Secrets of the BRAIN

How do people think and learn? Why, faced with danger, do some choose to fight, others to flee?

Mark Nichols

Smith knows he is in trouble. He has problems at home, his job performance has been slipping and his confidence is shot. Now, he has been summoned to the office of that steely-eyed new boss, the one who has left a string of middle-management corpses in his wake since he launched a downsizing shakeup of the firm. At the appointed hour Smith threads his way nervously through a labyrinth of corridors, then climbs a flight of stairs to the more gracious hallway that leads to the boss's office. Suddenly, he is gripped by a fear so total that it nearly freezes his limbs. A voice inside his head screams: "Don't go in there—if you don't go in, he can't fire you." But another part of his brain is telling him that the consequences of running away might be even worse. By now, he is at the boss's door. Fingers trembling, he reaches for the knob and . . .

And what? Does Smith open the door, step inside and face the consequences? Or, consumed by fear, does he draw back and beat an ignominious retreat? What is more—and this is what fascinates scientists—how does the human brain weigh the conflicting claims of intellect and raw animal fear to arrive at a decision? Tony Phillips, who heads the psychology department at the University of British Columbia (UBC) in Vancouver, is trying to solve that riddle. The answer, he says, may lie in an intricate interplay of feedback loops within the brain. And the organ that in the end directs poor Smith to face the boss or flee could be a tiny teardrop-shaped collection of brain cells located behind the frontal lobes called the nucleus accumbens. "Our ability to imagine different courses of action and their consequences is quintessentially human," says Phillips. "Now, we may be close to figuring out the answer to a fundamental puzzle—the nature of the interface between human thought and action."

Scientists around the world are tackling age-old mysteries of the brain and beginning to solve such puzzles as how memory works and why some people's psyches can withstand the kind of horrific experiences that traumatize others. "We are trembling on the edge of an enormous explosion of understanding," says Robert Adamec, a research professor in the psychology department at Memorial University in St. John's, Nfld. "Things are moving so fast right now that in 10 years I may look back on some of the ideas I have now as somewhat foolish."

As researchers venture across one of science's last frontiers, they are boosted by brain-scanning technology that allows them, for the first time, to watch events unfold inside the brain. Alan Evans, who heads the Montreal Neurological Institute's brain-imaging centre, is part of the U.S. Government-sponsored Human Brain Project, dedicated to assembling a comprehensive structural and functional map of the human brain. In Evans's study, technicians are using magnetic resonance imaging (MRI) equipment to peer inside the skulls of 450 people, compare the differences in shapes and sizes of individual anatomies and come up with a diagram of the typical human brain.

Ever since the Montreal brain surgeon Wilder Penfield carried out pioneering experimental work during the 1940s and 1950s, Canadian researchers have been strong contributors to the neurosciences—and today they are playing prominent roles in brain research. One current realm of Canadian specialization is a drive to find out why most brain cells, unlike those in other parts of the human body, do not regenerate after injury. Discovering ways to make neurons grow again in stroke- or disease-damaged brains could pave the way for improved treatments or even cures for such dreaded neurodegenerative conditions as Parkinson's, Huntington's and Lou Gehrig's diseases, which begin in the brain and cripple and kill over time. "We're on the threshold of an era," says William Tatton,

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director of Dalhousie University's Neuroscience Institute in Halifax, "where for the first time we may be able to intervene effectively in neurological diseases."

Despite cutbacks in government funding, Canadian laboratories are also engaged in studies aimed at understanding the brain's cognitive abilities—the functions that enable humans to think, learn and remember. In a series of dramatic findings during the past decade, Sandra Witelson, a Hamilton-based researcher, has pinpointed structural differences between the brains of men and women, and between heterosexuals and homosexuals (see box "Boys, girls and brainpower"). In Vancouver, psychologist Robert Hare is using MRI to examine the brains of psychopaths, in an effort to find out why they display a stunning absence of conscience.

Exploring the human brain, and comprehending what is going on inside it, is a formidable task. And no wonder, considering the bewildering complexity of the brain, a 3.3-lb. lump of tissue contalning between 50 billion and 100 billion brain cells. In a living brain, individual cells—also known as neurons—routinely make contact with as many as 10,000 other cells in an incredibly complicated electrochemical interplay that scientists are just beginning to grasp.

