THE MICROSCOPE • Vol. 61:4, pp 169–179 (2013)

CRITICAL FOCUS

Brian J. Ford

Brainstorm: New Insights on Human Intelligence

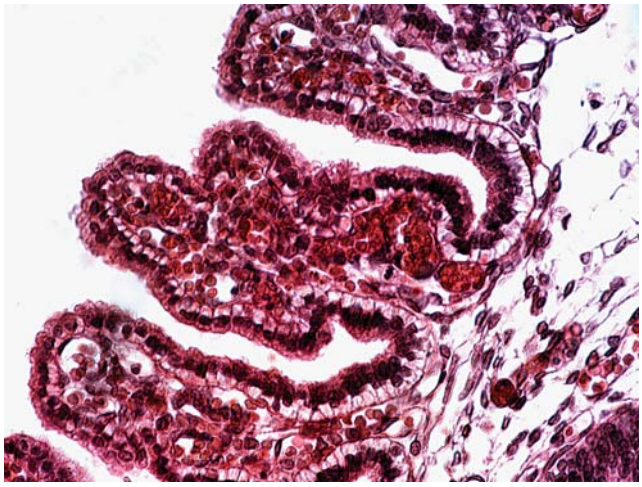
Today's well-funded research into the human mind is founded more on myth rather than a curiosity for exploring what goes on inside the brain's cells.

This time we are going to revolutionize the way we look at the brain, so let's start with a quiz to stimulate those neurons. Which is the odd one out: Prince Albert, Barack Obama, Margaret Thatcher or the Emperor of Japan?

Here are some background facts. Prince Albert was Queen Victoria's consort, and died aged only 42 in 1861, leaving her distraught. Born in Germany, as Prince Albert of Saxe-Coburg and Gotha, he married Victoria when he was 20; she was a year older. He pioneered bringing science and technology to the people. President Barack Obama was born in Honolulu, Hawaii, and graduated from Columbia University and Harvard Law School, where he was president of the *Harvard Law Review.* He became U.S. president at 47, and in April 2013 he launched the BRAIN Initiative to foster American research in neuroscience. Margaret Thatcher was Britain's most prominent post-war prime minister. She graduated from Oxford University in 1947 with a science degree, entered parliament at 24 and became prime minister at 53. She often said she was more pleased to be the first scientist to become prime minister, rather than the first woman. Finally, the Emperor of Japan Akihito is the 125th emperor of his line and was educated (notably in English studies) by Elizabeth Janet Gray, an American librarian and author from Philadelphia. She had married Morgan Fisher Vining of the University of North Carolina, and turned to the Quaker faith after he was killed in an automobile accident. Emperor Akihito acceded to the throne in 1989 and has been an advocate of popularizing science and bringing its benefits to the people.

Give up? The answer is — Margaret Thatcher. She was the only one of the four who was a scientist, yet was the only leader whose policies disadvantaged science. The other three are known as great advocates of scientific enquiry, even though they weren't scientifically trained. Thatcher studied X-ray crystallography under Professor Dorothy Hodgkin, though did nothing to support science when in power. On her death, *New Scientist* said it had been expected that she would encourage science. "It didn't work out that way," said the magazine. "Thatcher's hard-nosed policies on privatization and manufacturing led to a dramatic reduction in research activity. … Spending on research and development has never fully recovered." Mrs. Thatcher, the scientist, did more harm to science than any other Western leader.

Although none of the other leaders was a science graduate, each worked to promote scientific endeavor for the benefit of the public. Prince Albert was always keen to be completely up-to-date with the latest scientific developments and engineering — he was the driv-



Complex interrelationships exist between the eosin-stained erythrocytes in fine capillaries and the neurons (stained with hematoxylin) of the rat cerebellum. This section of a neonate rat, which I prepared when a student in the department of zoology at Cardiff University in Wales, U.K., offered much study material in contemplating the architecture of the brain.

ing force behind the Great Exhibition of 1851, held in the awesome Crystal Palace (at that time the world's largest glass building), and he is commemorated through the Royal Albert Hall in central London, which was originally called the Central Hall of Arts and Science when it opened in 1867. The Emperor of Japan is a modern-day equivalent of Prince Albert in that he is keen to see science brought to the public. Like his father, he is fascinated by marine biology and has published learned papers on the family Gobiidae, the gobies. When I was introduced to Emperor Akihito at the Linnean Society in London we discussed his abiding enthusiasms for biology and marine biology in particular. He sees scientific awareness as a birthright, a key to complete educational fulfillment and a necessary concomitant of building an informed future population.

President Obama has a similar respect for science, and he recently announced $100 million federal funding for neuroscience, which is clearly a pointer to the future of American research. The program's name BRAIN is an acronym: Brain Research through Advancing Innovative Neurotechnologies (once again, the word came first and the description was contrived to fit it). This isn't the largest program of research in the field of biology and is a small sum compared with the $2.7 billion that the Human Genome Project cost the American taxpayer between 1990 and 2005. What makes this program unusual is the identification of the president with the project: This is a major scientific initiative that is being promoted as revealing how brains work, which has been launched by the head of state and has his personal seal of approval. It's also a matter of interest for public welfare. Obama's BRAIN initiative closely resembles programs by Prince Albert in Victorian England and Emperor Akihito in present-day Japan and shows how you can bring the leader into the laboratory to play a key role in promulgating science.

Except for one thing: Our understanding of the brain is founded on myths and misunderstanding. We admire the brain as a machine. To me, it's a community of beings, and this very different concept won't fit into the BRAIN initiative, which will perpetrate the fashionable trends rather than challenging them. The problem is that those who administer science and fund it are remote from the researchers. Academic science has changed in recent decades. As I foresaw 40 years ago in my book *Cult of the Expert*, it has switched from being a quest for nudging new knowledge from our begrudging world into an industrialized system for conniving wealthy funders into providing largesse for those with nothing better to do. The merits of research are no longer simply determined by the altruism of the academic or the benefits they bring; now it rests on column inches in the press and dazzlingly incomprehensible grant applications bursting with buzz-words. Support is often given by people who are coerced into a belief system imposed by those with specialist knowledge, who can sell them a concept much as replacement windows or used automobiles are marketed to the unwary.

