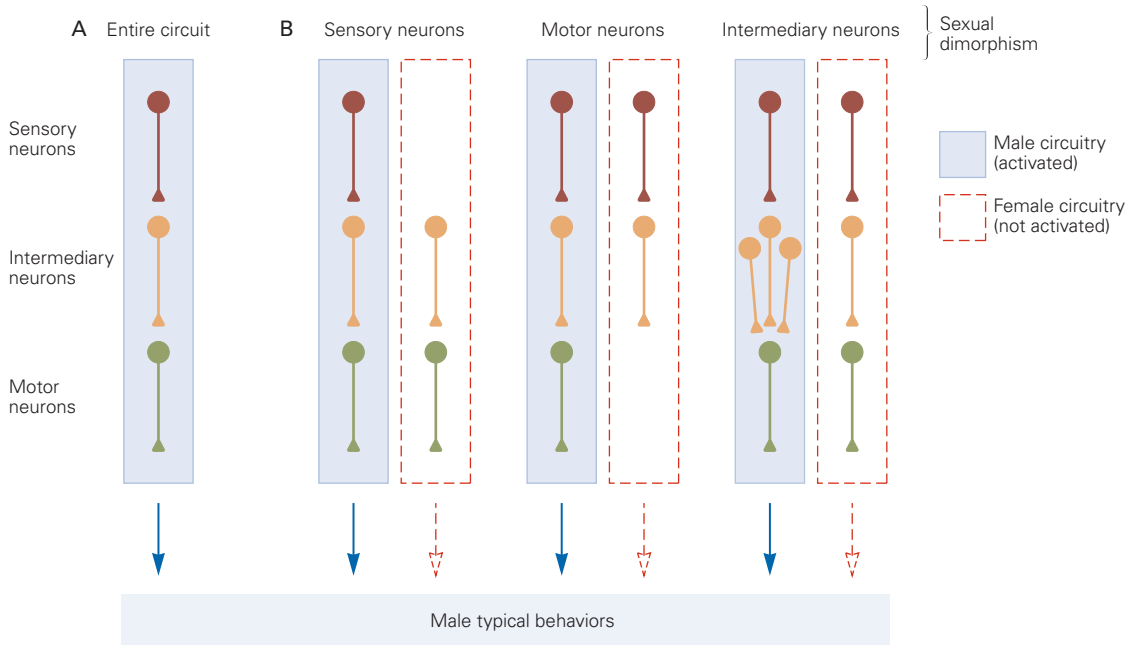

Figure 51–11 Possible circuit configurations that underlie sex differences in behavior. Neural circuit diagrams can be configured to generate sex differences in behaviors. Although it is possible to envision a neural circuit entirely exclusive to one or the other sex, most behaviors are shared between the sexes, and the current consensus is that sex differences in behavior or physiology reflect sexual dimorphisms in key neuronal populations embedded within an otherwise shared neural circuit. Such sexual dimorphisms have been found at the level of sensory neurons, motor neurons (as discussed for spinal nucleus of the bulbocavernosus neurons), or neurons interposed between sensory and motor pathways (such as the BNST and the sexually dimorphic nucleus of the preoptic area).

to male-typical levels. Thus, the perinatal surge of testosterone acts largely via aromatization into estrogens to masculinize the brain, whereas in adult life, both testosterone and estrogen facilitate the display of male-typical social interactions (Figure 51–12A).

These findings imply that male mice lacking androgen receptor exclusively in the nervous system should not only have male genitalia but also exhibit male patterns of social behavior, albeit at reduced intensity. This has in fact been borne out nicely by genetic engineering studies in mice; such mutant male mice indeed appear indistinguishable externally from control males, but they exhibit male-type sexual and aggressive behaviors with diminished intensity. However, there is growing evidence that the developmental control of masculinization of the brain by estrogen has shifted during evolution such that testosterone may be the predominant masculinizing agent in primates, including humans.

