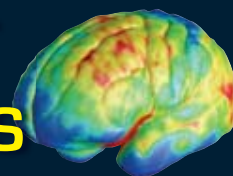


Why Prediction Markets Beat Political Polls (*page 38*)

SCIENTIFIC AMERICAN

Brain Power
**BEYOND
NEURONS**

page 54



March 2008

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The End of Cosmology

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is disappearing as the
universe expands

Space Wars

How Weapons in Orbit
Put the Earth at Risk

Quantum Computers

Problems That Even
They Can't Solve

Bluefin Tuna

Are We Eating These
Fish to Extinction?



White Matter

Although scientists have long regarded the brain's white matter as passive infrastructure, new work shows that it actively affects learning and mental illness • • • **By R. Douglas Fields**

KEY CONCEPTS

- White matter, long thought to be passive tissue, actively affects how the brain learns and dysfunctions.
- Although gray matter (composed of neurons) does the brain's thinking and calculating, white matter (composed of myelin-coated axons) controls the signals that neurons share, coordinating how well brain regions work together.
- A new type of magnetic resonance technology, called diffusion tensor imaging (DTI), has for the first time shown white matter in action, revealing its underappreciated role.
- Myelin is only partially formed at birth and gradually develops in different regions throughout our 20s. The timing of growth and degree of completion can affect learning, self-control (and why teenagers may lack it), and mental illnesses such as schizophrenia, autism and even pathological lying.

—The Editors

Imagine if we could peek through the skull to see what makes one brain smarter than another. Or to discover whether hidden traits might be driving a person's schizophrenia or dyslexia. A new kind of imaging technique is helping scientists observe such evidence, and it is revealing a surprise: intelligence, and a variety of mental syndromes, may be influenced by tracts within the brain made exclusively of white matter.

Gray matter, the stuff between your ears your teachers chided you about, is where mental computation takes place and memories are stored. This cortex is the "topsoil" of the brain; it is composed of densely packed neuronal cell bodies—the decision-making parts of nerve cells, or neurons. Underneath it, however, is a bedrock of "white matter" that fills nearly half of the human brain—a far larger percentage than found in the brains of other animals. White matter is composed of millions of communications cables, each one containing a long, individual wire, or axon, coated with a white, fatty substance called myelin. Like the trunk lines that connect telephones in different parts of a country, this white cabling connects neurons in one region of the brain with those in other regions.

For decades neuroscientists exhibited little interest in white matter. They considered the myelin to be mere insulation and the cables inside it little more than passive passageways. Theories about learning, memory and psychiatric disorders centered on molecular action inside the neurons and at the famous synapses—the tiny contact points between them. But sci-