MIND GAMES

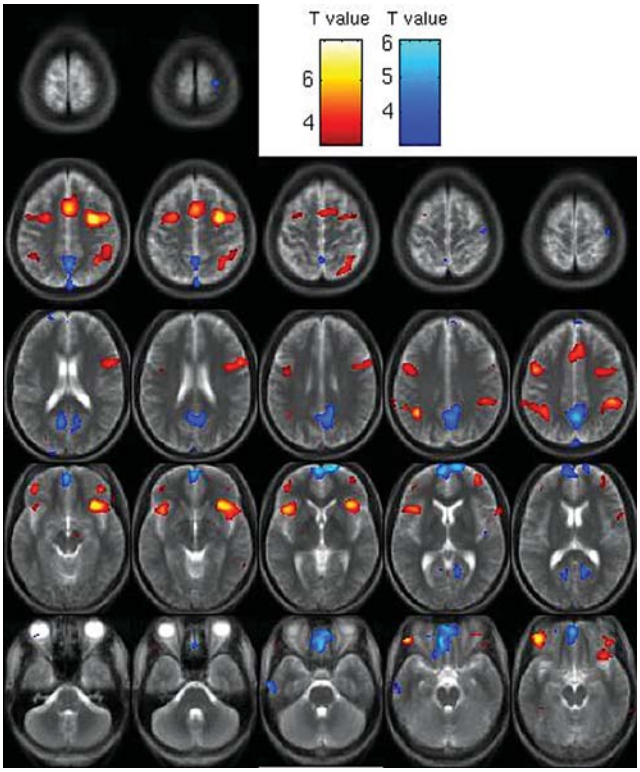
So it is with neuroscience. Tinkering with the brain and watching its activity are so exciting, and the research provides such a sense of allure that it is easy to see how a head of state might be beguiled. It's also extremely simple to do: Buy a grand machine, slide in your specimen and publish the rainbow-hued images that result. Funneling money into this kind of brain research has a sense of futurism about it — though in fact we have created more rumors than reality in neuroscience and much of our knowledge is based on transient models and flawed concepts. By funding this enterprise, BRAIN runs the risk of deepening the divisions between research and reality. Obama didn't have advisers pointing him to areas of research that are poised for breakthroughs and starved of cash. He had cunning campaigners, who understood that his team knew what neuroscience meant and could sense that

espousing something so pervasive in society is a surefire winner of electoral support.

Neuroscience persists in a mechanistic view of the mind, fails to reconcile human activity with that in the vast realm of living cells and tends to cloak its vague pretensions in high-flown language that seeks to dignify our superficial understanding with weighty prose. Researchers have become hung up on what happens between nerve cells: Modern models of the mind are all about connectivity. In my view, the focus of neurobiology should be on what goes on within the cells as much as between them. It is as though we are trying to interpret interactions by peering inside a telephone exchange, when what we should be doing is studying the callers. If funding were allocated for this revolutionary approach I'd be content. In fact, the money will go to promote people who are comfortable in the orthodoxy of today's perceived perspectives. It always does. Academia exists to perpetrate exclusivity and conventional comfort, not to break down barriers or revolutionize revelations. If anything needs fundamental revision, it's neuroscience. It won't get it this way.

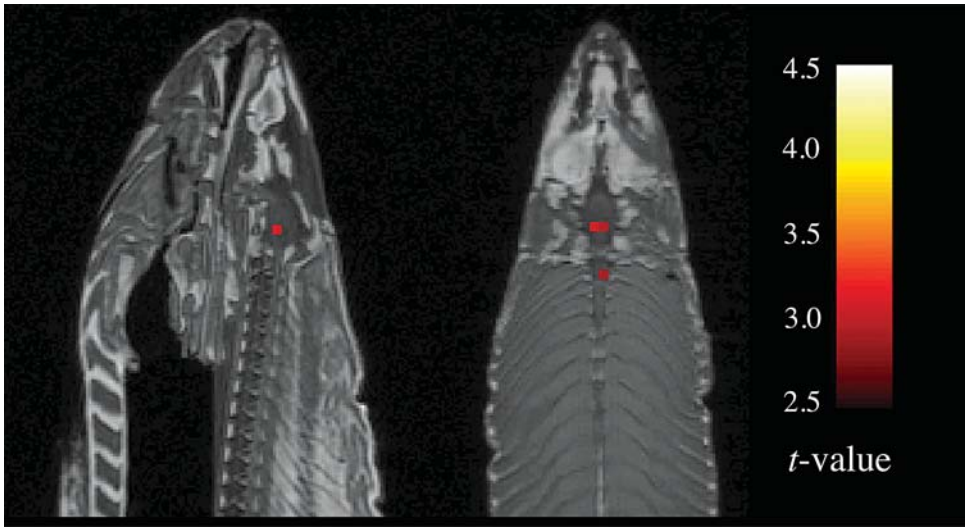
One of the greatest breakthroughs came in 1991, when Functional Magnetic Resonance Imaging was announced. Magnetic Resonance Imaging had slowly evolved since being patented in Russia in 1960. MRI emerged as an effective technique only in 1977. Functional magnetic resonance imaging (fMRI) was centered on the detection of changes in blood oxygenation. When hemoglobin is saturated with oxygen it appears brighter on a scan. However, deoxyhemoglobin is paramagnetic so it is affected by magnetic fields and changes the image produced by protons in an MRI scan. This was harnessed to show oxygenation levels in tissues by Dr. Ogawa Seiji of the AT&T Bell Laboratories in New Jersey during the early 1990s. Areas of the brain where the cells were highly active had long been known to correlate with changes in oxygenation. This is obvious; neurons demand high levels of energy and cannot store metabolic reserves like glucose, so they trigger increased flow of oxygenated blood that is taken to be proportional to metabolism of the cells. Using fMRI, the magnitude of blood flow across different areas of the brain is considered to correlate closely with mental activity.