How do the actions of the limited number of sex hormones modulate the display of a large array of complex social interactions such as courtship vocalizations (similar to songbirds, many animals, including mice, vocalize as part of their mating ritual), sexual behavior, marking (the propensity of animals of many species to claim territory with pheromones secreted in bodily fluids), and aggression? As described earlier in this chapter, sex hormones bind to cognate receptors to modulate gene expression in target cells. These steroids are available at different times, amounts, and places in the brain of the two sexes. Accordingly, sex hormone–regulated genes are expressed in sexually dimorphic patterns that are also different for different brain regions. These genes regulate differentiation and adult function of neural circuits along male- or female-typical lines (Figure 51–12B).

Experimental inactivation of such sex hormone–regulated genes reveals that individual genes influence only a subset of the sexually dimorphic social interactions without altering the entire behavioral program of males and females. Thus, an additional emerging theme is that sex hormones control differentiation and function of neural circuits in a modular manner, with different sex hormone–regulated genes acting in distinct neuronal populations to regulate separate aspects of male- or female-typical behaviors. In short, there is no single neuronal population that governs

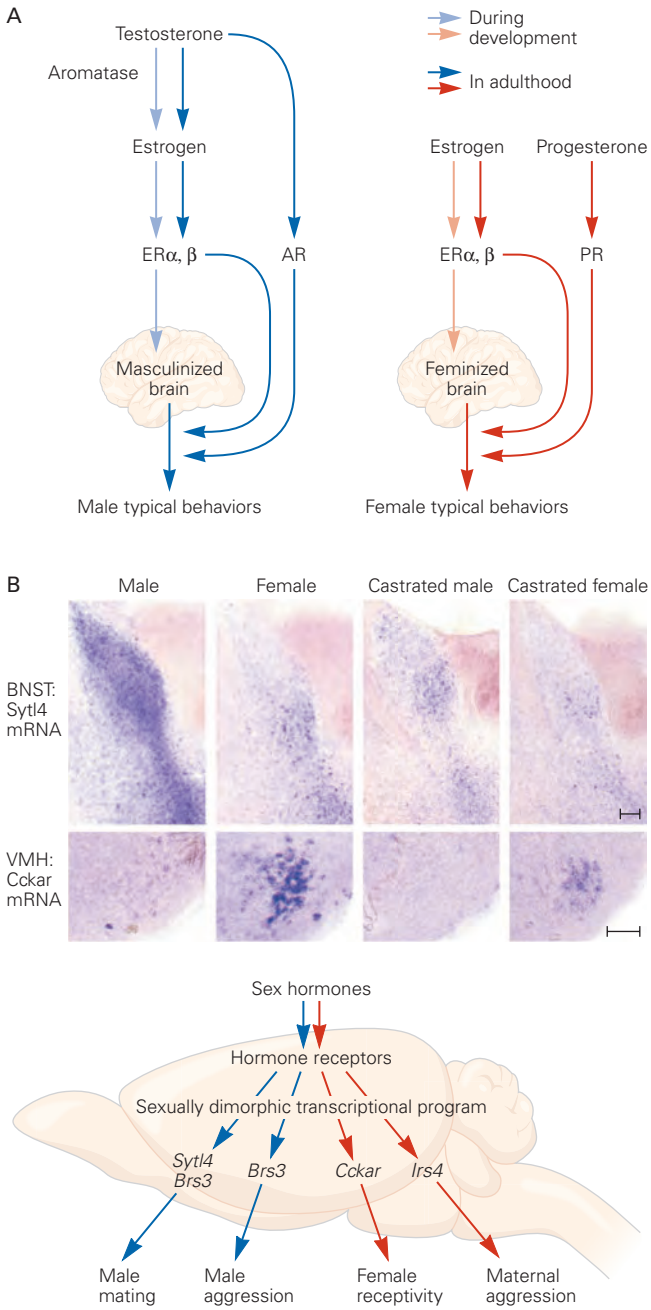

Figure 51–12 Mechanisms whereby sex hormones influence development and function of the nervous system.

