0013-7227/04/$15.00/0
Printed in U.S.A.

Endocrinology 145(3):1063–1068

doi: 10.1210/en.2003-1504

Minireview: Sex Differences in Adult and Developing Brains: Compensation, Compensation, Compensation

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Despite decades of research, we do not know the functional significance of most sex differences in the brain. We are heavily invested in the idea that sex differences in brain structure cause sex differences in behavior. We rarely consider the possibility that sex differences in brain structure may also prevent sex differences in overt functions and behavior, by compensating for sex differences in physiological conditions, *e.g.* gonadal hormone levels that may generate undesirable sex differences if left unchecked. Such a dual function for sex differences is unlikely to be restricted to adult brains. This review will entertain the possibility that transient sex differences in gene expression in developing brains may cause permanent differences in brain structure but prevent them as well, by compensating for potentially differentiating effects of sex differences in gonadal hormone levels and sex chromosomal gene expression. Consistent application of this dual-function hypothesis will make the search for the functional significance of sex differences more productive. (*Endocrinology* 145: 1063–1068, 2004)

Classical View on the Function of Neural Sex Differences

ASK ANY NEUROSCIENTIST why there are sex differences in the brain, and you will likely hear that such differences generate differences in reproductive behavior, the control of gonadotropic hormones, or sex differences in cognitive functions. Intuition tells us that sex differences in brain structure beget sex differences in brain function. There is nothing wrong with that. If, for example, a brain area has three times more cells that produce a specific neurotransmitter in one sex *vs.* the other, and if these cells send, accordingly, three times denser projections to target neurons in another area, stimulation of these cells will probably cause sex-specific responses in the target neurons. The naked eye is not likely to detect these sex differences in function as they occur at the molecular and cellular level. Whether such differences always manifest themselves as differences in behavior or in other functions that can be monitored at the organismal level (which I will call overt functions in this review) remains to be seen.

If one tries to link well-known neural sex differences with differences in overt functions, problems rapidly mount, but less so for the spinal cord than for the brain. Some of the best known neural sex differences concern differences in number and size of motoneurons in the medulla and spinal cord, which often can be linked to well-known sex differences in the function of target muscles. For example, the spinal nucleus of the bulbocavernosus (SNB) in rats and mice, which is readily visible in males but difficult to detect in females, innervates muscles that are found at the base of the penis and are absent or only vestigial in females (1). Not only might a recording electrode in the spinal cord detect many more firing motoneurons in males, this difference generates overt sex differences in genital responses so obvious that most neuroscientists do not feel challenged to study the structure-function relationship in greater detail. Similarly, sex differences in medullary motoneurons that innervate muscles of the larynx in clawed frogs (2), or muscles of the dewlap in green anoles (3), have been linked to more frequent and intense use of these structures during courtship in males.

Higher up in the central nervous system, the increased variety of cell types and complexity in connections obscure the relationship between structure and function of sexually dimorphic structures. Some neural sex differences, however, still trigger similar intuition as does the sex difference in the SNB. This is especially true for the vocal control areas of zebra finches and canaries, in which robust sex differences in brain morphology were first detected (4). Males of these species have larger nuclei, denser connections, more synapses, *etc.*, than females at virtually every level of the vocal control system (5). The structure-function relationship seems obvious: males sing; females don't, or sing very little. Females may still need the system for perception of song (6, 7), but the differential in the number and size of cellular features may buy males the ability to sing complex song. This fits with naturally occurring variability in sex differences in song control nuclei, which are less pronounced or even absent in vocal control systems of species where females sing as well as males (5). An exception, however, is the African bush shrike, *Laniarius funebris.* Even though the complexity of male and female song does not differ, males still have larger vocal control areas than females (8). This anomaly should keep us on our toes. The link between song production and size of the vocal control nuclei may not be as simple as it first appeared.

Compared with bird song control areas, it has been much more frustrating to determine the function of the sexually

Abbreviations: AVP, Arginine vasopressin; GABA, γ-aminobutyric acid; MPN, medial preoptic nucleus; MPOA, medial preoptic area; PR, progesterone receptor; SDN, sexually dimorphic nucleus of the preoptic area; SNB, spinal nucleus of the bulbocavernosus; TH, tyrosine hydroxylase; VMN, ventromedial hypothalamic nucleus.

