exposing female fetuses to exogenous testosterone causes masculinization of behavior, and in the absence of exogenous testosterone, female-typical behavior develops. This observation of behavioral phenotype is consistent with the endocrinology of gonadal phenotypic determination: Female phenotype can be regarded as a “default” developmental pathway that ensues unless there is significant androgenic exposure.

An important body of research has investigated whether humans exhibit androgenic prenatal programming of neurobehavioral sex differences, as observed in other mammals. Measuring the effects of prenatal testosterone is a difficult challenge in human studies, as the experimental manipulations typical of animal research are obviously unethical for human research. In this entry, reference is made to research involving direct measures of amniotic testosterone levels, prenatal exposure to therapeutic exogenous hormones, and studies of individuals with endocrine disorders.

Behavior and Cognition

An important category of sex differences concerns behavior and activity interests and preferences across the life span, such as children’s toy preferences and adults’ career preferences, which generally exhibit strong associations with measures of prenatal testosterone. This field of inquiry is led by research performed by Simon Baron-Cohen and Melissa Hines, who have demonstrated that amniotic testosterone is negatively correlated with empathy and positively correlated with restricted interests (one or more overriding specific interests) in boys during childhood, but no effects were found in age-matched girls in these studies. Some studies demonstrate a positive association between amniotic testosterone and male-typical play for children of both sexes, although others have found no such effect. Females exposed to unusually high concentrations of prenatal testosterone due to the genetic disorder classic congenital adrenal hyperplasia (CAH) exhibit masculinization of behavior even in light of the observation that parents encourage sex-typical play more for their CAH daughters than their unaffected daughters. During childhood, compared with unaffected girls, CAH girls more often choose male-typical play styles and male playmates and play more with male-typical toys and less with female-typical toys, with the degree of masculine preferences corresponding to the degree of prenatal androgen exposure. CAH girls report greater preference for male-typical and less preference for female-typical activities during adolescence compared with unaffected peers, and CAH adult women exhibit greater preference and prevalence in male-typical careers than unaffected women.

Sex differences are apparent in various cognitive traits and abilities, such as male advantages in mathematics and spatial ability (e.g., mental rotation, navigation) and female advantages in spatial location and verbal skills (e.g., verbal learning, memory, fluency, perceptual speed, vocabulary, reading, writing, speech). Work led by Jo-Anne Finegan and Sheri Berenbaum has been particularly influential in demonstrating that these differences appear to be in part attributable to prenatal testosterone exposure. One study of 7-year-old girls performing mental rotation found that those who had higher (compared with lower) amniotic testosterone
performed better, but this pattern was not consistent across other measures of spatial ability. Across the life span, females with CAH appear to have superior spatial ability compared with unaffected peers, with enhanced spatial ability corresponding to the degree of prenatal androgen exposure. Evidence has been inconsistent in demonstrating associations with prenatal testosterone for mathematical ability, and evidence is weak or unsupportive for other cognitive sex differences. Females with CAH exhibit less empathy and more physical aggression than unaffected peers, but no differences in dominance have been detected. A now unfavored therapy for miscarriage prevention involves administration of progestins during pregnancy, which are in some cases androgenic. Children exposed prenatally to androgenic progestins exhibit greater physical aggression than untreated peers.

Sexual Orientation and Gender Identity

The categories of greatest neurobehavioral sex differences are sexual orientation and gender identity, with the overwhelming majority of female sex individuals exhibiting female gender identity and sexual attraction to males, and vice versa. Evidence generally supports a negligible contribution of prenatal hormone exposures to sexual orientation and gender identity, with the caveat that scientific inquiry into these topics is severely limited because cultural stigmas are a barrier to scientific interest, funding, and self-report. Another barrier to investigating this topic is that CAH studies are of only limited use because the sexual behaviors of women with CAH may be affected by genital abnormality, potentially masking the effects of prenatal endocrine programming. Nonetheless, work by Hines as well as Heino Meyer-Bahlburg demonstrates that compared with unaffected peers, women with CAH appear to be less sexually attracted to men, with the degree of sexual attraction to men negatively correlated with the degree of prenatal androgen exposure. There is less evidence for a positive association of prenatal androgen with sexual attraction to women, partly explained by the association of CAH with generally reduced sexual interest. Another source of information is studies of XY individuals with complete androgen insensitivity syndrome. These individuals lack any (including prenatal) responsiveness to androgens, have male internal and female external reproductive structures, and typically identify as female. Females with complete androgen insensitivity syndrome exhibit sexual orientation that is no different from the general female population, suggesting that androgen exposure (rather than the Y chromosome) is necessary to promote male-typical sexual orientation; but it remains unclear whether prenatal or postnatal exposure is responsible for this effect.

Because psychosocial stress affects adrenal hormone production (including that of testosterone), the effect of maternal stress during pregnancy on the offspring’s sexual orientation has been investigated. Results have been inconclusive, with some suggesting that maternal stress during pregnancy is associated with increased rates of homosexuality in male and female offspring and others finding no such effects. A small number of studies have investigated prenatal estrogen exposure and sexual orientation in populations who were exposed during fetal development to another, now discredited therapy for miscarriage prevention, the synthetic estrogen diethylstilbestrol. Most studies converge to suggest that individuals exposed to diethylstilbestrol do not exhibit different sexual orientation from unexposed peers.

