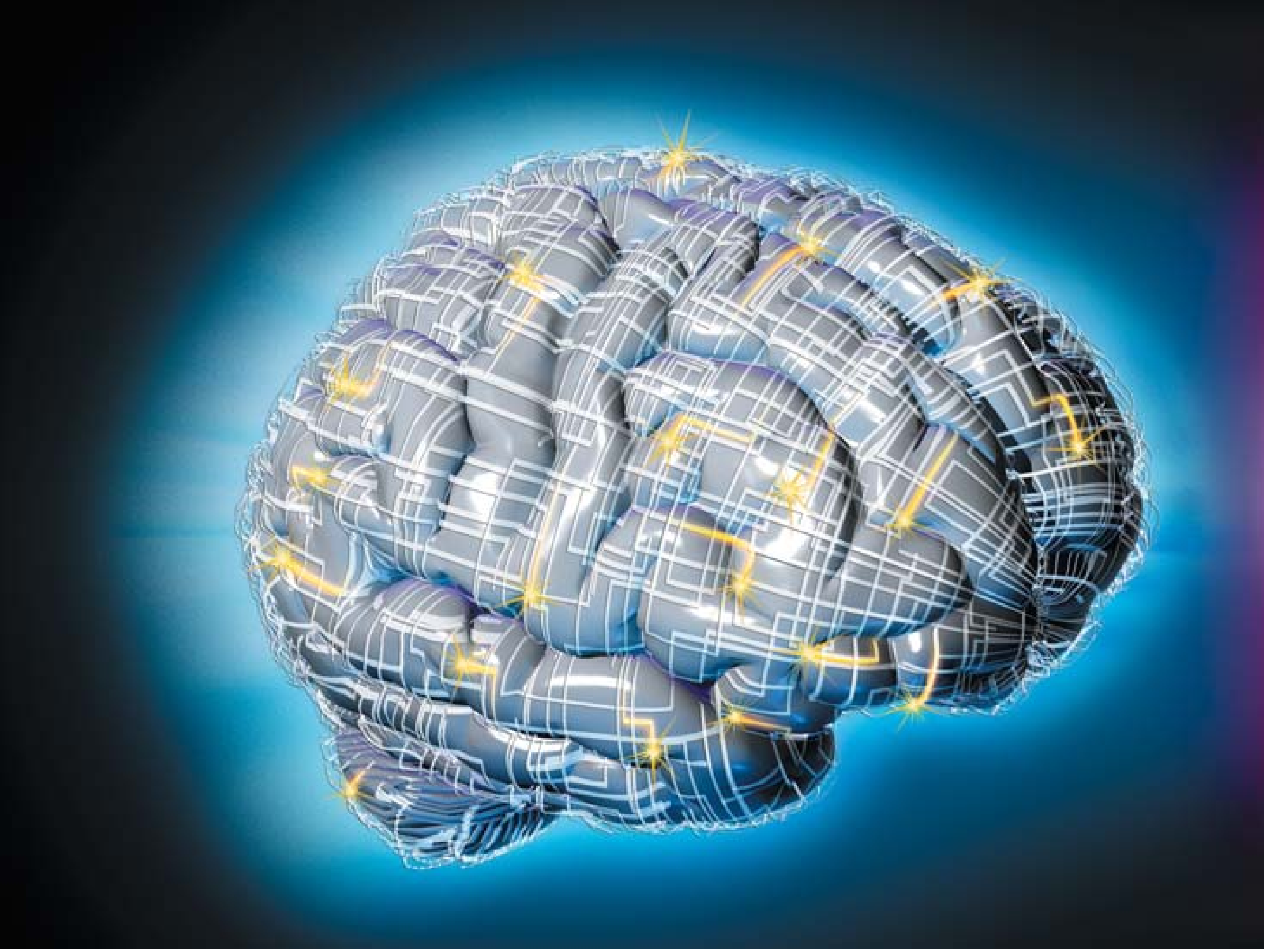


HIS BRAIN,

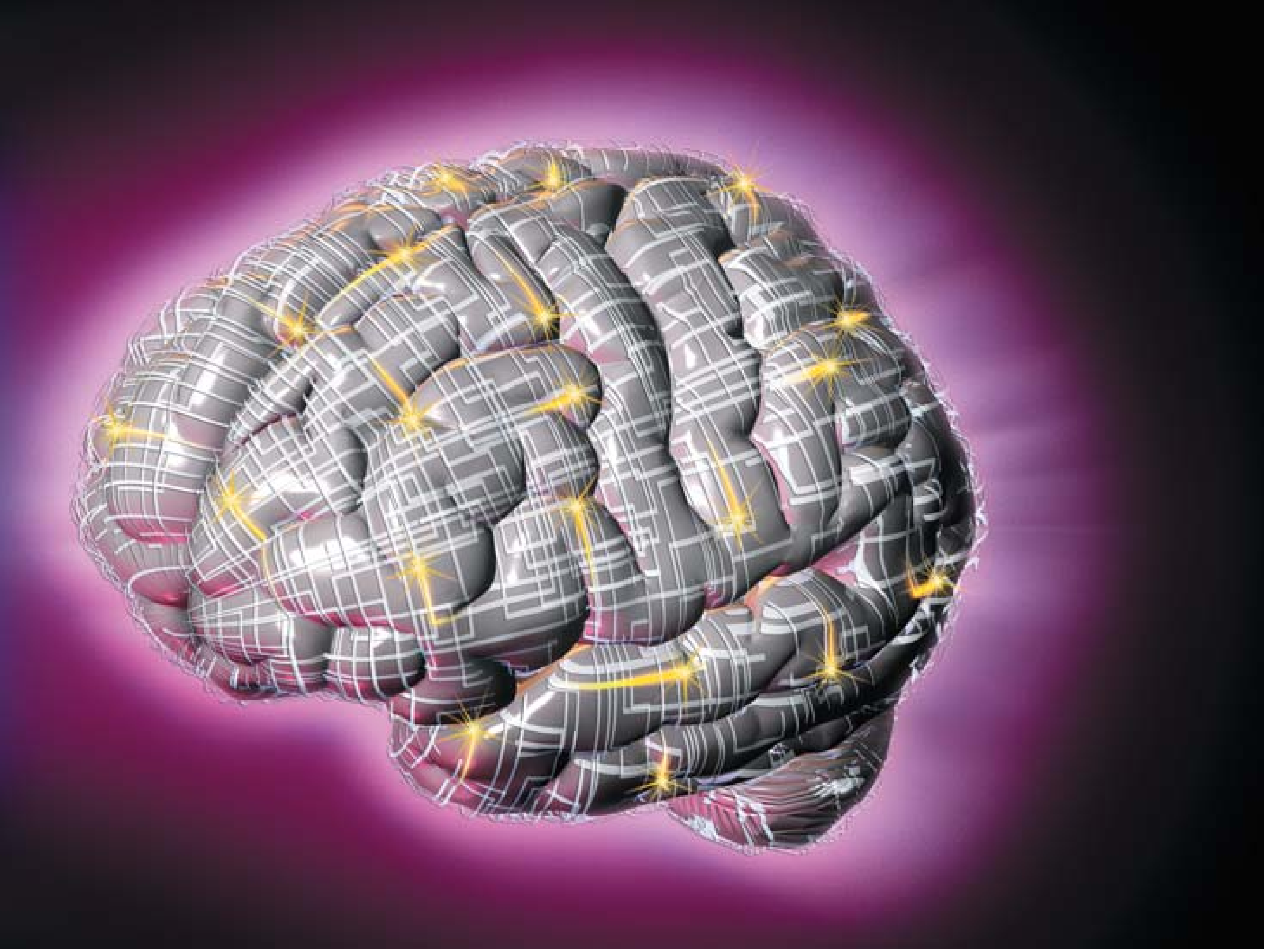
It turns out that male and female brains differ quite a bit in architecture and activity. Research into these variations could lead to sex-specific treatments for disorders such as depression and schizophrenia

BY LARRY CAHILL

On a gray day in mid-January, Lawrence Summers, the president of Harvard University, suggested that innate differences in the build of the male and female brain might be one factor underlying the relative scarcity of women in science. His remarks reignited a debate that has been smoldering for a century, ever since some scientists sizing up the brains of both sexes began using their main finding—that female brains tend to be smaller—to bolster the view that women are intellectually inferior to men.

To date, no one has uncovered any evidence that anatomical disparities might render women incapable of achieving academic distinction in math, physics or engineering [*see box*

SLIM FILMS



HER BRAIN

on page 47]. And the brains of men and women have been shown to be quite clearly similar in many ways. Nevertheless, over the past decade investigators have documented an astonishing array of structural, chemical and functional variations in the brains of males and females.

These inequities are not just interesting idiosyncrasies that might explain why more men than women enjoy the Three Stooges. They raise the possibility that we might need to develop sex-specific treatments for a host of conditions, including depression, addiction, schizophrenia and post-traumatic stress disorder (PTSD). Furthermore, the differences imply that researchers exploring the structure and function of the brain must take into account the sex of their subjects when analyzing their data—and include both women and men in future studies or risk obtaining misleading results.

