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Evidence and Implications From a Natural Experiment of Prenatal Androgen Effects on Gendered Behavior

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Abstract

Sex and gender are key to people's lives, and are the focus of scientific and popular interest and controversy. Sex-related psychological characteristics reflect more than socialization; they are influenced by sex hormones present during sensitive periods of development, particularly androgens that are present prenatally. Studies of females with congenital adrenal hyperplasia (CAH) show how prenatal androgens affect behavior across the life span; these hormones have large effects on interest and engagement in gendered activities, moderate effects on spatial abilities, and relatively small (or no) effects on gender identity, gender cognitions, and gendered peer involvement. In addition to showing the complexity of androgens' effects on gendered behavior, studies of females with CAH provide an opportunity to test theories of gender development, gain insight into how nature and nurture work together, and examine mechanisms of development. The implications of this work have often been misunderstood, so we consider what it means—and does not mean—for biology to influence gender-related behavior.

Keywords

congenital adrenal hyperplasia, differences of sex development, gender development, gender identity, interests, natural experiments, peers, prenatal androgens, spatial abilities

"Is it a boy or a girl?" is typically the first question for new or expectant parents, often answered with elaborate gender-reveal parties. This emphasis on sex and gender reflects its enduring role in people's lives: how they think and feel about themselves, and how they are seen and treated by others. Not surprisingly, psychological aspects of sex and gender generate considerable scientific and popular interest and controversy. In this article, we consider the psychological science of sex and gender, focusing on the role of hormones present early in life, and what the science means for the ways that people are treated.

Sex and Gender Matter[1]

Psychological aspects of gender are neither monolithic nor absolute; people cannot be classified as female or male on the basis of one characteristic, or even a constellation of characteristics. Nevertheless, sex differences are among the largest effects in psychology (Beltz et al., 2020). Sex differences vary in size across characteristics: They are very large for choice of social partners (e.g., playmates and romantic partners), large for activity interests (e.g., childhood toy play, adult hobbies, occupations) and the incidence of some psychopathology (e.g., conduct disorder, depression), moderate for spatial abilities and some social behaviors (e.g., aggression), and small for personality; in comparison, sex differences in height are very large, and typical psychological effects are small to moderate. (Arguments that psychological sex differences are neither large nor meaningful [e.g., Hyde, 2005] fail to compare these differences with other psychological effects and minimize characteristics with large sex differences.)

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Explanations for Gendered Characteristics

Sex-related characteristics are traditionally ascribed to experience. Boys and girls receive different socialization pressures from parents, peers, and the broader world (Blakemore et al., 2009). Children also use social cues to develop and apply gender schemas, effectively socializing themselves (Martin & Ruble, 2004).

Nevertheless, socialization is not independent of biology. Genes and physiology influence psychological characteristics, and those related to gender are no exception. Sex steroid hormones, in particular, play a prominent role. Compelling evidence from many nonhuman species shows that androgens and estrogens present during early development are major contributors to sex differences in behavior, as they are to reproductive anatomy and function (Wallen, 2009).

The same general process operates in people. Exposure to hormones, especially androgens, during sensitive periods of development, especially prenatal life, organizes the brain in ways that contribute to gender development. As described in this article, these effects are complex, and some characteristics are affected more than others; this complexity makes an interesting story.

Of course, it is not possible or ethical to manipulate hormones in people, and effects of hormones cannot typically be separated from effects of socialization. Fortunately, natural experiments provide an effective tool, via studies of people with differences in sex development, in whom there is separation of hormonal and rearing sex. Most of this work involves females with classic congenital adrenal hyperplasia (C-CAH) due to 21-hydroxylase deficiency. They are chromosomally female (46,XX) but, because of a genetic mutation, are exposed to excess adrenal androgens beginning early in gestation and are typically born with masculinized genitalia that are subsequently modified by surgery; they are usually diagnosed and treated shortly after birth, and so have low female-typical postnatal androgens and are reared as girls (Merke & Auchus, 2020).

