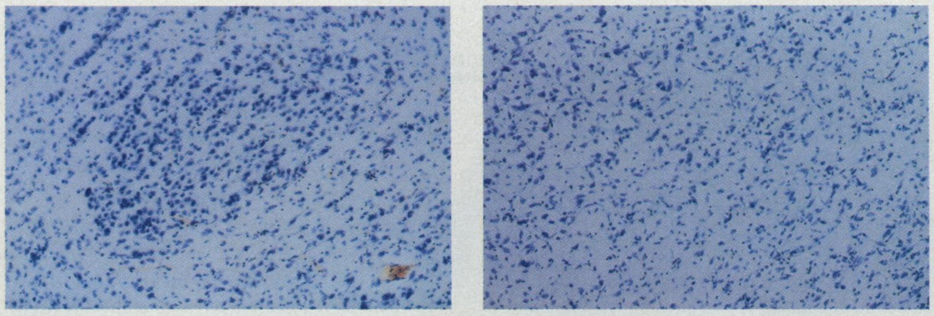


Missing cells. *Oval collection of cells in hypothalamus from heterosexual man* (left) *are absent in homosexual man* (right).

slices, but researchers argue about what is the most reliable measure of size—the volume measurements used by LeVay, or actual cell counts. There is also the nagging possibility that some unknown factors may influence the size of the structures, according to one of the major players in the field, Dick Swaab, a neuroscientist at the Netherlands Institute for Brain Research in Amsterdam.

Despite his words of caution, Swaab says he is glad to hear of LeVay's finding, because it builds on his own group's discovery, reported last year in *Brain Research*, of the first known structural difference between the brains of homosexual and heterosexual men. Swaab's team found that the suprachiasmatic nucleus (SCN), a part of the brain that governs daily rhythms, is twice as large in homosexual men as it is in the typical heterosexual brain.

But the suprachiasmatic nucleus is not known to play a role in sexual behavior, LeVay points out. So while it might be influenced by the same factors that cause homosexuality, it is less likely than the anterior hypothalamus to be part of the cause. Gorski postdoc Allen agrees that the anterior hypothalamus is "exactly where we would expect some nucleus that may control [sexual orientation] to be located."

But what factors might influence the development of this part of the brain? A possible answer comes from studies in rats, which also have a sexually dimorphic area in their anterior hypothalamus, larger in males than in females, that governs sexual behavior. In rats, the development of the area is dependent on testosterone levels before and immediately after birth. Male rat pups that are castrated at birth, reducing their testosterone levels, have a smaller sexually dimorphic nucleus than normal males, and when they grow up they show less male-type sexual behavior, such as mounting. Testosterone injections enlarge the nucleus in female pups. The resulting adults show more "male" sexual behavior.

Extending that kind of data to humans involves a huge step, but that's just the step some researchers are trying to take. Sandra J. Witelson and her colleagues at McMaster University have found lesbians to be twice as likely as heterosexual women to show left-hand preference on a variety of tasks; gay men also show such a tendency. Since studies of people with abnormal sex-hormone levels suggest that handedness is a brain feature that can be influenced by sex hormones during brain development, Witelson says her team's results suggest there "might be atypical brain organization" in homosexuals, also caused by atypical sex-hormone levels.

In a paper in the current issue of *Psychoneuroendocrinology* (v.16, p.131), Witelson proposes that the brain is a mosaic of areas that may respond to sex hormones at various times during early development. Typical female or male hormone levels would produce a typical female or male brain, she says. But unusual levels of sex hormones at any given time may switch the development of susceptible brain areas. "This could cause different areas in the same brain to undergo different sexual differentiation," says Witelson. Depending on levels and timing, sex-hormones could influence handedness, sexual orientation, or other characteristics.

Witelson emphasizes that her model is speculative, based on a rather eclectic assortment of data. But that model—and LeVay's finding—raises questions that offer a program for future research. Does INAH-3 have sex-hormone receptors, for example, indicating that it could be influenced by those hormones? And when during brain development does the difference between the sexes emerge?

No matter how such questions are answered, it may be difficult ever to establish that INAH-3 or any other brain structure actually causes homosexuality, or to rule out the possibility that childhood or adolescent experience may have altered the size of INAH-3 in homosexuals. But Witelson, for one, is not discouraged. "The important [point] is that several independent studies have shown that various brain structures are different between people of different sexual orientation," she says. And Swaab agrees with Witelson that this is what one would expect. The difference between homosexuals and heterosexuals, he quips, "should be in the brain, not in the heart."