Sculpting the Brain

NOT SO LONG AGO neuroscientists believed that sex differences in the brain were limited mainly to those regions responsible for mating behavior. In a 1966 *Scientific American* article entitled "Sex Differences in the Brain," Seymour Levine of Stanford University described how sex hormones help to direct divergent reproductive behaviors in rats—with males engaging in mounting and females arching their backs and raising their rumps to attract suitors. Levine mentioned only one brain region in his review: the hypothalamus, a small structure at the base of the brain that is involved in regulating hormone production and controlling basic behaviors such as eating, drinking and sex. A generation of neuroscientists came to maturity believing that "sex differences in the brain" referred primarily to mating behaviors, sex hormones and the hypothalamus.

Several intriguing behavioral studies add to the evidence that some sex differences in the brain arise before a baby draws its first breath.

That view, however, has now been knocked aside by a surge of findings that highlight the influence of sex on many areas of cognition and behavior, including memory, emotion, vision, hearing, the processing of faces and the brain's response to stress hormones. This progress has been accelerated in the past five to 10 years by the growing use of sophisticated noninvasive imaging techniques such as positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI), which can peer into the brains of living subjects.

These imaging experiments reveal that anatomical variations occur in an assortment of regions throughout the brain. Jill M. Goldstein of Harvard Medical School and her colleagues, for example, used MRI to measure the sizes of many cortical and subcortical areas. Among other things, these investigators found that parts of the frontal cortex, the seat of many higher cognitive functions, are bulkier in women than in men, as are parts of the limbic cortex, which is involved in emotional responses. In men, on the other hand, parts of the parietal cortex, which is involved in space perception, are bigger than in women, as is the amygdala, an almond-shaped structure that responds to emotionally arousing information—to anything that gets the heart pumping and the adrenaline flowing. These size differences, as well as others mentioned throughout the article, are relative: they refer to the overall volume of the structure relative to the overall volume of the brain.

Differences in the size of brain structures are generally thought to reflect their relative importance to the animal. For example, primates rely more on vision than olfaction; for rats, the opposite is true. As a result, primate brains maintain proportionately larger regions devoted to vision, and rats devote more space to olfaction. So the existence of widespread anatomical disparities between men and women suggests that sex does influence the way the brain works.

Other investigations are finding anatomical sex differences at the cellular level. For example, Sandra Witelson and her colleagues at McMaster University discovered that women possess a greater density of neurons in parts of the temporal lobe cortex associated with language processing and comprehension. On counting the neurons in postmortem samples, the researchers found that of the six layers present in the cortex, two show more neurons per unit volume in females than in males. Similar findings were subsequently reported for the frontal lobe. With such information in hand, neuroscientists can now explore whether sex differences in neuron number correlate with differences in cognitive abilities—examining, for example, whether the boost in density in the female auditory cortex relates to women's enhanced performance on tests of verbal fluency.

Such anatomical diversity may be caused in large part by the activity of the sex hormones that bathe the fetal brain. These steroids help to direct the organization and wiring of the brain during development and influence the structure and neuronal density of various regions. Interestingly, the brain areas that Goldstein found to differ between men and women are ones that in animals contain the highest number of sex hormone receptors during development. This correlation between brain region size in adults and sex steroid action in utero suggests that at least some sex differences in cognitive function do not result from cultural influences or the hormonal changes associated with puberty—they are there from birth.

Inborn Inclinations

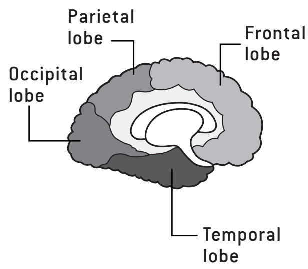
SEVERAL INTRIGUING behavioral studies add to the evidence that some sex differences in the brain arise before a baby draws its first breath. Through the years, many researchers have demonstrated that when selecting toys, young boys and girls part ways. Boys tend to gravitate toward balls or toy cars, whereas girls more typically reach for a doll. But no one could really say whether those preferences are dictated

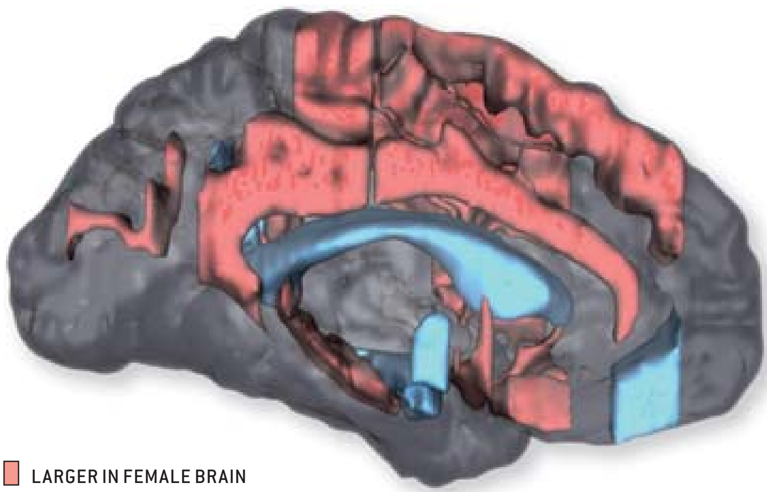
Overview/*Brains*

- Neuroscientists are uncovering anatomical, chemical and functional differences between the brains of men and women.
- These variations occur throughout the brain, in regions involved in language, memory, emotion, vision, hearing and navigation.
- Researchers are working to determine how these sex-based variations relate to differences in male and female cognition and behavior. Their discoveries could point the way to sex-specific therapies for men and women with neurological conditions such as schizophrenia, depression, addiction and post-traumatic stress disorder.