What is clear is that out of that welter of neuronal activity human consciousness and thought somehow emerge. Much basic brain research is devoted to trying to find out exactly what is happening when electrical impulses flow through a neuron and trigger a discharge of chemicals across the gap—or synapse, between brain cells. It is that synaptic contact that gives rise to mental activity—by mobilizing millions of brain cells in specific regions that scientists are increasingly linking to specialized roles. The frontal lobes, for example, are the part of the brain that anticipates events and weighs the consequences of behavior, while deeper brain regions, including the seahorse-shaped hippocampus and the nearby amygdala, are associated with such things as memory, mood and motivation.

In the case of Smith—the anxiety-ridden employee on his way to see his boss—UBC's Phillips thinks that some brain circuits may be locked in a kind of neural competition in which some can override others. While the hippocampus helps Smith to chart a course through physical space, the amygdala is urgently warning him of possible peril. But that can change if the fear generated by the amygdala becomes strong enough to somehow override the messages coming from other brain regions.

Outside the boss's office, that very thing threatens to happen. As the amygdala becomes more insistent, the frontal lobes—which perform executive planning functions in the brain—warn that to turn and flee could be even more career-threatening than to face the boss. Phillips thinks that the final decision

THE GOD MACHINE

During the past decade, psychologist Michael Persinger and his assistants have ushered more than 500 volunteers into a soundproof chamber, placed a strange-looking helmet on their heads and then, from a console outside the chamber, exposed their brains to a rhythmic bombardment by low-intensity electromagnetic waves. Persinger, a psychology professor at Laurentian University in Sudbury, Ont., hopes that this unorthodox treatment can be used eventually to help people suffering from such problems as depression, chronic pain and epilepsy by correcting electrical irregularities in the brain. But he is equally interested in the fact that many of his subjects react to the electromagnetic exposure by experiencing unusual auditory and visual sensations. Some people even sense that there is someone or something with them in the chamber, a "presence" they describe as God—or the devil. "Ultimately," says Persinger, "human experience is determined by what is happening in the brain. And the experience of God can be generated by a process that has nothing to do with whether God exists or not."

According to Persinger, electromagnetic brain events of the kind his helmet reproduces may account for many spiritual and paranormal experiences, including visitations by angels, demons or aliens. How can this happen? Persinger says that a person's sense of self arises from language functions, which are usually centered in the left hemisphere. But a variety of factors, including stress, fatigue and depression—and artificial stimulation by Persinger—can alter the brain's normal electrical functioning and produce a sense of "otherness." When this occurs mainly in the left hemisphere, he says, the subject is likely to feel that the presence is benign or god-like. But when the same event is mainly in the right hemisphere, which is concerned with vigilance, the brain is more likely to interpret the presence there as being alien or demonic.

In his experiments, Persinger uses a specially wired motorcycle helmet, which British journalist Ian Cotton donned in 1993 while researching a book on evangelical Christianity entitled *The Hallelujah Revolution*. After Persinger's team provided temple-bell sound effects, reported Cotton, "I was actually in a line of solemn Tibetan monks, grave-eyed, brown cowls around their heads. I too was a Tibetan monk, and what I realized was that I always had been."

Born in Jacksonville, Fla., Persinger—now a Canadian citizen—left the United States in 1969 to avoid being drafted for service in Vietnam. He does not have a high opinion of organized religion. "If you look at the history of human behavior," he says, "it is evident that many wars were caused by rival concepts of God." Reacting to his work, fundamentalist Christians have mounted small protests at Laurentian. Persinger talks at times as though God might be no more than a neurological accident. But he is careful to hedge his bets. "I am interested in the part of the brain that *mediates* the God experience," he says. Does that mean the God experience could be caused by the *presence* of God? Replies Persinger: "It's a possibility."

M.N.

is made by the nucleus accumbens, perhaps with the help of the frontal lobes. Now, Phillips' research team is trying to find out exactly how that happens by studying rats, whose brains are in many ways scaled-down versions of human ones. "The nucleus accumbens is a very sophisticated switching system," says Phillips. "And somehow, the strongest signal reaching it can determine what orders go out to initiate action."

