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# The Genetics of Sex Differences in Brain and Behavior

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## Abstract

Biological differences between men and women contribute to many sex-specific illnesses and disorders. Historically, it was argued that such differences were largely, if not exclusively, due to gonadal hormone secretions. However, emerging research has shown that some differences are mediated by mechanisms other than the action of these hormone secretions and in particular by products of genes located on the X and Y chromosomes, which we refer to as direct genetic effects. This paper reviews the evidence for direct genetic effects in behavioral and brain sex differences. We highlight the `four core genotypes' model and sex differences in the midbrain dopaminergic system, specifically focusing on the role of *Sry*. We also discuss novel research being done on unique populations including people attracted to the same sex and people with a cross-gender identity. As science continues to advance our understanding of biological sex differences, a new field is emerging that is aimed at better addressing the needs of both sexes: gender-based biology and medicine. Ultimately, the study of the biological basis for sex differences will improve healthcare for both men and women.

### Keywords

Sexual differentiation; brain anatomy; sex differences; sexual orientation; gender identity; sex chromosomes; SRY; dopamine; behavior

## 1 INTRODUCTION

Men and women are different in many ways. These differences include both biological phenotypes [e.g. 1] and psychological traits [e.g. 2]. Some of these differences are influenced by environmental factors [3; 4]. Yet, there are fundamental differences between the sexes that are rooted in biology.

Of particular interest are sex differences that have been identified in the brain. Although the brains of men and women are highly similar, they show consistent differences that have important implications for each sex. That is, brain sex differences uniquely affect biochemical processes, may contribute to the susceptibility to specific diseases, and may influence specific behaviors. Such biological differences should never be used to justify discrimination or sexism. However, we believe that a thorough understanding of these



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differences can inform researchers and clinicians so that they can better address important issues. Two examples include how genetic sex can lead to differences between the sexes in the etiology and the progression of disease and how differences in neural development may result in differences in cognition and behavior.

In this paper, we will review sex differences in brain and behavior that are not due to the action of hormones secreted by the gonads—which has been the dominant mechanism associated with such differences—but from what we term `direct genetic effects.' These are effects that arise from the expression of X and Y genes within non-gonadal cells and result in sex differences in the functions of those cells. First, we will highlight some sex differences at the biological level and at the psychological level. Then, we will review the `classic' view that dominated the field of sex differences—that most sex differences, especially those concerned with reproductive physiology and behavior, were due to the action of hormones produced by the gonads. Next, we will present the emerging view that `direct genetic effects' play an important role as well. Finally, we will discuss novel approaches to studying sex differences by focusing on unique groups of individuals: people with sex-chromosome variations (e.g., Klinefelter's Syndrome and Turner Syndrome), people with genetic mutations in the sexual development pathway, people with an atypical sexual-orientation, and people who experience a cross-gender identity.

## 2 BIOLOGICAL SEX DIFFERENCES

There are many biological differences between males and females that are beyond the obvious differences at a gross, macro level (e.g., height, weight, and external genitalia). Specifically, there are several important physiological differences that have critical implications including the susceptibility to different diseases and the ability to metabolize different medications. In this section we will highlight some sex differences in neuroanatomy and neurochemistry.

### 2.1 Neuroanatomy

The two sexes have similar but not identical brains. Most brain studies have focused on gross manifestations of these differences—namely the size of specific regions or nuclei. Yet, there is mounting evidence of sex differences at a finer level including differences in synaptic patterns [5; 6] and neuronal density [7; 8; 9]. It is beyond the scope of this article to provide a comprehensive review of all known neuoranatomical differences. We have provided notable sex differences in the rat brain in Table 1. There are also excellent resources for those who are interested in delving deeper into this topic [10; 11; 12].

We have chosen to focus on neuroanatomical differences in the rat because the biological significance and origins of these differences are much clearer than in humans. Neuroanatomical differences in humans are also well-studied although ethical reasons preclude the experimental manipulations that have led to the findings detailed in Table 1. This significantly limits the conclusions that can be drawn from any observations made in humans.

Although these neuroanatomical differences are intriguing, most are limited because the practical or functional significance of these findings are unknown. Discovering the significance of these differences is often difficult, even in rodents. de Vries and Sodersten have eloquently outlined the challenges facing researchers who want to understand the link between sex differences in structure and behavior [13]. A highly relevant case study highlighted in their review concerns the sexually dimorphic nucleus of the preoptic area (SDN-POA). The preoptic area (POA) has been implicated in the regulation of male copulatory behavior [14], but the link (if any) between the sex difference in SDN-POA size

and behavior remains elusive. Masculinizing the size of the SDN-POA in female rats does not result in a corresponding masculinization and defeminization of behavior [15]. Instead, the SDN-POA may be related to inhibition of female sexual behaviors [16; 17], which might not have been an obvious hypothesis given what was known about the POA previously. As science and technology continue to advance, we will eventually know how to make sense of the mounting evidence of sex differences in the brain. For now, it is reasonable to suspect that such differences may help account for observed sex differences in behavior, neurological diseases, and cognitive abilities. SDN-POA) exist, and the interpretation of the data is often more complicated than this summary implies.

### 2.2 Neurochemistry

Males and females exhibit different patterns of transmitting, regulating, and processing biomolecules. Table 2 presents some of the neurochemical sex differences that have been identified. As a specific example, we focus below on the monoaminergic system, which has been implicated in several neurological diseases and mental disorders that differentially affect men and women.

Monoamines are a class of small-molecule neurotransmitters that are involved in the control of a variety of processes including reproduction and sexual behavior [51; 52], respiration [53], and stress responses [54]. Monoamines have also been implicated in numerous mental disorders, including ones that differentially affect men and women [55; 56]. Likewise, sex differences in the monoaminergic systems in the rat are well-documented. Reisert and Pilgrim provided a comprehensive review of arguments for the genetic bases of these differences [57].

Monoamines are subdivided into two groups—catecholamines and indolamines—based on their molecular structure. The main catecholamines are dopamine (DA), norepinephrine (NE) and epinephrine, which are synthesized from the amino acid tyrosine. Figure 1 highlights some of the known sex differences of the dopaminergic system. Regulation of dopamine can potentially control the levels of the other two catecholamines as they are derived from dopamine.

Catecholamines are released by the adrenal glands usually in response to stress, which affects males and females differently. For instance, chronic physical stress impairs memory in male rats only [58]. The sexes also show differing neurochemical responses: Dopamine activity is upregulated in males only whereas norepinephrine is upregulated in females only (Figure 1A). Sex differences have also been found in the regulation and modification of dopamine (see Figures 1B and 1C). Specifically, the enzyme tyrosine hydroxylase (TH), which is involved in dopamine synthesis [59], is regulated by *Sry*—the male sex determination gene—which is not present in females. Additionally, levels of norepinehrine in the amygdala differ between the sexes as a result of age. Thus, it is likely that brain catecholaminergic responses to stress might also differ between the sexes.

Another monoamine is serotonin, which is an indolamine. Unlike catecholamines, serotonin is derived from the amino acid tryptophan. The serotonergic system shows sex differences (Figure 2), though many of these differences remain unlinked to behavioral differences between men and women. Nevertheless, differences in this system likely have consequences given the link between serotonin and numerous mental disorders [60; 61].

## 3 PSYCHOLOGICAL AND BEHAVIORAL SEX DIFFERENCES

In addition to biological differences, men and women differ in many psychological and behavioral aspects. For instance, men perform better on specific visuospatial aspects (e.g.,

mental rotation) compared to women; and women perform better on specific verbal tasks (e.g., verbal fluency) compared to men [88]. Furthermore, there is a large sex difference in sexual interests and behaviors, such as interest in casual sex, interest in multiple sex partners, and interest in visual-sexual stimuli (e.g., pornography) [89; 90]. Other examples are summarized in Table 3.

Some contend that these differences are due to social systems and gender socialization [cf. 91; 92; 93] . Nevertheless, biological traits likely contribute to many sex differences. Thus, a thorough understanding of the main determinants involved in expression of such sex differences can help us better explain the relationship between brain, behavior, and environment. In addition, it allows us to determine how one's sex potentially influences the risk of developing disorders that manifest and progress differently in men and women. Such knowledge can better inform the treatment of these diseases. Tables 3 and 4 illustrate several factors (*e.g.* hormones and genes) that may be causally linked to expression of sex differences in behavior and disease, respectively.

## 4 THE CLASSICAL VIEW ON SEX DIFFERENCES

Researchers have examined what contributes to the differences we see between males and females. Certainly for humans, social environments influence some of these differences. For instance, social stratifications (e.g., social class and the distribution of social power) and social rules (e.g., customs and traditions) may affect the ability for people to access educational resources or to engage in certain behaviors [205; 206]. However, social factors alone do not contribute to all differences seen between males and females—especially regarding biological differences [207].

The life sciences have elucidated many factors that contribute to sex differences. In this section, we briefly review the classical view that gonadal hormones contribute to most, if not all, sex differences after gonadal differentiation. We will then present some findings that have challenged this view.

