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How Early Hormones Shape Gender Development

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Abstract

Many important psychological characteristics show sex differences, and are influenced by sex hormones at different developmental periods. We focus on the role of sex hormones in early development, particularly the differential effects of prenatal androgens on aspects of gender development. Increasing evidence confirms that prenatal androgens have facilitative effects on male-typed activity interests and engagement (including child toy preferences and adult careers), and spatial abilities, but relatively minimal effects on gender identity. Recent emphasis has been directed to the psychological mechanisms underlying these effects (including sex differences in propulsive movement, and androgen effects on interest in people versus things), and neural substrates of androgen effects (including regional brain volumes, and neural responses to mental rotation, sexually arousing stimuli, emotion, and reward). Ongoing and planned work is focused on understanding the ways in which hormones act jointly with the social environment across time to produce varying trajectories of gender development, and clarifying mechanisms by which androgens affect behaviors. Such work will be facilitated by applying lessons from other species, and by expanding methodology. Understanding hormonal influences on gender development enhances knowledge of psychological development generally, and has important implications for basic and applied questions, including sex differences in psychopathology, women's underrepresentation in science and math, and clinical care of individuals with variations in gender expression.

Why are the sexes different? How does the prenatal environment set the stage for postnatal development? How does behavior result from transactions between the brain and the social world? All three questions are the focus of contemporary work in the behavioral sciences, and they converge in questions regarding prenatal sex hormone effects on gender

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Conflict of Interest

Nothing declared

development, which includes characteristics that show sex differences and that relate to being female or male.

Foundation

Human work linking hormones and behavior borrows heavily from work in nonhuman species showing that exposure to sex hormones early in development has permanent effects on sex-related behavior, and reproductive anatomy and function [reviewed in 1,2,3]. Thus, early development represents a sensitive period for hormones to organize the brain.¹ Studying prenatal hormonal influences on gender development is challenging: hormones cannot be manipulated experimentally, and human behavior is strongly influenced by social context.

Fortunately, several methods are available to meet these challenges, as shown in Table 1. Evidence using those methods has accrued to demonstrate that levels of androgens during prenatal development are related (in varying degrees) to characteristics that show sex differences; this evidence is described in recent reviews [4–6], and summarized in Table 2 (Column 1). Recent progress, discussed below and summarized in Table 2 (Column 2), has examined the limits of the effects, and considered the psychological and neural mechanisms mediating them. Ongoing and planned work involves expansion of those themes, novel methods, and incorporation of recent lessons from animal studies. Given the challenges of studying these questions, this field moves more slowly than many others, so we extend our review beyond the past two years.

Nature and Psychological Mechanisms of Prenatal Androgen Effects on Gendered Behavior

Confidence has increased that early androgens affect gender development, in light of recent studies that confirm, extend, and clarify previous findings. Most promising, research has moved from asking whether hormones influence human behavior to asking how they do so.

Activity interests and participation – from childhood toy preferences to adult hobbies and occupations – continue to be strongly linked to prenatal androgen exposure [e.g., 7,8], with two notable recent findings. First, androgen effects on interest and engagement in male-typed occupations was seen to have economic consequences: women with exposure to high levels of prenatal androgens due to congenital adrenal hyperplasia (CAH) were more likely than controls to have income in the top 20th percentile, reflecting employment in male-typical, higher-paying jobs (despite having lower education, and more psychosocial problems) [9]. Second, the sensitive period for androgen effects on activity interests was extended to the early postnatal months, as seen in links between parent-reported child play and urinary testosterone during the first six postnatal months [10], and penile length at a similar time (marking the postnatal testosterone surge also known as mini-puberty) [11].

¹In nonhuman and human primates, androgens facilitate masculinization during the prenatal period [reviewed in 3,75]. Estrogens probably do not have effects during prenatal development because both sexes are exposed to estrogens from the mother [76], but they may have effects at later sensitive periods. Therefore, our terminology reflects the focus on androgens, while acknowledging the potential role for estrogens (and perhaps other hormones) at other periods.

Speculations about the affective and cognitive processes that underlie children's sex-typed toy preferences have been stimulated by evidence that those preferences are paralleled in rhesus monkeys (male monkeys, like boys, strongly preferred wheeled toys, whereas female monkeys, like girls, had variable preferences, leading to sex differences in preference for wheeled versus plush toys) [12, 13]. Recent work has documented early sex differences in propulsive movement (hitting versus cradling an object), with sex-typed activities suggested to develop "from socialization mechanisms that build on a male predisposition to imitate propulsive motion" [14, p. 262]. Furthermore, sex differences in occupational choices (e.g., male-predominance in science and engineering, female-predominance in social service) appear to be driven in part by androgen effects on interest in things versus people [15].