SIZABLE BRAIN VARIATION

Anatomical differences occur in every lobe of male and female brains. For instance, when Jill M. Goldstein of Harvard Medical School and her co-workers measured the volume of selected areas of the cortex relative to the overall volume of the cerebrum, they found that many regions are proportionally larger in females than in males but that other areas are larger in males (*below*). Whether the anatomical divergence results in differences in cognitive ability is unknown.





SOURCE: JILL M. GOLDSTEIN *Harvard Medical School and Brigham and Women's Hospital, Connors Center for Women's Health and Gender Biology;* BASED ON JILL M. GOLDSTEIN ET AL. IN *CEREBRAL CORTEX,* VOL. 11, NO. 6, PAGES 490–497; JUNE 2001

by culture or by innate brain biology.

To address this question, Melissa Hines of City University London and Gerianne M. Alexander of Texas A&M University turned to monkeys, one of our closest animal cousins. The researchers presented a group of vervet monkeys with a selection of toys, including rag dolls, trucks and some gender-neutral items such as picture books. They found that male monkeys spent more time playing with the "masculine" toys than their female counterparts did, and female monkeys spent more time interacting with the playthings typically preferred by girls. Both sexes spent equal time monkeying with the picture books and other gender-neutral toys.

Because vervet monkeys are unlikely to be swayed by the social pressures of human culture, the results imply that toy preferences in children result at least in part from innate biological differences. This divergence, and indeed all the anatomical sex differences in the brain, presumably arose as a result of selective pressures during evolution. In the case of the toy study, males—both human and primate—prefer toys that can be propelled through space and that promote rough-and-tumble play. These qualities, it seems reasonable to speculate, might relate to the behaviors useful for hunting and for securing a mate. Similarly, one might also hypothesize that females, on the other hand, select toys that allow them to hone the skills they will one day need to nurture their young.

Simon Baron-Cohen and his associates at the University of Cambridge took a different but equally creative approach to addressing the influence of nature versus nurture regarding sex differences. Many researchers have described disparities in how "people-centered" male and female infants are. For example, Baron-Cohen and his student Svetlana Lutchmaya found that one-year-old girls spend more time looking at their mothers than boys of the same age do. And when these babies are presented with a choice of films to watch, the girls look longer at a film of a face, whereas boys lean toward a film featuring cars.

Of course, these preferences might be attributable to differences in the way adults handle or play with boys and girls. To eliminate this possibility, Baron-Cohen and his students went a step further. They took their video camera to a maternity ward to examine the preferences of babies that were only one day old. The infants saw either the friendly face of a live female student or a mobile that matched the color, size and shape of the student's face and included a scrambled mix of her facial features. To avoid any bias, the experimenters were unaware of each baby's sex during testing. When they watched the tapes, they found that the girls spent more time looking at the student, whereas the boys spent more time looking at the mechanical object. This difference in social interest was evident on day one of life—implying again that we come out of the womb with some cognitive sex differences built in.

Under Stress

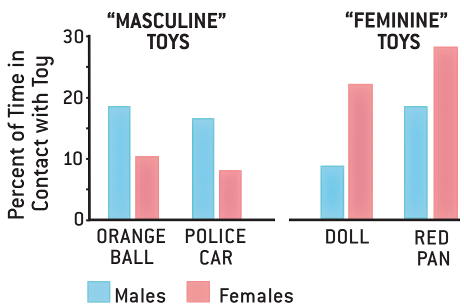
IN MANY CASES, sex differences in the brain's chemistry and construction influence how males and females respond to the environment or react to, and remember, stressful events. Take, for example, the amygdala. Goldstein and others have reported that the amygdala is larger in men than in women. And in rats, the neurons in this region make more numerous interconnections in males than in females. These anatomical variations would be expected to pro-

THE AUTHOR

LARRY CAHILL received his Ph.D. in neuroscience in 1990 from the University of California, Irvine. After spending two years in Germany using imaging techniques to explore learning and memory in gerbils, he returned to U.C. Irvine, where he is now an associate professor in the department of neurobiology and behavior and a Fellow of the Center for the Neurobiology of Learning and Memory.

WIRED PREFERENCES?

