Brain boosting: It's not just grey matter that matters

18 February 2015 by Teal Burrell
Magazine issue 3009. Subscribe and save
For similar stories, visit the The Human Brain Topic Guide

Inside your head, another brain is hiding in plain sight – one that responds to your cognitive needs and self-heals. It's time to make the most of your myelin

RECENTLY, my friend's cable TV went out. She fiddled with the box: resetting, unplugging and re-plugging. When that failed, she called the cable company. They examined things at their end – and came up short. Frustrated, she retreated to another room, where she discovered her cat had ripped apart a piece of the wire. It wasn't the ends that needed fixing; it was the part in the middle.

A similar revelation is under way in neuroscience. For years, changes in the brain – whether from learning to ride a bike, taking a Prozac, or sinking into Alzheimer's disease – have been attributed to the activity of neurons and the small chemical junctions between them, called synapses. Targeting synapses is like fiddling with the connections at either end or calling the cable company. But ignoring the wiring in between may be a mistake.

"All ideas about communication and plasticity in the nervous system were focused on the synapse," says Douglas Fields at the National Institutes of Health in Bethesda, Maryland. That's starting to change, as he and other neuroscientists realise that neurons alone are not enough to explain our brain's plasticity – its ability to learn, adapt, and form new memories.
What it comes down to is myelin, the fatty sheath that envelops most neurons. We are used to thinking of it like insulation along a cable — allowing electrical impulses to zip along faster. But we are learning that this fatty layer is not like a wire's insulation, installed uniformly and left unattended. Instead, it is dynamic and autonomous, customising itself to match the brain's demands. The cells that produce it respond in real time to our cognitive needs: new insulation is laid down to help the brain master a skill; a frayed section can be replaced. What's more, these additions and renovations continue well into adulthood. This new kind of plasticity has come as a shock to many researchers. Bill Rebeck at Georgetown University in Washington DC has been a professor of neuroscience for over a decade, but when he heard about it last year, he was gobsmacked. "Wait, really?" was all he could mutter.

And plasticity is just the start. Because they are not nerve cells, which are notoriously hard to tinker with, we might be able to tweak them manually to give the brain an extra boost when needed, or to help mend the damage behind conditions such as multiple sclerosis. It turns out a most vital part of our cognitive potential has been hiding in plain sight.

To better understand why myelin is so important, you need to look at how information travels around the brain. A neuron sends electrical impulses zipping down long projections called axons to the synapse, a small gap that chemicals called neurotransmitters travel across. These relay the signal to neighbouring neurons (see diagram). Myelin keeps the information tightly confined within the axon, allowing a speedy trip.

Wired for learning

The substance is thought to have evolved to allow animals to react quickly. But myelin does more than just speed up our reflexes, it is also crucial to learning, development and behaviour. "Ultimately it allows us to have clever brains," says William Richardson, who studies neuronal plasticity at University College London.

Hints about the role of myelination in cognitive abilities come from the way it is produced during our lifetime. A small amount is made as we develop in the womb, but after birth it takes off, and we see surges as infants learn to crawl, walk and talk. By about age 4, the rate of myelination slows, and teenagers still have the prefrontal cortex left to myelinate — an area crucial for planning and consideration of consequences. Until then, processing in the prefrontal cortex is slow and inefficient and teens remain precariously impulsive. The finer circuitry is complete by the time we reach our 40s, but from the 60s onwards the coverings start to fray and degenerate, which fits with the common experience of cognitive decline as we age. As myelin degenerates, the signals get fuzzier.

Until recently, scientists thought insulating the prefrontal cortex was the final hurrah for myelin. Plasticity was then down to the neurons, and synapses between them. For instance, the number of neurotransmitter receptors increase in a synapse the more that pathway is used, which enables the brain to adapt according to learning or experience. As a result, our quest to understand cognitive decline, and the potential for activities that boost brain power, has focused on grey matter, the part of the brain and spinal cord packed with the neuron cell bodies and synapses.
But Heidi Johansen-Berg at the University of Oxford began to wonder about white matter, the area of our brain that is rich in myelin-covered axons. "It seemed like an overlooked but obviously very important structure in the central nervous system," she says. It wasn't until 2009 that she could investigate, with the help of a new neuroimaging method called diffusion MRI, which accurately measures human white matter in the living brain.