Spatial abilities are facilitated by exposure to high levels of prenatal androgens. Performance on several spatial tests was higher in two samples of females with CAH compared to typical females [16,17]. Inconsistencies in early studies were clarified: androgen facilitation of spatial abilities may be countered by adverse effects of the disease during early life [17]. Converging evidence comes from typical samples. Spatial abilities were positively related to amniotic testosterone in girls for one measure, but not two others, perhaps due to small sample [18]. Spatial performance was also higher in females with a male co-twin than a female co-twin, thought to reflect transfer of testosterone during gestation [19,20]; importantly, one study controlled for postnatal socialization effects by showing that females with a (non-twin) brother did not have better spatial ability than those with a sister [19].

Sex-related psychiatric disorders are suggested to result, in part, from sex hormones. Prenatal androgens have been invoked to explain male predominance of externalizing disorders, such as attention-deficit hyperactivity disorder (ADHD) [e.g., 21] and substance use, and of autism [e.g., 22]; it is not specified when prenatal androgens trigger ADHD or autism, although genes presumably play a role. Population registry-based studies of psychiatric morbidity in individuals with CAH in Sweden produced results not easily reconciled with early androgen effects. Although girls and women with CAH had a higher rate of substance misuse than female controls, the rate was also higher than male controls; moreover, other conditions that show female predominance (stress and adjustment disorders) were increased, but ADHD and autism spectrum disorders were not [23]. Boys and men with CAH also had higher rates of psychiatric disorder than controls [24].

Overall, the increased psychopathology seen in males and females with CAH reflects the limitations of natural experiments (i.e., other disease factors contribute to behavior), so it is important to note indirect evidence for prenatal androgen effects on some forms of sex-related psychopathology. Consistent with male predominance of substance use and female predominance of disordered eating, females with a male co-twin had more alcohol use [25,26], and less disordered eating [27] than females with a female co-twin; importantly, these studies included siblings to control for postnatal environmental effects. "Autistic" traits were associated with amniotic testosterone [28], but interpretation is not simple because some traits show sex differences in the normal range and would be expected to relate to prenatal hormones for that reason.

Neural Substrates of Prenatal Androgen Effects on Gendered Behavior

Neuroimaging has come to human behavioral neuroendocrinology, as to other areas of behavioral science, with increasing interest in aspects of brain anatomy and activation that are related to sex and sex hormones [reviewed and discussed in 29]. In a magnetic resonance imaging (MRI) study of typical boys aged 8–11, brain structures that show sex differences were examined in relation to amniotic testosterone, with effects for regional gray matter volume in some areas, but not to midsagittal corpus callosum size [30,31]. The behavioral significance of the effects is not clear (anatomy was not examined in relation to behavior). It is also unclear why girls were not studied since they were included in other aspects of the study linking amniotic testosterone to behavior.

Brain activation patterns during cognitive and affective tasks were also examined in relation to prenatal androgens in natural experiments and a typical sample, with most using functional MRI. (Few studies considered potential confounding effects of postnatal androgens.) Evidence for androgen effects on two aspects of sex-typed brain responses comes from women with complete androgen insensitivity syndrome (CAIS) who have a Y chromosome but do not have effective androgen exposure (due to lack of functional androgen receptors). In two separate samples, women with CAIS had female-typical brain responses to mental rotation [32] and to sexually-arousing stimuli [33]; their brain activation patterns were different than those of men and similar to those of typical women, consistent with their low androgen responsiveness and not with possessing a Y chromosome.

Other studies linking androgens to brain activation were not as clear. For example, in a positron emission tomography study, women with and without CAH did not differ in neural response to olfactory stimuli [34].

Several studies focused on characteristics related to psychopathology, consistent with the approach of understanding psychiatric disorders in terms of underlying dimensions of observable behavior and neurobiology [35–37]. For example, the male predominance of childhood-onset externalizing problems suggests that early androgens masculinize reward systems. In one set of studies focused on emotion in faces [38,39], girls with CAH had greater amygdala activation while viewing negative facial emotions and less hippocampal activation while recalling emotional faces than did typical girls, but the groups also differed in performance. In a study of typical boys (those whose structure was described above), amniotic testosterone was linked to striatal responses to valenced facial cues, and to behavioral approach (on a questionnaire measure of impulsivity/fun-seeking, drive, and reward responsivity) through striatal activity (but not directly to behavioral approach, perhaps due to low statistical power) [40]. Interpretation would have been enhanced with data from girls to evaluate sex differences and because testosterone is often seen to have within-sex effects in females [4].