At Memorial, Adamec is trying to understand why horrific events affect the brains of some people so severely that they develop the condition known as post-traumatic stress disorder—typified by the depression, anxiety and anger that afflicts some war veterans. From human and animal studies, Adamec has concluded that people who have anxious personalities to begin with are probably more likely to suffer lasting damage from involvement in shocking or violent events. "There is something about the way a person's brain is wired that is relevant," says Adamec. "And if an event leads to a lasting increase in anxiousness, there must be a lasting alteration in some brain circuits."

Using rats, Adamec is now trying to discover which brain circuits are affected—and how. The problem probably involves changes in the flow of several of the 100 or so chemical neurotransmitters that carry messages between brain cells. One of the culprits, says Adamec, may be a neurotransmitter known as CCK, which is associated with panic attacks. The zone in which traumatic events leave their indelible mark may be a circuit involving a number of brain regions, including the amygdala, which is involved in memories of emotion-laden experiences, and the hypothalamus, which regulates bodily functions, including responses to stress. Adamec's ultimate hope: that by understanding how post-traumatic stress disorder arises, scientists may be able to find a way to intervene—after a potentially traumatic shock—with drugs that can prevent permanent changes from occurring in the brain.

Federal cutbacks are putting a strain on brain funding. Ottawa has announced plans to slice $4.4 million over the next three years from the current $33 million it devotes to brain-related research. At the sam time, federal agencies increasingly are favoring medically oriented discoveries that could help to reduce health-care costs while producing jobs and profits. "I think there is a deliberate attempt by government," says Warren Bull, executive director of the federally backed Canadian NeuroScience Network, "to insist that there be a practical payback."

A discovery by Toronto brain researchers could provide that kind of payback by trimming the estimated $2.3 billion spent treating schizophrenia. The problem with some of the most effective anti-psychotic drugs used to treat the disease, says Shitij Kapur, a research scientist at the Clarke Institute of Psychiatry, "is that the side-effects are so horrible that patients become convinced that the drug is an enemy, and stop taking it." When that happens, patients often lapse into psychosis and have to be hospitalized.

Using PET (for positron emission tomography) brain-scanning technology, Kapur and other scientists at the Institute tracked two widely used anti-psychotic drugs—haloperidol and risperidone—in the brains of schizophrenics. The researchers found that in most cases the drugs worked—and with fewer of the side-effects that can include extreme restlessness and muscular stiffness—when taken at doses well below those often prescribed.

Most scientists believe that schizophrenia is caused by excessive activity of a chemical called dopamine, which helps transmit messages between brain cells—and that anti-psychotic drugs work by blocking receptors that are activated by dopamine. Watching drugs flow through patients' brains, the researchers could see that a drug dose of between two milligrams and six milligrams blocked about 70 per cent of the dopamine receptors, while doses as high as 50 mg only marginally increased the blockage. If Kapur and his colleagues

