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Neuroscience. To Learn is to Myelinate

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The adult mammalian brain requires the production of new glial cells and myelin for learning

Learning triggers neuronal changes in the brain that contribute to information acquisition and memory formation, including the activity and strength of existing synapses, the formation of new synapses, and possibly the birth of new neurons (1). Therefore, it is not surprising that neurons have been seen as the sole components of the nervous system, capable of responding to experience and responsible for learning and long-term behavioral plasticity. However, this notion is being challenged by recent findings on glial biology. On page 318 of this issue, McKenzie et al. (2) add to this argument by revealing that the generation of new oligodendrocytes—one of the brain's non-neuronal cell types—is required for learning a complex motor skill. The finding advances our understanding of brain plasticity and points to roles for glia and myelin in cognitive function.

Oligodendrocytes generate myelin, the insulating membrane that covers many neuronal axons and facilitates the propagation of electrical signals along neuronal circuits. Although oligodendrocytes and the myelin they create were assumed to be static, recent studies indicate that myelin is much more malleable than once thought. Imaging studies have shown that various forms of learning correlate with structural changes in the human brain's white matter, and animal studies have demonstrated oligodendrocyte and myelin changes in response to social and environmental conditions (3). These observations raise the possibility that myelin is highly dynamic and that changes in myelination are important components of brain plasticity.

Oligodendrocytes send out multiple cellular processes that attach and ensheath axons with concentric layers of compacted cellular membrane to form myelin (see the figure). Myelination increases the speed by which electrical impulses travel along neuronal processes, and differences in the degree to which axons are myelinated affect the timing of the flow of information between neurons. The composition of myelinated axons in the brain is heterogeneous; axons may be highly myelinated, not myelinated, or incompletely myelinated, and the pattern of myelination may vary along a single axon (4). Most myelination in the mammalian brain occurs during early life. At that stage, oligodendrocyte progenitor cells (OPCs) give rise to oligodendrocytes, which go on to myelinate axons as they mature. Remarkably, a high density of OPCs remains in the adult brain long after the developmental period of myelination is complete. Adult OPCs retain the capacity to differentiate into myelinating oligodendrocytes in response to injury or demyelinating

diseases, such as multiple sclerosis (5). These precursor cells may also give rise to newly generated oligodendrocytes to remodel myelin along previously myelinated axons in the adult brain (6). Yet, the potential functional importance of this apparent reservoir of undifferentiated cells for plasticity in the normal brain has been a mystery. McKenzie et al. sought to determine whether adult-born oligodendrocytes are necessary for learning to occur. They observed that young adult mice that learn to run on a “complex running wheel” with irregularly spaced rungs have a transient elevation in OPC proliferation and production of adult-born oligodendrocytes in the corpus callosum, an axodense area of the brain connecting the two cerebral hemispheres. To analyze the contribution of new oligodendrocyte formation to motor learning, the authors used genetically modified mice in which they had eliminated the ability of OPCs to make new oligodendrocytes without affecting preexisting oligodendrocytes or myelin. They achieved this by inactivating the myelin regulatory factor (*Myrf*) gene in adult OPCs. *Myrf* encodes a protein required for OPCs to differentiate into mature myelinating oligodendrocytes. McKenzie et al. discovered that mice lacking the capacity to form new oligodendrocytes also failed to develop an effective running strategy in the complex running wheel. By contrast, when mice were allowed to train on the complex running wheel before *Myrf* inactivation, they performed comparably to normal control mice. This indicates that although the production of new oligodendrocytes is not required for information retrieval, it is critical for learning new motor behavior.

How is learning linked to changes in myelination? OPCs express numerous receptors that make them responsive to neurotransmitters. OPCs can also respond to neuron-derived mitogens and trophic factors such as neuregulin-1 (*NRG1*) and brain-derived neurotrophic factor (*BDNF*), whose release is modulated by neuronal activity. Interestingly, cell-culture experiments have shown that *NRG1* and *BDNF* influence whether neuronal activity stimulates myelination (7). In vivo optogenetics studies have also shown that elevated neuronal activity increases OPC proliferation and oligodendrocyte number in an area of the brain involved in motor learning in vivo (8). Accordingly, neuronal circuits that are preferentially recruited during learning may signal to adjacent OPCs to differentiate into myelinating oligodendrocytes. This could lead to increased strength of connectivity and efficiency of information flow along circuits as a new motor behavioral pattern emerges. Thus, it is possible that activity-dependent myelination might be toggled on and off under different physiological contexts.

How might differences in myelin generation affect cognitive function more generally? And is myelin plasticity a universal aspect of learning or is it confined to systems involved exclusively in adaptive motor behaviors? The answers to these questions have broad implications for the understanding of how cognitive function is influenced by conditions that affect myelin. Several psychiatric illnesses, such as schizophrenia and bipolar disorder, are associated with defects in myelin (9). Moreover, myelin appears to be particularly vulnerable to adverse life experiences, such as social isolation (10, 11). The discovery that new myelin generation is essential for learning may help explain some of the cognitive disturbances associated with psychiatric disorders or the absence of strong social support. Furthermore, the efficiency with which OPCs differentiate into myelinating

oligodendrocytes appears to decrease with age (12), raising questions about how changes in myelin plasticity might contribute to age-associated cognitive decline.

The evidence that glia can be influenced by experience, and that this process is essential for behavioral changes and cognition, has brought us to an exciting paradigm shift that opens up a new vast frontier that might help to explain the mechanisms of learning. This may bring us closer to developing new treatments for neurological and neuropsychiatric disorders.

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