This is a simplistic interpretation because the single reading usually taken has little reliable scientific relevance to the actual behavior of the brain. Random fluctuations can cause such signals to be generated and so can changes in tissue composition. A regular scientific study would amass data on normal blood flow parameters and correlate those with perturbations caused by external stimuli. In much of the research, a single data set is used for both initial and end-point analysis, and this "double-dipping" provides meaningless results. A study published by doctors Nikolaus Kriegeskorte, W. Kyle Simmons, Patrick Bellgowan and Christopher Baker in *Nature Neuroscience* (Vol. 12:5 pp 535–540, 2009) concluded that almost half the papers published on fMRI had fallen into the trap, making their conclusions meaningless. In one case, neuroscientist Dr. Craig Bennett placed a dead salmon into an MRI scanner at Dartmouth, NH (to calibrate the device) and found a signal from the central nervous system. His observation made worldwide news. "It was only because there are areas of fat in those regions," he now tells me. There could be no more telling example of the misleading impression a single MRI image can create.



Functional magnetic resonance imaging (fMRI) displays areas of false color in brain scans. This example appeared on the science blog by Chris Chatham. Changes in blood flow are correlated with cerebral activity and many workers take the results to indicate how the neurons are behaving. Controls are rarely used, and the reliance of the published results can be questioned.

There is a vogue for correlating attitudes and traits with specific areas of the brain. It is like a modern ver-



Because his new MRI scanner needed testing, Dr. Craig Bennett of U.C. Santa Barbara tells me that they normally use mineral oil for calibration but he decided on a whim to pick up a supermarket salmon and use that instead. The results made worldwide news: The brain of the decidedly dead fish lit up as though it were alive. "The result was due to fat in the specimen," he says. There could be few better examples of the need for care in interpreting fMRI results.

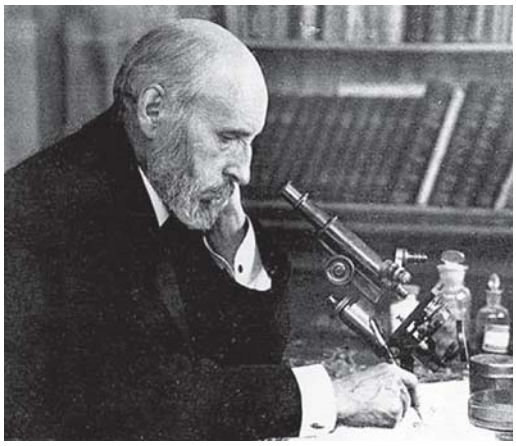
sion of phrenology, where Victorian practitioners perceived the personality of the patient by studying the lumps and bumps on the skull. In fMRI, rainbow-colored images are obtained of the brain when people are thinking or are scared, when they try to recall a memory or experience a sensation. Thus the amygdala is the area of the brain that is correlated with anxiety, so scans showing activity in that region have been regarded as images of neuroticism. Areas of the prefrontal cortex have been identified with psychopathic traits, so beautifully colored images showing altered blood flow have been used to claim that we are observing the roots of antisocial behavior. Yet controls are not rigorous; the changes we make visible may be random events not correlated with what the cells themselves are doing. Even if the results are relevant, they may be the consequence of abnormal brain activity instead of its cause. The value of the hardware that produces the scans is vast; the scientific merit of the pretty pictures is negligible.

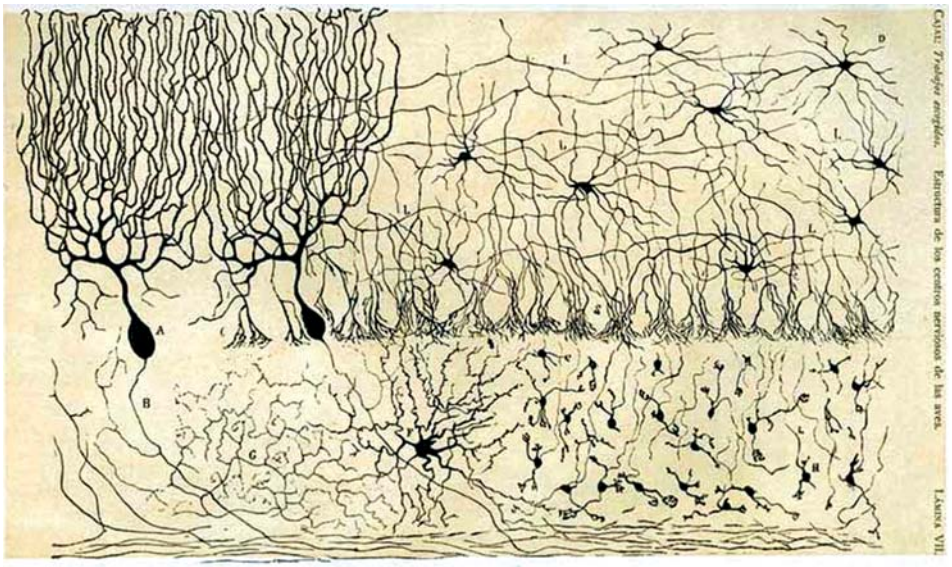
'MISSING HUGE THINGS'

I am no longer the only one who thinks so. Dr. John Ioannidis of Stanford University School of Medicine now says: "I wouldn't put much trust in most of this literature … neuroscience is in serious trouble." Professor Jack Gallant of the Helen Wills Neurosciences Institute at University of California at Berkeley insists: "We are missing huge things." Doctors Edward Vul and Harold Pashler of University of California at San Diego coined the term "voodoo correlations" for these errors in interpretation and found that half a sample of fMRI studies were "seriously defective." Cognitive neuroscientist Dr. Tal Yarkoni of the University of Texas, Austin, says the idea of correlating fMRI scans with real brain function is a "pipe dream."