■ MARCIA BARINAGA

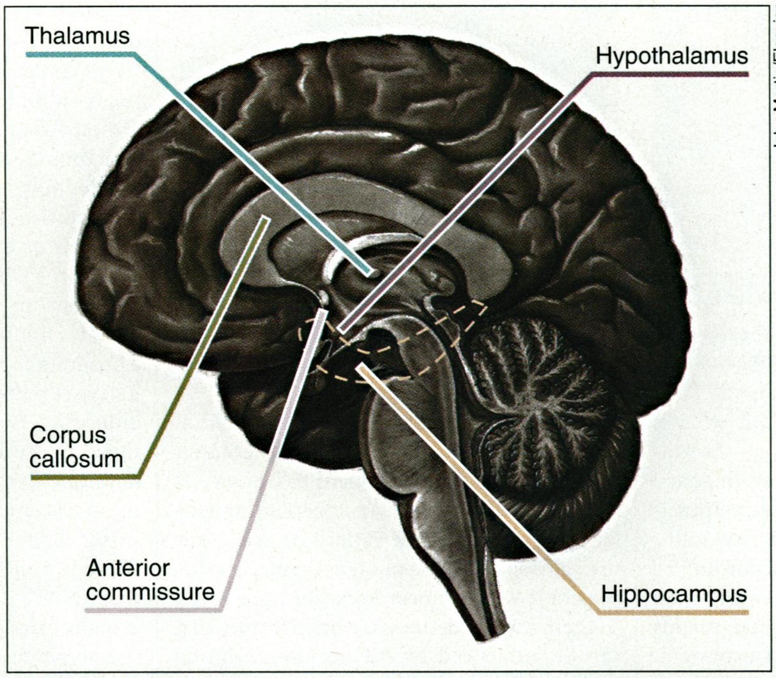
The Brain as "Sexual Organ"

When Oxford University anatomists Geoffrey Raisman and Pauline Field set out to study the differences between the brains of male and female rats in the late 1960s, most researchers were skeptical. The prevailing view was that male and female brains were alike. "People just didn't believe these significant structural differences existed," recalls Rockefeller University neuroscientist Bruce McEwen, who studies sex differences in rodent brains. But the pair forged ahead and, 20 years ago this month, published a study in *Science* that was the first to show conclusively a structural difference in the brains of male and female mammals: Male rats have fewer synapses connecting two parts of the hypothalamus than females do. McEwen says it's only since Raisman's and Field's study, which he calls "monumental," that researchers "have felt there could be structural sex differences in the brain."

Raisman and Field were quickly joined in these studies by an entire new generation of researchers who entered the field just in time to make use of high-tech tools that could show them the brain in minute detail. Electron microscopes gave a view of differences in autopsied brain structures the size of the period at the end of this sentence. Noninvasive imaging techniques, such as magnetic resonance imaging (MRI), helped show the interior of living heads for the first time. At the same time, rodent studies reached a new level of sophistication, allowing researchers to trace the way sex hormones work.

As a result of data gathered with these new tools during the 1970s and 1980s there is now a solid body of data indicating sex differences in the brains of almost every mammalian family examined so far: rodents, birds, monkeys, and—most recently and most intriguingly—human beings. "I see more and more studies involving different species and different parts of the brain," says McEwen. "Without question, these differences do exist, because they have been documented at the synaptic level and at the biochemical level." In the human brain, such differences have now been observed in three major structures—the hypothalamus, the anterior commissure, and the corpus callosum—as well as in lesser areas (see table).

But if anatomical differences between male and female brains have been conclusively documented, their functional significance is far from clear. Indeed, attempts to explain differences in behavior between men and women in terms of their brain anatomy have ignited major controversies (see story on p. 959). Obviously, some of the anatomical differences have a role in controlling the reproductive functions of the two sexes. But some may not, prompting researchers to speculate that they have roots in strong evolutionary pressures on the sexes during prehistory when the brain was expanding rapidly. Such theories are, for the moment, mostly speculation. But what is not conjecture is the rapidly expanding body of evidence showing that the brain is a sexual organ.



John Martin/Elsevier

VIVE LA DIFFÉRENCE

BRAIN REGION	SEX DIFFERENCES	COMMENTS
HYPOTHALAMUS		Strongest data on sex differences in humans come from this region
Sexually Dimorphic Nucleus (SDN)	2.5 times larger in men	5 times larger in male rats than in female rats
Other Interstitial Nuclei	2 of 4 nuclei are larger in men	May include SDN
THALAMUS		
Massa Intermedia	More often absent in men than in women	Difficult to quantify differences
CORPUS CALLOSUM		
Splenium	More bulbous in women	Conflicting data
Isthmus	Larger in women	
	Entire callosum shrinks with age in men—but not in women	
ANTERIOR COMMISSURE	Larger in women	Little data
HIPPOCAMPUS	11% larger in polygynous male voles—no larger in monogamous male voles	MRI scans are soon to be done in humans

The observed differences begin at the level of whole organ. "We should not forget that the entire brain *is* a sex difference," says Dick Swaab of the Netherlands Institute for Brain Research in Amsterdam. Men's brains are on average larger than women's by 15%—about twice the difference in average body size between men and women.

