

of the BRAIN

*MOUNTING EVIDENCE
SUGGESTS THAT GLIAL
CELLS, OVERLOOKED FOR
HALF A CENTURY, MAY BE
NEARLY AS CRITICAL TO
THINKING AND LEARNING AS
NEURONS ARE*

By R. Douglas Fields

GLIAL CELLS [red] outnumber neurons nine to one in the brain and the rest of the nervous system.

The recent book *Driving Mr. Albert* tells the true story of pathologist Thomas Harvey, who performed the autopsy of Albert Einstein in 1955. After finishing his task, Harvey irreverently took Einstein's brain home, where he kept it floating in a plastic container for the next 40 years. From time to time Harvey doled out small brain slices to scientists and pseudoscientists around the world who probed the tissue for clues to Einstein's genius. But when Harvey reached his 80s, he placed what was left of the brain in the trunk of his Buick Skylark and embarked on a road trip across the country to return it to Einstein's granddaughter.

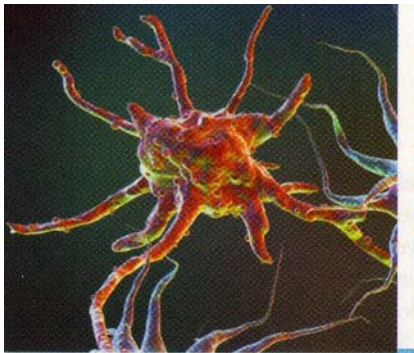
One of the respected scientists who examined sections of the prized brain was Marian C. Diamond of the University of California at Berkeley. She found nothing unusual about the number or size of its neurons (nerve cells). But in the association cortex, responsible for high-level cognition, she did discover a surprisingly large number of nonneuronal cells known as glia—a much greater concentration than that found in the average Albert's head.

An odd curiosity? Perhaps not. A growing body of evidence suggests that glial cells play a far more important role than historically presumed. For decades, physiologists focused on neurons as the brain's prime communicators. Glia, even though they outnumber nerve cells nine to one, were thought to have only a maintenance role: bringing nutrients from blood vessels to neurons, maintaining a healthy balance of ions in the brain, and warding off pathogens that evaded the immune system. Propped up by glia, neurons were free to communicate across tiny contact points called synapses and to establish a web of connections that allow us to think, remember and jump for joy.

That long-held model of brain function could change dramatically if new findings about glia pan out. In the past several years, sensitive imaging tests have shown that neurons and glia engage in a two-way dialogue from embryonic development through old age. Glia influence the formation of synapses and help to determine which neural connections get stronger or weaker over time; such changes are essential to learning and to storing long-term memories. And the most recent work shows that glia also communicate among themselves, in a separate but parallel network to the neural network, influencing how well the brain performs. Neuroscientists are cautious about assigning new prominence to glia too quickly, yet they are excited by the prospect that more than half the brain has gone largely unexplored and may contain a trove of information about how the mind works.

See Me,

THE MENTAL PICTURE most people have of our nervous system resembles a tangle of wires that connect neurons. Each neuron has a long, outstretched branch—an axon—that carries electrical signals to buds at its end. Each bud emits neurotransmitters—chemical messenger molecules—across a short synaptic gap to a twiglike receptor, or dendrite, on an adjacent neuron. But packed around the neurons and axons is a diverse population of glial cells. By the time of Einstein's death, neuroscientists suspected that glial cells might contribute to information processing, but convincing evidence eluded them. They eventually demoted glia, and research on these cells slid into the backwater of science for a long time.



Astrocyte glia activate distant neurons to help form memories.

Neuroscientists failed to detect signaling among glia, partly because they had insufficient analytical technology but primarily because they were looking in the wrong place. They incorrectly assumed that if glia could chatter they would use the same electrical mode of communication seen in neurons. That is, they would generate electrical impulses called action potentials that would ultimately cause the cells to release neurotransmitters across synapses, igniting more impulses in other neurons. Investigators did discover that glia had many of the same voltage-sensitive ion channels that generate electrical signals in axons, but they surmised that these channels merely allowed glia to sense indirectly the level of activity of adjacent neurons. They found that glial cells lacked the membrane properties required to actually propagate their own action potentials. What they missed, and what advanced imaging techniques have now revealed, is that glia rely on chemical signals instead of electrical ones to convey messages.

Valuable insights into how glia detect neuronal activity emerged by the mid-1990s, after neuroscientists established that glia had a variety of receptors on their membranes that could respond to a range of chemicals, including, in some cases, neurotransmitters. This discovery suggested that glia might communicate using chemical signals that neurons did not recognize and at times might react directly to neurotransmitters emitted by neurons.