After this article was written and was about to go to press, a distinguished neuroscientist from the University of California at Irvine announced findings that substantiate my views. For more than 20 years, Professor James Fallon has studied PET and EEG scans of psychopaths' brains and correlates them with genes believed to code for aggression. One of his anonymized brain scans scored highly on all scales yet turned out to be his own. Fallon is a kindly and competitive individual, and his initial response was that the PET scanner had malfunctioned. Double-checking the results showed that his own brain — on the basis of every scientific finding — was that of a violent psychopath. The genetic evidence could be explained by the fact that Fallon is distantly related to Lizzy Borden, but the other findings throw doubt on our current conventions. Many researchers are starting to conclude that the great majority of the published conclusions are meaningless. They have cost millions to obtain.

Yet I believe there is a deeper problem that has yet to be addressed. Much attention is focused on activity at the synapses, where the dangling axons and dendrites of neurons meet but never quite touch. It is the action potential, the electrical signal that a neuron transmits, that is considered to reveal the roots of mental processes in the brain. Neurotransmitters, the best known of which is acetylcholine, are believed to hold the secret. In recent decades a range of neurotransmitters has been discovered, including biogenic amines such as dopamine and histamine, peptides like somatostatin and the opioids, a variety of





Italian physician Camillo Golgi (far left) discovered in 1873 that a reaction between silver nitrate and potassium dichromate gave him a stain that revealed neurons and their extensions as dark objects against an amber background. Golgi concluded that all neurons were interconnected but abandoned this view in his acceptance speech for the Nobel Prize, which he was awarded in 1906 jointly with Spanish pathologist Santiago Ramón y Cajal (near left). The modern concept of the neuron emerged from Cajal's work. Using Golgi's stain, Cajal recognized that neurons do not make direct contact through the axons that seem to connect them. His doctrine still underpins modern neurology. The brains of birds were studied by Cajal, and these detailed studies (bottom) portray the network revealed by using the Golgi stain. Cajal proposed that it was the interaction of neurons through the synapses that underpinned cerebral activity, a view that persists. However, I think that the crucial processing goes on within each neuron instead of between them.

amino acids from aspartate to glycine and even the ubiquitous nitric oxide.

BRAIN STAIN

The gap at the synapses is a couple of micrometers across and was first recognized by the diligent microscopy of nerve cells carried out by the brilliant Spanish microscopist Dr. Santiago Ramón y Cajal in 1899. Cajal stained brain tissue with the silver nitrate technique devised by the Italian microscopist Dr. Camillo Golgi. This colored the neurilemma (the membrane covering each neuron) intense black against an amber background, allowing the outline of the cells to be clearly delineated. Cajal's research coined the "neuron doctrine" which, in present-day terms, stipulates:

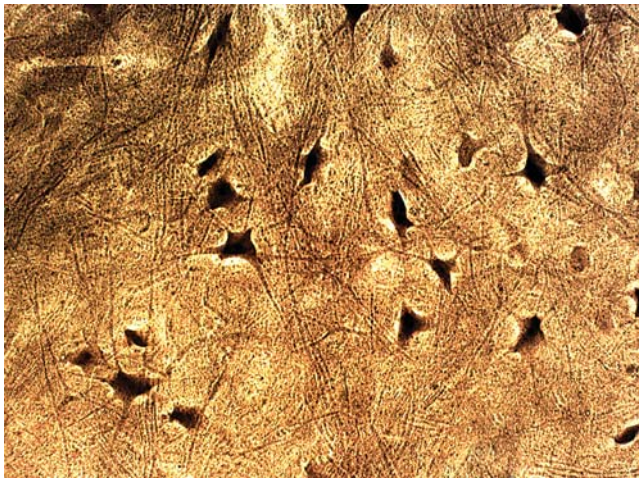
1. The neuron is the structural and functional unit of the nervous system.

2. Neurons are individual cells that are anatomically distinct from other neurons.

3. The neuron has three parts: soma (cell body), dendrites and axon. The axon has terminal arborizations, which make close contact with dendrites of other neurons.

4. Conduction of nerve impulses is unidirectional and follows axipetal polarization.

The dendrites are the branches of the neuron which pick up signals from other cells and transmit them in to the soma, whereas the axon is the fiber that carries away the post-processing impulses from the neuron. Those major developments were made under curious circumstances with which microscopists will easily identify. Golgi discovered his revolutionary staining technique in 1873 while working in his kitchen at home, not in a laboratory, and Cajal could publish his research only in a journal that he edited and published



The rendering of the soma of each neuron, black and opaque with Golgi's silver nitrate stain, has diverted our attention from what goes on within. In this human brain section, I have photographed a group of motor neurons under brightfield illumination. Although the morphology of the cells and their connections can be clearly seen, the complex internal structure of the neurons themselves remains obscured.

Water molecules in the axons between neurons can be visualized by diffusion spectrum imaging. The scan, with a spatial resolution of 400 µm, takes 24 hours to complete. The color coding is related to the orientation of the fibers. Our interest in network theory gives such images considerable topicality, though they do not reveal what data-processing occurs within the cells themselves.

