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Change in the Brain's White Matter:

The role of the brain's white matter in active learning and memory may be underestimated

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"Gray matter" is only one of two types of brain tissue; the other "white matter" is rarely mentioned. Yet white matter makes up half the human brain and has not been thought to be important in cognition or learning outside the context of pathology. That view could change. Imaging and cellular and molecular studies are revealing white matter plasticity with possible implications for normal cognitive function and psychological disorders.

White matter, which lies beneath the gray matter cortex, is composed of millions of bundles of axons (nerve fibers) that connect neurons in different brain regions into functional circuits. The white color derives from the electrical insulation (myelin) that coats axons (see the figure). It is formed by nonneuronal cells, oligodendrocytes, which wrap up to 150 layers of tightly compressed cell membrane around axons. Myelin is essential for high-speed transmission of electrical impulses, and its damage can impair conduction and consequently, sensory, motor, and cognitive functions. The human brain continues to undergo myelination until at least the third decade of age, and the frontal regions of the cerebral cortex, which carry out higher-level executive functions, are the last to become myelinated.

Learning involves changes in strength of synapses, the connections between neurons in gray matter. But human brain imaging using magnetic resonance imaging (MRI) has revealed structural changes in white matter after learning complex tasks. This raises the question of whether white matter responds to experience in a manner that affects neuron function under normal circumstances, thereby affecting information processing and performance. There are a few intriguing observations related to this possibility. For example, structural changes in white matter correlate with the number of hours a professional musician practices (1). The greatest changes were seen in parts of the brain that were not yet fully myelinated. Similarly, adult subjects showed increased white matter structural organization in a brain region important for visuo-motor control 6 week after learning to juggle (2). And in a study of adults learning to read, the volume, anatomical organization, and functional connectivity of white matter tracts linking cortical regions important for reading were increased (3). Whether these changes in white matter structure affect neuron function directly by altering transmission of information required for acquiring a skill is not clear. However, the observations do show that learning a new skill is associated with altered white matter structure in the mature brain.

Histological studies on experimental animals should clarify whether the white matter changes seen by MRI after learning are caused by myelination of unmyelinated axons, increased thickness of myelin on axons that are already myelinated, alterations in axon caliber, branching, or crossing, or other cellular changes. MRI analyses of Japanese macaques have shown, for example, large structural changes in white matter in the cerebellum after training them to use a rake to retrieve a food reward (4). The extent of change correlated with the speed of learning the skill. Studies on rats raised in enriched environments that provide social interaction and novel objects for exploration revealed

robust cellular changes in gray and white matter that include vascular tissue, glia, neurons, and increased myelination (5). Whether myelin has a primary role in the increased information processing in such animal models should be further explored, as observations such as those in the rat-environment studies may have implications for understanding brain development during early childhood experience.

It is unclear whether experiences regulate myelination into adulthood. The size of the corpus callosum brain region increased by 10% in adult rats that were placed in an enriched environment for several months, but this was caused by an increased volume of another type of glial cell (astrocytes) as well as unmyelinated axons, possibly as a result of axon sprouting (6). The same treatment increased the volume of myelinated axons in the corpus callosum of juvenile animals. Thus, more axons appear to become myelinated as a result of experience during the developmental period when myelination is most active. Still, 29% of myelin-forming oligodendrocytes in adult mice develop from oligodendrocyte progenitor cells (OPCs) after sexual maturity (7). Perhaps this supply is generated for repair or possibly for myelination associated with learning. Interestingly, the cell division cycle of OPCs increases by 8 hours for every day of age from birth (8), indicating that the ability to form new oligodendrocytes decreases with age. This parallels the normal decline in human cognition and decrease in white matter volume after the age of 50 (9).

One of the largest categories of genes whose expression changes during sleep includes genes that control oligdendrocyte development and myelination (10). The reason for this is unclear, but sleep is linked to consolidating memory. Mutations in oligodendrocyte genes have been identified as possible risk factors for depression and schizophrenia (11), and disruption of specific genes in mouse oligodendrocytes correlates with behavioral changes resembling schizophrenia in humans (12). Mental disorders are currently understood to be disorders of synaptic transmission, but oligodendrocytes could perhaps contribute to aberrations in transmission.

How do oligodendrocytes know which axons are electrically active? Can impulse activity affect myelination? Three mechanisms have been identified that regulate myelination or the development of myelin-forming glia in response to electrical stimulation of axons in vitro. Specific frequencies of electrical impulses control the amount of L1 CAM present on unmyelinated axons, a cell adhesion molecule that is necessary for myelination (13). The neurotransmitter adenosine 5′-triphosphate (ATP) is released from axons and activates receptors on astrocytes, causing them to release a cytokine (leukemia inhibitory factor) that stimulates myelination by mature oligodendrocytes (14). Adenosine derived from hydrolysis of released ATP promotes OPC development and thus increases myelination (15). Although synapses have been detected on OPCs, raising speculation that synaptic communication could stimulate myelination, neuron-OPC synapses are lost as OPCs mature to a premyelinating stage (16). Also, a nonsynaptic mechanism for ATP release from axons has been identified (17).

White matter is essential for impulse conduction, and so the concept of white matter plasticity widens the scope of investigation beyond the synapse in considering transmission of information through neural networks that are critical for learning complex skills and higher-level cognitive function in the absence of pathology. Perhaps white matter differences that correlate with scoring on intelligence quotient tests (18) and certain psychiatric conditions (11) can be attributed in part to a direct role for white matter in learning and cognitive function. But much work needs to be done to explore these interesting possibilities. This includes determining the nature of the white matter structural changes observed and assessing whether these changes affect electrical impulse transmission and/or synchrony of neuronal firing in a manner that affects information processing.

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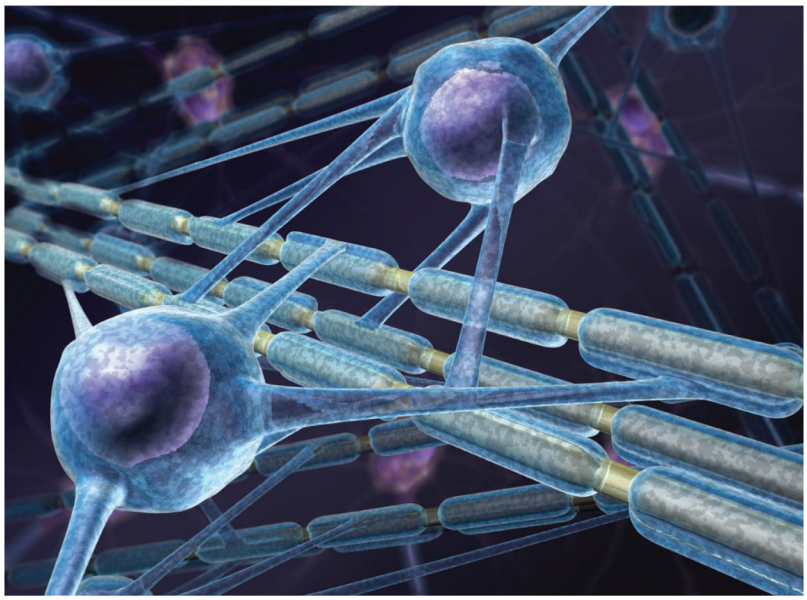

1. . White matter

Myelin that coats and insulates neuronal axons may control the propagation of electrical impulses in a manner that affects information processing.