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# Glial Biology in Learning and Cognition

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## Abstract

Neurons are exquisitely specialized for rapid electrical transmission of signals, but some properties of glial cells, which do not communicate with electrical impulses, are well suited for participating in complex cognitive functions requiring broad spatial integration and long-term temporal regulation. Astrocytes, microglia, and oligodendrocytes all have biological properties that could influence learning and cognition. Myelination by oligodendrocytes increases conduction velocity, affecting spike timing and oscillations in neuronal activity. Astrocytes can modulate synaptic transmission and may couple multiple neurons and synapses into functional assemblies. Microglia can remove synapses in an activity-dependent manner altering neural networks. Incorporating glia into a bicellular mechanism of nervous system function may help answer long-standing questions concerning the cellular mechanisms of learning and cognition.

## Keywords

memory, astrocyte, microglia, oligodendrocyte, myelin, synaptic plasticity, neuron–glia interactions

The cellular mechanisms of learning and memory remain obscure despite being one of the most intensely studied nervous system processes; part of the reason for this may be failure to adequately explore how non-neuronal cells in the brain (glia) may participate in these processes. Although electrical signaling is the backbone of brain function, neurons working alone seem to provide only a partial explanation for complex cognitive processes, especially those requiring broad temporal and spatial scales of integration. This was the consensus of a recent workshop held at the National Science Foundation in Arlington, Virginia, which assembled an international team of experts on learning and memory together with experts on glia.<sup>1</sup>

Glia do not generate electrical impulses, and as a consequence they are largely absent from thinking about how information is processed in the brain. Glial cells are regarded as support cells that maintain neurons in optimal condition, but rapidly accumulating evidence is provoking a re-examination of this presumption as being too narrow (Fields 2009). Glial cells far exceed neurons in cellular diversity, cell numbers, and functions, and they can regulate neuronal activity in many ways (Clarke and Barres 2013). However, because neuroscience developed historically from methods that monitor electrical signaling in brain cells, other forms of cell–cell communication in the brain have been relatively neglected. The objective of this recent workshop was to synthesize the latest information and consider whether incorporating glial biology

into the cellular mechanisms of learning and cognition may provide new avenues for research to help solve long-standing problems in these fields. This brief review article summarizes the consensus that a better understanding of the cellular basis of learning and cognition can develop from a shift toward considering information processing as a bicellular mechanism that incorporates glia.

It is well established that learning is highly dependent on states of arousal, attention, motivation, sleep cycle (Meltzoff and others 2009), and the prior history of experience (Hulme and others 2013). Also, new events must be coupled together with multimodal aspects of an experience and integrated with existing memories (Komorowski and others 2013). Thus, interactions within populations of neurons locally and across distant

