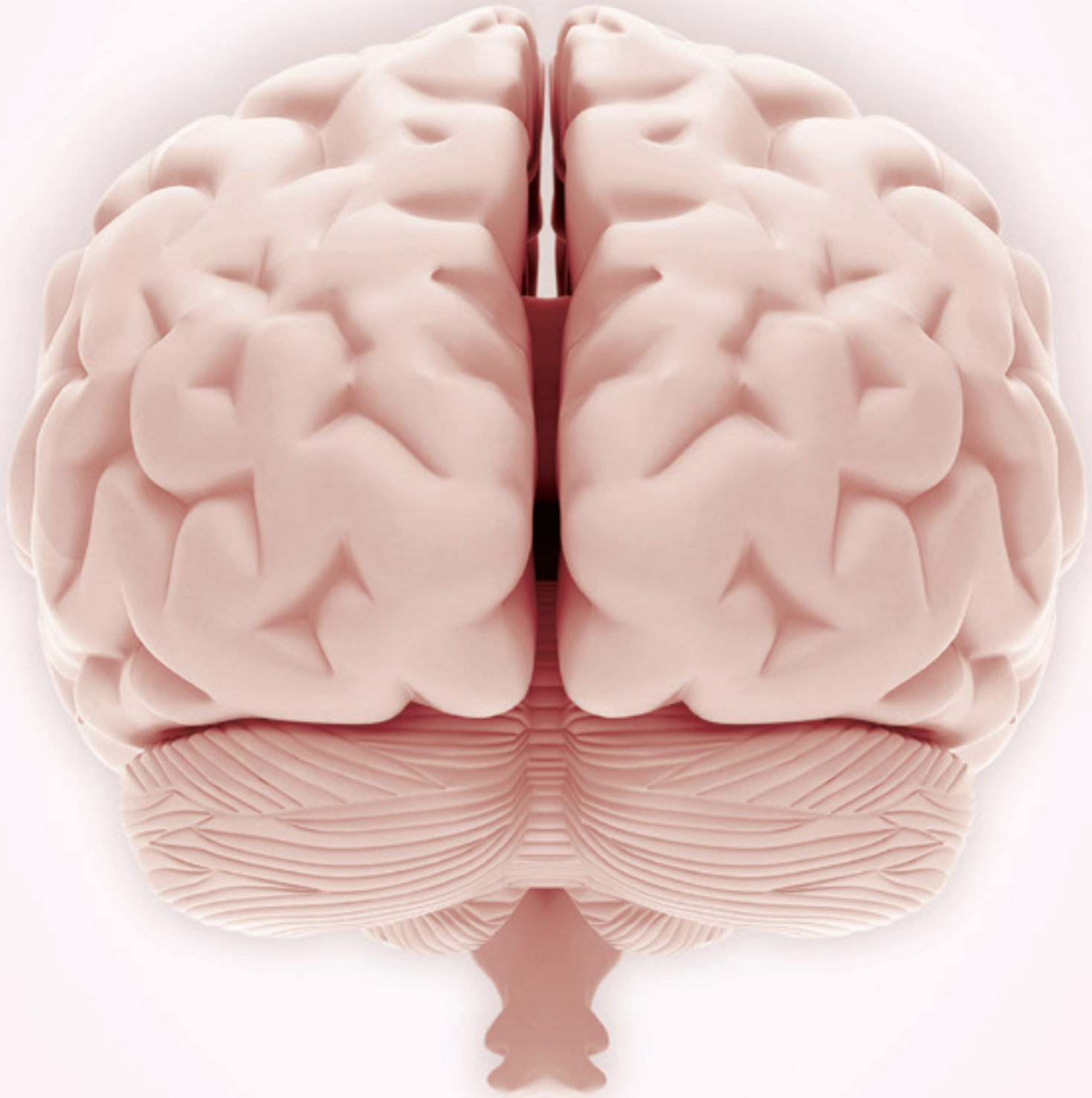
SPECIAL EDITION

The New BRAIN



MACLEAN'S

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Introduction

Join us for a giant brainstorming session on what the world's neuroscience superstars are keeping top of mind

Now that science has decoded DNA—parsed our cellular bits almost down to the last variation—it may seem as if biology has been completely conquered by man's hunger for knowledge.

But every time the prefix "neuro" is typed out, as it is with increasing frequency, it is clear there is one frontier left: the brain. Once the domain of philosophers, phrenologists, priests and psychiatrists, the command centre of the body is being scrutinized by some of the finest scientific minds of our times. The seat of human thought and intelligence is also the origin of our basest urges, from eating to sex to fear of scary things that might kill us. And though we know how some of it works, we don't completely understand the mechanisms that allow the collection, sorting, interpretation, storage and dissemination of a mind-boggling amount of information, all accomplished by three pounds of tissue with the consistency of soft tofu.

In the beginning, there was autopsy. Defective brains were dissected and examined for anatomical reasons for everything from insanity to dementia.

In 1934, neurosurgeon Dr. Wilder Penfield founded the Montreal Neurological Institute, where he perfected the Montreal procedure, best known as the "I smell burnt toast" experiment (later immortalized in a Heritage Minute). In an effort to find the source of a patient's epilepsy, he opened her skull under local anaesthesia and probed her brain as she was conscious and talking. In this way, he discovered many functions of unmapped areas of the brain, including the source of memory, not to mention olfactory memories.

Then, in 1953, H.M., the most studied amnesiac in history, agreed to a partial lobotomy to cure his epilepsy. When U.S. doctors removed part of his brain, they erased his ability to form new memories. Some of the pioneering research on H.M. was also done at the Montreal Neurological Institute by Brenda Milner and her student Suzanne Corkin, who just published a book about his life.

York University cognitive scientist Shayna Rosenbaum, 37, featured in *The New Brain*'s Q&A, was so inspired by the work with H.M. that she switched from law to psychology and dedicated her career to memory disorders.

Now magnetic resonance imaging (MRI), which provides a picture of the brain, and functional MRI (fMRI), which identifies the areas of increased blood flow (and therefore the parts of the brain that are working on tasks), have become the workhorses of neuroscience. But the technology and the science that flows from it is not without its skeptics, as Colby Cosh reports in this special issue. As researchers claim to peer into our craniums, some even going so far as to suggest they can tell what we're thinking, the neuroskeptics are proving the field is littered with overhyped, unreproduceable studies that do little more than make headlines. Sample sizes, selection of MRI data and statistical biases all play into each and every announcement of an advance in brain research.

In *The New Brain*, *Maclean's* features some of the most intriguing ideas about the most complex organ of the body.

It explores the discovery of glial cells, once thought to be the neuron's useless accomplice, but now considered its partner. It reports on exciting research on obesity, including a theory that the more weight you pack on, the harder it is for your brain to work, especially when choosing between healthy and unhealthy foods. Alzheimer's, ADHD, autism and post-traumatic stress disorder—some of the developed world's most prominent medical puzzles—are examined through the prism of the latest research.

Please join us for a brainstorming session on what the latest neuroscience superstars—at home and abroad—are thinking about the brain, from the incredible story of one Canadian soldier's recovery from a traumatic brain injury (an axe to the head) to the Calgary neuroscientist who is helping Parkinson's patients walk again by tapping into music's deep connection to reward and motivation. ♣

The glia club

Once dismissed as ‘glue,’ glial cells, neuron’s little brother, have become the lodestone of brain research. But is it a good idea for scientists to herd in one direction?

In this beginning, too, there was darkness. It was 1991, and Richard Robitaille had flicked off the lights in a cluttered laboratory at the Medical Sciences Building of the University of Toronto—the better to see a tiny, phosphorescent glow he hoped would appear beneath the lens of his battered microscope. Robitaille, a post-doctoral researcher in neurobiology, hoped to witness a Holy Grail moment in brain science: the reaction within a neuron that triggers the synaptic flash. The origin, in short, of our ability to think, to feel, to act.

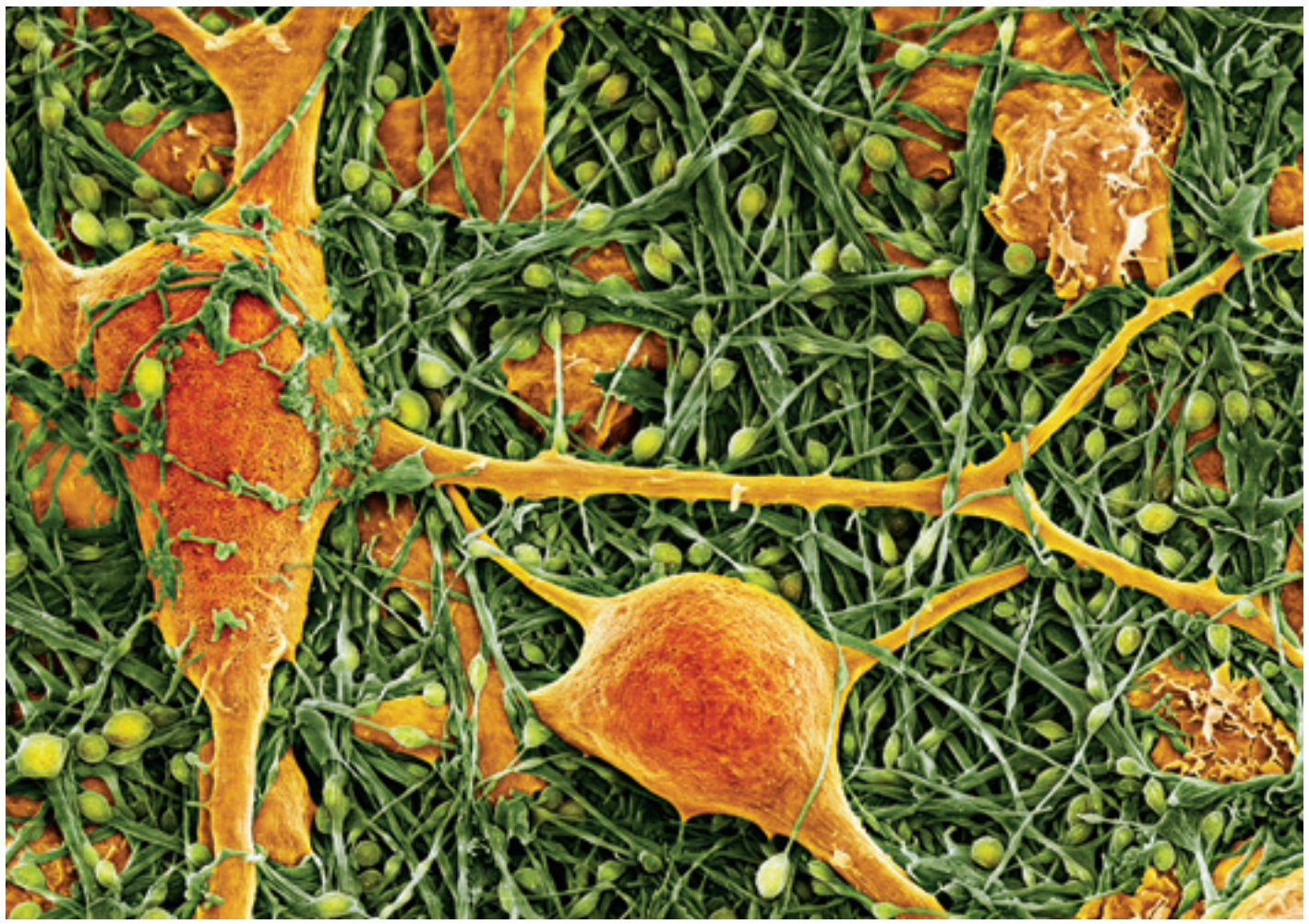
Scientists had long pondered this mystical chain of events, but only recently had they figured out a way to watch it in real time. By dosing neuronal cells with a chemical agent, they could make calcium inside the cells emit light. Calcium is important, because it is the medium through which cells send signals—a kind of instant messaging service that launches the whole neuromuscular process. If all went as planned, Robitaille would get to watch it in action, inside a unique kind of neuron that serves as the junction between nerves and muscles. So he trained his lens on the cell’s synaptic compartment and he waited.

There was light all right. But not from the inside of the synaptic chamber. Instead, a green glow rose from the formation of so-called “glial” cells that surrounded the nerve-muscle cell. Robitaille was annoyed: glia were regarded as little more than handmaids to neurons, the real stars of brain science. Glia

were insulators, waste removers, fillers and bonders (the name derives from the Greek word for “glue”). Now, inexplicably alight with calcium, they were obstructing Robitaille’s view of what he really wanted to see. “We went home disappointed that day,” he recalls. “Bloody glial cells. I think I used the F-word.”

Only later, over coffee, did his supervisor ask a question that changed the course of Robitaille’s career. What if the glia were lighting up for a reason?

It’s the sort of tale heard often in the two and a half decades since glial cells emerged Cinderella-like from the shadows of neuroscience. During the same period, researchers at Yale University and at the National Institutes of Health in Washington were watching the same light reaction witnessed by Robitaille. And they were experiencing the same sense of disbelief. If glia were using calcium as a signalling mechanism, they reasoned, that would suggest they perform some higher function. And if they were performing some higher function, then a century’s worth of brain science—premised on the belief that neuronal cells were the things between our ears that mattered—just might be obsolete.



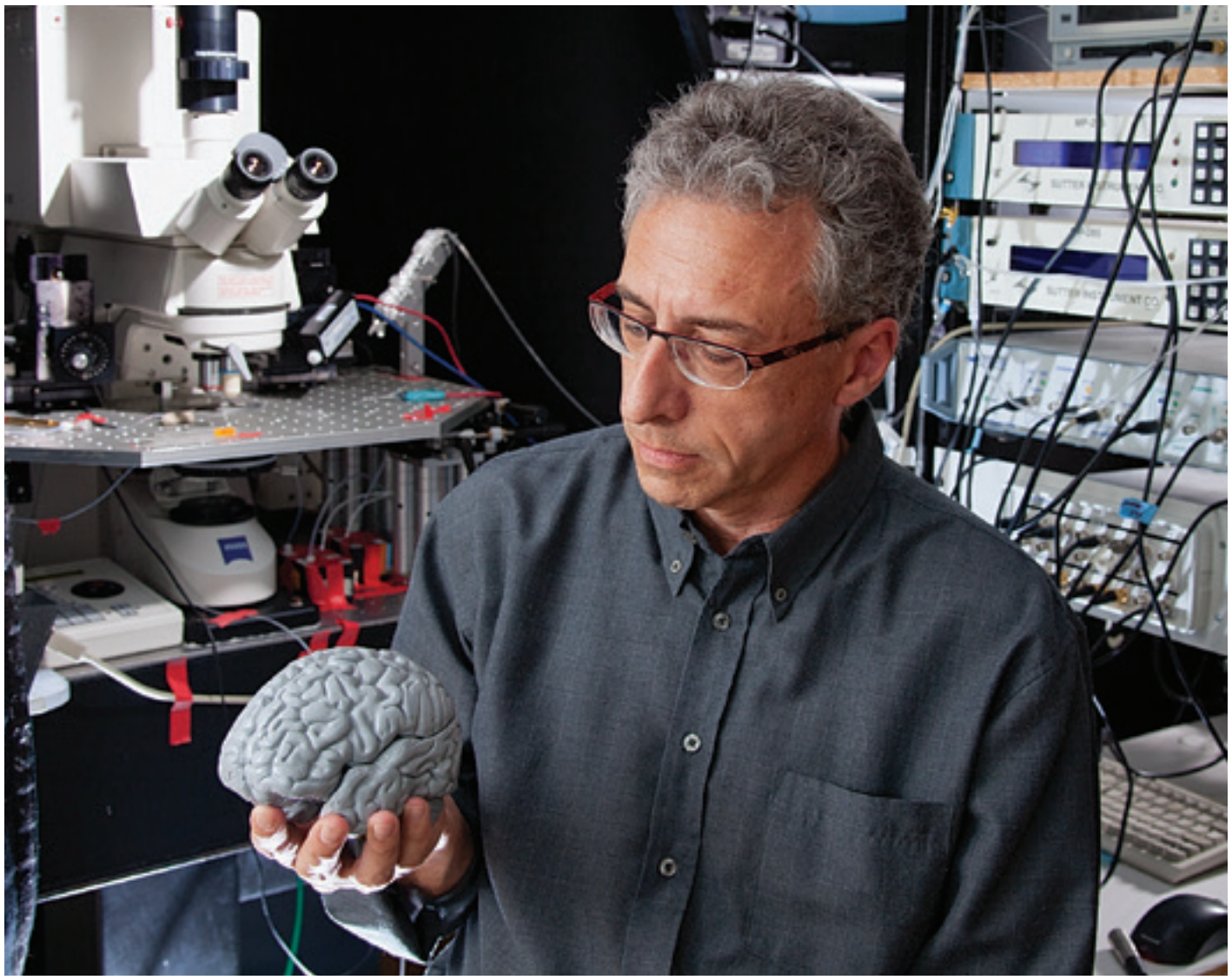
Aha! moment: ‘It was like nature tapped you on the shoulder and revealed a secret,’ says Douglas Fields, a pioneer in glial cell research (THOMAS DEERINCK/NCMIR/SCIENCE SOURCE)

A cascade of research followed. Glial cells were found not only to "listen in" on the activities of neurons, but to relay information about those happenings among themselves. Some studies suggested they play a coordinating role in the so-called "regional" brain activities once ascribed exclusively to neurons—advanced functions like thought, memory and decision-making. A few researchers, including Robitaille, explored the potential role of glia in nerve disorders like Lou Gehrig's disease and multiple sclerosis. Wherever the research led, excitement followed. "It was like nature had tapped you on the shoulder and revealed a secret," says Douglas Fields, a pioneer in glial cell research and author of *The Other Brain*, a 2010 book on the subject. "These are the sorts of moments that scientists live for."

Today, it is possible to argue that glial cells have eclipsed neurons as the fashionable avenue of brain science. Published papers on them number in the tens of thousands, while research foundations have opened their vaults to fund research in the field. Some models have elevated glia to the status of "partner" to neurons in the business of higher thought, and no inquiry into brain or nervous function can exclude the possibility that glia exert some influence. Wherever there are neurons, after all, there are glial cells, too.

For science historians, this is an object lesson on the blinkering effect of received wisdom: for 100 years, neurological experts worked on the basis of a "Neuron Doctrine"—written, published and expanded—that declared the primacy of neurons in the nervous system. Now, it turns out they were looking at a half-formed picture of the brain and its processes—"like a house," as one researcher put it, "without the stucco, the bricks and windows." The revision of that model has proven an epic task, making stars out of glial cell experts while wounding the egos of traditionalists. It has generally sent brain science off in new and unexpected directions, creating the kind of buzz that irresistibly raises the selfsame question that should have been nagging at neuroscientists for the past few decades: is our new fixation blinding us to something else?

YOU CAN UNDERSTAND why early anatomists passed them over. The sheer dynamism of neurons fascinated Victorian-era scientists, who by the end of the 19th century had recognized electricity as a means of signalling between cells throughout the nervous system. Ever since, electricity has provided a seductive metaphor for the inscrutable source of our thoughts and actions. In the popular mind, the synaptic "spark" has come to represent life itself.



'Moving onward': Richard Robitaille, from the Université de Montréal, is exploring the role of glia in such nerve disorders as Lou Gehrig's disease (PHOTOGRAPH BY ROGER LEMOYNE)

Yet even then, there were clues to the importance of glial cells. For starters, they outnumber neurons in the human brain by a factor of nine, which seems a lot of matter to waste on bubble-wrap (this may be the origin of the discredited theory that we use only 10 per cent of our brains). What's more, the distinctive anatomy of glial cells—some bulbous, some tentacled—clearly suggested a purpose beyond propping up and insulating neurons. "There were anatomists at the time who said they really must be more than glue," says Stephen Smith, a Stanford University professor who led breakthrough research on glia in the late 1980s. "Unfortunately, that's where it ended."

Indeed, eight more decades would pass before a pivotal sign presented itself, an unintended bequest from the greatest mind of the 20th century. Albert Einstein's last gift to science was his prodigious brain, salvaged by the pathologist who autopsied him and parsed out over the decades to pretty much anyone who asked. One piece made its way to the University of Cali-

fornia at Berkeley, where a renowned neuroanatomist named Marian Diamond compared it to samples from 11 other adult male brains. In 1985, Diamond announced an intriguing discovery: Einstein's brain matter had 73 per cent more glial cells by volume than the average of the others.

Diamond stopped short of declaring abundant glia the fount of genius. But her observation sent a jolt through what Fields describes as the "scientific backwater" of glial cell research. The calcium-imaging experiments followed, and in 1990 Smith, then working at Yale, reported that a specific kind of glial cells called astrocytes appeared to react to neuronal firing by spreading waves of calcium among themselves. The implications were gobsmacking. All this time, researchers had assumed glial cells were deaf, dumb and mostly inert because they couldn't transmit electrical signals. But it turns out they communicate ("discuss," Fields says) through chemical signalling—in response, no less, to neurons themselves.

Smith's study formed the basis of a cover story in *Science* magazine and the gold rush of glia research was on. Subsequent studies indicated that astrocytes can not only listen in on neurons but also send signals *back* to them, which bolstered belief among scientists that they are key players, even coordinators, of higher thought. About the same time, astrocytes became linked to intelligence. The higher a creature ranks on the evolutionary chain, studies showed, the more astrocytes it has in its cerebral cortex, and the larger they tend to be. Earlier this year, a team of U.S. researchers published a study suggesting that mice injected with human astrocytes learned better and remembered better than normal mice. It was, declared one of the study's co-authors, "a profoundly surprising and unexpected finding."

All of this triggered a period of self-examination, as neuroscientists considered how much more complex their models had just become. It is something most scientific fields undergo at some point. In genetics, for example, researchers dismissed the 98 per cent of human DNA that does not encode proteins as "junk DNA" before recent studies found it interacts with nearby genes. They're still trying to determine why, but they do know that non-coding DNA can be responsible for inherited diseases, suggesting that it is more active than previously thought. Suffice to say, no one calls it junk any more.