***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

dimorphic nucleus of the preoptic area (SDN) in rats, which is several times larger in males than in females (9). A prime candidate for the function of this sex difference seems to be male sexual behavior because the SDN is conveniently situated in the medial preoptic area (MPOA), which controls this behavior (10). However, lesioning the SDN barely puts a dent in sexual behavior of experienced males, and neonatal manipulations that affect the development of male sexual behavior leave the SDN morphology unchanged and vice versa (11–13). A quarter century and well over a hundred papers later, we know a lot more about the development of the SDN, but we have not gotten an inch closer to revealing the functional significance of its sex difference (13).

Dual-Function Hypothesis for Neural Sex Differences

I believe that one of the biggest stumbling blocks in finding the functional significance of sex differences in the brain is that we are stating our hypotheses too narrowly. A number of years ago, we proposed that sex differences in brain structure might serve at least two functions (14–16). They may indeed generate differences in overt functions and behavior, but they may just as well do the exact opposite, that is, they may prevent sex differences in overt functions and behavior by compensating for sex differences in physiology. The need for such compensation is clear in behaviors shown by both sexes that depend on specific hormonal conditions in one sex that never occur in the other, for example, parental behavior in prairie voles.

Prairie voles form stable pair bonds in which both parents take care of the pups (17). Once pups are born, males and females show no qualitative difference in parental behavior with the exception of nursing (18). In female rodents, hormonal changes associated with pregnancy prime the brain for parental behavior (19). Female prairie voles are no exception. As virgins, they are unresponsive to pups or even infanticidal, but exposure to gonadal steroids makes them parental (20). In contrast, males are spontaneously responsive to pups, and castration does not eliminate parental responsiveness (18, 20). In gonadally intact males, however, parental behavior depends on activation of arginine vasopressin (AVP) receptors in the lateral septum (21). Interestingly, there is an enormous sex difference in the AVP innervation in voles. Female voles have hardly any AVP fibers in their septum, whereas males have a dense AVP fiber network (14). A similar sex difference is found in the number of AVP mRNA-expressing cells in the bed nucleus of the stria terminalis, which forms the origin of septal AVP innervation (22). Therefore, prairie vole males, which do not become pregnant and therefore never will be exposed to the hormonal changes associated with pregnancy, may have compensated by using the male-biased AVP innervation to stimulate parental responsiveness (Fig. 1).

The hypothesis that sex differences in the brain may generate sex differences in some overt functions and behaviors as well as prevent them in others is perfectly falsifiable. The first part of the hypothesis predicts that blocking the function of sexually dimorphic systems prevents or blunts sex differences in some overt functions; the second part predicts that doing so generates sex differences in other overt functions,