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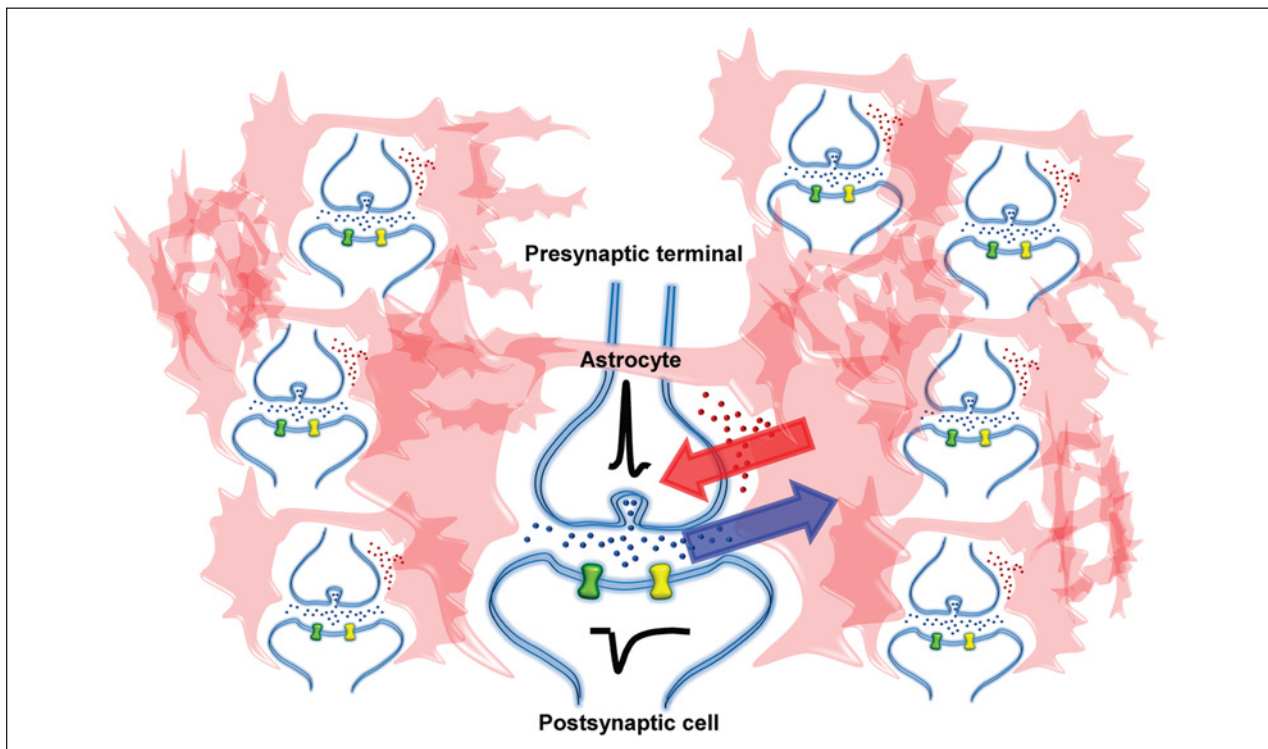
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**Figure 1.** A single astrocyte (pink) can ensheath tens of thousands of synapses; modulate synaptic transmission by the release (red arrow) and removal (blue arrow) of neurotransmitters and neuromodulatory substances, and by controlling ion concentration and modulating blood flow locally. Coupling of neurons into functional assemblies by astrocytes could increase information processing and implicates astroglia in complex cognitive function, such as perception and memory. Modified from Navarrete and Araque (2011).

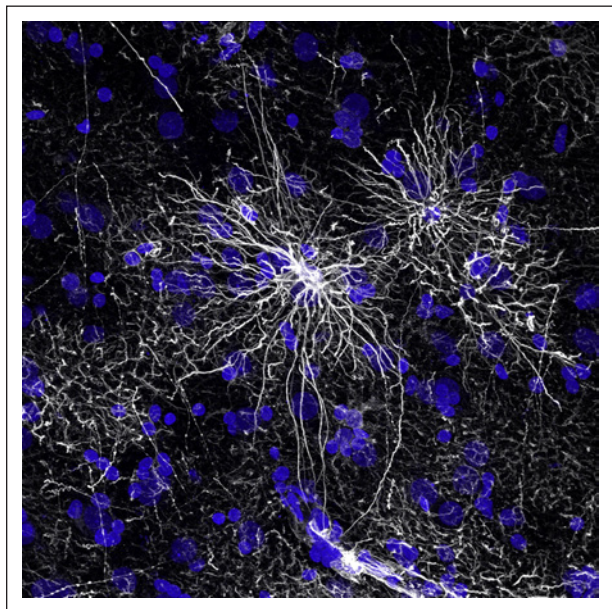
regions of the brain are essential in all but the most rudimentary forms of learning. Moreover, this broad spatial integration is achieved across exceedingly wide temporal scales ranging well beyond the millisecond to seconds of electrical signaling in neurons, to encompass instead hours, days and months, which are well suited to the temporal dynamics of glial communication and plasticity.