These oversights perpetuate themselves, say experts, due to limitations and biases built into the whole pursuit of science. One is technology: while there were visible clues pointing to functions for glia, only new imaging tech-

niques developed in the 1980s revealed the cells' use of calcium as a signal, notes Stephen Smith, the Stanford professor. Another is the gravitational effect of discovery. Every breakthrough offers new and exciting opportunities to advance a specific theory, building a critical mass of minds and resources around it. At best, this phenomenon creates clusters of excellence; at worst, it leads to tunnel vision.

Einstein's brain matter had 73 per cent more glial cells by volume than the average of 11 other adult male brains, a scientist found

Carl Craver, a philosophy professor at Washington University in St. Louis, Mo., believes that's exactly what happened in neuroscience. In brain research, he notes, the process for getting approval and money is subject to the same subtle biases as all disciplines, and those biases discourage radical thinking. "People trying to get their first jobs or trying to get grants have to play to their audience," Craver says. "If the audience is senior academics who believe in a certain framework, it's risky to try to tempt them to go in unprecedented directions." In rare cases, he says, shocking results can dislodge that conservatism, "but there are institutional facts about science that can make change slow and difficult."

The flip side of that conservatism? Irrational exuberance, where an advancement is treated as the missing piece of a long-unfinished puzzle. And there have been times when the mania over glial cells has taken on that feel. They have been linked through research in recent years to a stunning array of nerve, brain and muscle afflictions, from epileptic seizures to chronic pain to sleep disorders. The field got a dose of realism, however, when a respected researcher named Ken McCarthy rose at a conference three years ago in Amsterdam to announce results suggesting the excitement might be misplaced.

McCarthy had genetically engineered mice whose astrocytes didn't signal that they were properly using calcium. He found that the neuronal transmission in their brains was not affected. In other words, there was no meaningful interaction between astrocytes and neurons. McCarthy was apologetic: he'd set out to prove the interaction, saying, "I would love to be able to show you

that." Other glia experts raised concern about the design of the study.

Still, an aura of caution descended on the discipline, with pioneers like Fields reminding the public that glial cells neither supersede nor work without neurons. "The emerging view is that it's a partnership between these two cells that makes the whole system work," he says. "You can't say one is more important than the other. The important concept is that glia contribute something new, something different."

For researchers like Robitaille, now at the Université de Montréal and recognized as a leader in his field, that knowledge is enough to sustain another career's worth of lab work. He recently completed a paper that attempts to explain McCarthy's adverse findings and he hopes his work on Lou Gehrig's disease could lead to medical breakthroughs. "There are few neuronal diseases where glial cells are not involved," he notes. "But we've always looked at them from a very neurocentric perspective. We're going to be moving onward." It will require perseverance and—unscientific though it might sound—a certain amount of faith, he acknowledges. Venturing into the unknown is a test of the soul as well as the intellect. Seeing the light is merely the first step. **CHARLIE GILLIS**

How to build a brain

A philosopher and engineer has created the most complex simulated brain in the world. On $30,000 a year.

Chris Eliasmith is a shaggy-haired, former military brat who was born in Ottawa, lived in a different city every four years, and eventually pursued an impressive academic career. Not only is he a professional engineer, he is a philosopher, too. It's not exactly the kind of thing you expect from a guy who, at first glance, looks like he fronts the house band at your local pub.

Though he was always fascinated by the brain, his parents insisted he study something practical, hence the engineering degree from the University of Waterloo. After that, he was free to pursue his passion, and that's how he ended up with a Ph.D. in philosophy from Washington University in St. Louis in 2000.

Now the director of the Centre for Theoretical Neuroscience at Waterloo, Eliasmith is obsessed with the human brain, and has spent a career figuring out how it works. All those years of schooling prepared him for his greatest achievement so far: creating a "biologically-based cognitive architecture"—in other words, a computer model that doesn't look like a brain, but acts like a brain. In May, Eliasmith published a book, *How to Build a Brain*, that lays out in painstaking detail the mechanics of the simulation.

Although he speaks a different language with his colleagues in the lab, Eliasmith can explain the complexity of neuroscience to the layperson. At the TEDx Waterloo conference last year, this is how he described it: "We know that every time we learn something new, play a fast-paced game of hockey, or utter a sentence like this one, these are the results of the electrochemical

maelstrom going on in between our ears," he said.

Eliasmith wants to explain that maelstrom. That's why he built the Semantic Pointer Architecture Unified Network—or SPAUN for short. The brain simulator can memorize lists of numbers, do simple arithmetic, and write out the solutions. But it does more than simple math. Eliasmith can kill neurons in the simulator—mimicking a stroke, or Parkinson's disease, or the effects of aging. That damage impairs SPAUN's functioning just as it would impair a human brain, which allows scientists to learn how the real brain works. Eliasmith, the Canada Research Chair in theoretical neuroscience, and his team are currently working on a more advanced simulation that, unlike the current model, will be able to learn and remember problem-solving strategies.

Magnificent obsession: Chris Eliasmith's simulator can remember lists of numbers, do simple math and scribble out the solutions (PHOTOGRAPH BY KOUROSH KESHIRI)

When Eliasmith and his team demonstrate SPAUN's power at conferences, people barely believe what they're seeing, even if they're only looking at a two-dimensional brain on a screen. After a pattern-identification problem flashes on the monitor, SPAUN figures out the solution using its virtual neurons, and scribbles out the response.

In fact, SPAUN runs on a supercomputer that doesn't look all that different from a standard CPU, which sits in a nondescript room in his lab in Waterloo. The problem is the supercomputer, though powerful, takes 2½ hours to do one second of simulated brain work. That's the very real glitch Eliasmith and his team have hit: They need more powerful supercomputers to advance the work. These aren't in the modest budget, which includes a five-year research grant of $30,000 a year plus a smattering of funding secured by his band of post-docs and graduate students.

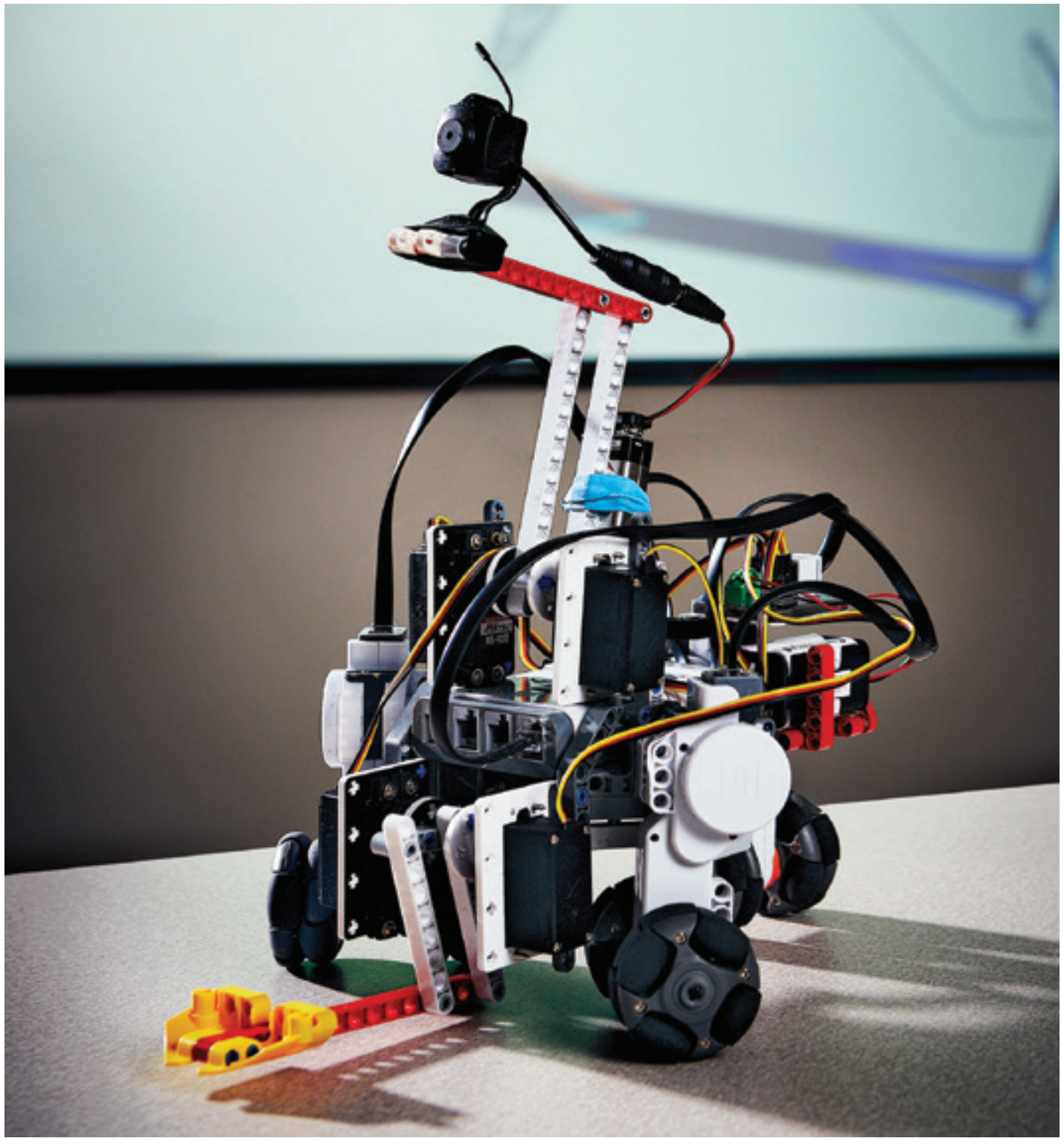
Still, the Canadians made a splash after Eliasmith and his team published their work in the November 2012 issue of the journal *Science*. But their reputation had preceded them: The team in Waterloo has already started working with a group of hardware engineers at the University of Manchester led by acclaimed scientist Steve Furber, the school's ICL professor of computer engineering. The Manchester team is building an artificial brain on a platform called SpiNNaker that could eventually simulate up to a billion neurons—still only a fraction of the 85 billion neurons in a human brain, but a leap ahead of SPAUN's 2.5 million neurons.

"I'm very impressed with SPAUN," says Furber. "It's clearly the most sophisticated cognitive neural system that anybody has constructed to date." Now the teams are collaborating. Eliasmith's Nengo software, which brings SPAUN to life, will be matched to SpiNNaker's increasingly powerful hardware and, eventually, produce a superior modelling platform. "Our roles in this are almost perfectly complementary," says Furber. Eliasmith is working on a similar project with Stanford University.

In global terms, the Waterloo team are overachievers, given their small budget. Their colleagues in Europe and the United States, on the other hand, are on the cusp of an explosion in brain research. Two massive undertakings could blow the door wide open: the Human Brain Project, based in more than 80 institutions in Europe—including Furber's lab—and fuelled by $1.6 billion from the European Union, and the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) initiative in the United

States, announced by President Barack Obama in April with a pledge for $100 million in initial funding.

The two programs, both in early stages, aspire to accomplish different, though related, objectives. Eliasmith says the European program aims to build enormous models of the brain that simulate the work of billions of neurons, while the American initiative will comprise an equally huge data-gathering effort.



Proof of concept: A simpler, robotic version of SPAUN, affectionately called Spazbot, is used to test the brain model in the natural environment (PHOTOGRAPH BY KOUROSH KESHIR)

What that means, says Jean-François Gariépy, a postdoctoral fellow in

Duke University's cognitive neuroscience centre, is that the Human Brain Project could produce powerful theoretical models of the brain. The BRAIN project, on the other hand, will focus on collecting data in the real world. If it's successful, the U.S. initiative could give scientists "new levels of access to the details of actual functioning brains," says Eliasmith.

"Can we sit there and watch a hundred or a thousand neurons at the same time that an animal is performing a task? That would give us unprecedented levels of detail, and levels of information, about interactions between brain areas."

Gariépy, who hails from Sainte-Sophie, Que., says both projects have unlimited potential.

'For biology, it's probably the biggest moon shot that we've made. It seeks to do things that we don't know are possible yet.'

"If you want to compare them to anything that's been done in biology, I would say it's the most concerted and ambitious effort done in this century," he says. "It doesn't compare to shooting for the moon, but for biology, it's probably the biggest moon shot that we've made. It seeks to do things that we don't know are possible yet."

Eliasmith's work lies at the intersection of these enormous global undertakings. "I still sincerely believe that SPAUN is the only large-scale model that actually connects the data to the behaviour," Eliasmith says.

"If you think the connection between the low-level neural data [produced by the Europeans] and the high-level behavioural data [produced by the Americans] is important, then I still believe SPAUN is really far ahead." Furber has immense confidence in his future. "SPAUN is very unlikely to be Chris's last word on the subject," he says. "Others will see it, and be inspired by it, and attempt to do better. At the same time, I'm sure Chris will attempt to improve on it."

Where the team in Waterloo falls short is, obviously, money. They don't benefit from a pool of resources nearly the size of what's on offer south of the border and overseas. But that could change, in part due to federal investment in the new Canada Brain Research Fund, which has gone mostly

unheralded since it was first announced in the 2011 federal budget.

The money was pledged to Brain Canada, a non-profit that rose from the ashes of the former Neuroscience Network Centre of Excellence, which saw its federal funding eliminated in 1998. Soon after, says Brain Canada president and CEO Inez Jabalpurwala, the organization started to fund research that treated the brain as "one system" that's "not just divided by a bunch of diseases."

A decade later, the group approached the feds for financial support. The government responded with a commitment to match every dollar raised by Brain Canada, up to $100 million, over six years.

Mark Bisby, a Brain Canada adviser, says it could end up funding Canadian research in the larger European and American initiatives. The Human Brain Project has set aside money for "open calls" that allow international researchers to get a piece of the action. As for the BRAIN initiative south of the border, Jabalpurwala says the federal government is encouraging Canadian participation.

Brain research is officially in vogue, and Eliasmith's SPAUN is at the forefront of brain simulation. As billions are spent on brain modelling around the world, no one can ignore the stunning accomplishment of the plucky team from Waterloo—a group of post-docs and grad students led by an Air Force brat who decided he wanted to build a brain. **NICK TAYLOR-VAISEY**

Mad beauty

A conceptual photographer dusts off the jars of a brain collection from a Texas mental hospital

Patients were piling up at the former State Lunatic Asylum in Austin. For 30 years, from the 1950s onward, the once-revered institution had become an overcrowded repository for people who were unable to survive on their own. Patients lived and died there. Many were autopsied. And often their disfigured brains were immersed in jars of toxic preservatives.

"I was dumbfounded," says Austin photographer Adam Voorhes, describing the moment he first saw the brains tucked away in a closet at the University of Texas two years ago. The 34-year-old freelance magazine photographer was there to photograph a healthy brain for a *Scientific American* feature story. That's when he saw the collection of brains bequeathed to the school in the 1980s by what is now the Austin State Hospital. "You walk into this storage closet and there's this floor-to-ceiling, wall-to-wall, glass-covered case filled with these large glass jars with brains," he says.

The worn labels on the 100 jars revealed nothing more than the date of death or autopsy and the diagnosis, often scribbled in Latin: Down syndrome, Alzheimer's and meningitis. Voorhes was surprised by how many patients were not mentally ill. Other medical conditions included water on the brain, epilepsy and syphilis.

The contrast between the healthy brain and those stacked in front of him was stark. The preserved brains were different in size, colour and shape. As he peered through the murky solution, it was obvious some had been the

object of study. And in some jars there were bits of lung and kidney—presumably from the same patient. Voorhes contemplated a book of photography; for the text he recruited 38-year-old freelance writer Alex Hannaford.

"It was fascinating to look at these brains and try to imagine the kinds of lives these people were living up until their death," Hannaford says.

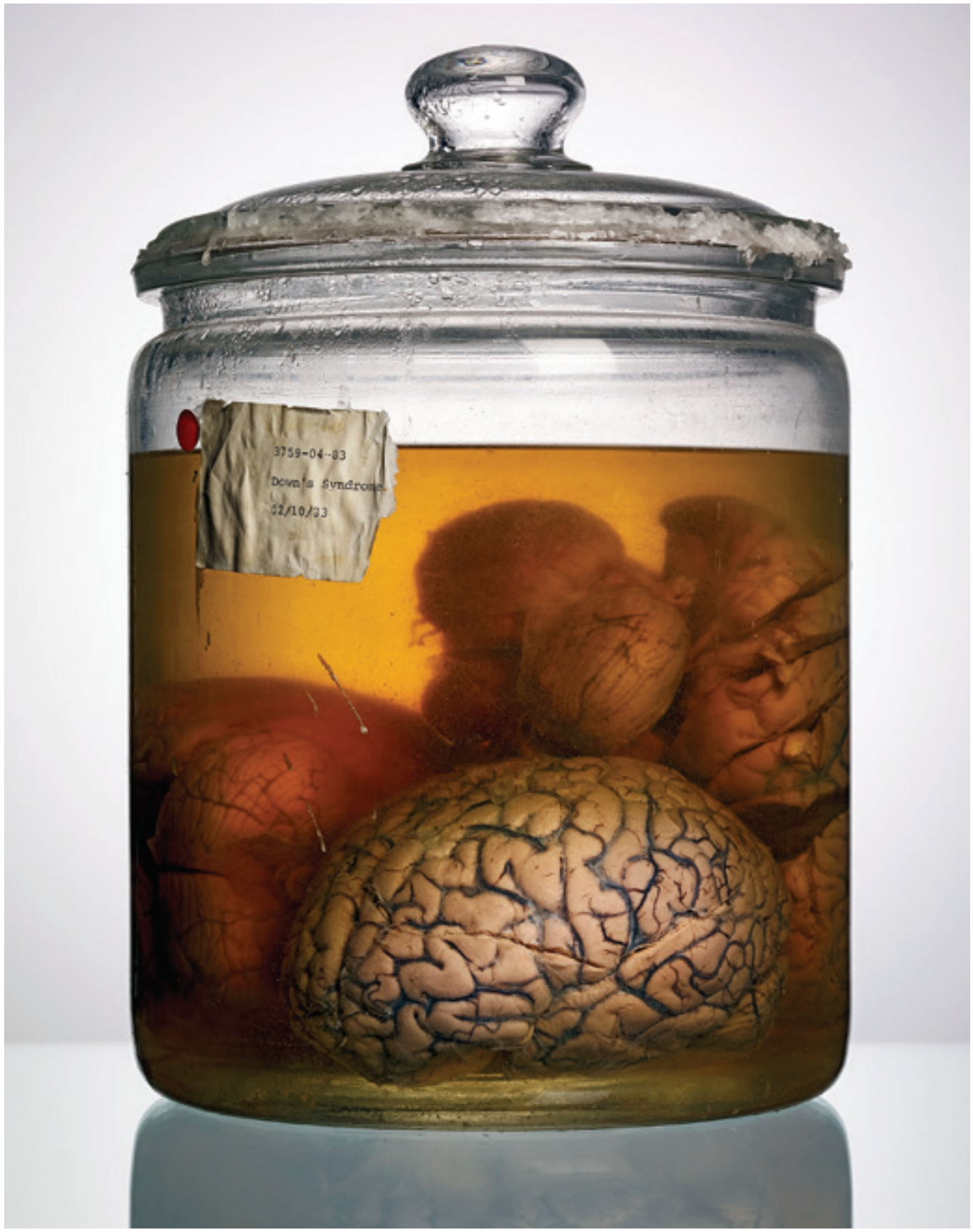
But as he dug into his research he discovered the hospital had destroyed the medical records years ago. The project became "a bit of a sleuthing adventure," he says—a mystery he admits has never really been solved. Instead, the photographer, known for his conceptual images, and the writer will publish a book chronicling the history of the hospital from the late 1800s to the early 1980s.

Both Hannaford and Voorhes are convinced the brains could provide insight into a variety of illnesses, especially as advancements in technology such as MRI scans and DNA sequencing can reveal more of their stories.

"We understand how the heart works. We know exactly what it does and why it does it. But we do not fully understand the brain," says Voorhes.

Meanwhile, he feels the brains have endured enough. The patients suffered in life. In death their brains were extracted, dissected and subsequently abandoned for decades. But it took Voorhes's quirky eye to reveal the strange beauty in the dusty jars. **DAVID GRAHAM**

Brains in jars: Like many specimens in the University of Texas collection, this one belonged to a patient without a mental illness. The diagnosis was Down syndrome.

