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## ARTICLE

### *The End of Sex as We Know It*

Bruce S. McEwen and Elizabeth Norton Lasley

Are male and female brains different in ways that relate not just to sexuality and reproduction, but to intellectual potential, talents, and interests? Recent neuroscience research is showing that, from the earliest stages of development, male and female brains seem to differentiate themselves in ways that suggest *vive la difference* may mean more than we thought.



#### *About the Authors:*

**Bruce S. McEwen, Ph.D.**, is professor and head of the Laboratory of Neuroendocrinology at The Rockefeller University, where his research focuses on the actions of stress and sex hormones on the brain and immune system. He is the author of *The End of Stress As We Know It* (Dana Press/Joseph Henry Press, 2002).

**Elizabeth Norton Lasley** is a science writer who specializes in neuroscience. Formerly a senior editor at Dana Press, her freelance articles have appeared in many publications including *Science*. She co-authored *The End of Stress As We Know It* (Dana Press/Joseph Henry Press, 2002) with Bruce McEwen, Ph.D.



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by Bruce S. McEwen, Ph.D.,  
and Elizabeth Norton Lasley

# The End of Sex as We Know It

*Recently, research has shown that male and female brains are different in ways that go well beyond sex and reproduction. True, some of the research was limited to nonhuman mammals. But discoveries about how genes, hormones, and the environment operate to differentiate the brains, behavior, and vulnerabilities of the sexes—with effects on learning, memory, abilities, and behavioral traits—are potentially so far-reaching for our thinking about humans that neuroscientist Bruce McEwen asks whether this is “the end of sex as we know it.”*

After the protests that greeted Harvard’s President Lawrence Summers when he raised provocative questions about how brain differences might affect the roles of men and women in science, it is difficult to believe that any public figure will ever again dare mention the subject of differences in intellectual potential between the sexes. But President Summers was not rehashing old stereotypes to the effect that women are too emotional or distracted when they menstruate. It is easy to reject that kind of straw man; however, it is also easy, much too easy, to embrace the soothing and supposedly uncontroversial assertion that, in areas not directly concerned with sexual behavior and reproduction, the sexes are essentially indistinguishable.

Men and women have obvious differences, but, increasingly, research is showing that the differences go far beyond the obvious. Although today’s research is still far from supporting any general assessment of each sex’s innate abilities and their possible consequences for intellectual capacities, no informed scientist—and certainly no brain scientist—can pretend significant differences do not exist. From the beginning, brain development takes sharply divergent paths depending on sex. The male brain tends to be larger and contain more cells; the cerebrum and amygdala (areas associated with analysis and fear, respectively) are larger in men. In women, although the brain is smaller overall, the connective tissue linking the brain’s hemispheres is thicker, perhaps supporting the quicker integration of information and emotion.

What these facts mean in terms of intelligence and ability is not yet clear, nor is it clear exactly how much is innate or socially conditioned. We do know that, on average, women score higher than men in tests involving empathy and language tasks, and baby girls talk earlier than boys, with bigger vocabularies. Men, however, tend to do better than women on college-level math tests and tests of mechanical skill. Evidence

for differences like these has proved quite consistent and robust over time.\*

Neuroscience is complicating this picture, even as it clarifies it, and, in the past 5 to 10 years, many long-held dogmas have fallen. It was commonly held that the sex hormones, estrogen and testosterone, mainly influenced sexual differentiation and reproductive behavior, working mostly through brain centers involved with those processes: the hypothalamus, pituitary gland, and parts of the amygdala. We are now learning that the whole nervous system is responsive to sex hormones, and these hormones influence an impressive array of processes: learning and memory, mood, attention, fine-motor control, seizure susceptibility, pain, and recovery from damage as a result of stroke and Alzheimer's disease. Moreover, neuroscience is now showing that experience changes the structure and circuitry of the adult brain and that hormones play a role in this by acting synergistically with the brain's own chemical neurotransmitters. Scientists also used to think that all sex differences depended on the effects of estrogen and testosterone. Now several studies have implicated the sex chromosomes in aspects of behavior and brain structure that are outside the influence of sex hormones.

