A TALE OF TWO HALVES

Since the 1960s, researchers have been scrutinizing a handful of patients who underwent a radical kind of brain surgery. The cohort has been a boon to neuroscience — but soon it will be gone.

BY DAVID WOLMAN

In the first months after her surgery, shopping for groceries was infuriating. Standing in the supermarket aisle, Vicki would look at an item on the shelf and know that she wanted to place it in her trolley — but she couldn't. "I'd reach with my right for the thing I wanted, but the left would come in and they'd kind of fight," she says. "Almost like repelling magnets." Picking out food for the week was a two-, sometimes three-hour ordeal. Getting dressed posed a similar challenge: Vicki couldn't reconcile what she wanted to put on with what her hands were doing. Sometimes she ended up wearing three outfits at once. "I'd have to dump all the clothes on the bed, catch my breath and start again."

In one crucial way, however, Vicki was better than her pre-surgery self. She was no longer racked by epileptic seizures that were so severe they had made her life close to unbearable. She once collapsed onto the bar of an old-fashioned oven, burning and scarring her back. "I really just couldn't function," she says. When, in 1978, her neurologist told her about a radical but dangerous surgery that might help, she barely hesitated. If the worst were to happen, she knew that her parents would take care of her young daughter. "But of course I worried," she says. "When you get your brain split, it doesn't grow back together."

In June 1979, in a procedure that lasted nearly 10 hours, doctors created a firebreak to contain Vicki's seizures by slicing through her corpus callosum, the bundle of neuronal fibres connecting the two sides of her brain. This drastic procedure, called a corpus callosotomy, disconnects the two sides of the neocortex, the home of language, conscious thought and movement control. Vicki's supermarket predicament was the consequence of a brain that behaved in some ways as if it were two separate minds.

After about a year, Vicki's difficulties abated. "I could get things together," she says. For the most part she was herself: slicing vegetables, tying her shoe laces, playing cards, even waterskiing.

But what Vicki could never have known was that her surgery would turn her into an accidental superstar of neuroscience. She is one of fewer than a dozen 'split-brain' patients, whose brains and behaviours have been subject to countless hours of experiments, hundreds of scientific papers, and references in just about every psychology textbook of the past generation. And now their numbers are dwindling.

Through studies of this group, neuroscientists now know that the healthy brain can look like two markedly different machines, cabled together and exchanging a torrent of data. But when the primary cable is severed, information — a word, an object, a picture — presented to one hemisphere goes unnoticed in the other. Michael Gazzaniga, a cognitive neuroscientist at the University of California, Santa Barbara, and the godfather of modern split-brain science, says that even after working with these patients for five decades, he still finds it thrilling to observe the disconnection effects first-hand. "You see a split-brain patient just doing a standard thing — you show him an image and he can't say what it is. But he can pull that same object out of a grab-bag," Gazzaniga says. "Your heart just races!"

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Work with the patients has teased out differences between the two hemispheres, revealing, for instance, that the left side usually leads the way for speech and language computation, and the right specializes in visual-spatial processing and facial recognition. "The split work really showed that the two hemispheres are both very competent at most things, but provide us with two different snapshots of the world," says Richard Ivry, director of the Institute of Cognitive and Brain Sciences at the University of California, Berkeley. The idea of dichotomous consciousness captivated the public, and was greatly exaggerated in the notion of the 'creative right brain'. But further testing with split-brain patients gave a more-nuanced picture. The brain isn't like a computer, with specific sections of hardware charged with specific tasks. It's more like a network of computers connected by very big, busy broadband cables. The connectivity between active brain regions is turning out to be just as important, if not more so, than the operation of the distinct parts. "With split-brain patients, you can see the impact of disconnecting a huge portion of that network, but without damage to any particular modules," says Michael Miller, a psychologist at the University of California, Santa Barbara.

David Roberts, head of neurosurgery at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, sees an important lesson in split-brain research. He operated on some of the cohort members, and has worked closely with Gazzaniga. "In medical school, and science in general, there is so much emphasis on large numbers, labs, diagnostics and statistical significance," Roberts says — all crucial when, say, evaluating a new drug. But the split-brain cohort brought home to him how much can be gleaned from a single case. "I came to learn that one individual, studied well, and thoughtfully, might enable you to draw conclusions that apply to the entire human species," he says.

