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Your neurons are whirring with movement like clockwork. Understanding how it works may give us a new way to tinker with the brain

ONE of the first things William "Jamie" Tyler does when I meet him is show me a video of "one of the most devastating knockouts ever in boxing". In a 1990 clash, American pugilist Julian Jackson knocked his English counterpart Herol Graham unconscious with a right hook. Graham's lights went out before he hit the floor.

Tyler is a boxing fan who once worked out at the Harvard Boxing Club. But that's not why he's showing me the video. Instead, as a neuroscientist at Virginia Tech, Tyler uses it to highlight a problem: such knockouts are a bit of a mystery in our accepted understanding of the brain. We think of the brain as a biochemical and electrical organ, so how can a mechanical event, such as a punch to the face, cause unconsciousness? "We know without a doubt that there is no electrical transfer from that boxer's leather glove to that man's face. It's a mechanical impulse wave and [yet] he's unconscious," says Tyler. "Granted it's extreme, but it demonstrates how mechanically sensitive the brain is."

While no one is questioning whether brain cells use electrical and biochemical signals to talk to each other, Tyler and others think that's only part of the story. It seems neurons are also hooked together in a mechanical network, like the cogs in a finely tuned clock. The forces that pass between them might be an unknown way for our brains to store memory and adapt quickly to new circumstances - ensuring that they always run like well-oiled machines.

Not only could this help us probe age-old questions about what makes our thoughts go round, it also offers immediate practical benefits. For one thing, understanding disruptions to these mechanical processes might help us address certain types of brain injury. It could even be possible to tinker with the brain's mechanics using sound waves, which promises to lead to non-invasive therapies for disorders such as epilepsy.

The notion of a mechanical brain has its origins in the mistaken ideas of the 2nd century Greek physician Galen, who proposed that ventricles in the brain pumped fluids through nerves to control the body's functions. Even as recently as the 17th century, René Descartes propounded a similar theory for how the brain functions. It wasn't until the 18th and 19th centuries that it became clear that nerves carried electrical signals. This culminated in the 1950s when Alan Hodgkin and Andrew Huxley showed how these electrical signals, called action potentials, are transmitted along nerve fibres.

But around the time that Hodgkin and Huxley were doing their Nobel prizewinning work, hints began to emerge that mechanical processes may be involved after all. The first clue came from observations of cuttlefish nerves, which seemed to shrink and swell when stimulated by a small electric current. The finding went largely unnoticed for decades until, in 1980, Ichiji Tasaki of the National Institute of Mental Health in Bethesda, Maryland, and colleagues saw something similar in nerves taken from the claws of blue crabs: as the action potential travelled along the nerve, so did a mechanical wave (Science, vol 210, p 338).

The finding helped to explain the energy exchange as a neuron fires. Hodgkin and Huxley had modelled the action potential as an electrical circuit. Such a circuit dissipates heat, but this is not what was experimentally observed: there is no overall heat loss during the propagation of a nerve impulse. However, if the nerve impulse could be treated as a mechanical wave in which heat is both released and absorbed (with no net loss), the energy accounting squared up nicely.

Perhaps more importantly, it showed that our nervous system is buzzing with movement - albeit at the nanometre scale - setting the scene for a mechanical understanding of the brain.

As well as mechanical waves moving along nerves, researchers have looked at the forces passing between neurons in the synapses. Here signals travel from one neuron to another through the release of charged ions and neurotransmitters. These molecules cross the gap to reach a small mushroom shaped spine on the "dendrite" of the next neuron (see diagram). This then relays the message onwards, starting a new chain of activity.

Importantly, dendritic spines are flexible - a fact that piqued the interest of Francis Crick, the co-discoverer of the structure of

DNA. In the early 1980s, he hypothesised that the spines might twitch as neurons exchanged information, and that the changes in their shapes might somehow alter the strength of the signal passed between two neurons. These movements, he speculated, could even play a role in storing memories. No one had the technology to watch the synapse in action at the time but, by 1998, films made by powerful microscopes showed that dendritic spines do indeed move and change shape within seconds, just as Crick had predicted.

The cogs and wheels driving these movements were elusive, but a decade of research has suggested several possibilities, which Tyler recently outlined in a paper for Nature Reviews Neuroscience (vol 13, p 867). We now know, for instance, that dendrites are full of a protein called actin, which can either assemble into large polymers or fall apart into smaller units, depending on the circumstances. This process generates forces that may be strong enough not just to bend the dendritic spine, but also to make it contract or expand.

Crucially, the dendritic spine on one side of a synapse is linked to the axon terminal on the other side by a chain of adhesive proteins. This means that when a dendritic spine moves, so does the axon terminal - with potentially important consequences. Taher Saif of the University of Illinois at Urbana-Champaign and colleagues have shown that the greater the force applied to an axon terminal, the greater the number of neurotransmitter molecules that are available for release across the synapse. In this way, the movements could alter the strength of the signal and consequently the plasticity of the synapse - key changes that might be a means of storing information during learning and memory.

That's not all. There could even be communication between neighbouring synapses. Tyler points out that neighbouring dendritic spines lie upon the same bed of actin and small rods called microtubules, which can store elastic energy like a spring. As one spine is stimulated, it seems to release chemicals that trigger changes to this structure, which pushes or pulls its neighbouring spines, shifting the balance of forces in their synapses.