### 4.1 The Role of Gonadal Hormones

Sexual development in mammals can be divided into two main components: sex determination and sex differentiation [208]. `Sex determination' is the process by which the bipotential gonad develops into either a testis or an ovary, which depends exclusively on genetics. `Sex differentiation' is the development of other internal reproductive structures, the external genitalia, and non-gonadal sex differences. Unlike sex determination, sex differentiation is driven by gonadal hormones. It was widely believed that sex differences that emerged after sex determination were largely due to the actions of gonadal hormones. Examples of this pervasive view include writings from Lillie in 1939 (“[T]he mechanism of sex differentiation is taken over by extracellular agents, the male and female hormones.” [209]), Jost in 1970 (“The developmental analysis of the body sex characteristics reveals a hormonal control.” [210], Morris et al. in 2004 (“[A] single factor—the steroid hormone testosterone— accounts for most, and perhaps all, of the known sex differences…”[14]) and Zhao et al. in 2010 (“[T]he sexual phenotype of individuals is dependent on the gonad…” [211]). We will use the term `classical view' to refer to this hypothesis.

The classical view was based on decades of compelling research demonstrating the organizational and activation effects of gonadal hormones in vertebrates [212; 213]. `Organizational effects' refer to the permanent, irreversible changes during development that organize the body in either a male- or female-typical pattern. For instance, the neonatal surge of testosterone in male rodents leads to life-long changes in the synaptic pattern of the ventrolateral ventromedial hypothalamic nucleus [47]. `Activational effects' refer to the

short-term changes that occur in the body depending on the presence or absence of specific hormones. An example of this is the requirement for the presence of both estrogen and progesterone to induce or “activate” lordosis in female rats [214].

Recently, it was found that gonadal hormones might not be the sole contributor to male- and female-typical development. Genes encoded on the sex chromosomes that directly act on the brain to influence neural developmental and sex-specific behaviors have been identified—an example of what we describe as direct genetic effects [215; 216]. When we use this term, we refer to effects arising from the expression of X and Y genes within non-gonadal cells that result in sex differences in the functions of those cells or target cells. Such direct genetic actions are wide-ranging and can include effects of locally produced hormones or other non-hormonal messenger molecules. For example, sex differences arising in the brain from differential paracrine secretion of neurosteroids would be considered a direct genetic effect. The commonality among these actions is that they are not dependent on mediation by hormones secreted by the gonads. In many cases, the identity of the messenger molecules have yet to be identified. This review will now focus on examples in which sex differences in behaviors are unlikely to be influenced by only the action of gonadal hormonal secretions and may in fact be due to direct genetic effects.

### 4.2 Exceptions to the Classical View

The idea that factors other than the gonadal hormone milieu could account for sex differences first gained credence from research performed on the zebra finch. In zebra finches, males exhibit courtship behaviors that are unique to their sex. Specifically, they possess the ability to sing a distinct courtship song. This male-specific ability has been attributed to several brain regions that are larger in males compared to females [217; 218]. Given the hypothesis that such differences must have been the result of sex-specific hormones, several researchers unsuccessfully attempted to alter the courtship behavior of finches by manipulating hormone levels [219]. For example, it was shown that castrated male zebra finches were not significantly different from intact male zebra finches in terms of song development [220]. Furthermore, female zebra finches that developed testes continued to develop feminine song circuitry and did not exhibit masculine song behavior [221; 222].

Several other experimental manipulations led researchers to question the role of hormones. For instance, Jacobs *et al.* treated female zebra finches with estrogen at the beginning of hatching given that estrogen induces male sexual differentiation in the zebra finch neural song system [223]. Interestingly, estrogen treatment was not able to cause full masculinization of the neural circuitry of the zebra finch song system (the song circuitry was still smaller compared to control males) [224; 225] and supraphysiological doses of estrogen were required for full masculinization [226]. Similarly, it was shown that inhibiting the action of estrogen by using aromatase blockers in males did not completely prevent the male differentiation pathway [217; 227; 228; 229; 230].

The discovery of a rare type of zebra finch provided further support for a new hypothesis regarding sexual differentiation: The bilateral gynandromorphic finch has male-typical phenotypes on one half of the body (e.g., plumage, testis, and song circuitry) and female-typical phenotypes on the other half of the body. Each half of such finches is either entirely genetically male or genetically female. Thus, each side contains the sex-specific genes necessary for the development of the corresponding sex-specific traits. In this model, while the gonadal hormonal actions in producing sex differences in the brain cannot be completely ruled out (both sides of the neural song system were larger than that of normal females), their influences cannot fully explain the differences observed between the left and right sides of the brain. Given this explanation, the most reasonable theory is that endogenous genetic

differences in the brain cells themselves can also contribute to the unequal differentiation of the two sides producing sex differences through their local action within the brain [231].

Recent work on gynandromorphic chickens strengthens the case that the classical view largely does not apply to sexual differentiation in birds. Zhao et al. showed that the `sex identity' (or the expression of sex-specific phenotypes) of somatic cells in birds is determined by the sex chromosome complement of those cells and not the gonadal hormonal environment [211; 231]. In mammals, transplantation of somatic cells from one sex into the gonad of the other sex reverses the sex identity of the donor somatic cells. For example, XX cells can develop into functioning Sertoli cells while XY cells can become functioning granulosa cells [232; 233]. However, this is not the case in the chicken as male donor cells introduced into the developing ovary continued to express a male-specific marker and were excluded from `functional' structures of the host gonad. The host and donor somatic cells were exposed to the same hormones, but they responded differently based on their respective sex chromosome complement.

A second exception to the classical view that we highlight below concerns the development of the tammar wallaby. As with brain development, gonadal hormones drive the sex-specific development of the external genitalia in most mammals. Specifically, androgens promote the development of male genitalia. However, the formation of reproductive structures in the tammar wallaby appears to be independent of gonadal hormone control and is solely due to the effect of sex chromosome complement.

The tammar wallaby is a marsupial that is much smaller than the kangaroo. During fetal development, the production of testosterone, which would typically masculinize mammalian fetuses, does not occur in these marsupials until about the fourth or fifth day after birth [234; 235; 236; 237]. Yet, signs of sex-specific reproductive structures (e.g., scrotum, mammary gland, and pouch formation) can be observed as early as several days before birth. In mammals, the development of male-specific structures, is thought to be completely dependent on the action of androgens [208]. Experiments that increased or decreased the action of testosterone or estrogen in the tammar wallaby had no significant effect on the development of the external genitalia [238; 239]. This suggested that such differences were not under gonadal hormone control.

A case similar to the gynandromorphic zebra finch has also been reported in tammar wallabies: This consists of wallabies that are XX on one side of the body and XY on the other side of the body. Such wallabies develop a hemipouch on the XX side and a hemiscrotum on the XY side even after exposure to circulating gonadal hormones [226; 240; 241]. As with the zebra finch, such cases challenged the view that all sex differences were due to hormones produced by the gonads.

## 5 AN EXPANDED VIEW ON SEX DIFFERENCES

In light of scientific findings, such as with the zebra finch and the tammar wallaby presented above, the field of sex differences has now come to encompass studies that examine gonadal hormone as well as genetic origins of these differences. One of the most significant challenges in studying the establishment of sex differences in animal models has been the difficulty in separating gonadal sex from chromosomal sex. These two parameters almost always correlate in an animal.

In the following section, we highlight the `four core genotypes' model, which has proven to be a powerful tool in teasing out the effects of gonadal versus chromosomal sex and enabling researchers to overcome this confound. We then discuss in-depth sexual differentiation and sex differences in the midbrain dopaminergic system, focusing

specifically on the role of *Sry*. We discuss the implications that these differences may have on the development of this system as well as neurological health implications.

### 5.1 The `Four Core Genotypes' Model

A 2×2 mouse-model was developed to separate the effects of gonadal sex from chromosomal sex. This model, known as the `four core genotypes' (FCG), allows researchers to establish the relative contribution of sex chromosomes and hormones in sexual differentiation as well as the interaction between the two. Arnold and Chen recently reviewed this model [242]. Here we highlight some of the model's basic concepts.

Figure 3 depicts the effect of the presence or absence of *Sry*—a 12kb region on the Y chromosome that is responsible for testis determination—using the FCG model. An XY mouse should develop testes; however, if *Sry* is deleted from the Y chromosome (symbolized by $Y^{-}$) then the mouse will develop ovaries [243]. If the *Sry* gene is inserted into any chromosome of an XX mouse (symbolized by $XX^{Sry}$), then the mouse will develop testes. Finally, if *Sry* is deleted from the Y chromosome of an XY mouse and then inserted into one of its autosomes (symbolized by $XY^{-Sry}$), then it will develop testes.

$XY^{-Sry}$ mice are fully fertile because the presence of *Sry* promotes testes development. $XX^{Sry}$ mice lack some of the genes required for sperm production, which are found on the Y chromosome [244], and therefore do not appear to be fertile. However, they have small testes and are fully masculinized in terms of measures of male copulatory behavior, social exploration behavior, and sexually dimorphic neuroanatomical structures in the septum, and lumbar spinal cord.