Overall, the zeal for neuroimaging studies has yet to be matched by findings, with few clear and consistent patterns regarding androgen effects on brain structure and activation. Advances will likely come from studying neural systems underlying sex-related behavior and likely to be influenced by androgens, and directly linking brain measures to behavior.

But, links between hormones and neural systems do not necessarily imply causality; for example, a brain region may be larger or more active during a specific task in women with versus without CAH simply because that region changes in response to behavior or environmental input that differs between the groups. Furthermore, a given behavioral endpoint may emerge through a variety of trajectories; androgens may affect the path to an outcome but not necessarily the outcome itself (the sexes may get to the same outcome through different paths) [e.g., 41].

Ongoing Work & Future Directions

This is an exciting time to study how hormones shape gender development. The field is poised for some significant advances, and we highlight topics that represent opportunities based on animal studies, tantalizing recent findings noted above, and related trends in other areas of science.

First, there is need to understand variations in androgen effects across behaviors and across people. For example, why is gender identity less affected by early androgens than are activity interests; what differentiates the women with CAH who are bisexual from the majority who are heterosexual; why would high prenatal androgen levels produce autism in some children, ADHD in others, and normal development in most?

Second, findings from animal studies [e.g., 41–46] can be used to guide work in human beings, as illustrated with some examples. The importance of later sensitive periods for hormone effects, such as puberty and pregnancy [e.g., 43, 46] might be tested in studies of cognition and affect in children receiving drugs to suppress puberty because of precocious puberty or gender identity concerns, and in women raising biological versus adopted children (the latter differentiates changes due to pregnancy hormones from childrearing). The evidence for a behavioral role of genes on the sex chromosomes [e.g., 42,45] can be extended to human behavior by studying women with CAIS. The notion that the sexes use different paths to get to the same outcome [e.g., 41] might be understood through studies combining neuroimaging and behavioral measures, e.g., identifying sex differences in links between brain activation during a cognitive task and performance on a related task outside the scanner.

Third, it is important to pursue additional windows into prenatal androgen exposure. Natural experiments, particularly CAH and CAIS, have yielded valuable data, but they are not perfect. (Unfortunately, most criticisms [e.g., 47] are narrow, ignore the consistency of the evidence, and fail to capture the difference between cause and effect [discussed in 48]). Methods involving direct measures of prenatal hormones (e.g., from amniotic fluid) have both promise and pitfalls [49]. Importantly, most methods relying on indirect indicators of prenatal hormones create more confusion than clarification. It is time to stop using digit ratio to mark variations in prenatal androgen exposure because such use is not supported by evidence [as detailed elsewhere, 50,51,52]. For example, in one study [50], women with CAIS who have no effective androgen exposure had only moderately feminized digit ratio compared to men, were not significantly different from typical women (who have some effective androgen exposure), and showed variability in digit ratio despite minimal

variability in androgen exposure; furthermore, digit ratios did not even provide high discrimination between control men and women, despite the marked sex difference in prenatal androgen exposure. It is necessary to obtain validity data on other purported markers, such as otoacoustic emissions, before using them on a large scale [53].

Promising measures include aspects of genital anatomy, which reflect early androgen action, and thus are likely to relate to later behavior in people as they do in nonhuman animals. Anogenital distance reflects prenatal androgen exposure [54–57], although it may be modified by postnatal androgen [58], and has been linked to boys' parent-reported play in one study [11]. Penile length, especially change during the first months of life, may mark the early postnatal testosterone surge in boys, and has also been linked to parent-reported play [5,11].

Fourth, we need to understand how hormones work jointly with socialization to influence gender development [48]. Children are socialized in ways that reflect their characteristics, and the social world does not affect all children equally with regard to gender development [e.g., 59,60]. Girls with CAH provide a unique opportunity to uncouple effects on gender development of biological and rearing sex, to ask how girls with CAH are socialized (e.g., whether they are socialized in female-typical ways consistent with their rearing sex and identity, or in atypical ways in relation to their masculinized activity interests), and whether socialization has different effects on girls with and without CAH [8,48,61]. This question is ideally suited for biomarkers: imagine what we could learn if we could easily identify children at birth in terms of their early androgen exposure and then study how they elicit different socialization and respond differently to the same socialization.