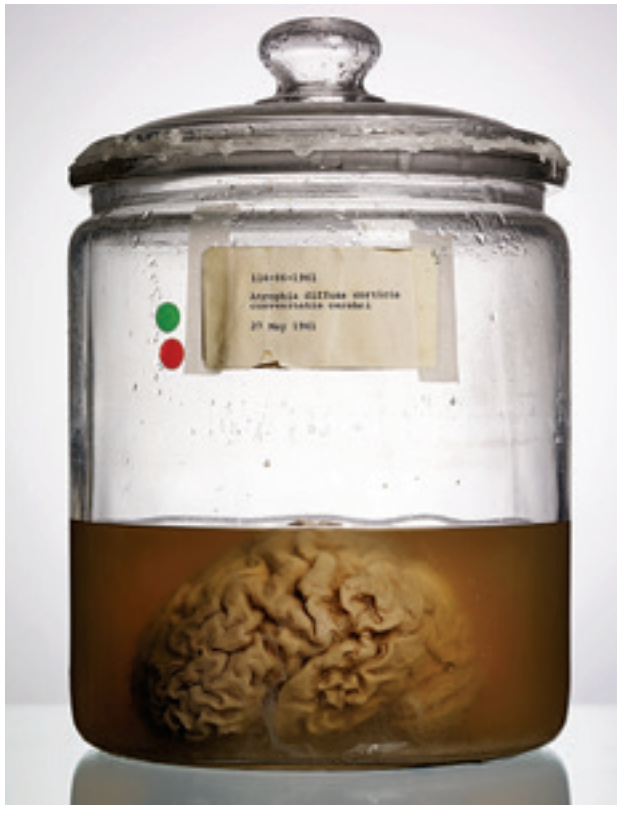


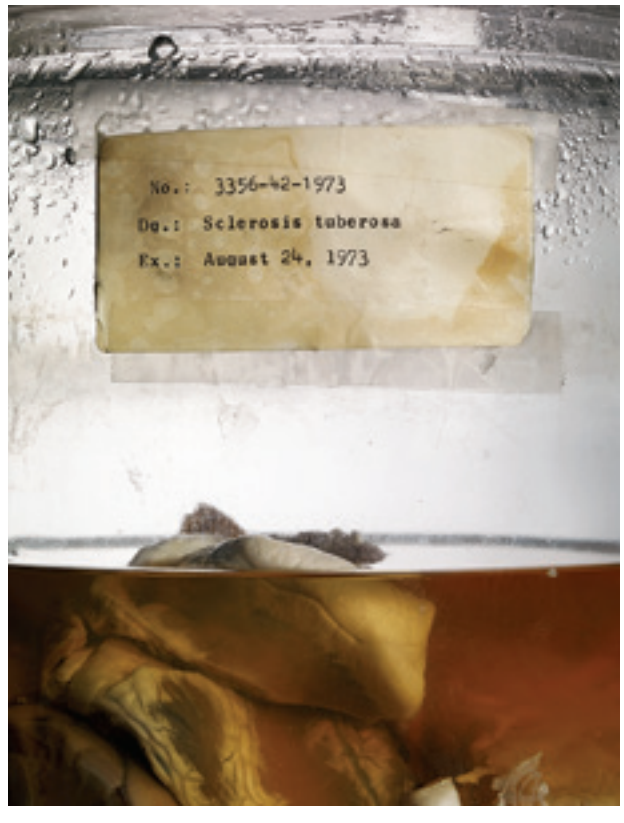
True colours: ‘A normal brain is this beige colour, but the hemorrhaged brains have got these black lines between the nodules’ — author Alex Hannaford

‘It was fascinating to look at these brains and try to imagine the kinds of lives these people were living up until their death’ — author Alex Hannaford

Mysterious matter: The medical charts from the mental hospital were destroyed, and many brains bequeathed to the University of Texas have gone missing

After being abandoned for decades, photographer Adam Voorhes's quirky eye revealed the strange beauty in the dusty jars





Crude vessels: Voorhes, who wore a respirator to protect his lungs from the toxic fumes given off by the preservatives, was surprised by how primitive some of the containers were: 'Some of the jars were cracked and there was just a simple wax used as a seal, or even Saran wrap. I just felt, "Why isn't this being taken more seriously?" '

They grow up so fast

The latest research on a baby's remarkable brain development, from recognizing right and wrong to the gift of memory

While it seems all they do is cry and poop and feed and sleep, your baby's brain is working far harder than yours—and neuroscientists are paying attention. Here's the newest research on a baby's remarkable brain development before the tender age of four.

In the womb: Even before the first breath, the fetal brain is forming all its main structures and creating synapses among its 100 billion nerve cells. But because it is undergoing such major construction, it is susceptible to neurodevelopmental disorders. Society talks much of alcohol and sushi, but an often-overlooked culprit of long-term effects on the baby brain is a more mundane and common influence: maternal stress. "Infants who are highly stressed [because their mothers are] highly stressed during pregnancy end up with measurably smaller brains," says Dr. Jean Wittenberg, head of the infant psychiatry program at the Hospital for Sick Children in Toronto. Excess cortisol and adrenalin, produced by the body in response to stress, "damage vital regions—such as the hippocampus and amygdala—areas responsible for learning, memory and emotional responses," according to a report from Harvard University's National Scientific Council of the Developing Child.

'Baby morality': At three months, infants may be capable of distinguishing between right and wrong, according to Yale's Infant Cognition Center (GETTY IMAGES)

Birth: "People don't talk about birth as a milestone," explains David Dyment, clinical geneticist at the Children's Hospital of Eastern Ontario in Ottawa, "but even then, at time zero, there are expectations—movement, sucking, balance between wakeful moments and sleep." Getting there takes time. New research from Columbia University Medical Center using data from school-age children in New York found that the longer a baby stays in the womb, the better the likelihood of academic achievement. Compared to those born at 41 weeks, babies born at 37 weeks were a third more likely to have reading difficulty and 19 per cent more likely to have problems doing math. For Dyment, this makes sense: "Certainly, a child born prematurely is at greater risk for medical conditions, including bleeding in the brain, which may cause developmental issues." Dr. Stephen Miller, head of neurology at the Hospital for Sick Children, thinks birth age might be the most important: "If you're

looking for a single predictor of how well a baby will do, look at their gestational age of birth."

3 months: Now smiling and waving arms and legs around, baby is showing the first signs of personality. It may, according to psychologist Karen Wynn at Yale's Infant Cognition Center, be capable of distinguishing between right and wrong. In a 2011 experiment, babies watched a puppet show: As one puppet struggled to remove a toy from a box, a nice puppet helped out. In a repeat scene, a mean puppet slammed the box shut. Given the choice, more than three-quarters of five-month-olds chose the good puppet. Wynn tried the same experiment on three-month-olds, who voted with their eyes. "Babies, even at three months, looked toward the nice character and looked hardly at all… toward the unhelpful character," Wynn explained in a *60 Minutes* segment that aired last year. Critics were quick to poke holes in her theory of "baby morality"—babies had already watched Mom and Dad helping them for three whole months—but Wynn seemed convinced. "Study after study after study, the results are always consistently babies feeling positively toward helpful individuals in the world," she said.

6 months: Good news for baby, not so good for parents: "By six months, babies can't be soothed by people who are not their primary caregivers," says Dr. Wittenberg at Sick Kids. For some, this represents the root of "baby consciousness"—the moment baby can recognize himself as different from other people, and that those people are different from each other. Consciousness is a relative and subjective term, but in April, French researchers sought to measure the pattern of consciousness—that is, a sensory cue followed by a spike in electrical activity—in babies as young as five months via baby-sized EEG caps. Two-thirds of squirmy subjects refused to co-operate, but the remaining 80 revealed the same pattern as adults, albeit slower. It took babies 1.3 seconds to recognize an unfamiliar face, whereas adults can do the same in 0.3 seconds.

9 months: Before the nine-month mark, point your finger at a baby and she will look at your finger; after nine months, she'll look where you're pointing. "Baby can recognize now that there's an intention," says Wittenberg. More fascinating, however, is that she may actually feel it. Since 2009, researchers at the University of London have used electrodes to record nine-month-

old brains as they watched people reach for toys. The babies' motor region was activated as if they themselves were doing the reaching. This suggests predictive behaviour, or that "they observe or anticipate other people's actions, even when these are actions they cannot yet do themselves," explains lead researcher Victoria Southgate. "This mechanism is crucial for collaborative activity with others," she adds. Which really means that playtime just became more fun.

1 year: By one year, the brain has nearly doubled in size. Neural connections are strengthening, so some eager parents start to fine-tune baby's future skills. They're not wrong: Researchers at McMaster University in Hamilton found very early musical training led to one-year-olds who communicated better (through pointing and gesturing), smiled and soothed more and showed larger and earlier brain responses to sound. The study compared infants who took interactive music classes between six and 12 months (which included singing lullabies and playing percussion) with infants who attended classes where music merely played in the background. "Past studies of musical training have focused on older children," says Laurel Trainor, director of the McMaster Institute for Music and the Mind. "Our results suggest that the infant brain might be particularly plastic with regard to musical experience." Others aren't persuaded (and baby music lessons will not guarantee you've got a budding musician): "Do babies understand beats and timing? No," says Dyment. "But can they recognize music and have favourite songs? Absolutely."

18 months: In a 2011 TED conference talk, developmental psychologist Alison Gopnik described her findings of "the broccoli-Goldfish" study. Gopnik placed two bowls—one of tasty Goldfish crackers, one of raw broccoli—in front of 15- and 18-month-olds. All babies preferred the crackers. Then a researcher made yummy noises as she eyed the veggies, before putting out her hand and asked for food. "The question is: What would the babies give her? What they liked or what she liked?" Eighteen-month-olds shared the broccoli, despite their preference for crackers. (Fifteen-month-olds, meanwhile, stared blankly, then offered up the crackers just the same.) At 18 months, says Gopnik, "babies discover this really profound fact about human nature: We don't always want the same thing. And what's more, they felt they could do things to help others get what they want."

2 years: By age two, the brain is about 80 per cent of its adult size and is already strengthening well-used connections and eliminating others. “You get this pruning effect of connections between neurons, which will continue until adolescence,” says Dyment. You also get the gift of memory. Experts once scoffed at memories before age three or four—when the hippocampus is adequately formed—but new research challenges that. In a 2011 New Zealand study, 46 kids as young as two played happily with a “magic shrinking machine,” where a pulled lever turned full-sized toys into smaller versions (memorable, for a kid). Six years later, most had forgotten the whole event, but nine had strong recollections, two of those from children barely two at the time. A longitudinal study at Memorial University in Newfoundland asked 140 children between four and 14 to describe their earliest memories. Two years later, they asked again. “Younger children’s earliest memories seemed to change, with memories from younger ages being replaced by memories from older ages,” says psychology professor Carole Peterson, who led the study. “But older children became more consistent in their memories as they grew older.”

3 years+: Just a year away from full size, the brain has experienced what Sick Kids neurologist Dr. Miller calls “an explosion of development.” His Sick Kids colleague Dr. Margot J. Taylor cautions that “not all children reach their milestones on time, and how can we tell ahead of time which children will require extra help to stay on track?” To do so, Taylor’s team has been following a group of pre-term infants (born two or more months early) up to age four, comparing brain imaging at birth to ongoing behaviour, cognitive and language assessments. Preliminary results suggest that changes in the brain detectable at birth may be correlated with developmental difficulties four years later, so early intervention may aid in social and motor skills, expression of needs and desires and enhanced academic success. “Looking at the developing brain can help us identify the most vulnerable children before their difficulties come to light,” she says. **ROSEMARY COUNTER**

Gone baby gone

Why don't we remember anything from earliest childhood? It's called infantile amnesia.

Elise Troister's first memory, at age 5, goes like this: she's at a friend's house, swinging on a swing set in the backyard, when a "black fluffy dog" approaches and tries to bite her feet as they scrape the ground. "The dog keeps trying to catch my feet," she says. "Eventually I start to cry." She remembers this vividly, and yet, when asked about the time she took her first step, or said her first word, Troister, a 23-year-old Toronto artist, draws a blank. Why? Because like the majority of adults on this planet, she cannot remember anything before the age of 3½. In other words, Troister has childhood amnesia, a scientific term for our murky childhood memories, or what researchers Carole Peterson and Duyen T.K. Nguyen described in a 2010 study as "the absence or scarcity of memories about very early life events." The theory goes that sometime during childhood development, we lose the ability to access our earliest memories. But the question remains: Why does it happen?

One of the thinkers to tackle this question—he coined the term "infantile amnesia"—was Sigmund Freud. In the early 1900s, Freud surmised that the "veil of amnesia" is a kind of security blanket. We repress our earliest memories, he argued, because they are inherently inappropriate: sexually charged and/or rife with social taboos. "From his [Freud's] point of view," says Peterson, "you had the Oedipal complex, the Electra complex. People have inappropriate thoughts about parents. He thought they were repressing them."

One in, one out: We're prodigies at making memories before about age four, but because of heightened brain activity, it's harder for us to retain them (ANDREW TOLSON)

It's an interesting theory, like most things Freudian; but also like most things Freudian, it has its weak spots. In the first place, the theory is a classic logic trick: the things we can't remember from early childhood may indeed be taboo in nature, but if we can't remember them, how do we know? And anecdotally speaking, sometimes the early memories that linger longest are in fact the creepiest. Sasha Downer, a 24-year-old Richmond Hill, Ont., fashion writer, reports that her first memory is of her baby brother defecating on her grandmother's head while she was holding him aloft—an image Downer might have been spared if the "veil of amnesia" was up and running.

Recently, other more credible (if not as entertaining) childhood amnesia theories have surfaced: some purely "hard science," others anthropological. One of the most current and fascinating explanations belongs to Paul Frankland of the Hospital for Sick Children in Toronto. Children, he says, eventually lose their earliest memories because "neurogenesis"—the creation of new neurons in the brain—changes their brain circuitry as they age. When we're young, our brains are in a state of information flux: we're constantly learning and experiencing new things. We're prodigies at mak-

ing memories at this point, but because of the heightened activity in our brains, it's apparently much harder for us to retain them. As we age, this process decelerates and our ability to retain memories increases.

To prove the theory, Frankland's research team accelerated neurogenesis in the brains of adult mice—to mimic the heightened brain activity of infant mice—and stalled it in infant mice—to mimic the brain activity of their elders. The results were uncanny. With neurogenesis reversed, infant mice retained more memories and adult mice became more forgetful.

Where does language figure in this process? "Some psychological theories would argue that infantile amnesia is related to the development of language," says Frankland, "but the fact that we see very much the same type of forgetting in infant animals argues that it can't just be language."

Maybe, but for Peterson, language is the one constant. "If you can talk about it [a memory] in a coherent way you are more likely to remember it," she says. "If it's emotionally neutral it's more likely to be forgotten."

According to Elise Troister—she of the backyard swing memory—not only did her parents talk to her frequently about the dog incident over the years, they also showed her a home video of it regularly, sparking the memory and enabling its preservation. Peterson's 2009 study, which she conducted with Yubo Hou at Peking University and Qi Wang at Cornell, revealed that children whose parents talk to them frequently about their individual experiences are more likely to remember their early childhood later in life.

Peterson and her team also discovered that parents in North America are more likely to trigger early childhood memories than parents in Asia—China in particular. In China, theorizes Peterson, it's considered uncouth and at odds with "Confucian values" to talk endlessly about your child's unique attributes and experiences, something that comes naturally to us in the West.

The result? The North American kids in Peterson's study were better at recalling episodes from early childhood than their Chinese counterparts. "This was our first cue that it's not just the memory system doing its thing," she says. "There are social variables affecting childhood amnesia." And Peterson believes there are definite benefits to a robust early childhood memory: "A person's identity is tied up with the story they tell about themselves," she says.

Embedded in this idea is another one that might be just as salutary: the knowledge that our memories may not be determined by science alone, but by the stories that we tell one another. **EMMA TEITEL**

(EMMA KIM/GETTY IMAGES)

Memory and gender

We know that memory loss happens to just about all of us at some point in our lives, whether as babies or as octogenarians, but does it affect men and women equally?

Researchers at McMaster University tried to answer this question by conducting a memory-themed battle of the sexes. Their findings may account for the stereotype that men don't "notice the little things." According to Jennifer Heisz, one of the researchers on the Females Scan More than Males study, women tend to "scan" faces better than men, giving way to better memories for facial recognition. "The way we move our eyes across a new individual's face affects our ability to recognize that individual later," she was reported as saying. "Women look more at new faces than men do, which allows them to create a richer and more superior memory."

How do the sexes differ when it comes to infantile amnesia, the loss of

memory before ages 3 to 4? According to a Canadian study from 2010, “almost all investigations of infantile amnesia have been conducted with adults, and gender differences favouring women are frequently found.” In other words, some studies have found that women are better at recalling early childhood memories than men. (When studies are done on children, however, the gender difference is not yet identifiable.) For now, it appears women may be winning the memory war. **EMMA TEITEL**

The young and the restless

No one knows why autistic kids are often night owls, but their parents can take heart: science is looking at some biological causes based in the brain

Three or four times a week, Malcolm would go on a rampage in his room until two in the morning, systematically tossing all of his toys and clothing around, stripping his bed and either yowling or shouting with glee. Then his brother, Piers, would wake up around three, ready to start his day. “Some nights I would sleep on the floor in Piers’s room, and other nights I don’t think I slept at all,” says Stephanie Pocock, the mother of the two Ottawa boys, both of whom have autism.

While sleeping problems are common among children, for mothers and fathers of children with autism spectrum disorder (ASD) bedtime can be a nightmare. It’s difficult to get these kids to bed, and when they wake before morning, even harder to get them back to sleep. The frustration and anxiety and stress on both sides contribute to more sleepless nights.

Autism is a complex disorder that affects brain development, which leads to trouble communicating and interacting socially. Of the one in 150 to 160 children diagnosed with autism, experts estimate that anywhere from almost half to three-quarters will develop some form of sleep disorder. In some instances they get up in the middle of the night. Others on the autism spectrum function normally with significantly reduced hours of sleep, behaviour that continues to baffle researchers.

"It is a challenging area partly because you are using things like EEG to record sleep," says Isabel Smith, associate professor of pediatrics and psychology at Dalhousie University in Halifax, referring to the graphing of electrical activity in the brain. "It is a lot to ask of a child with ASD and a parent to have them come to a sleep lab to do these types of studies."

Sleepless nights: Malcolm Pocock, who has autism spectrum disorder, used to go on a rampage in his bedroom until two in the morning (PHOTOGRAPH BY RÉMI THÉRIAULT)

AT THE UNIVERSITY of Alberta, Dr. Lonnie Zwaigenbaum is studying the link between sleep disorders and stress in 363 Canadian children. The associate professor and director of autism research and pediatrics says preliminary studies suggest a close relationship between sleep, a child's behaviour and parental stress, meaning that sleep challenges can predict the future severity of behavioral problems. For that reason he believes autism requires both behavioural and medical treatments, and that when doctors diagnose autism they should also assess the child for sleep disorders.

"I think until recently people just thought of the symptoms of autism in terms of difficulties communicating and difficulties interacting with people," says Zwaigenbaum. "But there are additional challenges surrounding physical and emotional health. They are not part of the definition, but could impact the way a child functions or participates."

One of the common theories to explain sleep problems is that children with

autism make less melatonin in their brain, or do not make it at the proper time. Melatonin is the neurohormone produced by the pineal gland that regulates the circadian clock. Production is increased in darkness and reduced in light.

'Under control': Now seven years old, Malcolm doesn't trash his room any longer, though he still won't go to bed before 10 or 11 p.m. (PHOTOGRAPH BY RÉMI THÉRIAULT)

There have been no concrete studies on the effect of melatonin supplements on children, though a small U.S. study of 24 children (a sample size too small to be statistically significant) did help determine effective doses as well as recommend a dose 30 minutes before bedtime. However, doctors don't know how it works and if there are any long-term side effects.

"We know that it is the levels within the brain that influence the sleep cycle, but we are still learning about the relationships between the bloodstream,

in which melatonin is absorbed, and the brain," says Zwaigenbaum.

Despite the lack of information, it is still a popular sleep treatment. "We use melatonin on occasion," says Pocock. "I've been told there is no long-term research about possible implications, but when you are dealing with a seven-year-old child who is getting three hours of sleep at night, that is bad for their health."

'It is a lot to ask of a child with ASD and a parent to have them come to a sleep lab to do these types of studies. It's a big investment.'

The other possibility is that melatonin production may be influenced by gene mutations in autistic children. For example, the gene and enzyme N-Acetylserotonin O-methyltransferase, also known as ASMT, transforms the protein normelatonin into melatonin. In cases of sleep disorders, it is possible that the gene is mutated and does not create the proper enzyme to complete melatonin synthesis.

Another theory is that sleep problems are related to iron deficiencies, which can be more common in autistic kids because they can be extremely picky eaters and/or have gastrointestinal problems. Iron is thought to be involved in the synthesis of dopamine, a neurotransmitter involved in motor function. Dr. Beth Malow, director of the sleep disorders division of the Vanderbilt University Medical Center in Tennessee, is studying iron deficiencies and restless-leg syndrome in autistic children. "The hope is that you can treat the iron, which may be low in these kids due to dietary preferences, and that can make a huge impact in terms of their sleep."

WITH NO CONCRETE biological reason for the sleepless nights, parents resort to strict bedtime routines, which work, although they are taxing: it took six months for Pocock to move Piers's bedtime to 8 p.m. from 7 p.m. Now nine years old, Piers has begun to sleep through the night, and his brother Malcolm, 7, doesn't trash his room anymore, although he still won't go to bed until 10 or 11.

In Calgary, Tanis Anderson, the mother of five-year-old Melia, is still awoken by screams at 4 a.m. on the dot, and it can take upwards of half an hour to calm her daughter before she can return to bed.

"Even though I'm still not getting a full night's sleep, I feel like I have it under

control," she said of Melia, who has Rett syndrome, a severe neurological disorder on the autism spectrum. "Or maybe I'm just used to it." **KATHERINE DECLERQ**

Crying out for attention

How one psychologist is offering hope to parents worried about the stigma, safety and side effects of ADHD medication

Attention deficit hyperactivity disorder is one of the most-studied childhood mental-health conditions, and yet its cause is still poorly understood. While researchers hunt for the combination of genetic and environmental factors that raise the risk of developing ADHD, parents seek ways to improve the child's well-being, including behavioural interventions that may be more effective than medication in the long run. But access to children's mental health care and behavioural programs come with long wait-lists and other barriers, so families drop out.

Patrick McGrath wants to change that. The child psychologist and professor at Dalhousie University in Halifax started a mental health call centre, staffed with trained non-professionals who coach the parents of children diagnosed with moderate ADHD and other disorders. Last year, Strongest Families, a non-profit, served 900 parents with children aged four through 12 across the country. "We teach very specific skills," says McGrath, its CEO. For instance, "noticing the good" reinforces good behaviour and casts positive attention on the child. "As my mother used to say, and she had 10 kids, it's better to be noticed for murder than not be noticed at all."

They help parents establish good routines and clear expectations, as well as provide acknowledgements and rewards for kids when they do things properly, and issue appropriate—but not harsh—consequences for misbehaviour.

"It's not rocket science, but it has to be done very explicitly," says McGrath.

"Our contribution is not that we're using parent training, which has been done by many, but that we're doing it at a distance." Health districts in Nova Scotia, Ontario, Alberta and British Columbia currently offer the service.

'The quick fix': Parents of children with attention deficit hyperactivity disorder often stop pursuing other options when medication is prescribed (NICOLE HILL/RUBBERBALL/CORBIS)

In fact, behavioural interventions are recommended for all children diagnosed with ADHD. But often parents stop pursuing other options when medication is prescribed. "There is a tendency toward the quick fix, but parents should take the relative calm of the child and the family to do something more about it," says Dr. Philippe Robaey, a psychiatrist who heads a clinic on ADHD and disruptive behaviour at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa.

The success of behavioural interventions offers hope to parents who worry about the stigma, safety and side effects of ADHD medications. "Hearing your child has ADHD is not easy," says Dr. Alice Charach, a psychiatrist and head of the Attention Deficit and Related Disorders Clinic at the Hospital for Sick Children in Toronto, whose neuropsychiatry team assesses about 180 new families a year (with a seven-month waiting list). "It's a whole other step to hear you have to use medication and not want to. It's a big decision."