### Connecting All the Parts: Glia in Spatial Integration

All types of glia can respond to and influence neurotransmission in several ways. The three major glial cell types in the brain, astrocytes, oligodendrocytes and microglia, communicate with each other and with neurons by using neurotransmitters, other small molecules, and gap junctions. Oligodendrocytes greatly increase the speed of electrical transmission through nerve axons by forming the axonal myelin sheath and clustering ion channels at nodes of Ranvier where action potentials are generated (Nave 2010). Microglia prune synapses in part by monitoring synaptic transmission (Wake and others 2013), thus they rewire neural connections in accordance with

neuronal function (Schafer and others 2012). Astrocytes can regulate synaptic transmission between neurons by modifying the concentration of extracellular potassium, controlling local blood flow, releasing and taking up neurotransmitters and other neuromodulatory substances, delivering nutrients to neurons, and altering the geometry and volume of extracellular space between brain cells; all of these could coordinately couple neurons into functional assemblages.

The large spatial domain over which astrocytes and oligodendrocytes can couple and regulate neuronal activity is at odds with traditional thinking of learning where synapse-specific modification is paramount. Restricting plasticity mechanisms to individual synaptic connections is thought to increase the capacity for information storage and learning, but global changes may help organize the memory, and in a combinatorial manner increase storage capacity. If astrocytes modulate synaptic strength and couple domains of synapses into functional assemblies, the degrees of freedom for information storage are multiplied beyond synapse-specific coding (Fig. 1). Astrocytes do have anatomical and physiological properties that may impose a higher order organization on information processing in the brain. The volume of human astrocytes is



**Figure 2.** Astrocytes from human cerebral cortex can be distinguished from those of mice by the increased complexity of branching and much larger size (proportionately) that enables human astrocytes to interact with up to 2 million synapses across multiple cortical layers. Courtesy of Nancy Ann Oberheim, Takahiro Takano, and Maiken Nedergaard, University of Rochester, New York.

almost 20-fold larger than their rodent counterparts, enabling human astrocytes to integrate input from a comparably staggering number of synapses (~2M compared with 0.1M in rodent brain) (Oberheim and others 2006) (Fig. 2). Curiously in the gray matter regions of cerebral cortex and hippocampus, astrocytes are organized in non-overlapping domains (Bushong and others 2002); the significance of this tile-like organization is completely unknown.

Similar large-scale changes, as opposed to point-to-point changes in neuronal synaptic connections, may also participate in other aspects of information processing and cognition that are not currently understood from a strictly neuronal perspective. For example, when we see an object against a background, our visual system assigns the inside and outside of the bounding edges separating the figure from the ground (Fig. 3). This is a difficult computational problem in computer vision because it involves global information that cannot be decided locally (Zucker 2012). How does the brain do this? Although the importance of astrocytic domains is far from being fully understood, astrocytes in a receptor-mediated pathway can modulate extracellular  $K^+$  and regulate neuronal spiking activity (Wang and others 2012). A single astrocyte, acting via purines, produce an UP state (persistent depolarization resulting in high-frequency firing) in a sizable population



**Figure 3.** Figure-ground illusions, as in this Raven-Bear drawing illustrate how border regions become grouped together with the object that is perceived, even as the figure and ground reverse in such illusions. This assignment of neuronal activity at borders in conjunction with the figure that is perceived requires rapid global analysis of the entire scene. Such global analysis and coupling of large domains of neurons is difficult to explain using neuromodeling of synapse-specific plasticity and connectivity. The large spatial domain of astrocytes coordinately regulating hundreds or thousands of synapses and neurons simultaneously, could contribute to complex cognitive operations required for analysis of global features for perception and other types of large-scale analysis. The raven-bear logo is reprinted with permission of Alaska Geographic.

of neighboring neurons (Poskanzer and Yuste 2011). Effects of this kind working in conjunction with synaptic plasticity could create neuronal clusters that become associated with particular input signals. Computer simulations of molecular diffusion in the neuropil show that astrocytes are highly effective in limiting the spread of glutamate released at synapses. This same approach could be used to explore the modulation of synaptic activity by glial regulation of extracellular  $K^+$  (Kinney and others 2013).