These questions represent pieces of the large puzzle to identify the neural, psychological, and developmental paths linking prenatal androgens to behavior, and studying how varying trajectories develop from the interplay of hormones and the social environment at different sensitive periods, as represented in Figure 1. The figure highlights the hypothesized biological and psychosocial contributors to gender development, and how different paths can lead to similar endpoints; for example, male-typed activity interests may result primarily from increased exposure to prenatal androgens for some girls (such as those with CAH), but from gendered socialization experiences for other girls. The figure also calls attention to the interplay between biological and social processes, and the psychological and neural mechanisms that mediate links between causes and outcomes. But, empirical evidence is needed to test most of the paths in the figure; most extant data concern simple links between behavior and prenatal androgens or gendered socialization.

Relevance to Important Psychological Questions

There are broad implications of identifying how hormones shape gender development, as illustrated in Figure 1. Sex and gender are crucial to identity and a range of characteristics, psychological and physical, in health and disease [62,63]. Prenatal programming provides a window into development and, ultimately, an opportunity to facilitate optimal development [e.g., 64,65]. Gender development clearly represents the interplay of biology and

socialization, so provides a nice model for psychological development more broadly. We illustrate with several examples.

First, sex matters for mental illness susceptibility, prevalence, age of onset, and form. It is likely that understanding how hormones contribute to sex-related psychopathology will provide information fundamental to the development of personalized interventions [35–37].

Second, controversy surrounds the causes of women's underrepresentation in science, math, engineering, and technology (STEM) careers [e.g., 66,67]. There is little doubt that social structure (e.g., discrimination, child care policies) contributes to the problem [e.g., 68], but it is likely that sex differences in interests also play a role. Prenatal androgen effects on the tendency to prefer careers that involve things versus people [15] reinforce other suggestions [69,70] that women might be engaged by STEM when emphasis is placed on its social relevance.

Third, optimal care of children with variations in gender expression (e.g., disorders of sex development, transgender identity) requires more evidence on the ways that hormones are modified by genes and social factors, best studied in systematic, long-term follow-up studies [71]. A pressing question concerns the development and causes of gender identity: it is not simply related to prenatal androgens [as confirmed recently, 72,73], and appears to be plastic, with adolescence a key period for the development of nonnormative identity [74].

Conclusions

Work on hormonal influences on gender development provides a nice model for understanding psychological development in general. Identifying mechanisms by which sex and gender matter can tell us about the ways that the prenatal environment primes us to elicit and respond to our social worlds, and how our biology and experiences transact across development to shape brain structure and function that guide behavior.

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Highlights

Prenatal androgens influence sex-related characteristics to varying degrees

Androgens facilitate male-typed activities through interest in things vs. people

Androgens are associated with some aspects of brain structure and activation

Current work is focused on interplay of hormones and social environment

Relevant to questions regarding sex-related psychopathology, prenatal programming

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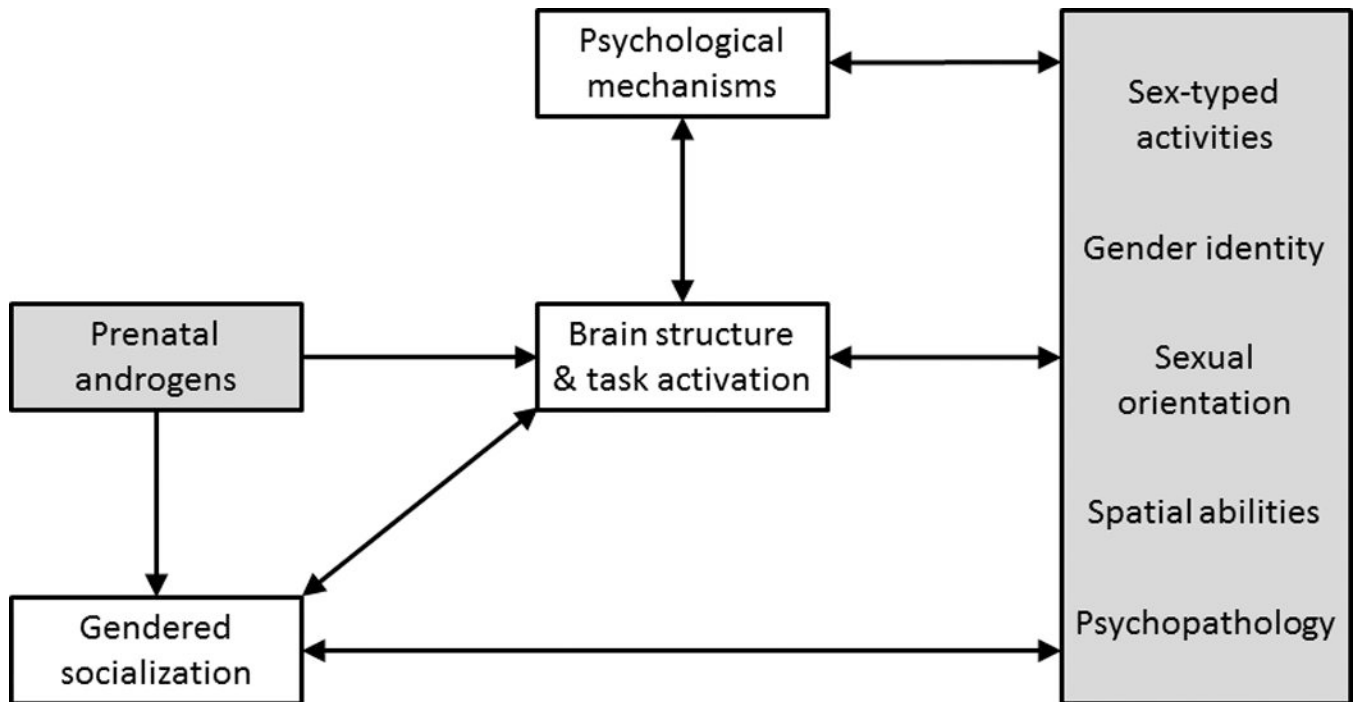