Right now, the research is raising as many questions as it is answering, at least when it comes to definite conclusions about human behavior and many brain functions. It goes without saying, or should, that the

existence of important sex-based brain differences does not mean in any way, shape, or form that a stronger or more intelligent sex exists. Several animal studies, however, are clarifying the specific differences in males and females and how chemistry, genetics, and the environment play their parts in creating divergent results depending on sex. Scientists suspect that the observable differences in performance of men and women in various areas are produced by some combination of genetic and environmental influences that bring about the distinct, sometimes dramatic, divergence in pathways of brain and behavior that is emerging from new research.

#### **BEYOND TESTOSTERONE**

Research is challenging a central dogma of reproductive biology: that sex differences arise just from the gonadal steroid hormones, estradiol and testosterone. Estrogen is the female sex hormone made primarily in the ovaries but also synthesized in lesser quantities in males. Estrogen's most potent form in the body is called estradiol. Testosterone is the male sex hormone made primarily in the testes but also synthesized in small quantities in the ovaries.

The standard thinking in science has been that the "default" sex of mammals is female. If an embryo has a male Y chromosome (inherited from the father), a kind of gene that produces a so-called transcription factor, located on that chromosome, will signal the gonads to develop into testicles. The testicles will produce the male hormones, chiefly testosterone, which will give rise to all male traits, both anatomical and

\* See, for example, "A Scientist Dissents on Sex and Cognition," by Doreen Kimura, *Cerebrum*, Fall 2000.

behavioral, and suppress the development of female characteristics such as female-typical reproductive behaviors.

Although a wealth of research supports this view, as far as it goes, scientists have long suspected that gonadal hormones are not the whole story, that at least some important sex differences, particularly those in the brain, are induced directly by the genes and appear well before the sex organs even emerge. Research in the early 1990s showed that when brain cells were taken from male and female mouse embryos and cultured separately, the resulting cell lines had sex-specific biochemical signatures before any difference in testosterone levels was apparent. For instance, the resulting cell lines of female mouse embryos contained significantly more dopamine-producing cells than were observed in males.

Then, in 2002, Arthur Arnold, Ph.D., his colleagues at the University of California, Los Angeles, and scientists in London bred a strain of mouse with an unusual Y chromosome. The chromosome was missing the gene called *Sry*, which triggers the emergence of testes. Mice with a Y chromosome that is missing *Sry* do not develop testes, but rather ovaries, and are thus defined as female, meaning that their genetic sex (male) does not match their gonadal sex (female). By patching *Sry* onto an adjacent, non-sex chromosome, the researchers created a mouse that had testes, but lacked *Sry* in its normal location on the Y chromosome. They then bred these males with normal (not genetically altered) females, producing offspring of four distinct types. The offspring lacking *Sry* developed into two types

of females (defined as having ovaries): One type possessed two X chromosomes, and one possessed XY chromosomes (genetically male). The mice with *Sry* developed into two types of males (defined as having testes): One possessed two X chromosomes (genetically female), and one possessed XY chromosomes. These offspring made it possible for researchers to compare the effects of XX and XY chromosomes independently of the presence of testes or ovaries and the gonadal hormones.

Although many sex differences in the brain and behavior of these mice depended on the presence of ovaries or testes, and thus on gonadal hormones, certain behavioral traits and brain structures were related specifically to the genetic sex of the mice. For instance, genetically male mice (XY), regardless of the presence of testes, were more masculine in terms of certain brain structures than were genetically female mice. Also, behavioral differences that depended on the presence or absence of the Y chromosome were observed in mice with testes. These results imply a direct contribution of sex chromosomes to sex differences in the brain.

More evidence of sex differences came the following year. Eric Vilain, M.D., Ph.D., and his coworkers at the University of California, Los Angeles, analyzed differences in genes expressed in developing male and female mouse brains 10 days after conception—before the gonads begin to form. They found more than 50 genes with a pattern of expression strikingly different between male and female mice. Although it is premature to draw conclusions about male and female behavior, or any other

aspect of brain function, particularly in humans, the results are intriguing. For example, several genes linked to the Y (male) chromosome are believed to be risk factors for aggressive behavior in mice, and one such gene, known as *Dby*, was highly expressed in the embryonic male brains.

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The researchers surmised that the genes they had identified “may be fundamental factors that trigger differences between male and female brain development before the production of gonadal hormones.”