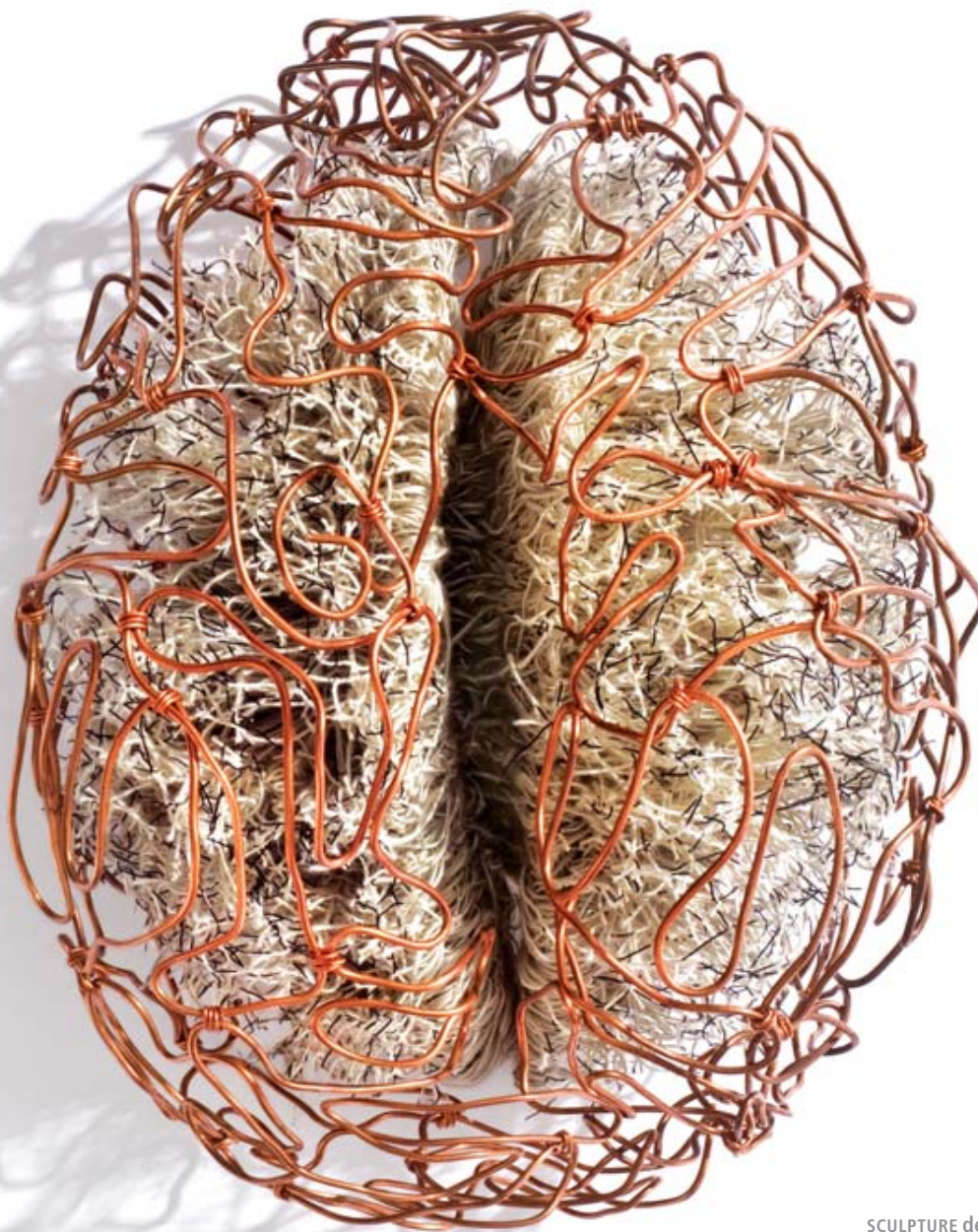
entists are now realizing that we have underestimated the importance of white matter in the proper transfer of information among brain regions. New studies show that the extent of white matter varies in people who have different mental experiences or who have certain dysfunctions. It also changes within one person's brain as he or she learns or practices a skill such as playing the piano. Even though the neurons in gray matter execute mental and physical activities, the functioning of white matter may be just as critical to how people master mental and social skills, as well as to why it is hard for old dogs to learn new tricks.

More with Mastery

The myelin that gives white matter its color has always posed mysteries. For more than a century scientists looked at neurons through their microscopes and saw long fibers, the axons, extending from a neuronal cell body to a neighboring one, like an outstretched, elongated finger. Each axon was found to be coated with a thick crystalline gel. Anatomists surmised that the fatty covering must insulate axons like rubber sheathing along a copper wire. Strangely, however, many axons, especially the smaller filaments, were not coated at all. And even along insulated fibers, gaps in the insulation appeared every millimeter or so. The bare spots came to be known as nodes of Ranvier, after French anatomist Louis-Antoine Ranvier, who first described them.

Modern investigation has revealed that nerve impulses race down axons on the order of 100 times faster when they are coated with myelin—

Matters



SCULPTURE BY MARGIE McDONALD, PHOTOGRAPHED BY FRANK ROSS

SCULPTURE depicts overhead view of brain's cortex (*copper*) and white matter core.

and that myelin is laid on axons somewhat like electrical tape, wrapped up to 150 times between every node. The substance is manufactured in sheets by two types of glial cells. These cells are not neurons, but they are prevalent in the brain and nervous system [see “The Other Half of the Brain,” by R. Douglas Fields; *SCIENTIFIC AMERICAN*, April 2004]. An octopus-shaped glial cell called an oligodendrocyte does the wrapping. Electrical signals, unable to leak out through the sheath, jump swiftly down the axon from node to node. In nerves outside the brain and spinal cord, a sausage-shaped glial cell called a Schwann cell forms myelin.

Without myelin, the signal leaks and dissipates. For maximum conduction velocity, the insulation thickness must be strictly proportional to the diameter of the fiber inside. The optimal ratio of bare axon diameter divided by the total fiber diameter (including the myelin) is 0.6. We have no idea how oligodendrocytes

Myelin is laid down until age 25 or so, one reason teenagers do not have adult decision-making abilities.