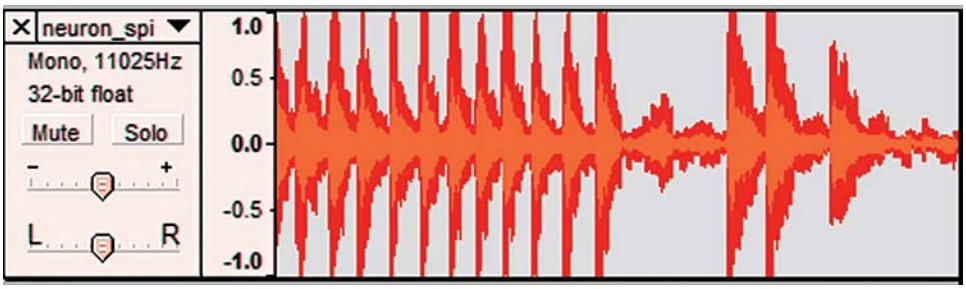
himself. Self-help underpins so much microscopy.

Cajal's techniques gave him an unprecedented view of the neural network, and the resonances of his meticulous mapping have come down to us today. Regrettably, it has placed severe conceptual constraints on how we model the mind. We have never moved on from probing the neural network and are largely unaware of what else we need to study. For example, because the glial cells in the brain have no dendrites or axons that can be stained by the Golgi method, they have been largely overlooked. They are widely dismissed as comprising the substance holding the brain together — indeed the Greek term glia (γλια) simply means "glue." Because of Cajal's legacy of studying the interrelationships of neurons, we still concentrate on what happens at the nerve cell synapses rather than what goes on inside, though I am certain that the thinking goes on within neurons rather than between them. Neurons process information; they act as thoughtful entities. Yet they can handle inputs only when they arrive as impulses from other neurons in the brain or from sensors. Should you poke a neuron in the course of research, it elicits no response whatever — it acts as if it were dead.

Although the neuron spike signals are widely regarded as digital impulses, I have analyzed them to show that they are modulated. Most of the mathematical theory in computational neuroscience is based solely on the temporal patterns of these spikes, but I am certain this is misleading. It is not the timing of the signals that matters but the subtle variations in their nature. Those pulses are not mere markers; they are the little words each neuron speaks.

Before we can question what cerebral activity is, we should know how we recognize it. There are clear flaws in correlating blood flow and oxygenation levels with the intensity of neuronal behavior, though our techniques for monitoring cell activity are in themselves limited because we resort to detecting electrical impulses. The brain is monitored through an electroencephalogram (ECG). We try to shock the brain back into normalcy by using an electrical discharge. The passage of a signal emitted by a neuron is detected as an (electrical) action potential, and the research leaves an overriding impression that the brain runs on electricity, and that alone. No wonder neuroscientists analogize the brain to an electrical device like a computer.

It is certainly true that you can detect electrical action potentials emanating from living cells. Those neural spike signals are abundantly present in neurons, where they are emitted at around 40Hz. They are widely regarded as digital electronic emanations and are treated as such, though electrical activity is easy to exaggerate. You can plug electrodes between the dirt and the tree in which it grows and detect a similar electrical potential difference. Is this the energy of life? It's tempting to assume, but it cannot be so. If you plug an electrode into the ground and another in



Impulses from neurons cultured *in vitro* can be played back as audio files. The result is a buzzing sound we designate as "neuron spikes." Current theories interpret these as temporally mediated, and analysis of firing rates dominates the work of senior scientists in President Barack Obama's BRAIN program. In my research, I have spaced the "spikes" so that their complex internal modulations can be visualized. The results may indicate how neurons communicate.

the wall of my house, you will pick up precisely the same kind of electrical signal. It varies with the weather, yet nobody would assume that the house was alive. These potentials are not the meaning of life; rather, we are detecting the movement of solutes and charged ions that are related to it. Alterations in electrical-field activity correlate with changes in molecular structure consequent upon the neuron's inner workings, so the electrical signals we detect are merely an indicator, not the essence of living.

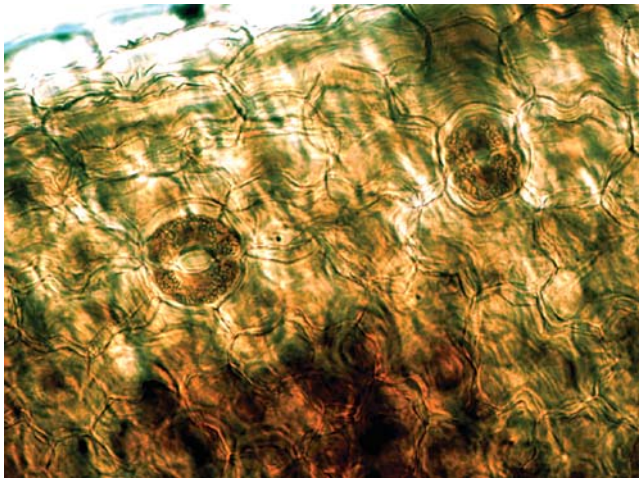
COMPLEXITY BEYOND COMPUTERS

Computers have long been celebrated for performing actions that are beyond the capacity of humans, but that is an absurd claim. A pair of scissors and a stapler can do things that no person can achieve; so can something simple like a thumb tack or complex like a car. Human inimitability is no arbiter of inherent superiority. What neurobiology forgets is that the brain is composed of living cells, and these essentially autonomous organisms embody extraordinary abilities that few people stop to study. The intricate choreography of the entire brain confers upon it remarkable and unknowable power, and it is the capacity of each living cell that produces the result. Only by studying the lives of cells can we start to understand ourselves.

It was always clear to me that the brain was not, in any sense, like a computer. It could only be so if neurons were simple, solid-state devices; instead, they are subtle, flexible, responsive, inconceivably complex creatures. Should you insist on clinging to that traditional model, you must abandon its simplicity because if the brain has any electronic analogue then it should be envisaged as a community of separate computers, not just one. Even in this model, the brain is incalculably more complex than anyone can currently conceive. Computers are deterministic, while the behavior of living organisms is opportunistic and mediated by circumstance.

