

## NEUROSCIENCE

# Glia — more than just brain glue

Nicola J. Allen and Ben A. Barres

**Glia make up most of the cells in the brain, yet until recently they were believed to have only a passive, supporting role. It is now becoming increasingly clear that these cells have other functions: they make crucial contributions to the formation, operation and adaptation of neural circuitry.**

## How do glia differ from neurons?

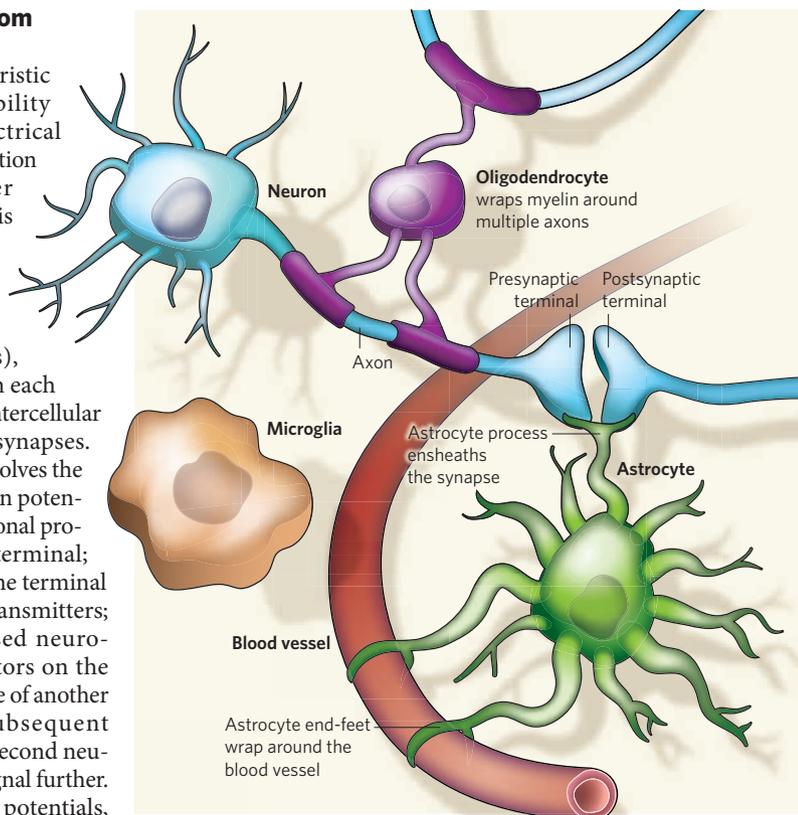
The defining characteristic of a neuron is its ability to transmit rapid electrical signals in the form of action potentials. All other neural cells that lack this property are categorized into a broad class termed glia. Neurons are arranged in networks (circuits), and communicate with each other via specialized intercellular adhesion sites called synapses. Neuronal signalling involves the propagation of an action potential down a neuron's axonal process to a presynaptic terminal; the depolarization of the terminal and release of neurotransmitters; binding of the released neurotransmitters to receptors on the postsynaptic membrane of another neuron; and the subsequent depolarization of this second neuron, propagating the signal further. Glia do not fire action potentials, but instead surround and ensheath neuronal cell bodies, axons and synapses throughout the nervous system.

## Are all glia the same?

No. On the basis of morphology, function and location in the nervous system, there are several classes of glia. In mammals, for example, glia are classified as microglia, astrocytes and the related Schwann cells and oligodendrocytes (Fig. 1).

## Where do they originate from?

Glia and neurons mainly share a common origin — precursor cells derived from the embryonic germ layer known as the neuroectoderm. A notable exception is microglia, which are part of the immune system and enter the



**Figure 1 | Glia-neuron interactions.** Different types of glia interact with neurons and the surrounding blood vessels. Oligodendrocytes wrap myelin around axons to speed up neuronal transmission. Astrocytes extend processes that ensheath blood vessels and synapses. Microglia keep the brain under surveillance for damage or infection.

brain from the blood circulation early in an organism's development.