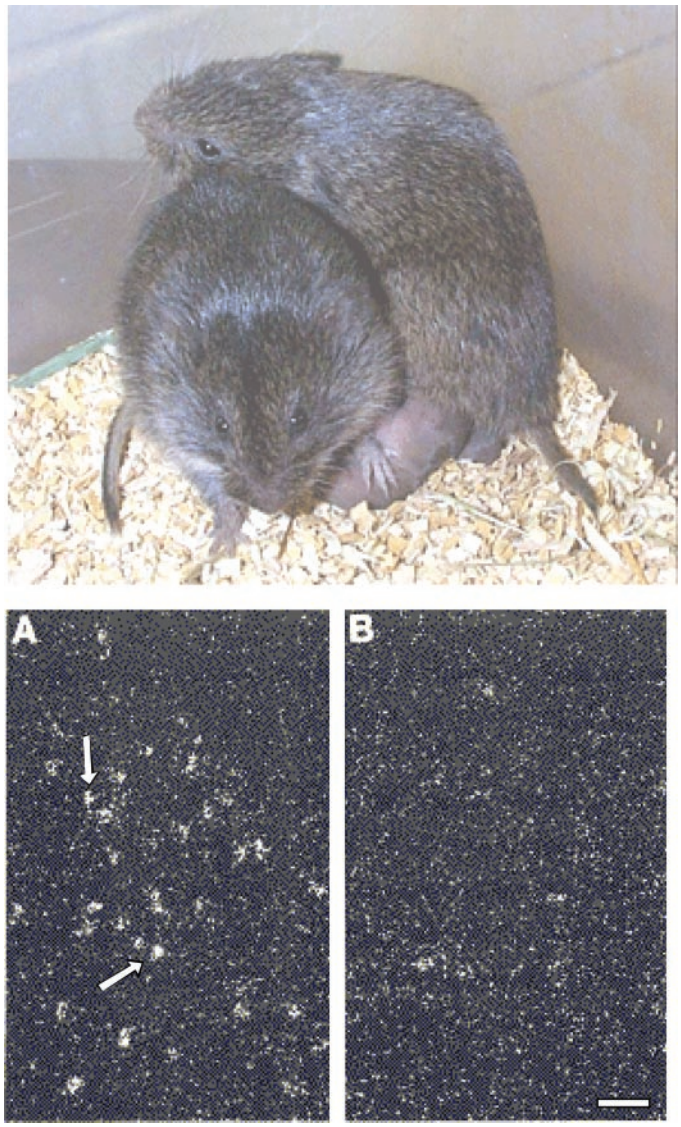

FIG. 1. The *top panel* shows a male and female prairie vole sharing time in taking care of their young. The *bottom panel* shows dark-field illuminated sections with many more cells labeled for vasopressin mRNA in the bed nucleus of the stria terminalis of a male (*left*) than of a female prairie vole (*right*). *Bar*, 25 μm.

where such differences did not exist before. Support for the second part of the hypothesis was obtained well before we had stated the dual-function hypothesis. The sexually dimorphic septal AVP innervation had already been shown to be involved in aggressive behavior in rats, a sexually dimorphic behavior (23). This fits the first part of the hypothesis. Septal AVP had also been implicated in social recognition memory in males, a behavior performed equally well by males and females (24). Treating rats with an AVP antagonist, however, blocked social recognition memory in males but not in females, thereby inducing a sex difference where there was none before (25).

More recent studies have shown that manipulating sexually dimorphic neurotransmitter or hormonal systems affects pair bonding and parental behavior differently in male and female prairie voles (26–28). This suggests that the neuro-

chemical and hormonal underpinnings of social behavior may differ even in cases where these behaviors are remarkably similar between the sexes. For example, intracerebroventricular injections of an AVP antagonist blocked pair bonding in male but not in female prairie voles, whereas the opposite was true for an oxytocin antagonists (26). Humans are not an exception. Strokes in the same brain regions can have different outcomes in men and women (29–31), and functional imaging studies suggest that men and women use cortical regions differently even for functions that do not differ themselves (32–35). Ironically, the hypothesis that the neurochemical underpinnings of non-dimorphic behaviors may also differ in humans seems to be tested all the time when medical practitioners prescribe psychoactive drugs in similar dosages to men and women to treat behavioral disorders (36). Even though the disorders may present similar symptoms, many of the drugs act on neurotransmitter systems that are sexually dimorphic, such as the central serotonin innervation (37). For that reason alone, the effectiveness of these treatments may differ. However, few researchers monitor the results of these inadvertent experiments (36).

Significance of the Dual-Function Hypothesis for Sexual Differentiation

There is no reason to restrict the dual-function hypothesis of sex differences in brain structure to adult brains. We are tempted to see sex differences in gene expression during development as factors contributing to sexual differentiation (13, 38, 39). We have to be cautious, however, because the opposite could be true as well; such differences may prevent undesirable sexual differentiation of brain structure. In some cases, however, the link with sexual differentiation is very tempting. For example, on postnatal d 8, male rats express higher levels of the cell survival-promoting Bcl-2 protein in the MPOA than do females (40). Because the MPOA contains the SDN, this difference corresponds well with the lower levels of apoptosis in the SDN in males *vs.* females on postnatal d 8 (41). In mice, overexpression of Bcl-2 indeed blunts sexual differentiation of structures such as the SNB (42), where differentiation depends on sex differences in the rate of programmed cell death (43). Therefore, the sex difference in Bcl-2 expression may indeed contribute to differentiation of the SDN.

