Medical Xpress

Neurons feel the force—physical interactions control brain development

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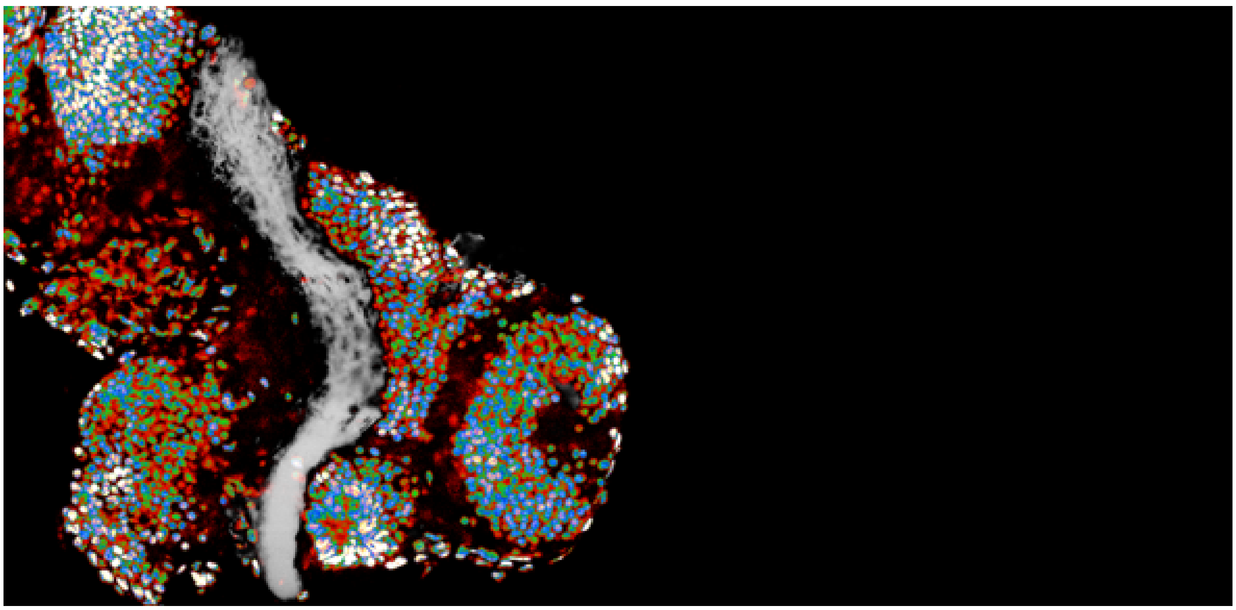

Brain of a frog embryo. The coloured structures are cell nuclei (containing DNA), the white structure in the center corresponds to the optic tract, which contains the neuronal axons studied. Credit: Eva Pillai

Researchers have identified a new mechanism controlling brain development: that neurons not only 'smell' chemicals in their environment, but also 'feel' their way through the developing brain.

Scientists have found that developing nerve cells are able to 'feel' their environment as they grow, helping them form the correct connections within the brain and with other parts of the body. The results, reported in the journal *Nature Neuroscience*, could open up new avenues of research in brain development, and lead to potential treatments for spinal cord injuries and other types of neuronal damage.

As the brain develops, roughly 100 billion neurons make over 100 trillion connections to send and receive information. For decades, it has been widely accepted that neuronal growth is controlled by small signalling molecules which are 'sniffed' out by the growing neurons, telling them which way to go, so that they can find their precise target. The new study, by researchers from the University of Cambridge, shows that neuronal growth is not only controlled by these chemical signals, but also by the physical properties of their environment, which guide the neurons along complex stiffness patterns in the tissue through which they grow.

"The fact that neurons in the developing brain not only respond to chemical signals but also to the mechanical properties of their environment opens many exciting new avenues for research in brain development," said the study's lead author Dr Kristian Franze, from Cambridge's Department of Physiology, Development and Neuroscience. "Considering mechanics might also lead to new breakthroughs in our understanding of neuronal regeneration. For example, following spinal cord injuries, the failure of neurons to regrow through damaged tissue with altered mechanical properties has been a persistent challenge in medicine."

We navigate our world guided by our senses, which are based on interactions with different facets of our environment—at the seaside you smell and taste the saltiness of the air, feel the grains of sand and the coldness of the water, and hear the crashing of waves on the beach. Within our bodies, individual neurons also sense and react to their environment – they 'taste' and 'smell' small chemical molecules, and, as this study shows, 'feel' the stiffness and structure of their surroundings. They use these senses to guide how and where they grow.

Using a long, wire-like extension called an axon, neurons carry electrical signals throughout the brain and body. During development, axons must grow along precisely defined pathways until they eventually connect with their targets. The enormously complex networks that result control all body functions. Errors in the neuronal 'wiring' or catastrophic severing of the connections, as occurs during spinal cord injury, may lead to severe disabilities.

A number of chemical signals controlling axon growth have been identified. Called 'guidance cues,' these molecules are produced by cells in the tissue surrounding growing axons and may either attract or repel the axons, directing them along the correct paths. However, chemical guidance cues alone cannot fully explain neuronal growth patterns, suggesting that other factors contribute to guiding neurons.

One of these factors turns out to be mechanics: axons also possess a sense of 'touch'. In order to move, growing neurons must exert forces on their environment. The environment in turn exerts forces back, and the axons can therefore 'feel' the mechanical properties of their surroundings, such as its stiffness. "Consider the difference between walking on squelchy mud versus hard rock – how you walk, your balance and speed, will differ on these two surfaces," said Franze. "Similarly, axons adjust their growth behaviour depending on the mechanical properties of their environment." However, until recently it was not known what environments axons encounter as they grow, and Franze and his colleagues decided to find out.

They developed a new technique, based on atomic force microscopy, to measure the stiffness of developing Xenopus frog brains at high resolution – revealing what axons might feel as they grow through the brain. The study found complex patterns of stiffness in the developing brain that seemed to predict axon growth directions. The researchers showed that axons avoided stiffer areas of the brain and grew towards softer regions. Changing the normal brain stiffness caused the axons to get lost and fail to find their targets.

In collaboration with Professor Christine Holt's research group, the team then explored how exactly the axons were feeling their environments. They found that neurons contain ion channels called Piezo1, which sit in the cell membrane: the barrier between cell and environment. These channels open only when a large enough force is applied, similar to shutter valves in air mattresses. Opening of these channels generates small pores in the membrane of the neurons, which allows calcium ions to enter the cells. Calcium then triggers a number of reactions that change how neurons grow.

When neuronal membranes were stiffened using a substance extracted from a spider venom, which made it harder to open the channels, neurons became 'numb' to environmental stiffness. This caused the axons to grow abnormally without reaching their target. Removing Piezo1 from the cells, similarly abolishing the axons' capacity to feel differences in stiffness, had the same effect.

"We already understand quite a bit about the detection and integration of chemical signals" said Franze. "Adding mechanical signals to this picture will lead to a better understanding of the growth and development of the nervous system. These insights will help us answer critical questions in developmental biology as well as in biomedicine and regenerative biology."

More information: David E Koser et al. Mechanosensing is critical for axon growth in the developing brain, *Nature Neuroscience* (2016). DOI: 10.1038/nn.4394