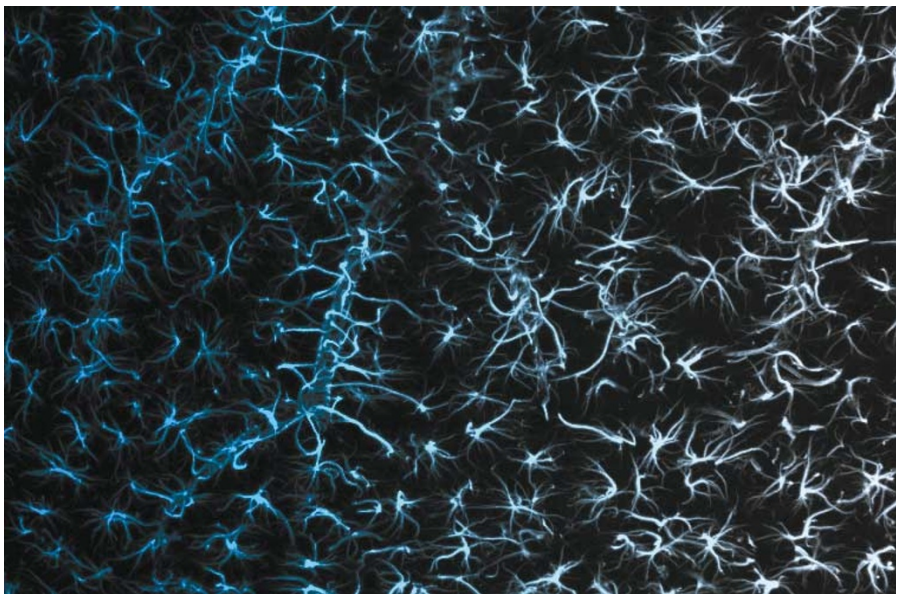
The best supporting actors

Glial cells were long thought to play a peripheral role in the theatre of the brain. But some neuroscientists now believe that they are intimately involved in the way the brain processes information. Bas Kast charts the cells' move into the limelight.



T. TAKANO/M. NEDERGAARD

Stars of the show: glia such as these astrocytes are being linked to information processing in the brain.

Until ten years ago, glial cells seemed destined for a life of anonymity. Despite being the most numerous type of cell in the human brain — outnumbering neurons by ten to one — glia were seen as little more than packing material. For most researchers, it was the chemical and electrical signals used by neurons to communicate that were the key to understanding the brain.

But glial cells are now high on the neuroscience agenda. A series of studies in the 1990s showed that these cells do communicate with neurons, leading some researchers to suggest that our picture of how the brain processes information needs to be revised. For the small band of scientists who have devoted their careers to studying glia, the surge in interest is long overdue. "Finally," says Maiken Nedergaard, a neurophysiologist at New York Medical College in Valhalla, "glia are starting to receive the attention they deserve."

Glial cells come in different types, but all were originally thought to play menial roles. One such function, holding brain tissue together, earned the cells their name — glia derives from the Greek word for glue. Some glia wrap themselves around neurons, providing electrical insulation. Others, such as the star-shaped astrocytes that are the focus of much of the new work, have been implicated in a range of jobs. These include supplying neurons with nutrients[1] and maintaining the levels of ions used by neurons in signalling[2].

Unsung heroes

One of the reasons glial cells have been neglected is that they do not generate electrical pulses. Such voltage pulses are used by neurons as part of their communication system. They are sent along a fibre, called an axon, that projects from the neuron's body. Experimental techniques for studying these pulses revealed little of interest when applied to glia, and the lack of pulses led most researchers to assume that the glia were not involved in information processing.

But electrical pulses are only part of the brain's communication system. Once a pulse reaches the end of an axon, it triggers the release of chemicals called neurotransmitters. These diffuse across the synapse — the gap between the axon and the 'dendrite', the receiving fibre of the target neuron. Once across, they dock with special proteins, known as receptors, on the dendrite's membrane. Some receptors can react to the arrival of neurotransmitters by opening channels in the dendrite's wall, allowing ions to flow into and out of the cell.