A. Masculinization of the nervous systems occurs in at least two distinct steps: a developmental organizational phase largely controlled by estrogen signaling and a postpubertal activational phase controlled by estrogen and testosterone signaling via their cognate hormone receptors to regulate gene expression. (Abbreviations: **AR**, androgen receptor; **ER**, estrogen receptor; **PR**, progesterone receptor.)

B. Histological images show sexually dimorphic expression patterns of *Sytl4* mRNA in the bed nucleus of the stria terminalis (**BNST**) and *Cckar* in the ventromedial hypothalamus (**VMH**) of adult mice. Expression of these genes is clearly different in unmanipulated males and females and dramatically altered upon experimental removal of sex hormones from the circulation following castration in adult life. Both the BNST and VMH regulate mating and aggression in the two sexes.

Current thinking about how sex hormones regulate sex differences in behavior is illustrated in the diagram below. Molecular studies have identified many genes, such as *Sytl4* and *Cckar*, whose expression is sexually dimorphic in the adult brain and controlled by sex hormones. Many such genes, when experimentally mutated in mice via genetic engineering, regulate distinct components of sexually dimorphic behaviors but not the entire repertory of social interactions. In other words, sex hormones control sexually dimorphic behaviors in a modular genetic manner. (Reproduced, with permission, from Xu et al. 2012.)

gender-typical behaviors; rather, the neural control of distinct behaviors is distributed across multiple different neuronal populations.

This modular control of sexually dimorphic behaviors fits well with our thinking that most circuits are shared between the males and females and that sex differences in behavior arise from key neural populations that alter circuit function in a male- or female-typical fashion. It seems likely that neurons exhibiting sexually dimorphic molecular or anatomical features represent such key neuronal populations.

The Human Brain Is Sexually Dimorphic

Are sex differences between the brains of male and female mammals also present in humans, and if so, might they be functionally important? Early studies

revealed that a few structures are markedly larger in men. These include Onuf's nucleus in the spinal cord, the homolog of the SNB in rodents (Figure 51–7); the BNST, implicated in rodent mating behavior (Figure 51–4); and the interstitial nucleus of the anterior hypothalamus 3 (INAH3), related to the rodent SDN-POA discussed earlier (Figure 51–13).

Advances in high-resolution magnetic resonance imaging (MRI) and histology have uncovered more subtle structural and molecular dimorphisms in the