Overview/Glia

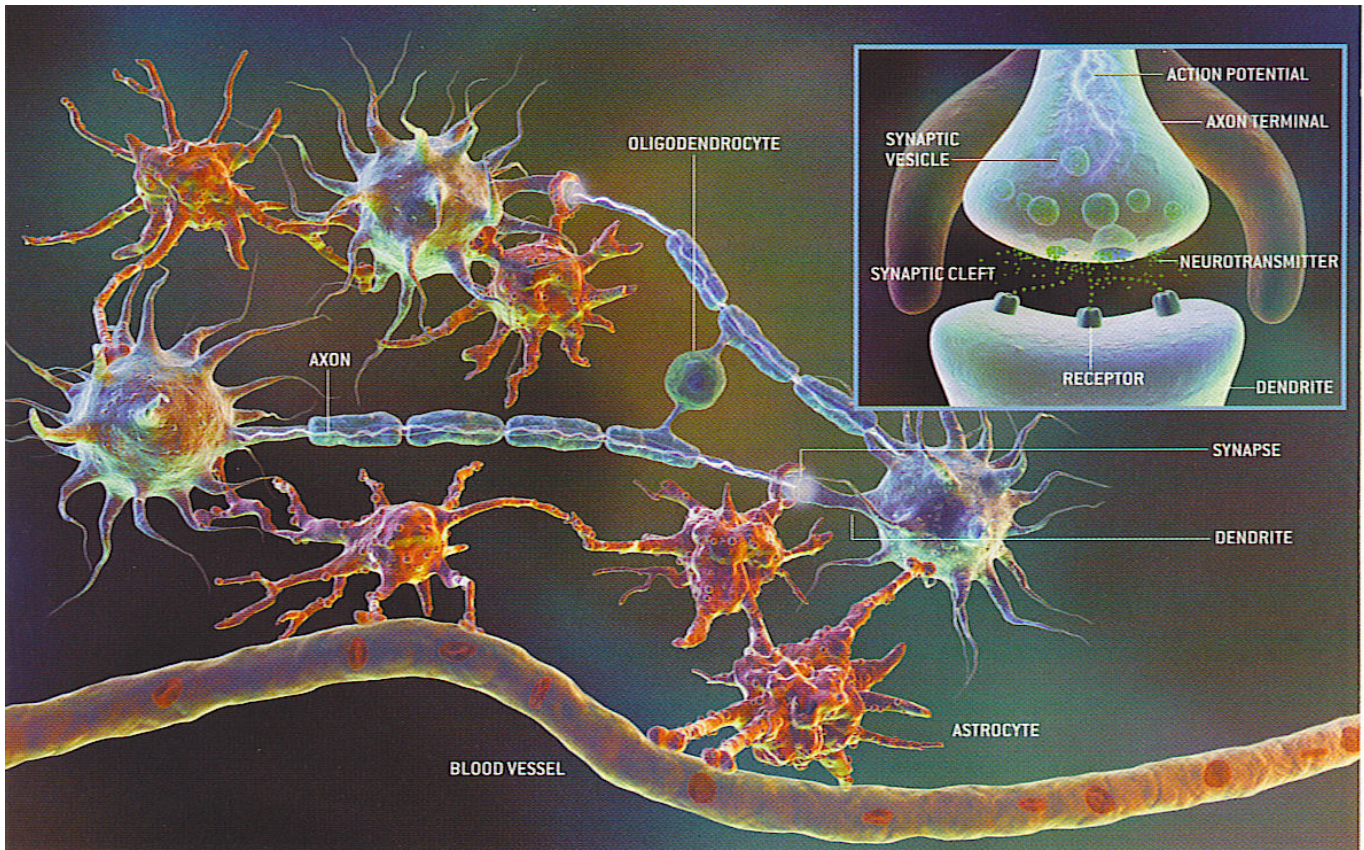
- For decades, neuroscientists thought neurons did all the communicating in the brain and nervous system, and glial cells merely nurtured them, even though glia outnumber neurons nine to one.
- Improved imaging and listening instruments now show that glia communicate with neurons and with one another about messages traveling among neurons. Glia have the power to alter those signals at the synaptic gaps between neurons and can even influence where synapses are formed.
- Given such prowess, glia may be critical to learning and to forming memories, as well as repairing nerve damage. Experiments are getting underway to find out.