Females with and without C-CAH can be compared to investigate whether early androgens masculinize human behavior; differences between the groups implicate hormones as contributors to the behaviors of interest, whereas similarities implicate socialization (or other aspects of biology that are female typical, such as sex chromosomes). In most studies, females with C-CAH are compared with unaffected females (ideally sisters, to control for genetic and environmental background). Sometimes, they are compared with females with nonclassical CAH (NC-CAH), a mild form of the disorder that is manifest only postnatally and characterized by female-typical (low) prenatal androgens and female-typical genitalia; females with NC-CAH provide a behavioral comparison for females with C-CAH because they also have a disease and receive medical treatment.

Androgens Differentially Affect Gendered Characteristics

Figure 1 summarizes findings from studies of girls and women with C-CAH. Females with C-CAH are masculinized on some, but not all, behaviors, and are not as masculinized as typical males; the findings emphasize the multidimensional nature and causes of gender. In general, androgens influence personal characteristics the most, and gender identity and cognitions the least; social relationships show an intermediate influence reflecting the combined effects of personal characteristics and identity. The strength of the evidence also varies across behaviors. (This review is not exhaustive, but focuses on characteristics with the strongest evidence, often confirmed by multiple methods and investigators. Fig. 1 includes some behaviors not discussed here.)

Gender-typed activities and interests

The biggest differences between females with and without C-CAH are in activities and interests. Consistent findings are seen across ages, countries, and types of assessment (observation, daily reports of time use, global self-reports, parent reports, drawings; reviewed in Berenbaum & Beltz, 2011, 2016). We illustrate these effects here using data from our own studies. When we observed children ages 3 through 12 playing with a standard set of toys (including toys typically preferred by boys, toys typically preferred by girls, and toys liked by both sexes), we found that preferences of girls with C-CAH were in between those of typical girls and boys (Berenbaum & Snyder, 1995): They played more with boys' toys (vehicles, Lincoln Logs) and less with girls' toys (dolls, makeup) than did their sisters without CAH, but not as much as boys did. When observational data were combined with questionnaire responses, the difference between girls with and without C-CAH was very large, and there was little overlap between these groups. In a study of 10- through 13-year-old girls with C- and NC-CAH, we again used multiple measures of activity interests and participation, including daily interviews of time use and questionnaires. The group difference was large and consistent with effects of prenatal androgen exposure: Compared with girls with NC-CAH, girls with C-CAH were more male typed and less female typed in their activity interests and participation (Berenbaum et al., 2018).