$XY^{-Sry}$ mice can be mated with XX females to produce the four types of offspring (XX, $XY^{-}$, $XX^{Sry}$, and $XY^{-Sry}$) that can then be used to assess the impact of a mouse's chromosomal and gonadal sex on different phenotypes. That is, if there is a difference between mice that carry the *Sry* gene (i.e., $XX^{Sry}$ and $XY^{-Sry}$) versus those that do not (i.e., XX and $XY^{-}$), then the observed difference can be attributed to the gonadal type and/or presence of *Sry*. On the other hand, if there is a difference between mice that have the Y chromosome (i.e., $XY^{-}$ and $XY^{-Sry}$) versus those that do not (i.e., XX and $XX^{Sry}$), then the observed difference can be attributed to complement of sex chromosomes (XX versus XY).

**5.1.1 Limitations of the FCG model—**Some possible limits to the FCG model have been suggested. One possible limit is that the size, morphology, and function of the gonads are not exactly the same in XX and XY mice of the same gonadal type (e.g. $XX^{sry}$ vs. $XY^{-sry}$). Consequently, the level of gonadal hormone secretions in FCG mice may differ during critical periods of development—a confound that has yet to be investigated. Yet, numerous phenotypes that are responsive to the organizational effects of gonadal hormones (including sexually dimorphic brain structures) do not differ in XX and XY mice of same gonadal type [37,57,80,42], indicating that XX and XY mice of the same sex are likely experiencing similar levels of gonadal secretions. For example, measurements of circulating testosterone in XX and XY males found no difference in testosterone levels between the groups [245].

A second limit relates to the biochemical and molecular environment. That is, one cannot rule out the effect of prenatal hormonal secretions, the influence of adult circulating hormones produced by the gonads or other tissues, acute fluctuations in hormonal levels, and the influence of the *Sry* transgene (i.e., the potentially higher expression-level of the *Sry* transgene in $XY^{-Sry}$ animals versus XY mice). For example, the *Sry* transgene could hasten the early stages of testis organogenesis in $XY^{-Sry}$ males. Furthermore, several phenotypes have been found to differ between XY and $XY^{-Sry}$ males. However, it is not known whether

these differences are caused by the effect of *Sry* on androgen production or by some other mechanisms that are not mediated through the action of gonadal hormones.

To address these limits, it is best to rule out the effect of circulating gonadal hormones. An effective approach would be to first gonadectomize the mice followed by an administration of equivalent doses of gonadal steroid hormones. This is particularly important in the case of $XY^-$ females since their level of ovarian steroid hormones differ from that in the XX wild type females [245]. Nevertheless, a major limitation still remains: It will not be obvious whether the sex difference attributed to the complement of sex chromosomes within cells is caused by (a) gene or genes encoded on the Y chromosome; (b) higher dosage of X genes particularly the ones that escape X inactivation in XX animals [246]; or (c) the paternal imprint of the genes encoded on the X chromosome in XX animals, which changes the expression of these genes to exhibit a female-specific pattern [219; 247]. If one determines that the sex difference in phenotype is due to the sex chromosome complement, then the next step would be to discover the nature of the gene or genes involved and identify whether those genes are encoded on the X or Y chromosome and how and where they mediate their role [216].

Notwithstanding these potential limitations, a variety of sex differences have been examined using the FCG model. We review three of these.

**5.1.2 Lateral septum—**One clear example of the role of sex-chromosome genes in brain phenotypes can be found in the lateral septum. The lateral septum is part of the limbic system and is involved in stress-related behaviors. This nucleus is denser in male brains compared to female brains. However, it was found that the vasopressin fiber density was greater in the lateral septum of $XY^{-Sry}$ and $XY^-$ mice compared to XX and $XX^{Sry}$ mice [215]. In addition, an examination of vasopressin fiber densities in animals with the same sex chromosome complement indicated a role for the action of gonadal steroid hormones. No interaction was observed between gonadal sex and sex chromosomes [216].

**5.1.3 Addiction—**On average, women use addictive drugs at lower levels than men, but women become addicted to drugs more rapidly than men [248]. Based on the FCG model, Quinn et al. showed that this difference could be attributed to the differences in the complement of the sex chromosomes and not to the gonadal secretions and/or the expression of the *Sry* gene. XX mice developed habitual behavior more rapidly than the XY animals independent of their gonadal phenotype and even after gonadectomy. This implies that neither gonadal sex nor circulating steroid hormones exert major effects on the development of habit-driven behavior in mice [182].

**5.1.4 Aggression—**Males typically exhibit more aggressive behaviors compared to females [249; 250; 251]. Recent reports have shown that aggression latencies are strongly influenced by the simultaneous action of gonadal hormones and sex chromosomes. Using the four core genotypes model, it was found that a significant interaction exists between the two variables. In this model, the XX females appeared to be slower at displaying aggressive behavior on their first encounter with an intruder compared to animals in all other groups [215].

### 5.2 Direct Role of Sry in Brain Sex Differences

Sex differences in the brain may contribute to some of the psychological and behavioral differences we observe between the sexes. Furthermore, they may influence the susceptibility to different diseases. For instance, Parkinson's disease—a neurodegenerative disease that impairs motor function and speech—affects more men than women. Research

has established a link between Parkinson's disease and a loss of dopaminergic neurons in the substantia nigra [252]. Such losses disrupt dopamine pathways, which leads to many of the symptoms associated with Parkinson's disease.

Robust sex differences have been observed in the development, activity, and number of dopaminergic neurons. The data described below represents a clear example of a sex difference in the brain that has a strong genetic component.

**5.2.1 Dopaminergic neurons in rodents—**Sex differences in dopaminergic neurons have been found prior to exposure to gonadal steroid hormones. During *in utero* development, rat embryos are exposed to a plasma surge of hormones around embryonic day 17 or 18 (E17 or E18). Yet, as early as E14, dissociated cell cultures of dopaminergic neurons obtained from male and female rat brainstems were found to be fundamentally different in their morphology and function prior to exposure to gonadal steroid hormones [57]. Furthermore, females had higher numbers of dopaminergic, tyrosine hydroxylase-immunoreactive (TH-ir) cells in the midbrain; and their mesencepahlic and diencepahlic neurons produced more dopamine when compared to males. On the other hand, soma measurements of diencephalic neurons from male cultures contained larger dopaminergic neurons. Although it is difficult to make accurate measurements of hormonal levels in the embryonic brain, it is unlikely that there is a huge sex difference due to gonadal hormone exposure at this stage as the rat gonad only *begins* to differentiate at this point. Therefore, this suggests a contribution of sex chromosome complement and/or sex-specific gene expression.

These differences are not altered even when gonadal hormone levels are manipulated. Specifically, treatment with estradiol and testosterone does not eliminate the observed sex differences in number, size, or function of the dopaminergic cells. Similar findings were later replicated in a study using mesencephalic cultures from the NMRI strain of mice [253]. Collectively, these observations strongly support the idea that some of the sex-specific properties of the dopaminergic neurons appear to be under the control of non-hormonal mechanisms.

**5.2.2 The Y chromosome's role in dopaminergic neuron development—**A study utilizing the four core genotype model further strengthened the case that a genetic component largely accounts for these sex differences. Carruth et al. cultured mesencephalic neurons from E14 animals representing each of the groups from the four core genotypes [50]. Cultures from $XY^{-}$ and $XY^{-Sry}$ animals developed significantly more TH-ir neurons compared to the XX and $XX^{Sry}$ animals. However, gonadal sex did have a small effect: Animals that had *Sry* (and hence testes) were associated with a higher number TH-ir cells compared to those without *Sry*. Due to the design of the four core genotypes model, it is difficult to separate the direct effects of *Sry* from its indirect effects on dopaminergic neurons or their precursors (e.g., through testis determination and the subsequent hormonal secretions).

The data pertaining to sex differences in dopaminergic neuron development show sex differences in distinct directions and so are difficult to interpret. In cultures from E14 rats and NMRI mice, the sex difference is the reverse of what was seen with the four core genotypes. However, rather than invalidating the findings, the conflicting information highlights the complex interactions between genetics and gonadal hormones in leading to the sex differences that are observed. First, the differences between data from NMRI mice and the four core genotypes may be attributable to strain differences. Data from the former study indicate that genetic background can significantly affect whether a sex difference is observed [253]. Carruth et al. had outbred their mice onto the MF1 background [50]. In

regards to the differences seen between cultures from rats and the four core genotypes, one possible explanation is that both androgens and the Y chromosome are needed to lead to the number of dopaminergic neurons being higher in males. Support for this hypothesis comes from our own studies where we see that the number of dopaminergic neurons in the rat substantia nigra is higher in *adult* males [49]. Additionally, the finding that the presence of testis was associated with a higher number of these neurons fits with our hypothesis. There are also important distinctions in the timing of the cultures in relation to gonadal development: while both studies cultured E14 neurons, the bipotential gonad has already differentiated into a testis to a larger extent in the mice [254; 255] than in the rat at this gestational stage [256]. As such, the hormonal environment from which these cultures were derived may not be the same, which could account for some of the disparity in the direction of the sex difference. An elaboration of the hypothesis presented above is that it is not just the testes and androgens that are essential but also *Sry*, the gene that initiates testicular development. Using a rat model, our laboratory has found evidence that this may be the case and showed that *Sry* has a direct effect on the expression of TH in the substantia nigra [49].