## What is known about the evolution of glia?

Glia are evolutionarily conserved, being present in one form or another in most species examined, from the simplest invertebrates to humans. The proportion of glia seems to be correlated with an animal's size: the tiny nematode worm has only a few glia; some 25% of the fruitfly brain consists of glia; the mouse brain

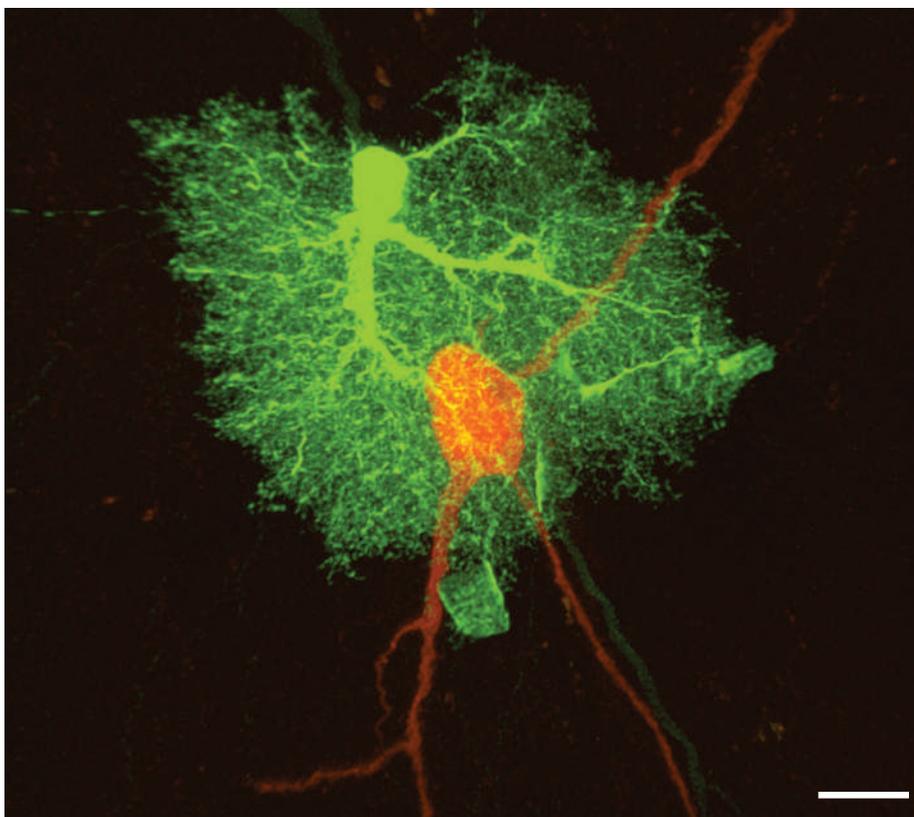
has roughly 65% of these cells; the human brain has about 90%; and the elephant brain consists of some 97% glia. As animals have evolved, glia have become not only more diverse and specialized, but also essential: without them neurons die. Furthermore, astrocytes in the human cerebral cortex are much more complex than those of other mammals, and are thought to be involved in information processing.

## So what exactly do glia do?

Lots of things. The traditional view has been that glia look after neurons and maintain their proper functioning, having a somewhat passive role themselves. Established functions of glia include supporting neurotransmission, maintaining ionic balance in the extracellular space, and insulating axons to speed up electrical communication. But emerging research suggests that glia, particularly astrocytes, also have an active role in brain function and information processing — both during development and in adulthood.

## What is the specific function of microglia?

These resident immune cells of the nervous system survey the brain for damage and infection, engulfing dead cells and debris. Microglia have also been implicated in synaptic remodelling during the development of the nervous system, when they are proposed to remove inappropriate synaptic connections through the process of phagocytosis. Moreover, they are activated in many neurodegenerative diseases, but whether they are helpful or harmful in these conditions is a matter of debate.



**Figure 2 | An astrocyte in action.** This micrograph shows a protoplasmic astrocyte (green) enveloping the cell body and the processes of a neuron (red). The bushy nature of astrocytes, evident in this image, allows them to form distinct domains in the brain. Scale bar, 10  $\mu\text{m}$ . (Image courtesy of M. Ellisman and E. Bushong, Univ. California, San Diego.)

### What do oligodendrocytes and Schwann cells do?

In vertebrates, these cells are essential for rapid electrical communication between neurons and their targets. Oligodendrocytes (in the central nervous system) and Schwann cells (in the peripheral nervous system) produce a lipid-rich membrane called myelin, which enwraps axons, thereby speeding up the conduction of electrical impulses. In the absence of myelin, the conduction velocity of an action potential is directly proportional to the diameter of the axon. This means that the final size of an animal would be limited by the fact that its axons would eventually become prohibitively large. The evolution of myelin has allowed animal size to increase without a corresponding increase in axon diameter, enabling rapid thought and action. Besides, myelination induces clustering of ion channels, thereby further enhancing conduction velocity. 'Demyelination' — due to damage to oligodendrocytes and Schwann cells — leads to various diseases, including multiple sclerosis and hereditary sensorimotor neuropathy.