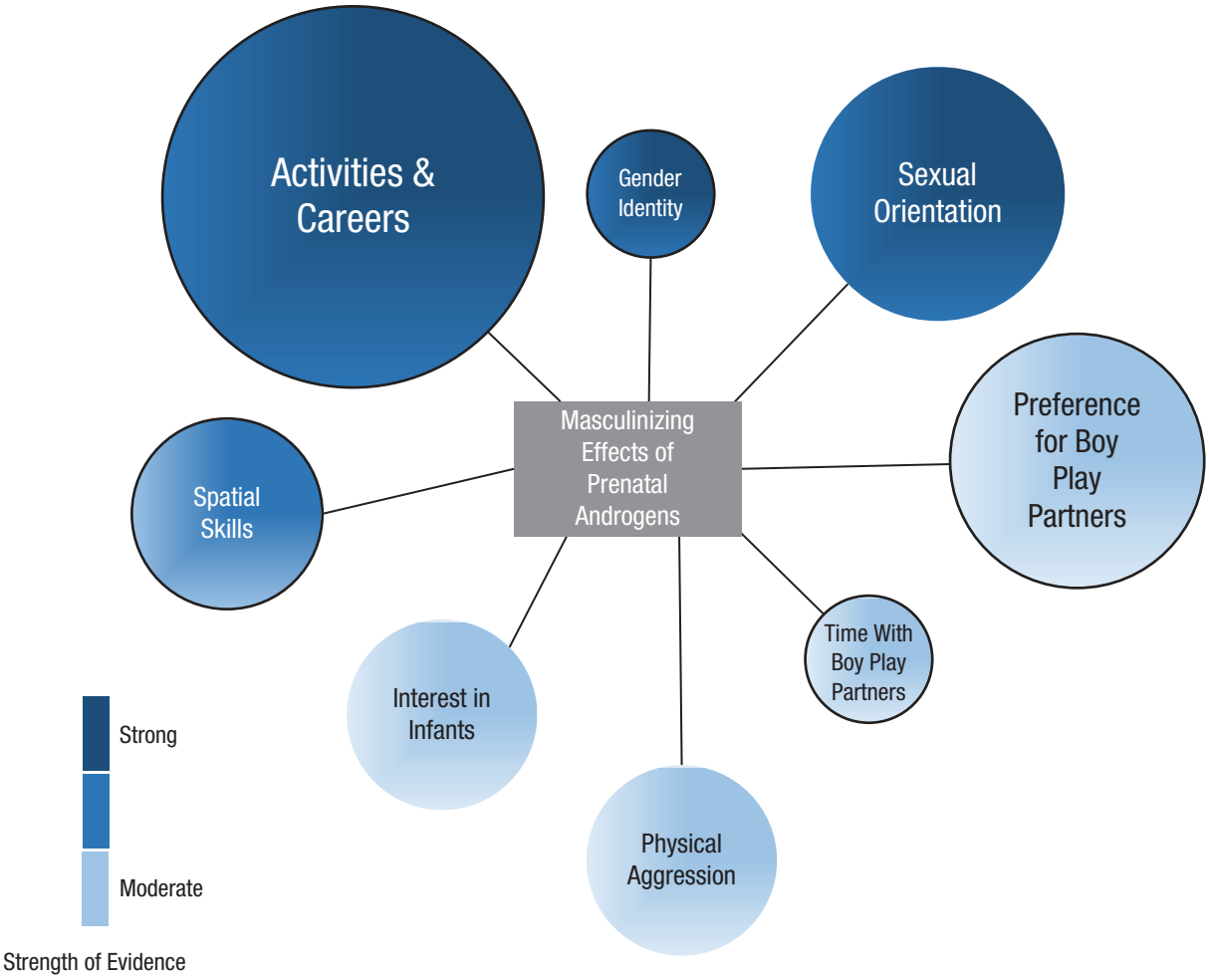

Fig. 1. Visual depiction of the extent to which prenatal androgens masculinize human behavior, as revealed through studies of girls and women with congenital adrenal hyperplasia (CAH). This summary is based on evidence extracted from several reviews (Berenbaum & Beltz, 2011, 2016; Peckins & Beltz, 2020) and focuses on behaviors that have been studied most extensively and results that have been replicated recently. Behaviors considered in this article are represented by nodes with thick black outlines, the size of each node reflects the relative size of the effect (bigger nodes indicate larger effects), and the shading of each node reflects the strength of the evidence supporting the effect (darker shading indicates greater strength of the evidence).

The male-typed interests of females with C-CAH continue into later adolescence and adulthood; there are large differences between females with and without C-CAH on global questionnaire measures of hobbies and leisure activities (e.g., sports and building things vs. dance and crafts), independently replicated across countries (see Berenbaum & Beltz, 2011, 2016, for reviews). Differences extend to occupations. In a study of career interests, we found that interest in male-typical occupations was reported more often by adolescent and adult females with C-CAH than by their unaffected sisters, and this reflected greater interest in occupations involving things (e.g., chemist, carpenter) than in those involving people (e.g., teacher, designer; Beltz et al., 2011). Interests are manifest in occupational selection: Results of a study in Sweden (Frisén et al., 2009) showed that women with C-CAH were more likely than women without CAH to work in jobs in which men dominate and to earn more money (a finding consistent with salary disparities in male- vs. female-dominant jobs).

Androgens appear to affect activities in a dose-dependent fashion. Females with C-CAH who had the highest prenatal androgen exposure (inferred from genotype or disease factors) have the highest interest and engagement in male-typed activities and careers (e.g., Beltz et al., 2011; Berenbaum et al., 2000; Frisén et al., 2009).