**5.2.3 Sry is a direct effector of TH expression—***Sry* is the gene on the Y chromosome that directs the bipotential mammalian gonad to develop as testes—hence, its name: Sex determining region on Y. *Sry* is the founding member of the Sox family of proteins, which play a major role in a wide range of biological processes such as neurogenesis, hematopoiesis, and neural crest development [257]. *Sry* contains a high mobility group (HMG) box domain and shows little conservation from mouse to human outside this stretch of about 80 amino acids [258].

The HMG box forms a domain that induces a sharp bend in the DNA [259]. It is proposed that this bending of the DNA enhances recruitment of specific transcriptional factors. In line with this hypothesis, *Sry* has two nuclear localization signals within the HMG domain [260] and its ability to activate transcription in vitro has been demonstrated [261].

Recently, researchers have used genome-wide surveys to identify targets of *Sry* in the gonad. The most widely known target of *Sry* is *Sox9* [262]. Two other notable targets of *Sry* are *Cbln4* [263], which codes for the cerebellin precursor; and *MAO A*, which codes for monoamine oxidase A [264]. Wu and colleagues also found that *MAO A* was upregulated by Sry in the BE(2)C neuroblastoma cell line suggesting that *MAO A* may be a neural Sry target [264].

Most studies on *Sry* expression have focused on the gonad and *Sry*'s subsequent effects on sex determination and differentiation [265]. In the developing mouse embryo, *Sry* is expressed between E 10.5 and E 12.5 in the developing genital ridge, prior to overt testis differentiation [266]. Until recently, it was thought that *Sry* had no role other than sex determination. However, *Sry* expression has been found in numerous tissues outside of the testis (see below) and this expression in the adult male rat is now known to have biologically significant effects. *Sry*'s crucial role in the regulation of the catecholaminergic system is one of the best examples of a direct genetic regulator of a trait that differs between the sexes.

**5.2.4 SRY in the brain—**Clépet et al. were the first to perform a survey of *SRY* expression in human tissue outside of the gonads [267]. In fetal tissue, *SRY* was seen in the brain, adrenal, heart, and pancreas. In adults, transcription was detected in the kidney, heart, and liver. This study also showed that *SRY* was expressed in the teratocarcinoma cell line NT2/D1, which was derived from adult male tissue and which can be used as a model for dopaminergic neurons. When NT2/D1 was induced to differentiate into neurons by retinoic acid, *SRY* expression remained.

*SRY* expression in the human adult brain was not surveyed until 1998. Mayer, Lahr et al. showed that *SRY* mRNA was present in the hypothalamus, frontal, and temporal cortex of only the adult male [268]. *Sry* mRNA is also found in the adult male mouse brain where it can be detected in the midbrain (including the substantia nigra) and hypothalamus in all developmental stages [269].

**5.2.5 SRY and the regulation of TH expression—***Sry* has a biologically significant role in the brain in at least one instance—the regulation of tyrosine hydroxylase (TH) [49; 270]. In a 2004 study, Milsted, Serova et al. found that *Sry* is a regulator of TH gene transcription [270]. The study looked at *Sry*'s role in relation to TH in both the brain and the adrenal medulla. They demonstrated that *Sry* and TH mRNA were co-localized in the locus coeruleus, substantia nigra, and ventral tegmental area of the male rat (Figure 4A). They then used a luciferase reporter assay to show that *Sry*'s ability to upregulate TH expression is dependent on the AP1 binding sites in the promoter of TH.

The *in vivo* significance of those findings was shown and expanded upon by a study from our laboratory. By *in situ* hybridization, we were able to determine the spatial distribution of *Sry* mRNA within the rodent brain [49]. Specific labeling of *Sry* was observed in the substantia nigra, medial mammillary bodies of the hypothalamus, and the cortex of male rats only. These transcripts were translated and co-localized with the TH protein—all neurons in the substania nigra positive for *Sry* were also positive for TH. Knocking down *Sry* expression in the male rat substania nigra led to 38% fewer TH-immunoreactive neurons and introduced a significant asymmetry in limb use where the animals strongly favored the usage of their ipsilateral limbs (Figures 4B and 4C). The reduction in TH-ir neurons was not due to neural degeneration and is most likely due to a reduction in TH expression. There was also a 26% decrease in TH-ir cells in the striatum when *Sry* expression was knocked down in that region. TH-ir neuron number was not affected in females infused with the *Sry* antisense cocktail.

The nature of *Sry*'s modulation on TH remains unclear. The results of the study by Milsted, Serova et al. argue that the TH response to *Sry* is likely an indirect one [270]. Our data indicate that there may be both direct and indirect mechanisms [49].

The identification of a specific function for *Sry* in the dopaminergic system, specifically, and the brain, generally, is still absent. Additionally, comprehensive temporal and spatial expression studies need to be performed on brain *Sry* expression. Another largely unanswered question concerns the identity of a female-specific `compensatory' factor for *Sry*.

We have shown that the attenuation of *Sry* expression in males results in detrimental motor effects and that females have lower levels of TH neurons [49]. However, female rats do not go through life exhibiting motor dysfunction. The higher susceptibility of men to Parkinson's disease also implies that this factor exists and might have protective effects against the nigrostriatal degeneration that is the hallmark of Parkinson's [252]. Estrogens are a viable candidate for this factor – short-term injections of estradiol benzoate lead to an increase in TH mRNA [271] and ovariectomy results in loss of TH-positive neurons [272].

## 6 NOVEL APPROACHES TO STUDYING SEX DIFFERENCES

Traditional animal models have played an invaluable role in advancing our understanding of sex differences. In particular, scientists are able to conduct experimental manipulations that would be unethical on human subjects. However, research on specific groups of people has addressed some complex questions. In this section, we focus on research conducted on four

such groups: people with sex-chromosome variations, people with genetic mutations of the sexual development pathway, people attracted to the same sex, and those with cross-sex gender identity. For readers interested in learning more about disorders of sex development, several comprehensive resources exist [208; 273].

### 6.1 Genetic Disorders of the Sex Chromosomes

The most obvious genetic difference between females and males is their sex chromosome complement (i.e., XX and XY). Various human sex chromosome disorders exist, which might be considered a human model for sex chromosome effects similar to the four core genotypes. The most common variants in men involve additional X or Y chromosomes: Klinefelter's Syndrome (47,XXY); and 47,XYY Syndrome. In women, the most common variants entail the addition or absence of X chromosomes including 47,XXX; 48,XXXX; and Turner Syndrome (45,X).

Chromosomal abnormalities can highlight the role that sex chromosomes play in the phenotypic differences typically seen between 46,XY men and 46,XX women. For instance, adolescent girls with Turner Syndrome are more likely to have social difficulties compared to 46,XX girls [274], which may be partly related to facial and emotional-processing impairments [275]. Furthermore, 46,XX girls score better than boys on tests of social cognitive skills [276]. The fact that both 46,XY boys and 45,X girls experience more social adjustment problems compared to 46,XX girls suggests the presence of a genetic locus involved in social cognitive skills on the X chromosome. Data from Skuse *et al.* [277], suggest that this locus may be subject to imprinting. Significant differences between 45,$X^{p}O$ Turner-syndrome girls (in which the X was of paternal origin) and 45,$X^{m}O$ girls (in which the X was maternally derived) in terms of social skills have been reported. 45,$X^{p}O$ had superior social competence and better social skills than 45,$X^{m}O$ girls suggesting that the genes in this locus are expressed only from the paternal X. This could potentially be one of the reasons why boys are more susceptible to disorders such as autism that affect social adjustment and social skills such as language. In boys the X is only of maternal origin and therefore this locus would be silenced.

In other cases, however, the characteristics of individuals with sex chromosome abnormalities may augment the expected sex difference. On average, men in the general population have better visuospatial skills than women, and women have better verbal skills than men—which suggests that increased dosage of X chromosome genes may contribute to these skills. However, women with Turner Syndrome have impaired visuospatial abilities yet greater language skill compared to control women [278; 279].

The role of the Y chromosome in psychosexual differentiation is still unclear. Work by McCarty et al. indicates that genes on the Y chromosome outside of *SRY* and the pseudoautosomal region have “no obvious role…on psychosexual differentiation in genetic males [244].” This is difficult to ascertain because (a) the incidence of XY gonadal dysgenesis is extremely rare, estimated to be 1 in 20,000 [280]; and (b) these individuals have been poorly studied in regards to sexual differentiation of the brain.

### 6.2 Androgen Insensitivity Syndrome

The role of the Androgen Receptor (AR) in brain sexual differentiation has been discussed in patients with Androgen Insensitivity Syndrome (AIS). AIS is an X-linked recessive disorder that is seen in 1 out of 20,400 live male births [281]. There are two forms of AIS: Complete (cAIS) and Partial (pAIS). People with Complete AIS are genetically male (46, XY with undescended testes) but phenotypically female. However, individuals with Partial AIS typically have ambiguous genitalia.