### And what about astrocytes?

Put simply, astrocytes allow neurons to function (Fig. 2). They contribute to homeostasis in the brain by providing neurons with energy and substrates for neurotransmission. They act as physical barriers between the synaptic

connections of neighbouring neurons, and remove excess neurotransmitter molecules from the extracellular space, allowing discrete and precise encoding of synaptic signals and neurotransmission. Recently, unexpected roles for astrocytes have been identified — they seem to be involved in the formation of synapses and in modulating synaptic function through bidirectional communication with neurons. For this reason, the next few questions are dedicated to this, currently the 'hottest' type of glia.

### How exactly do astrocytes contribute to homeostasis in the brain?

Astrocytes control blood flow through their numerous fine processes, which form close associations with both blood vessels and neurons. In response to enhanced neuronal activity, astrocytes signal to blood vessels about the need for regional increases in blood flow, which results in enhanced delivery of oxygen and glucose to the active brain region. Analysis of such changes in blood flow forms the basis of the study of brain function by functional magnetic resonance imaging (fMRI). Besides regulating blood flow, astrocytes ferry glucose and oxygen from blood to neurons. It is hypothesized that they convert glucose into lactate. Lactate is then exported to neurons, where it is converted to pyruvate to produce the cell's energy molecule ATP. Astrocytes are also responsible for

terminating the action of neurotransmitters secreted by neurons and for mediating their recycling back to neurons in a process known as the glutamate–glutamine cycle.

### Are all astrocytes the same?

No. These cells are broadly divided into two groups — protoplasmic astrocytes found in the brain's grey matter and fibrous astrocytes of the white matter. Protoplasmic astrocytes are intimately associated with neuronal cell bodies and synapses, whereas fibrous astrocytes are associated with neuronal axons. Furthermore, types of protoplasmic astrocyte differ between the various regions of grey matter; even within a single brain region, neighbouring astrocytes are probably different. This is not surprising, because, if they are to fulfil different functions, these cells must adapt to specific brain regions. Exact functional differences between the various types of astrocyte remain elusive.

### Do astrocytes talk to each other?

Yes. They communicate with each other through waves of calcium ions, propagating information over large distances. Stimulation of one astrocyte can cause a calcium response in a subset of neighbouring astrocytes, with no response in other subsets, indicating the presence of distinct networks of astrocytes organized in a mosaic pattern. Although individual astrocytes occupy distinct domains, and cellular projections from neighbouring astrocytes do not overlap in the adult brain, these cells are linked together by structures in their cell bodies called gap junctions.

### Do they communicate with neurons too?

Bidirectional communication does indeed occur between neurons and astrocytes. Individual astrocytes can make contact with and ensheath thousands of synapses formed between many different neurons. This means that synapses don't consist of just a pre- and postsynaptic neuronal element, but that many also have an astrocytic projection that envelops the synapse. This close spatial relationship has led to the term tripartite synapse, to acknowledge the astrocyte's contribution (Fig. 3). The synaptic localization of astrocytes means they are ideally placed to monitor — and respond to — synaptic activity. Moreover, astrocytes possess many of the same neurotransmitter receptors as neurons, and neurotransmitter release by neurons activates calcium-based signalling cascades in astrocytes. Astrocytes then release neuroactive substances, signalling back to neurons to form a feedback loop. The different types of molecule secreted by astrocytes can either inhibit or enhance overall levels of neuronal activity.

### Do any types of glia receive direct neuronal input?

Possibly. Cells expressing the proteoglycan NG2, which are thought to be oligodendrocyte

precursor cells, have been shown to receive direct synaptic signals from neurons, some of them even firing action-potential-like signals in response. The significance of this innervation is not known. Does it influence the decision of NG2-expressing cells to become oligodendrocytes, or even neurons? And could it result in the recruitment of NG2 cells into specific neural networks?

### What is the role of glia in embryonic brain development?

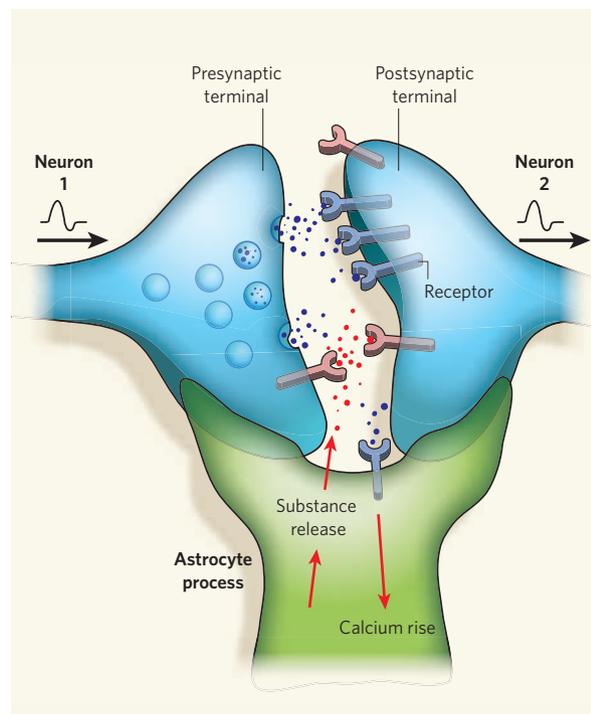
Some glia give rise to neurons, and others guide neurons to their correct location in the nervous system — so they are essential for brain development. During embryonic development, a specialized type of glia called radial glia divide to form neural progenitor cells. Moreover, the long processes of radial glia span the cortex, providing tracks along which newly generated neurons migrate to reach their correct location. Once all neurons are in place, the processes of radial glia degenerate and they form cortical astrocytes. Besides guiding neurons to their correct location, glia provide a scaffold along which axons grow. They perform this pathfinding function through both attractive and repulsive interactions with receptors present on the axon.