## Glia in Learning and Memory

Glia can affect both the encoding and consolidation of memory. Activation of intracellular  $Ca^{2+}$  signaling in astrocytes can augment or suppress both excitatory and inhibitory synaptic transmission and influence state dependent changes in cortical activity during, for example, sleep (Halassa and others 2009) and working memory. Recent evidence obtained *in situ* and *in vivo* has shown that astrocytic signaling participates in some

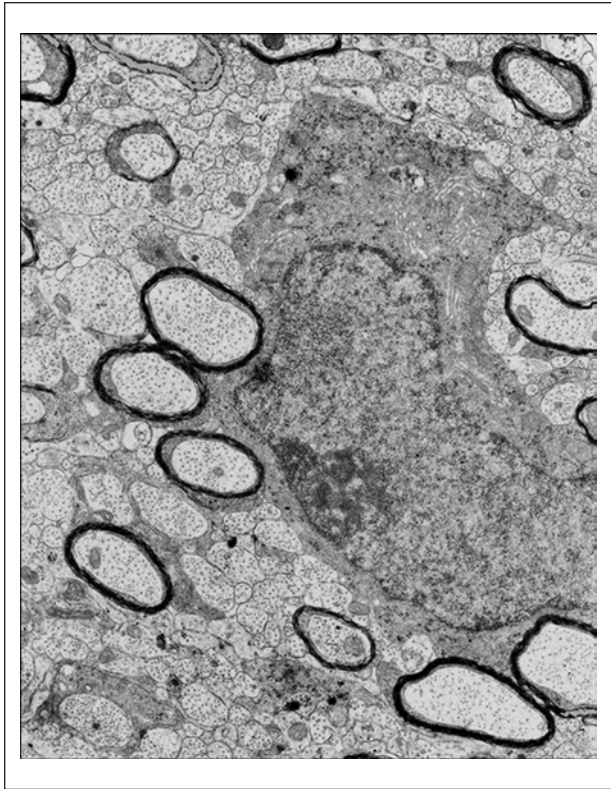


forms of synaptic plasticity (i.e., cholinergic-induced long-term potentiation (LTP) in cortex and hippocampus (Navarrete and others 2012); spike-timing dependent cortical plasticity, hippocampal long-term depression (LTD) and working memory (Han and others 2012)). Transient disruption of the flow of energy substrates from astrocytes to neurons has little effect on learning but severely impairs the later formation of long term memory (Suzuki and others 2011). Astrocytes associated with blood vessels shuttle ions and energy substrates between neurons and the blood stream and regulate local blood flow, which in turn modulates neuronal function (Moore and Cao 2008). Moreover, microglia, oligodendrocytes, and astroglia are primary sources for extracellular matrix components now thought to play critical roles in late stages of LTP and memory consolidation (Babayán and others 2012). Recently, humanized chimeric mice, in which a large proportion of mouse astrocytes were replaced with human astrocytes, were found to exhibit increased synaptic plasticity and faster learning (Han and others 2013).

### The Importance of Timing

The temporal coincidence in firing of multiple inputs converging onto a neuron is fundamental to most rules of learning and synaptic plasticity. Thus the physiological mechanisms underlying learning will be strongly influenced by conduction delays. Similarly, oscillations and waves of neuronal activity link neuronal firing in phase-locked mode with other neurons and such oscillatory activity during sleep is important in memory consolidation (Buzsáki 2006). Astrocytes influence neuronal membrane potential and excitatory and inhibitory synaptic transmission underlying neural oscillations locally, and oligodendrocytes provide rapid impulse propagation for long-range oscillations and synchrony of spike time arrival between distant populations of neurons.

Myelination of axons by oligodendrocytes (Fig. 4) enables saltatory conduction between nodes of Ranvier, which greatly increases the speed of impulse propagation. Accumulating evidence indicates several forms of activity-dependent signaling between axons and myelinating glia that control myelination of specific axons (Wake and others 2011; Fields 2013), suggesting a hitherto unexplored mechanism of experience-dependent plasticity and learning (Fields 2008). The consequences of altering conduction velocity by myelin plasticity has been modeled recently and the results indicate profound effects on neural network function would result in terms of spike time arrival, oscillation frequency, phase coupling, and brain wave propagation (Pajević and others 2013). Recent data from human brain imaging by MRI, notably using diffusion tensor imaging, has revealed structural changes in myelinated tracts after learning a wide range of tasks