Today, the split-brain patients are getting on in years; a few have died, one has had a stroke and age in general has made them all less fit for what can be taxing research sessions of sitting, staring and concentrating. The surgery, already quite rare, has been replaced by drug treatments and less drastic surgical procedures. Meanwhile, imaging technologies have become the preferred way to look at brain function, as scientists can simply watch which areas of the brain are active during a task.

But to Miller, Ivry, Gazzaniga and others, split-brain patients remain an invaluable resource. Imaging tools can confirm, for example, that the left hemisphere is more active than the right when processing language. But this is dramatically embodied in a split-brain patient, who may not be able to read aloud a word such as 'pan' when it's presented to the right hemisphere, but can point to the appropriate drawing. "That gives you a sense of the right hemisphere's ability to read, even if it can't access the motor system to produce speech," Ivry says. "Imaging is very good for telling you where something happens," he adds, "whereas patient work can tell you how something happens."

2 A CABLE, CUT

Severing the corpus callosum was first used as a treatment for severe epilepsy in the 1940s, on a group of 26 people in Rochester, New York. The aim was to limit the electrical storm of the seizure to one side of the brain. At first, it didn't seem to work. But in 1962, one patient showed significant improvement. Although the procedure never became a favoured treatment strategy — it's invasive, risky, and drugs can ease symptoms in many people — in the decades since it nevertheless became a technique of last resort for treating intractable epilepsy.

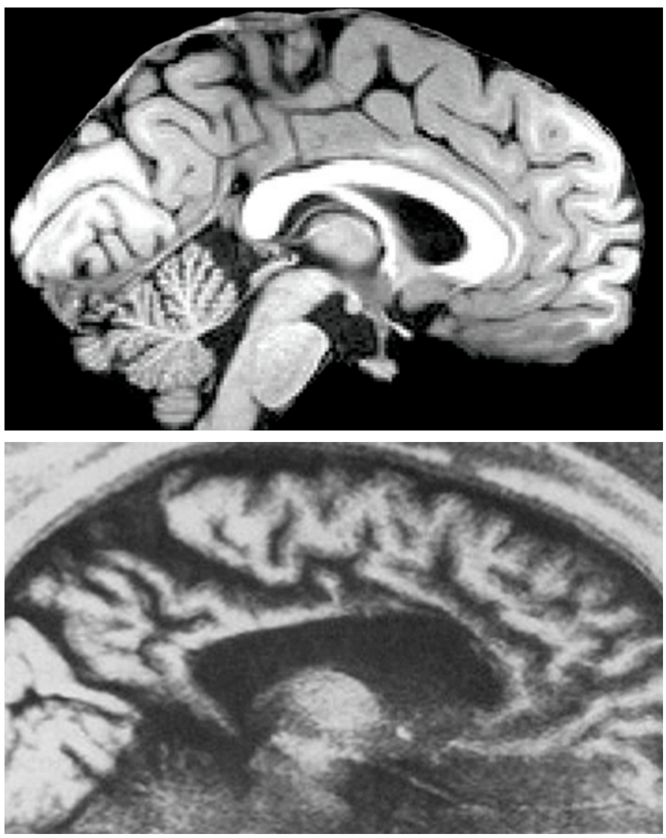
To Roger Sperry, then a neurobiologist and neuropsychologist at the California Institute of Technology, and Gazzaniga, a graduate student in Sperry's lab, split-brain patients presented a unique opportunity to explore the lateralized nature of the human brain. At the time, opinion on the matter was itself divided. Researchers who studied the first split-brain patients in the 1940s had concluded that the separation didn't noticeably affect thought or behaviour. (Gazzaniga and others suspect that these early sections were incomplete, which might also explain why they didn't help the seizures.) Conversely, studies conducted by Sperry and colleagues in the 1950s revealed greatly altered brain function in animals that had undergone callosal sections. Sperry and Gazzaniga became obsessed with this inconsistency, and saw in the split-brain patients a way to find answers.