Vervet monkeys observed by Gerianne M. Alexander of Texas A&M University and Melissa Hines of City University London displayed toy preferences that fit the stereotypes of human boys and girls: the males (*top photograph*) spent more time in contact with trucks, for example, whereas the females (*bottom photograph*) engaged more with dolls (*graphs*). Such patterns imply that the choices made by human children may stem in part from their neural wiring and not strictly from their upbringing.



duce differences in the way that males and females react to stress.

To assess whether male and female amygdalae in fact respond differently to stress, Katharina Braun and her co-workers at Otto von Guericke University in Magdeburg, Germany, briefly removed a litter of Degu pups from their mother. For these social South American rodents, which live in large colonies like prairie dogs do, even temporary separation can be quite upsetting. The researchers then measured the concentration of serotonin receptors in various brain regions. Serotonin is a neurotransmitter, or signal-carrying molecule, that is key for mediating emotional behavior. (Prozac, for example, acts by increasing serotonin function.)

The workers allowed the pups to hear their mother's call during the period of separation and found that this auditory input increased the serotonin receptor concentration in the males' amygdala, yet decreased the concentration of these same receptors in females. Although it is difficult to extrapolate from this study to human behavior, the results hint that if something similar occurs in children, separation anxiety might differentially affect the emotional well-being of male and female infants. Experiments such as these are necessary if we are to understand why, for instance, anxiety disorders are far more prevalent in girls than in boys.

Another brain region now known to diverge in the sexes anatomically and in its response to stress is the hippocampus, a structure crucial for memory storage and for spatial mapping of the physical environment. Imaging consistently demonstrates that the hippocampus is larger in women than in men. These anatomical differences might well relate somehow to differences in the way males and females navigate. Many studies suggest that men are more likely to navigate by estimating distance in space and orientation ("dead reckoning"), whereas women are more likely to navigate by monitoring landmarks. Interestingly, a similar sex difference exists in rats. Male rats are more likely to navigate mazes using directional and positional information, whereas female rats are more likely to navigate the same mazes using available landmarks. (Investigators have yet to demonstrate, however, that male rats are less likely to ask for directions.)

Even the neurons in the hippocampus behave differently in males and females, at least in how they react to learning experiences. For example, Janice M. Juraska and her associates at the University of Illinois have shown that placing rats in an "enriched environment"—cages filled with toys and with fellow rodents to promote social interactions—produced dissimilar effects on the structure of hippocampal neurons in male and female rats. In females, the experience enhanced the "bushiness" of the branches in the cells' dendritic trees—the many-armed structures that receive signals from other nerve cells. This change presumably reflects an increase in neuronal connections, which in turn is thought to be involved with the laying down of memories. In males, however, the complex environment either had no effect on the dendritic trees or pruned them slightly.

But male rats sometimes learn better in the face of stress. Tracey J. Shors of Rutgers University and her collaborators have found that a brief exposure to a series of one-second tail shocks enhanced performance of a learned task and increased the density of dendritic connections to other neurons in male rats yet impaired performance and decreased connection density in female rats. Findings such as these have interesting social implications. The more we discover about how brain mechanisms of learning differ between the sexes, the more we may need to consider how optimal learning environments potentially differ for boys and girls.

Although the hippocampus of the female rat can show a decrement in response to acute stress, it appears to be more resilient than its male counterpart in the face of chronic stress. Cheryl D. Conrad and her co-workers at Arizona State University restrained rats in a mesh cage for six hours—a situation that the rodents find disturbing. The researchers then assessed how vulnerable their hippocampal neurons were to killing by a neurotoxin—a standard measure of the effect of stress on these cells. They noted that chronic restraint rendered the males' hippocampal cells more susceptible to the toxin but had no effect on the

SOURCE: GERIANNE M. ALEXANDER AND MELISSA HINES IN *EVOLUTION AND HUMAN BEHAVIOR*, VOL. 23, NO. 6, PAGES 467–479; NOVEMBER 2002. USED WITH PERMISSION FROM ELSEVIER females' vulnerability. These findings, and others like them, suggest that in terms of brain damage, females may be better equipped to tolerate chronic stress than males are. Still unclear is what protects female hippocampal cells from the damaging effects of chronic stress, but sex hormones very likely play a role.

The Big Picture

EXTENDING THE WORK on how the brain handles and remembers stressful events, my colleagues and I have found contrasts in the way men and women lay down memories of emotionally arousing incidents—a process known from animal research to involve activation of the amygdala. In one of our first experiments with human subjects, we showed volunteers a series of graphically violent films while we measured their brain activity using PET. A few weeks later we gave them a quiz to see what they remembered.