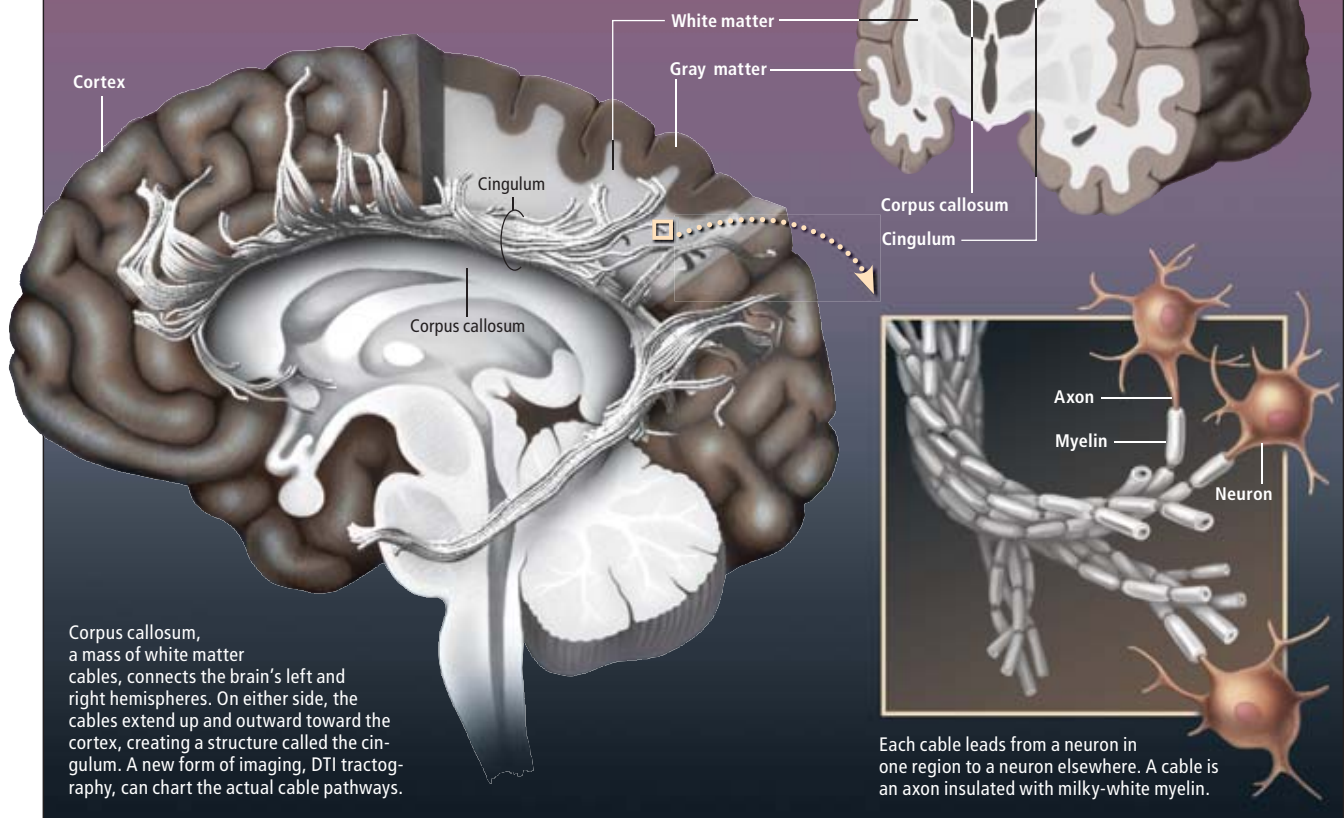
“know” whether 10 or 100 layers of insulation are required to create the proper thickness on axons of different diameters. But recently biologist Klaus-Armin Nave of the Max Planck Institute for Experimental Medicine in Göttingen, Germany, discovered that Schwann cells detect a protein called neuregulin that coats axons, and if the amount of this protein is augmented or inhibited, the Schwann cell will wrap more or fewer sheets of myelin around the axon. Interestingly, many people who suffer bipolar disorder or schizophrenia have a defect in the gene that regulates production of this protein.

The wrapping occurs at different ages. Myelin is prevalent only in a few brain regions at birth, expands in spurts and is not fully laid until age 25 or 30 in certain places. Myelination generally proceeds in a wave from the back of the cerebral cortex (shirt collar) to its front (forehead) as we grow into adulthood. The frontal lobes are the last places where myelina-

[BASICS]

WHAT IS WHITE MATTER?

White matter fills nearly half the brain. It consists of millions of cables (*white*) that connect individual neurons (*gray matter*) in different brain regions, like trunk lines connecting telephones across a country.



JEN CHRISTIANSEN (illustration); DEREK JONES/Cardiff University (cingulum tractography)