MAPPING THE MIND

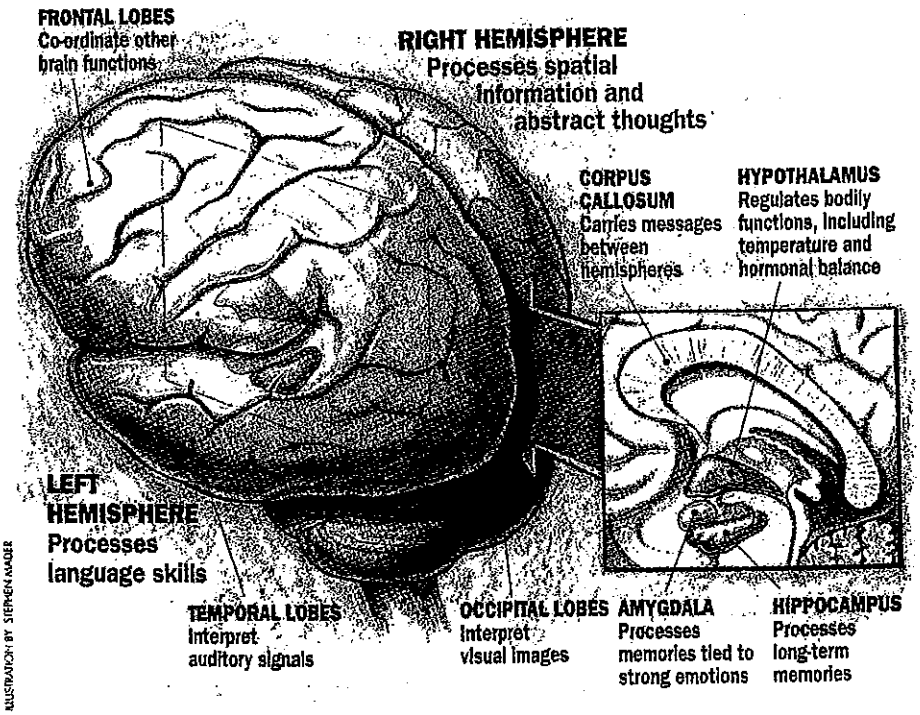

ILLUSTRATION BY STEPHEN MADER

can persuade other scientists that they are right, their finding could improve the lives of schizophrenics while saving millions of dollars by reducing drug and hospital costs.

In another project, Canadian scientists are looking for answers to one of the brain's most painful mysteries—the inability of a damaged brain or spinal cord to heal like a cut finger or a broken bone. There is a period in human development when this is not true: brain cells in unborn babies and infants up to the age of about 2 can regenerate themselves. That is why doctors try to reverse the effects of cell death in Parkinson's disease by transplanting fetal tissue into victims' brains (see box, "The Debate over Fetal Tissue"). But for most people with brain or spinal cord injuries, or other neurodegenerative diseases like Huntington's and Alzheimei's, little can be done to bring dead cells back to life.

About four years ago, Sam Weiss, an associate professor of anatomy and pharmacology at the University of Calgary, and graduate student Brent Reynolds made a discovery that may point to a way of growing new cells in the human brain. They found an inactive cell in the brains of mice that, when prodded into action, behaves like the rapidly reproducing stem cells found in human and animal bone marrow. The burning question now is whether similar cells exist in the human brain.

If they do—and Weiss says there is "some evidence" to support that conclusion—scientists may be able to grow them in a culture to generate millions of new cells, which could be transplanted into the brains of people suffering from neurodegenerative diseases. Even better, adds Weiss, it may be possible "to turn on the stem cells, and persuade them to begin reproducing themselves right inside the brain." To exploit the commercial possibilities of the discovery, the University of Calgary, with the backing of American and Swiss pharmaceutical companies, in 1992 set up a Calgary-based company called NeuroSpheres Ltd., which now employs about 20 people.

John Steeves, a professor of neurobiology at UBC, thinks that a substance called myelin, which forms a coating around neurons that helps speed up communications among cells, may play a role in preventing cell regeneration in damaged brain and spinal cords. Studying the neural circuitry of chickens, Steeves noticed that myelin begins to form about a week before the baby birds are born, just as the spinal cord nerve cells lose their ability to regenerate. Does that mean, Steeves wondered, that one of the roles of myelin is to stabilize neural circuits in a young organism by halting cell replication? If so, he reasoned, then preventing myelin production might encourage cell regeneration.

In an experiment, Steeves and members of his research team injected proteins that suppressed myelin formation into adult chickens whose spinal cords had been severed. "To my amazement," says Steeves, "we got regeneration in about 20 per cent of the damaged cells." It is too early, says Steeves, to try to apply

THE DEBATE OVER FETAL TISSUE

Sometime within the next six weeks, Dr. Ivan Méndez and his surgical team at the Victoria General Hospital in Halifax will pool nerve cells from two, three or perhaps four aborted fetuses and implant them in the brain of a patient with Parkinson's disease. The controversial operation will mark phase two of the team's study of the incurable neurodegenerative disorder. At least nine more patients will follow, with a report expected in late 1997. The theory behind the implants—first tried in Sweden in 1988—is to substitute fetal nerve cells that are capable of growing for damaged adult cells that cannot regenerate. It is, says Méndez, "like replacing a faulty chip in your computer."