To test her idea, Johansen-Berg turned to a 2004 study, which had found that learning a new skill such as juggling changed the density of grey matter – an example of classic synaptic plasticity. Johansen-Berg decided to recreate the study, and measure changes in white matter too. A group of volunteers agreed to learn how to juggle, and after six weeks, brain scans showed that their myelin had increased more than that of a control group who had no training (Nature Neuroscience, vol 12, p 1370).

"We saw a change not only in the grey matter but also in the underlying white matter pathways, suggesting that these pathways strengthen in some way as a result of experience," says Johansen-Berg. The changes to white and grey matter took place over different timescales, suggesting two separate processes. Johansen-Berg thinks the increase in white matter would have enabled faster conduction along the circuits coordinating juggling. What's more, the effect was seen in everyone who learned to juggle, regardless of how good they became, which means it is the learning process itself that is responsible.

This was the first study to reveal that training can alter white matter in healthy adults, and it opened the door to a plethora of similar findings. Since then, numerous activities have been linked to extra myelin, from learning to read, to meditating, and learning a new skill like playing the piano or another language.

To investigate these changes more closely, Richardson turned to rodents. Rather than juggle, he made mice run on a complicated wheel, with rungs removed in a random pattern. Watching the struggling mice is a pitiful sight – their legs slip through the bars, their paws feel desperately into empty space. But after just a few days, they look like they've been doing it forever. So was myelin the key?

Myelin is formed by oligodendrocytes, octopus-shaped cells with long arms that wrap thin layers of fat 50 to 100 times around the axon, preventing electrical signals from slipping out, and expediting the conversation between brain regions (see diagram). The cells are made throughout life by oligodendrocyte precursor cells (OPCs), which tile the brain, ready to morph when needed.

When Richardson bred mice that couldn't produce oligodendrocytes – or new myelin – in adulthood, the mice weren't able to get used to the wheel, even after a week of practice.

Further proof of the essential role of myelin in learning complex skills came last year. Michelle Monje at Stanford University in California turned to another relatively new technology, optogenetics, which involves breeding mice with light-sensitive genes. This allows unprecedented control over neurons using pulses of light. Monje used it to activate a particular set of neurons that made the mice run in anticlockwise circles. After a while, they became slightly more efficient with the left paw, and when Monje inspected the brains of the mice, she found that new myelin had been laid down in these circuits. Crucially, she was able to show that repeatedly activating specific neurons led to changes in the surrounding myelin rather than changes within neurons, so it was this that was critical to making the circuits more efficient.

Richardson and Monje's papers, both published in 2014, distinguish myelin plasticity as a second type of plasticity – distinct from the better-known synaptic version. Although more studies will be needed in humans, the findings have important implications for learning and memory. Well-used pathways get more myelin, as shown in the juggling study, speeding up the signals and making the brain more efficient. Being more efficient, these pathways are also more likely to be used next time around. "It's not only that information is stored in the plasticity of synapses, but actually in the myelin as well," says Gabriel Corfas at the University of Michigan in Ann Arbor. If you are learning Mandarin, for instance, myelination would help you remember the right character faster and more intuitively. "This gives a new dimension to the amount of information and the types of information the nervous system can store," Corfas says. The importance of these and other non-neuronal cells has led Fields to term them our "other brain".

While we now know that stimulating the brain in various ways can boost myelin production, so too can the insulation be lost, emphasising that the brain is a "use it or lose it" organ. If electricity isn't flowing, the myelin can degrade, and this can lead to psychological and social problems (see "Social networks"). If the brain were a city, and myelin the insulation on wires connecting the buildings, some parts would end up in the dark. A lack of myelin is implicated in conditions like autism, in mental illnesses such as schizophrenia, and in spinal cord and traumatic brain injuries.

And there is a further twist. It turns out that myelin production is in part controlled by packets of messenger chemicals that are relayed through the blood. Could we use these messengers to give struggling brains a boost, rather than trying to manipulate brain cells directly, which is notoriously hard?
Brain boosting: It's not just grey matter that matters - life - 18 February 2015 - New Scientist

That's the thinking behind the work of Richard Kraig, at the University of Chicago. His team discovered that small packets of proteins and RNA in the blood known as exosomes influence myelin production.