To prove such assertions, scientists first had to show that glia actually do "listen in" on neuronal communication and take action based on what they "hear." Earlier work indicated that an influx of calcium into glial cells could be a sign that they had been stimulated. Based on that notion, investigators devised a laboratory method called calcium imaging to see whether glial cells known as terminal Schwann cells—which surround synapses where nerves meet muscle cells—were sensitive to neuronal signals emitted at these junctions. The method confirmed that Schwann cells, at least, did respond to synaptic firing and that the reaction involved an influx of calcium ions into the cells.

But were glia limited only to eavesdropping on neuronal activity, by scavenging traces of neurotransmitter leaking from a synapse? More general-function Schwann cells also surround axons all along nerves in the body, not just at synapses, and oligodendrocyte glia cells wrap around axons in the central nervous system (brain and spinal cord). At my National Institutes of Health lab, we wanted to know if glia could monitor neural activity anywhere as it flowed through axons in neural circuits. If so, how was that communication mediated? More important, how exactly would glia be affected by what they heard?

To find answers, we cultured sensory neurons (dorsal root ganglion, or DRG, cells) from mice in special lab dishes equipped with electrodes that would enable us to trigger action potentials in the axons. We added Schwann cells to some cultures and oligodendrocytes to others.

We needed to tap independently into the activity of the axons and the glia to determine if the latter were detecting the axon messages. We used a calcium-imaging technique to record visually what the cells were doing, introducing dye that fluoresces if it binds to calcium ions. When an axon fires, voltage-sensitive ion channels in the neuron's membrane open, allowing calcium ions to enter. We would therefore expect to see the firing as a flash of green fluorescence lighting up the entire neuron from the inside. As the concentration of calcium rose in a cell, the fluorescence would get brighter. The intensity could be measured by a photomultiplier tube, and images of the glowing cells could be digitized and displayed in pseudocolor on a monitor in real time—looking something like the radar images of rainstorms shown on weather reports. If glial cells heard the neu-



ronal signals and did so in part by taking up calcium from their surroundings, they would light up as well, only later.

Staring at a computer monitor in a darkened room, my NIH colleague, biologist Beth Stevens, and I knew that after months of preparation our hypothesis was about to be tested with the flick of a switch. When we turned on the stimulator, the DRG neurons responded instantly, changing from blue to green to red and then white on a pseudocolor scale of calcium concentration, as calcium flooded into the axons. Initially, there were no changes in the Schwann cells or oligodendrocytes, but about 15 long seconds later the glia suddenly began to light up like bulbs on a string of Christmas lights [see illustration on page 59]. Somehow the cells had detected the impulse activity in the axons and responded by raising the concentration of calcium in their own cytoplasm.

Glia Communicating with Glia

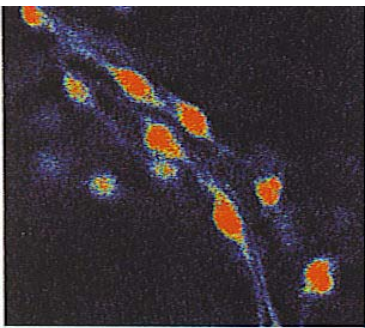
THUS FAR WE HAD confirmed that glia sense axon activity by taking in calcium. In neurons, calcium activates enzymes that produce neurotransmitters. Presumably, the influx in glial cells would also activate enzymes that would marshal a response. But what response was the cell attempting? More funda-

mentally, what exactly had triggered the calcium influx?

Clues came from previous work on other glial cells in the brain known as astrocytes. One of their functions is to carry nutrients from capillaries to nerve cells; another is to maintain the optimal ionic conditions around neurons necessary for firing impulses. Part of the latter job is to remove excess neurotransmitters and ions that neurons release when they fire. In a classic 1990 study, a group led by Stephen J. Smith of Yale University (now at Stanford University) used calcium imaging to show that the calcium concentration in an astrocyte would rise suddenly when the neurotransmitter glutamate was added to a cell culture. Calcium waves soon spread throughout all the astrocytes in the culture. The astrocytes were responding as if the neurotransmitter had just been released by a neuron, and they were essentially discussing the news of presumed neuronal firing among themselves.

