

Glial Cells Are More Than Our Brain's "Glue"

"Glial cells may contribute to many diseases of the brain," says Fred Hutchinson Cancer Center researcher Aakanksha Singhvi. And glia may play a central role in sensory response.

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When it comes to brain cells, neurons get the most attention.

Their central role in our thoughts, sensations and behaviors has captivated scientists. But neurons are only half the story: glia, specialized brain cells that ensure topnotch neural function, make up about 50% of our brain's cells. Historically, attention paid to neurons has left glia overshadowed and overlooked — to our detriment.

"In the last few years there has been growing appreciation that glial cells may contribute to many diseases of the brain, from epilepsy to Alzheimer's," said Fred Hutchinson Cancer Center neuroscientist [Aakanksha Singhvi, PhD](#), who is at the forefront of a scientific reassessment of glial cells' importance. "Glia are about half the cells in your brain. So if you don't understand how they organize into or control the [neural] network, that's a big knowledge gap."

She's working to bridge that gap. On Feb. 27 in the journal *Cell Reports*, Singhvi and her team, led by graduate student Sneha Ray, [published insights](#) that will help scientists build a more holistic — and clinically relevant — picture of how brains work.

Using tiny worms called nematodes, they revealed how an individual glial cell independently regulates different neurons and helps integrate sensory information flowing through separate neural circuits.

Ray discovered that a single glial cell uses different molecules to communicate with different neurons. Careful clustering of these molecules ensures that the glial cell can conduct a distinct "conversation" with each neuron. Through these molecular interlocutors, glia can "coach" neurons, influencing how they respond to environmental cues like temperature and smell.

But this study from Singhvi's group also shows that glial cells do more than give individual neurons notes. Ray, with fellow Singhvi Lab graduate student Pralaksha Gurung, found that glia help neurons play well together, even across circuits designed to detect different environmental cues. A glial molecule that controls the worm's temperature-sensing neuron can also influence how the

animal smells — no synapse required.

“It’s the first very clear indication that a glial cell is going to put specific molecules to specific contact sites to regulate those neurons, at the single-cell level, with consequences to how the animal will behave,” Singhvi said.

She and her team propose that glia across species use the same strategy to communicate with neurons and influence how information is processed across different sensory circuits. In this way, glia may play a central role in animals’ responses to complex sensory worlds.

Ray’s insights were honored by the Genetic Society of America, which gave her the 2024 Sydney Brenner Best PhD Thesis Award, an annual recognition of the world’s best doctoral work in nematodes. She’ll formally receive her award during [The Allied Genetics Conference 2024](#) in Washington, DC.

Glia: stepping into the light

Less glitzy than neurons that literally pulse with electricity, glia were easy to overlook by scientists investigating the nervous system. It seemed clear that glia played a purely supporting role; neuroscientists dismissed them as a mere “glue” that help neurons stick together, or “nursemaids” that provide neurons sustenance but not guidance.

Singhvi is among the cadre of neuroscientists leading the charge to reevaluate glia.

“How is the brain put together? We don’t really understand it from a glial perspective,” she said. “If we don’t understand glia, we don’t understand how the brain is organized into a network.”

Complex organisms like humans have more than one type of glia, each of which interacts with numerous neurons. Glial cells called astrocytes stretch out many tendrils toward nearby neurons.

“A single astrocyte glia interacts with a hundred-odd neurons in the human brain by some estimates,” Singhvi said. But, she said, a given glial cell may interact with an individual neuron in many sites: “An astrocyte may make in the range of 100,000 contacts.”

To unearth glial cells’ basic biology, Singhvi helped pioneer the use of minuscule nematodes, called *Caenorhabditis elegans*. These worms are unusual: each worm has exactly the same number of cells, including neurons. This phenomenon allowed scientists to create incredibly detailed maps of *C. elegans* cells — including neurons and glia — that apply to every animal.