Many more sex differences in developing brains are less easy to explain. For example, around birth, male rats express much higher levels of progesterone receptor (PR) in the MPOA than do females (44) (Fig. 2). This sex difference starts to disappear once the ovaries become active (45). It is tempting to suggest that PR may cause the sexually dimorphic development of the medial preoptic nucleus (MPN). Indeed, blocking PRs neonatally reduces male rat sexual behavior as well as the sex difference in MPN volume (46, 47). However, there cannot be a simple relationship between the sex difference in PR expression and differentiation of the MPN, because mice have the same sex difference in PR expression as do rats (48) but do not develop clear sex differences in the MPOA (49). Thus, if the sex difference in PR can contribute to the differentiation of the MPN, mice tissue either is insensitive or fosters sexually dimorphic processes that blunt its sexual differentiation or make it different from that in rats.

There are more areas where transient sex differences in gene expression do not map on to gross sex differences in the adult brain. For example, immediately after birth, large sex differences are found in γ-aminobutyric acid (GABA) neurotransmission in the ventromedial hypothalamic nucleus (VMN) and the arcuate nucleus but not in the MPOA (50, 51). The VMN and arcuate nucleus express gonadal steroid receptors as prominently as does the MPOA during development and therefore appear to be equally likely targets for the differentiating effects of gonadal steroids (52, 53). However, morphological and neurochemical sex differences are much more prominent in the MPOA than in the arcuate nucleus and the VMN (13). Perhaps the sex difference in GABA neurotransmission in the VMN and arcuate nucleus prevents the development of gross morphological and neurochemical differences in these areas.

It is not difficult to imagine scenarios that would require compensatory sexually dimorphic gene expression. For example, target cells provide important trophic support to afferent neurons (54, 55). So one could postulate that sexually dimorphic cell death in one group of neurons should not automatically lead to similarly biased death in cells that project to these neurons. One way to prevent cell death in these areas might be to stimulate temporarily the expression of cell survival-promoting factors such as Bcl-2.

To add one layer of complexity, one should wonder whether sex differences, such as the one in PR expression in the MPN, serve to increase sex differences as well as prevent them. Both possibilities may coexist, just as the sex difference in AVP innervation may prevent sex differences in some behaviors (for example, social recognition memory and pa-

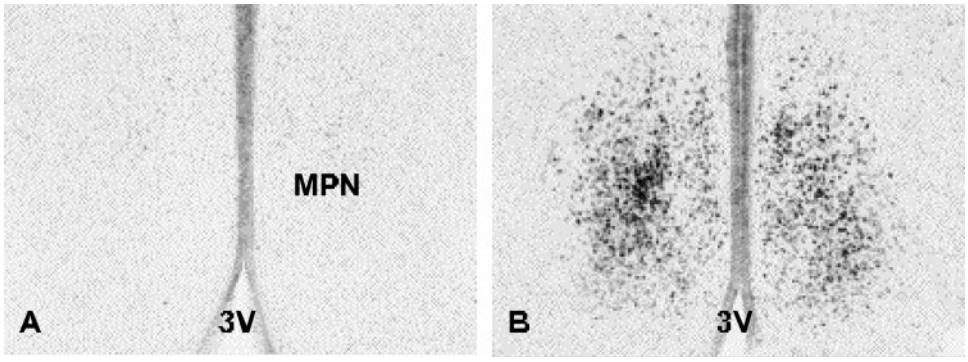

FIG. 2. Sex difference in the expression of progesterone in the MPN of a neonatal male (A) and female (B) rat. Note the abundance of PR-immunoreactive nuclei in the male but not the female MPN. 3V, Third ventricle.

rental behavior) and generate them in others (for example, aggressive behavior) (14). Likewise—although I suggested that sex differences in GABA neurotransmission may possibly prevent gross morphological sex differences in the VMN and arcuate nucleus—blocking GABA synthesis interferes with the development of sexually dimorphic reproductive behaviors (56). Quite likely, the combination of all the differently expressed factors in a given developing brain region amounts to a highly complex, multilevel combinatorial code. Even if this code would signal a region to develop similarly in males and females, it may have to do so in a sexually dimorphic manner, simply because it may have to compensate for inputs or target fields that are already different in males and females.