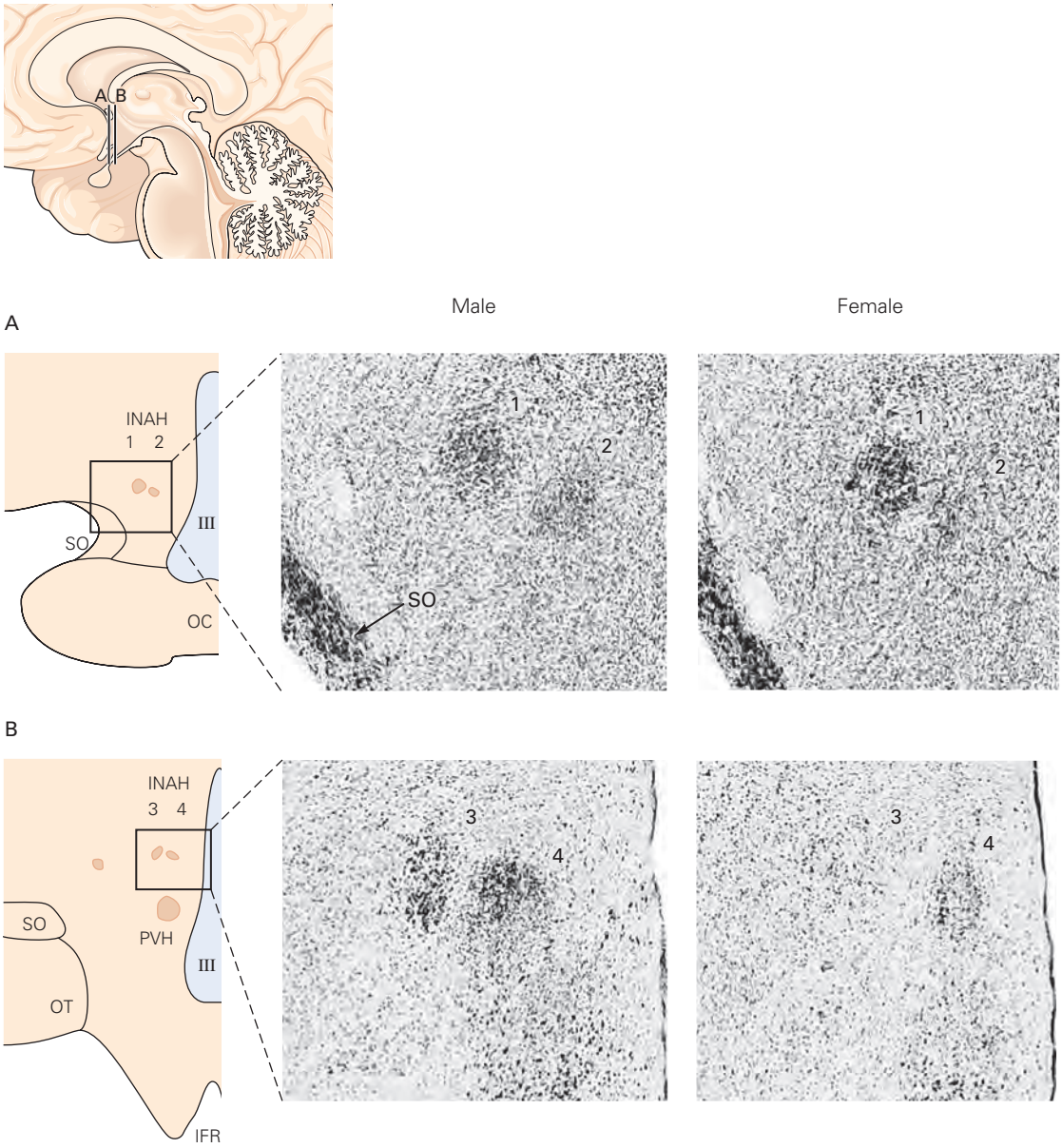

Figure 51–13 Sexual dimorphism in the interstitial nucleus of the anterior hypothalamus (INAH) 3 in the human brain. The human hypothalamus contains four small, discrete neuronal clusters, INAH1 to INAH4. The photomicrographs show these nuclei in adult male and female brains. While INAH1, INAH2, and INAH4 appear similar in men and women, INAH3 is significantly larger in men. The section in part **A** is 0.8 mm anterior to the section in part **B**. (Abbreviations: **IFR**, infundibular recess; **III**, third ventricle; **OC**, optic chiasm; **OT**, optic tract; **PVH**, paraventricular nucleus of the hypothalamus; **SO**, supraoptic nucleus.) (Adapted, with permission, from Gorski 1988.)

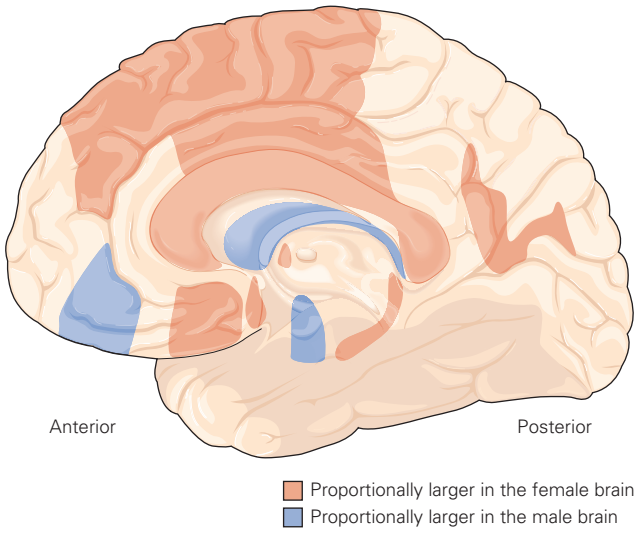

Figure 51–14 Sexual dimorphism is widespread in the adult human brain. A magnetic resonance imaging study measured the volume of many brain regions in adult men and women. The volume of each region was normalized to the size of the cerebrum for both sexes. Sex differences were significant in many regions, including several cortical areas that likely mediate cognitive functions. (Adapted, with permission, from Cahill 2006. Copyright © 2006 Springer Nature.)