Male brains don't start out bigger, though: The brains of human babies are the same size until age 2 to 3. After that, male brains grow faster until age 6, when the full brain size is reached. Many researchers think this pattern reflects the fact that the basic structure of the brain is female and it is modified when male sex hormones kick in. "There is a large body of evidence, mainly in rodents, indicating that the default brain in mammals is female, and that androgens must be present very early in life to masculinize both genitalia and brain," writes University of Western Ontario neuropsychologist Doreen Kimura, in the *Encyclopedia of Neuroscience*.

Studies in rodents have shown that as male hormones surge through the growing brain, they apparently home in on a few key areas—such as the hypothalamus, which is the source of pituitary hormones and is responsible for sexual response and mating behavior. They effect their changes especially on a structure known as the sexually dimorphic nucleus (SDN), a cubic millimeter of tissue that is exquisitely sensitive to testosterone and estrogen. Gorski's UCLA team discovered the SDN in rats in 1977 and was rapidly "scooped" in its search for the same feature in humans by Swaab, says Gorski. Both groups found that the SDN is five times as large in normal male rats as in females, and Swaab has found in 100 human brain autopsies that it is 2.5 times larger in men than in women.

In a remarkable set of followup studies, Gorski's group found that when testosterone is withheld by castrating rat pups, their brains look like those of females: Half their SDN neurons die within 24 hours. "It's very exciting," says Gorski. "But we can reverse this by giving a single injection of testosterone on day 1, or on days 2, 3, 4, or 5 after birth. But if we wait to day 6, we get nothing." By contrast, "by giving androgens to the female, we can make her SDN grow as big as the male's." Although the function of the SDN is unknown, Swaab speculates that it may play a role in male gender identity and in mounting behavior.

The body of data on the hypothalamus—from both animal and human studies—is larger than that for any other brain structure. But for humans alone, another brain region has so far been the most extensively studied. "The corpus callosum shows several sex differences," says Sandra J. Witelson, a behavioral neuroscientist at McMaster University, referring to the bundle of nerve fibers connecting the brain's right and left hemispheres. Yet although it is clear there are differences between males and females in the corpus callosum, researchers don't always agree on what those differences are. Early in the 1980s, one team that studied autopsied brains reported that the splenial portion of the corpus callosum is larger—or at least more bulbous—in women than in men.

But Witelson reviewed the 10 other studies done of the splenium since then and found that the majority find no sex difference in that part of the corpus callosum. Witelson has found, however, that a different region—the isthmus—is larger in women. "This is surprising because all other parts of the corpus callosum are larger in men," she says. While the corpus callosum starts out to be larger in men, it decreases in size with age, while in women it stays the same—at least until age 70, Witelson reported in the 18 July *New England Journal of Medicine*.

Sex differences in the anatomy of the corpus callosum likely reflect sex differences in cortical structure. This, in turn, could underlie the sex differences that have been documented in cognition and patterns of lateralization, such as women's greater use of both hemispheres for some language skills.

That interpretation dovetails nicely with observed differences in the anterior commissure, another band of fibers connecting the cerebral hemispheres, and in the massa intermedia, a band of gray matter and fiber that connects the right and left halves of the thalamus. While the data are sketchier for these areas than for the corpus callosum, Gorski's team found that the massa intermedia tends to be absent altogether in men more frequently than it is in women. While the function of the massa intermedia isn't known, some early NIH studies have found a correlation between the presence of it and I.Q. scores (with different patterns in men and women). Says Witelson: "Obviously, intelligence isn't situated in the massa intermedia, but it could be correlated with other anatomical features that are relevant to some aspects of intelligence."

Although evidence of anatomical differences between male and female brains is accumulating fast, many researchers think the surface has barely been scratched. "People haven't [looked in other regions] so far," says Swaab. They should, he says, "because brain weight is already sexually dimorphic. That leads me to expect that differences will be found all over the brain."

One of the most promising regions for future study is the hippocampus, a temporal lobe structure that is thought to participate in memory and spatial processing. Studies of the hippocampus could go beyond documenting differences into the key puzzle of why male and female brains have evolved differently. That possibility is hinted at by intriguing studies of the hippocampus in wild rodents conducted by University of Pittsburgh anthropologist Steven J.C. Gaulin. "If the hippocampus was critically important in spatial processing, then I wondered if you could see something as gross as size differences in the hippocampus of males and females," says Gaulin.