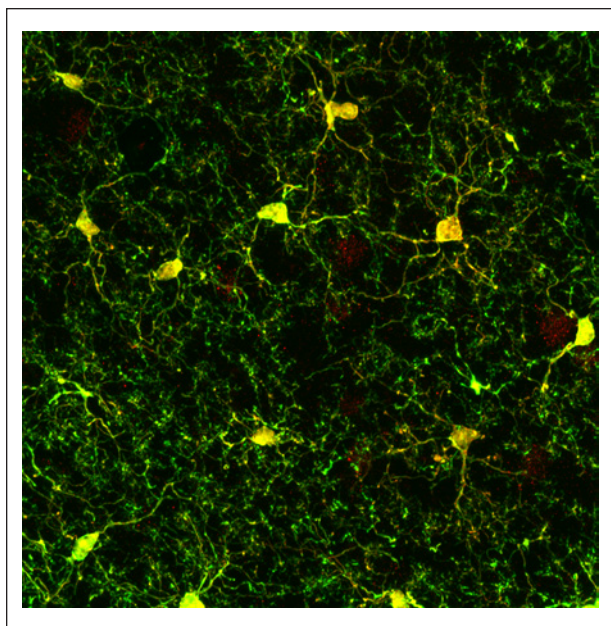


**Figure 4.** The layers of myelin formed around axons by oligodendrocytes greatly increase the velocity of impulse conduction. The formation of myelin is influenced by impulse activity in axons, which would alter information processing greatly as a consequence of changes in spike time arrival and oscillations of neural activity. Shown here is a cross section of an optic nerve during development with several axons undergoing myelination by an oligodendrocyte, which can be distinguished by the dark cytoplasm. Courtesy of Wiebke Moebius and Klaus Armin-Nave, Max-Planck Institute, Göttingen.

(Zatorre and others 2012). The cellular basis of these changes in white matter is being investigated, but present evidence supports some contribution by glia (astrocytes and myelin).

### Adult Neurogenesis

Adult neurogenesis is influenced by environmental experience (Glasper and others 2012), and contributes to memory formation (Sahay and others 2011), but adult gliogenesis has received much less attention. Astrocytes produce growth factors that modulate neural stem cell differentiation (Barkho and others 2006), and thus regulate neurogenesis. Oligodendrocyte progenitor cells (NG2 cells) are the largest population of dividing cells in the adult brain, suggesting a possible role in myelination in the adult brain (Young and others 2013) that could contribute to optimal information processing.



**Figure 5.** Microglia in the hippocampal region. In addition to their immunological role, microglia participate in activity-dependent remodeling of synaptic connections. Courtesy of Lindsay De Biase and Antonello Bonci, National Institute on Drug Abuse, Baltimore, Maryland.

## Future Challenges

Current knowledge about astrocytes, oligodendrocytes, and microglia and their dynamic changes is rudimentary in comparison to neurons, and little effort has been made to include glia into realistic computational modeling. Computational models that consider activity-dependent changes in the timing of intercellular communication (such as provided by myelination) need to be developed and incorporated together with the broad spatial and temporal dynamic interactions between networks of astrocytes and neurons. Because neuroscience developed from a focus on electrical signaling in neurons, both conceptual and technical advances are necessary to understand the function of glia in learning and cognition. A potential route toward accelerating progress in this field emerged from the meeting: rather than relying on indirect measurements performed in neurons to ascertain glial function, cell biological approaches to directly assess the chemical signals of glia will likely benefit research.

Viewing the cellular basis of brain function as bicellular rather than monocellular may bring a new understanding of brain function, broadening without undermining current understanding. In many respects glia are far more complex than neurons and difficult to study. Adult neurons do not divide, differentiate, migrate, or engage in such a wide range of multitasking roles as glia.

Microglial involvement in activity-dependent synaptic pruning (Tremblay and others 2010) illustrates this difficulty, because their immune system function provokes numerous cellular changes that engage these cells in circuit remodeling by releasing cytokines, reactive oxygen species, growth factors, enzymes and other substances when the brain is exposed for an experiment (Fig. 5). Such multitasking responses in glia can perturb the processes being measured. It is this complexity of glial biology, however, that likely contributes much of the intriguing complexity evident in learning and cognition in the human brain.

## Declaration of Conflicting Interests

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