AIS is caused by mutations in the androgen receptor (*AR*) gene [282]. There is an important difference in the behavioral phenotype between humans and rats with Complete AIS. Humans with Complete AIS are female-typical in their play behavior and sexual orientation [283]. In contrast, XY rats with *AR* mutations behave sexually like wild-type males and have a male-typical partner preference [283]. The reasons behind this difference remain unclear although the implication is that androgens play an important role in masculinizing the human brain. However, we cannot completely discount the role of estradiol as the expression of aromatase (which converts testosterone to estradiol) is dependent on androgen signaling via AR [284].

## Sexual Orientation

Of all behavioral differences between males and females, partner choice is one of the most pronounced. With very few exceptions in the Animal Kingdom, males typically choose females to mate with, and females typically choose males to mate with. Although sexual selection is a driving force of evolution, little is known about the molecular basis of partner preference.

Human sexual orientation is a complex phenotype to study. Part of this difficulty comes from the accurate assessment of sexual orientation [285; 286], especially when researchers depend on self-identification, which may be mediated by numerous social and psychological factors [287; 288; 289]. Nevertheless, most people report primarily opposite-sex or heterosexual attractions. Yet, a significant number of people (approximately 2–6%) report predominantly homosexual attractions [290].

The distribution of sexual behavior differs between men and women. In men, the distribution is largely bimodal [291]. That is, men are either attracted to one sex or the other. Although there is disagreement regarding bisexuality among men [292], physiological research has found that very few men (even those who openly identify as bisexual) show comparable physical attraction to both men and women [293]. The distribution is more complex in women, in which the fraction of women that show exclusive same-sex attraction is lower than men (1–3%), but many more women than men report erotic fantasies towards both sexes [294].

In this section we will highlight some of the biological research that has focused on same-sex attraction. A more thorough review is available for interested readers [295].

**6.2.1 Neuroanatomy differences in sexual orientation—**Neuroanatomical differences have been reported for three brain regions based on sexual orientation in human males: the arginine vasopressin neuronal population of the suprachiasmatic nucleus, which was larger in gay men than in male and female controls [296]; the third interstitial nucleus of the anterior hypothalamus (INAH-3), which is smaller in gay men and more similar in size to female controls [297]; and the anterior commissure, which is larger in gay men than in control males and females [298]. The most discussed anatomical finding was in INAH-3 [297]. Although subsequent researchers reported inconsistent findings [299], a comparable difference was found in sheep [300].

Approximately 8–10% of the domestic ram population has been found to sexually prefer other males. Unlike other animal models showing atypical sexual behavior, these male-oriented rams mount and ejaculate on other males versus simply exhibiting a passive stance (i.e., lordosis). Consequently, they are an ideal animal model of male homosexuality because their coital behavior is masculine but their sexual partner preference is feminine.

An analogue of the sexually dimorphic nucleus (ovine SDN or oSDN)—a hypothalamic nucleus thought to be involved in mate selection—was identified in the sheep brain [300]. The oSDN was found to be larger in female-oriented rams compared to male-oriented rams (MORs), and ewes; the latter two groups had oSDN's comparable in size. It was hypothesized that the oSDN corresponds with human INAH-3, which suggests that the relevant neuroanatomical pathways are conserved between mammalian species.

**6.2.2 The role of prenatal androgens—**One of the main hypotheses on the determinants of sexual orientation was that same-sex attraction was the result of atypical sex-hormone levels during gestation. Studies in rodents and ferrets showed that pre- or perinatal hormonal manipulation could lead to changes in partner preference, sexual behavior, and coital performance largely controlled by the hypothalamus [301; 302]. Yet, extending this hypothesis from animal research to humans is difficult in our opinion. Atypical sexual behavior in rodents is hard to equate to human sexuality. For example, the induction of lordosis in male rats does not change their *partner preference*. Instead, what changes is the rat's *entire sexual behavior*, which is different from sexual orientation. Rather, an animal that consistently chooses same-sex partners—such as the abovementioned ram whose adult hormone levels are within the male-typical range [303]—would be a better model. Furthermore, the treatment necessary to change the sexual behavior of rodents goes far beyond any naturally occurring variation in androgen levels [304], and as such is unlikely to reflect natural causes of human variation in sexual orientation. Additionally, hormonal manipulations have failed to make male animals mount other males.

Case studies on humans with various genetic defects in the androgen pathway show only limited support for the hypothesis. There are no reports showing an increase in attraction to men in hypovirilized XY individuals relative to the general population. This implies that disruption of the androgen pathway does not have a strong effect on male sexual orientation. The role of androgens in female sexual orientation appears more complex. Women with congenital adrenal hyperplasia (CAH) experience abnormal activity of the embryonic adrenal glands. This leads to a much higher exposure of female fetuses to androgens, greatly exceeding female-typical levels. The exposure is often high enough to cause some degree of genital masculinization. Several studies have found that CAH women reported more same-sex sexual activity and that more self-identified as homosexual compared to the general population, which suggests that typical female sexual development is disrupted by extreme prenatal androgen exposure [305]. It is important to note that while women with CAH reported more gender atypical attitudes, interests, and behavior, the majority still identified as heterosexual. The role of androgens in the sexual orientation of lesbian women who have no genital masculinization is still unclear.

Two studies looked at genetic variation in genes related to the steroid pathway. A candidate gene study on the human androgen receptor gene [306] and one on the aromatase gene (CYP19) [307] found no evidence that variations in these genes play a role in variations in human sexual orientation. A variety of anthropomorphic measures have been used as indirect measures of prenatal androgen exposure, but results have been inconsistent. A recent prospective study showed no correlation between maternal circulating androgen concentration at 18 and 34 weeks of gestation and digit ratio in girls [308]. An in depth discussion of these studies and a speculation on their widely varying results falls outside of the scope of this manuscript. For a review on the often cited 2D:4D finger-length ratio in sexual orientation, see McFadden et al. [309]. Finally, studies retrospectively examining the influence of stressful events during pregnancy have been inconclusive [310; 311]. Therefore we believe that there is little evidence that naturally occurring variations of prenatal circulating gonadal hormones within one sex play a role in determining variants of sexual orientation although diverging views have been expressed on this topic.

**6.2.3 The genetics of sexual orientation—**Evidence is mounting that there is a strong genetic component influencing sexual orientation. Family studies [312; 313; 314; 315] have found an increased rate of homosexuality among siblings and in the maternal uncles of gay men (a median rate of 9% for brothers of gay men) [316]. Although the concordance rates of homosexuality in monozygotic twins vary depending on ascertainment methods [313; 317; 318; 319], twin studies have found that there is a substantial genetic component in the development of sexual orientation.

There has been limited molecular genetics research. In 1993, Hamer et al. reported that male homosexuality was more often on the mother's side of the family versus the father's side [291]. A linkage scan showed significant linkage of male homosexuality to the X-chromosome region Xq28 [291]. This finding was subsequently replicated by two studies [294; 320] but not by an independent group [321]. However, a meta-analysis of the results across all four studies yielded an estimated level of Xq28 allele sharing between gay brothers of 64% instead of the expected 50% [322]. Nevertheless, the exact gene(s) involved has (have) yet to be identified.

A different method also implicated the role of the X-chromosome. Unlike male cells, female cells contain two X-chromosomes. Consequently, each female cell randomly inactivates one X-chromosome during embryogenesis to create dosage compensation: The inactive chromosome remains inactive in all resulting daughter cells [323]. If inactivation is completely random, this means that in a population of female cells the maternal X will be inactivated in 50% of the cells whereas the paternal X is inactive in the remaining half. If a particular X chromosome, whether maternal or paternal, is inactivated in more than 90% of cells, that individual is considered to be extremely skewed in regards to X-inactivation. Mothers with gay sons were found to have extreme skewing of X-inactivation when compared to mothers with no gay sons: Skewing in mothers with one gay son = 13/97 or 13%; skewing in mothers with two or more gay sons = 10/44 or 23% [324]. This suggested an involvement of the X chromosome in the molecular mechanisms of sexual orientation. Arguably, the effect of the X-chromosome gene(s) or mechanisms that influence sexual orientation in the sons is visible in the blood of their mothers.

A genome-wide linkage scan on gay-brother pairs showed suggestive linkage to loci on chromosome 7 and 8 [325]. A maternal origin effect was found near marker D10S217, located at 10q26, with significant linkage for maternal meioses but no paternal contribution. This result suggested the presence of a maternally-expressed, paternally-silenced imprinted gene for sexual orientation in 10q26. The relatively small sample size ($N = 456$) likely underpowered this study. However, a larger linkage scan on 1000 homosexual male sibling pairs is currently underway (A.R. Sanders, personal communication).

The presence of a possible imprinted gene on chromosome 10 is particularly interesting. Previously reported evidence of maternal loading of sexual orientation transmission was initially used to implicate the X-chromosome in human sexual orientation, but it could just as well indicate epigenetic factors acting on autosomal genes. A role for imprinted genes in human sexual orientation was hypothesized earlier [326].