Working with University of Utah animal behavioralist Lucia Jacobs, he studied the behavior of three species of voles: polygynous wild meadow voles, a species in which the males travel farther than females to find mates—an activity that requires considerable spatial processing—and prairie voles and pine voles that are monogamous and stayed by the sides of their mates. On autopsying the rodents, the pair found the polygynous males' hippocampi were 11% bigger on average than those of females. But the monogamous males' hippocampi were no bigger than the females.' Says Gaulin: "I think this is the only sex difference in the mammalian brain for which we have a plausible evolutionary function that has been tested."

Although it might seem that there's a huge evolutionary distance between a vole and a man, "the obvious next step is to use MRI to image the hippocampus in humans," says University of Arizona psychobiologist Lynn Nadel, a specialist in the hippocampus.

Whether ideas derived from work on voles can be applied directly to humans or not, the observed differences between men's and women's brains are no doubt there for solid evolutionary reasons. Says Gaulin: "If you look at the present-day organisms as bearing the stigmata of their polygynous past, such as higher male metabolism rates, larger male body size, and higher male aggressiveness, then it's not at all implausible for us to bear other marks of it in the brain." Now that anatomical differences are being established, surely one of the next key steps will be to understand why those differences came into being. ■ ANN GIBBONS

Is "Gender Gap" Narrowing?

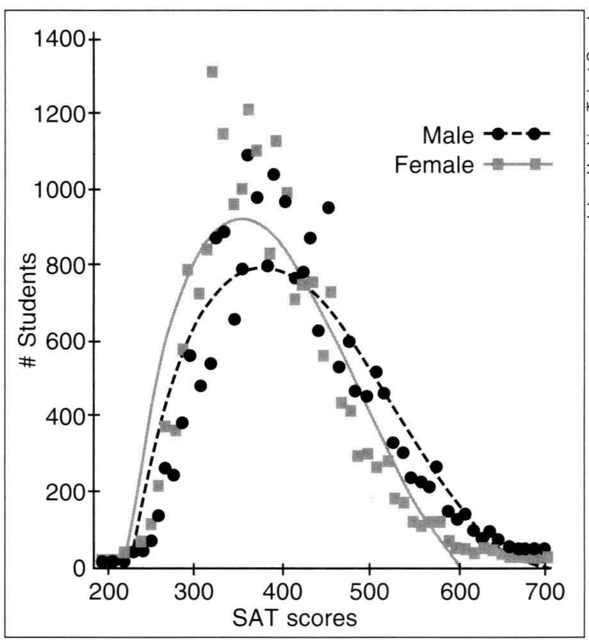
Do males and females have different kinds of intellectual abilities? That notion, which has probably prevailed through most of recorded history, has undergone sharp alterations as a result of both scientific and political developments in the last 3 decades. And particularly now, when "political correctness" has become a hot button, this area of research is something of a political minefield.

The starting point for this debate is a large body of evidence, accumulated over many decades, suggesting that there are some differences in cognition and perception between men and women. Generally speaking, test results show that females are somewhat better at verbal expression, while males have a persistent advantage in certain quantitative and spatial abilities. (These generalizations were the main ones that emerged from the first major attempt to synthesize the literature, *The Psychology of Sex Differences*, written in 1974 by Eleanor Maccoby and Carol Nagy Jacklin.)

But are these differences "real?" And are they diminishing? Both questions are currently being fiercely debated. Indeed, in the opinion of one researcher, psychologist Diane Halpern of the University of Southern California, "The hostile and politically charged climate surrounding sex differences research has called into question the possibility of ever obtaining bias-free research."

Within this supercharged atmosphere, there's something of a polarity between biologically and socially oriented researchers. Those at the biological end of the spectrum, such as behavioral neuroscientist Sandra Witelson of McMaster University in Ontario, think it's obvious that biology has a role in cognitive sex differences. "The neurobiological evidence is continuing to mount...there are too many incontestable findings—things that have to have consequences in behavior and thinking." (See story p. 957.) In fact, she says, "if one didn't observe these sex differences, one would hypothesize that they must exist."

But more socially oriented investigators—such as psychologist Janet Hyde of the University of Wisconsin—flatly disagree. "We've constructed theories of sex differences in the brain to account for differences in abilities," says Hyde. But now, she argues, the gender gap in test scores is waning. "We've come to question the very existence of the phenomenon the brain theories were constituted to explain."



Johns Hopkins Talent Search

Mathematical gap. *Math scores of precocious 12-year-olds show boys predominate at the top.*

Getting a grip on the available data is not easy: Male-female differences in cognition are often subtle, they change according to age and ability level, and standardized tests are crude tools for resolving questions about sex differences they weren't designed to measure. As a result, even a slight change in a test question can result in a big change in "effect size"—the proportion of a standard deviation by which the sexes differ. Furthermore, generalizing about "verbal ability" obscures the fact that this category includes a va-