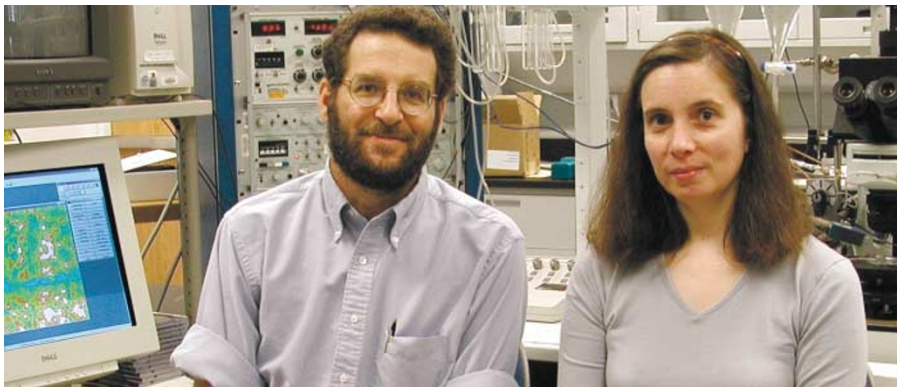
Astrocytes wrap themselves around some types of synapse, and so come into contact with the neurotransmitters that flow across the gap. Evidence dating back to the 1970s shows that glia have receptors for neurotransmitters similar to those on neurons, but neuroscientists had never seen glia use them.

In the late 1980s, research began to reveal that receptors on glial cells could react to glutamate, a common type of neurotransmitter, by opening channels in the glial cell's membrane[3,4]. In 1990, Ann Cornell-Bell and her colleagues, then at Yale University in New Haven, Connecticut, showed that glial cells in laboratory cultures use their receptors to receive signals from neurons[5]. Cornell-Bell found that the channels opened by glutamate on the glial-cell membrane allow external calcium ions to flow into the cell. At the same time, the cells release calcium ions from internal stores. The combined effect is a rapid increase in the level of calcium ions inside the glial cell.

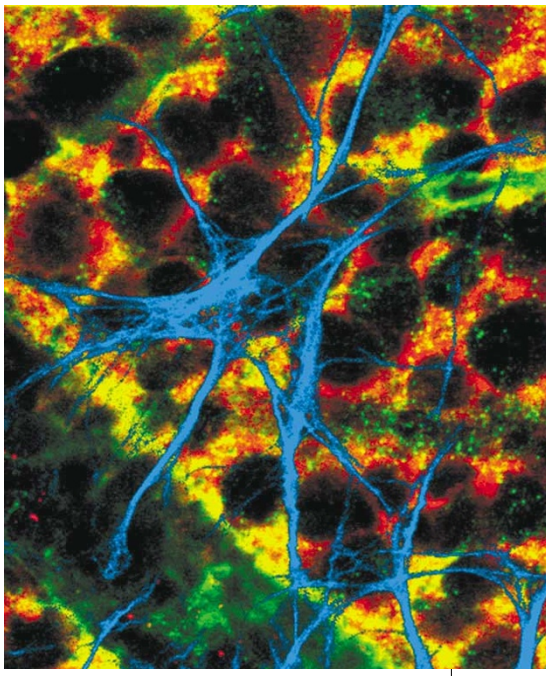
The Yale team also showed that a rise in calcium levels in one glial cell triggers similar increases in neighbouring cells. These cells, in turn, pass the signal on, causing a wave of rising calcium levels to pass through the local network of glia. Not only were neurons communicating with glial cells, but the glia seemed to be sending signals among themselves.

A series of studies has now shown that the calcium wave is mediated by two different signals[6]. One of these uses gap junctions, areas where two neighbouring glia come into direct contact. The release of calcium ions from the glia's internal stores is controlled by a series of different molecules. These can

Brain power: Maiken Nedergaard speculates that glial cells could be involved in cognition.



Eyes down: Eric Newman and Kathleen Zahs have found evidence that in retinas (right), the calcium waves passing through astrocytes (shown in blue) can influence the way neurons react to light.



P. KOFUJI/E. NEWMAN/K. ZAHS

flow over gap junctions and trigger the release of calcium ions in adjoining cells. In addition, the rise in calcium levels causes the glia to release adenosine triphosphate (ATP), the molecule used by cells to carry energy. ATP molecules can diffuse across extracellular space and, by opening receptor channels, trigger increases in calcium levels in the glia they come across. This provides a means for the calcium wave to jump between cells that do not make direct contact.

By the early 1990s, many neuroscientists were convinced that neurons could talk to glia, and that glia could talk among themselves. Later that decade, evidence emerged for the final link in the network — signal transmission from glia to neurons.

In 1994, Nedergaard[7] showed that rising calcium levels in astrocytes were followed by a similar increase in calcium levels in nearby neurons. The signal appears to be transferred across gap junctions between the two cells. The same year, Philip Haydon, then at Iowa State University in Ames, described how glutamate emitted from glia can dock with nearby neurons and raise calcium levels in those cells[8].

