



To learn is to myelinatePatrick Long and Gabriel Corfas *Science* **346**, 298 (2014); DOI: 10.1126/science.1261127

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tion could, in essence, ban DTC genetic testing as we have known it in Europe. Whether a website providing information regarding a genetic test is advertisement per se, or simply informational, may be debatable.

These articles in the proposed regulation are likely to strengthen the trend of DTC companies incorporating physicians into their model of test provision, as well as redirecting their advertising efforts (including continuing medical education) to health care professionals. This may present problems related to impartiality similar to those observed with prescription drugs, especially when clinicians are recruited, trained by, and often remunerated by the companies selling the services (12).

Inclusion of a health care professional, even a clinical geneticist, does not necessarily safeguard against all the concerns

"If the proposed regulation is approved, it is not obvious that crossing the Atlantic will make it easier for companies."

surrounding scientific validity or clinical validity raised by the proposed regulation and the FDA. Given the speeds at which new tests are being developed and at which new technologies allow for genotyping and sequencing, it is unreasonable to expect that simply adding a medical professional will solve all problems raised by DTC genetic testing. Not only are such professionals not currently prepared to interpret all genetic tests offered by DTC companies, but their involvement does not necessarily assure that tests offered will have appropriate quality and/or benefit to the users.

Although a decision of the Council of the EU was originally planned before the May 2014 European elections, only a June 2014 meeting providing guidance for future work has taken place (13), with further debates and negotiations to follow. If the proposed IVD regulation is accepted by the Council, it will clearly affect the way genetic testing is being offered beyond the clinic. It will also potentially affect the clinicians who will be sought by consumers for genetic testing prescriptions. The future of European DTC genetic testing companies-and of non-European companies in the EU marketmay also be heavily affected by coming policy decisions. For example, companies may want to broaden their sales outside the United States into foreign markets, in order to circumvent FDA demands. This was showcased recently when 23andMe announced it would resume selling its Personal Genome Service in Canada (14). If the proposed regulation is approved, it is not obvious that crossing the Atlantic will make it easier for companies (15). ■

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NEUROSCIENCE

To learn is to myelinate

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

By Patrick Long and Gabriel Corfas

earning 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 precur-

sor cells may also give rise to newly generated oligodendrocytes to remodel myelin along previously myelinated axons in the adult brain (6).

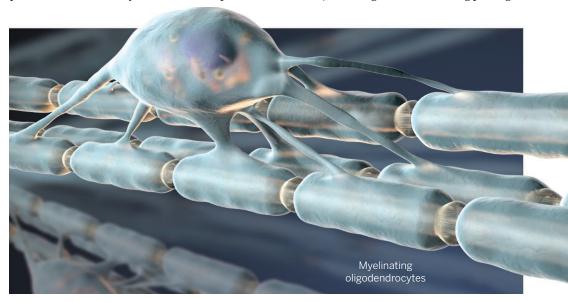
Yet, the potential functional importance of this apparent reservoir of undifferentiated cells for plasticity in the normal brain has been a mystery. McKenzie et al. sought to determine whether adult-born oligodendrocytes are necessary for learning to occur. They observed that young adult mice that learn 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 axondense area of the brain con-

necting 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

elin. 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



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 my-

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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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