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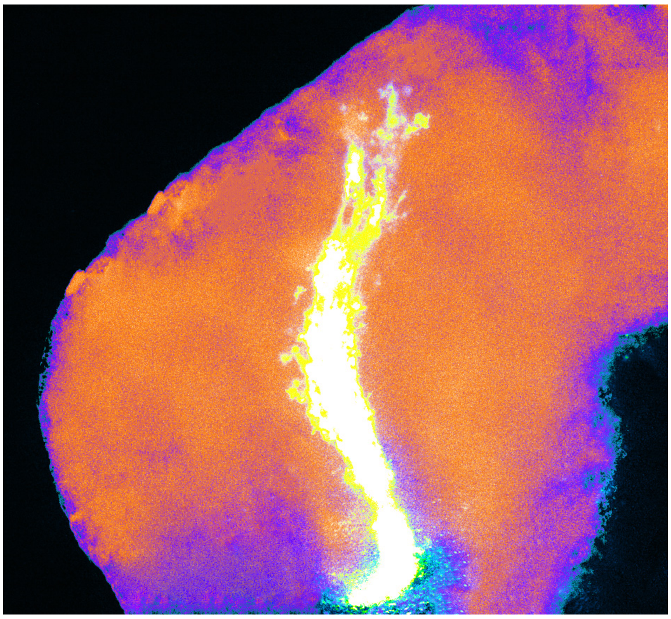
# Beyond Chemistry: How Mechanical Forces Shape Brain Wiring

**During brain development, neurons extend long processes called axons. Axons link different areas of the brain and carry signals within it and to the rest of the body. Growing axons “wire up” the brain by following precise paths through the tissue. Their navigation depends on chemical signals and the physical properties of their surroundings. How these signals work together has remained largely unknown. An international team of scientists has now shown that tissue stiffness controls the production of key signalling molecules in the brain. This discovery, recently published in *Nature Materials*, reveals a fundamental link between mechanical forces and chemical signalling. It could help scientists understand how other organs and body systems develop and may inform new medical approaches.**




In frog brains (orange-blue), developing axons from the eye (yellow-white) follow a specific path to reach their final destination. Along the way, they make a characteristic turn. This turning is mediated by both chemical and mechanical signals. The exact nature of this chemo-mechanical coupling is what the researchers in this study aimed to understand.

Scientists have long known that chemical signals, such as gradients of signalling molecules, guide tissue growth and development. More recent work has shown that physical cues, such as tissue stiffness, directly influence how cells and tissues behave as well. What is less understood is how these mechanical and chemical cues work together to steer development.

Researchers of the Max-Planck-Zentrum für Physik und Medizin (MPZPM), the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), and the University of Cambridge have uncovered fundamental mechanisms at play in the developing brain. By using *Xenopus laevis* (African clawed frogs), a well-established model system, the team found that tissue stiffness regulates the expression of key chemical cues, and that this process is controlled by the mechanosensititve protein Piezo1. The team of researchers led by Prof. Kristian Franze found that increasing tissue stiffness induces the expression of chemical signals that are typically absent in those regions. Semaphorin 3A is one such chemical signal. Crucially, this response only occured when levels of Piezo1 were sufficiently high. “We didn’t expect Piezo1 to act as both a force sensor and a sculptor of the chemical landscape in the brain,” said study co-lead Eva Pillai, a postdoctoral researcher at the European Molecular Biology Laboratory (EMBL). “It not only detects mechanical forces – it helps shape the chemical signals that guide how neurons grow. This kind of connection between the brain’s physical and chemical worlds gives us a whole new way of thinking about how it develops.”



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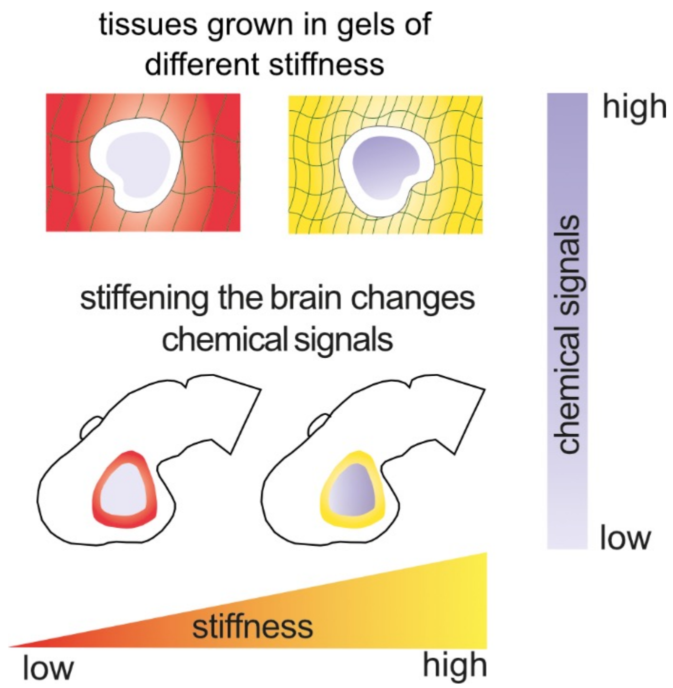
The loss of Piezo1 not only affects chemical signalling but also the mechanical integrity of the tissue itself. When Piezo1 levels are attenuated, the abundance of key cell-adhesion proteins such as NCAM1 and N-cadherin decreases. These molecules are essential for maintaining cell-cell contacts – which glue cells together. "What's exciting is that Piezo1 doesn't just help neurons sense their environment – it helps build it," said Sudipta Mukherjee, study co-lead and postdoctoral researcher at FAU and MPZPM. He and Pillai were both doctoral students at the University of Cambridge, where the project was initiated. "By regulating the levels of these adhesion proteins, Piezo1 keeps cells well connected, which is essential for a stable tissue architecture. The stability of the enviroment in turn, influences the chemical environment."






Dissected frog brain tissues were cultured in gels of different stiffness (soft: red, stiff: yellow), the expression of key chemical signals increased in gels of higher stiffness. When soft parts of the developing frog brain were compressed and thereby stiffened, for a long time (6 hours), the expression of chemical signals were similarly increased.

**Protein with a dual mission: sensor and modulator**

The study suggests Piezo1 is a dual-function protein: both a sensor that translates mechanical signals from the environment into cellular responses, and a modulator that helps structure the mechanical environment itself.

These findings have broad implications for both developmental biology and disease research. Misguided neuronal growth is linked to congenital and neurodevelopmental disorders, while tissue stiffness also plays a role in the progression of diseases such as cancer. By showing that mechanical cues shape chemical signalling, the study opens exciting new avenues for understanding development and tackling disease.

"Our work shows that the brain's mechanical environment is not just a backdrop – it is an active director of development," said senior author Kristian Franze. "It regulates cell function not only directly, but also indirectly by modulating the chemical landscape. This study may lead to a paradigm shift in how we think about chemical signals, with implications for many processes from early embryonic development to regeneration and disease." The findings reveal that tissue stiffness influences chemical signalling over long distances, altering the behaviour of cells far from the site of the original mechanical stimulus. This study highlights mechanical forces as a powerful regulator of development and organ function.



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*The **Max-Planck-Zentrum für Physik und Medizin** is conceived as a joint effort between the Max-Planck-Institute for the Science of Light (MPL), the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) and the Universitätsklinikum Erlangen (UKER). The new scientific center aims to apply advanced methods from experimental physics and mathematics to basic biomedical research with an emphasis on the intercellular microenvironment. Learn more at mpzpm.mpg.de.*



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