Perhaps, but brain surgery has proved nowhere near as simple. Gone is the optimism that greeted fetal-tissue implants in the late 1980s. Inconsistent results have led doctors to believe the implanted neurons—which secrete dopamine, a chemical messenger lacking in Parkinson's patients—will have to be supplemented with other treatments. And no one knows whether the grafts can survive the undiscovered brain-cell killer behind the illness. On top of that, abortion opponents continue to denounce the operations as yet another indignity against the unborn.

Halifax surgeons performed the first fetal-tissue implant in Canada in 1991, followed by four more to complete phase one of their study. In December, 1994, Méndez and company—still the sole Canadian team in the field—announced they would expand their research after all patients showed a lessening in the severity of their symptoms and their deterioration slowed. They all still require medication, however. Unlike phase one, phase two involves implanting cells in two locations of the brain instead of one.

A major stumbling block continues to be cell survivability. "If you don't know how many cells survive, you don't know how much you have to put in." Méndez says. To date, doctors have relied on indirect evidence from brain scans. But last April, *The New England Journal of Medicine* reported on an autopsy that showed implanted fetal cells had survived and grown in the brain of a 59-year-old male Parkinson's patient.

If such surgery proves beneficial to Parkinson's patients, it could eventually be used to treat epilepsy, Huntington's disease or brain and spinal cord injuries. Meanwhile, studies are under way in the United States, Sweden and France that may defuse the controversy over using fetal cells. Scientists are now growing genetically engineered cells in culture, hoping they can provide a limitless supply—and new hope—for victims of brain disease.

DAN HAWALESHKA

Boy, girls and brainpower

The sexes differ in more than appearance

It began almost by accident. In an effort to uncover the causes of dyslexia, psychologist Sandra Witelson decided in 1970 to conduct an experiment involving dyslexic and other children at a Hamilton grade school. Because dyslexia affects mostly males, Witelson planned to use boys only. "But the girls wanted to join in, so they could get to miss some of their regular classes too," says Witelson. "So we included girls." The purpose of the experiment was to see whether some mental functions in dyslexic children—such as language skills or spatial perception—favor one or the other of the two brain hemispheres, as they do in most people. What Witelson found was that dyslexic children have fewer right-left brain differences than other kids—and that, where they exist, the differences were far more pronounced in boys than in girls. That discovery, published in 1976, sent a tremor through the world of brain research. The reason: Witelson's finding suggested that differences between male and female behavior might not be due simply to social conditioning, but rather to biological differences in the brains of men and women.

Certainly there is ample anecdotal evidence to suggest that conclusion. And studies have shown that women often *do* possess superior verbal skills, while men are frequently better at things like mathematics and map reading. But now, the 55-year-old Witelson and a handful of other researchers have begun to produce concrete and mounting evidence of physical differences in the brains of men and women, as well as in the brains of heterosexuals and homosexuals. Typically, in a study published last May, Witelson, a professor in the psychiatry department at Hamilton's McMaster University, reported that in a part of the temporal lobe associated with language skills, women's brains contained up to 11-percent more brain cells than men's brains.

That does not necessarily mean that women are smarter than men—but it does show that they are different. As Witelson notes,—her findings challenge the politically correct dogma that "except for anatomical differences in men's and women's bodies, everything else is supposed to be the same, except where things have been distorted by social forces." If there are physical brain differences between the sexes, adds Witelson, "it may be better to recognize this and deal with it, rather than pretending that we are all the same."

A native of Montreal, Witelson studied psychology at McGill University, where she became interested in childhood learning disabilities. When American researchers in the late 1960s reported that brain regions in the left and right hemispheres often varied in size, Witelson wondered whether the disparities were related to the distribution of brain functions in the two hemispheres. Officials at the U.S. National Institutes of Health in Bethesda, Md., were interested in the same question and, in 1976, they offered to fund scientists to investigate it. Witelson and a McMaster colleague bid on the multimillion-dollar NIH contract—and won.

The three-year grant set the stage for a series of studies by Witelson and her scientific partners that have shed light on the differences between brain hemispheres—and between male and female brains. From the male point of view, one of Witelson's most disturbing discoveries was reported in 1991. She found that as men grow older, the corpus callosum—a brain region that provides communications between the hemispheres—begins shrinking. The biggest surprise was that the study, based on post-mortem examinations of 23 male and 39 female brains, showed virtually no shrinkage of the female corpus callosum. In a current study, Witelson is trying to determine what effect the shrinkage has. "Clearly, whatever is happening in the corpus callosum is not of great consequence for most men," she says. "Lots of men do very well in their later decades."