The U.S. Centres for Disease Control says one in 10 children between the ages of four and 17—or 5.4 million kids—had been diagnosed with ADHD by 2007, according to reports from their parents. That was a 22 per cent increase over 2003. In Canada data is murkier, but figures from the National Longitu-

dinal Survey of Children and Youth suggest that 2.6 per cent of three- to nine-year-olds have been diagnosed, up 50 per cent from 2001. Roughly two-thirds of children with ADHD in Canada and the U.S. are prescribed medication.

Some physicians and advocacy groups have applauded the increase in diagnoses, chalking them up to better recognition of the disorder. Others say widespread misdiagnosis due to hasty assessments by inexperienced professionals, or from efforts to keep a disruptive child in school, has put kids on medications they don't need.

There's some evidence to support this. Studies of school-aged children in the U.S. and British Columbia found the youngest children in a class, those born just before the admissions cutoff date, are more likely receive a diagnosis of ADHD and take medication. "In some cases a lack of maturity is being mistaken for a medical diagnosis," says Richard Morrow, a research analyst at Therapeutics Initiative, an organization that studies drug safety and effectiveness at the University of British Columbia. Still, Robaey believes "we miss a lot of kids with ADHD."

Earlier diagnosis and intervention has long-term benefits. The child will do better in school, won't feel stupid, be labelled a problem, and get bullied, says Charach. But it's difficult to tell if an unco-operative preschooler who throws temper tantrums has ADHD or another behavioural disorder. "Parent behaviour training makes as much of a difference as medication in preschoolers," says Charach. The medications usually prescribed for ADHD, stimulants containing methylphenidate, sold as Ritalin and Concerta, or amphetamine, sold as Adderall, aren't approved by Health Canada for use in children under six, because few studies have been done in this age group. Even so, about 60 per cent of Canadian preschoolers diagnosed with ADHD are prescribed medication off-label.

Most children with ADHD do benefit from medication, but finding the right drug and dosage takes time. The CHEO clinic skips the guesswork by doing a four-week trial for each child, putting them on either a placebo, or a low-, medium-, or high-dose medication for a week at a time. No one knows the dosage for a given week. Parents and teachers complete daily online questionnaires about the child's appetite, mood and ability to focus, collecting the drug's positives and negatives. At the end of the trial, the parents and physician identify the child's best week—and Robaey reveals the dosage. "This is the child's physiology, this is what the child needs," says Robaey. "If the pla-

cebo week was as good as the others, maybe he doesn't need medication."

If the behavioural training is as important to ADHD treatment as medication, the Halifax-based distance coaching could make a huge difference for the family and for the community. "If we put one kid back on the trajectory of success to become a productive member of society, he will pay for dozens of interventions," says McGrath. "We can design approaches to treatment that fit their needs, not those of the psychologist or the mental health system." **HANNAH HOAG**

Mind the age gap

Previously dismissed as lesser or defective, new research is revealing that the teenage brain is just as powerful as any adult's

Just a few years ago, the teen brain was largely dismissed as all gas and no brakes. Research dwelled on its immature prefrontal cortex—the executive-control centre that tells teens to, say, drive slower or wear a condom—and increased sensitivity to the rush that risk provides.

But new research is telling a different story. As advancing magnetic resonance imaging (MRI) technologies prove neuroplasticity is an ongoing phenomenon, the idea of the teen brain as lesser or defective is being challenged.

"There's no deficit in capacity between the teenage and adult brain," says Howard Sercombe, the sociology professor at the University of Strathclyde in Glasgow who uses the gas-and-brakes analogy. "In terms of computing power, the teenage brain is an adult brain." Sercombe works alongside neurophysiologists in an effort to understand young brains, which are more agile when it comes to creating new neural pathways . "Teenagers have the unique combination of maximum computing power and maximum flexibility."

Harnessing the power and potential of the teen brain has huge implications for mental health. Leading the way is the Saguenay Youth Study, a large, longitudinal study of teenagers in Quebec that began almost 10 years ago.

Back in 2003, Guillaume Collard, now a 26-year-old student and sous-chef from Saguenay, noticed an ad at his high school for the study. Like many teenagers, Collard was driven by a mix of boredom and altruism. "I wasn't involved in much of anything, and my social conscience made me want to get involved," he says.

Teen spirit: 'We collected data over many years from more than 1,000 teenagers aged 12 to 18,' says Dr. Tomas Paus of the Saguenay Youth Study (MUAMMER MUJDAT UZEL/GETTY IMAGES)

So, for modest compensation, Collard enrolled in the Saguenay study, which measured everything from memory and cognition to cardiovascular and metabolic health. "There were meetings at school, a test on the computer, a written test," says Collard. "Then we had medical tests at the hospital, where we saw specialists."

One of those specialists was neuroscience pioneer Dr. Tomáš Paus, the director of the project. “We collected data over many years from more than 1,000 teenagers aged 12 to 18,” says Paus, a senior scientist with Baycrest Health Sciences’ Rotman Research Institute in Toronto. But his study, which explores gene-environment interactions, would never work in a genetically varied and multicultural city like Toronto. “When you’re interested in genetics, you want less heterogeneity, both in genetics and cultural habits.”

Paus moved his work 200 km north of Quebec City to Saguenay, a picturesque region known for whale watching along its fjord, at the confluence of the St. Lawrence River. Here, the Founder Effect—a loss of genetic variation when a population remains relatively isolated—has created a “blank slate” for genetic testing.

With funding from the Canadian Institutes of Health Research and the Canadian Foundation for Innovation, Paus measured the blood pressure, heart rate, body compositions, lipid levels, glucose and sex hormones of the Saguenay teenagers. Each participant also did six hours of cognitive tests, including a self-reported lifestyle and mental-health questionnaire, and MRI scans. They’re now in the process of scanning and testing the participants’ parents.

The result is a scientist’s dream: a wealth of specific, intricate data with limitless potential for extraction. More than 30 studies have already been published using Dr. Paus’s research. One linked prenatal exposure to cigarette smoke to the accumulation of 33 per cent more abdominal fat in the children as teenagers. The teenagers whose mothers smoked while pregnant were also more likely to experiment with drugs and alcohol, suggesting smoking may interfere with the brain’s ability to evaluate rewards.

Another found adolescents with higher resistance to peer pressure showed more activity in the prefrontal cortex, suggesting stronger connections between decision-making parts of the brain. Chip Limeburner, 20, who participated in the study between the ages of 10 and 15, remembers his experience fondly. “So many of the tests—brainteasers, tangrams—were like games. And hey, it was a day off school.”

The Saguenay Youth Study reflects a new interest in the teen brain by experts in many fields. For Amir Levine, an adult and child psychologist studying adolescent brain development at the Centre for Addiction and Mental Health in Toronto, adolescence is a fork in the road. “People are starting to understand the period as a critical point in time where you can change

the course of mental illness," says Levine. Dramatic changes in white matter, depending on their trajectory, can make any situation much better or way worse.

Many mental illnesses are manifested in adolescence and early adulthood. "The majority of people who will become depressed will have symptoms in adolescence; most people who suffer from addiction begin experimenting in adolescence," he says. Serious disorders such as schizophrenia often show up in young adults. Studies like Paus's, says Levine, "are a huge undertaking and very expensive, but they enable people to ask many different questions. They can identify risk factors years in advance."

Take, for example, dementia, which is only party genetic. "Fifty per cent of cases are attributable to modifiable conditions—midlife obesity, hypertension, diabetes," says Paus. For anyone predisposed to the condition, controlling their environment (through physical activity, eating habits or restricting alcohol use) could prevent onset. "If you know your weak spot, if you know you're genetically vulnerable to dementia, then you'll know what risk factors to modify and how."

This is what Paus calls "personalized prevention." Others have called it "P4 medicine" (that is, predictive, personalized, preventative and participatory). "If you're able to predict the risk for you, you're also able to understand and intervene," says Paus. Depression, addiction and anxiety, for example, could be pre-treated with cognitive therapy, medications and modified risk factors. Nurture the teen brain, and you might mould it into a healthier one.

But, like all innovations, personalized prevention raises some concerns. "My only reservations about individual profiling is that it's unlikely to be cheap," says Sercombe. "This is a world where little kids don't have clean water but a middle-class white man can pay to know he's got a 70 per cent chance of dying early if he doesn't keep an eye on his prostate."

Then there's the issue of practicality, says Levine. "With adolescence, which is already a very small window of time, you have to get their parents' consent and you have to find kids to reliably come in and participate." When it comes to habits and personality tests, teens are notorious for selective truths and wishful thinking. Or worse. "I remember falling asleep in the MRI machine once when I was supposed to be paying attention," confesses Limeburner. "They had to re-do the test."

Luckily, he's much more interested now: Limeburner is a second-year

McGill University student majoring in neuroscience. He's even working with the leftover data from the very study he participated in. "I've obtained the images of my own brain," he says. At 20, Limeburner's no longer an adolescent, but he hasn't lost his teenaged sense of humour: "I'm thinking of printing them on a T-shirt." **ROSEMARY COUNTER**

No brawn, no brains

Genetics may decide your upper and lower limits for cognitive fitness, but exercise can really pump up your grey matter

In January, Jen Graybeal, the director of public relations at Overit Media, instituted hourly exercise breaks for the roughly 30 employees who work at the digital media agency in Albany, N.Y. Crunches at 10 a.m., leg lifts at 11 a.m. and a power walk at lunch. The afternoon ushered in lunges, push-ups, jumping jacks and arm dips. And the whole group capped off the afternoon with a freestyle dance session at quitting time. The optional, but widely adopted, exercise program started as a way to get fit, but Graybeal found it had the added benefit of boosting creativity among her team members. “It’s like hitting refresh on your web browser,” she says. “It clears your head of what you’re doing at that particular moment. I sometimes find that when we’re exercising, we’re able to think up different ideas and pitch angles for our clients; it’s an opportunity to come up with fresh ideas.”

Although looking good and preventing cardiovascular disease are some of the key reasons people run, swim and play tennis, it turns out that the brain also benefits from aerobic exercise. And those rewards come regardless of age, says Jennifer Heisz, a newly recruited assistant professor at McMaster University who studies the cognitive neuroscience of exercise.

Cognitive ability—that great big bucket of brain-related tasks that include attention, memory, language acquisition and use, learning, problem solving and decision making—rises like a gentle hill through childhood, peaks during young adulthood and then, around 30, starts to decline, dropping off steadily in the senior years. At that point, what matters most is whether you sink below

a functional threshold, or the point where you can no longer drive, get dressed and do all the other activities required of independent living.

Move it: Only 15 per cent of Canadian adults are active for the recommended 150 minutes of moderate- to vigorous-intensity aerobic activity per week (PHOTOGRAPH BY RYAN MCVAY)

That rise and fall over time is more of a wide brush stroke than a thin pencil line, representing the range of abilities your brain can have at any given age. “Your genetics, your biology, defines your upper and lower limits, but your lifestyle can really push you around in that range,” says Heisz. “And exercise is a key thing that can help individuals get to the upper limit, the upper range, where everyone wants to be.”

On the whole, our brains are as out of shape as our bodies. A 2011 Statistics Canada report found that only 15 per cent of Canadian adults are active for the recommended 150 minutes of moderate- to vigorous-intensity aerobic activity per week.

Scientists have long searched for evidence of the “healthy body, healthy mind” adage. Studies tracking middle-aged and older adults consistently

turn up evidence showing that regular exercise is associated with better brain function, although the studies evaluate cognition from so many perspectives that a cause-and-effect relationship is hard to prove.

Still, older adults who exercise tend to have better executive function than their couch-potato peers. They're better at focusing on the information that's important and filtering out the noise, says Heisz. In real life, that means they can follow the plot of a movie or the flow of conversation, and can plan ahead. In one measure of executive function, fit older adults scored almost as well as younger adults.

But it's the younger adults, those in their prime, who are most worried about their brain health, says Art Kramer, a neuroscientist and director of the Beckman Institute at the University of Illinois in Urbana-Champaign. When he looked into who was buying computerized brain games, he found it wasn't the older folks, it was the fortysomethings. But the training effects of these games are very narrow. "If you're training someone in memory, you don't get the transfer to decision making, or perception, or so forth," he says.

'The interesting thing about exercise is that it has effects all over the brain ... You see improvements across the board.'

Not a lot of research has looked for the brain benefits for middle-aged, normal adults. Kramer studies the effects of long-term exercise programs on the brains of children and older adults, but bets middle-agers would see a similar effect.

Kids with high fitness levels have bigger hippocampi, which are tiny, sea-horse-shaped structures tucked into the base of each lobe of the brain. "It plays an important role in what we call relational memory," he says. "When you meet someone, you remember their name, what they look like, and what you talk about."

In older adults, the hippocampus usually shrinks by one to two per cent annually, which is associated with increased risk of cognitive impairment. But exercise can offset that loss, says Kramer. One study published earlier this year found that adults who were in better shape in their 40s and 50s were less likely to receive a dementia diagnosis later in life. But an accompanying

editorial remarked that you'd need to do five or more hours of exercise a week to lower the risk of dementia even a bit.

Animal research shows that exercise begets new neurons in the hippocampus. It stretches the neuron's protrusions, allowing it to make new connections with other neurons and promote the flow of information. It rolls out new routes for blood flow through the brain and releases chemicals with acronyms such as BDNF, IGF-1 and VEGF, which help the brain adapt to new challenges.

"The interesting thing about exercise is that it has effects all over the brain—various measures of cognition, short-term and long-term memory, decision making, attention, executive function. You see improvements across the board," says Kramer.

But what everyone really wants to know is whether your Sunday-morning run can boost your IQ. The jury's still out on that one, but Kramer, who has a treadmill in his office, is looking at it in children and older adults. "If you really want broad improvements in your ability to think well, take a hike," he says. **HANNAH HOAG**

Obese and obtuse

This may come as no surprise to dieters, but new research suggests that the fatter you are, the fuzzier your thinking, especially when it comes to healthy food choices

For decades, people who struggled with their weight were told it was a lack of willpower that stopped them from controlling their appetites. But new research suggests a shortage of brainpower might be an even bigger problem. A flabby body it seems, can lead to a flabby mind.

"When you get unhealthy, what happens is that areas of your brain get less efficient," says Tim Verstynen, director of the cognitive axon lab at Carnegie Mellon University in Pittsburgh. "Usually it's around how you make a decision and how you get a reward."

In fact, it's possible that obese people are caught in a feedback loop, with their unhealthy choices making them less likely to steer away from fattening foods or unnecessary snacks.

The brain is the body's undisputed energy hog, weighing in at less than 1.5 kg, yet gobbling up 20 per cent of our oxygen supply, 25 per cent of the glucose and 15 per cent of all blood flow. Not surprising, given that something as simple as choosing a breakfast cereal requires a kind of high-level, executive communication that engages multiple areas of the mind. In his own research, Verstynen, a psychologist, has been looking at how that "cross-talk" travels across white matter, the brain's connective network, by taking scans of water levels in nerve fibres called axons. Correlating those images with the subject's body-mass index, he and his team have concluded that the bigger the gut, the less going on upstairs.

"As you become more and more obese, particularly around the midriff, the white-matter signal goes down," Verstynen explains. It's a reduction, he postulates, that is due to a chronic inflammation of the myelin, a sheath that insulates our brain's wiring.

Burger on the brain: Recent studies suggest there's a measurable drop-off in a person's cognitive abilities as their weight goes up (SHUTTERSTOCK)

It's not yet fully clear how such signal disruptions affect the obese, but some recent studies suggest there's a measurable drop-off in cognitive abilities as weight goes up. Last summer, French and British researchers published a paper in *Neurology* reporting the result of a project that tracked the health of 6,400 people over a decade, and had the participants, aged between 35 and 55, do memory and other brain tests three times. What they found is that people who were obese and showed other metabolic changes, such as high cholesterol, blood sugar or blood pressure, showed a 22.5 per cent faster decline in their test scores than those with normal weight and good health.

And last fall, at an international neurology conference, Verstynen presented preliminary findings from a still-unpublished project in which he and his colleagues monitored the brain activity of 29 adults. Participants were shown

the names of colours on a screen and asked to identify the shade they were printed in, rather than the colour they referred to (e.g., the word red, printed in blue). Functional magnetic-resonance imaging revealed that subjects with a high body-mass index showed more brain activity than leaner participants, suggesting they had to work harder to come up with the right answer.

Verstynen likens such reductions in cognitive function to the fogginess one feels after a late night, rather than some precipitous drop in intelligence. But even such a small change could have big consequences, especially if it complicates the decision-making process or impairs impulse control.

We're loving it, unwittingly: Some scientists believe we are hard-wired to eat as many calories as possible and fast food taps into that craving (JIM RITTERHOUSE/FLICKR)

Still, such changes would only partially explain the role the brain plays in obesity. For scientists are really sure of only one thing: Eating is at once our simplest urge and our most complex process. Blood sugar, energy levels, hormones, daily rhythms and even our evolutionary past all play a part in stimulating and suppressing our appetites. (One hypothesis, first put forth 50 years ago, suggests excessive weight gains can in part be explained by a reward system that's still geared to hunter-gatherers. The brain places a premium on high-calorie foods, storing up for lean times that never come in prosperous nations.)

Complex body systems that track energy and satiety levels are constantly providing peripheral signals to the brain about our fuel needs. Much of the monitoring occurs in the hypothalamus, a primitive, almond-sized area we share with all vertebrates. Sitting directly above the brain stem, it synthesizes and secretes neurohormones that, in turn, control a large variety of func-

tions and behaviours, including sleep, thirst, hunger, body temperature, heart rate and the fight-or-flight response.

Then there are higher brain centres—the insula, amygdala, striatum and orbitfrontal cortex—associated with stimuli, emotions, rewards and memory, which also add pieces to the eating puzzle. Dr. Alain Dagher, a neurologist and researcher at the Montreal Neurological Institute, has been studying the effects that ghrelin, a hormone produced by the stomach, has on hunger. Secreted when the gut is empty, it makes the sight of food more appealing. In a 2009 study, Dagher and his team administered ghrelin intravenously, then showed pictures of various foods to subjects while they sat in a scanner. What they found was a significant uptick in activity in the primary and secondary visual cortices compared with those who hadn't been given the hormone. "It seems to change the motivational value of pictures," he explains, "and affect our decision-making as we evaluate the available food options."

Dagher is among those who are convinced that the body's age-old circuitry remains wired for calories, rather than taste or healthfulness, a belief that is buttressed by a growing number of studies suggesting that the popularity of fast food is directly tied to how it stimulates our brains. In a paper published this spring, researchers from three U.S. institutions described what happened when they placed 30 teenagers in MRI machines and showed them TV shows and commercials. Food ads for brands such as McDonald's and Cheerios caused greater activation of brain areas associated with attention, reward and taste than non-food ads for things such as cars, telephones and insurance. And afterward, the teens demonstrated better recall and higher opinions of the food commercials than the non-food ones.

A similar study of younger children, published in the *Journal of Pediatrics* last fall, looked at the effects of corporate logos on brain activity. It found that all subjects showed more action in their reward centres when exposed to fast-food brands. But the obese children also showed higher levels of activity in their cognitive-control areas than children of healthy weights, suggesting they might be more vulnerable to that type of advertising. Dagher suspects such findings simply confirm something that fast-food companies have known for years. "I think they're probably ahead of us, to be honest," he says. "All they have to do is get you to try it, and then the body remembers."

But with obesity now a global epidemic—the World Health Organization estimates there are more than 300 million people who meet the medical cri-

teria, and a further 700 million who can be classified as overweight—the question becomes how we might best work around our brains. Diets are clearly hit and miss. Dagher notes that ghrelin levels actually spike when people try to starve themselves, or are experiencing stress, while a forthcoming British study, previewed last fall, seems to show that skipping a meal actually increases the brain's desire for high-calorie foods.

And our understanding of the intricate, interlinked processes that affect our appetites is still too limited to offer much hope of a pharmacological breakthrough. Rimonabant, a promising anti-obesity drug that blocked a hunger-controlling cannabinoid receptor in the brain, was pulled from the market in 2009 after it was found to provoke severe depression and suicidal thoughts.

Food ads for brands such as McDonald's caused greater activation of brain areas associated with attention than non-food ads

One potential path was unveiled in April by researchers at the University of East Anglia in Norwich, England, who published a paper outlining their discovery of stem cells that generate appetite-adjusting neurons. The cells, known as tanacytes, are found on the floor of the third ventricle, one of four connected, fluid-filled cavities within the brain. Mohammad Hajihosseini and his colleagues were able to prove the cells were reproducing and migrating to neighbouring regions by injecting tiny amounts of dye into the brains of mice and tracing its progression. It's an important breakthrough because scientists previously believed humans were born with a set number of appetite neurons. And if they malfunctioned or died—one of the suspected root causes of eating-related disorders such as obesity and anorexia—the damage was permanent. "It means that these circuits aren't set for life, like most of the other areas of the brain. They're malleable," says Hajihosseini. "And we now have a mechanism to replace them if we wanted to."

Eventually. There's still the question of whether these neurons turn the appetite on or off, as well as which genes regulate their biology and make them divide—and at what age, and for what reasons, humans stop naturally producing them. There are five or 10 years, the lead researcher estimates, of heavy scientific lifting before we might be able to talk about interventions.

A more direct and probably more effective way to combat the obesity epidemic is to cut off the foods that are feeding it—calorie-rich, low-nutrition snacks, sugary drinks and ever-more mind-blowing fast-food innovations. (Pizza Hut now offers cheeseburger-stuffed crusts at its Middle East locations and hot-dog-stuffed ones in the U.K.) "It's going to take new public policy to change things," says Montreal's Dagher, "just as we saw with the tobacco industry 10 or 20 years ago."