Some neuroscientists wondered whether the communication occurred because calcium ions or related signaling molecules simply passed through open doorways connecting abutting astrocytes. In 1996 S. Ben Kater and his colleagues at the University of Utah defused that suspicion. Using a sharp microelectrode,

GLIA AND NEURONS work together in the brain and spinal cord. A neuron sends a message down a long axon and across a synaptic gap to a dendrite on another neuron. Astrocyte glia bring nutrients to neurons as well as surround and regulate synapses. Oligodendrocyte glia produce myelin that insulates axons. When a neuron's electrical message (action potential) reaches the axon terminal (*inset*), the message induces vesicles to move to the membrane and open, releasing neurotransmitters [signaling molecules] that diffuse across a narrow synaptic cleft to the dendrite's receptors. Similar principles apply in the body's peripheral nervous system, where Schwann cells perform myelination duties.



Schwann glia could be key to treating nerve diseases such as MS.

ASTROCYTES REGULATE SIGNALING across synapses in various ways. An axon transmits a signal to a dendrite by releasing a neurotransmitter (green)—here, glutamate. It also releases the chemical ATP (gold). These compounds then trigger an influx of calcium (purple) into astrocytes, which prompts the astrocytes to communicate among themselves by releasing their own ATP. Astrocytes may strengthen the signaling by secreting the same neurotransmitter, or they may weaken the signal by absorbing the neurotransmitter or secreting proteins that bind to it (blue), thereby preventing it from reaching its target. Astrocytes can also release signaling molecules (red) that cause the axon to increase or decrease the amount of neurotransmitter it releases when it fires again. Modifying the connections among neurons is one way the brain revises its responses to stimuli as it accumulates experience—how it learns. In the peripheral nervous system, Schwann cells surround synapses.

they cut a straight line through a layer of astrocytes in culture, forming a cell-free void that would act like a highway separating burning forests on either side. But when they stimulated calcium waves on one side of the break, the waves spread to astrocytes across the void with no difficulty. The astrocytes had to be sending signals through the extracellular medium, rather than through physical contact.

Intensive research in many laboratories over the next few years showed similar results. Calcium responses could be induced in astrocytes by adding neurotransmitters or by using electrodes to stimulate the release of neurotransmitters from synapses. Meanwhile physiologists and biochemists were finding that glia had receptors for many of the same neurotransmitters neurons use for synaptic communication, as well as most of the ion channels that enable neurons to fire action potentials.

ATP Is the Messenger

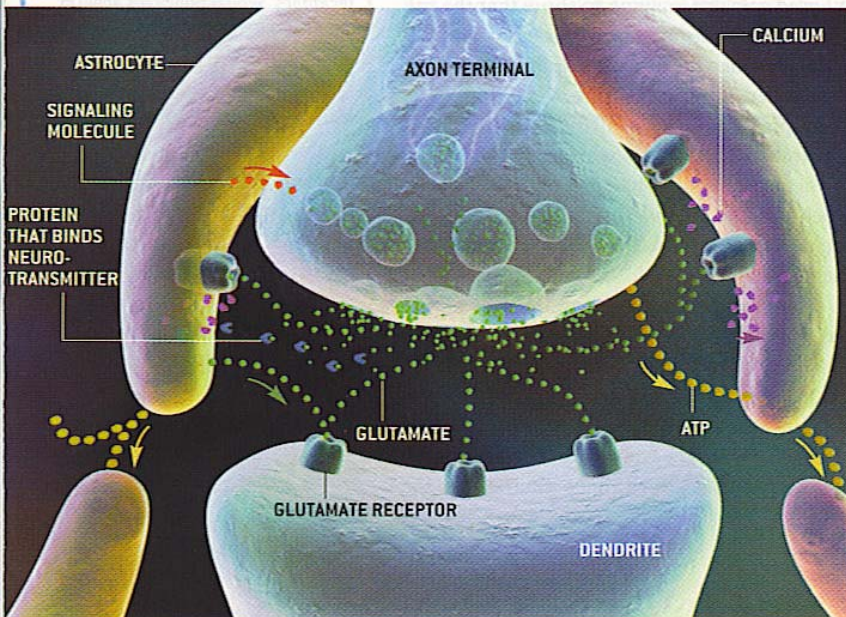
THESE AND OTHER RESULTS led to confusion. Glial communication is controlled by calcium influxes, just as neuronal communication is. But electrical impulses trigger calcium changes in neurons, and no such impulse exists in or reaches glia. Was glial calcium influx initiated by a different electrical phenomenon or some other mechanism?

In their glial experiments, researchers were

noticing that a familiar molecule kept cropping up—ATP (adenosine triphosphate), known to every biology student as the energy source for cellular activities. Although it makes a great power pack, ATP also has many features that make it an excellent messenger molecule between cells. It is highly abundant inside cells but rare outside of them. It is small and therefore diffuses rapidly, and it breaks down quickly. All these traits ensure that new messages conveyed by ATP molecules are not confused with old messages. Moreover, ATP is neatly packaged inside the tips of axons, where neurotransmitter molecules are stored; it is released together with neurotransmitters at synapses and can travel outside synapses, too.