Gender identity

It is important not to generalize and conclude that prenatal androgens strongly affect all psychological

characteristics. In particular, females with C-CAH generally have female-typical gender identity. Although some conversations focus on gender identity as innate and stable, data show that it develops across time and cannot be easily attributed to genes or specific aspects of physiology, including androgens (for discussion, see Berenbaum, 2018). Among females with C-CAH, the vast majority (90%–95%) report female binary identity (when asked to report their identification as either female or male), although the number who express gender dissatisfaction or male identity is greater than in unaffected females; furthermore, girls and women with C-CAH are somewhat less female identified than those without CAH when assessed using continuous measures of gender identity (Berenbaum & Bailey, 2003). In contrast to activities, gender identity is not strongly associated with inferred degree of prenatal androgen exposure (Berenbaum & Bailey, 2003; Meyer-Bahlburg, 2013). Studies of transgender individuals (whose gender identity differs from their natal or assigned sex) also provide little evidence for influences of androgens, other physiological processes, or specific genes (for discussion, see Berenbaum, 2018).

In line with these studies showing female-typical gender identity in females with C-CAH, another study found that females with C- and NC-CAH had typical gender cognitions (Endendijk et al., 2016). *Gender cognitions* refers broadly to knowledge and application of gender stereotypes, beliefs, and values (e.g., women should obey husbands, it is best for men to do important jobs). Typical gender cognitions coexisted with gender-atypical (male-typed) activity interests and engagement, which suggests that females with C-CAH have standard knowledge and endorsement of stereotypes, but may not adhere to them, at least with respect to activities; this is consistent with observational data showing weak links between gendered attitudes and behavior in typical samples (for discussion, see Ruble et al., 2006).

Play partners

The dissociation between activities and identity in girls with C-CAH provides an excellent opportunity to study their influences on gendered peer interactions (Martin et al., 2011). Put simply, if peer interactions are based on behaviors such as play with boys' toys, girls with C-CAH should play with boys; but, if peer interactions are based on identity and cognitions, they should play with girls. Early data from questionnaires and experimental tasks revealed a greater preference for boy playmates among girls with C-CAH than among typical girls. These differences were modest in size and much smaller than the large differences between these groups in activities and the huge difference in playmate choice between typical girls and boys, whose preferences are essentially nonoverlapping (for discussion, see Berenbaum et al., 2018).

Peer relationships are best studied in the social world, so we obtained diary reports of time spent with other girls and with boys. Girls with C- and NC-CAH did not differ significantly in time spent with either boys or other girls, and few girls in either group spent much time with boys (Berenbaum et al., 2018). Time spent with other girls was related to both activities and gender identity and cognitions; prenatal androgens contributed to decreased time spent with other girls through its masculinizing effect on activities, but for girls with C-CAH, female-typed cognitions were still positively related to time spent with other girls. Further study is needed to understand why girls with C-CAH report some preference for boy playmates but spend little time with them; possible explanations may involve, for example, boys' reluctance to play with girls or the recognition by girls with C-CAH that boys' play extends beyond the activities the girls prefer (e.g., it includes rough-and-tumble play they do not prefer; Hines & Kaufman, 1994).

Cognitive abilities

Most cognitive studies of females with CAH have focused on spatial abilities, which show moderate to large sex differences. If prenatal androgens contribute to the typical male superiority in these abilities, then females with C-CAH should have better spatial abilities than unaffected females. We found such differences, and our results also suggested that spatial skills were partly enhanced by male-typed activity interests (Berenbaum et al., 2012; Resnick et al., 1986). Nevertheless, the evidence is not entirely consistent: Two meta-analyses offer conflicting conclusions (Collaer & Hines, 2020; Puts et al., 2008). Variations across studies likely reflect methodological issues that limit detection of what is a modest difference and factors associated with the disease that may counteract androgens' effects (Hampson & Rovet, 2015). Most studies have found that females with C-CAH have better spatial abilities than unaffected females (a finding consistent with hypotheses) or that the two groups do not differ significantly.