central nervous system. For example, structures such as the fronto-orbital cortex and several gyri—including the precentral, superior frontal, and lingual gyri—occupy a significantly larger volume in adult women compared to a cohort of adult men (Figure 51–14). Moreover, the frontomedial cortex, amygdala, and angular gyrus volumes are larger in men compared to women. Thus, there are likely to be many sexual dimorphisms in the human brain.

Sexual Dimorphisms in Humans May Arise From Hormonal Action or Experience

What remains unclear is how these brain dimorphisms arise and how they relate to behavior. They might arise early from the organizational effects of hormones or later as a result of experience. Sex differences arising before or soon after birth could underlie behavioral differences, whereas those that arise later in life might be results of dimorphic experiences. Answers to these questions are fairly clear in a few cases. For example, studies of the development of neural circuits responsible for penile erection and lactation in rodents translate readily to humans.

Two recent observations suggest that enduring effects of experience on behavior first studied in animals (Figure 51–10) are also relevant to humans. First, as discussed in Chapter 49, children raised for lengthy periods in orphanages with little individual care have long-lasting defects in a variety of social behaviors. Even years after placement in foster homes, these children have on average lower levels of oxytocin and vasopressin in their serum than children raised with biological parents. Second, people who have suffered abuse as children often grow up to be poor parents. Postmortem studies have shown that adults who had been abused as children exhibited greater promoter methylation of their glucocorticoid receptor genes than adults in control populations. Although these studies are new and require replication, they provide tantalizing hints at the biological mechanisms that underlie the lifelong effects of early parental care.

Dimorphic Structures in the Brain Correlate with Gender Identity and Sexual Orientation

In contrast to progress in mapping the biological bases of some relatively simple sexually dimorphic behaviors in people, differences in sexual partner preference and gender identity remain poorly understood. Little progress has been made in relating sex differences in cognitive functions to structural differences in the brain, in part because the very existence of cognitive differences remains a matter of controversy; if they exist at all, they are small and represent differences in means between highly variable male and female populations. On the other hand, several lines of evidence have connected clear differences in gender identity and sexual orientation to dimorphic structures in the brain.

Early insight into this issue came from observation of people with single-gene mutations that dissociate anatomical sex from gonadal and chromosomal sex, such as CAIS, CAH, and 5α-reductase deficiency (Table 51–1). For example, girls with CAH experience an excess of testosterone during fetal life; the disorder is generally diagnosed at birth and corrected. Nevertheless, the early exposure to androgens is correlated with subsequent changes in gender-related behaviors. On average, girls with CAH tend to have toy preferences and engage in play typical of boys of equivalent age. There is also a small but significant increase in the incidence of homosexual and bisexual orientation in females treated for CAH as children, and a significant proportion of these females also express the desire to live as men, consistent with a change in gender identity. These findings suggest that early organizational effects of steroids affect gender-specific behaviors independent of chromosomal and anatomical sex.

In 5α-reductase II deficiency and CAIS, many of the affected males show completely feminized

external genitalia and are mistakenly raised as females until puberty. Thereafter, their histories diverge. In 5α-reductase II deficiency, the symptoms arise from a defect in testosterone processing largely confined to the developing external genitalia. At puberty, the large increase in circulating testosterone virilizes the body hair, musculature, and most dramatically, the external genitalia. At this stage, many but not all patients choose to adopt a male gender. In CAIS, in contrast, defects arise from a body-wide defect in the androgen receptor. These patients commonly seek medical advice after they fail to menstruate at puberty. Concordant with their feminized external phenotype, most CAIS patients express a female gender identity and a sexual preference for men. They opt for surgical removal of the testes and hormonal supplementation appropriate for females.