In 1999 Peter B. Guthrie and his colleagues at the University of Utah showed conclusively that when excited, astrocytes release ATP into their surroundings. The ATP binds to receptors on nearby astrocytes, prompting ion channels to open and allow an influx of calcium. The rise triggers ATP release from those cells, setting off a chain reaction of ATP-mediated calcium responses across the population of astrocytes.

A model of how glia around an axon sense neuronal activity and then communicate to other glia residing at the axon's synapse was coming together. The firing of neurons somehow induces glial cells around an axon to emit ATP, which causes calcium intake in neighboring glia, prompting more ATP release, thereby activating communication along a string of glia that can reach far from the initiating neuron. But how could the glia in our experiment be detecting the neuronal firing, given that the axons made no synaptic connections with the glia and the axonal glia were nowhere near the synapse? Neurotransmitters were not the answer; they do not diffuse out of axons (if they did, they could act in unintended places in the brain, wreaking havoc). Perhaps ATP, which is released along with neuro-



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transmitters when axons fire, was somehow escaping along the axon.

To test this notion, we electrically stimulated pure cultures of DRG axons and then analyzed the medium. By exploiting the enzyme that allows fireflies to glow—a reaction that requires ATP—we were able to detect the release of ATP from axons by seeing the medium glow when axons fired. We then added Schwann cells to the culture and measured the calcium responses. They also lit up after axons fired an action potential. Yet when we added the enzyme apyrase, which rapidly destroys ATP—thereby intercepting the ATP before it could reach any Schwann cells—the glia remained dark when axons fired. The calcium response in the Schwann cells had been blocked, because the cells never received the ATP message.

ATP released from an axon was indeed triggering calcium influx into Schwann cells. Using biochemical analysis and digital microscopy, we also showed that the influx caused signals to travel from the cells' membrane to the nucleus, where the genes are stored, causing various genes to switch on. Amazingly, by firing to communicate with other neurons, an axon could instruct the readout of genes in a glial cell and thus influence its behavior.

Axons Control Glia's Fate

TO THIS POINT, work by us and others had led to the conclusion that a glial cell senses neuronal action potentials by detecting ATP that is either released by a firing axon or leaked from the synapse. The glial cell relays the message inside itself via calcium ions. The ions activate enzymes that release ATP to other glial cells or activate enzymes that control the readout of genes.

This insight made us wonder what functions the genes might be controlling. Were they telling the glia to act in ways that would influence the neurons around them? Stevens set out to answer this question by focusing on the process that prompts production of the myelin insulation around axons, which clearly would affect a neuron. This insulation is key to the conduction of nerve impulses at high speed over long distances. Its growth enables a baby to gradually hold up its head, and its destruction by diseases such as multiple sclerosis causes severe impairment.

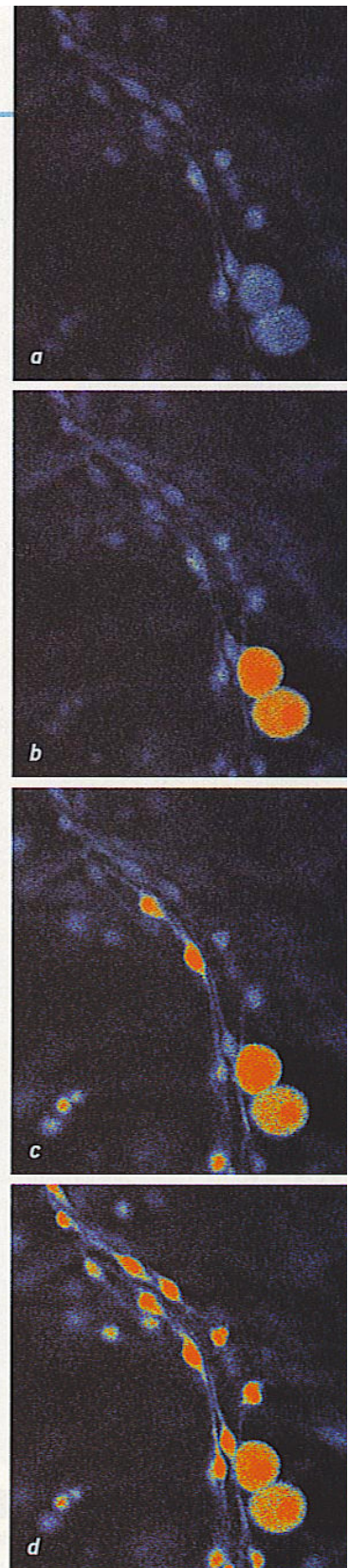
We turned to myelin because we were curious about how an immature Schwann cell on an axon in the peripheral nervous system of a