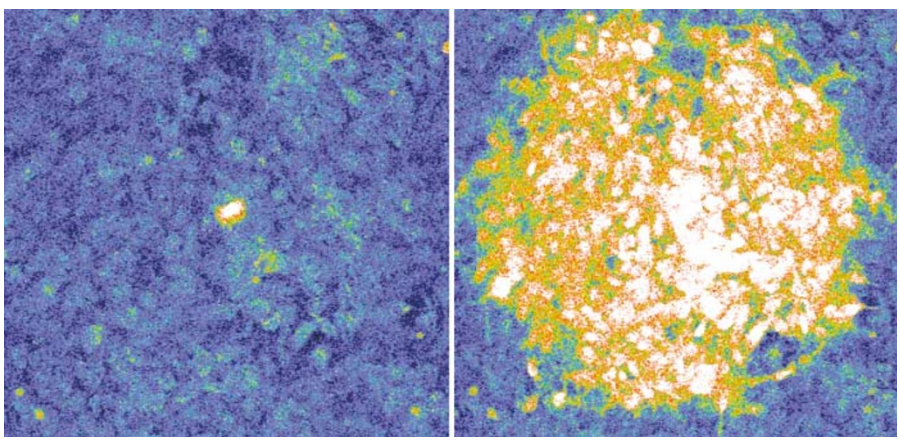
More recently, researchers have started to suspect that the way in which glia wrap themselves around synapses might affect the flow of neurotransmitters. Knut Petter Lehre of the University of Oslo and Dmitri Rusakov of the Institute of Neurology in London are working on a detailed study of the distribution of glia around synapses. Initial results suggest that the glia wrap themselves tightly to the receiving dendrite, but leave more gaps around the transmitting axon.

Dimitri Kullmann, one of Rusakov's colleagues at the Institute of Neurology, suggests that the close association with the dendrite helps to restrict neurotransmitters to their main target. But by leaving gaps around the axon, glia allow the signal to diffuse back around its sides. Here the neurotransmitters can dock with receptors, perhaps providing a feedback loop by which the signalling cell can regulate its own firing.

Three's a crowd

The transformation of neuroscientists' perception of glia has led Haydon, now at the University of Pennsylvania in Philadelphia, to suggest that the classic picture of the synapse needs to be redrawn. He believes that glia surrounding the junction between two neurons should be seen as the third member of a 'tripartite synapse'[9].

Studies of glial cells in retinas taken from rats support this view. In 1997, Eric Newman and Kathleen Zahs of the University of Minnesota in Minneapolis showed that the calcium wave originally seen in cell culture by Cornell-Bell also occurred in the rat retinas[10].



M. SIMARD/M. NEDERGAARD

Surf's up: a calcium wave spreading out from a single cell (left) to hundreds of neighbouring glia.

The following year, the same researchers showed that this calcium wave influences how neurons in retinas respond to light[11]. The neurons fire when exposed to light, and Newman and Zahs saw that many of the cells fired less frequently as the calcium wave passed. This was just the kind of interaction between glia and neurons that Haydon was proposing.

Later the same year, Richard Robitaille from the University of Montreal in Canada, provided evidence for a three-way synapse in a living animal[12]. He studied the neuromuscular junction in frogs. This specialized synapse is the point at which neurons meet muscles, and neurotransmitters released here control muscle movements.

If neurons at the junction are induced to fire repeatedly for long enough, the amount of neurotransmitter released by each pulse starts to decline. Researchers were not sure why this happens, but most assumed that the process was controlled by chemicals in the neurons or the synapse.

Robitaille injected GDPβS, a substance that inactivates chemical messengers known as G-proteins, into the glial cells that surrounded the synapse. G-proteins play a key role in the signalling pathway that leads to increased calcium levels. With the G-proteins disrupted, the glia could not react to neurotransmitters in the normal way.

Robitaille found that the decline in neurotransmitter release stopped when the G-proteins were inactivated. The process seems to be controlled, at least in part, by the glial cells surrounding the synapse. Robitaille speculates that the glia could be acting as a brake on the emission of neurotransmitters, preventing neurons from using up all of their supplies.

Evidence for a tripartite synapse in the mammalian brain comes from studies of

Three-way split: Philip Haydon says glial cells are involved in communication at the synapse.

astrocytes in slices of brain tissue taken from the hippocampus, an area involved in the formation of memories. When one neuron fires repeatedly, the strength of the effect it has on connecting neurons can increase with time. This effect, known as potentiation, is thought to be important in learning and has been observed at synapses in the hippocampus and elsewhere in the brain.

Potential difference

In 1998, Nedergaard and her colleague Jian Kang described how astrocytes can control potentiation at hippocampal synapses[13]. They identified synapses at which repeated firing caused potentiation. They then showed that they could induce potentiation by stimulating astrocytes around the synapse, and prevent normal potentiation by applying a drug to astrocytes that disrupted their functioning.

Other researchers are trying to redraw our picture of the synapse in different ways. Read Montague, a theoretical neuroscientist from the Baylor College of Medicine in Houston, Texas, suggests that by isolating the area around the synapse, glia may be assisting a hitherto undiscovered form of neurotransmission.