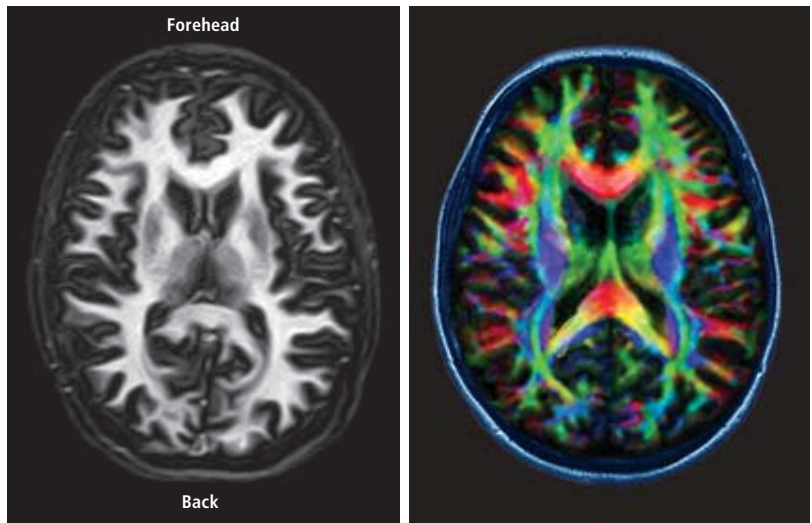
CONVENTIONAL MRI machine (top) can roughly depict white matter (bottom left, white areas). But a new MRI process called DTI shows structure in greater detail (bottom right); red and yellow indicate more highly organized white matter.

tion occurs. These regions are responsible for higher-level reasoning, planning and judgment—skills that only come with experience. Researchers have speculated that skimpy fore-brain myelin is one reason that teenagers do not have adult decision-making abilities. Such observations suggest that myelin is important to intelligence.

Presumably the brain does not finish wrapping human axons until early adulthood because, throughout that time, axons continue to grow, gain new branches and trim others in response to experience. Once axons are myelinated, the changes they can undergo become more limited. Still, for a long time a question remained: Is myelin formation totally programmed, or do our life experiences alter the degree of wrapping and thus how well we learn? Does myelin actually build cognitive ability, or is cognition simply limited in regions where it has not yet formed?

Piano virtuoso Fredrik Ullén decided to find out. Ullén also happens to be an associate professor at the Stockholm Brain Institute in Sweden. In 2005 he and his colleagues used a new brain-scanning technology called diffusion tensor imaging (DTI) to investigate the brains of professional pianists. DTI is done with the same kind of magnetic resonance imaging machines found in hospitals but involves a different type of magnetic field and different algorithms to create the many brain-image slices that are assembled into a three-dimensional picture. The slices display the vectors (mathematically defined as tensors) of water that diffuses in tissue. In gray matter the DTI signals are low because water diffuses symmetrically. But water diffuses asymmetrically along bundles of axons; this irregular pattern illuminates white matter, exposing the major highways of information that flow among brain regions. The more tightly packed and heavily coated with myelin the fibers are, the stronger the DTI signal.

Ullén found that in professional pianists, certain white matter regions are more highly developed than in nonmusicians. These regions connect parts of the cerebral cortex that are crucial to coordinated movement of the fingers with areas involving other cognitive processes that operate when making music.



He also found that the more hours a day a musician had practiced over time, the stronger the DTI signals were in these white matter tracts; the axons were more heavily myelinated or tightly packed. Of course, the axons could simply have expanded, requiring more myelin to maintain the optimal 0.6 ratio. Without performing an autopsy, the question remains open. The discovery is important, however, because it shows that when learning a complex skill, noticeable changes occur in white matter—a brain structure that contains no neuronal cell bodies or synapses, only axons and glia. Studies on animals, in which brains can be physically examined, show myelin can change in response to mental experience and a creature's developmental environment. Recently neurobiologist William T. Greenough of the University of Illinois at Urbana-Champaign confirmed that rats raised in “enriched” environments (with access to abundant toys and social interaction) had more myelinated fibers in the corpus callosum—the hefty bundle of axons that connects the brain's two hemispheres.

[THE AUTHOR]



R. Douglas Fields is chief of the Nervous System Development and Plasticity Section at the National Institute of Child Health and Human Development. He has written several articles for *Scientific American*, most recently in the August 2007 issue on how sharks zero in on prey by sensing extremely weak electrical fields emitted by fish.

COURTESY OF R. DOUGLAS FIELDS (Fields); PHILIPS HEALTHCARE (machine); ZEPHYR/PHOTO RESEARCHERS, INC. (color scan); JOE GALLIVAN/Ulster Medical and Surgical Specialists (black-and-white scan)

KNOWN DISEASES

Faulty or missing myelin in the central nervous system can cause several debilitating diseases, including:

MULTIPLE SCLEROSIS
(degeneration of central nervous system)

CEREBRAL PALSY
(severely impaired muscle control)

ALEXANDER DISEASE
(destruction of central nervous system)

These results seem to jibe with DTI studies performed by neuroscientist Vincent J. Schmithorst of Cincinnati Children's Hospital, which compared white matter in children ages five to 18. A higher development of white matter structure, Schmithorst found, correlates directly with higher IQ. Other reports reveal that children who suffer severe neglect have up to 17 percent less white matter in the corpus callosum.