Taken together, the findings portend a seismic shift in scientific thought—away from a strictly hormonal theory of sex-based brain differences and toward one that allows for the direct effect of genes. As a final note, the work also raised questions about the role of the prenatal environment. Many scientists maintain that a person’s hormone levels are influenced by the balance of hormones surrounding him or her in utero. These hormone levels could be produced either by the mother or, in the presence of more than one embryo, by hormones from the neighboring fetus. Vilain’s findings challenge at least the theory that other fetuses are an influence, because differences in the mouse brains were apparent before any of the

embryos began producing sex hormones. In short, although the new research described does not prove that differences between men and women are set from the moment of conception, it does suggest that the initial divergence between male and female cannot be attributed solely to testosterone.

### **...BUT ALSO A WIDE ROLE FOR TESTOSTERONE**

Another assumption challenged in recent years is that sex hormones are limited in their action to matters of sex and reproduction. Scientists are discovering that sex hormones can influence the brain in many other ways. Sex hormones operate by activating receptors within specific types of brain cells. Their action during critical periods of brain development adds on to those already set in place in embryonic life via the Y chromosome and further causes male and female brains to develop differently.

An early sign of these diverging pathways, which eventually lead to different traits in adulthood, comes from research conducted at the end of the 1990s on how testosterone alters the way neurons respond to one of the brain’s main neurotransmitters, gamma-aminobutyric acid (GABA). GABA’s effects are generally inhibitory, meaning that it slows the firing activity of neurons instead of exciting it (as does the excitatory neurotransmitter glutamate, for example). Many medications that treat seizures, which involve excessive brain cell activity or excitation, work by prolonging the effects of GABA. But circumstances exist in which GABA can be excitatory, and these depend on how the cells that receive the GABA signal respond, especially in early brain development.

Anthony Auger, Ph.D., Margaret McCarthy, Ph.D., and their colleagues at the University of Maryland found that, during a perinatal period when the brain is sensitive to testosterone, this hormone extended the period during which GABA functioned in an excitatory manner. In males, the neurotransmitter's effects were predominantly excitatory in the hypothalamus and parts of the hippocampus; GABA was inhibitory in the same regions in females but was excitatory in another area, the arcuate nucleus, for both sexes. These sex differences in the developing brain give rise to differences in brain processes, such as brain cell proliferation and survival, the excitability of neurons, and the formation of the contact points between neurons, known as synapses. According to the researchers, the varying effects of GABA enable neurons in male and female brains to respond in different, even opposite, ways to the same stimulus.

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Male and female brains also differ in the number of neurons, especially in certain areas. Newborn mammals, including humans, are born with more brain cells than they need; in the period after birth, a normal and

tightly orchestrated process of cell death refines and sculpts the brain into what will be its adult form. This cell death is known to have different patterns in male and female mammals. Nancy Forger, Ph.D., of the University of Massachusetts and her colleagues have shown that testosterone plays a role in controlling the process of cell death in the developing brain.

Once again, though, hormones are not the whole story. When Forger tallied the neurons in the brains of mice missing a gene called *Bax*, she found that as a result of the gene's absence, the usual sex-based differences in two key brain areas were eliminated. Importantly, however, this effect was only true for the total cell number; the females still had more dopamine-producing cells than the males. The finding shows *Bax* to be a juncture in the pathway through which cell death shapes the male and female brain, but it suggests, too, that the sex differences in the female brain are also controlled by mechanisms independent of *Bax*.

#### **ESTROGEN'S OTHER EFFECTS**

Testosterone's role in the nervous system, including its varying effects on the sexes, has a counterpart in the role of the female hormone. In the adult female brain, for example, natural amounts of estradiol facilitate fine-motor control and improve reaction times and balance. They do so by acting on the cerebellum and, in part, by regulating the activity of dopamine in other brain areas. But, contradictorily, high doses of estradiol actually inhibit the dopamine system. In the early days of birth control pills, when high doses of estrogen were

used as contraceptives, they exacerbated the symptoms of Parkinson's disease in women with the disorder by inhibiting the action of dopamine. (Parkinson's is a disorder that involves a loss of dopamine function in controlling movements.)

Only later, when estrogen levels in contraceptives were drastically reduced, did it become clear that normal levels of estrogen aided, not inhibited, functioning of the dopamine system.