As a consequence of prevailing attitudes, neurons have long been modeled as binary switches, as "go" or "no-go" gates, and are often analogized to transistors. Yet it always seemed to me that they were more complex than that, and I could easily see intimations of how we behaved in the workings of the cell. Back in 1970, in the first textbook I wrote, entitled *Microbiology and Food*, I had a section headed "Man as Microbe". By 1976, on pages 136–137 of my book *Microbe Power,* I was setting out the basis of my views. I had described the intricacies of protist behavior and then brought the neuron into the discussion:

> Perhaps a single brain cell can carry out some of the integrative processes of thought and memory within its own structure (that is intraneuronal, as opposed to interneuronal activity). Brain models have tended to become firmly based on the go or no-go principle but if that is all neurons can do, then surely they would have to be the most primitive and non-enterprising cells in our bodies. In reality they are nothing of the sort. They are so highly specialized that they have lost even the ability to multiply, so that a person loses brain cells steadily throughout life, and they are never replaced. Additionally, we know that the resting nerve cells of the brain consume relatively large amounts of energy foodstuffs, which is a second pointer to highly specialized activities taking place. Perhaps brain cells behave in a more complex manner than we have suspected in the past.



Stomata are the openings in the surfaces of leaves through which gases are exchanged. For all the apparent simplicity of the paired guard cells that control each opening, they respond to light, vibration, chemical changes, etc., revealing much the same spectrum of senses as those we ourselves possess. In this image, the example on the left is open, whereas the one on the right is almost closed. These are stomatal cells responding to local conditions and reacting autonomously.

Those ideas were expanded in a summary communicated at the Minds and Machines conference at the Cambridge Philosophical Society in December 1992, and then in 1998 I presented a major synthesis at the Inter/Micro conference in Chicago. My talk in August that year was "On the Intelligence of Microbes." Further research was published as "Revealing the Ingenuity of the Living Cell" (*Biologist,* Vol. 53:4, pp 221–224, 2006), while the definitive paper was published as "On Intelligence in Cells: The Case for Whole Cell Biology" (*Interdisciplinary Science Reviews*, Vol. 34:4, pp 350–365, 2009). These publications called for a reappraisal of our approach to research on cells and the neuron in particular.

My reasoning was twofold. First, I posited that the neuron — being such a highly specialized entity — could not reasonably be confined to carry out simplistic switching functions. Secondly, I saw such bewildering complexity in the way single cells behave in nature. This was an era when the electron microscope was forging ahead and the quest was always for greater resolution. The dawn of the electron microscope curtailed the study of living cells. Scientists were now looking at dead specimens and cell biologists were peering ever deeper inside the cell, observing the minutest structural components, without stopping to consider how the entire cell behaved when alive. This rush towards a reductionism paradigm has underpinned biology for over a century and is misplaced. Instead of patiently observing entire cells, so many scientists were fractionating them to analyze their constituent parts. It was like an ornithologist trying to understand bird behavior by peering through a magnifying glass at a plate of scrambled eggs. We had lost sight of the whole cell, living its busy life, and that always remained a focus of my research. Reductionism is a trap for the unwary. Don't simply scrutinize the symbols on the musical score — celebrate the song.

It led me to campaign for us to study, not the fragments within cells, but living cells in the round. To follow my "Interdisciplinary Science Reviews" paper, I published an article appealing for "whole cell biology" in *The Biologist* (February 2010) and then in *New Scientist* (April 24, 2010). Wherever one looks there is evidence of cognitive and intelligent behavior by single cells, behavior that richly resembles human life.

Since the ancients wrote on humanity we have celebrated our triumph over nature through the five senses: sound, sight, touch, taste and smell. The earliest description of these senses lies in the ancient Tamil text Tolkappiyam, which dates back some 2,300 years. The senses were remarked upon by the Greeks and Romans, and by Shakespeare's time they had become the "five wits" of humanity. Victorian microscopists mused that cells seemed to embody the senses thought to be characteristic of humanity. More recent texts point out that these human attributes exist in other forms of life, citing the organs of sense on the appendages of butterflies, so they can taste where they stand, and the remarkable olfactory senses of dogs and sharks. Some write of the Venus fly-trap *Dionaea muscipula* as also possessing sophisticated senses. *Dionaea* certainly creates an action potential in response to mechanical stimulation. Reading these accounts you gain the impression that many forms of life possess the senses on which we pride ourselves.

STOMATA STUDIES

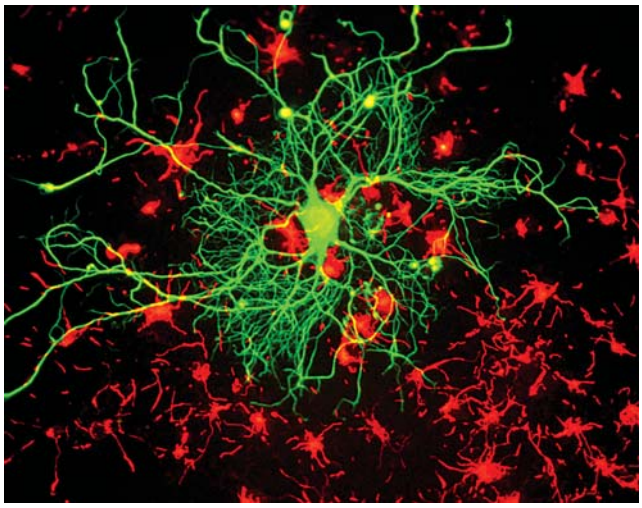
Now come with me down the microscope. This will give budding neurologists something exciting to think about. We will look at a single stomatal guard cell. The stomata are the minute breathing pores in the surfaces of leaves that regulate gas exchange with the atmosphere, and two guard cells control the size of each aperture, which changes as conditions alter and as the needs of the plant vary from time to time. These cells respond to vibration and to light. They react to chemical stimuli and changes of gases in the atmo-

sphere, and respond when touched. Run your eye along the list again and you will see the guard cells' version of all those human senses. We are not as unusual as we think. Consider it further, and deeper realities emerge; the stomata regulate the inner milieu of each leaf and do so with expert precision. I first studied them in the early 1960s, and soon became aware that they are exhibiting extraordinary abilities to respond to the eternal shifts in balance as the plant moves through its life from minute to minute, though we have little understanding of how they do it.