The mystery of how the brain controls—and sometimes diverts—our appetites will probably take much longer to fully unravel. As Tim Verstynen points out, it was only a decade ago that researchers began to suspect there was a link between obesity and reduced cognition. It's too soon to even say whether differences in the brain cause obesity, or obesity causes changes in the brain. (The most likely answer seems to be both.) "We're just at the beginning of this," he says. "We're still trying to figure out what questions to ask." **JONATHON GATEHOUSE**

The hidden costs of conflict

What happens when the horror of war slams into a brain predisposed to PTSD? With new research on different fronts, glimmers of hope

Cpl. Greg Shand landed in Afghanistan for his first tour of duty in September 2008. He was a mobile support equipment operator, a "trucker," who drove all kinds of vehicles, including the Bison armoured personnel carrier, a hulking eight-wheeler designed to carry infantry, often venturing beyond the safety of the base. Mostly, he transported "anything to keep the battle going, from personnel right down to dry socks." But Shand was also part of a crew that recovered vehicles that had been hit with improvised explosive devices (IEDs) and rocket-propelled grenades. "Nine times out of 10 there was a fatality or an injury, so there was the body mess as well inside of it."

Shand held things together and says others complimented him on his performance under pressure. He never broke down. Instead, he "bottled everything up," he says. But after his tour ended in 2009 and he returned home, it started to spill out. He was hostile, drank heavily and worked reluctantly. During the eulogies at ramp ceremonies, he wondered why he had survived. He couldn't string together more than two or three good nights of sleep in a couple of weeks. "I'd wake up from nightmares, soaked." Sleep disturbances are one of the hallmarks of post-traumatic stress disorder, a severe anxiety widespread among military veterans and others who have survived conflict.

Months of terror and depression passed before Shand was diagnosed with PTSD in early 2010.

Working under a barrage of mortar shells, evacuating the injured and the dead, or killing others, causes stress, triggers fear, and enhances the strength of an emotional memory as it is stored in the brain. Many people who experience traumatic events recover and go on to have normal lives. But others develop PTSD and continue to feel fear and anxiety months and years after the trauma occurred. Once thought of as purely psychological conditions, scientists are finding that PTSD and other brain disorders may be rooted in the brain itself. If that's true, then there's hope that it may be a target for therapy.

Prime concern: The Canadian Forces estimate that eight per cent of personnel deployed to Afghanistan have been diagnosed with PTSD (HUGH GENTRY/REUTERS)

In the United States, PTSD has become a prime concern. An estimated one in five veterans—roughly 460,000—who served in the Iraq and Afghanistan wars have PTSD and/or depression. The Canadian Forces estimate that eight per cent of personnel deployed to Afghanistan have been diagnosed with PTSD, although it acknowledges the true rate is likely greater. Refugees and displaced people, victims of rape, assault and torture, and survivors of car accidents and other disasters also experience high rates of PTSD. Even people who witness horrific events can be affected. Despite Canada's small military, few natural disasters and relatively low rates of violent crime, McMaster Uni-

versity researchers estimate that 9.2 per cent of Canadians have had PTSD.

When soldiers come home, or when refugees land in a new country, they bring their fears with them. Some try to hide it. Then a door slams and brings on a flashback, with shaking and sweaty palms, a pounding heart, and rising blood pressure. Fear is a normal and protective emotion—part of the fight or flight response. But in some cases it gets out of hand. For those with PTSD, it means reliving the trauma through flashbacks and nightmares, skipping out on barbecues to avoid people or situations that trigger reminders, and difficulties sleeping and concentrating, or feeling jumpy and agitated.

Some people get by on medications to control the symptoms of PTSD, but psychologists consider cognitive behavioural therapy (CBT) to be the gold standard for treatment. "It's actually as good as medication or even better," says Alain Brunet, a clinical psychologist at the Douglas Mental Health University Institute in Montreal. But it's expensive, and for it to work well it requires a highly trained person. There's also a risk of relapse.

CBT, explains Brunet, relies on a type of learning called extinction. "It's like getting back on a horse after you've fallen off. It's a new form of learning, where you learn that there is nothing to be afraid of," he says. CBT is akin to laying a new memory on top of the old one, gradually quieting the first one over time. The trouble with CBT is that to work, the patient and therapist have to tease out all the different contexts that trigger an attack, which can sometimes be impossible.

More recently, scientists have been chasing drug treatments that modify the way memories are stored in the brain. During clinical trials, Brunet coaxes his patients to relive their traumatic experiences under the influence of a well-known hypertension drug called propranolol. The drug modifies the way the memory is re-stored in the brain, removing some of the emotional component. "You remember everything, but it's less intense, and intensity is very much what PTSD is about," says Brunet. He's wrapping up a pair of small, randomized placebo-controlled clinical trials—the best kind—testing propranolol to treat PTSD, as well as a trial in Nepal with torture survivors. "This is very close to a cure," he says.

Brunet's research hinges on a new way of thinking about memory storage. Scientists used to think that long-term memories, including fear memories, persisted forever, perhaps fading somewhat over time like ink on a page. But about a decade ago, Karim Nader, then a postdoctoral researcher at New

York University, performed experiments that showed that when animals recall a fear memory, it is briefly shifted to short-term storage before it is built up again from scratch and resaved. It was akin to copying a note before throwing away the original. Nader, who is now a neuroscientist at McGill, realized he could manipulate the fear memory with a drug similar to propranolol during recall and prevent the original memory's reconsolidation. "We have a tool and we can say we're going to block memory storage in the emotional system," he says. "It's more crazy than you can imagine."

After the battle, a new war: Many veterans have struggled to receive benefits because there was no clear cause for the symptoms of PTSD (DAVID LEESON/THE DALLAS MORNING NEWS)

Not everyone who experiences a traumatic event develops PTSD. Many display resilience, an observation that has led scientists to hunt for the biological factors that might predict who might develop PTSD and who might not, or identify ways to spur recovery. Brain-imaging studies have found differences in the way the brains of people with PTSD process emotional information. The amygdala, a brain region strongly involved in emotional memory, particularly fear, tends to be hyperactive in people with PTSD, whereas parts of the prefrontal cortex, which helps keep the amygdala in check, shows less activity. It's almost as though in the PTSD brain, the prefrontal cortex can't reel in the amygdala, leaving it to run emotionally amok.

Twin studies have found that even the unaffected twin can show these changes, a sign that there may be some genetic predisposition to developing

PTSD. Scientists have looked for such genes in thousands of survivors, such as Armenian children who survived a school-flattening, magnitude-6.8 earthquake in 1988; Rwandans who fled to refugee camps during the 1994 genocide; and American soldiers deployed to Iraq. Collectively these studies have identified changes in several genes, including a pair of genes involved in the production of serotonin—a brain chemical that regulates mood, sleep and alertness—and one called PRKCA, which is associated with better memory. In June, Raul Andero Galí and Kerry Ressler, from Emory University in Atlanta, and their colleagues, identified a fear-regulating gene called OPRL1 and noted that traumatized non-military civilians carried an altered version. They also identified a drug that acts on the receptor produced by the OPRL1 gene and could reduce the formation of fear memories in animals.

Scientists are finding that other conflict-related disorders including Gulf War illness and possibly some cases of depression may not be psychological but due to brain damage instead. Over 25 per cent of the nearly 700,000 veterans deployed to the 1990-91 Persian Gulf War and 15 per cent of non-deployed veterans have developed pain, fatigue, headaches and other complaints. Many veterans have struggled to receive benefits because there was no clear cause for the symptoms. Earlier this year, in a brain-imaging study of 31 Gulf War veterans, scientists at Georgetown University Medical Center in Washington found the nerve fibres that interpret the signals for pain and fatigue were degraded in the vets compared to controls. In another study, researchers at Boston University studied the brains of four deceased military veterans who had been exposed to blasts or concussions, and found they all showed evidence of chronic traumatic encephalopathy (CTE)—dead and drying neurons, clumps of defective proteins and plaques, and tangled glial cells—the same degenerative brain disease identified in many professional football and hockey players who had had concussions during their careers.

A decade ago, few understood the hidden changes that had occurred in the brain after a traumatic experience. Doctors and psychologists could only treat the symptoms, often using medications to mask the depression, anxiety and attention difficulties survivors experienced. Now, there's hope that combinations of drugs and therapy can undo the symptoms or prevent them altogether.

"If things continue to go well, they might supersede traditional pharmacological approaches," says Brunet. **HANNAH HOAG**

Team Trevor

How one soldier's brutal encounter in Afghanistan is changing the way experts look at brain repair

Ryan D'Arcy is a neuroscientist, inventor and a challenger of conventional wisdom. Trevor Greene is a former competitive rower, journalist and Canadian army captain, forcibly retired. They come to brain-injury recovery from different perspectives, but have arrived at the same conclusion: When it comes to rewiring a traumatically wounded brain, the impossible is now possible.

For D'Arcy, a professor at Simon Fraser University and research chair in Multimodal Technology for Healthcare Innovation at Surrey Memorial Hospital, his work is on the cutting edge of brain research and imagery. And for Greene, well, it was his brain that was cleaved with an axe by a young Taliban-inspired fighter in an Afghan village more than seven years ago, so the issue of recovery is as personal as it gets for him, along with his wife, Debbie Greene, and their young children, Grace and Noah.

At 12 intervals over three years, D'Arcy, with Stephen Lindsay, a cognitive psychologist at the University of Victoria, have used a functional magnetic resonance imaging (fMRI) machine to peer into Greene's brain, charting his physical and mental recovery. A man so grievously wounded that he once seemed doomed to a twilight life in a long-term-care facility is instead the human face of a research project charting new approaches to brain repair and tossing out accepted time limits on the window for recovery. Where he was once virtually immobile, he is now able to use a walker and, with assistance, struggles the length of the eight-metre-long living room of his home

in Nanaimo, B.C. “For weeks now, we have been turning the corner and doing laps, with minimal rest to build my endurance,” says Greene.

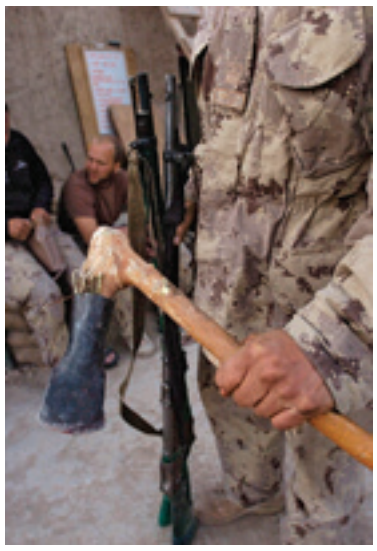
Survivor: After being attacked with an axe while on duty in Afghanistan, Greene is now the face of groundbreaking medical research (PHOTOGRAPH BY KEVIN LIGHT)

Every month brings hard-earned victories that, viewed cumulatively, seem near-miraculous. His mental acuity is razor-sharp, as is his spoken and written command of language. The axe blow’s greatest damage was to a part of the brain controlling movement. “What we did see across the 12 scans was a systematic increase in the amount of brain activation in the motor areas that are governing Trevor’s ability to move and walk again,” says D’Arcy. He is working with “Team Trevor” on a research paper he believes offers new strategies and more optimistic outcomes for patients who have suffered strokes or other brain trauma. Among the findings:

The recovery time window

"What people are uniformly told is that you can expect a tiny amount of change in the short window after an injury," says D'Arcy, adding that the accepted convention is that brain recovery ends after six months, or a year at most. "That really draws a picture of a very pessimistic downward [performance] curve," he says. "Trevor's curves [as charted over 12 fMRIs] are exactly the opposite. If you were investing in the stock market, this is the sort of curve you'd want to see."

Greene offers a soldier's saltier take on his progress. "We are correcting the bulls--t in the scientific textbooks that purport how, after six months, recovery from brain injury stops and compensation strategies have to be planned," he writes via email. "My brain is still rewiring after seven years fer chrissakes, and I'm making steady gains. I hate to think how the doctors give up after six months and, more important, the patient."



'Steady gains': 'My brain is still rewiring after seven years,' says Greene, whose head was cleaved with an axe by a young Taliban-inspired fighter (RICK MADONIK/TORONTO STAR/CP; STEVE PUDDICOMBE/CBC/CP)

The power of imagination

D'Arcy calls Greene's decision to imagine he was back at his old sport of rowing while he was in the fMRI machine one of the study's most exciting discoveries, one that could have far-reaching impact for rehabilitation specialists. The machine, which measures increases in blood oxygenation and flow, showed that areas of the brain that activate muscles used in rowing were being fired by Greene's visualization. Athletes use imagery to imprint an act or skill, and Greene, by constantly imagining himself straining in a rowing shell, is rewiring his brain in a similar way. The evidence so far is that the body will eventually follow the paths he builds from visualization. "We started with the fun-

damental idea that we will see changes in the brain before we see recovery of the ability," says D'Arcy. "That is something we know to be true."

The medicine of motivation

Greene says visualization is something everyone can do; that the "progress I've made can be applied to others facing recovery from brain injury." D'Arcy is more cautious about its universal application. "It's certainly too early to say that. But you can start to know where you need to focus your efforts. You need to focus on: Are they motivated?" In this, Greene has a clear goal: to walk again—not to mention the focus of an athlete and a soldier. Also in Greene's corner is the exceptional work and support that Debbie pours into his recovery, and the series of brain scans, each showing improvement and feeding momentum.

Is Greene an exception? "I think, yeah, no doubt he is," says D'Arcy. Anyone who has witnessed both Trevor and Debbie tough through one of his brutal rehabilitation sessions can attest to that. "If you can get a circumstance where somebody can be as focused and as motivated, then that can create the means for change," says D'Arcy. His message to survivors of head trauma: "Recovery from brain injury becomes your new elite sport."

Unlike most research papers that use anonymous subjects, this one will include the Greenes as co-authors. Their hope is it will inspire brain-trauma survivors, and those who treat them, to follow a soldier's path back from the brink. **KEN MACQUEEN**

Crunch time

With concussions taking a toll, athletes are donating their brains and enrolling in 'live brain' studies

New research showing that "heading" a soccer ball can damage cognition in high school players has added the sport to the growing litany of athletic endeavours—football, wrestling, diving, skiing, hockey—whose competitors are at high risk of concussion. Despite resistance from professional leagues, the medical community has sounded alarms about sports-related brain trauma, which, according to one study, affects millions of players in North America every year. Once considered reversible injuries whose symptoms healed with time, concussions are now known to have serious effects on the brain. Researchers think they may cause inflammation, neurotransmitter release and other problems. Recent studies have linked repeated concussions—even what doctors call symptomless "subconcussive impacts"—to CTE (chronic traumatic encephalopathy), the Alzheimer's-like constellation of cognitive ills that can include depression and dementia.

Whether concussion always leads to CTE is controversial, however. A study of the brains of six CFL players with histories of multiple concussions showed only three had the disease, according to a May paper in *Frontiers in Human Neuroscience* by Lili-Naz Hazrati of the University of Toronto's Tanz Centre for Research in Neurodegenerative Diseases. But co-author Charles Tator says that doesn't mean we shouldn't stop concussions before they happen.

"The emphasis has to be on prevention, because we don't have good treatments," says the Toronto neurosurgeon. Tator founded the Canadian Sports

Concussion Project, as well as the Allison Project, the latter with 18-year-old former snowboarder and concussion sufferer Allison Haggart. And former WWE wrestler Christopher Nowinski's concussion led him to co-found Boston's non-profit Sports Legacy Institute, which will soon release hit-count guidelines to help limit impacts on child players. A total of 17 NFL players, both living and dead, have donated their brains to researchers, and New Brunswick hockey player Bob Lemieux is enrolled in live brain studies at the University of Toronto.

Although the most high-profile figure to be felled by concussion is perhaps the Pittsburgh Penguins' superstar captain Sidney Crosby, the spotlight is also increasingly shifting to women, among them, Canadian speed skater Kristina Groves, a four-time Olympic medal winner. **SARAH BARMAK**

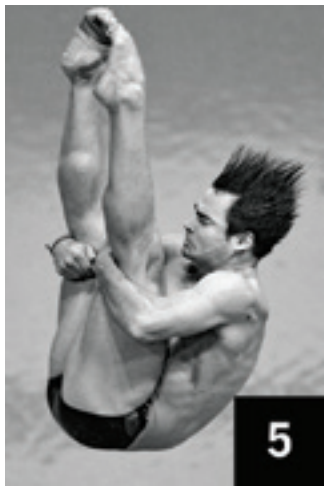
Muhammad Ali: The American heavyweight champ known as 'the Greatest' (right) has arguably done the most to bring attention to the sad effects of repeated head injuries. His form of early-onset dementia has been called 'dementia pugilistica'—literally, 'boxer's dementia.' (MANNY MILLAN/SPORTS ILLUSTRATED/GETTY IMAGES)

1. Soccer: Male players may get the spotlight, but they aren't the only ones suffering debilitating head injuries. Two-time U.S. Olympic gold medallist Cindy Parlow Cone (left) suffered her first soccer-related concussion in 2001. The former player scored more than 50 per cent of her goals with her head.

2. Skiing: U.S. alpine ski racer Lindsey Vonn missed a slalom in the 2011 World Cup finals after suffering a minor concussion in training. She was controversially cleared for a super-G race days later and took silver, though she said she had skied "in a fog."

3. Hockey: Eric Lindros, the retired hockey star, suffered enough concussions—starting at age 17—that he worried about being labelled "concussion-prone." Born in London, Ont., Lindros lectures and was the subject of a feature on concussions in ESPN The Magazine and Maclean's. (His younger brother Brett, a New York Islanders first-round pick, ended his career at 20 after two severe concussions in 1995.)

4. Baseball: Baseball may not be known for its head injuries, but tell that to Blue Jays pitcher J.A. Happ, whose head was bloodied by a line drive during an early May game this year against Tampa Bay. Although a CT scan revealed he avoided a concussion, Happ sustained a skull fracture and had to take weeks off the mound. (REUTERS; GETTY IMAGES; AP)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5. Diving: Canadian two-time Olympic medallist Alex Despatie concussed himself after banging his head on the diving board during a practice in Spain in the summer of 2012.

6. Snowboarding: "Snowboarding isn't worth it," Gretchen Bleiler, the American 2006 Olympic silver medallist, moaned after suffering a severe concussion, fracturing an eye socket and breaking her nose during a 2012 training session. Bleiler dropped out of the 2013 Winter X Games.

7. Hockey: Sidney Crosby gamely opted to return to the ice after a blind-side hit from the Washington Capitals' David Steckel during the Winter Classic on Jan. 1, 2011. After another hit knocked him head-first into the boards days later, Crosby suffered from headaches, light sensitivity and mental fog that took him from the game for nearly two years at the peak of his abilities, becoming the poster child for concussions.

8. Football: Lamar Campbell, the former Detroit Lions player, says two things were behind his decision this year to donate his brain to Boston's Center for the Study of Traumatic Encephalopathy after his death. One is the suicide last year of former linebacker Junior Seau. The other is Campbell's young son, in case he decides to follow in dad's cleats. (REUTERS; GETTY IMAGES; AP)

Forget what you know

After 150 years, groundbreaking new neuroscience research may finally be able to change the way we think about general anaesthesia

Anaesthesiologist Beverly Orser calls this the surgical era, a time when most of us, at some point, will go under the knife. Regardless of the procedure, invasive surgeries involve anaesthetic drugs. Long the quiet backdrop to monumental advances in medicine thanks to the coma-like state it induces, general anaesthesia is itself increasingly under the microscope.

Scientists know it affects the entire nervous system, not only sedating us, but erasing our memories of the surgery and blocking our pain. But after more than 150 years of putting people to sleep and waking them up, we still don't know exactly how it works.

Mounting research is delving into the long-term impact of different drugs—including links to memory loss and learning impairment—and scientists are probing down to the cellular level to figure out what molecular mechanisms are involved.

At her University of Toronto's labs, Orser's research centres around gamma-aminobutyric acid (GABA) subtype A receptors, thought to play a key role in inducing unconsciousness by restricting a neuron's ability to respond to stimulating messages and inhibiting communication in the brain (the same receptors are targeted by Valium). As a practising anaesthesiologist at Sunnybrook Health Sciences Centre in Toronto, Orser administers the drugs that allow doctors to slice through skin and tissue, saw through bone and stitch a patient back up again who won't remember a trace of the trauma.

Sleepy science: After more than a century of putting people to sleep and waking them up, we still don't know exactly how general anaesthesia works (FUSE/GETTY IMAGES)

In the operating room, anaesthesia has evolved into a "sophisticated art form," in Orser's words, and anaesthesiologists may choreograph doses of five different drugs or more—one administered intravenously first to put the patient to sleep (propofol and etomidate, for example) and another inhaled through a mask to keep them under for the duration of the surgery (most likely isoflurane, sevoflurane or desflurane). Higher-risk procedures require even more complex mixtures.

Anaesthetics, which suppress automatic functions like breathing, blood pressure and heartbeat, are extremely powerful drugs, Orser notes, and there's not a great deal of difference between a therapeutic dose and a lethal one. But long after any therapeutic effect has worn off, it is entirely possible that our brains might not be the same.

"For a long time we were thinking anaesthesia is safe and reversible," says Zhongcong Xie, a researcher and anaesthesiologist at Massachusetts General Hospital, where the use of anaesthesia in surgery was first demonstrated in 1849. "That may not be case." Compelling research is linking anaesthesia and surgery to Alzheimer's-like effects in aging brains, and learning and

memory impairment in fetal and developing brains.

Research published in the *Annals of Neurology* in 2012 by Xie's colleague at Massachusetts General Hospital, Yiying Zhang, showed that isoflurane may lead to cell death in the brain by damaging mitochondria, the power producers of cells, and that could mean lasting damage to memory and learning functions. Yet the study found desflurane did not have the same effect.

"We were surprised, because initially we were thinking these two drugs have a very similar structure," says Zhang. She notes follow-up studies on small groups of people found similar results.

"We need more data to either rule in or rule out the contribution of isoflurane and other anaesthetics to the pathology of Alzheimer's disease, and the instance or severity on learning and memory function after surgery," says Xie.

In a recent study in mice at Orser's labs, researchers tested the memories of mice after exposure to isoflurane, putting them in cages with familiar and unfamiliar objects—like toy trucks, Lego blocks or action figures—and found the drug impaired short-term recognition of the toys. Orser notes short-term memory loss is already a well-documented outcome of surgery and general anaesthesia, with one in three people showing cognitive dysfunction 24 hours after surgery. Three months after surgery, that figure is still one in 10. Yet Mayo Clinic researchers have rejected any connection between anaesthesia and Alzheimer's disease based on a broad study of 900 people's health records in Minnesota. The study, published in 2012, compared two sets of patients over the age of 45, one group with dementia, the other without. It found the rates of surgery, and thus exposure to anaesthesia, were the same, at about 70 per cent.