Currently, scientists have evidence that estradiol, which is produced by the ovaries and also made from testosterone in both male and female brains, stimulates the dopamine system more readily in females than in males, but the inhibitory effects of high doses of estradiol are seen in both sexes.

Scientists also know that the masculine characteristics of the developing brain crucially depend on estradiol. The male brain can convert testosterone to estradiol in both early life and adulthood. In the developing brain, estradiol derived from testosterone leads to marked variations between the sexes in the neurotransmitters and hormones released by the hypothalamus, as well as their receptors. For example, the hypothalamus secretes dopamine into the pituitary gland to trigger the production of the hormone prolactin. This hormone stimulates the release of milk in nursing mothers and may contribute to the calming effects that breastfeeding has on mother and child. Males produce some prolactin, as well, and studies in rats suggest that injections of the hormone can relieve anxiety. Much to the disappointment of tired mothers, though, prolactin does not result in breastfeeding

capabilities in males. Estradiol is also a powerful growth factor that nourishes neurons in the fetal and newborn brain, influencing cell survival and migration and helping neurons to form the points of connection known as synapses. In the adult brain, estrogen encourages the birth of new neurons, a process called neurogenesis, and protects against the destructive effects of stroke, heart disease, and Alzheimer's disease. Yet, estradiol is also capable of promoting cancerous growth in the reproductive organs and increasing the risk of strokes. We still have much to learn about the safest doses and means of delivering estradiol so as to maximize benefits and minimize risks.

But, here again, the sex hormones are not the only chemical players involved. In the developing rat brain, estradiol works through one of the prostaglandins to produce male-type behaviors. (Prostaglandins are hormone-like substances better known for their role in inflammation and pain sensitivity.) Essentially, this prostaglandin normally works with testosterone to tell the brain to "be a man." When Stuart Amateau, M.D., Ph.D., and Margaret McCarthy of the University of Maryland treated newborn male mice with low doses of indomethacin (a prostaglandin blocker), the animals' brains were unable to respond to testosterone as adults, seriously impairing mating behavior. They also found that increasing the levels of prostaglandin in females resulted in a full range of male-type behaviors (with the obvious exception of ejaculation). Although Amateau and McCarthy's research suggests a link between prostaglandins and sexual differentiation, the researchers caution that

their conclusions may not apply in humans.

Another example of the many influences in how the developing brain differentiates depending on hormones came in March 2005.

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Emilie Rissman, Ph.D., of the University of Virginia Medical School and colleagues at the Swedish Karolinska Institute found that male mice bred without one of the lesser-understood estrogen receptors, ER beta, grew up behaving like normal males. However, the same mice, when given injections of estrogen, responded with female-type behaviors such as lordosis, a female posture indicating readiness to mate.

#### **HOW ESTROGEN PROTECTS THE BRAIN**

So far, we have discussed research on how genes, hormones, and body chemistry change the developing brain and asked what the changes might mean for behavior. Coming from the other direction, scientists also observe differences between males and females, then try to explain them by reference to differences in male and female brains and the role of sex hormones and other players. For instance, in humans and animals alike, females have less brain damage from stroke and other injuries than do males. This seems to be due to higher concentrations

of estrogens in the brain. A 1995 study that synthesized a variety of research results concluded that estrogen replacement therapy protected women against stroke, and animal studies show that estradiol, in particular, helps to contain stroke-induced brain damage from ischemia (oxygen deprivation).

Just how this protection works is not entirely clear, but some clues are emerging. One is an enzyme, aromatase, that converts testosterone to estradiol through a process known as aromatization. Besides testosterone from the testes, a hormone known as DHEA (dehydroepiandrosterone), produced by the adrenal glands, can be converted to testosterone and can also be aromatized. Because females make some testosterone as well as some DHEA, aromatase is important in females as well as in males. In 2003, Louise McCullough, Ph.D., of Johns Hopkins University and her coworkers found that, when female mice underwent an experimental form of stroke, the brain injury was greater in mice bred with the aromatase gene deleted (a process that creates what is called a “knockout”). But when another group of mice also lacking the aromatase gene received a compensating dose of estradiol, which they could not produce themselves, the ischemic damage was prevented.