We discovered that the number of disturbing films they could recall correlated with how active their amygdala had been during the viewing. Subsequent work from our laboratory and others confirmed this general finding. But then I noticed something strange. The amygdala activation in some studies involved only the right hemisphere, and in others it involved only the left hemisphere. It was then I realized that the experiments in which the right amygdala lit up involved only men; those in which the left amygdala was fired up involved women. Since then, three subsequent studies—two from our group and one from John Gabrieli and Turhan Canli and their collaborators at Stanford—have confirmed this difference in how the brains of men and women handle emotional memories.

The realization that male and female brains were processing the same emotionally arousing material into memory differently led us to wonder what this disparity might mean. To address this question, we turned to a century-old theory stating that the right hemisphere is biased toward processing the central aspects of a situation, whereas the left hemisphere tends to process the finer details. If that conception is true, we reasoned, a drug that dampens the activity of the amygdala should impair a man's ability to recall the gist of an emotional story (by hampering the right amygdala) but should hinder a woman's ability to come up with the precise details (by hampering the left amygdala).

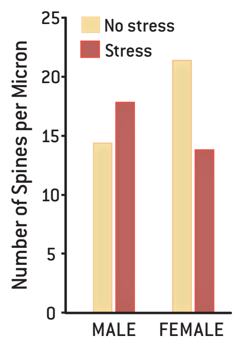
Propranolol is such a drug. This so-called beta blocker quiets the activity of adrenaline and its cousin noradrenaline and, in so doing, dampens the activation of the amygdala and weakens recall of emotionally arousing memories. We gave this drug to men and women before they viewed a short slide show about a young boy caught in a terrible accident while walking with his mother. One week later we tested their memory. The results showed that propranolol made it harder for men to remember the more holistic aspects, or gist, of the story—that the boy had been run over by a car, for example. In women, propranolol did the

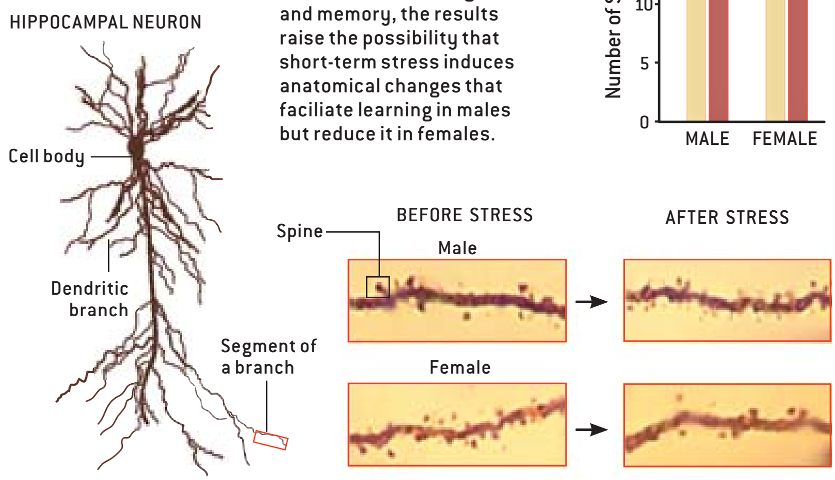
THE STRESSED HIPPOCAMPUS

The hippocampus in male rats reacts differently to both acute and chronic stress than does the same structure in females.

ACUTE STRESS

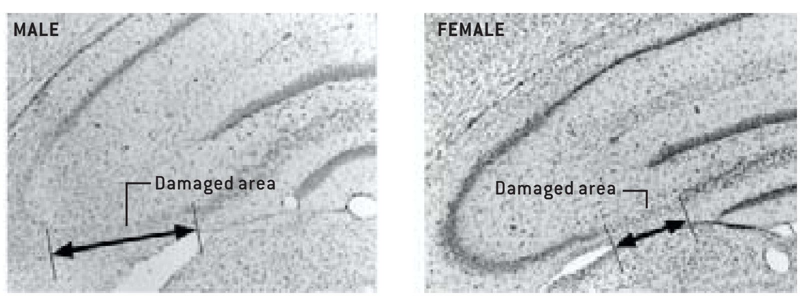
Short-term stress caused the density of dendritic "spines" in hippocampal neurons to increase in males but to decrease in females (*micrographs* and *graph*) studied by Tracey J. Shors of Rutgers University and her colleagues. The spines are the sites where dendrites receive excitatory signals from other neurons. Because the hippocampus is involved in learning and memory, the results raise the possibility that short-term stress induces anatomical changes that faciliate learning in males but reduce it in females.