Dual-Function Hypothesis and Sex Chromosomal Effects

The need for compensation gets an entirely new dimension when one considers that sex chromosomal genes may directly affect brain development (57, 58). Whereas gonadal steroids target especially neurons that express steroid receptors, every cell in the brain may express sex chromosomal genes in a sexually dimorphic manner. Sex differences in sex chromosomal gene expression could result from the different dosage of X chromosomal genes, sex differences in X-Y genes (homologous genes on the X and Y chromosome that are located on chromosomal areas that do not recombine and therefore differ somewhat in structure), and parental imprinting of X chromosomal genes (57). Because such differences have indeed been found in developing brains (59), they may also serve to induce or prevent sexual differentiation of the brain. If true, this may explain a number of findings that do not fit the idea that sex differences in the developing brains always contribute positively to sexual differentiation of neural tissue. For example, Veney *et al.* (60) recently discovered that the calcium-binding protein, neurocalcin, is expressed transiently at much higher levels in the developing telencephalon of female than of male zebra finches, especially in areas that do not develop gross morphological sex differences. As sex chromosomal genes appear to influence sexual differentiation of song control areas directly (57, 61), the authors' suggestion that the sex difference in neurocalcin expression may prevent rather then induce differentiation (60) rings true. This raises the intriguing possibility that interference with neurocalcin functioning during development might induce sex differences normally not found in bird brains.

Another interesting phenomenon is that cultures of mesencephalic cells harvested on embryonic d 14 differ in the number of cells that will express tyrosine hydroxylase (TH) depending on the sex of origin (62, 63). Carruth *et al.* (64) provided convincing evidence that sex chromosomal complement and not previous exposure to gonadal hormones determines the level of TH expression *in vitro*, by using mice in which sex chromosomal complement was manipulated independent of gonadal sex. Female mice either had a pair of X chromosomes, or an X and a Y chromosome minus the testis-organizing Sry gene; males had the same two sets of chromosomes but also an Sry transgene on an autosomal gene, which triggered testis development. Cultures from XX mice developed more TH neurons than did XY cultures regardless of the sex of origin. Interestingly, this difference does not appear *in vivo* (65). One possible explanation is that something about the internal milieu prevents XX- and XY-specific gene expression from inducing sex differences in mesencephalic cells *in vivo*. A much more intriguing possibility is that XX- and XY-specific gene expression occurs also *in vivo*, perhaps to compensate for effects of factors derived from other brain regions that would have caused undesirable sexual differentiation if left unchecked. Even though this type of thinking requires several levels of abstraction, all the ideas generated are in principle testable. For example, one could identify the elements on X and Y chromosomes that cause the differences in TH expression *in vitro*. Equating the influence of these elements in XX and XY animals should eliminate the difference *in vitro* and induce a difference *in vivo*.

Differentiation *vs.* Compensation

Although the idea that sex differences at the molecular and cellular level, whether caused by sex chromosomal expression or by gonadal hormone levels, may generate as well as prevent sex differences in overt functions and behavior may be new in the field of brain sexual differentiation, it has been addressed in other domains of biology. For example, the silencing of transcription of genes on one of the two X chromosomes, a process called X-inactivation, is a female-specific process and evolved presumably to prevent deleterious effects of sex differences in the dosage of X-specific gene expression. These sex differences were the consequences of deterioration of Y chromosomal genes during evolution of the heteromorphic sex chromosomes (66, 67). Evolution apparently involves a constant tug-of-war between XY and XX cells, creating on the one hand sex differences in gene expression meant to differentiate XY and XX cells in some tissues (which is essential, for example, for the differentiation of the gonads), while on the other hand keeping XY and XX cells as equivalent as possible in other tissues (which is important for processes that depend on X- and Y-specific genes but that take place in tissues that have equivalent functions in males and females). The very fact that single genes often control distinct and not necessarily related processes in different cell types means that sex differences in the expression of those genes may produce adaptive effects in some but maladaptive effects in other tissues. Evolution is likely to favor the emergence of sexually dimorphic processes that would counter the latter effects. It would be remarkable if brains were an exception.

Acknowledgments

I thank Nancy Forger and Jan Thornton for critically reading the manuscript and giving very helpful suggestions.

Received November 6, 2003. Accepted November 26, 2003.

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This work was supported by NIH Grants RO1-MH47538 and K02-MH01497.

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***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**