

Emerging roles of glial cells in neuroscience

January 26 2016, by James Fink

When we think of the brain, we often think of the amazing things it is capable of—from conjuring up wild dreams to mastering foreign languages. At the same time, we may also think of devastating neurological diseases like Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis (ALS) that arise when different parts of the brain are disturbed. Underlying these processes and diseases are groups of cells, intricately connected to one another, and constantly communicating, like a large social network. Their goal is to update one another on the state of our brain, our body, and our environment. Historically, most neuroscience research has focused on the neuron, however, there are other important cell-types in the brain. These include astrocytes – cells known to support neurons and their environment, oligodendrocytes – cells that myelinate neurons and speed up the transmission of signals between them, a process that goes awry in Multiple Sclerosis, and microglia, which act as the immune cell of the brain, cleaning up debris and providing local surveillance in the nervous system. Although these cell types have generally been viewed as support cells, secondary to the neurons of the brain, research in the past decade has started to shine some new light on these underrated elements, suggesting that these other cells participate in a variety of complex processes important for proper brain function.

Astrocytes at the synapse

Though for most of their history they were thought to be strictly supportive of [neurons](#), providing a scaffold-like structure and aiding in the metabolism of extracellular substances, the role of astrocytes turns

out to be much broader and more complex. For one, astrocytes are intricately associated with the connections between neurons, termed synapses. At synapses, neurons are able to communicate with one another via the release of packets of chemicals, known as neurotransmitters, essentially integrating and processing information and allowing the brain to carry out its second to second functions. We now know that astrocytes are also able to participate in this communication directly via their own release of neurotransmitters, which can act on neurons at a given synapse. They may also uptake these neurotransmitters and metabolize them. The specific location of astrocytes near synaptic contacts combined with their ability to release neurotransmitters means that these cells are ideally positioned to "overhear" conversations between neurons and provide their own input, changing the conversation if need be.

Good evidence exists for this sort of role for astrocytes. A paper published in 2012 showed that astrocytes play a major role in a specific type of plasticity in the brain known as "spike-timing dependent synaptic plasticity". Specifically, it was shown that astrocytes are able to sense specific signals from neurons at the synapse, and then, via an increase in calcium within the astrocyte itself, release neurotransmitter back onto one of the neurons and control how much transmitter that neuron releases in the future. We can think of this process as a conversation whereby the astrocyte acts as a mutual friend moderating a conversation between two arguing friends (the two neurons at the synapse). In this way the astrocyte is able to control the conversation, toning it down or maybe even provoking the argument. Plasticity, a term used to describe changes in the strength of connections between neurons, is an important process in the brain and is thought to contribute to learning and memory. Therefore, astrocytes probably play an important role in these processes. In support of this, another recent study engrafted human glial progenitors into neonatal mice. This transplant resulted in better plasticity and improved learning in these animals, suggesting that

increased complexity of human astrocytes may contribute to more advanced information processing.

A 2016 paper published in *PLOS ONE* also aimed to investigate astrocyte involvement in learning and memory, though this study took a more indirect approach. In the study, Tadi et al. studied mRNA levels of molecules associated with metabolic coupling between astrocytes and neurons as well as molecules associated with astrocyte biochemical processes. By studying learning and memory in mice via a maze paradigm, the authors measured the levels of these pre-selected molecules in the hippocampi from these animals, an area of the brain associated with learning, memory, and spatial navigation. The authors found that, following learning, there was an upregulation of genes associated with neuron-astrocyte coupling. This evidence suggests that metabolic coupling between neurons and astrocytes is important for learning and memory.

Activity-dependent myelination

Oligodendrocytes are cells that form the fatty sheaths that cover axons of neurons passing through the brain. These sheaths are responsible for insulating the axon and speeding up the signals traveling down neuronal processes in the same way insulation surrounds wires associated with electrical appliances in our households. Each individual oligodendrocyte may have large numbers of processes extending from their cell body, each of which are capable of forming a myelin sheath. In this way, a single oligodendrocyte is capable of providing myelin to a lot of neurons. Moreover, these cells are abundant in the white matter of the brain, the underlying neural tissue filled with what is essentially intersecting highways of axons traveling to and from the brain. Also, oligodendrocytes and myelin are important for neuron survival. Loss of myelin can eventually lead to death and loss of axons in the brain, impairing communication between different brain areas. Similar to the

situation between astrocytes and neurons, it is now known that oligodendrocytes and neurons are also metabolically coupled, allowing these cells to exchange materials such as lactate and use this for ATP production. Such a role goes well beyond the original thoughts about oligodendrocyte function.

Oligodendrocyte precursor cells (OPCs), the immature versions of the oligodendrocyte, are also able to "listen in" on the conversations between neurons, gauging their activity. OPC involvement in this communication may help them remain poised to mature into myelinating oligodendrocytes and form sheaths around neurons in an activity-dependent manner. This means that if activity between neurons increases, oligodendrocytes may myelinate these neurons, improving the transmission of signals between them. There is also evidence that oligodendrocytes contribute to the conversation between neurons. A May 2015 paper in PLOS ONE suggests that OPCs are capable of producing "neuromodulatory factors". The evidence for this comes from looking at expression levels of neuromodulatory proteins prostaglandin D2 synthase and Pentraxin 2.

Synaptic Pruning

Microglia cells are another interesting cell type associated with the central nervous system. Traditionally involved with immune system-related surveillance as well as homeostatic processes, such as engulfing waste particles and other debris, the other roles of these [cells](#) have also been further investigated in the past decade. A new role for microglia is starting to emerge.

Early in brain development, neurons form an overabundance of connections or synapses—a scenario that may act as sort of an "anything is possible" wiring diagram of the brain. This large number of synapses may contribute to the ability to adjust to the unexpected environments

and circumstances we may be born into. As our brains begin to develop, taking in new information from our surroundings, this excessive connectivity has been shown to be "trimmed". Studies over the past two decades have indicated that microglia are highly active/motile in [brain](#) regions experiencing such "trimming", also known as "synaptic pruning". Moreover, microglia have also been observed making contact with synapses, specifically those that show diminished size, suggestive of an active process of synapse elimination.

The future of glia

Clearly, scientific understanding of glial cell function is drastically changing. The findings outlined in this post, combined with the hundreds of creative papers profiling new complex roles of [astrocytes](#), oligodendrocytes, and microglia paints a picture in which neuronal cross-talk is constantly under the influence of other [cell types](#). This picture makes it clear that understanding plasticity and neural information processing in detail will be a tall task. How will we be able to tease apart the role each cell is playing, especially when all of them are playing similar roles in the communication between neurons? Either way, this new era of glial cell biology is an exciting one, full of possibility for discovery.

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