CHRONIC STRESS

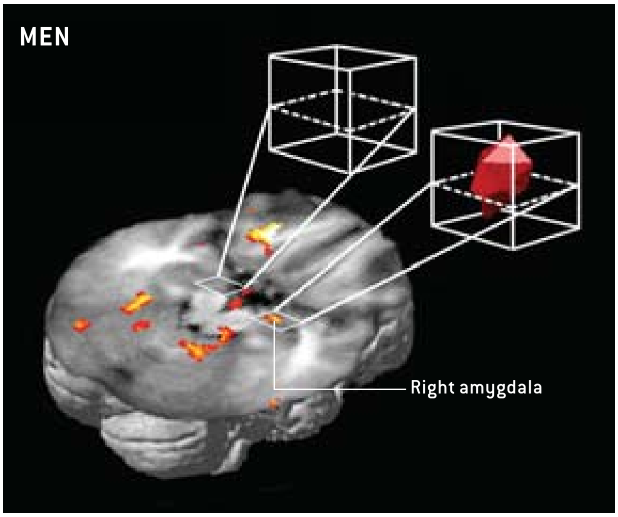
Long-lasting stress, in contrast, may leave the male hippocampus more vulnerable to harm. When Cheryl D. Conrad, J. L. Jackson and L. S. Wise of Arizona State University exposed chronically stressed rats to a nerve toxin, males, but not females, suffered more damage than same-sex controls did. The micrographs below are from stressed subjects.

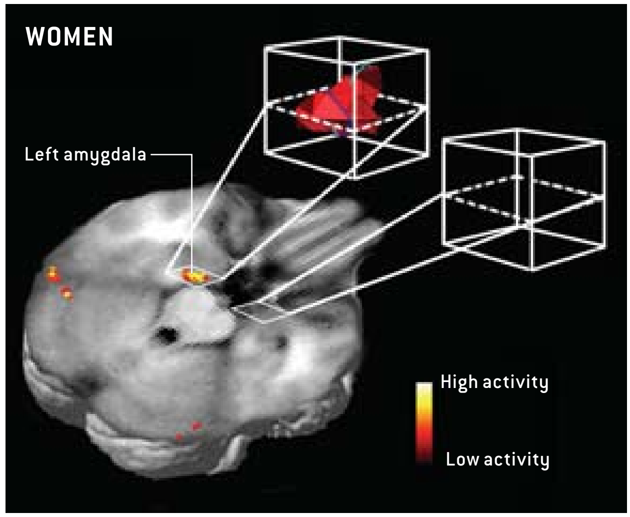


SOURCE: T. J. SHORS, J. FALDUTO AND B. LEUNER IN *EUROPEAN JOURNAL OF NEUROSCIENCE*, VOL. 19, PAGES 145–150; JANUARY 2004 (*top*);
SOURCE: CHERYL D. CONRAD *Arizona State University* (*bottom*)

THE AMYGDALA AND EMOTIONAL MEMORY

In research by the author and his collaborators, the amygdala, crucial for memory of emotional events, reacted differently in men and women who viewed emotionally arousing slides, such as of a decaying animal. Men who reported strong responses showed greatest activity in the right hemisphere amygdala (*left scan* and *schematic*) and the most accurate recall two weeks later, whereas the women who felt most worked up and showed the best recall displayed greatest activity in the left amygdala (*right panel*). Further studies by the team suggest that the hemispheric sex differences in amygdala activity cause women to be more likely to retain details of an emotional event and men more likely to remember its gist.





converse, impairing their memory for peripheral details—that the boy had been carrying a soccer ball.

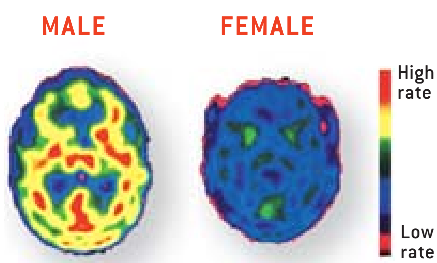
In more recent investigations, we found that we can detect a hemispheric difference between the sexes in response to emotional material almost immediately. Volunteers shown emotionally unpleasant photographs react within 300 milliseconds—a response that shows up as a spike on a recording of the brain's electrical activity. With Antonella Gasbarri and others at the University of L'Aquila in Italy, we have found that in men, this quick spike, termed a P300 response, is more exaggerated when recorded over the right hemisphere; in women, it is larger when recorded over the left. Hence, sex-related hemispheric disparities in how the brain processes emotional images begin within 300 milliseconds—long before people have had much, if any, chance to consciously interpret what they have seen.

These discoveries might have ramifications for the treatment of PTSD. Previous research by Gustav Schelling and his associates at Ludwig Maximilian University in Germany had established that drugs such as propranolol diminish memory for traumatic situations when administered as part of the usual therapies in an intensive care unit. Prompted by our findings, they found that, at least in such units, beta blockers reduce memory for traumatic events in women but not in men. Even in intensive care, then, physicians may need to consider the sex of their patients when meting out their medications.

Sex and Mental Disorders

PTSD IS NOT the only psychological disturbance that appears to play out differently in women and men. A PET study by Mirko Diksic and his colleagues at McGill University showed that serotonin production was a remarkable 52 percent higher on average in men than in women, which might help clarify why women are more prone to depression—a disorder commonly treated with drugs that boost the concentration of serotonin.