Many types of cell release exosomes as a way of delivering specific messages to other cells: they are part of the body's vast communication network. Kraig began to wonder about the roles of exosomes on brain function after reading that transferring the blood of young mice into old mice can reverse their cognitive decline.

He has now shown that exosomes produced in the blood are taken up by OPCs in the brain. Their message is the "trigger to make the myelination go", says Kraig. That raises the exciting possibility that a blood transfusion packed with the right exosomes could help treat multiple sclerosis (MS), in which myelin is attacked by the immune system.

OPC-regulating exosomes are dispensed whenever the brain is stimulated in new ways, such as during exercise and learning. They may be one reason why physical and mental activity help ward off diseases like Alzheimer's. But while advice to exercise the body and mind is not new, for many people it is not that simple – if you have MS, for instance. Kraig hopes that treating people with donor exosomes might improve myelination enough to enable them to exercise, and thus boost exosomes and myelination themselves.

Another disease, amyotrophic lateral sclerosis (ALS), is not normally associated with myelin. It is characterised by the death of neurons that control muscles. But in 2013, Dwight Bergles at Johns Hopkins University in Baltimore, Maryland, showed in mice that oligodendrocytes die before the neurons. Late in the disease, more than half of them had died. "This is a massive reorganisation of myelin. It is very stressful for neurons and can induce them to degenerate," Bergles says.

He has now found that in people with ALS, OPCs seem to have difficulty converting to oligodendrocytes. The key to an ALS cure may lie in preventing the initial oligodendrocyte loss, or helping OPCs to morph properly.

There is still much to be worked out, and many of the animal studies need to be confirmed in humans. But as Corfas said at the Society for Neuroscience conference in Washington DC last November, "It's an exciting time. The way we think about myelin is changing." Indeed, if we can uncover enough, this type of research might even yield an actual wonder drug, says Richardson, one that makes us smarter, speeding up the rate of learning.

In the meantime, the message is clear. "Keep learning, keep your mind active," Richardson says. Kraig recommends learning new things, like a new piano piece, as well as keeping up with ordinary activities like taking a walk. If it's an unfamiliar route, with changing scenery and the requirement to memorise the way home, that's all to the good. So embrace a new hobby. And then another. It should help keep the electricity flowing a little better, a little longer.

This article appeared in print under the headline "Meet your other brain"

Social networks
After the Romanian Revolution in 1989, the dismal reality of the country's orphanages was revealed: 170,000 children had been crowded into impoverished institutions, largely abandoned, and left without human contact. A few years later, even after being adopted into good homes, the children struggled with low IQ, depression, anxiety, and social and behavioural problems. Brain studies revealed the wiring between regions wasn't as efficient; the myelin was lacking.

Almost accidentally, Gabriel Corfas, now at the University of Michigan in Ann Arbor, discovered an analogous phenomenon in young mice. He was originally planning on studying something else – solo mice were a control – but the isolated mice turned out to be too interesting to resist. The oligodendrocytes of socially deprived mice looked deprived themselves, with scrrawnier arms that didn't wrap as many times around the axons (see main story).

"Information is flowing more slowly along these circuits," says Corfas. "You could expect it would produce functional and behavioural problems." Just like the orphans, the mice had poor memories and problems interacting with other mice.

Social deprivation can cause problems in adults as well, but unlike in young animals, the damage seems reversible. Similar issues in friendless adult mice are reversed when they are given cage mates.

Untangling the wires
Your instant guide to white matter

http://www.newscientist.com/article/mg22530090.600-brain-boosting-its-not-just-grey-matter-that-matters.html?full=true&print=true#VOcvnfhF-Ps
Myelin Fatty layers of insulation around the main tendril of a nerve cell – the axon. Produced by cells called oligodendrocytes

White matter The part of the brain and spinal cord packed with myelin-covered axons. It appears white because of the fat in myelin

Grey matter The part of the brain and spinal cord rich in cell bodies of neurons and synapses

Synapses The narrow spaces between neurons where chemical neurotransmitters are released, transmitting information to the next neuron

OPCs Oligodendrocyte precursor cells – turn into oligodendrocytes

Oligodendrocytes Octopus-like cells that produce myelin around a nerve fibre

Teal Burrell is a science writer based in Washington DC