The duo's first patient was a man known as W. J., a former Second World War paratrooper who had started having seizures after a German soldier clocked him in the head with the butt of a rifle. In 1962, after W.J.'s operation, Gazzaniga ran an experiment in which he asked W.J. to press a button whenever he saw an image. Researchers would then flash images of letters, light bursts and other stimuli to his left or right field of view. Because the left field of view is processed by the right hemisphere and vice versa, flashing images quickly to one side or the other delivers the information solely to the intended hemisphere (see 'Of two minds').

For stimuli delivered to the left hemisphere, W.J. showed no hang-ups; he simply pressed the button and told the scientists what he saw. With the right hemisphere, W.J. said he saw nothing, yet his left hand kept pressing the button every time an image appeared. "The left and right didn't know what the other was doing," says Gazzaniga. It was a paradigm-blasting discovery showing that the brain is more divided than anyone had predicted[1].

Suddenly, the race was on to delve into the world of lateralized function. But finding more patients to study proved difficult. Gazzaniga estimates that at least 100 patients, and possibly many more, received a corpus callosotomy. But individuals considered for the operation tend to have other significant developmental or cognitive problems; only a few have super-clean cuts and are neurologically healthy enough to be useful to researchers. For a while, Sperry, Gazzaniga and their colleagues didn't know if there was ever going to be anyone else like W.J..

But after contacting neurosurgeons, partnering with epilepsy centres and assessing many potential patients, they were able to identify a few suitable people in California, then a cluster from the eastern part of the United States, including Vicki. Through the 1970s and the early



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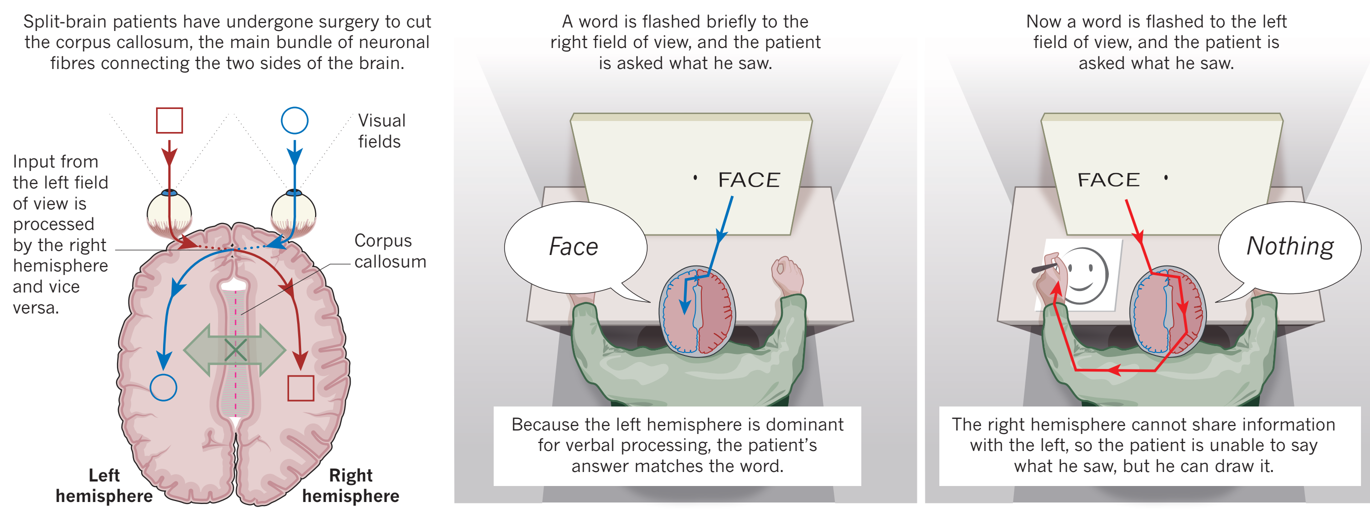
M. GAZZANIGA

The callosum tissue seen in a healthy brain (bright white in top image) retracts after a corpus callosotomy, leaving just the ventricle (black).

OF TWO MINDS Experiments with split-brain patients have helped to illuminate the lateralized nature of brain function.



1980s, split-brain research expanded, and neuroscientists became particularly interested in the capabilities of the right hemisphere — the one conventionally believed to be incapable of processing language and producing speech.