A similar situation might prevail in addiction. In this case, the neurotransmitter in question is dopamine—a chemical involved in the feelings of pleasure associated with drugs of abuse. Studying rats, Jill B. Becker and her fellow investigators at the University of Michigan at Ann Arbor discovered that in females, estrogen boosted the release of dopamine in brain regions important for regulating drug-seeking behavior. Furthermore, the hormone had long-lasting effects, making the female rats more likely to pursue cocaine weeks after last receiving the drug. Such differences in susceptibility—particularly to stimulants such as cocaine and amphetamine—could explain why women might be more vulner-



PET SCANS, such as those above made by Mirko Diksic and his colleagues at McGill University, reveal that the brains of males produce serotonin at a faster rate than those of females. Serotonin influences mood, so the finding may help make sense of the observation that more women than men suffer depression.

LARRY CAHILL ET AL. IN *LEARNING AND MEMORY*, VOL. 11, NO. 3; 2004. USED WITH PERMISSION (*top*); MIRKO DIKSIC *Montreal Neurological Institute, McGill University*, FROM *PNAS*, VOL. 94, PAGES 5308–5313, ©1997 NATIONAL ACADEMY OF SCIENCES USA (*bottom*) able to the effects of these drugs and why they tend to progress more rapidly from initial use to dependence than men do.

Certain brain abnormalities underlying schizophrenia appear to differ in men and women as well. Ruben Gur, Raquel Gur and their colleagues at the University of Pennsylvania have spent years investigating sex-related differences in brain anatomy and function. In one project, they measured the size of the orbitofrontal cortex, a region involved in regulating emotions, and compared it with the size of the amygdala, implicated more in producing emotional reactions. The investigators found that women possess a significantly larger orbitofrontal-to-amygdala ratio (OAR) than men do. One can speculate from these findings that women might on average prove more capable of controlling their emotional reactions.

In additional experiments, the researchers discovered that this balance appears to be altered in schizophrenia, though not identically for men and women. Women with schizophrenia have a decreased OAR relative to their healthy peers, as might be expected. But men, oddly, have an increased OAR relative to healthy men. These findings remain puzzling, but, at the least, they imply that schizophrenia is a somewhat different disease in men and women and that treatment of the disorder might need to be tailored to the sex of the patient.

A Gray Matter

Harvard University president Lawrence Summers struck a nerve in many people early this year when he raised the possibility that brain biology might help to explain why fewer women than men flourish in scientific careers. Nancy Hopkins, a biologist at the nearby Massachusetts Institute of Technology, was so offended by his musings that she walked out of the conference at which he was speaking.

What does the research say? Evidence linking inequities in anatomy to intellectual ability is hard to come by. For starters, sex differences in performance on standardized tests of general intelligence are negligible, with insignificant differences sometimes favoring women, sometimes favoring men. And although neuroscientists are discovering a multitude of sex-related differences in brain structure and function, no one can at present say whether these differences have any influence on career success in science—or, if they do, how their effect might compare with that of cultural factors.

LAWRENCE SUMMERS met a news crew this past February as he headed to a Harvard faculty meeting.

It is possible, however, that the brains of men and women might achieve their equivalent general intelligence in somewhat different ways. One recent study, for example, suggests that the sexes might use their brains differently when solving problems such as those found on intelligence tests. In this work, Richard Haier and his co-investigators at the University of California at Irvine and the University of New Mexico used a combination of MRI scanning and cognitive testing to develop maps that correlate gray-matter volume and white-matter volume in different parts of the brain with performance on IQ tests. Gray matter consists of the cell bodies of neurons that process information in the brain; white matter is made up of the axons through which one nerve cell relays information to another cell. The team found links between gray- or white-matter volume and test performance in both sexes, but the brain areas showing the correlations differed between men and women.

These findings have not yet been replicated. Even if they are, though, researchers will still have an unsolved question on their hands: What, if anything, might such differences have to do with how men and women reason? *—The Editors*

Sex Matters

IN A COMPREHENSIVE 2001 report on sex differences in human health, the prestigious National Academy of Sciences asserted that "sex matters. Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research."

Neuroscientists are still far from putting all the pieces together—identifying all the sex-related variations in the brain and pinpointing their influences on cognition and propensity for brain-related disorders. Nevertheless, the research conducted to date certainly demonstrates that differences extend far beyond the hypothalamus and mating behavior. Researchers and clinicians are not always clear on the best way to go forward in deciphering the full influences of sex on the brain, behavior and responses to medications. But growing numbers now agree that going back to assuming we can evaluate one sex and learn equally about both is no longer an option. SA

RICK FRIEDMAN *Corbis*

MORE TO EXPLORE

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