MOVIE MADE using scanning-laser confocal microscopy [later colorized] shows that glial cells respond to chattering neurons. Sensory neurons [two large bodies, 20 microns in diameter] (a) and Schwann glial cells [smaller bodies] were mixed in a lab culture containing calcium ions [invisible]. Dye that would fluoresce if calcium ions bound to it was introduced into the cells. A slight voltage applied to the neurons prompted them to fire action potentials down axons [long lines], and the neurons immediately lit up (b), indicating they had opened channels on their membranes to allow calcium to flow inside. Twelve seconds later (c), as the neurons continued to fire, Schwann cells began to light up, indicating they had begun taking in calcium in response to the signals traveling down axons. Eighteen seconds after that (d), more glia had lit up, because they had sensed the signals. The series shows that glia tap into neuronal messages all along the lines of communication, not just at synapses where neurotransmitters are present.

fetus or infant knows which axons will need myelin and when to start sheathing those axons and, alternatively, how it knows if it should transform itself into a cell that will not make insulation. Generally, only large-diameter axons need myelin. Could axon impulses or ATP release affect these decisions? We found that Schwann cells in culture proliferated more slowly when gathered around axons that were firing than around axons that were quiet. Moreover, the Schwann cells' development was arrested and myelin formation was blocked. Adding ATP produced the same effects.

Working with Vittorio Gallo and his colleagues in the adjacent NIH lab, however, we found a contrasting situation with the oligodendrocyte glia that form myelin in the brain. ATP did not inhibit their proliferation, but adenosine, the substance left when phosphate molecules in ATP are removed, stimulated the cells to mature and form myelin. The two findings indicate that different receptors on glia provide a clever way for a neuron to send separate messages to glial cells in the central or peripheral nervous system without having to make separate messenger molecules or specify message destinations.

Better understanding of myelination is important. Every year thousands of people die and countless more are paralyzed or blinded because of demyelinating disease. Multiple sclerosis, for example, strikes one in 700 people. No one knows what exactly initiates myelination, but adenosine is the first substance derived from an axon that has been found to stimulate the process. The fact that adenosine is released from axons in response to axon firing means activity in the brain actually influences myeli-

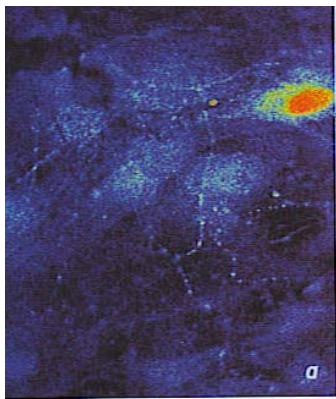


Myelination in the CNS in Response to
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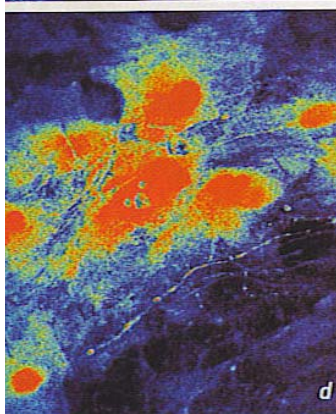
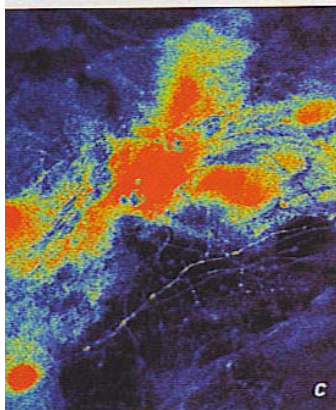
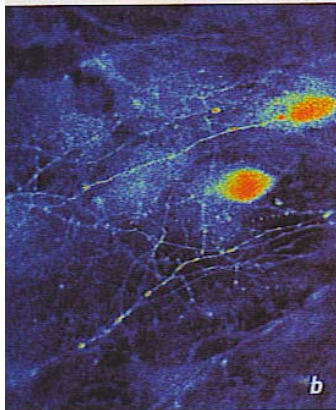
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HOW DO GLIA communicate? Glia called astrocytes (a) and sensory neurons (not shown) were mixed in a lab culture containing calcium ions. After a neuron was stimulated to fire action potentials down long axons (lightning bolts) (b), glia began to light up, indicating they sensed the message by beginning to absorb calcium. After 10 and 12.5 seconds (c and d), huge waves of calcium flux were sweeping across the region, carrying signals among many astrocytes. Green to yellow to red depicts higher calcium concentration.



nation. Such findings could mark paths to treatment. Drugs resembling adenosine might help. Adding adenosine to stem cells could perhaps turn them into myelinating glia that are transplanted into damaged nerves.