Figure 1. Simple process model delineating the link between prenatal androgens and sex-typed behaviors (gray boxes) by considering neural and psychological mediators of the link and including the influence of gendered socialization (white boxes) on the process. Path magnitudes change with development and vary for different behaviors, contexts, and individuals.

Table 1**Key Methods for Studying Androgen Effects on Gender Development**

Natural Experiments	Strengths	Limitations	Used to Study
Congenital Adrenal Hyperplasia (CAH)	Separation of prenatal androgens and rearing (social) sex in girls	Physical virilization Abnormalities in other hormones (e.g., glucocorticoids)	Prenatal androgens versus rearing in girls and women
Complete Androgen Insensitivity Syndrome (CAIS)	Separation of prenatal androgens and sex chromosomes	Confounding of androgens and rearing (social) sex (both female-typical)	Prenatal androgens versus genes on the sex chromosomes
Typical Samples	Strengths	Limitations	Used to Study
Amniotic Hormones	Natural variations in hormones No confounding disease factors	Single sample of hormones at varying gestational ages Selected sample	Effects of within-sex variations in prenatal hormones
Opposite-Sex Twins	Natural variations in hormones No confounding disease factors	Unclear whether and how hormones transferred between fetuses Twins share postnatal social environment	Effects of within-sex variations in prenatal hormones
Genital Anatomy	Natural variations in androgens Measured postnatally	No direct evidence linking anatomy to prenatal androgens in human beings	Effects of within-sex variations in prenatal and early postnatal androgens
Digit Ratio	Easy to measure Differs in groups known to differ in prenatal androgen exposure	Does not reflect within-sex variation in prenatal androgen exposure	Should not be used

Summary of Prenatal Androgen Effects on Gender Development

Table 2

	Reviewed in 2011		Confirmed in Recent Studies?	
	Effect Size	Evidence	Effect Size	Evidence
Activity Interests & Participation				
	large	Natural Expt Amniotic T	large	Natural Expt Amniotic T
				+++ ---
Gender Identity	small	Natural Expt	small	Natural Expt
				+++
Sexual Orientation	moderate	Natural Expt	Natural Expt	
				+++
Spatial Abilities	small-moderate	Natural Expt OS twins	small-moderate	Natural Expt OS Twins Amniotic T
				+++ ++ +
Psychopathology:				
“Autistic” Traits	moderate	Natural Expt Amniotic T	large	Amniotic T
				+
Autism Diagnosis			no effect	Natural Expt
				+
Substance Use			small	OS Twins
				+
Disordered Eating			small-moderate	OS Twins
				+

Modified from [4].

Source (of evidence): Natural Expt: Natural experiments (e.g., CAH); Amniotic T: Typical samples with direct measure of testosterone in amniotic fluid; OS Twins: Typical samples of opposite versus same-sex twins

Strength (of evidence), based on number of studies and ability to infer causation about androgen from design (e.g., more weight given to data from natural experiments than twins): + weak; ++ moderate; +++ strong; --- insufficient new evidence