This study yielded another insight worth mentioning. Normal female mice whose ovaries had been removed also showed less stroke-induced damage than the aromatase knockouts with or without ovaries. This finding suggests that estrogen from the ovaries is not the brain’s only source of estradiol. In early 2004, findings from the University of Tokyo yielded evidence for a



brain source of estradiol. Neurons, particularly those in the hippocampus, are equipped with a set of enzymes that can convert cholesterol (which occurs naturally in the brain) into estradiol. Working with hippocampal tissue from male rats, Suguru Kawato, Ph.D., and his colleagues mapped a relay by which cholesterol is ferried inside the neuronal membrane and converted to estradiol.

Along with the aromatase-knockout studies by McCullough, this evidence implies that the brain can make estradiol “on demand,” albeit in amounts too small to substitute for what the ovaries make or what may arise from DHEA or testosterone in the circulation. Nevertheless, these small amounts of estrogens may be the brain’s way of trying to protect itself from excitotoxicity, the process of neuronal cell death caused by overactivation of excitatory neurotransmitter receptors, such as NMDA (N-methyl-D-aspartate), which can occur during stroke. Interestingly, activation of NMDA receptors stimulates estrogen production. NMDA receptors become activated not only during normal neural activity but also when a stroke or a seizure occurs. This interaction may contribute to the added protection observed in female brains in stroke or injury.

### **ESTROGEN AND MEMORY**

Similar to estrogen’s role in neuroprotection, it was suspected that estrogen plays an important role in memory. As far back as the late 1970s, researchers in my laboratory (Bruce McEwen) and elsewhere began to think that estrogens might help protect and improve memory. Neuroendocrinologist Victoria Luine, Ph.D., and I administered estradiol to

rats whose ovaries had been removed. The treatment led to raised levels of acetylcholine (a neurotransmitter involved in attention and memory and which is depleted in patients with Alzheimer’s disease). Other investigators have linked increased acetylcholine production with improved attention and better memory. This link is backed by research in humans by Barbara Sherwin, Ph.D., at McGill University, who observed that women whose ovaries had been removed complained of deficits in their memory.

Sherwin and others have also shown that in healthy women estrogen enhances certain types of memory, including recall of information received verbally. In addition, estrogen treatment was shown to protect against Alzheimer’s disease. Victor Henderson, M.D., and Annlia Paganini-Hill, Ph.D., at the University of California, Los Angeles, studied more than 8,000 women and found that the risk of developing Alzheimer’s disease was sharply reduced in women who took estrogen replacement therapy during and after menopause. Richard Mayeux, M.D., of Columbia University found that elderly women taking estrogen after menopause were less likely to develop Alzheimer’s and women who showed signs of the disease did so at a much later age. A group of 450 women from the Baltimore Longitudinal Study of Aging showed a similar reduction in risk for those taking estrogen replacement therapy. Studies in the recent Women’s Health Initiative, however, showed that estrogen treatment may not be helpful, and can even be harmful, once the process of Alzheimer’s disease has begun. In addition, because estrogen can increase excitatory

activity in the brain, it is not a treatment option for women with epilepsy.

### **HOW ESTRADIOL OPERATES IN THE HIPPOCAMPUS**

The studies of estrogen and memory debunked the idea that estradiol regulates only reproductive processes, such as menstruation, pregnancy, and lactation. There was also a further implication. In regulating reproductive processes, estrogen acts mainly in the hypothalamus and pituitary. But those brain areas are not much involved with memory. Scientists reasoned that if estrogen also affects memory, they should look for evidence of estrogen actions in a part of the brain that does handle memory: the hippocampus. This sea horse-shaped structure is the principal hub of both memory and emotion; it is one of the brain's most adaptable, malleable, changeable areas, and, it turns out, estrogen helps provide those characteristics.

Because the hippocampus is the seat of spatial and navigational memory, animals that store food—squirrels, for example—have a larger hippocampus than would otherwise be expected. Imaging studies of humans who are skilled at complex spatial tasks show enlargement in this area, too. What is more, one of the first symptoms of Alzheimer's disease, which disrupts the circuitry in the hippocampus, is forgetting where one is or how to get home. Beyond spatial and navigational memory, the hippocampus is also responsible for declarative memory (for facts and figures) and contextual memory (where and when). Working in tandem with another brain area, the amygdala, the hippocampus helps seal emotionally

charged events into the brain. If you can recall exactly where you were when something charged with emotion occurred—the 9/11 terrorist attacks, for example—the hippocampus is producing the instant contextual recall. If the memory causes you to feel as shocked and sick as you did at the time of the event, you are feeling the effects of the amygdala.