Outside the Neuronal Box

EXPERIMENTS IN OUR LAB and others strongly suggest that ATP and adenosine mediate the messages coursing through networks of Schwann and oligodendrocyte glia cells and that calcium messages are induced in astrocyte glia cells by ATP alone. But do glia have the power to regulate the functioning of neurons, other than by producing myelin?

The answer appears to be “yes.” Richard Robitaille of the University of Montreal saw the voltage produced by synapses on frog muscle become stronger or weaker depending on what chemicals he injected into Schwann cells at the synapse. When Eric A. Newman of the University of Minnesota touched the retina of a rat, waves of calcium sent by glia changed the visual neurons’ rate of firing. Studying slices of rat brain taken from the hippocampus—a region involved in memory—Maiken Nedergaard of New York Medical College observed synapses increase their electrical activity when adjacent astrocytes stimulated calcium waves. Such changes in synaptic strength are thought to be the fundamental means by which the nervous system changes its response through experience—a concept termed plasticity, suggesting that glia might play a role in the cellular basis of learning.

One problem arises from these observations. Like a wave of cheering fans sweeping across a stadium, the calcium waves spread throughout the entire population of astrocytes. This large-scale response is effective for managing the entire group, but it cannot convey a very complex message. The equivalent of “Go team!” might be useful in coordinating general activity in the brain during the sleep-wake cycle or during a seizure, but local conversations are necessary if glial cells are to be involved

in the intricacies of information processing.

In a footnote to their 1990 paper, Smith and his colleagues stated that they believed neurons and glia carried on more discrete conversations. Still, the researchers lacked experimental methods precise enough to deliver a neurotransmitter in a way that resembled what an astrocyte would realistically experience at a synapse. In 2003 Philip G. Haydon of the University of Pennsylvania achieved this objective. He used improved laser technology to release such a small quantity of glutamate in a hippocampal brain slice that it would be detected by only a single astrocyte. Under this condition, Haydon observed that an astrocyte sent specific calcium signals to just a small number of nearby astrocytes. As Haydon put it, in addition to calcium waves that affect astrocytes globally, “there is short-range connectivity between astrocytes.”

In other words, discrete astrocyte circuits in the brain coordinate activity with neuronal circuits. (The physical or biochemical factors that define these discrete astrocytic circuits are unknown at present.) Investigation by others has also indicated that astrocytes may strengthen signaling at synapses by secreting the same neurotransmitter the axon is releasing—in effect, amplifying the signal.

The working hypothesis that Haydon and I, along with our colleagues, are reaching from these discoveries is that communication among astrocytes helps to activate neurons whose axons terminate relatively far away and that this activity, in turn, contributes to the release of neurotransmitters at distant synapses. This action would regulate how susceptible remote synapses are to undergoing a change in strength, which is the cellular mechanism underlying learning and memory.

Results announced at the Society for Neuroscience’s annual meeting in November 2003 support this notion and possibly expand the role of glia to include participation in the formation of new synapses [see box on opposite page]. Some of the findings build on research done two years earlier by Ben A. Barres, Frank W. Pfrieger and their colleagues at Stanford, who reported that rat neurons grown in culture made more synapses when in the presence of astrocytes.

Working in Barres’s lab, postdoctoral students Karen S. Christopherson and Erik M. Ullian have subsequently found that a protein called thrombospondin, presumably from the

astrocyte, was the chemical messenger that spurred synapse building. Thrombospondin plays various biological roles but was not thought to be a major factor in the nervous system. The more thrombospondin they added to the astrocyte culture, though, the more synapses appeared. Thrombospondin may be responsible for bringing together proteins and other compounds needed to create a synapse when young nerve networks grow and therefore might contribute to the modification of synapses as the networks age.

Future experiments could advance our emerging understanding of how glia affect our brains. One challenge would be to show that memory—or a cellular analogue of memory, such as long-term potentiation—is affected by synaptic astrocytes. Another challenge would be to determine precisely how remote synapses might be influenced by signals sent through astrocyte circuits.