What accounts for the different outcomes? Among many possibilities, one is that the dramatic change in behavior in 5α-reductase II patients at puberty results from the effects of testosterone acting on the brain. In CAIS patients, these effects do not occur because androgen receptors are absent from the brain. Clearly, however, this explanation does not rule out social and cultural upbringing as important factors in determining gender identity and sexual orientation.

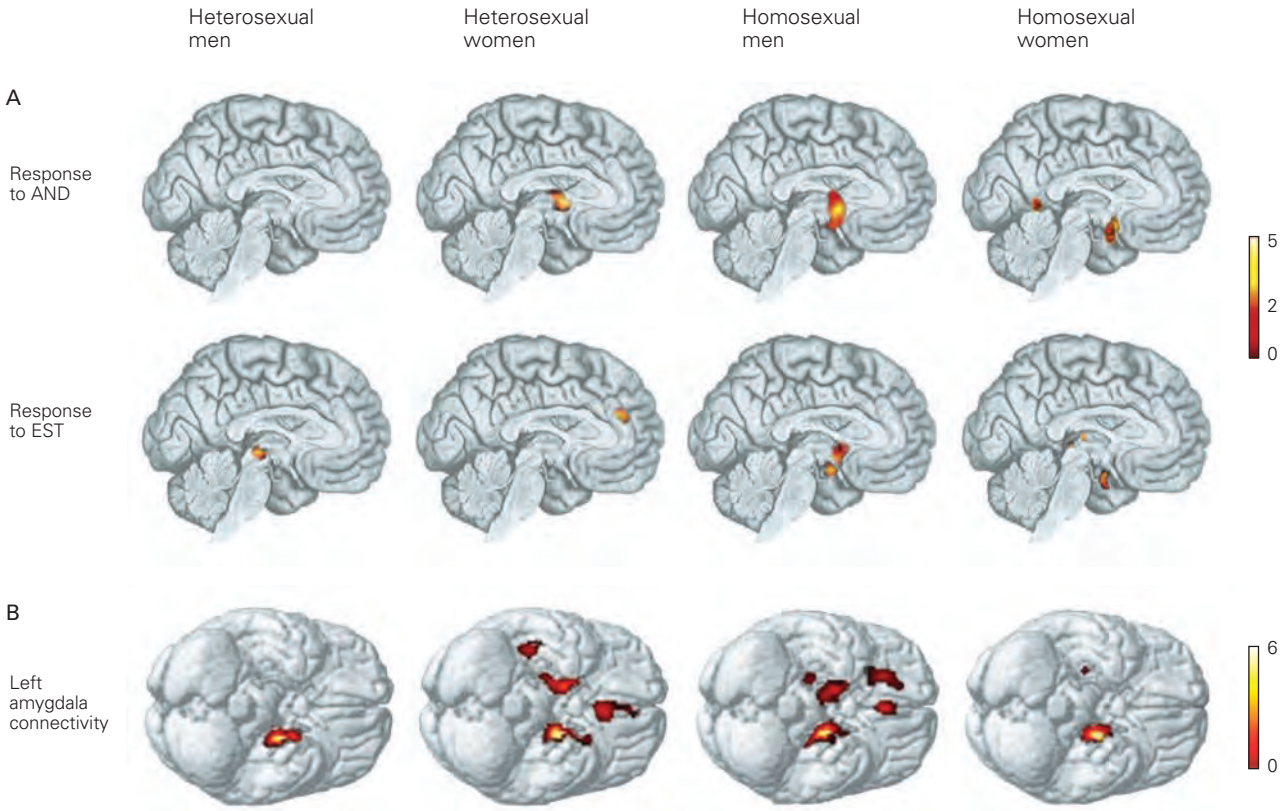

Figure 51–15 Some sexually dimorphic patterns of olfactory activation in the brain correlate with sexual orientation.