In the search for estrogen's effects in the hippocampus, Catherine Woolley, Ph.D., in our Rockefeller University laboratory in the early 1990s, discovered an important link: Estradiol induced new synapses in the hippocampus, a process known as synaptic remodeling. She also noticed that a related hormone, progesterone, has the opposite effect, decreasing synapses in the post-ovulatory phase of the cycle. Other work has shown that memories that involve the hippocampus show an increase after exposure to estradiol and a decrease after progesterone. Moreover, Woolley demonstrated that estradiol specifically increases the number of synapses on the "terminals" known as dendritic spines. Estradiol has a powerful influence on dendritic spine density. During the five-day estrous cycle of the rat, for example, spine density can fluctuate by as much as one-third; the greatest density occurs when estrogen levels are highest, just before estrus. Under normal conditions, females in this high estrogen phase learn conditioned responses faster than they do in other phases of the estrous cycle. Dendritic spines are the points of contact among many excitatory cells in the brain, especially in the hippocampus and cerebral cortex, where one cell may form as many as 20,000 synapses with others. Because the

spines enable cells to link after a stimulus from the environment, creating new spines and modifying spine function may be one mechanism through which memories are formed.

### **A SURPRISE ABOUT HOW ESTROGEN WORKS**

Now that scientists had established that estrogen influences the number of spine synapses in response to stimuli such as stress, their next logical question was, how? The thinking was that hormones act by docking into their respective receptors in the cell nucleus, thereby triggering the expression of various genes, such as those that make the uterus grow. Unfortunately, that model failed to explain the effects of estrogen on dendritic spines in the hippocampus. The main stumbling block was that, although research since the early 1980s had shown that the effects of estrogen on the hippocampus are as impressive as on other parts of the brain known to be rich in estrogen receptors located in the cell nucleus (parts of the hypothalamus, for example), the hippocampus, viewed by the light microscope, contained almost no estrogen receptors. Or so everyone thought.

But it turned out that scientists were looking in the wrong place in the hippocampus as well as in the dopamine producing regions of the brain. They assumed that estrogen receptors, like all steroid hormone receptors, would be found in brain cell nuclei. But studies in the late 1990s showed estrogen receptors in other parts of the cell. The receptors were visible by light microscope in cultured cells, but the observations were not really believable until confirmed by

much more powerful electron microscopy. The impetus to this intensified search came from discoveries of investigators working with cancer cells that showed rapid effects, clearly not of genes, that were mediated by the same type of estrogen receptors that are found in cell nuclei. This was puzzling enough to challenge the dogma of cell-nuclear receptors that had a stranglehold on the field. In 2001, a team led by Teresa Milner, Ph.D., of Cornell University and me (Bruce McEwen), along with Stephen Alves, Ph.D., in my laboratory, used antibodies that fastened onto estrogen receptors, coupled with electron microscopy, to find that estrogen receptors do indeed exist in hippocampal neurons at many sites outside the nucleus, including axons and dendrites. Now, at last, we had the beginnings of an explanation for the response of hippocampal neurons, which apparently lacked nuclear estrogen receptors, to estradiol and the ability to generate new synaptic connections. We now have reason to believe that estrogen acts locally, at receptors at the outposts of the neuron, without having to go back to the command center in the nucleus. Indeed, the local control of synapses, including the synthesis of proteins at synapses directed by local activity, is one of the features that may contribute to the formation of memories.

Although the hippocampus is deficient in the type of nuclear estrogen receptors found in the hypothalamus, pituitary, and reproductive organs, it does have estrogen receptors located in other parts of the nerve cell that act much more like the receptors for the chemical neurotransmitters that regulate the electrical activity within the brain.

What estradiol does is to orchestrate a collaboration between excitatory and inhibitory neurons in the hippocampus to increase the actual connections between nerve cells. Males, like females, have at least some of these so-called non-nuclear estrogen receptors, but they do not show spine synapse formation in the hippocampus unless the actions of testosterone on the brain are blocked at birth.