### And how do they contribute to the formation of neural networks?

They do so by aiding synapse formation and possibly synapse elimination. Astrocytes, for instance, induce synapse formation in several classes of neuron, both by direct contact with neurons and by secreting factors that regulate synapse formation as well as pre- and postsynaptic functions. But such actions are not restricted to astrocytes. Oligodendrocytes and Schwann cells also induce synapse formation between neurons. It is not clear how such glial signals act: do they provide a permissive environment for synapse formation at sites predetermined by neurons, or do they actively instruct neurons where to form synapses? As mentioned previously, microglia are also implicated in the removal of inappropriate synaptic connections and so in fine-scale ‘sculpting’ of neuronal networks.

### Do glia play a part in disease?

Glia can be a help or a hindrance in disorders of the nervous system, and their malfunction has been implicated in many such diseases. For example, following spinal-cord injury, astrocytes form a glial scar that acts as a barrier to the regeneration of damaged axons. Moreover, in the neurodegenerative disease amyotrophic lateral sclerosis, astrocytes secrete a toxic factor that kills motor neurons — those involved in muscle function. And astrocytes can sometimes become cancerous, giving rise to brain tumours called gliomas. Also, as mentioned earlier, oligodendrocytes are the target of an autoimmune attack in multiple sclerosis that causes demyelination. Unexpectedly, profound



**Figure 3 | A tripartite synapse.** Astrocytes express many of the same receptors as neurons. When neurotransmitters are released from the presynaptic terminal of a neuron, astrocytic receptors are thought to be activated, leading to a rise in calcium ions in the astrocyte and the release of various active substances, such as ATP, which act back on neurons to either inhibit or enhance neuronal activity. Astrocytes also release proteins, which control synapse formation, regulate presynaptic function and modulate the response of the postsynaptic neuron to neurotransmitters.

loss of oligodendrocytes and myelin has been reported in clinical depression.

### What experimental models are used to study glia?

Studying the role of glia in nervous-system function is difficult because, in most organisms, glia are essential for neuronal survival and so their removal causes neuronal death. Therefore, much of what we know about glia has come from studies of isolated mammalian glia maintained *in vitro*. Although such analysis is useful and has taught us much about the basic properties of glia, it cannot tell us how glia interact with other cell types. Electrophysiological and calcium imaging studies using mammalian brain slices have begun to provide insight into both glia–neuron interaction and the role of glia in the activity of neuronal networks. Also, with advances in live imaging techniques, such as *in vivo* two-photon microscopy, glial activity and its correlation with blood flow and behaviour can be monitored in living animals. Studying small model organisms, including worms, fruitflies and fish, is another powerful approach that has allowed dissection of the role of glia in nervous-system function by means of genetic engineering.

### So what is left to learn about them?

Lots! Although the recent resurgence of interest in glia has led to many exciting and unexpected discoveries about the roles of these cells in the nervous system, such findings are almost certainly just the tip of the iceberg, and there are many outstanding questions. How exactly do glia participate in the formation and functioning of neuronal networks? Do glia have essential functions beyond supporting and interacting with neurons? What is the extent of astrocytic networks? How

crucial are these networks, and can they process information in the absence of neurons? How do glia contribute to disease, and might they be a potential target for drugs?

### Why the resurgence of interest?

A historical difficulty with studying glia has been the ‘neuro-centric’ view of the brain, implicit in the name of the discipline: neuroscience. Fortunately, there is a growing appreciation of the importance of other cell types in the nervous system and their symbiotic relationship with neurons, with no single cell type now being viewed as more important than the others. By examining how all of these cells work together, neurobiologists hope to make more rapid progress in understanding how the nervous system forms, functions, adapts and can be repaired. ■

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