One of the most replicated findings in sexual orientation research is known as the `fraternal birth order effect': Each older brother increases the odds of male homosexuality by approximately 33% [327; 328]. This is relative to the baseline frequency of homosexuality, and the odds of being homosexual are about twice as high for the fourth-born son relative to the first-born son. Yet, this finding is not so simple: The effect is only influenced by older brothers born via the same mother, it is not influenced by the number of older sisters, and it only seems to be true for right-handed homosexual men [329]. The dominant hypothesis for

this effect, which lacks empirical support, is that each successive male pregnancies increases the mother's immunity against male-specific antigens expressed by the fetus [330; 331], and this immune response affects any subsequent male fetuses. Although this phenomenon does not directly implicate genetics, at the very least it demonstrates a biological basis for human male sexual orientation and suggests the immune system as an alternative, gonadal hormone-independent mechanism through which sex differences can be mediated.

Altogether, there is mounting evidence for a genetic role of human sexual orientation. The overwhelming dominance of heterosexual behavior in the animal kingdom points at a tight molecular regulation of this trait.

### 6.3 Gender Identity

Gender identity, or our sense of maleness or femaleness, plays an important role throughout our development affecting both our sense of self and our relationships [295; 332; 333]. Our gender identity and the roles ascribed to that gender are heavily influenced by social factors [e.g. 334]. Most people adopt a gender identity congruent with the sex assigned at birth, which remains constant throughout life [206]. The best approach to study the biological basis of gender identity is to study individuals who develop a cross-gender identity—in particular transsexuals.

Zhou et al. were the first to describe a sex difference in the central subdivision bed nucleus of the stria terminalis (BSTc) in humans and a potential biological marker for gender identity [335]. The type and direction of the sex difference mirrored that of the rat: the volume of the BSTc is larger in men than in women. The study also found that the BSTc of male-to-female (MtF) transsexuals is female-sized but the interpretation of this finding is complicated. The MtF subjects used in the study had all received estrogen therapy so it remains unclear if the sex difference is related to gender identity or hormonal exposure since estrogens can modify the structure of the brain. A second confound is the relatively small size of the sample pool as the authors were only able to gain access to tissue from six MtF transsexuals.

The literature on the genetic basis of transsexualism is extremely limited. Although there are reports of families where several members identify as transsexuals [336], such reports are rare. There are few twin case studies, and they have reported differing concordance rates for transsexualism [337; 338; 339; 340]. Since no systematic twin study has been reported, it is impossible to separate genetic from environmental influences. Consequently, there is no clear support for a genetic basis of transsexualism at this point.

A number of chromosomal abnormalities have been reported in transsexuals [341; 342; 343; 344]. In all cases, sex chromosomes were involved. The most common association was with disomy-Y (47,XYY). However, because of the relatively high frequency of sex chromosome aneuploidy (1 in 900 males for XYY; [345]) a statistically significant association with transsexualism has not been shown.

A small number of candidate genes have been studied for transsexualism. A recent study looked at a polymorphism in the gene coding for 5-alpha reductase and found no assocation in a sample of MtF and female-to-male (FtM) transsexuals [346]. The same group found a significant association between a single nucleotide polymorphism in the CYP17 gene (which encodes the 17α-hydroxylase enzyme) in FtM transsexuals but not MtF transsexuals [347]. However, their sample size was small and they reported a significant difference in allele distribution between male and female controls as well, shedding doubts on these results.

A small study of MtF transsexuals in a Swedish population studied repeat sequences in or near the androgen receptor gene, the estrogen receptor beta gene, and the aromatase gene. They found an association between MtF transsexualism and a dinucleotide CA polymorphism in the estrogen receptor beta (ERb) gene [348]. However, a larger study of MtF transsexuals failed to replicate the ERb results and instead found a significant association with the androgen receptor repeat[349]. This, too, was not replicated by a subsequent research team [350]. Overall, the significance of these genetics studies remains unclear.

## 7 CONCLUSION

There are many differences between men and women. In this review, we have focused on brain sex differences because of the role that they play in people's health and behavior. Historically, it was believed that such differences were solely due to gonadal hormone secretions. Yet, emerging research is also implicating direct genetic effects.

The next challenge will be to first elucidate the molecular mechanisms by which these direct genetic effects on sex differences arise. One way to address this question will be to manipulate gene dosage in specific tissues and at specific times of development by using targeted approaches in genetically modified animals. Another critical issue will be to understand how compensation mechanisms between the sexes operate. de Vries proposed that observed molecular sex differences may compensate for other sex differences rather than generating differences between males and females themselves [351]. It will be crucial to tease out whether small imbalances influence specific differences in neuropsychological function. Finally, it will be essential to translate our knowledge of sex differences to improve the quality of medical and psychological care.

As science continues to advance our understanding of sex differences, a new field is emerging focused on better addressing the needs of men and women: gender-based biology and medicine. The ultimate aim of this field is to translate scientific data into practical applications that are effective for each sex [352]. From tailoring preventive screenings to treating sex-specific illnesses, this field recognizes that “one-size-fits-all” healthcare has its limits. Rather, our biological sex is an important variable that must be considered in our mental and physical health.

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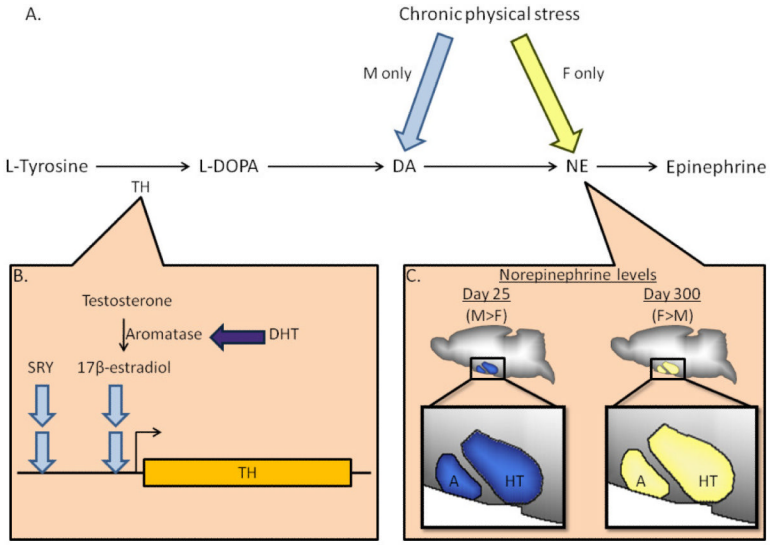


**Figure 1.**

The catecholaminergic pathway is sexually differentiated TH: Tyrosine hydroxylase, L-DOPA: L-dihydroxyphenylalanine, NE: norepinephrine. **(A)** Chronic physical stress results in sexually dimorphic responses. Dopamine (DA) activity is upregulated exclusively in males flight blue arrow) while norepinephrine activity is upregulated exclusively in females (yellow arrow) [58]. Only males experience impaired memory. **(B)** Control of TH expression differs between the sexes. SRY, the testis determining gene, which is not found in females, directly regulates TH expression in males [49; 270]. 17β-estradiol increases TH expression only in males flight blue arrows) [353]. Aromatase activity is more responsive to dihydrotestosterone (DHT) in males than in females (dark blue arrow) [354]. **(C)** Male rats have higher NE levels than female ones in the amygdala (A) and hypothalamus (HT) early in life [62]. When the rats reach day 300, the direction of this difference is reversed.

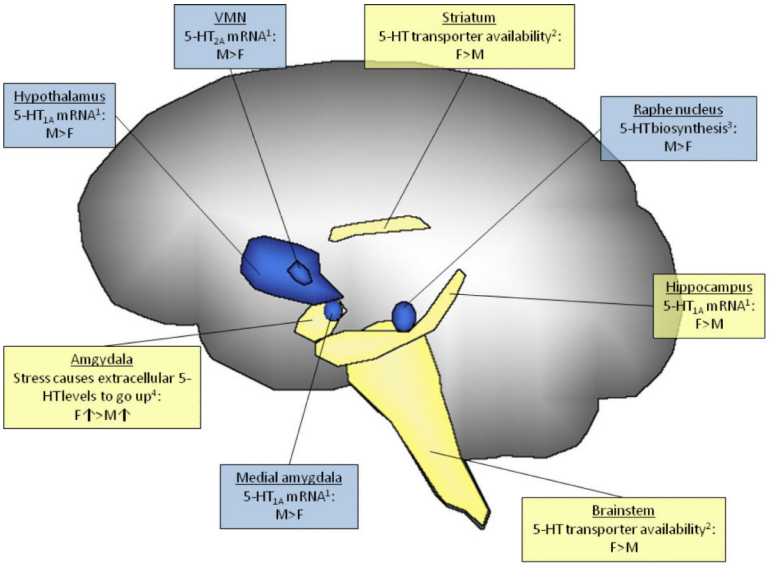


**Figure 2.**

Serotonin (5-HT) is sexually differentiated on multiple levels. In addition to the differences illustrated above, some of the loci that influence 5-HT levels in the blood are also sexually dimorphic [66]. References: 1 - [67], 2 - [68], 3 - [65], 4 - [69].