Stimulating Change

Such findings strongly suggest that experience influences myelin formation and that the resulting myelin supports learning and improvement of skills. But to be fully convinced of that conclusion, investigators need a plausible explanation of how abundant myelin can enhance cognition, as well as some direct evidence that defects can impair mental abilities.

My lab has uncovered several ways in which an individual's experiences can influence myelin formation. In the brain, neurons fire electrical impulses down axons; by growing neurons from fetal mice in culture dishes equipped with

platinum electrodes, we can impose patterns of impulses on them. We found that these impulses can regulate specific genes in neurons. One of the genes causes production of a sticky protein called L1-CAM that is crucial for pasting the first layer of membrane around an axon as myelin begins to form.

We also found that glia can "listen in" on impulses shooting through axons and that the traffic heard alters the degree of myelination; a type of glial cell called an astrocyte releases a chemical factor when it senses increased impulse traffic. This chemical code stimulates oligodendrocytes to form more myelin. Children who succumb to Alexander disease, a fatal childhood disorder causing mental retardation and abnormal myelin, have a mutation of an astrocyte gene.

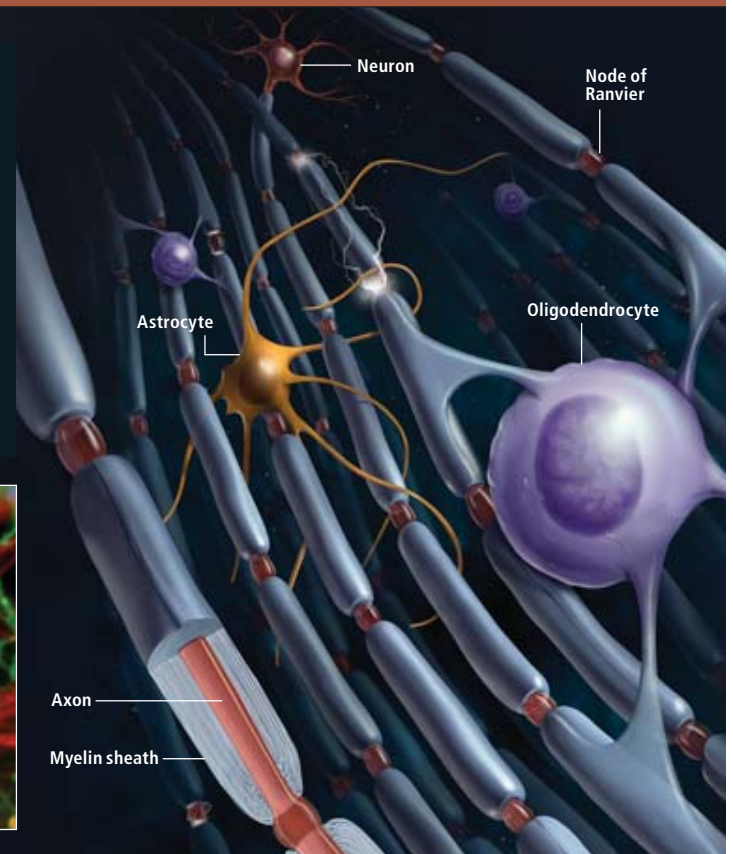
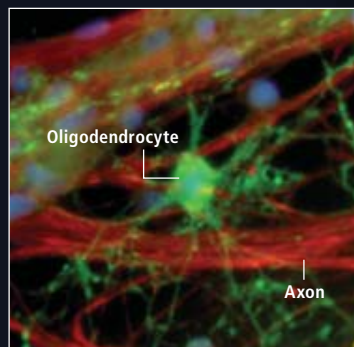
Logic, too, helps to explain how white matter can influence cognitive ability. It might seem that, by analogy to the Internet, all information in the brain should be transmitted as quickly as possible. That would mean all axons should be equally myelinated. But for neurons, faster is

VARSHA SHUKLA (micrograph); ALAN HOOFRING (NH Medical/Arts) (illustration)

[HOW IT WORKS]

MYELIN FORMATION

Long axons insulated with myelin carry signals between neurons faster than unmyelinated axons. Oligodendrocyte cells manufacture the fatty membrane and wrap the axon with 10 to 150 layers. Different factors can stimulate the myelination process; often astrocyte cells "listen in" on the signals traveling along axons and relay chemical messages to the oligodendrocytes. Below, a microscope shows axons in red being wrapped.



not always better. Information must travel enormous distances between brain centers. Each center carries out its particular function and sends the output to another region for the next step of analysis. For complex learning, such as learning the piano, information must be shuttled back and forth among many regions; information flowing over different distances must arrive simultaneously at one place at a certain time. For such precision to occur, delays are necessary. If all axons transmitted information at the maximum rate, signals from distant neurons would always arrive later than signals from neighboring neurons. An impulse typically takes 30 milliseconds to travel from one cerebral hemisphere to the other through myelinated axons in the corpus callosum, compared with 150 to 300 milliseconds through unmyelinated axons. None of the corpus callosum's axons are myelinated at birth, and by adulthood 30 percent remain that way. The variation helps to coordinate transmission speeds.