A. Positron emission tomography imaging was used to identify brain regions that were activated when subjects sniffed androstadienone (**AND**) or estratetraenol (**EST**) compared to nonodorous air. AND activated several hypothalamic centers in the brains of heterosexual women but not men, whereas EST activated several hypothalamic centers in heterosexual males but not females. Patterns of activation in the hypothalamus of homosexual men were similar to those of heterosexual women in response to AND, whereas similar patterns of activation were found in heterosexual men and homosexual women in response to EST. The color calibration on the right shows the level of putative neural activity. Because the same brain sections were selected to compare, the figure does not illustrate maximal activation for each condition. (Adapted, with permission, from Berglund, Lindstrom, and Savic 2006; Savic, Berglund, and Lindstrom 2005.)

B. Heterosexual and homosexual subjects were scanned while breathing unscented air, and a measure of covariance was used to estimate connectivity among regions. In heterosexual women and homosexual men, the left amygdala was strongly connected to the right amygdala, whereas connectivity remained local in heterosexual men and homosexual women. (Adapted, with permission, from Savic and Lindstrom 2008.)

A second set of studies probing the biology of sexual orientation assessed responses to pheromones. Pheromone perception in humans is quite different from that of mice and is likely a less important sense. Humans do not have a functional VNO, and most of the genes implicated in pheromone reception in the mouse VNO, such as *trpc2* and those encoding VNO receptors, are absent or nonfunctional in the human genome. To the extent that humans do sense pheromones, they appear to use the main olfactory epithelium and bulb. Chemicals that appear to be human pheromones include androstadienone (AND), an odorous androgenic metabolite, and estratetraenol (EST), an odorous estrogenic metabolite. AND is present at 10-fold higher concentrations in male sweat compared to female sweat, whereas EST is present in the urine of pregnant women. Both compounds can produce sexual arousal—AND in heterosexual women and EST in heterosexual men—even at concentrations so low that there is no conscious olfactory perception.

Brain areas activated by AND and EST have been identified by positron emission tomography (PET) imaging. When AND is presented, certain hypothalamic nuclei are activated in heterosexual women but not heterosexual men, whereas when EST is presented, adjacent regions containing clusters of nuclei are activated in men but not in women (Figure 51–15A). In homosexual men and women, there is a reversal of hypothalamic activation: AND but not EST activates hypothalamic centers in homosexual men, and conversely, EST but not AND activates those areas in lesbian women. Heterosexual and homosexual brains therefore appear to process olfactory sensory information in different ways.

Do sexually dimorphic structures in homosexual brains correlate with anatomical sex or sexual orientation? Imaging studies have provided support for the view that the brains of homosexual men resemble those of heterosexual woman and that the brains of homosexual women resemble those of heterosexual men (Figure 51–15B). Moreover, the volume of the sexually dimorphic BNST is small in male-to-female transsexuals compared to men, whereas female-to-male transsexuals appear to have a larger BNST compared to women (Figure 51–16). It is not clear, however, whether the structural dimorphism in these individuals is a consequence or a cause of gender identity or sexual orientation.

The male mouse counterpart of the human BNST plays a critical role in recognizing the sex of *other* mice and guides subsequent social interactions, such as aggression with males and mating with females. Thus, a region linked to gender identity in the human brain plays an important role in sex recognition in rodents.

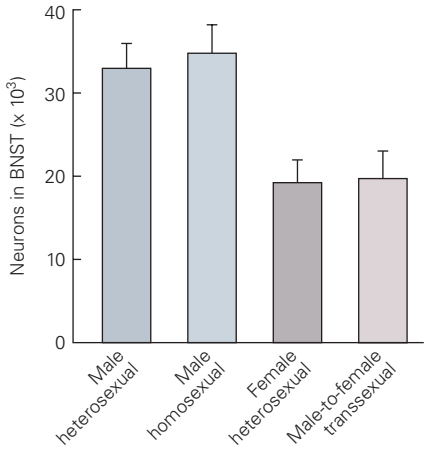

Figure 51–16 Sexual dimorphism in the bed nucleus of the stria terminalis (BNST) in humans. The nucleus has significantly more neurons in men compared to women regardless of male sexual orientation. Similar to women, male-to-female transsexuals have fewer neurons than men. In the one female-to-male transsexual brain available for postmortem analysis (not shown in the bar graph), the number of neurons is well within the normal range for men. (Adapted, with permission, from Kruijver et al. 2000.)