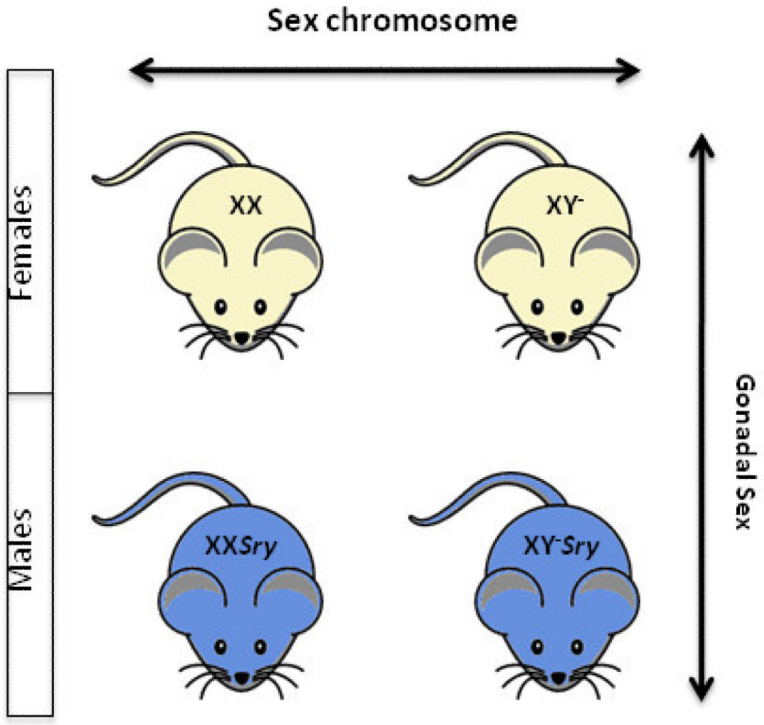


**Figure 3.**
2×2 comparison in the four core genotypes model. In this comparison, the factors are gonadal sex and sex chromosome complement.

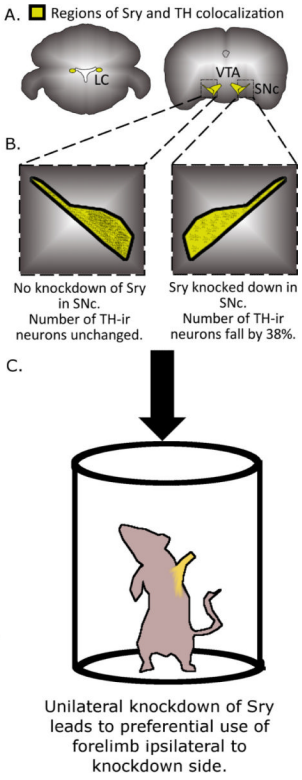


**Figure 4.**

*Sry* regulates tyrosine hydroxylase (TH) levels and motor behavior. **(A)** Sry and TH colocalize in the locus coeruleus (LC), ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) [49; 270]. **(B)** Knockdown of Sry expression in the SNc leads to a reduction in the number of TH-immunoreactive (TH-ir) neurons. Unilateral infusion of antisense oligodeoxynucleotides (ODN) against *Sry* decreased the number of TH-if neurons by 38% compared to the contralateral side infused with sense ODN [49]. **(C)** Unilateral downregulation of TH expression by Sry leads to asymmetric limb use. Animals preferentially used the forelimb ipsilateral to the side of the antisense ODN infusion (preferred limb highlighted in yellow) [49].

## Table 1

Selected neuroanatomical sex differences in the rat.

| Structure/Region | Known roles | Sex difference | Basis of difference |
|---|---|---|---|
| Sexually dimorphic nucleus of the Preoptic Area (SDN-POA) | The POA is implicated in the regulation of male copulatory behavior [14]. Lesions of the SDN alone slow acquisition of this behavior. Potential human equivalent is INAH-3 [18]. | 2.6 times larger in males [19]. | Perinatal aromatized androgen decreases neuronal apoptotic rates in males [20]. |
| Anteroventral Periventricular Nucleus (AVPV) | Involved in regulating the luteinizing hormone surge in females [20] and male copulatory behavior [21]. | 2.2 times larger in females with a higher cell density [22]. | Degeneration of cells in this region is greater in males [23] due to prenatal action of androgen |
| Bed Nucleus of Stria Terminalis (BNST) | Plays a role in the control of male sexual behavior [24], release of gonadotropin [25], and modulation of stress [26; 27]. | The principal nucleus (BNSTp) is larger in volume in males [28]. | The larger volume in males is due to sexually different apoptotic rates caused by testosterone [29]. |
| Corpus Callosum | Conducts information between the two halves of the cortex [30]. | Larger in neonatal males [31]. | Organizational effects of testosterone lead to masculinization while feminization appears to be dependent on estrogens [32; 33]. |
| Arcuate Nucleus (ARC) | Helps regulate the estrus cycle [34], appetite and body weight [35]. | Neurokin-B neurons innervate capillary vessels in the ventromedial ARC in post-pubertal males only [6]. | Dihydrotestosterone is responsible for the masculine projection pattern [36]. |
| Amygdala | Strongly associated with emotion, decision-making and Pavlovian conditioning [37]. | Adult males have a larger medial nucleus than adult females [38]. | Treatment of females with estradiol masculinizes this nucleus [38]. |
| | | The posterodorsal aspect of the medial amydala is 65% larger in males [39]. | Activational effects of circulating androgens accounts for the larger region in males [40]. |
| Cerebral cortex | Connected to a wide range of processes from memory [41] to language [42] to emotional processing [43]. | Right posterior cortex is thicker than left but only in males [44]. | Gonadal hormones play a role in maintaining the sex difference (ovariectomy masculinizes the cortex of females) [44]. |
| Ventromedial Hypothalamic Nucleus (VMN) | Involved in the control of lordosis, mounting, and norepinephrine release [45].<br>High concentrations of steroid receptor mRNA have been observed in the ventrolateral VMN [46]. | Females have less synapses in the ventrolateral VMN compared to males [8]. | Organizational effects of aromatized testosterone appear to be crucial in establishing the masculine trait [47]. |
| Substantia nigra pars compacta | Made up almost entirely of dopaminergic neurons.<br>Dopamine is involved in control of motor activity [48]. | Females have 20% fewer dopaminergic neurons [49]. | A genetic component has been demonstrated in mice [50]. |

*Note: This table highlights some prominent sex differences in the rat brain but it is by no means exhaustive. Conflicting evidence concerning the examples reported here (particularly in the SDN-POA) exist, and the interpretation of the data is often more complicated than this summary implies.

## Table 2

Selected neurochemical sex differences in the brain.

| Neurochemical system/pathway | Known roles | Species | Selected sex differences |
|---|---|---|---|
| Cathecolamines (also see Figure 1) | Involved in the control of a variety of processes including reproduction and sexual behavior [51; 52], respiration [53], and stress responses [54]. | Rat | Male have higher norepinephrine (NE) levels in the amygdala and hypothalamus at day 25. Direction of this sex difference is reversed at day 300 [62]. |
| | | | In response to chronic physical stress, dopamine (DA) activity is upregulated only in males whereas NE activity is increased only in females [58]. |
| | | Human | Women appear to be more dependent than men on NE for long-term emotional memory formation [63]. |
| Serotonin | Modulates a wide variety of processes including mood, aggression, perception, reward, and attention [64]. | Rat and human | Sex differences in the serotonergic system are found at multiple levels [65; 66; 67; 68; 69]. See Figure 2 for an illustration of some of these differences. |
| Aromatase | Plays a key role in sexual differentiation of the brain by converting testosterone to 17β-estradiol[70]. | Rat | Aromatase activity is higher in males than females in many regions including the anterior hypothalamus, BNST and POA [71]. |
| | | | Only males experience spikes in the expression of brain-specific and total aromatase during embryonic development and shortly after [72]. |
| Vasopressin (VP) | VP in the central nervous system (CNS) has been linked to learning, memory and motor behavior [73]. It has also been connected to the control of social behaviors such as pair-bonding, parenting and aggression [74]. | Rat | The number of vasopressin-positive cells is 2 to 3 times higher in males than in females [75]. |
| | | | Vasopressin-positive projections are also 2 to 3 times denser in males [75]. |
| | | | Intrahypothalamic release of VP due to an increase of plasma osmolality is higher in females. [76] |
| | | Human | Some studies have found that plasma VP concentrations are higher in men than in women [73]. |
| Cholinergic system | The cholinergic system helps regulate the sleep-wake cycle and modulates synaptic plasticity implicated in memory, learning, and development [77; 78]. Sex differences are found at many points in the cholinergic system [reviewed in 73]. | Rat | Levels of acetylcholine (ACh) are higher in females, regardless of estrous cycle, than in males [79]. The maximal level of Ach in females was found at proestrus. |
| | | | The binding affinity of muscarinic Ach receptors is lower in females than in males [80]. Estrogens appear to modulate the binding activity of these receptors [81]. |
| | | Human | Men are more sensitive to cholinergic stimulation than women [82]. |
| Opioid system | Opioids are a class of chemical for which receptors are found throughout the CNS [83; 84]. | Rat and mouse | Generally, μ and κ class opioids seem more effective in males than females although in some cases the effectiveness is equal [86]. In a minority of cases, they are more effective in females. |
| | | Human | μ-opioids appear more effective in women than in men [86]. |
| | | | μ-opioids show significantly higher binding potential in women in the amygdala, thalamus and the cerebellum |

| Neurochemical system/pathway | Known roles | Species | Selected sex differences |
|---|---|---|---|
| | Opioids exert an analgesic effect and also play a role in stress response and reproduction [85]. | | [87]. The sex difference in the first two regions is reversed after menopause. |