### **THE HIPPOCAMPUS FUNCTIONS DIFFERENTLY IN MALES AND FEMALES**

We have talked a good deal about the hippocampus and how estrogen may affect its role in memory, but all discussion has related to females. Does this mean that in this brain area males are at a disadvantage because of the more prominent role of testosterone in their brains? It turns out that males also show synaptic remodeling, which does not appear to be simply the result of the conversion of testosterone to estradiol in the brain. Research by Csaba Leranth, M.D., Ph.D., at Yale University, and Neil MacLusky, Ph.D., at Guelph University in Canada, suggests that testosterone itself is pivotal. In fact, the hippocampus of a mature male rat appears to be unable to respond to estradiol. Yet, in males, testosterone appears just as capable as estradiol in females to directly induce spine synapses to form.

Another sex-dependent variation observed in the hippocampus relates to activation of the flight-or-fight response. Emotionally charged experiences are more readily remembered. To make it more likely that a person will remember a dangerous situation and so avoid that danger in

the future, the hippocampus is full of receptors for the stress hormone cortisol. Although this holds true for both male and female brains, the effects of acute stress are different—and sometimes opposite—for males and females, particularly during learning tasks. After the stress of a mild shock to the tail, male rats being trained to associate an eye blink with a tone predicting a puff of air perform better, whereas when females undergo the same stress, performance is impaired. Other studies link the enhanced performance in males to testosterone, whereas the impairment in females seems to be related to impaired action of estradiol.

In an elegant 2001 study, Tracey Shors, Ph.D., and her colleagues at Rutgers University connected memory, stress, spine density, and estrogen. Working with rats, the team showed that after the stress of a mild shock to the tail, dendritic spine density in the hippocampus was enhanced in males but reduced in females. The decrease in the females did not occur immediately after the stressor but did so within 24 hours. However, this decrease was only observed at the time of proestrus, the period immediately before the time when the female is most receptive to mating. This finding seems to suggest that females are especially sensitive to stressful experiences when estrogen levels are high. It should be noted that proestrus, a period when the female is “in heat,” occurs in most mammals, but not in humans. Still, examined along with previous research, the finding positively links memory formation to the density of dendritic spines in the hippocampus—and,

in females, implicates estrogen in the way these spines respond to stress.

As noted before, the research by Leranth and MacLusky at Yale University showed that, in the male rat hippocampus, androgens, such as testosterone, can also cause dendritic spine density formation, and that they do so directly without being aromatized into estradiol. In a study published in the journal *Neuroscience* in 2005, Milner and I and colleagues at Merck Research Laboratories found that androgen receptors, too, are located in extranuclear, as well as certain cell nuclear, sites in hippocampal neurons, suggesting that the changes brought about by estradiol and testosterone are similar but not identical. As we have already noted, the male hippocampus does not respond to estradiol by making new synapses unless the developmental actions of testosterone are blocked at birth, in which case it will show estrogen-induced synapse formation. Yet, male response to testosterone and

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testosterone secretion is increased in male rats undergoing acute shock stress.

In the studies by Tracey Shors discussed earlier, the ability of acute stress to increase spine synapses in the hippocampus may well

be the result of the surge of testosterone brought about in response to the stressor. Yet female rats show impairment of synapse formation when subjected to the same type of shock stress. It is important to note, though, that a temporary decrease in dendritic spines and memory does not necessarily mean that the brain is being damaged. In fact, the decrease may be a protective response, putting spine production on hold until the stress has passed—making females more resilient in the long term even if the short-term effects on memory are deleterious. This notion further emphasizes the fundamentally different organization of the stress response system of the hippocampus in male and female rats.

#### **HOW MIGHT THIS APPLY TO MEN AND WOMEN?**

It is difficult to extrapolate from biochemical and animal findings to human behavior. The work by Shors and others, for example, clearly suggests that males and females respond differently to stress, as measured by effects on memory. Because men respond better to stress, as measured by effects on memory. So it is almost irresistible to conclude that, at least in this area, men really are from Mars and women are from Venus. On a more realistic note, the idea that different responses are developmentally programmed and also influenced by hormones in adult life may help us understand why women suffer more depression, while men suffer more substance abuse and antisocial behavior. The research also helps explain the well-documented finding that women are likely to take much harder the struggles associated

with advancement in academia and industry—more likely to do something else rather than “try and try again.” One can argue that a woman’s perspective includes other things in life that are as important as the job; one can also argue that women are less able to handle stressors, as are the female rats.