Perhaps just as crucial are the nodes of Ranvier. In the past few years scientists have con-

cluded that far from being mistakes, the nodes act as intricate, bioelectric repeaters—relay stations that generate, regulate and rapidly propagate electrical signals along an axon. By studying owls' excellent hearing, neurobiologists have shown that during myelination the oligodendrocytes insert more nodes than are optimal for fast signaling along certain axons to slow signals traveling along them.

Clearly, the speed of impulse transmission is a vital aspect of brain function. We know that memory and learning occur when certain neuronal circuits connect more strongly. It seems likely that myelin affects this strength, by adjusting conduction velocity so that volleys of electrical impulses arrive at the same neuron simultaneously from multiple axons. When this convergence occurs, the individual voltage blips pile up, increasing the strength of the signal, thus making a stronger connection among the neurons involved. Much more research must be done to explore this theory, but there is no doubt that myelin responds to the environment and participates in learning skills.

SUSPECTED ILLNESSES

Abnormal myelin formation is suspected of contributing to several mental illnesses, including:

SCHIZOPHRENIA
(delusions, hallucinations)

AUTISM
(impaired communication and emotional detachment)

BIPOLAR DISORDER
(periods of mania alternating with periods of depression)

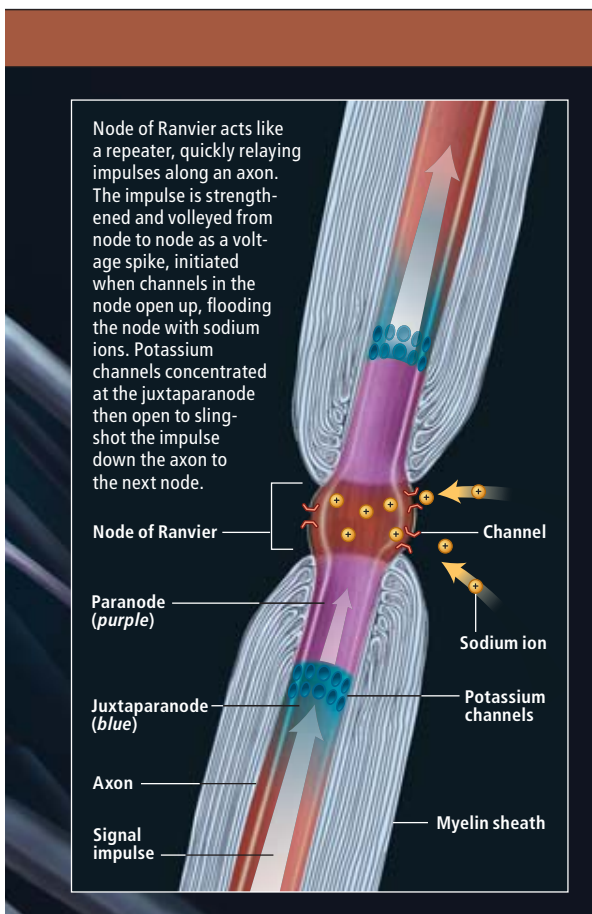
DYSLEXIA
(spelling, reading or more general language disorder)

Learning and Mental Illness

With this new perspective, it is not hard to imagine how faulty transmission could lead to mental challenges. After decades of searching gray matter for the causes of mental disabilities, neuroscientists now have circumstantial evidence suggesting that white matter plays a role. Dyslexia, for example, results from disrupted timing of information transmission in circuits required for reading; brain imaging has revealed reduced white matter in these tracts, which could cause such disruption. The white matter abnormalities are thought to reflect both defects in myelination and developmental abnormalities in neurons affecting these white matter connections.

Tone deafness results from defects in higher-level processing in the cerebral cortex where sounds are analyzed; psychologist Kristi L. Hyde of McGill University has found that white matter is reduced in a specific fiber bundle in the right forebrain of tone-deaf individuals. Furthermore, recent research by Leslie K. Jacobsen of Yale University indicates that exposure to tobacco smoke during late fetal development or adolescence, when this bundle is undergoing myelination, disrupts the white matter. The structure, as seen by DTI, correlates directly with performance on auditory tests. Nicotine is known to affect receptors on oligodendrocytes

Myelin responds to the environment and participates in learning, in part by strengthening neuronal connections.



that regulate the cells' development. Exposure to environmental factors during crucial periods of myelination can have lifelong consequences.