Alternative Explanations

The pattern of results we have described is best explained by differential effects of androgens across different behaviors. C-CAH is not a perfect experiment, however, and alternative explanations must be considered. In particular, parents' response to girls' virilized

genitalia (resulting from high prenatal androgens) and aspects of the disease or treatment warrant consideration. Parenting does not seem to lead to gender-atypical play: Observational data show that parents do not encourage male-typed behavior in girls with C-CAH and may encourage female-typed behavior (Pasterski et al., 2005). Disease and treatment factors are unlikely explanations because they would affect more than gendered characteristics and would also affect females with NC-CAH and males with C-CAH, who are behaviorally similar to typical same-sex counterparts, as seen in the studies we have described. An exception is spatial abilities, which may be reduced in both females and males with C-CAH as a result of disease complications. Further, it is possible that the small effects seen in some characteristics (e.g., gender identity) reflect the moderate (not male-typical) androgen levels to which females with CAH are exposed.

Other evidence against alternative explanations comes from converging findings in individuals with other differences in sex development (e.g., Batista et al., 2019; Callens et al., 2016; Meyer-Bahlburg, 2013). Additional evidence against alternative explanations from typical samples is suggestive, but not yet compelling (Berenbaum & Beltz, 2016).

Value of Studies of CAH

Studies of females with C-CAH do more than confirm the results of studies of nonhuman animals showing long-term masculinizing behavioral effects of hormones present during sensitive periods of development; they provide opportunities to understand psychological processes broadly. The complexity of androgens' effects revealed in studies of females with C-CAH raises interesting questions about moderators. Biological moderators likely include other aspects of physical differentiation that are female typical in C-CAH. Social moderators likely include processes shared with typical females, and studies of such moderators have the potential to reveal how nature and nurture work together; female-typical socialization may be modified in response to androgen-influenced characteristics.

Mechanisms of gender development can be tested in females with C-CAH, primarily owing to the dissociation of identity and other gendered characteristics not found in typical females. For example, findings noted above show that identity is important to the ways that people think about gender, supporting cognitive perspectives; that peer interactions are influenced by both behavior and identity; and that spatial skills are facilitated by activities.

Studies of females with C-CAH may also reveal mechanisms underlying androgen-influenced behavioral sex differences. For example, interest in toy vehicles may relate to predisposition to imitate propulsive movement (hitting vs. cradling an object; Benenson et al., 2011) and preferences for engaging with objects over people (Beltz et al., 2011). Some mechanisms may be shared with other primates; rhesus monkeys show sex-related object preferences paralleling human toy preferences (Hassett et al., 2008). It is possible that underlying mechanisms involve physiological processes outside the brain.

Considerable attention has focused on neural mechanisms, but sex differences in the brain alone provide little information about the origins of psychological sex differences (for discussion, see Beltz et al., 2020). Behavior is subserved by the brain, so psychological sex differences are reflected in the brain. The brain changes in response to input (from the environment and physiological systems). Thus, neural sex differences might cause or result from behavior. Neural sex differences are most meaningful when directly tied to psychological sex differences.

Implications of Hormonal Influences on Behavior

Gendered psychological characteristics are unquestionably influenced by prenatal androgens, but to varying degrees. Nevertheless, the science is often ignored, criticized, or misinterpreted, for two primary reasons. First, biological explanations have unfortunately been used in selective and distorted ways to support social policies that hurt girls and women, even though biologically influenced differences do not justify discrimination and inequality. Second, biological influences are often taken as evidence that something is "determined," even though biology is not immutable, and causes are separable from modifiers. Thus, gender equality does not require ignoring evidence for biological influences on sex differences, or insisting that sex differences are socially constructed (Berenbaum, 2017). We elaborate these points in Figure 2 and illustrate them with the example of career choice.

Figure 2 lists four primary ways in which biological influences on gender development are misunderstood, along with examples that counteract and correct the errors. First, biology is not deterministic. In most cases, biology influences a characteristic but is not fully causative. Furthermore, genetically influenced physiological processes are routinely altered by behavior; for example, diet and exercise reduce disease risk. Biology may be less deterministic than social factors, as illustrated by the difficulties eliminating racism. Second, causes are often different from modifiers; characteristics that are strongly influenced (or even determined) by genes are often changed by actions of individuals or social