As is the case with the sexual dimorphism of the mouse BNST discussed earlier, hormonal influences are also thought to underlie the dimorphism of the human BNST.

If prenatal influences do lead to dissociation of sex from gender, are those influences genetic? Other than the rare syndromes described earlier, attempts to find genetic bases for sexual orientation or gender identity have not been productive. Claimed genetic contributions are small and claims of associations with specific genomic loci have not been replicated. Thus, while the current weight of evidence favors some contribution of early, even prenatal, factors in these processes, their cause and relative importance remain unknown.

Highlights

1. In humans and many other mammals, the sex determination pathway directs differentiation of the bipotential gonad into testes in males and ovaries in females. The *SRY* gene on the Y chromosome directs the gonad to form testes, whereas the absence of *SRY* enables the gonad to differentiate into ovaries.
2. Sex steroid hormones produced by the gonads—testosterone by testes and estrogens, and progesterone by ovaries—drive sexual differentiation of both the nervous system and the rest of the body.

3. Sex hormones act early during a critical window in development to irreversibly organize neural substrates for behavior in a sexually dimorphic manner, whereas in adult life, these hormones act acutely and reversibly to activate sex-typical physiological and behavioral responses.
4. During the critical window, testes produce a transient surge of testosterone that masculinizes the developing bipotential nervous system. By contrast, the ovaries are quiescent during this period, and it is thought that the absence of sex hormones enables the nervous system in this period to differentiate along a female-typical pathway.
5. Many of the actions of testosterone that masculinize the nervous system occur following its conversion to estrogen locally at the site of action. There is evidence to suggest that in humans and other primates testosterone also acts directly via its cognate hormone receptor to effect masculinization of the neural substrates of behavior.
6. Sex hormones control sexual differentiation of neural pathways by utilizing cellular processes such as apoptosis, neurite extension, and synapse formation that are employed widely during other developmental events.
7. Sex hormones bind to cognate hormone receptors that modulate gene expression. Such genes in turn regulate the cellular processes that result in sex differences in neuronal number, connectivity, and physiology.
8. Many neuronal populations that are sexually dimorphic by morphological and other criteria have been identified in the vertebrate brain over the past few decades. Functional studies show that these regions influence some, but not all, sexually dimorphic behaviors.
9. Recent molecular studies have identified many sex hormone–regulated genes whose expression patterns are sexually dimorphic. These genes as well as the neurons they are expressed in regulate sexually dimorphic social behaviors in a modular manner. In other words, individual genes and the neuronal populations that express them modulate one or a few sexually dimorphic behaviors so that the control of these behaviors is distributed among many different neuronal groups.
10. Such sexually dimorphic neuronal populations are likely embedded within neural circuits found in both sexes, and they are thought to guide behavior along male- or female-typical patterns.
11. Both sensory stimuli and past experience profoundly regulate the display of sexually dimorphic behaviors. In some cases, the influence of past experience can extend across the life span of the animal.
12. Pheromones guide choice of sexual partner in rodents. There is evidence from imaging studies that men and women may also show sexually dimorphic neural responses to male and female pheromones and that these responses can align with sexual orientation; in these cases, however, it is unclear if the neural responses are learned responses based on past experience.
13. There are many sex differences between the brains of men and women, and in some instances, these sex differences align with gender in adult life rather than gender assigned at birth. In these cases, it is not clear whether the sex differences causally reflect gender identity or are a result of it. These issues are difficult to disentangle at present.

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