Schizophrenia is now understood to be a developmental disorder that involves abnormal connectivity. The evidence is multifold. Doctors have always wondered why schizophrenia typically develops during adolescence—but recall that this is the primary age when the forebrain is being myelinated. The neurons there have largely been established, but the myelin is changing, making it suspect. In addition, nearly 20 studies in recent years have concluded that white matter is abnormal (possessing fewer oligodendrocytes than it should) in several regions of the schizophrenic brain. And when gene chips—tiny diagnostic devices that can survey thousands of genes at a time—recently became available, researchers were startled to discover that many of the mutated genes linked to schizophrenia were involved in myelin formation. White matter abnormalities have also been found in people affected by ADHD, bipolar disorder, language disorders, autism, cognitive decline in aging and Alzheimer's disease and even in individuals afflicted with pathological lying.

Of course, underdeveloped or withered myelin could be a result of poor signaling among neurons, not necessarily a cause. After all, cognitive function does depend on neuronal communication across synapses in the cortex's gray matter, where most psychoactive drugs act. Yet

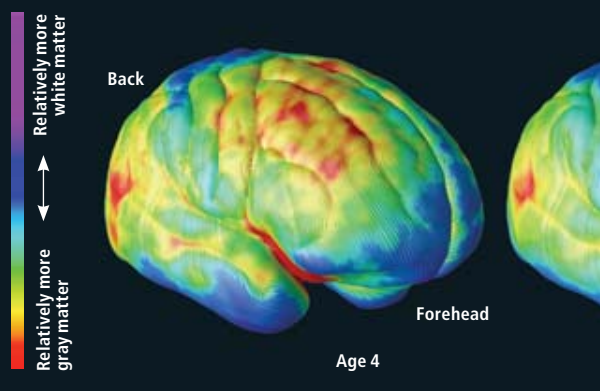


PROFESSIONAL PIANISTS have more highly developed white matter in certain regions than nonmusicians do, suggesting it affects learning. Furthermore, it is more extensive in pianists who begin regular practice before age 11 than in those who start during their teens or later, indicating that critical periods exist for superior skill acquisition.

[DEVELOPMENT]

THE BRAIN MATURES

Few axons are covered with myelin at birth. More are insulated over time, from the back of the cerebral cortex to the front. The sequence here, by Paul Thompson of the University of California, Los Angeles, depicts the pruning of neurons and the relative increase in myelin. Basic functional areas such as vision (*back*) are completed before age 4, followed by language and, last, self-control (*forehead*).



To reach world-class status in certain intellectual or athletic skills, an individual must start young.

optimal communication among brain regions, which is also fundamental to proper cognition, depends on the white matter bedrock connecting the regions. In 2007 Gabriel Corfas, a neurologist at Children's Hospital Boston, showed that experimental disruption of genes in oligodendrocytes—not in neurons—of mice causes striking behavioral changes that mimic schizophrenia. And the behavioral effects involve one of the same genes, *neuregulin*, found to be abnormal in biopsies of schizophrenic brains.

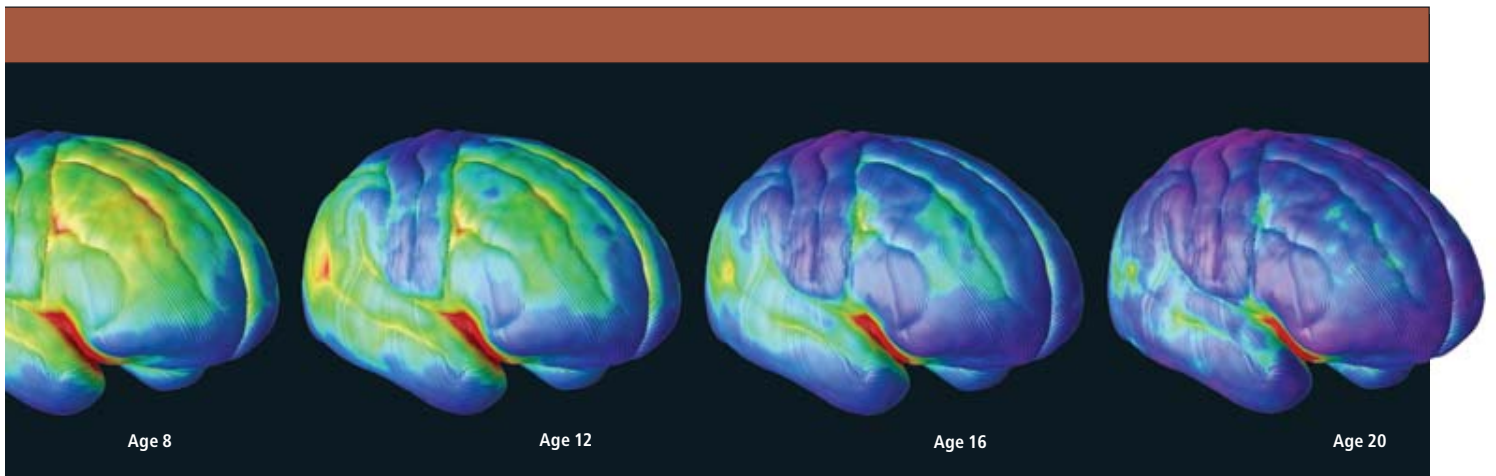
The chicken-and-egg question of whether changes in myelin alter neurons or whether changing neuronal patterns alter myelin will be settled the same way such dilemmas always are: with the acknowledgment that there is a close interdependence between the two mechanisms. Myelinating glia can respond to changes in axon diameter, but they also regulate that diameter. And they can determine whether or not a given axon survives. In multiple sclerosis, for example, axons and neurons can die after myelin is lost as a result of the disease.