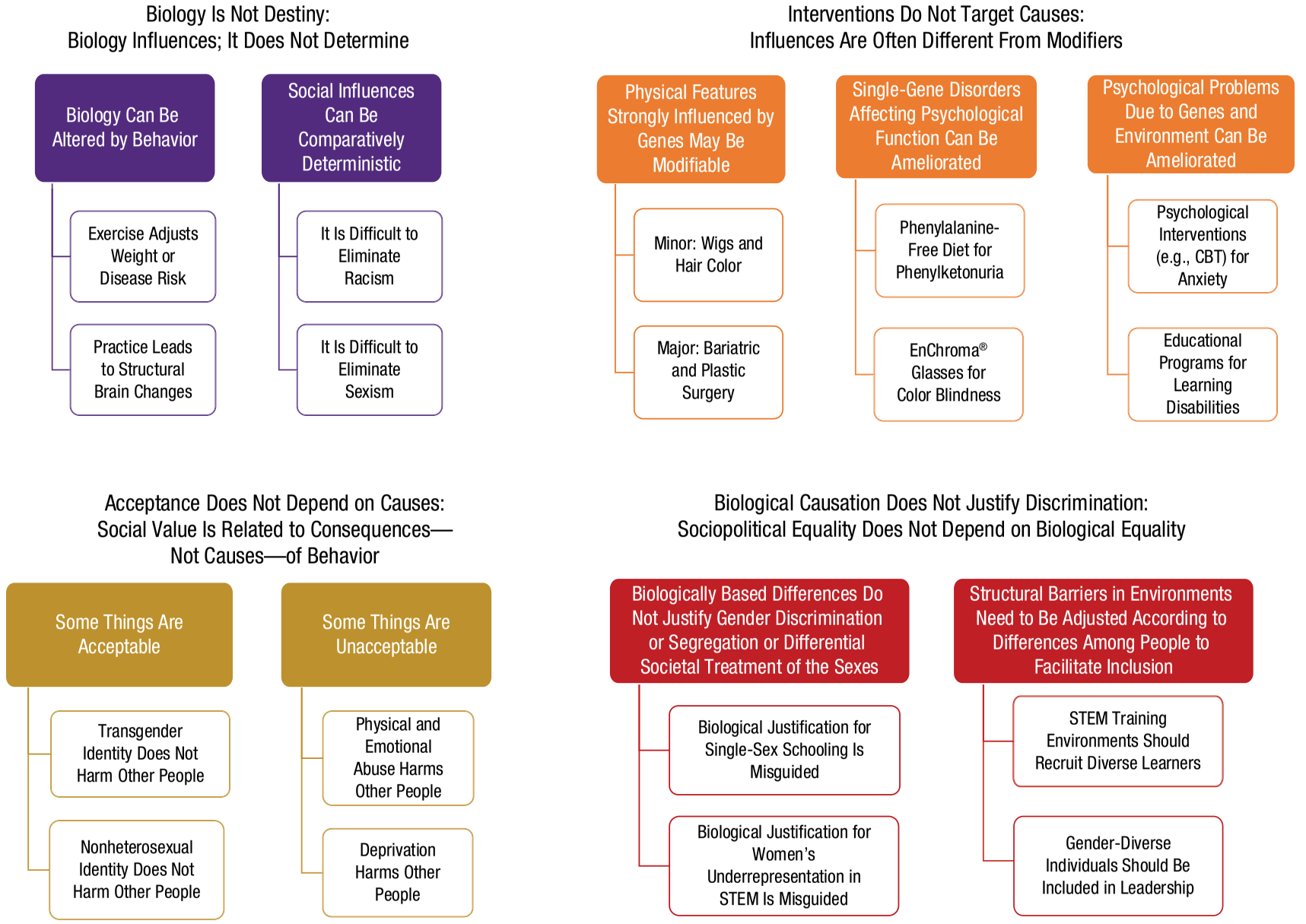

Fig. 2. List of the implications of biological, including hormonal, influences on behavior, highlighting inferences biology does not permit. CBT = cognitive behavior therapy; STEM = science, technology, engineering, and mathematics.

systems. For example, color blindness can be fixed with special glasses; hair can be dyed to change its color. Third, social acceptance of behavior should depend on its consequences, not its causes. For example, people with nonheterosexual identities do not harm society, but those who commit violent acts do. Fourth, discrimination is never justified. Biological justifications for social exclusion reflect prejudice, not science.