Perhaps it should not be surprising that astrocytes can affect synapse formation at a distance. To form associations between stimuli that are processed by different circuits of neurons—the smell of a certain perfume, say, and the emotions it stirs about the person who wears it—the brain must have ways to establish fast communication between neuronal circuits that are not wired together directly. If neurons are like telephones communicating electrically through hardwired synaptic connections, astrocytes may be like cell phones, communicating with chemical signals that are broadcast widely but can be detected only by other astrocytes that have the appropriate receptors tuned to receive the message. If signals can travel extensively through astrocyte circuits, then glia at one site could activate distant glia to coordinate the firing of neural networks across regions of the brain.

Comparisons of brains reveal that the proportion of glia to neurons increases greatly as animals move up the evolutionary ladder. Haydon wonders whether extensive connectivity among astrocytes might contribute to a greater capacity for learning. He and others are investigating this hypothesis in new experiments. Perhaps a higher concentration of glia, or a more potent type of glia, is what elevates certain humans to genius. Einstein taught us the value of daring to think outside the box. Neuroscientists looking beyond neurons to see how glia may be involved in information processing are following that lead.

GLIA CONTROL SYNAPSES

FOR YEARS, scientists assumed that only neurons specify the connections they make to other neurons. But evidence shows that glia can strongly influence how many synapses a neuron forms and where it forms them.

Ben A. Barres and his colleagues at Stanford University found that when they grew neurons from a rat's retina in a lab culture devoid of glial cells known as astrocytes, the neurons created very few synapses. When the researchers added astrocytes or culture medium that had been in contact with astrocytes, synapses formed abundantly. Barres could see the synapses and count them through a microscope as well as detect them by recording electrical activity (a sign that signals were flowing through synapses) with a microelectrode. He then detected in the medium two chemicals that are released by astrocytes to stimulate synapse formation—a fatty complex called apoE/cholesterol and the protein thrombospondin.

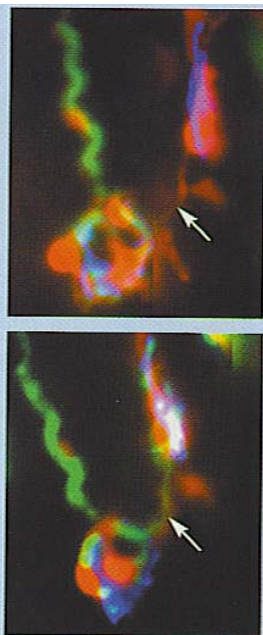
Meanwhile Jeff W. Lichtman's group at Washington University recorded muscle synapses in mice over several days or weeks as they formed and as they were removed during development (the time when unneeded synapses get pruned) or after injury. When the images were spliced into a time-lapse movie, it appeared that both synapse formation and elimination were influenced by nonneuronal cells, seen as ghostlike forces acting on the axon terminal.

Most recently, Le Tian, Wesley Thompson and their associates at the University of Texas at Austin experimented with a mouse that had been engineered so that its Schwann glia cells fluoresced. This trait allowed Thompson's team to collaborate with Lichtman's group and watch glial cells operate at the junction where neurons meet muscle—a feat previously not possible. After a muscle axon is injured or cut, it withdraws, but a cluster of neurotransmitter receptors remains on the recipient side of a synapse. Investigators knew that an axon can regenerate and find its way back to the abandoned receptors by following the Schwann cells that remain.

But what happens if the axon cannot find its way? Tracking the fluorescence, Thompson's group saw that Schwann cells at intact synapses somehow sensed that a neighboring synapse was in trouble. Mysteriously, the Schwann cells sprouted branches that extended to the damaged synapse, forming a bridge along which the axon could grow a new projection to the receptors (photographs).

This work clearly shows that glia help to determine where synaptic connections form. Researchers are now trying to exploit this power to treat spinal cord injuries by transplanting Schwann cells into damaged spinal regions in lab animals.

—R.D.F.



GLIA CAN GUIDE the formation of synapses. Neurobiologist Le Tian severed a muscle nerve synapse in a mouse whose cells had been engineered to fluoresce. Two days later (top) Schwann glia cells (dark red) had formed a bridge across the divide (arrow). In another two days (bottom), an axon (green) had regrown along the bridge to create a synapse.

MORE TO EXPLORE

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Also see the journal *Neuron Glia Biology*: www.journals.cambridge.org/jid_NGB