Remodeling Old Age

Whatever the mechanism, as our brain matures from childhood to adulthood the precision of connections among regions improves. How well the connections are made may dictate how well we can learn certain skills at certain ages.

Indeed, Ullén's studies of accomplished pianists revealed an additional finding: white matter was more highly developed throughout the brains of individuals who had taken up the instrument at an earlier age. In people who learned after adolescence, white matter development was increased only in the forebrain—the region that was still undergoing myelination.

This finding suggests that the insulating of



Age 8

Age 12

Age 16

Age 20

nerve fibers in part determines age limits for learning new skills—windows of opportunity, or critical periods, when certain learning can occur or at least can occur readily. Learn a foreign language after puberty, and you are destined to speak it with an accent; learn the language as a child, and you will speak it like a native. The difference occurs because the brain circuits that detect speech rewire according to the sounds we hear only as a child. We literally lose the connections that would allow us to hear sounds unique to foreign languages. In evolutionary terms, the brain has no reason to retain connections to detect sounds that it has never heard after years of childhood. Critical periods are also one of the main reasons adults do not recover as well from brain injuries as children do.

Specialists have identified specific protein molecules in myelin that stop axons from sprouting and forming new connections. Martin E. Schwab, a brain researcher at the University of Zurich, revealed the first of several myelin proteins that cause young sprouts from axons to wither instantly on contact. When this protein, which he named Nogo (now referred to as Nogo-A), is neutralized, animals with a spinal cord injury can repair their damaged connections and recover sensation and movement. Recently Stephen M. Strittmatter of Yale found that the critical period for wiring the brains of animals through experience could be reopened by blocking signals from Nogo. When the protein is disrupted in old mice, the critters can rewire connections for vision.

If myelination is largely finished in a person's 20s, however, does that contradict recent claims that the brain remains plastic throughout middle and old age? For example, studies show that

mental exercise into a person's 60s, 70s and 80s helps to delay the onset of Alzheimer's. And how does a person's wisdom increase over the decades? Answers are still forthcoming. Researchers have not yet looked for myelin changes in older animals. Other experiments suggest myelination continues into our mid-50s but on a much subtler level.

Certainly white matter is key to types of learning that require prolonged practice and repetition, as well as extensive integration among greatly separated regions of the cerebral cortex. Children whose brains are still myelinating widely find it much easier to acquire new skills than their grandparents do. For a range of intellectual and athletic abilities, if an individual wants to reach world-class level he or she must start young. You built the brain you have today by interacting with the environment while you were growing up and your neural connections were still myelinating. You can adapt those abilities in many ways, but neither you nor I will become a world-class pianist, chess player or tennis pro unless we began our training when we were children.

Of course, old geezers can still learn, but they are engaged in a different kind of learning involving the synapses directly. And yet intensive training causes neurons to fire, so the potential exists for that firing to stimulate myelination. Perhaps someday, when we fully understand when and why white matter forms, we can devise treatments to change it, even as it grows old. To deliver on that speculation, we would need to find the signal that tells an oligodendrocyte to myelinate one axon and not another one nearby. That discovery, buried deep underneath the gray matter, awaits unearthing by future explorers. ■

➔ MORE TO EXPLORE

Myelination: An Overlooked Mechanism of Synaptic Plasticity?
R. Douglas Fields in *Neuroscientist*, Vol. 11, No. 5, pages 528–531; 2005.

Extensive Piano Practicing Has Regionally Specific Effects on White Matter Development.
Sara L. Bengtsson et al. in *Nature Neuroscience*, Vol. 8, No. 9, pages 1148–1150; September 2005.

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T. Ishibashi et al. in *Neuron*, Vol. 49, No. 6, pages 823–832; March 16, 2006.

How to Grow a Super Athlete.
D. Coyle in *Play Magazine*, (*New York Times Sports*) March 4, 2007. Available at www.nytimes.com/2007/03/04/sports/playmagazine/04play-talent.html