Gazzaniga can tick through the names of his "endlessly patient patients" with the ease of a proud grandparent doing a roll call of grandchildren — W.J., A.A., R.Y., L.B., N.G.. For medical confidentiality, they are known in the literature by initials only. (Vicki agreed to be identified in this article, provided that her last name and hometown were not published.)

On stage last May, delivering a keynote address at the Society of Neurological Surgeons' annual meeting in Portland, Oregon, Gazzaniga showed a few grainy film clips from a 1976 experiment with patient P.S., who was only 13 or 14 at the time. The scientists wanted to see his response if only his right hemisphere saw written words.

In Gazzaniga's video, the boy is asked: who is your favourite girlfriend, with the word girlfriend flashed only to the right hemisphere.

> **"I HAVE A HARD TIME SAYING IT'S ALL OVER."**

As predicted, the boy can't respond verbally. He shrugs and shakes his head, indicating that he doesn't see any word, as had been the case with W.J.. But then he giggles. It's one of those tell-tale teen giggles — a soundtrack to a blush. His right hemisphere has seen the message, but the verbal left-hemisphere remains unaware. Then, using his left hand, the boy slowly selects three Scrabble tiles from the assortment in front of him. He lines them up to spell L-I-Z: the name, we can safely assume, of the cute girl in his class. "That told us that he was capable of language comprehension in the right hemisphere," Gazzaniga later told me. "He was one of the first confirmation cases that you could get bilateral language — he could answer queries using language from either side."

The implications of these early observations were "huge", says Miller. They showed that "the right hemisphere is experiencing its own aspect of the world that it can no longer express, except through gestures and control of the left hand". A few years later, the researchers found that Vicki also had a right-hemisphere capacity for speech[2]. Full callosotomy, it turned out, resulted in some universal disconnections, but also affected individuals very differently.

In 1981, Sperry was awarded a share of the Nobel Prize in Physiology or Medicine for the split-brain discoveries. ("He deserved it," Gazzaniga says.) Sperry died in 1994, but by that point, Gazzaniga was leading the charge. By the turn of the century, he and other split-brain investigators had turned their attention to another mystery: despite the dramatic effects of callosotomy, W.J. and later patients never reported feeling anything less than whole. As Gazzaniga wrote many times: the hemispheres didn't miss each other.

Gazzaniga developed what he calls the interpreter theory to explain why people — including split-brain patients — have a unified sense of self and mental life[3]. It grew out of tasks in which he asked a split-brain person to explain in words, which uses the left hemisphere, an action that had been directed to and carried out only by the right one. "The left hemisphere made up a post hoc answer that fit the situation." In one of Gazzaniga's favourite examples, he flashed the word 'smile' to a patient's right hemisphere and the word 'face' to the left hemisphere, and asked the patient to draw what he'd seen. "His right hand drew a smiling face," Gazzaniga recalled. "'Why did you do that?' I asked. He said, 'What do you want, a sad face? Who wants a sad face around?'." The left-brain interpreter, Gazzaniga says, is what everyone uses to seek explanations for events, triage the barrage of incoming information and construct narratives that help to make sense of the world.

The split-brain studies constitute "an incredible body of work", said Robert Breeze, a neurosurgeon at the University of Colorado Hospital in Aurora, after listening to Gazzaniga's lecture last year. But Breeze, like many other neuroscientists, sees split-brain research as outdated. "Now we have technologies that enable us to see these things" — tools such as functional magnetic resonance imaging (fMRI) that show the whereabouts of brain function in great detail.

Miller, however, disagrees. "These kinds of patients can tell us things that fMRI can never tell us," he says.

SUBJECT OF INTEREST

Seated at a small, oval dining-room table, Vicki faces a laptop propped up on a stand, and a console with a few large red and green buttons. David Turk, a psychologist at the University of Aberdeen, UK, has flown in for the week to run a series of experiments.

Vicki's grey-white hair is pulled back in a ponytail. She wears simple white sneakers and, despite the autumn chill, shorts. She doesn't want to get too warm: when that happens she can get drowsy and lose focus, which can wreck a whole day of research.

During a break, Vicki fetches an old photo album. In one picture, taken soon after her surgery, she is sitting up in the hospital bed. Her hair is starting to grow back as black stubble and she and her daughter have wide smiles. Another page of the album has a slightly faded printout of a 1981 paper from *The Journal of Neuroscience* glued into it: the first published report involving data gleaned from Vicki, in which researchers describe how she, like P.S., had some capacity for language in her right hemisphere[4].