Witelson and her research partners illustrated another dimension of brain differences in November, 1994. In a study involving 21 people, they showed that part of the corpus callosum in the brains of some homosexual men was 13-percent larger than in the heterosexual men. That might explain why earlier studies, including some by Witelson, have found differences in the cognitive abilities of gay and straight men, including lower scores by gay men on tests of spatial perception. Witelson's findings involving the corpus callosum followed a 1991 U.S. study that reported physical differences between gay and straight men in the hypothalamus, a brain region associated with sexual behavior. Other American researchers have suggested that genetic factors may play a role in homosexuality.

Working in an area of science that is fraught with political implications, Witelson insists that she is interested only in the truth. "I think of myself as a scientist," she says, "not as a male or female scientist." Witelson, who has been married for 35 years to Hamilton eye doctor Henry Witelson, thinks there now is persuasive evidence that men's and women's brains "are actually different in some of the ways they are put together, anatomically and chemically." That will upset some people, she says, "because they assume that biology means things are immutable." But, she adds, "the fact is that upbringing and other environmental factors play a tremendously important role" in shaping the mind—a reminder that biology alone is not destiny.

MARK NICHOLS

the finding to humans. But it could point the way to a form of treatment that could help regenerate human neurons at some point in the future.

Over the past seven years, UBC neurobiologist Terry Snutch has made a series of discoveries that could pave the way for better drugs to treat conditions ranging from migraine headaches to manic-depressive illness and schizophrenia. Snutch's specialty is a family of proteins found on the surface of brain cells. The proteins act as channels for calcium, a mineral that plays a vital role inside neurons to trigger the flow of neurotransmitters used in the brain's messaging system. Snutch discovered that calcium channels are located on different parts of neurons—and each channel has a slightly different function.

What that means, says Snutch, is that the amount of calcium, and the flow of neurotransmitters it sets off, "can be controlled to a very fine degree." Some widely prescribed drugs used to treat a variety of illnesses act on calcium channels. Now, by designing drugs to target specific calcium channels, scientists may be able to eliminate some of the unpleasant side-effects—including the nightmares and fatigue caused by some migraine remedies.

Meanwhile, Canadian researchers are trying to solve the mystery of memory—a brain function that Endel Tulving, a Toronto brain researcher, considers to be "the thing that makes us human." Over the years, says Tulving, a senior neuroscientist at Toronto's Rotman Research Institute, investigators have tended to regard memory as a brain function that is simply involved in information storage. Tulving's model is more complicated. First of all, he says, there are two basic memory functions—encoding (taking the information in) and retrieval (getting it back out). In a theory developed over two decades, Tulving has also proposed that there are two different types of memory—semantic, which deals with such factual material as names, dates and the appearance of ordinary physical objects, and episodic memory, which enables people to re-experience the past.

Until recently, there was no way to test many of his ideas. But now Tulving and scientists at Toronto's Clarke Institute are using PET scans to see which parts of the brain handle different memory functions. They have already made an unexpected discovery: although memory is widely distributed throughout the brain, some functions are concentrated in one of the two brain hemispheres. The retrieval of semantic memory, for example, occurs mostly in the left frontal lobe, which makes sense because that side of the brain is strongly associated with language functions.

Tulving's theories may help explain why memories of past events are not always accurate or complete. For example, a bus driver's clever wisecrack might be recorded in an individual's episodic memory, perhaps with details of how the driver looked and the way he talked. At the time of the event, the bus's other passengers did little to engrave themselves in the subject's memory. So when the scene is recalled, the person's brain may sketch in generic passengers based on a general idea of what transit straphangers look like that is drawn from semantic memory.

Tulving admits that many of his ideas about how memory works are just that—ideas that have yet to be proved. "Memory is extraordinarily complicated," he says, "much more so than many people are willing to believe." He thinks that may be true of the brain itself—and that "some day we may discover that the brain works quite differently from what we imagine now." Luckily, one of the glorious paradoxes is that, for all its complexities, it is the human brain itself that may ultimately unlock the mysteries of the mind.