As for gender identity, evidence has been inconsistent on the programming effects of prenatal hormones. Approximately 3% of women with CAH prefer a male identity instead of female, a rate far greater than that of the general female population. However, women with CAH are no more likely to exhibit gender dysphoria based on the degree of exposure to prenatal androgens, suggesting that perhaps the enhanced rate of gender dysphoria among women...
with CAH is due to an aspect of CAH other than prenatal hormone exposure.

**Psychopathology**

Many psychiatric conditions are more prevalent in one sex than in the other. For example, autism spectrum disorders (ASD), obsessive-compulsive disorder, and Tourette syndrome are more common in males than in females, whereas eating disorders, schizophrenia, and most affective disorders are more common in females than in males. There is a vigorous debate among researchers on whether prenatal testosterone exposure could contribute to risk for ASD, obsessive-compulsive disorder, and Tourette syndrome, based on evidence that individuals who go on to develop these conditions often exhibit more male-typical behaviors as children (a trait positively associated with prenatal testosterone). Although prenatal testosterone exposure is associated with the normal range of variability for certain traits associated with these disorders, no direct evidence has linked these exposures with the disorders themselves. For example, prenatal testosterone has been associated with attention to detail and inversely associated with social skills, extreme deficits of which are symptoms of ASD, but the association of prenatal testosterone with ASD has been inconsistent (as of 2016, a Baron-Cohen 2015 study provides the only evidence in support of this possibility). Despite sex differences in prevalence, empirical studies have not supported evidence of prenatal sex hormone programming effects for eating disorder, schizophrenia, or bipolar disorder, and evidence has been inconsistent for depression and attention-deficit/hyperactivity disorder.

**Sex Differences in Programming Effects**

Male and female fetuses differ in the ways in which they respond to intrauterine conditions, with implications for gender development. Research led by Curt Sandman, Laura Glynn, and Elysia Davis demonstrates sex-based differences in both developmental responsiveness and developmental responses to maternal stress physiology. Their prospective, longitudinal studies of mother-child pairs followed beginning in early pregnancy lend insight into how the intrauterine endocrine environment over the course of gestation affects neurobehavioral development across the first decade of life. Sandman, Glynn, and Davis have observed sex differences in how fetal exposure to stress hormones affects neurobehavioral development.

During gestation, concentrations of the stress hormone cortisol in maternal circulation are significantly correlated with fetal cortisol exposure because the placenta has only a limited ability to regulate how much cortisol passes into the fetal compartment. Cortisol plays a critical role in normal fetal development, and variations in cortisol exposure represent an important mechanism of fetal programming.

**Male Fetuses Respond to Prenatal Stress With Developmental Delay**

Exposure to high levels of cortisol during early fetal development appears to affect males by altering developmental trajectories in ways that result in delayed maturation compared with females. Elevated maternal cortisol during early gestation was associated with delayed physical and neuromuscular development in male newborns and with impaired mental development in male 12-month-old infants; no such effects were found for females.

**Female Fetuses Respond to Prenatal Stress With Development of Anxiety- and Fear-Prone Behavioral Phenotypes**
While females appear to be more robust in avoiding male-typical developmental delays in response to prenatal stress, females exhibit higher rates of anxiety-related neurobehavioral phenotypes in response to prenatal stress. These differences can be detected as early as the fetal period, during which higher cortisol concentrations during late gestation are associated with greater responsiveness to challenge among female compared with male fetuses at 31 weeks’ gestation. Elevated gestational concentrations of cortisol and the placental stress hormone corticotropin-releasing hormone were associated with a more fearful temperament and distress behavior in female, but not male, infants. Among 6- to 9-year-old girls, but not boys, those who had been exposed to maternal pregnancy-specific anxiety during gestation exhibited poorer executive function and reduced gray matter volume in the brain regions associated with executive function, behavioral/emotional regulation, and inhibition (precursors of affective disorders). Elevated maternal cortisol in early gestation was associated with enlargement of the right amygdala and affective problems in preadolescent girls but not boys. These studies converge to suggest that females respond to signals of stress during the intrauterine phase of life by promoting neurobehavioral development of anxiety- and fear-related behaviors that are evident across infancy and childhood, with implications for psychopathology in adults.

**Sex-Dependent Responses to Prenatal Testosterone Exposure**

Male and female fetuses differ in neurobehavioral developmental responses to prenatal testosterone exposure. Among male children, amniotic testosterone has been positively associated with fear reactivity and brain lateralization for language function and negatively associated with empathy, variation of interests, and brain connectivity via the corpus callosum. No equivalent effects have been found in female children.

**Conclusion**

Many of the neurobehavioral differences that characterize gender norms in adulthood appear to have their roots in the prenatal phase of life. Also, male and female fetuses differ in their sensitivity and responses to specific intrauterine signals. It is important to note that in addition to prenatal influences, gender development is also influenced by hormone exposures and gene expression during other sensitive periods of development, particularly the neonatal and pubertal phases. Furthermore, prenatal influences on gender development interact with postnatal factors, including postnatal development, socialization, learning, and culture, to determine neurobehavioral gender phenotypes.

**See also** Biological Sex and Cognitive Development; Biological Sex and Mental Health Outcomes; Biological Sex and the Brain; Developmental and Biological Processes: Overview; Pregnancy; Testosterone

- women
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- sex trafficking
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