Some of the world's leading researchers—including Xie and Orser—noted the conflicting research, writing that "definite clinical data remains elusive," in an overview of recent research published by the *British Journal of Anaesthesia*. Still, they spent the majority of the paper dissecting the "large body of preclinical as well as some retrospective clinical evidence [that] suggests that exposure to general anaesthesia could be detrimental to cognitive development in young subjects, and might also contribute to accelerated cognitive decline in the elderly."

The paper highlighted mice and rat studies that paint a complex picture of general anaesthesia's impact on fetal and baby brains, where the timing of the dose, the type of anaesthesia and the length of exposure all affect devel-

opment in different parts of the brain in different ways.

Some research has found isoflurane and nitrous oxide (sometimes used in surgery) might change brain tissue in a fetus. Another study suggested sevoflurane might be toxic to young brains. The paper urged scientists to undertake more studies so anaesthesiologists can choose better drugs for the young and old. As Xie emphasizes: "This is a very new area."

That is less true for anaesthesiologist Emery Brown, who has spent the last 14 years mapping the brain's electrical activity under the influence of propofol in his lab, also at the Massachusetts General Hospital. "Everybody thinks [anaesthesia is] a black box, that this thing is so complicated because somehow it involves consciousness, that it can't be explained," he says. "And it turns out nothing could be further from the truth."

'Exposure to general anaesthesia could be detrimental to cognitive development in young subjects, and might contribute to decline in the elderly'

Brown believes neuroscience can help researchers understand anaesthesia. His groundbreaking work has earned him major U.S. research prizes, including the National Institute of Health's Pioneer award. "We can see the effects in the EEG [electroencephalogram], which relate directly to how the drugs work in the brain," he argues. "We have a very good idea of what happens under propofol anaesthesia. Why does propofol make you unconscious?"

The answer, he says, has to do with dramatic changes in the brain's electrical signals. Brown's research has shown that propofol does two things: it takes the cacophony of normal brain electrical activity and forces it into an unnatural, slow oscillation, a "hum down a phone line" that jams communication between the thalamus and cortex and cuts off communication within the cortex. Anaesthesiologists trained to look for those EEG patterns—including those working at Brown's hospital—use that as a measure to test that a patient is indeed unconscious.

"We started out looking systematically at propofol, but now we're looking at other drugs as well, because this is a totally tractable problem," he says.

"If you understand how [these drugs] work at a circuit level, not only do you learn things about anaesthesia, you learn something fundamental about

the brain," he says. "You get ideas of how you might produce therapies for some other problems, like sleep or depression."

Brown is even moving on to the question of how best to wake people up. His work has shown that giving the ADHD drug Ritalin to rats after anaesthesia might help brain function return to normal faster—potentially lessening side effects on memory or learning. He's now seeking funding to test the research on surgical patients.

Even with Brown's research, Orser says EEG monitors have yet to prove their worth to anaesthesiologists, and there really is no good monitor of the depth of anaesthesia—a crucial issue, because not everyone who appears "asleep" really is. About one or two in every 1,000 patients will experience some kind of awareness under anaesthetic drugs. In some cases the patient remembers hearing what was said in the operating room near the end of the surgery, but some people report feeling pain.

Perhaps the most illuminating consequence of our ignorance around anaesthesia is the slow progress in creating new and better drugs. "The aneasthetic that my grandchild might receive is awfully similar to what I might have received as a child," Orser notes. "Three generations, we're still using the same drugs."

Though they are generally safe, with a relatively low death rate that has plateaued at about one in every 300,000 patients, Orser envisions a future where general anaesthesia, like the ether it evolved from, is largely a drug of the past. In its place would be a series of drugs that address each of the desired effects in the brain—sedation, unconsciousness, immobility and amnesia. If anaesthesiologists can understand how general anaesthetics achieve these unique outcomes, "we might be able to move away from this global neuro-depressive strategy." Then, more than 150 years after anaesthesia fundamentally changed medicine, it would undergo a revolution of its own. **ROSEMARY WESTWOOD**

(VIVOSONIC INC)

The depths of sedation

It's a living nightmare: patients who can recount every second of their own surgery, from the first cut to the last stitch, unable to scream a warning from their frozen bodies.

Now a collaborative project between Vivosonic Inc. and a group of researchers in the University of Toronto's department of electrical and computer engineering will use the brain's response to sound waves to measure the depths of sedation in an effort to detect what is called anaesthesia awareness. One or two out of every 1,000 patients who are put under using general anaesthesia report some level of awareness, ranging from vague recollections of sounds or conversation to experiencing pain.

Vivosonic was formed in 1999 to market signal processing developments, technologies that measure the brain's response to sound. In Toronto, study participants listen to a repetitive sound through an earpiece or headphones,

both when they are awake and when they are asleep, while electrodes attached to the scalp monitor the brain's responses. In an effort to identify which sounds produce a response in consciousness, the researchers have completed preliminary tests on 20 people. They hope to test 200 more by 2014 before working with anaesthesiologists in the operating room. Right now, they're testing algorithms to clean up the signal and distinguish the brain's response to some auditory stimuli.

They hope the technology will not only be used as an early warning system for anaesthesiologists in cases of anaesthesia awareness, but also as a standardized tool to determine how much anaesthesia a patient should receive. "The trick is to do this in real time, as quickly as possible," explains Isaac Kurtz, vice-president of research and development at Vivosonic. "So if a patient is entering a state of arousal, you can catch it quickly." **KATHERINE DECLERQ**

Rx for music

Long known to soothe troubled souls, tunes help patients with Parkinson's, stroke and possibly autism

She was 72 when Bin Hu first met her, a Parkinson's patient losing self-confidence, and with it, the ability to walk. She dragged her feet like lead weights, and froze in her tracks whenever she saw something on the ground: a line, a mark, a mere crack in the pavement. It made her the perfect test subject. With masking tape and a projector, Dr. Hu laid down lines all over his lab floor. Then he asked, "Do you like to dance?"

"Oh yes," she said, "I love it. I've danced all my life."

"What's your favourite song for dancing?"

"ABBA," she told him, "*Dancing Queen*."

Hu cued it up and a remarkable thing happened. The woman, an artist by profession, rose from her chair and swayed to the music, dancing across the lines as if they didn't exist. But when the music stopped, she'd freeze again. Hu, a clinical neuroscientist with the Hotchkiss Brain Institute at the University of Calgary, moved the masking tape, turned the projector off and on, and even stripped the music down to its bare beats to see if it had the same effect. It didn't. "Without the music, she couldn't even stand up," said Hu. With it, she was a dancing queen.

Not long ago, the study of music and the brain was dismissed as an airy-fairy pursuit, not the sort of thing a serious scientist mentioned on a funding application. But the last decade has changed that. As scientists learn more about the human brain through imaging scans and novel experiments, music has emerged as a profound and inexpensive tool to affect brain function.

From Swedish pop songs to piano concertos, Broadway show tunes to hard-core rap, music—that marvellous, intangible tonic for the senses—is proving to be powerful medicine, capable of rewiring the brain, reshaping behaviour and healing the body.

Moving to the music: Parkinson's sufferer Sharon Strachan, 72, used to freeze trying to go down escalators, but now moves with ease thanks to her playlist (PHOTOGRAPHS BY CHRIS BOLIN)

Several studies have found that music can help stroke patients recover their memories, their attention skills, and their speech. "It's like magic," says Ryerson University's Frank Russo, a cognitive neuroscientist investigating music's therapeutic uses. "This person who can't speak, can sing." There's also evidence that music can boost the immune system and lower blood pressure in people who listen, along with slow deliberate breathing, for 30 minutes a day. One study found listening to music was more effective than anti-anxiety drugs in reducing patients' stress and cortisol levels before undergoing surgery. A study in the *Journal of the American Medical Association* this spring concluded that listening to soothing music significantly reduced stress and the need for sedatives for patients in intensive care. And in Calgary, where

doses of ABBA enabled a disabled woman to dance, Hu's experiment has evolved into a multi-city trial to help Parkinson's patients keep walking with nothing more than a special iPod and a 63-song playlist.

BIN HU NEVER set out to study music. He was interested in how the brain organizes itself into patterns that allow people to respond so rapidly in some situations: to flee from a fire or smile at a familiar face. His initial work focused on rats, showing that certain sensory stimuli, like hearing a song, can trigger reward circuits and motivate the animal to behave a specific way. Once a rat, for example, learns that certain sounds lead to food, it automatically scurries for the grub when it hears them. Change the sounds to ones that lead to a punishment, such as a shock to the foot, and you change the behaviour.

It was in rat brains that Hu first discovered "cue cells" that lie at the root of these responses, which, with time and repetition, produce automatic behaviour. Cue cells are a special type of neuron found deep in the thalamus, a primitive structure that is the recipient of sensory messages from the external world, be they sights, sounds or textures. Hu found the cue cells of the thalamus are on the frontlines of mediating the brain's responses, relaying information (like a switchboard) to be processed by different parts of the brain that deal with expectation and reward, decision-making and motor control.

'Maybe we can use the music to cue the pathway, and with enough cues, maybe it's possible to create a permanent connection'

The discovery showed for the first time how the brain uses a different kind of decision-making system for different kinds of movement. Deciding to leave your desk for a snack, say, is more deliberative than fleeing from fire. Deliberation requires more involvement from the highly evolved prefrontal cortex. But, Hu found, it's the cueing system that can lead to "highly automatic" motor reactions.

Published in the prestigious *Proceedings of the National Academy of Sciences* in 2004, the report drew the interest of famous British neurologist Oliver Sacks. Sacks, who lives in the U.S., was a visiting professor in Calgary in 2005, and is perhaps best known for his 1973 memoir-turned-movie

Awakenings, in which he discovered certain stimuli, such as human touch, music, and eventually the Parkinson's drug L-Dopa, could "awaken" patients who had been catatonic for years. What Sacks wanted to discuss with Hu was whether this cue system might explain "paradoxic movement"—those puzzling cases where people in wheelchairs can run from a fire alarm, or Parkinson's patients who can dance but not walk. It made Hu wonder if music could prompt the cueing system. Was it suggestive of a high-level pathway for pleasure in the brain?

Hu knew well the pathology of Parkinson's disease, a degenerative neurological condition that destroys dopamine-producing cells critical for movement, often resulting in telltale tremors. But dopamine is also the brain's pleasure chemical, the joy juice behind desire and the reward system, released any time we undertake activities our brains want us to repeat, like eating or having sex.

Was it possible that music could induce a dopamine release, one that could charge those reward circuits and motivate people to walk? Would Parkinson's patients be inclined to keep walking if it meant they could keep the music playing?

Hu knew time is no friend to Parkinson's patients. Within the first seven years, they tend to gain little benefit from drugs; at the 10-year mark they can lose balance and physical function; at 14 years, about 40 per cent are in a wheelchair.

"So right away, the thinking was, 'What if you could get a patient before they deteriorate?' " says Hu. "Could you help their brains to develop a new motor pathway response for walking, one triggered by music?"

The 2005 ABBA experiment inspired him to see music as "a powerful means of arousing the cueing networks, activating the brain reward and locomotion regions all at once."

As he began making plans to create a portable musical device for early Parkinson's patients and applying for grants that "didn't say anything about songs," on the other side of the country, researchers were gathering neurochemical proof that music does indeed tap into the brain's most primitive reward regions.

At the Montreal Neurological Institute, Robert Zatorre, a pioneer in music and brain research at McGill University, along with post-doctoral student Valorie Salimpoor, had used various imaging scans to see what happens to a

human brain on music. In *Nature Neuroscience* in 2011, they reported that a favourite piece of music triggers the same kind of dopamine release involved in the response to food or drugs, and in the same ancient brain regions.

Not only did dopamine levels surge while the 40 subjects experienced the "emotional peak" of a familiar instrumental piece, but it also happened in anticipation of hearing the music itself. Researchers also found a correlation between hearing familiar music and "the chills, or goosebumps," says Salimpoor, the study's lead author. "The research suggests that even before you hit the play button, you know when your favourite parts are building." These chills were confirmed by physiological readings that showed increases in subjects' heart rates, respiration, and body temperature while listening to the music's emotional peaks.

'Look at Baba go!': When Strachan's stride shortens or slows, the music stops, reminding her to move again; she now walks three kilometres a day (PHOTOGRAPHS BY CHRIS BOLIN)

"Music can be intensely pleasurable," says Salimpoor, now at Baycrest

Health Sciences' Rotman Research Institute in Toronto. "As pleasure increases, dopamine increases, and we like intense emotions. We enjoy the experience if there are no consequences; it's why we see horror movies, or ride roller coasters. It's all a controlled playground to feel these emotions."

More recently, Salimpoor and Zatorre showed that even the decision to purchase new music is mediated by the nucleus accumbens—a deep-brain structure central to dopamine production and the reward system, along with setting up predictions and expectations. The study, published in April in *Science*, involved test subjects listening to clips of new music on iTunes and having $10 to buy tracks they liked. Researchers found the more activity there was in the subjects' nucleus accumbens as they listened, the more likely they were to buy the song, and the more they were willing to pay for it.

Why music is so deeply embedded in the human brain's reward centres—as if it were the very first drug—remains a mystery. There's no obvious evolutionary advantage to the abstract pleasures of music. It won't fill your belly, make you strong, or fill your cave with people.

Jessica Grahn, a music neuroscientist at the University of Western Ontario, says one theory suggests that music and language evolved together, that language grew out of a kind of "musi-lang," grunting sounds, like notes, or cries uttered to convey information or emotion, which would have had clear survival advantages.

Another theory is that music evolved with the need to calm babies, allowing women to work hands free while singing and soothing the children on their backs. Even today, Grahn notes, most people are inclined to speak to babies in high, musical tones.

The theory that seems to have special currency in the modern drive to use music as therapy is that it was critical for social bonding. "It allowed synchronizing behaviour with another that doesn't cost anything. With music, you can bond in very large groups," says Grahn.

Humans have a sophisticated ability to match movements with rhythm, which she considers music's most important aspect. It's so closely linked to movement that brain imaging shows "even when people are just listening to music and sitting still, we still see the same motor areas activated as if they are moving."

For Russo at Ryerson, the social aspects of music give it a unique healing potential as people are inclined to mimic or mirror the actions of another.

With stroke patients who have lost speech, "The therapist will sing, 'Hi my name is John.' And while the patient is unable to say, 'Hi my name is John,' they can sing it."

"Listening on its own is not very helpful," he says, "In terms of rewiring the brain in some way it requires action." Stroke patients do eventually learn to speak without melody. Imaging research from Harvard University has found that as they learn to sing their words, new connections are forged between the left-brain areas usually involved in speech production, and the right side, known to be well-developed in professional singers.

Why music is so deeply embedded in the human brain's reward centres—as if it were the very first drug—remains a mystery

Knowing that music can also fire up the emotional rewards systems in the brain and foster social bonding has prompted Russo to explore the potential of singing as therapy in children with autism, who have social deficits, but "are also known to like music a lot."

To Salimpoor, the fact that "music developed spontaneously and independently across all cultures" suggests that it's "intrinsic to human nature to appreciate it." But there are those who believe that other species—whales, dolphins and birds, say—have their own form of musical appreciation that could help explain its roots in humans.

In 2009, Charles Snowdon, a psychologist at the University of Wisconsin at Madison, made the case that music is in the ears of the listener. To elicit a response from monkeys, for instance, Snowdon found he had to play them "monkey music." Working with David Teie, a cellist with the National Symphony Orchestra, the researchers composed 30-second audio clips specifically for the cotton-top tamarin, a small South American monkey.

Using the distinct sounds the tamarins make in response to fear, or threats, and other tracks based on pleasant calls that convey safety and happiness, the tamarins responded in kind. The fear-based music made them anxious and the soothing music relaxed them. Meanwhile, the only reaction logged to several samples of human music was a calming response to the heavy metal band Metallica.

But while it remains unclear whether musical appreciation is truly species specific, there's ample evidence that, among humans, musical appreciation is often culturally specific. In the 1980s, one U.S. study even found that American students had highly emotional responses to Air Supply's *Making Love Out of Nothing at All*, but study subjects in Germany, not so much.

Salimpoor says that the structure where musical memories are stored in the human brain even looks different in each person, depending she says, on the kinds of music a person has heard. Which is why the idea of using music as therapy can be tricky—one song will not benefit all.

IN 2010, HU teamed up with other researchers and engineers to develop a modified iPod Touch for Parkinson's patients called the Gait Reminder. It has headphones like any iPod, except this device is strapped to the thigh and also tracks movement, so that music plays only while the patient walks—and only in full stride. Any stop, or "shuffling" as Parkinson's patients know it, and the music shuts off. So if the patient likes the song, Hu says, they have to keep walking to keep it playing.

Hu had only two criteria for the playlist: the songs had to have lyrics, making the music "more emotional," and they had to give the listener chills, as a proxy to signify that critical dopamine release.

By September 2011, Hu was enrolling patients for the first trial. One of them was Sharon Strachan, a 72-year-old nurse who had cared for many Parkinson's patients over the years, and in 2003, was diagnosed with the disease herself. Her husband, Bruce, a board member with Alberta's Parkinson's Society, had heard about Hu's music project and Strachan decided to sign up.

By then, her eight-year battle with Parkinson's had taken a toll. A mother of two and grandmother to six, she often heard reminders from family members to "pick up her feet" when she walked, and there were comments from others that her face showed signs of the Parkinson's "mask"—void of expression as facial muscles slackened. She was tiring more easily, and then there was the freezing. "You know what was a struggle? I could go up an escalator, but I could never come down."

Strachan found pleasure in the Gait Reminder from the first day she strapped it to her leg a year and a half ago. With it, she now walks a brisk three kilometres a day, five days a week, in a nearby mall.

"It's really like being at a starting gate," she says, "You just start to walk

when the music plays." She tends to like any tune that's upbeat, and that includes most of the songs on the playlist. But she has her favorites—"that *Mamma Mia* by ABBA is a great one."

She sings along in her mind, and if her mind wanders and her strides shorten, the music stops, and she says to herself, "Sharon, step it up!"

"It increases your awareness. Even without the music now, I notice when I start to take shorter steps." Her average step size has increased, as has her pace, and the freezing at escalators is gone. But what's been especially gratifying is the feedback from others. Now her grandchildren say, "Look at Baba go!" Her daughter in California contacted Hu to ask, "Wow, what did you do to my mother? She's walking, she's smiling… I can even look at her face and see what she's thinking."

Monkey music: A cellist composed audio clips designed specifically for the cotton-top tamarin to help explain music's emotional roots (BRYCE RICHTER/UNIVERSITY OF WISCONSIN-MADISON)

Still, Hu does watch for side effects. "I am worried that there may be injuries," he says. "I worry that patients may do too much, and because they are old, they could be injured." Then he adds: "I constantly ask myself—are they addicted to it?"

After all, the music produces a dopamine release, boosts pleasure, confidence and dilutes inhibitions, all things that sound like the effects of an addic-

tive drug. For this reason, Hu says all 40 patients in the trial have their walking data recorded by the Gait Reminder and transmitted directly to his computer where he watches for signs of "compulsive walking." But so far, there are only signs of enjoyment.

Hu says early analysis shows nearly all patients who entered the trial with mild deficits have "showed significant improvement in step length, walking speed and arm swing." There have also been improvements in facial expressions and overcoming "freezing, or the fear of falling."

"The improvement in these symptoms seem long lasting and have not reversed back for more than a year," Hu says. The results are so promising Hu now has the go-ahead to expand the trial to 250 patients in Calgary, Edmonton, Lethbridge and Vancouver.

Still, the therapy doesn't work for everyone. Grahn notes that for some Parkinson's patients music can be an added stress and frustration; trying to keep pace with the rhythm while walking is its own struggle. But whether this is the result of the therapy, or the patient is simply not responding to a particular piece of music, is unknown.

Hu has since teamed up with Russo and his team in Toronto to dig into the science of the songs, to deconstruct them by beats per minute, their rhythms and their power to affect emotion. It's all in an effort to determine every patient's perfect playlist, and fire up her inner dancing queen. **CAROLYN ABRAHAM**

Fugue states

How brain damage that affects your memory can also affect how you imagine the future. An interview with cognitive neuroscientist Shayna Rosenbaum

When a mystery woman known only as “Linda” showed up last September at a downtown Toronto shelter, unable to remember who she was, reporters called local amnesia expert Shayna Rosenbaum, 37, a York University cognitive neuroscientist for insight. Professor Rosenbaum, who is affiliated with Baycrest Health Sciences, has just won the 2013 Canadian Association for Neuroscience Young Investigator Award. *Maclean’s* spoke with her about her research on the brains of patients with memory disorders. Amnesia can result from physical injury or psychological ailments and may be a symptom of a wide range of illnesses.

Q: *Did personal experience inspire your interest in memory?*
A: I was really taken by a few cases in undergrad [such as] H.M., a famous amnesiac; there was a book just released by neurologist Suzanne Corkin. I had never planned to go into psychology. I was planning to pursue a career in law. In my first year, psychology was my elective. I ended up deciding on psychology as my major at the University of Western Ontario and I was enrolled in law school. The summer following, I decided to continue on with my honours thesis and I didn’t look back. I was really taken by what I was learning. I looked at the effects of estrogen on memory in young women.

One personal story that inspired me was I’m a grandchild of Holocaust

survivors. I am always surprised by how strong emotional memory is. I didn't know much about my own history because of my grandparents not wanting to share what they had experienced. Memory can shape you, but the lack of memory almost shaped me more.

Personal history: As the grandchild of Holocaust survivors, neuroscientist Shayna Rosenbaum is fascinated by the strength of 'emotional memory' (ANDREW TOLSON)

Q: *You write about the role of injury to the hippocampus. Does memory loss always involve injury to that part of the brain?*
A: No. There are many parts of the brain involved in supporting memory. The hippocampus is a focus of research, because there's a direct connection between the formation and retrieval of memory and that structure. Regions of the frontal lobes, in fact, regions throughout the brain, form a network that supports memory.