Neuroscientists have recently found that voltage pulses sent down the axon can also travel 'backwards', away from the neuron's body and back into its dendrites[14]. When the pulse reaches a synapse, it opens channels in the dendrite's membrane, allowing calcium to flow in. By isolating the synapse, glia ensure that these small changes in the number of calcium ions in the gap are not rapidly diluted by calcium flowing in from other areas.

> The findings have upset the picture of the synapse as a one-to-one connection between neurons.

Montague argues that this allows the change in calcium levels in the synapse to be felt by the axon of the neuron on the other side of the junction. Several processes, including the release of neurotransmitters, are influenced by calcium concentrations. So the glia may be allowing neurons to communicate 'backwards' without releasing neurotransmitters.

Montague is now collaborating with his colleagues Dan Johnston and Rob Gereau at Baylor and Michael Friedlander of the University of Alabama at Birmingham to evaluate his ideas experimentally. "To show information processing without neurotransmitters would be a big result," he says, "but these are very difficult experiments to do."

The work of Haydon and Montague provides exciting new angles on how the brain may process information, but it poses a problem for researchers investigating how groups of neurons work together. Traditional models assume that the synapse is a one-to-one connection between two neurons. The new findings have disrupted this simple picture. Glial cells may communicate more slowly than neurons — voltage pulses can travel at up to 100 metres per second, over a million times faster than a calcium wave — but they are still sending information, and no one in the field is certain what the consequences of such transmissions may be.

Newman's work is a case in point. His studies suggest that glia in retinas influence the signals received by the brain's visual-processing areas, but he is at a loss as to what they could mean in terms of how humans or animals actually see. "At this point, we have no idea what this could mean for vision," he says. Nedergaard and Kang face a similar problem. "It's clear that glia can modulate hippocampal synapses, but we still don't have any direct evidence that they actually participate in memory and learning," says Nedergaard.

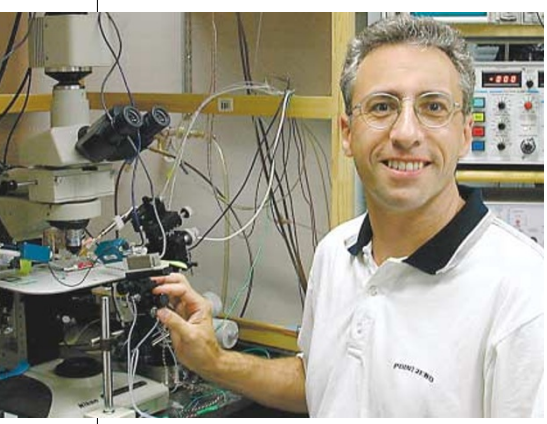
Thought patterns

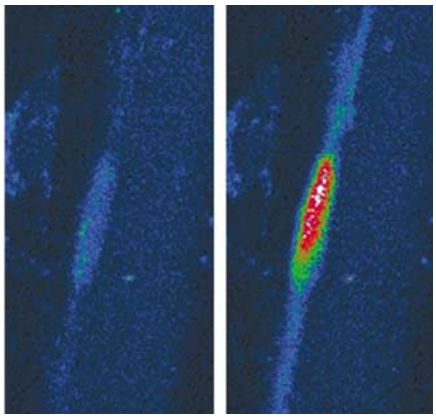
Comparisons between different species provide a further intriguing hint that glial cells may play a role in cognition. The ten-to-one ratio of glia to neurons in humans drops to one-to-one in rodents[15]. And the ratio is reversed in nematodes, with neurons outnumbering glial cells by almost six to one[16]. Nedergaard says that the pattern seems to work across all species — the greater the cognitive ability, the higher the ratio of glia to neurons. "It's therefore tempting to think that glial cells play a key role in higher cognitive functions," speculates Nedergaard.

Haydon likens the link between neurons and glia to that between lead actors and their supporting cast and stage hands[6]. The stars could not put on a play alone, and the more complex the performance, the more support is required. "If I think of the spectacular theatre our brains perform every single day, it's probably no coincidence that in our brain the backstage people outnumber the actors by a factor of ten," says Haydon.

Further probing of glial cells' abilities will be needed before neuroscientists can determine the accuracy of Haydon's analogy. But after the past decade's revelations about glial-cell function, the cells are now attracting the attention of a previously uninterested audience of neuroscientists. The backstage crew is finally getting its turn in the limelight. ■

Bas Kast writes for *Der Tagesspiegel* in Berlin.





Message service: by studying the links between neuron activity and the calcium response in glial cells (right), Richard Robitaille has found evidence that glia can exert an influence on neurons.

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