To simplify matters further, nematodes only have one type of glia. To learn more about how an individual glial cell interacts with several different neurons, Singhvi and Ray focused on a glial cell called AMsh. In every nematode, this glial cell sits at the tip of the animal’s nose and contacts the ends of the same 12 sensory neurons.

“It’s a one-stop shop for everything that the worm is using to ‘see’ the world outside,” Singhvi

said. “Each of those 12 neurons is actually doing different things for the animal.”

One of those 12 sensory neurons is AFD, which senses temperature. Singhvi and Ray zeroed in on temperature sensation as they began untangling the ways that glia and neurons communicate.

Clustering conversations

In prior work, Singhvi had discovered that KCC-3, a protein that transports potassium and chloride ions across cell membranes, is involved in temperature sensation in *C. elegans*.

In humans, KCC3 is required for proper brain development.

Singhvi has developed techniques that allow her to zero in on individual glia and the neurons they envelop using high-powered microscopes. Using these techniques, she and Ray quickly discovered that KCC-3 is not distributed equally along AMsh’s membrane. Instead, they saw that the ion transporter clustered in one spot along the interface between AMsh and AFD, even though it’s closely nestled near other neurons ensheathed by AMsh.

“We realized it’s sitting next to the temperature-sensing neuron — but not any of the others — which is essentially the glial cell knowing a half a micron [millionth of a meter] difference between the two neurons,” Singhvi said.

She and Ray discovered that this molecular clustering is not unique to KCC and AFD. The team detected at least three types of molecular clusters that connect AMsh to different sensory neurons.

“The glial cell is using molecules like KCC-3 to create specialized ion compartments specific for different neurons — and each one needs a different kind to work properly,” Singhvi said.

Her team showed that AMsh is not the only glial cell to group molecules like KCC-3 to facilitate separate communication with different sensory neurons, suggesting that this strategy is likely used by glia across species.

Ray and Singhvi also found that even though every neuron enveloped by AMsh senses a different environmental cue, the glial cell can help integrate information across circuits and allow neurons within one sensory circuit (like temperature) to influence the function of neurons within a different circuit (like those that smell specific odors). In this way, a single glial cell can help the worm respond to the bigger environmental picture, instead of merely helping neurons relay individual external cues.

From worms to humans

While we may seem to have little in common with worms, their neurons and glia work much like ours. So, a deeper understanding of how their glia help shape behaviors could help us better understand our own. Even worms must make complex decisions based on different, even competing, environmental cues, Singhvi noted.

“When you think about what it takes to be a nematode, it’s very complicated,” she said.

What does a worm do when it encounters a tantalizing scent that signals food — right when its environment starts getting dangerously warm? It must balance these different inputs and make a decision.

“The worm won’t burn — it’s too smart to burn,” Singhvi said.

And the compartmentalization that she and Ray uncovered is likely critical to a nematode’s — or human’s — ability to weigh important factors like heat and smell, she said.

“Our brains routinely process multiple inputs or sensory cues in parallel,” Singhvi said. “Our research showing that glia can be conduits between brain circuits will help us understand the different ways that the circuits can be disrupted.”

She noted that the same KCC-3 protein she studies in nematodes is also essential for brain function in humans. Disruptions of KCC-3 is linked to a severe brain development disorder called agenesis of the corpus callosum or [Anderman Syndrome](#), and to seizure susceptibility and neurodegeneration. Differences in brain circuits are linked to conditions such as autism, epilepsy and schizophrenia.

“The ability for the glial cell to keep these different compartments separate is important for the role of the glial cell if it’s talking to 1000 neurons,” she said. “It isn’t saying, ‘All of you be happy,’ or ‘All of you be silent.’ It’s able to have specific modulations of individual neurons at individual contact sites.”

This allows the animal to have multiple circuits working properly at the same time without confusing cross connections, and allows parallel circuits to work effectively.

“This is the essence of how the brain works,” she said.

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