Because I study patients, it's difficult to describe what a structure does if there are many structures damaged in a person, because it's difficult to map

the networks supporting memory. With neuroimaging, we can look at the networks. We usually start with the patient, and once we have a better understanding of whether a region is involved or not in supporting a certain form of memory, we follow up with other methods such as fMRIs (functional magnetic resonance images), where we can see, in a non-invasive way, regions of the brain.

Another reason for the focus on the hippocampus is because of that case of H.M., whose hippocampus and entire medial temporal lobe in both hemispheres were surgically removed to treat epilepsy. Although his seizures decreased, he was left with a severe form of memory impairment.

Aside from epilepsy, other conditions lead to hippocampal damage. Alzheimer's is known to affect the hippocampus very early on. It's responsible for the very obvious observation that patients with Alzheimer's lose memories of recent events, and as the disease progresses, very old memories are lost, as well.

Q: *In the case of "Linda," she seemed to have temporary total memory loss. We see movies where people lose their whole memory. Is that common?*

A: No, not at all. Memory is not one thing. Even H.M. had certain forms of memory that were left intact. That's what made him remarkable—despite his inability to remember events from one moment to the next, so if someone entered the room and left and then re-entered, he would never remember that person was there before—he could still learn new skills, such as mirror tracing or reading backwards text.

That woman, who I think turns out to have had a diagnosis of schizophrenia, her presentation sounds more like she had a form of functional amnesia, so it's not clear it was related to a part of the brain—there was a history of a psychiatric condition.

Strictly speaking, patients don't tend to lose all memory. They might lose memories of personal events, but not information or skills they had learned in the past.

Q: *So the hippocampus deals with spatial memory?*

A: That's what used to be believed: that it was specialized for spatial memory and, in humans, episodic memory, which is memory of personal events.

The reason I became very interested in the hippocampus is that, when I started to see patients who, like H.M., had hippocampal damage in both hemispheres, I found their episodic memory was severely impaired. But they

were able to get around in neighbourhoods they had experienced before the brain damage. That didn't jive with what was previously thought. So my early work looked in detail at whether very old spatial memories are disrupted following hippocampal damage. Mostly, it seems patients can navigate spatial relations in environments they've experienced.

Q: *What are you working on now that you're excited about?*

A: A lot of research shows that the hippocampus plays a necessary role in supporting episodic memory. It also seems to play a role in our ability to imagine the future. So not only do patients with hippocampal damage have difficulty remembering past events, they have tremendous difficulty imagining future events they might participate in.

There has been a lot of research on this topic, especially since some seminal work in 2007. But my students and I have been looking at the limits of this finding. Just like memory, imagining is not one thing. We've published studies showing that even patients who have difficulty imagining future events can still make decisions about the future.

Q: *When you talk about picturing the future, do you mean actually visualizing it?*

A: It's complex. It's unclear if the hippocampus plays a role in being able to visualize a scene. Some people think that's why such patients can't engage in such imagining, because they can't construct a spatial scene. Others, like me, think perhaps it relates to a more basic role in binding details together to form a narrative. So when you're imagining, you're telling a story or stringing together a series of details. This idea suggests that the role of [the hippocampus] is not limited to memory. Maybe what is called "amnesia" might not be a memory problem. It might be this more basic binding mechanism.

Q: *So amnesia is almost a larger phenomenon?*

A: Yeah, it possibly derives from something more basic. Turns out, there's another line of research showing these patients have difficulty discriminating objects, difficulties that extend beyond memory. You research three types of memory: spatial, semantic and episodic. You also look into their links; for example, spatial memory. We often find that our memories of facts are more easily triggered when we're in the place where we first learned them, or that hearing a song can trigger our memory of an event.

Q: *Tell me a little about these links.*

A: One structure of the brain that's been most associated with memory is very strongly connected to parts of the brain involved in emotion, olfaction

and other senses. Some believe the hippocampus acts as a pointer to all these details represented by those regions of the brain that help conjure up detailed memories and interact with each other, so that a cue like entering a room you had entered years ago triggers a vivid memory of something that happened just after, or a certain smell or tune could trigger a rich recollection.

Q: *What strategies help amnesiacs compensate for such changes?*

A: I mentioned that amnesiac people who have hippocampal damage seem to have intact semantic memory for facts. They accumulated this information over their lifetime and continue to accumulate it, although much slower and with more repetition. We have a paper that just came out with Jennifer Ryan, my colleague, on an individual named D.A., using the transverse patterning paradigm—it's akin to the game, "rock, paper, scissors." You have to learn the reward values of items: Let's say A is greater than B, and B is greater than C. We found D.A. seemed to spontaneously create his own strategy to learn the relation among [unfamiliar] items.

Second thing we've been looking at is something called the spacing effect or distributed practice. It is one in which you study an item repeatedly, but the further spaced those repetitions are, the better you are at remembering the item.

We also looked at personal semantic memory, or self-identity. Individuals with hippocampal damage still know themselves. They still have a representation of their likes and dislikes, and can acquire this, past the time of injury. There's something called the "self-reference effect," where if you learn information in relation to yourself, you're more likely to remember it, because you're learning it at a very deep level of processing.

I also look at the effects of healthy aging. In one study, we showed that older adults benefit from the self-reference effect. They remembered better if they were thinking about themselves in an everyday scenario.

There's the memory and aging program at Baycrest. They integrate findings from studies like ours and teach these strategies in programs, with sessions and homework. The biggest trick is trying to get these individuals to incorporate these strategies in everyday life. We know they're not just effective in lab settings. Even if they're effective just in grocery shopping, they can help individuals live independently. **SARAH BARMAK**

Ask the Alzheimer's experts

We all worry about dementia, some more than others. Even some 40-year-olds think they're getting Alzheimer's when they can't find their car keys. *Maclean's* asked Canada's top experts everything you wanted to know about Alzheimer's and dementia, and they answered.

1. What is the No. 1 question you get asked when you tell people at a cocktail party that you are an Alzheimer's/dementia researcher, and what is your answer?

Dr. Barry Greenberg
Director of strategy, Toronto Dementia Research Alliance

Greenberg: "How soon will we have a cure for Alzheimer's disease?" I answer that it will be difficult to "cure" Alzheimer's disease, because the degree of damage to the brain is already quite advanced by the time the first symptoms are noticed.

Dr. Serge Gauthier
Director, Alzheimer's disease research unit, McGill Centre of Aging

Gauthier: "My mother-in-law is getting forgetful. Can you see her?" I suggest that she should see her family doctor first, to be sure she is not on medications that affect concentration, has low B12 or thyroid function. Sleep apnea can also occur in women. It will be useful to have a measure of her memory using the MMSE (mini mental state exam) and/or the MoCA before she is referred to a memory clinic.

Frédéric Calon
Professor of pharmacy, Université Laval

Calon: It usually circles around what one can do to prevent Alzheimer's, because they are afraid that a loved one (or themselves) will be affected. This is sad because there is not much of an answer to give. This contrasts so much with most other diseases. I end up recommending eating well, exercising physically and mentally, and… supporting research!

2. Is living with Alzheimer's a nightmare or a blessing for the patient?

Gauthier: Most patients in the dementia stage of AD do not fully realize the impact of their cognitive impairment on their daily life. In that sense it is somewhat of a blessing to them, but not to the family who has to put restrictions on driving, using money, and eventually living alone.

Rémi Quirion
Chief scientist of Quebec

Quirion: A nightmare early on, when the patient realizes that something is going wrong and that is most painful. It can never be a blessing for anyone to suffer AD.

Calon: A disease that destroys one's personality cannot be a blessing. However, for some patients, their "new" personality can be relatively easy to live with.

3. What is the most promising research on the horizon today?

Calon: No one really knows. Clinicopathological studies are probably the way to go first, because we still need to define what is Alzheimer's disease exactly.

Quirion: Genetic studies and the impact of the environment (gene-society; epigenetics) on the development of AD will clearly demonstrate that AD is multi-factorial with many different subtypes. In a sense it's very much like hypertension, which can originate from problems with blood vessels, or the heart or the kidney or a mix of those. This will also mean that different treatments will have to be developed according to the subtype.

Greenberg: Prevention of the disease before the onset of dementia. Several prevention studies have been recently launched in selected individuals based on their genetic profiles or pre-symptomatic biomarker patterns.

We will be testing the hypothesis of disease prevention in such subjects with selected agents. The initial results of these studies will emerge within the next several years.

Unfortunately, the identification of potential pre-symptomatic subjects requires some combination of brain imaging and analyses of cerebrospinal fluid obtained through lumbar punctures (spinal taps), neither of which is applicable to treatments in the general population, as individuals without symptoms would not be undergoing such procedures as a routine. We will need further development of non-invasive and inexpensive pre-symptomatic diagnostic methods. This is an extremely active area of current research.

4. What do you personally do to protect your brain from dementia and Alzheimer's?

Quirion: I am a bad guy. I do not do much but of course exercise my brain in the context of my job. Now I must do the same for my body.

Gauthier: I am nice to my wife (married men have a reduced risk of Alzheimer's disease), red wine in moderation, low dose of blood pressure and cholesterol pills, lots of time with the grandchildren.

Greenberg: The best protection is good cardiovascular health, as the brain is the most highly vascularized organ in the body. There are also numerous studies that suggest healthy diets (the so-called "Mediterranean diet"), social engagement and challenging brain activity can delay onset. I've been involved in discussions that playing musical instruments or performing artistic tasks may have similar benefits, although this has not been tested.

In terms of what I personally do, the answer is simple: not nearly enough.

Larry Chambers
Scientific adviser, Alzheimer Society of Canada

Chambers: Because Alzheimer's disease and other dementias are chronic conditions that are very often implicated with vascular disease, I try to eat a balanced, heart-healthy diet and stay physically active as these are known to help reduce the risk of these diseases. By virtue of my work as a scientist, I keep my brain sharp.

5. How do you know when it's time to take a person exhibiting memory loss to the doctor? And how do you get them there when they insist there isn't a problem?

Quirion: [That's] a hard one, and when you recognize it, it is already very late. Best would be to do memory tests in the clinics on a regular basis with age.

Gauthier: As soon as there is a memory problem the person should see their family doctor. A "memory check-up" is I think quite acceptable to most people.

Greenberg: As quickly as possible when memory issues become evident. There are many causes of cognitive impairment that are treatable or preventable that are not due to degenerative diseases such as Alzheimer's. For example, there are drugs prescribed for unrelated causes that have so-called "anti-cholingeric" properties that can be substituted. Poly-pharmacy is a major issue in the aging population. The second question is more difficult with a less clear answer, as there is no cure for common stubbornness or self-denial.

6. What is the difference between Alzheimer's and dementia?

Dr. John Breitner
Psychiatry professor and director, Centre for Studies on Prevention of Alzheimer's Disease, Douglas Institute, McGill

Breitner: Alzheimer's disease is a condition that causes chronic and progressive deterioration and loss of brain function. As it progresses it causes decline in cognitive abilities (like memory, ability to plan and carry out complicated activities, even the ability to understand spoken or written language or to speak oneself). As people develop these difficulties they come to have dementia—a loss of multiple cognitive abilities that is severe enough to cause loss in daily function.

Incidentally, it's worth noting that Alzheimer's disease evolves through several decades of brain changes that are not yet severe enough to cause dementia or even milder losses of memory and other cognitive functions. That's important because this "pre-symptomatic" stage of

the disease is the time when we want to give treatments that can slow down the process.

7. Do personalities change with dementia and Alzheimer's? Can a grumpy person become sunny and vice versa? And what causes it?

Quirion: Yes, it happens especially early on when the patient realizes that something is happening, often leading to depression and/or aggressiveness.

Chambers: A person with Alzheimer's disease can become confused, suspicious or withdrawn. The person with dementia may be struggling with their loss of independence as a result of their declining functioning and abilities. This can lead to frustration, which may be expressed as cursing, complaining and increased irritability. A desire to regain some amount of control in the person's life may be expressed as being stingy or miserly. For example, the person may prepare a meal for two for a family gathering of eight and doesn't bother to tidy up before guests arrive.

8. If my father or mother had Alzheimer's does that mean I'll get it?

Breitner: You have something like a two- or threefold higher risk of developing Alzheimer's or dementia than a person of similar age and background who doesn't have this sort of family history. But it's important to remember that we're talking probabilities here. No one can tell for certain whether you will actually develop the dementia of AD. There are many other factors that can affect your risk.

Greenberg: No. Only about one per cent of cases are genetically inherited. The elevated risk in children of parents who were diagnosed with Alzheimer's disease is modest.

9. With the recent failure of Gammagard, once considered a promising treatment for Alzheimer's, and the fact that there hasn't been a new Alzheimer's drug in a decade, is there any hope for new treatments?

Gauthier: Definitively. Each "negative" study leads to knowledge about the natural history of Alzheimer's disease, changes in biomarkers, sensitivity of cognitive and functional measures.

Calon: Resilience is one of the key assets of most researchers. We cannot be deterred by bad news. There are many positive ways to look at things. Given the ridiculously low amount of investment in research (i.e. less than 0.2 per cent of spending on AD), researchers have done a lot in the last 30 years.

Chambers: At present, over 230 phase-three clinical trials are on international registers. Gammagard is just one of a multitude of treatments being explored by researchers. There is always hope, and we must remain hopeful. What science is currently telling us is that no single pharmaceutical substance is enough to alter the course of the disease.

10. Do you think a cure for Alzheimer's will be found in your lifetime?

Quirion: You know, cures are extremely rare in medicine. They occur for some infections but usually it is more like effective treatments that are discovered, not cures (just think of the treatments of most cancers, of hypertension, diabetes and many others).

Calon: A reasonable goal is to achieve something similar to what we have done with AIDS, finding a treatment that may not totally cure the disease, but at least dramatically slows down the pathological process. For AD, this would likely be a preventive treatment given to pre-identified high-risk individuals in order to delay the advent of symptoms by many years.

Chambers: Neurobiological science is the most expanded and largest field of science in the world today. The human brain is one of the most complicated entities known to man. At my age, I continue to be hopeful.

Language on the brain

The good news: Speaking a second language keeps Alzheimer's at bay.
The bad news: Bilingualism makes it harder to test for the disease.

The bilingual brain is a mental two-timer. One moment it appears faithful to a native tongue; the next, it's summoning a second language like it's a mistress on speed dial.

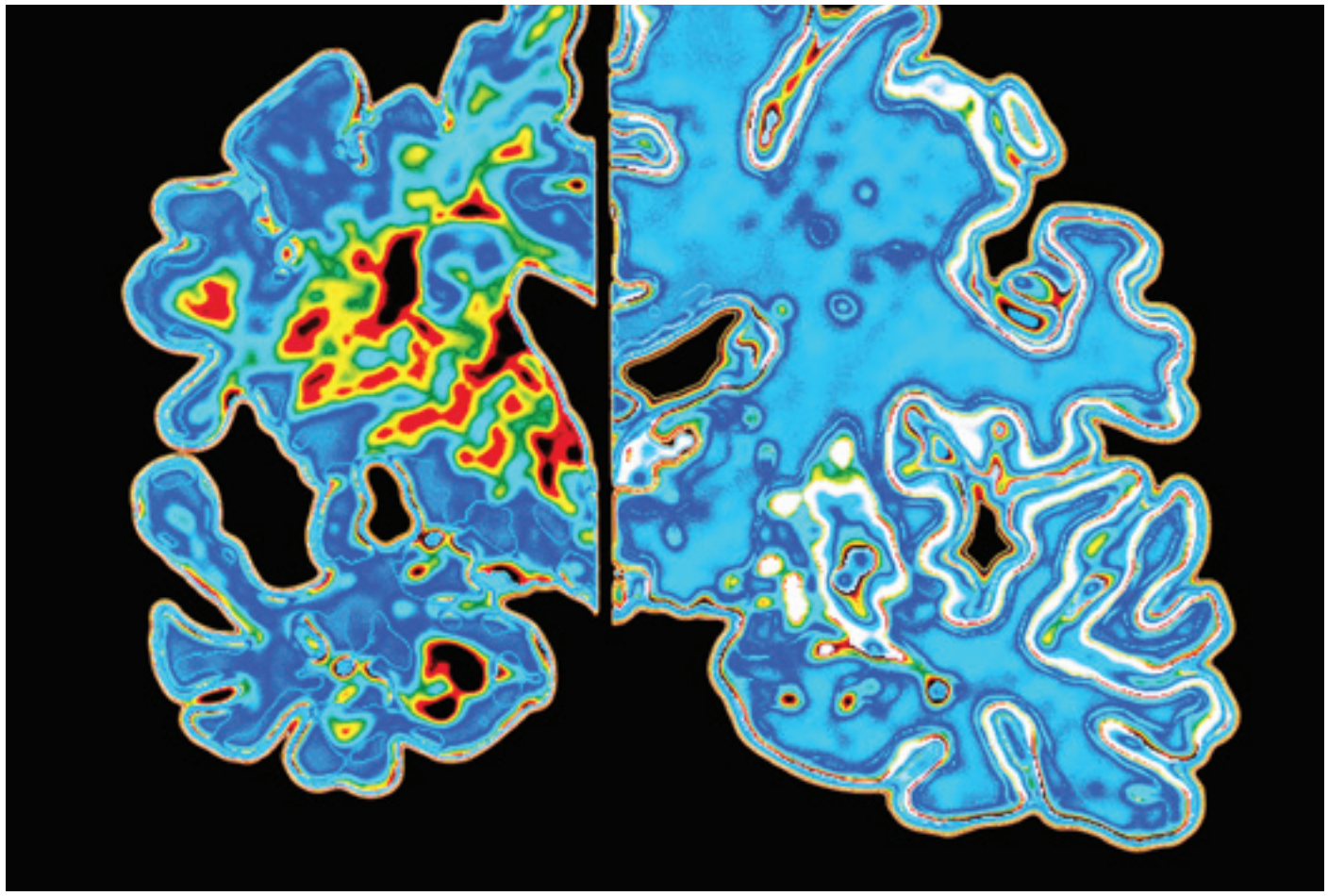
It's a cognitive juggling act that supports the idea that people who speak more than one language are slick multi-taskers. The probable reason, according to researchers, is their mastery of the brain's so-called executive function. The command centre that manages judgment, attention processes and task switching also allows bilinguals to toggle freely between systems of communication.

What happens, though, to that cerebral circuitry as we age? Studies indicate that fluency in another language bolsters our neurological wiring against the damaging effects of dementia. "It's called the 'bilingual advantage,' " says University of Ottawa psychology professor Vanessa Taler. "There are aspects of some higher-order cognitive processes that bilinguals are better at. We're interested in figuring out how it's a factor contributing to cognitive reserve."

Cognitive reserve refers to the brain's resiliency and ability to stave off clinical diseases such as dementia that might be due to greater connectivity between brain regions. Education, exercise, diet and social interactions can help build greater reserves, according to doctors.

As we age, hallmarks for Alzheimer's such as "senile plaques" deposit in the brain's grey matter, Taler said. Those protein buildups can disrupt signals in the brain."Neuroimaging methods can actually let you see the senile

plaques, the atrophy," she said. "The argument is that bilingualism helps you deal with it better."



Grey matters: The brain of an Alzheimer's patient (left) and a healthy brain (right). The damage is the same, but symptoms are delayed in bilinguals. (SCIENCE PHOTO LIBRARY)

In 2010, *Neurology* published an analysis of clinical records that suggested bilingualism can push back the onset of Alzheimer's symptoms by as much as five years. Last year a team of Toronto-based researchers detected the first physical evidence to support those findings, analyzing CT scans of multilingual patients, which showed that they were functioning at the same cognitive level as monolinguals even though their brains showed significantly more advanced symptoms of Alzheimer's.

Evidence that learning two languages can, to some degree, delay the onset of the disease is of particular significance in a bilingual and multicultural country like Canada, where close to one-fifth of the population is fluent in both official languages.

But there's a wrinkle. The very skill that helps delay cognitive impairment can also make it tricky to test. That's where Taler's work developing a French-English test for dementia comes in.

"We know there's a high prevalence of bilingualism in Canada, we know

there's an increasing population that's getting older, which is a primary risk factor of dementia, and yet we don't actually have good norms for testing bilinguals," she said. "This is what we're trying to figure out." The project, funded by the Alzheimer Society of Canada and based in Taler's lab at the Bruyère Research Institute in Ottawa, is working on a French-English diagnostic assessment. Part of the problem is bilinguals process language very differently than monolinguals, so they can't be assessed with the same baselines.

Maxed out: One language may be more impaired than another as Alzheimer's progresses, says Laura Moretta of Université Laval (SCIENCE PHOTO LIBRARY)

Ellen Bialystok, a York University psychology professor and leading expert on bilingualism and cognitive aging, said it's well established that there are "major significant vocabulary differences between monolinguals and bilinguals."

Most bilinguals tend to have more streamlined vocabularies, split between

both languages, and perform worse on language tasks than people fluent in only one language. Bilinguals may at times have less robust word power in both languages because their cognitive capacities for storing that much information gets maxed out.

Further, one language may be more impaired than another as Alzheimer's progresses, explained Laura Moretta, a speech therapist and assistant professor at Université Laval who is collecting francophone data for Taler's project. "Bilinguals can access one language and then the other, but when they have a problem in the brain, they're not affected in the same way," she said.

For example, some stricken with Alzheimer's may forget more of one language than the other. "That's why, when a patient is being assessed in one language, we may not be getting the full picture of their abilities or impairments," added Shanna Kousaie, a post-doctoral fellow at the Bruyère who is assisting Taler.

As for which words fade from cognitively impaired patients' memories first, they tend to be recently learned terms or least-used words. Proper nouns such as names usually slip away as language function deteriorates. Those names may get replaced by more vague pronouns like "him" or "her."

Taler added there is some evidence of "a disadvantage" for "biological kinds" of words, such as names for animals, possibly due to confusion over similarities in semantic features—many living creatures have four legs and fur, for instance.

She expects to have a working model of the computerized adaptive testing for French and English bilinguals finished in two years. In the meantime, her lab will gather data from 400 people to create algorithms for the test, which would present images such as a helicopter, jacket or window for a patient to identify using whichever language the subject chooses. Based on the responses—right or wrong, French or English, and the breadth of the vocabulary available—an algorithm would determine the next slide, with an adjusted difficulty level.