When pressed to share the most difficult aspect of her life in science, the perpetually upbeat Vicki says that it would have to be an apparatus called the dual Purkinje eye tracker. This medieval-looking device requires the wearer to bite down on a bar to help keep the head still so that researchers can present an image to just the left or right field of view. It is quite possible that Vicki has spent more of her waking hours biting down on one of those bars than anyone else on the planet.

Soon, it is time to get back to work. Turk uses some two-sided tape to affix a pair of three-dimensional glasses onto the front of Vicki's thin, gold-rimmed bifocals. The experiment he is running aims to separate the role of the corpus callosum in visual processing from that of deeper, 'subcortical' connections unaffected by the callosotomy. Focusing on the centre of the screen, Vicki is told to watch as the picture slowly switches between a house and different faces — and to press the button every time she sees the image change. Adjusting her seat, she looks down the bridge of her nose at the screen and tells Turk that she's ready to begin.

4 DEEP CONNECTIONS

Other researchers are studying the role of subcortical communication in the coordinated movements of the hands. Split-brain patients have little difficulty with 'bimanual' tasks, and Vicki and at least one other patient are able to drive a car. In 2000, a team led by Liz Franz at the University of Otago in New Zealand asked split-brain patients to carry out both familiar and new bimanual tasks. A patient who was an experienced fisherman, they found, could pantomime tying a fishing line, but not the unfamiliar task of threading a needle. Franz concluded that well-practised bimanual skills are coordinated at the subcortical level, so split-brain people are able to smoothly choreograph both hands[5].

Miller and Gazzaniga have also started to study the right hemisphere's role in moral reasoning. It is the kind of higher-level function for which the left hemisphere was assumed to be king. But in the past few years, imaging studies have shown that the right hemisphere is heavily involved in the processing of others' emotions, intentions and beliefs — what many scientists have come to understand as the 'theory of mind'[6]. To Miller, the field of enquiry perfectly illustrates the value of split-brain studies because answers can't be found by way of imaging tools alone.

In work that began in 2009, the researchers presented two split-brain patients with a series of stories, each of which involved either accidental or intentional harm. The aim was to find out whether the patients felt that someone who intends to poison his boss but fails because he mistakes sugar for rat poison, is on equal moral ground with someone who accidentally kills his boss by mistaking rat poison for sugar[7]. (Most people conclude that the former is more morally reprehensible.) The researchers read the stories aloud, which meant that the input was directed to the left hemisphere, and asked for verbal responses, so that the left hemisphere, guided by the interpreter mechanism, would also create and deliver the response. So could the split-brain patients make a conventional moral judgement using just that side of the brain?

No. The patients reasoned that both scenarios were morally equal. The results suggest that both sides of the cortex are necessary for this type of reasoning task.

But this finding presents an additional puzzle, because relatives and friends of split-brain patients do not notice unusual reasoning or theory-of-mind deficits. Miller's team speculates that, in everyday life, other reasoning mechanisms may compensate for disconnection effects that are exposed in the lab. It's an idea that he plans to test in the future.

As the opportunities for split-brain research dwindle, Gazzaniga is busy trying to digitize the archive of recordings of tests with cohort members, some of which date back more than 50 years. "Each scene is so easy to remember for me, and so moving," he says. "We were observing so many astonishing things, and others should have the same opportunity through these videos." Perhaps, he says, other researchers will even uncover something new.

Other split-brain patients may become available — there is a small cluster in Italy, for instance. But with competition from imaging research and many of the biggest discoveries about the split brain behind him, Gazzaniga admits that the glory days of this field of science are probably gone. "It is winding down in terms of patients commonly tested." Still, he adds: "I have a hard time saying it's all over."

And maybe it's not — as long as there are scientists pushing to tackle new questions about lateralized brain function, connectivity and communication, and as long as Vicki and her fellow cohort members are still around and still willing participants in science. Her involvement over the years, Vicki says, was never really about her. "It was always about getting information from me that might help others." ■

PHOTO BY MIKE MCGREGOR/CONTOUR BY GETTY

Michael Gazzaniga has worked with split-brain patients for 50 years.

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