Moreover, biology and socialization work together to shape behavior, as illustrated by career choice. Androgens' influences on interest and participation in gender-typed activities and on spatial abilities might contribute to sex differences in occupations—in some contexts. This does not mean that the sex differences are either inevitable or acceptable, and it is important to consider whether and how to change them. Most interventions focus on changing girls and women to increase their representation in STEM (science, technology, engineering, and mathematics) careers, but not on changing boys and men to increase their representation in nursing and social-service careers—a focus reflecting the premium placed on male-typed characteristics, although more people are needed in both types of careers. Popular programs aimed at increasing male-typed interests produce limited change and may actually restrict girls and women who have broader interests than boys and men do (McCabe et al., 2020). Promising alternatives focus on showing girls and women how STEM careers are compatible with their interests, for example, by emphasizing the social or communal nature of scientific work (Diekman et al., 2010).

Crucially, career outcomes depend not just on individuals' characteristics but also on social structures. Discrimination and unavailability of childcare may reduce participation by women with STEM interest and talent. Barriers are apparent in women's slow advancement even when they have chosen STEM careers and in their underrepresentation in fields that do not depend on sex-typed skills or interests (Meyer et al., 2015). Successful interventions focus on context, for example, by aiming to change masculine cultures and provide early experiences signaling that both sexes belong in STEM careers (Cheryan et al., 2017).

In considering the nature and causes of psychological sex differences, and potential modifications to them, it is important to recognize the role of values. For example, a reluctance to acknowledge hormonal influences on occupational interests and an emphasis on interventions to change those interests generally stem from the higher value and reward accorded to male-typed than to female-typed occupations. Rather than ignoring biological influences or designing interventions that primarily focus on changing girls and women, perhaps policymakers, educators, and researchers should now focus on interventions that recognize and reward characteristics that are female typed and the value of women's work.

Conclusions

CAH provides a natural experiment to advance understanding of gender, by revealing relative influences of prenatal hormones and socialization, and their interplay, and by enabling tests of psychological mechanisms. The complex behavioral effects of androgens highlight the multidimensionality of gender. Gender equality is compatible with evidence that hormones influence gendered characteristics.

Recommended Reading

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Berenbaum, S. A., Beltz, A. M., Bryk, K., & McHale, S. (2018). (See References). A report on a multimethod empirical investigation showing that prenatal androgens had effects on activities, but not peer play or gendered cognitions, in early-adolescent girls with congenital adrenal hyperplasia (CAH).

Berenbaum, S. A., Blakemore, J. E. O., & Beltz, A. M. (2011). A role for biology in gender-related behavior. *Sex Roles: A Journal of Research, 64*(11–12), 804–825. https://doi.org/10.1007/s11199-011-9990-8. A review of research on gender, highlighting the historical resistance to biological approaches, and what it means—and does not mean—for biology to influence gendered behavior.

Frisén, L., Nordenström, A., Falhammar, H., Filipsson, H., Holmdahl, G., Janson, P. O., Thorén, M., Hagenfeldt, K., Möller, A., & Nordenskjöld, A. (2009). (See References). A report on an empirical investigation of women with CAH in Sweden, showing dose-dependent effects of prenatal androgens on male-typed interests and careers.

Hampson, E. (2018). Regulation of cognitive function by androgens and estrogens. *Current Opinion in Behavioral Sciences, 23*, 49–57. https://doi.org/10.1016/j.cobeha.2018.03.002. A review of the effects of sex hormones on cognition that includes—but goes beyond—the effects of prenatal androgens to illustrate the ways in which androgens and estrogens affect spatial skills as well as working memory.

Transparency

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Note

1. Multiple rubrics to distinguish the terms "sex" and "gender" have been proposed (for discussion, see Blakemore et al., 2009). It is common to see "sex" used to refer to biological aspects of being male or female and "gender" used to refer to social or cultural aspects, but it is often impossible to make the distinction, as shown in this article. Other people use "sex" to refer to the categories of male and female, and "gender" to refer to judgments about the nature of differences between males and females, about roles, and about masculinity and femininity. We generally follow the latter approach, but use also "sex" to describe differences between girls and boys and between women and men; there are no values associated with our terminology.

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