Other theories of maleness and femaleness extend the notion of how broadly sex differences impact on the brain. Writing in the *New York Times* (“The Male Condition,” August 8, 2005), Simon Baron-Cohen, Ph.D., of Cambridge University noted that women are geared more toward empathizing—recognizing what other people are feeling or thinking and then responding to those feelings with an appropriate emotion. Men, he noted, go for systemizing—identifying the laws that govern how a system works, with the intention of controlling or predicting its behavior. In a provocative conclusion, Baron-Cohen, author of *The Essential Difference: The Truth About the Male and Female Brain*, cited the recent “Extreme Male Theory” of autism: that the disorder is essentially an exaggerated form of maleness, with an intense drive to systemize and an inability to empathize.

Shelley Taylor of the University of California, Los Angeles, reflects some of this same viewpoint in her book *The Tending Instinct*, in which she calls attention to the ability of females of many species to “tend and befriend,” instead of “fight or flight,” when confronted with dangers that are unpleasant but not life-threatening. The notion that women tend to nurture others more than do men may be explained by hormones other than estrogen. Oxytocin,

for example, is released in the female brain by childbearing, breastfeeding, cuddling, touching, and massage. It is also released in the brains of males involved in some of these activities. Kerstin Uvnas-Moberg, Ph.D., of the Karolinska Institute calls oxytocin the “calm and connection” hormone. She believes this system is fully as powerful as the fight-or-flight response. Some animal research supports the oxytocin story. Oxytocin and its counterpart, vasopressin, bring about widely different behaviors in the gentle, monogamous prairie vole, like long-term pair-bonding, compared with the aggressive and promiscuous montane vole. Furthermore, in lactating female rats with pups, oxytocin receptors induced by estradiol are responsible for the nurturing maternal care that determines the temperament of her offspring, according to work by Francis Champagne, Ph.D., and Michael Meaney, Ph.D., of McGill University.

The mothering properties of oxytocin appear to be intrinsic. Female rats that have never given birth show no interest in newborns and, when presented with foster pups, will ignore or even eat them. But scientists at the University of North Carolina showed in 1979 that oxytocin administered directly into the brains of these “bachelorette” rats can bring about maternal behavior, such as nest-building, licking, and protecting foster pups, within an hour. The rats’ ovaries had been removed, showing once again that there is more to the picture than estrogen; however, for the oxytocin treatment to work, the animals had to be “primed” with estrogen. These are important clues for a story that is yet to be elucidated. Indeed,

aside from the vole story and the mother rat, scientists are largely ignorant of the underlying neurobiology.

### THINKING AGAIN ABOUT THE BIG PICTURE

We return to where we began. Much research to date suggests that male and female brains operate in different ways and respond differently to the environment, but it is too soon to extrapolate much from the biochemical and animal findings to human behavior. So, yes, the state of the evidence means that President Summers's comments were controversial, largely an hypothesis. But the evidence already at hand is by no means irrelevant to the issue of what may be affecting the respective roles, choices, and achievements of men and women in various careers.

Unraveling the route the developing brain takes during sexual differentiation, and the roles of our genes, sex hormones, and other chemical actors in brain regions not previously thought to be sensitive to these factors, may eventually clarify how men and women differ in some intrinsic intellectual abilities, whether or not those differences will have any bearing on the success of a career. Beyond the intellectual, however, a more accurate understanding of how differences between the sexes are programmed during development, and influenced by sex hormones in adult life, may illuminate why women experience more depression and men have more substance abuse and antisocial behavior.

Indeed, sex differences and the effects of sex hormones are so widespread in the mammalian brain that, although much remains to be confirmed through research,

all domains of neural function are likely to somehow be affected. Scientists' best guess, at this time, is that men and women often can achieve the same results by using different strategies, suited to their respective abilities, that are very much based in individual differences but also show the impact of the sex differences we have described.

Such differences, of course, always harbor the potential to create misunderstanding, even conflict. For now, we must be satisfied that, although we have far to go to understand the detailed neurobiology associated with our own human behaviors, we already have more than enough new information and insight to begin reevaluating our stereotypes of the sexes, sex differences, and the ever-elusive notion of equality of the sexes. ■