While neurology is working out networks and pathways, I am watching complex interactions between cells and their surroundings. Those on a humble plant leaf can teach us many lessons, sure; but we perceive even greater wonders when we observe free-living microorganisms living their busy lives. I observe them building, just as we do; making decisions, much like us; selectively choosing a mate as people will; abandoning their daily activities for the pleasures of sex; and finding a way to solve problems, help a neighbor and adapt to unforeseeable situations. Many possess minute intracellular eyes, with a refractile lens and curved retinal cup. The essential activities that we can do, cells do too.

When I have said so in the past, people have retorted: "What about building the Washington monument?" yet there are single-celled creatures that construct homes for themselves like walls, ingeniously cemented together. "What cells can fly?" people will ask, though some cells (like the pollen grains of *Pinus*, the pine tree) have inflated floats that carry them aloft like balloonists. Single cells can search and find, copulate, seal themselves inside capsules, sense where they are, see where they're going and go hunting. Not only can they heal themselves, but they can reinstate their wounded neighbor. I believe that their instinctual ability to sense self and non-self may even be the root of the biological imperatives that drive humans to wage war against each other.

Whenever we see microorganisms described, their behavior is dismissed in shorthand that skates around the great imponderable questions that underpin their lives. Let us consider *Spirogyra*, an attractive filamentous alga common in lakes and ponds. During late summer, pairs of filaments lying close to each other will engage in sexual reproduction. This phenomenon of conjugation is typically described in terms such as: "Two filaments lie side by side and from each cell tubular protuberances known as conjugation tubes develop. They fuse producing a passage (the conjugation canal) through which cells from one filament move through to unite with those of the other. They are designated male and female, respectively. Once the cell bodies lie in the female filament they fuse together forming a resistant zygospore."



Fluorescence microscopy at the EnCor Biotechnology laboratories of the University of Florida provides this beautiful image of a neuron and surrounding glial cells. EnCor owner Dr. Gerry Shaw informs us these rat cells are stained with alpha-internexin. Although this multipolar cell shows so brilliantly, we are still restricted to seeing the shape of the neuron as little more than a silhouette.

All the published sources, in print and online, say something similar. Just consider what they miss. Tubular protuberances develop? How? These are algae we're speaking of. They are simple plants, yet here we are acknowledging that they join by sending out tubes that fuse. How do they detect each other's presence? What senses do they use? Where are the organelles that confer these senses? Nobody knows and (worse still) nobody is wondering how. These sensory stimuli result in the cell walls bulging towards each other. What regulates the growth of the tubes? How are the cellulose cell walls rendered soluble and then reformed? Which mechanisms are involved? We know of none. How do these algae have a sense of direction (the tubes develop precisely towards each other and are always meticulously aligned)? In what way do they fuse? How can the ends unite, and the separating septum dissolve away? We are erroneously taught that contractile vacuoles expel water from the male cell in order that hydrostatic pressure forces it through the conjugation canal. You see? A deterministic explanation once again — but that is not what we observe. The male cell crawls through eagerly, and there is a gap between the cell body and the cell wall so that no

pressure buildup is possible. Those vacuoles are produced by the male cell to expel water from its central vacuole and shrink down in volume, facilitating its passage through the canal. It does not move through because of a build-up of irresistible force but because it wants to. These cells are sensate and responsive. They are not digital devices .

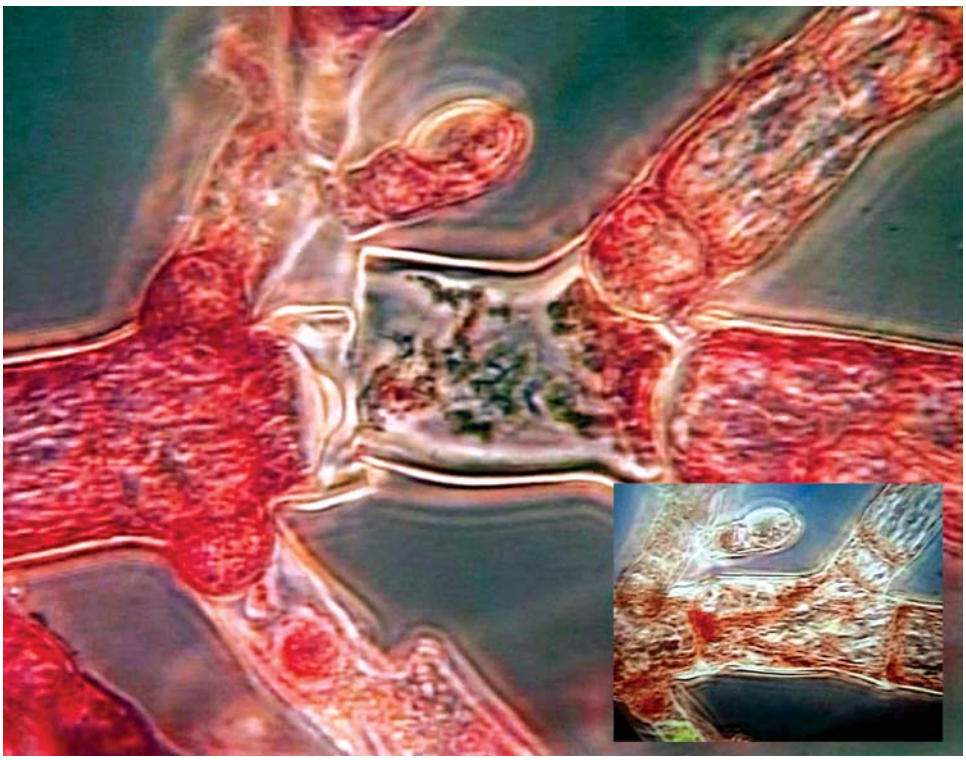
This is in itself a revelation, but I can go further because I am confident that cells clearly exhibit intelligence. Examples were reported in my 2006 paper for *The Microscope*, "Are Cells Ingenious?" (Vol. 52:3/4, pp 135–144). One crucial example had been researched in 1909 by Dr. Ivey Foreman Lewis of the University of Virginia. Lewis studied rhodophyte algae and described how they could undertake extraordinarily complex recovery after a cell in the colony was damaged. By 1916, Nels Quevli had published a book called *Cell Intelligence*, though he saw cells as being responsible for building complex structures rather than (as in my view) comprising them. During the 1970s, the research of I.F. Lewis was extended by two leading American phycologists, husband-and-wife team doctors Susan and Robert J. Waaland.