## Table 3

Sex differences in behavioral traits in humans.

| Trait | Sex Bias | Evidence for the role of hormones | Evidence for the role of genetic factors | Other factors affecting sex differences in behavior |
|---|---|---|---|---|
| Cognition | Men do better at spatial tasks [94] and mathematical problem solving [95]. Women do better on verbal fluency, articulation, and verbal memory tests [12]. | Prenatal hormone effects shown from studies of CAH, Turner's and androgen insensitivity syndromes [96] | No reliable evidence for the effect of sex chromosome genes proven from studies of Turner's and XX males [97] | Greater brain asymmetry in men for both verbal and non-verbal tasks [98; 99] |
| Play behavior-movement | There are sex differences in choice of toys, gender of the play partner, social play [100] and movement [101; 102; 103] | Testosterone influences juvenile play [104]<br>Prenatal androgen levels affect play behavior and movement [105; 106] | Genetics sex seems to affect play behavior more than prenatal hormone exposure [104] | Parents and other socializing agents (i.e. peers, community, and child's own cognitive processes) [107]<br>Developmental experience [108], visual information [109] affect movement organization |
| Language | Women perform better on episodic memory [110] and verbal fluency tasks, men are better at visuospatial processing [111; 112; 113]<br>Greater dependence of females on declarative memory and males on procedural memory [114; 115] | Estrogen influences word and declarative memory abilities in women [116; 117; 118; 119; 120; 121; 122; 123; 124]<br>Testosterone influences word memory in men [125]<br>Prenatal testosterone levels relate to language processing in girls [126] | Single nucleotide polymorphisms in the gene, brain derived neurotrophic factor (BDNF) affecting BDNF secretion rates, partly accounting for greater dependence of females on declarative memory and the sex differences observed in language-related tasks [127] | Greater degrees of left hemispheric lateralization of brain for language in males and the bilateral language processing in females [128]<br>Faster development of hippocampal brain regions in girls, activation of certain brain regions such as hippocampus and parahippocampal gyrus [129; 130] |
| Aggression | Foul language, imitation of aggressive models, violence and physical aggression more common in males [131] | Estradiol and progesterone influencing the serotonergic system [132; 133]<br>Weak association between testosterone and aggression in both sexes [134; 135]<br>High testosterone levels leading to increased verbal aggression and impulsivity in women [136; 137] | Association between serotonin transporter gene polymorphisms and greater impulsivity in males but not females [138]<br>Polymorphisms in monoamine oxidase-A (MAOA) gene associated with antisocial personality disorder and aggression in males [139] | Low self-control, high impulsivity and negative emotionality [140]<br>Sex-specific disparities in the neural circuitry of impulse control and emotion regulation, as well as serotonergic systems [141]<br>Larger orbitofrontal cortexes in women [142] |

## Table 4

Sex differences in neurological disease.

| Disease | Sex Bias | Evidence for the role of hormones | Evidence for the role of genetics | Other factors affecting sex differences in disease |
|---|---|---|---|---|
| Alzheimer's Disease (AD) | Women demonstrate higher AD prevalence at older ages [143; 144]. | Gonadal hormones implicated in gender-related cognitive deficits of AD but the interaction is complex [145] | APOE allele type [146; 147] (i.e. Less and slower rate of amyloid plaque formation in men due to APOE ε2 [148]) | Greater degeneration in areas of orbitofrontal cortex, middle and posterior cingulate cortex, hypothalamus, and mammilary bodies in men, and anterior thalamic in women [149]. |
| Parkinson's disease (PD) | Overrepresented in males [150; 151]<br>Age at onset is later in women [152].<br>Pathological symptoms of PD differ among males and females [153; 154; 155] | Most women manifest PD after menopause [156]<br>Estrogen affecting BDNF secretion [157]<br>Early life estrogen decline seems to be more important [158; 159; 160] | Linkage to X chromosome markers in 362 families, and to Xq28 in 443 discordant sibling pairs [161; 162]<br>Val66met polymorphism in BDNF in women [163] | Environmental factors [164]<br>Anatomical and structural differences in dopaminergic systems among males and females [107] |
| Autism | There is a high male to female ratio in the prevalence of autism [165] | Gonadal hormones affecting oxytocin (OT) and arginine vasopressin (AVP) receptors [166; 167] | Single nucleotide polymorphisms in the OT receptor in the Chinese Han [168] and American Caucasian population [169], SNPs in the vasopressin receptor (V1aR) gene [170; 171]<br>X-chromosome has effects on cognition and social aspects [172; 173] | Alterations in oxytocin or arginine vasopressin activity, and differential processing of the oxytocin precursor [174; 175; 176] |
| Addiction | Drug addiction more frequent in men [12]<br>Higher relapse rates, faster progression of compulsive drug abuse and dependence have in women [177; 178]) | Estradiol levels correlate with drug induced reinforcing behavior whereas progesterone levels are negatively associated with addiction [179; 180; 181] | Genes encoded on sex chromosomes can affect sex-related differences in addiction (the four core genotype mice) [182] | Neuroanatomical differences in motivation systems among males and females [107]<br>Sex-related alterations in the cortico-limbic-striatal system that mediates reward processing [183] |
| Depression | Women are twice as likely as men to develop depression during reproductive years [184] | Low estrogen levels in female rats mediated by influences on neurotransmitter levels [185]<br>Low testosterone levels associate with risk for depression in young and middle aged-men [186; 187] | Heritability rates estimated to be 70% [188]<br>Polymorphisms in serotonin gene, estrogen receptor 1 (ESR1) polymorphism in the presence of Val/Val genotype of the Val158Met polymorphism in the Catechol-O-methyl transferase (COMT) gene, longer CA repeats of human estrogen receptor 2 (ESR2), short CAG repeats in androgen receptor gene [189] | Maladaptive coping, pessimism, dependency, low self- esteem, victimization, sexual abuse, comorbid anxiety disorder more common in depressed women [190]<br>Early life events increase depression rates in adult women [191] |
| Anxiety disorders | The rate of anxiety disorders is higher in females [55]. The high comorbidity of these disorders with major depression helps account for the sex difference in depression [192]. | States of anxiety and panic have been reported to be affected by the menstrual cycle and pregnancy, implicating a role for estrogen and progesterone [55]. Pregnancy and lactation seem to alter | TheVal158alleleof COMT is associated with panic disorder in Caucasian women but not men [194]. In Asians, Met158 is associated with panic disorder in women but not men [194].<br>5*HTT*LPR is a polymorphism associated with anxiety in humans. The | Animal studies indicate females undergo less neurobiological changes in response to stress compared to males [193]. It is speculated that this indicates increased adaptability in males and hence lower |

| Disease | Sex Bias | Evidence for the role of hormones | Evidence for the role of genetics | Other factors affecting sex differences in disease |
|---|---|---|---|---|
| | | brain neurochemical system that affect anxiety and fear [193]. | orthologous polymorphism in rhesus macaques interacts with early adversity in a sexually dimorphic manner [195]. | prevalence of affective illness [193]. |
| Schizophrenia | more common in men than in women [196]<br>Age at onset is later in women, another smaller peak of onset during peri- and post-menopause [196; 197]<br>Pathological symptoms of schizophrenia differ among males and females (males experience more negative symptoms, greater decrease in emotion expression and recognition,, greater paranoid delusions in women) [198]<br>Lower chances of full recovery, and a poorer prognosis in men [196; 197]<br>Anatomical brain differences between male and female patients | This disease is not common before adolescence and puberty [199]<br>Male schizophrenics have higher levels of Luteinizing Hormone (LH) and testosterone than healthy subjects, and female schizophrenics higher levels of LH and lower levels of estrogen [200] | Eight ultra-rare variants in eight distinct miRNA genes in 4% of analyzed males with schizophrenia [201]<br>Relatives of females with schizophrenia demonstrate higher levels of the psychotic forms whereas relatives of schizophrenic men express lower rates of psychosis suggesting the presence of genetic heterogeneity [202]<br>Higher rate of CAG repeat expansions among families of female patients and not male patients [203] | Anatomical and structural brain differences among males and females [198]<br>Higher cortical levels in males as compared to females according to some studies [198]<br>Higher sensitivity of the dopamine system in men as compared to women (Normal males produce more striatal dopamine in response to an amphetamine challenge as compared to females) [204] |