No one has yet measured this transfer of movement in action, but there is indirect evidence that actin and microtubules do move in response to a spine's activity - and the scale and speed of these movements would be more than enough to tug or prod the neighbours, says Tyler. If so, the mechanism would add another route for signalling, perhaps helping synapses to coordinate their activity as we adapt to the situation at hand.

By controlling the flow of information in this way, such mechanisms could be crucial to tuning the neural networks that make our brain hum. But finding out for sure will be fiddly work - typically the forces extend over just 10 micrometres. So neuroscientists are turning to cutting-edge techniques such as magnetic particles, or laser beams that exert minuscule forces to tinker with these structures.

Tyler's interests, however, lie in a technique that may allow him to tweak the mechanics in the living brain. It started with a serendipitous observation while he was a graduate student. To liven up the long hours, Tyler played loud music, with a subwoofer placed next to the equipment recording electrical activity in neurons. To his surprise, he noticed spikes in neural activity each time the subwoofer boomed. "You'd see these synaptic events that seemed to correlate with the bass," says Tyler. "It was saying, 'Look! Mechanical vibrations in brain tissue can cause changes in neural activity'." But it didn't seem to be work worth publishing, so Tyler let it be.

Once in charge of his own lab at the Arizona State University in Tempe, Tyler revisited the issue. In 2008, his team took slices of mouse hippocampus and subjected them to low intensity, low frequency ultrasound waves - pressure waves that should jiggle the brain's mechanical structures. As suspected, it stimulated the neurons to fire, and increased the amount of neurotransmitter released at synapses.

Ultrasound therapy

The team next turned to live mice. By stimulating their motor cortices with pulses of ultrasound, they caused the mice to twitch their tails, forepaws and whiskers. They even implanted electrodes in the brains of the mice to confirm that spikes in neural activity accompanied the ultrasound stimulation (Neuron, vol 66, p 681).

The results seem to confirm the suspicions that external mechanical forces can interfere with processes in the brain, potentially answering that mystery of the boxing knockouts. If our synapses and neurons are tuned to fine mechanical forces, then a blow to the head might disrupt their signalling, forcing them to open up ion channels and activate receptors. "One theory is that it instantaneously opens all the potassium channels or all the sodium channels," says Tyler. "That would render you unconscious."

The idea of the mechanical brain is beginning to draw interest from other researchers. Randy King, now at the US Food and Drug Administration recently replicated Tyler's experiment to stimulate mice with ultrasound when he was at Stanford University in California. He believes that the low intensity of the waves rules out the possibility that the ultrasound is influencing brain activity via other mechanisms, such as heating. Instead, a real mechanical interaction must be taking place. "It's showing that we can activate the brain non-invasively. And that would be just huge for the entire field of neuroscience," says King.

One reason for excitement is the possibility of using ultrasound to treat brain disorders. Unlike deep brain stimulation, which uses implanted electrodes to treat Parkinson's disease and depression, it wouldn't require surgery. It can also stimulate deeper areas of the brain than other non-invasive methods, such as transcranial magnetic stimulation or transcranial direct current stimulation. That's because they use electrodes on the scalp to pass electric or magnetic fields through the skull, both of which have a fairly shallow reach.

Tyler has so far investigated whether ultrasound stimulation could stop epileptic seizures, in which lots of brain regions start firing in synchrony. In one of their first experiments along these lines, Tyler's team induced seizures in mice before applying ultrasound pulses to their skulls. The sound waves broke up the synchronous firing, ending the seizure. He has high hopes that the technique could be used to treat people with head injuries, who often have seizures. "What if you could develop a device that was an automatic external defibrillator, except for the brain, to treat brain injury?" says Tyler. "That's my vision."

The work has inspired Stuart Hameroff to test the technique on himself. An anaesthesiologist and consciousness researcher at the University of Arizona Health Sciences Center in Tucson, Hameroff first suggested to a colleague that they try the therapy to treat chronic pain. The colleague agreed, on one condition. "He looked at me and said, 'you have a nice shaped head, why don't we try it on you'," says Hameroff.

Mood lifter

So they did. They applied ultrasound to Hameroff's temple for 15 seconds. Nothing happened immediately. "But about a minute later, I

started to get a buzz, like I had a martini, and felt really good for about 2 hours."

This led to a pilot study in which 31 people who had chronic pain received 15 seconds of ultrasound over their posterior frontal cortex. Neither the doctor administering the treatment or the volunteer knew whether they were using ultrasound or a placebo. Those who received ultrasound reported a slight improvement in their pain, and their mood was enhanced for 40 minutes after the treatment (Brain Stimulation, vol 6, p 409).

Even so, Tyler and King agree there are safety issues to be worked out before ultrasound can be used as a treatment. King thinks we should be particularly careful. "If you damage the brain, it can be permanent. It's not like muscle, which if you damage might heal," says King. "It has huge implications if something goes wrong, and that would be bad for the whole field."

Tyler is impatient to resolve those safety issues quickly, since he believes the benefits of fiddling with the mechanical brain could stretch beyond the therapeutic applications. For example, since ultrasound can be so finely focused, it should be possible to study tiny regions individually. So you could put a subject in an fMRI scanner and stimulate an area to see how it talks to other parts of the brain. That could help us to build maps of the brain's connectivity, and the functionality of different regions, with unprecedented resolution.

So far, however, progress has been slow, and Tyler is frustrated with the difficulties of finding funding for big projects. "If you want to change something, you can do it in 200 years making very small steps, or you can do it in 10 to 15 years, making very large leaps," he says. And large leaps are what he is after. "We could be on the cusp of having a technique that will redefine the way we go about conducting human neuroscience."

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