The Rhodophyta are curious algae — none of their cells possess flagella, so even their gametes are unable to swim. For reasons like this they have always been regarded as evolutionarily primitive. Yet the Waalands' microscopical research had them studying the way these algae repair and regenerate themselves. Whereas Lewis had studied wild-state algae, the Waalands developed *in vitro* methods of culturing the algae and observing their behavior under laboratory conditions. When a cell in the colony is destroyed, they showed how neighboring cells move in and recreate the original. A group of Korean microscopists led by Professor In Kyu Lee subsequently looked at repair in three species, *Griffithsia japonica, Antithamnion nipponicum* and *Heterosiphonia pulchara*. Their work appeared in the *Korean Journal of Phycology* (Vol. 3:1, pp 15–27, 1988), and described in detail the ways in which the cells of these algae reinstated a damaged neighbor in the colony.

Nels Quevli was the first to write a book that incorporated the concept of "cell intelligence" in 1915. Even though he believed that cells managed to create elaborate multicellular structures, rather than comprise them, his approach was highly prescient. Little is known of him, though he deserves recognition for pioneering a viewpoint that remains neglected.

WHAT IS INTELLIGENCE?

Everyone recognizes intelligence when we encounter it, though attempting to define the term is controversial. The *Merriam-Webster Dictionary* defines it as "the ability to learn or understand or to deal with new or trying situations," while the *Oxford Advanced Learner's Dictionary* has "being able to store information and use it in new situations." This concept of solving an unforeseeable problem underpins many definitions of intelligence — and is precisely what these algae are doing. A cell can be destroyed with a steel needle on the microscope slide. Indeed, the filament can be entirely severed so the broken cell walls (devoid of contents) are left lying adjacent to each other. That could not happen in nature. Whatever causes the breakage of an algal filament — being stamped on by a walrus, or broken in a storm — will leave the severed ends a great distance apart. The only situation in which they can remain in juxtaposition is on the microscopist's slide. The adjacent cells are faced with an unprecedented situation yet they contrive to reinstate the damaged cell and restore the entire filament to life. This is precisely what the dictionaries stipulate as a prerequisite for intelligent behavior — these algal cells are dealing constructively with a new situation. By definition, that's intelligent. Extrapolating from a



This still frame captured by my colleague Dr. Jeremy Pickett-Heaps depicts the commencement of cell reinstatement by *Antithamnion sparsum*, a marine rhodophyte. The central cell has been destroyed using a steel needle, yet the cell to the left is beginning to produce a protuberance that will occupy the empty cell wall. Within 24 hours, the missing cell has been completely restored to full function (see inset). This reinstatement of a damaged cell involves complex mechanisms of detection, analysis, problem-solving and repair. We have no understanding of the nature of these intricate mechanisms, though they fit well with definitions of "intelligent" problem-solving.

"primitive" rhodophyte cell to the majesty of the human mind makes us realize that neurons will embody this inherent capacity for intelligence, though at a greatly enhanced level.

We cannot divine the workings of the brain by studying the networks they establish, any more than you will understand human behavior solely by peering at a map. We need to recognize the frailty of our comprehension. Those simplistic models founded on physics cannot reveal the machinations of the mind. The mechanisms I have described in living cells transcend anything we can grasp, and the huge amounts of money pouring into the BRAIN initiative will serve mainly to perpetrate present perceptions. The truth is that the biological systems we need to understand are not amenable to mathematical modeling or computer analysis; they are infinitely subtle and endlessly complex. Only the study of single cells and how they adapt reveals the extraordinary plasticity of the brain and points towards the revelation of us to ourselves. This is something modern science has never properly begun and, curiously, costs almost no capital expenditure at all.

Some say that computers are becoming close to emulating a living being. People cite the Turing test, in which an online conversation with a computer that seems as if it were with a real person could be taken to show that the machine was equal to a human brain. That's simple; just ask "Are you human?" or "Do you have an off switch?" to solve that one. Bearing in mind the lesson of the simple rhodophyte that repairs its neighbor, I would like to propose a radically different test that can alone really prove the point. Take three computers and line them up in a room. Then destroy the central one with a hammer. Rip out its components and throw them, with all the drives and cards, into the trash. Lock the door, and go home for the weekend. On Monday morning when you return, note the condition of the three computers. If the central one has been repaired and is functioning as it did before you laid into it with a hammer, with everything reinstated by the unaided activity of the two neighboring computers, then you can conclude that these computers are close to imitating life. If, on the other hand, the damaged computer is just as it was, then you will know it's merely a machine.

Neuroscience is fixated on computer emulations, on networks and on the pretty pictures that fMRI can create. None of these will take us where we need to go in our attempts to unravel the brain. There are much prettier pictures waiting down the microscope, which are produced for almost no cost at all. It is not investment of dollars we need — but observation of living cells and the study of the miracles they perform.