The test would have to be adapted for different language combinations, such as Cantonese and English, or Arabic and French.

"A bilingual has a lower vocabulary size in each language just due to being bilingual," said Taler. "That might lead you to think there's a problem, but it's not because their language skills are inferior. It's because they're managing two languages."

When Taler tested control subjects in a “choose your own language” scenario, 30 per cent of about 120 participants performed worse than subjects who were asked to respond in their stronger language. Two languages jockeying for words could cancel each other out, causing the participant to draw a blank, she theorized. **MATT KWONG**

5 ways to jog your memory

From ‘smart home’ tech to tiny cameras, research looks at a variety of novel ways to help boost retention

Memories are fallible, fleeting and maddening. One moment, a cluster of neurons in your brain is fusing together to store a specific experience; the next, the hippocampus goes dark and that sensory information has fluttered away. But what if there are ways to hack our minds and even train our powers of recall? Neuroscientists are experimenting with next-generation aids to strengthen our cognitive muscles and improve quality of life for Alzheimer’s patients and people with memory impairments. The toolkit includes a mechanism that tracks our eyeballs’ movements so we can learn how to better recognize faces, high-tech homes that speak to us, tiny wearable cameras that record visual memories in a snap, mind workout games and even virtual reality. **MATT KWONG**

Virtual reality

In a novel fusion of virtual reality with brain-scanning technology,

Dalhousie University neuroscientists led by Olav Krigolson are working with head-mounted displays to simulate driving conditions. The Halifax researchers attach an SX60 immersive helmet to a subject, then wire the person's scalp with electrodes to track brain signals as the subject learns from crash scenarios. The simulations could teach muscle-memory responses and implicit or unconscious memory, Krigolson says. His team received a $325,000 grant from the Canadian Foundation for Innovation to continue their research.

Smart homes

Washing your hands or locking the door at home might seem second nature. Not so for some patients living alone with dementia or Alzheimer's. Alex Mihailidis, a senior scientist with the Toronto Rehab Institute, has developed assistive "smart home" technology that automatically reminds seniors if a motion sensor determines they're confused or forgot a step in a task. The system delivers verbal instructions such as, "Turn the tap in front of you," and can address the person by name. Mobile robots can also play video tutorials. The artificial intelligence system has been tested in three nursing homes, and is being prepared for in-home trials.

Brain fitness games

Vancouver start-up Vivity Labs launched its Fit Brains Trainer app

for mobile devices last December. The app, which already has three million users, features logic puzzles, concentration games, math problems and other intellectual challenges. Clinical neuropsychologist Paul Nussbaum designed the challenges to exercise five major cognitive brain functions and enhance memory. Vivity Labs is consulting with psychology and cognitive science universities in B.C. and Ontario to study Fit Brains Trainer's impact on users' cognitive abilities.

Eye-tracking device

The eye-tracking device EyeLink II, developed by University of Toronto psychologist Eyal Reingold, is a key apparatus in Jennifer Ryan's lab. Ryan, the Canada Research Chair for the cognitive neuroscience of memory, monitors how EyeLink visors mounted to volunteers' heads track the patterns of their eye movements—an important factor in visual memory. She hopes understanding the way we process environments and recognize faces could help us train our gazes to focus differently, boosting retention.

Mini "lifelogging" cameras

The Vicon Revue, a tiny camera that can be worn like a pendant, takes viewer-perspective photos every 30 seconds. Microsoft's research division developed the device now used by psychology professor John Seamon's team at Wesleyan University in Connecticut. In Seamon's experiments, cognitively impaired patients at the Hartford Hospital's memory clinic wore

the cameras and walked around campus or watched a film. They reviewed their photos and, quizzed later, retained more memories than a group that wrote notes in a diary. Seamon theorizes that visual reminders taken from the viewer's perspective act as "a powerful trigger for recollection." The University of Toronto's TAGlab (Technologies for Aging Gracefully Lab) also used Vicon Revues for dementia research in 2010, studying the improved recall abilities of six seniors equipped with the cameras. The Vicon Revue is no longer in production as of 2013. A new model is being marketed under the name "Autographer." ♣

Neuro mania

‘This your brain on sports/music/pick a topic.’ Oh, neuroscience, the world is looking to you for all the answers. And everyone wants in on the game

Welcome to the Neuro Age. It was slow starting—the originating term, neuroscience itself, was only coined in 1962—but the new social explain-all has been spawning progeny at a rabbit-like pace lately. Much as the 20th century internalized *psyche*—we tossed around “psychodrama,” “psych out” and “psychopath” as everyday terms—the 21st has appended *neuro-* to a host of subjects once understood in social, philosophical or even religious terms.

Consider neurohistory, which explores how cultural structures interacted with and shaped our brain-body system.

Or neurophilosophy, which ponders the limiting effects our brains’ hardware imposes on the software of our ideas.

Or neuropsychiatry (weren’t psychiatrists and psychologists always interested in the brain? No: the mind), where researchers hope to use neuroscience to lay a factual floor under long-held assumptions about the links between organic brain developments and mental illness.

Neuro educationalists, whose new discipline combines neuroscience, psychology and educational theory to create improved teaching methods, are particularly enthusiastic about the potential of brain research. As Ken Kosik, a professor of neuroscience at the University of California at Santa Barbara, declared: “We need neuroscientists in schools: just like we have teaching hospitals, we need teaching schools.” Indeed, new academic foundations now

offer neuroscientific training to student teachers.

As always, where there is insight into human behaviour and motivation, there is economic opportunity: a thriving industry devoted to "brain-based learning" already supplies parents and teachers with games, books, models and software claiming to possess the key to unlocking the most stubborn student's educational resistance.

And even when their products are far from brain-oriented, neuromarketers of all stripes aim to fine-tune their salesmanship via the insights of neuroscience, especially those that show what features—of a person, place or thing—we seem hardwired to find attractive. (Call it neuroaesthetics: what your brain looks like on art.)

Throughout the social sciences, researchers are eager to attach "neuro" to their disciplines—neuroeducation, neurosociology, neuroanthropology—in an effort to turn them into hard sciences, bringing real explanatory power to dissecting the vagaries of the human condition, and thereby affecting learning, law, government and our very idea of what is normal or abnormal.

Publishing houses are pouring out the results: Amazon currently lists over 7,000 books with "neuro" in their titles and another 51,000 with "brain." The majority are for experts (*Principles & Practice of Neuro-Oncology*), but many are directed at ordinary readers (*Neuroscience for Dummies*).

"Some have done extraordinarily well lately," says Diane Turbide, publishing director at Penguin Canada, citing the constituent niches within the brain readership.

"The part we all want fixed," she says, in ourselves and our aging parents, has turned books like Toronto neurologist Tiffany Chow's *The Memory Clinic: Stories of Hope and Healing for Alzheimer's Patients and Their Families* into a bestseller, while *The Brain That Changes Itself*, a book about neuroplasticity by University of Toronto psychiatrist Norman Doidge, sold 100,000 copies in Canada alone.

That North America's greying boomers are now starting to contemplate death and the hereafter is surely a factor in keeping Dr. Eben Alexander's *Proof of Heaven: A Neurosurgeon's Journey Into The Afterlife* on the *New York Times* bestseller list for the past six months; a contrarian who argues against scientific belief that near-death experience is merely brain-based.

But it's not all a matter of personal concerns, Turbide adds. "There's clearly a thirst among the general reading public for an overarching theme, something that explains everything."

That desire has turned British neuroscientist Adrian Raine, author of *The Anatomy of Violence*, into a media presence. More than a half-century after Nazi eugenics theory made the subject toxic, talk about the biological roots of crime is respectable again. Neurocriminologist Raine points to the dangerous effects of trauma in the womb on fetal brains: children born to starving mothers, deprived of essential minerals and vitamins before birth, are 2.5 times more likely than their peers to test positive as teens for antisocial personality disorder.

Further advances in his field, Raine quite rightly predicts, will turn neurocriminology into the hottest of the hot-button neuro disciplines, touching as it does on some of our society's core concepts and values, including free will and fair legal punishment. These will soon be a matter, he writes, of neurolaw and neuroethics.

There will be others, though, like Montreal neuroscientist Mario Beauregard, author of *The Spiritual Brain*, who will discuss those issues within neuroreligion, neurocriminology's only rival for contentiousness. Neuroscientists, who for the most part stand by the mantra that "the mind is what the brain does," continue to search for physical roots to out-of-body experiences like those of Alexander. They scan the brains of everyone from Franciscan nuns

at prayer to meditating Buddhist monks in their attempts to establish the neural correlates of spiritual beliefs.

Their conclusions are challenged every step of the way by "non-materialist" colleagues like Beauregard and by neurotheologians, who find it quite understandable that God utilizes particular neural pathways. Just because particular areas of the brain light up as certain mental activities begin doesn't mean other areas—or other (spiritual) entities—are not eventually involved.

As made clear by the groaning bookshelves and the media attention garnered by Raine, Doidge and some of their peers, the neuro-explanation holds profound popular appeal. It suits us: our capabilities, our fears, our hopes, our view of ourselves. Physical causes for our failings, including those once thought moral or psychological, both lessen our responsibility and hold out the hope of cure, or at least prevention.

We may not have achieved it yet, but we have faith that neuro-certainty—finally understanding ourselves—is just the flare of a synapse away.

BRIAN BETHUNE

Headline acts

Biases built into brain studies mean results are often skewed before they're reported

A funny thing happened on the way to Jonah Lehrer's hanging. Last year, Lehrer, an insanely successful pop-neuroscience author, published a book called *Imagine: How Creativity Works*. Lehrer had larded up the book with fabricated quotes about songwriting from Bob Dylan, which was a poor choice. Dylan's rare public comments have been repeated, studied and cross-referenced so intensely that thousands of amateur Dylanologists were probably capable of spotting the lies. A freelancer named Michael Moynihan did the homework and received the glory. What was strange was how Moynihan's career-finishing blow brought neuroscientists out of the woodwork to criticize Lehrer, not for bad ethics, but for his glib, slovenly use of their research.

Christopher Chabris, a psychology prof at Union College in Schenectady, N.Y., had been one of the earliest Lehrer critics; after the dust settled, he complained that the Lehrer narrative had become a brilliant-youngster-makes-fatal-errors tale, when, in fact, "his explanations were inaccurate, overblown and often just plain wrong, usually in the direction of giving his readers counterintuitive thrills and challenging their settled beliefs." Another early critic, Columbia University psychiatrist Peter Freed, had written in 2011 that Lehrer's fans "want neuroscience to make as much sense as Jonah Lehrer's writing does, and the brain to be as unthreatening as Jonah Lehrer makes it… They want it to be like buying an iPhone. They want it to be intuitive and fun."

Those last eight words are a big hint. Bad things can happen when jour-

nalists and neuroscientists collide. It is not just neuroscience that we sometimes abuse, but neuroscience might have special problems making the step from the laboratory to the popular printed page. Consider what follows a friendly consumer warning.

This is your brain on pop journalism: Neuroscience can have special problems making the step from the laboratory to the printed page (DAVID PAUL MORRIS/THE BRAIN OBSERVATORY/BLOOMBERG/GETTY IMAGES)

Most of us could give a short, loose explanation of the scientific method: "Make experiments and look honestly at what you find." The form this generally takes nowadays is more specific: "Make experiments, and if you find something new or curious, figure out how likely it is that it could have appeared by chance alone." This is the basic reason for all those forbidding R-squareds and p-values in scientific papers: The authors are trying to show that they've found something intriguing that cannot be attributed to random variation, that isn't a one-off or fluke. This, in turn, is the reason for the emphasis science puts on reporting experiments in enough detail to be reproduced by somebody else.

But startling, counterintuitive new results are actually favoured at every step in the creation of popular-science literature. When it comes to selling books, newspapers and, yes, magazines, the rule is "the weirder, the better."

That goes double for brain research. Would you be reading these wonders if they had been written for a "Wonders of the spleen" issue?

Yet we typists are merely the last in a series of weirdness filters who aren't always oriented properly. By the time a science journalist hears about a finding, it has probably already been singled out by a public-relations flack at a research institution as being potentially newsy. The finding, in turn, may have been selected for publication by a scientific journal partly for attention-getting quirkiness. And, in turn, the result being published is probably the culmination of a long series of experiments, most of them "failed," on the part of the original investigator.

Jonah Lehrer (LYNN GOLDSMITH/CORBIS)

Scientists are supposed to be the guardians of their own integrity in this last regard—to correct sincerely for "multiple comparisons," which is the technical term for "throwing lots of stuff at the wall and seeing what sticks"—and to be conservative about judging whether results are reliably non-random. But functional magnetic-resonance imaging—the workhorse of neuroscience, which can identify areas of increased blood flow in the brain—is barely 20 years old. Its use has expanded fast, and trust in fMRI results has lately been undermined by a barrage of skeptical bombshells.

The most famous is a study now known to neurologists as the "Voodoo Correlations" paper—an insulting locution that was in the original title, but was deep-sixed in favour of the friendlier "puzzlingly high correlations"

before its 2009 publication in *Perspectives on Psychological Science*. The "Voodoo Correlations" name stuck anyway, because the preprint had caused a sensation after circulating online. The paper showed that many of the statistical connections between blood-flow results and psychological tests reported in the literature were stronger than they ought to have been, literally "impossibly high." Experimenters were routinely finding higher correlations between fMRI tests and measures of personality or emotion than either kind of test ordinarily has with itself when applied repeatedly.

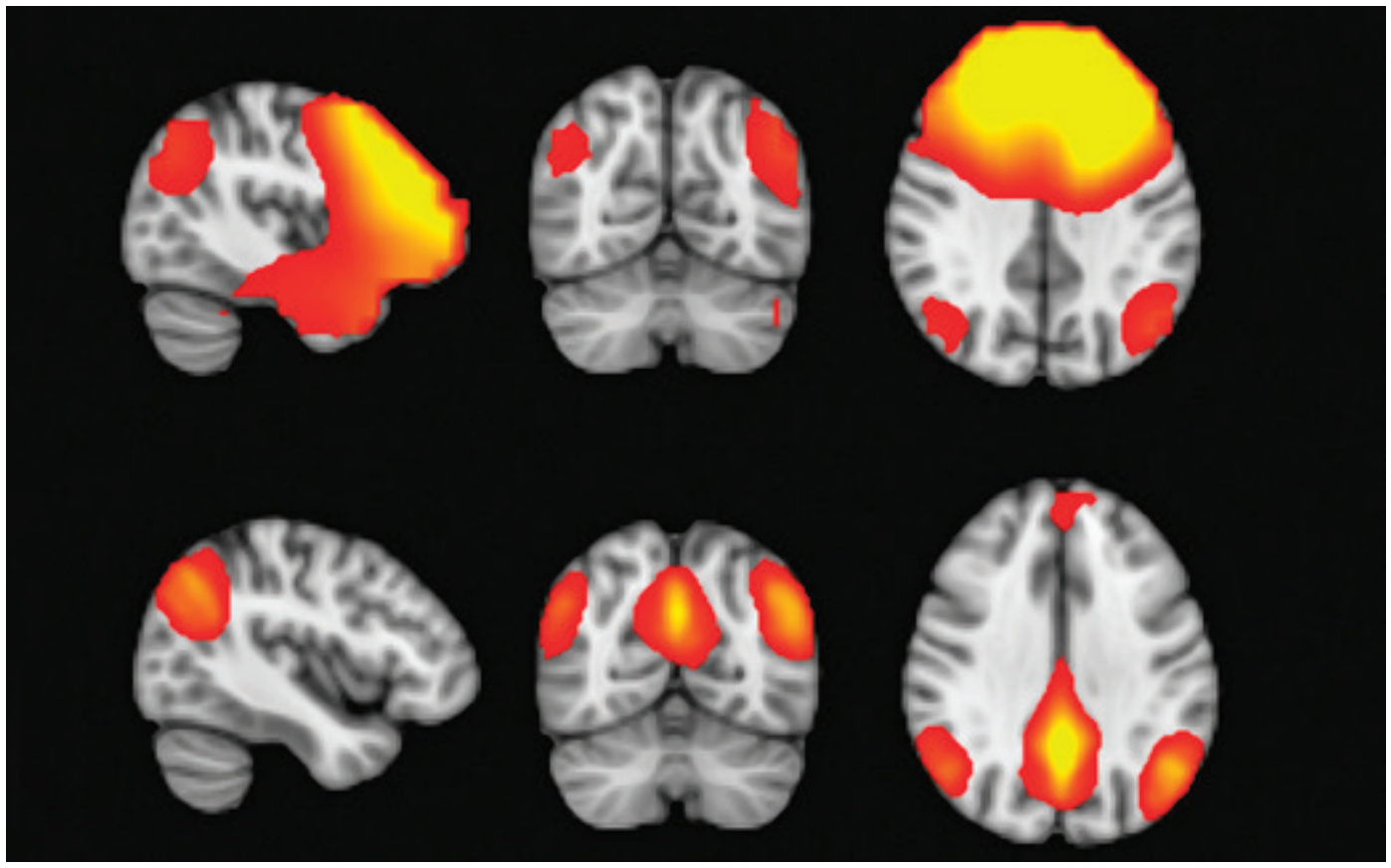
Jonah Lehrer's fans 'want neuroscience to make as much sense as Jonah Lehrer's writing does. They want it to be intuitive and fun.'

After sending out questionnaires to investigators, the authors of "Voodoo Correlations" discovered this was only possible because of endemic sampling bias. fMRI analysts were selecting promising subsets of thousands of voxels (the 3D analog of digital pixels) from their images, then naively reporting brain-image-to-behaviour correlations only between the "voxels of interest" in different test subjects, as if the uninteresting ones had never existed. In essence, the game was statistically rigged.

"Voodoo Correlations" has become an oft-cited landmark of neuroscience literature, and lead author Ed Vul, a brain-modelling specialist at the University of California-San Diego, notes that problems of inappropriate or bungled statistical hygiene are likely to arise when a scientific area of study first acquires the power of massive multidimensional data. When DNA sequencing became cost-effective, for example, genetics suffered analogous problems, and has learned more or less successfully to deal with them. "It's not the case that this particular issue no longer arises in neurology," he says. "But journal editors are very keenly aware of it now, and the rate at which it gets through is lower."

That is good news, but "Voodoo Correlations" was a reminder that there are many possible sources of false significance in research findings, and the authors had tackled only one. Uri Simonsohn, a social psychologist at the University of Pennsylvania's Wharton School, has been making international headlines as a fraud-busting statistics ninja, recently giving a cheeky new

name to an ancient problem: the issue of "researcher degrees of freedom." If an experimenter doesn't find the non-random statistical relationship he is looking for at first, he can make self-serving decisions on the fly and essentially pack many experiments into one: He can increase his sample, try different techniques of mathematical massaging, correct for or drop out different variables. This floods the literature with marginally "significant" findings actually due to chance, and the more researcher degrees of freedom a field has, the more error-prone its evidence base will be.



Using your head: Functional magnetic-resonance imaging—the workhorse of neuroscience—is barely 20 years old, and results have come under suspicion (SCIENCE PHOTO LIBRARY)

fMRI studies contain a terrifyingly huge quantity of researcher degrees of freedom. This was documented in October 2012 by a University of Michigan neuroscience grad student, Joshua Carp, whose literature review for the journal *Neuroimage* points out that fMRI studies are almost never done the same way twice. (He called the paper "The secret lives of experiments," a choice almost as daring as "Voodoo correlations.") Most of the research Carp checked out offered little or no useful detail about underlying methodological choices: Reproducibility is barely thought of. fMRI experimenters have very free rein in deciding how they fiddle with and group together signals from individual voxels, what statistical assumptions they incorporate into their work, what volunteers for brain pictures they accept or reject, even

what computer packages they use to crunch data.

Meanwhile, a different problem caught the attention of perhaps the top theorist of publication bias, Stanford's John Ioannidis. On April 10, Ioannidis and six co-authors published a study in *Nature Reviews Neuroscience* called "Power failure: why small sample size undermines the reliability of neuroscience." Scientists always want the largest sample they can get, because a true effect is more likely to meet the "probably not due to chance" criterion. But the Ioannidis group points out the often-neglected flip side: When some true effect exists, its apparent size can only be exaggerated by many small, underpowered studies, as opposed to one big one. If a barrage of small studies was launched to look for an odds ratio of 1:2 between psoriasis in Smiths and psoriasis in Joneses, the reported estimates would be scattered widely, ranging from less than one to perhaps two or even higher. But if only the "significant" effects got reported, which is effectively what happens when many labs are working in parallel on the same things, the overall average of the estimates would be much too high.

The authors call this the "winner's curse" and interrogate the neuroscience literature with it in mind. Are neuroscience studies characterized by small sample sizes? Very much so: They're damned expensive. Is this particularly true of fMRI and other neuroimaging studies? Yes it is: Those studies had even lower sampling power than animal-model experiments, in which there are usually tight ethical constraints on the number of subjects. Is the "winner's curse" problem big enough to affect the literature of neurology as a whole, to imply that much of it is exaggerated or false? Almost certainly.

The "Power Failure" paper repeats Vul's observation that genetics has already survived an analogous crisis. But it was no coincidence that the acceptance of statistical conservatism in genetics coincided with the crushing of early high hopes for genomic medicine. Thousands of robust relationships between particular mutations and particular diseases have now been documented—and some are useful guides to therapeutic action, as actress Angelina Jolie recently found out—but most known gene markers turn out to offer frustratingly elliptical hints, rather than clear causes of illness. Human traits known to be heritable, such as IQ or height, are turning out to be modified by large numbers of ultra-rare (and probably mutually interacting) gene variants rather than by lone, easy-to-spot ones. Gene-driven progress in medicine, once expected to proceed by great leaps, is now expected to be slow and incremental.

It is easy to imagine today's excitement over brain imaging ending the same way. "People sell fMRI as having potential for mind-reading," says Vul. "Well, fMRI averages the signals over a lot of space and a lot of time, and there are theoretical and practical limits to the technology. I don't know whether we'll get to the point where fMRI leads to findings that will allow us to predict human behaviour and intervene usefully on it. And you can't declare success until you get to that point." **COLBY COSH**

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