MAX-PLANCK-ZENTRUM
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Ein gemeinsames Forschungszentrum mit der FAU und dem Universitätsklinikum Erlangen

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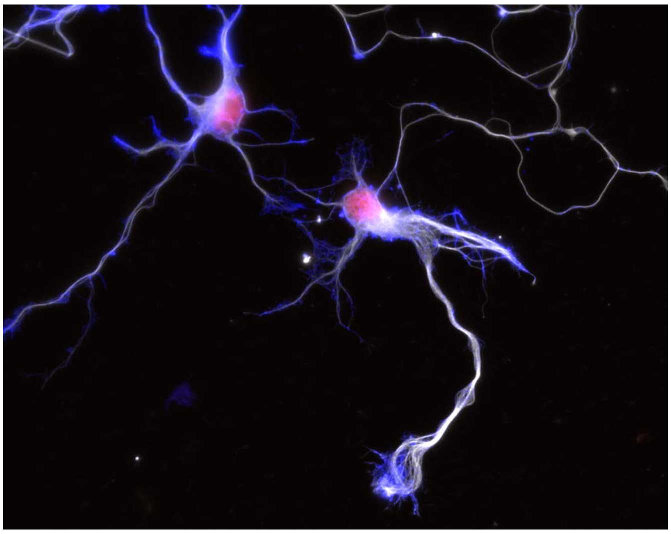
Is shaping brain activity a mechanical process? An international research team provides new insights

When thinking, the human brain performs a true masterpiece of information processing: around 100 billion neurons communicate with each other via approximately 100 trillion connections. An international team of researchers, including scientists from the Max-Planck-Zentrum für Physik und Medizin (MPZPM), has discovered that the mechanical properties of the developing brain influence both synapse formation and the emergence of electrical signals. The findings could open up new approaches to understanding neurodevelopmental disorders.

In the brain, highly specific connections called synapses link nerve cells and transmit electrical signals in a targeted manner. Despite decades of research, how synapses form during brain development is still not fully understood. Now, an international research team from the MPZPM, the University of Cambridge, and the University of Warwick has discovered that the mechanical properties of the brain play a significant role in this developmental process. In a study recently published in Nature Communications, the scientists showed how the ability of neurons to detect stiffness is related to molecular mechanisms that regulate neuronal development.

Synapse formation is regulated by local brain stiffness

The developing brain is generally very soft, like cream cheese, but its stiffness varies across regions. In African clawed frog (*Xenopus laevis*) embryos, the researchers found that softer regions exhibit higher synapse densities, while stiffer regions show lower densities. To test whether stiffness directly affects synapse formation, the team led by Prof. Kristian Franze, head of the Neural Mechanics Department at MPZPM and professor at Friedrich-Alexander-Universität Erlangen-Nürnberg and the University of Cambridge, artificially stiffened the brain and



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Immunostaining of cultured neurons
(red: cell nucleus; white: tubulin; blue: actin)

observed that synapse development was delayed across all regions. The scientists thus proved that mechanical properties actively influence how quickly and where synapses are formed in the brain. “This fundamentally changes our understanding of how the brain matures.” said Franze. “Until now, neuroscience has primarily focused on how chemical signals shape brain development. Considering mechanical cues provides a new perspective on brain development and may lead to new insights into neurodevelopmental disorders.” adds Dr. Eva Kreysing, lead author of the study and assistant professor at the University of Warwick.

Mechanosensitive protein delays synapse formation in stiff environments

To understand how neurons adapt to their environment at the molecular level, the team studied genetically altered neurons.

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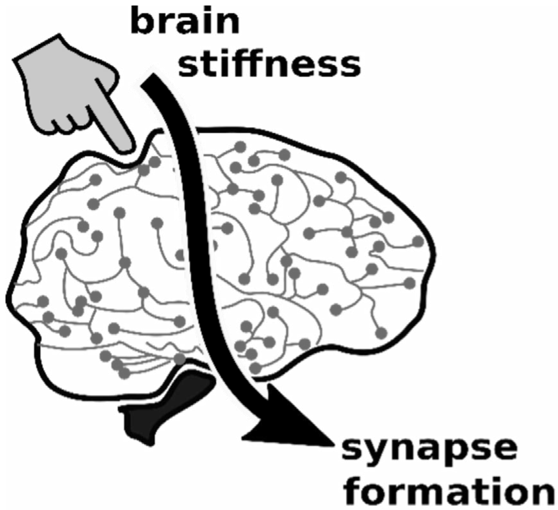
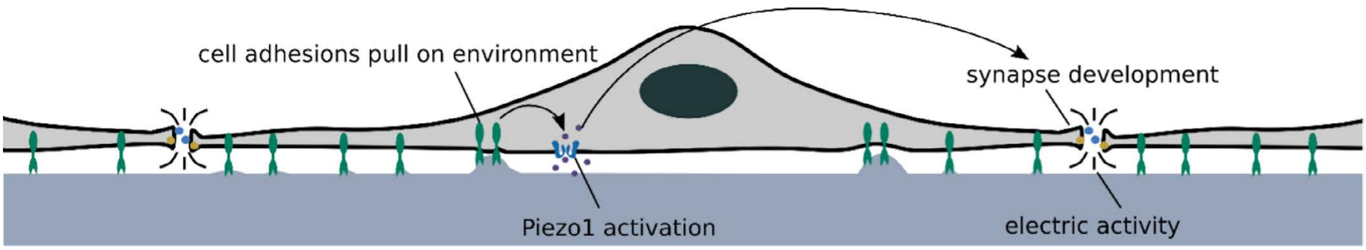
This allowed them to eliminate specific proteins from the neurons and examine processes such as synapse formation and electrical signalling under controlled conditions. The scientists found that both synapse formation and electrical activity depend on the stiffness of the environment. Neurons sense this stiffness through the mechanosensitive ion channel Piezo1. The researchers then measured the expression of thousands of genes and discovered that Piezo1 delays neuronal development in stiffer environments by reducing the expression of transthyretin, a protein recently shown to regulate synapse formation. By uncovering this pathway, the team revealed how stiffness sensing is linked to molecular mechanisms that guide neuronal development.

"These findings highlight the importance of mechanical signals in brain development and point to their potential role in neurodevelopmental disorders." concluded the third lead author, Thora Karadottir from the University of Cambridge, who also contributed significantly to the success of the project.

The identified signaling cascade that controls the stiffness-dependent development of nerve cells offers researchers new opportunities to investigate developmental disorders of the nervous system that could lead to conditions such as schizophrenia or autism.



The brain can be understood as a complex network of circuits. The individual units are neurons, while the synapses serve as nodes through which the neurons communicate with each other. The current study shows that more synapses form in particularly soft regions of the brain – and sheds light on the underlying molecular mechanism.



Neurons interact with their environment through cell adhesions, in part by exerting pulling forces. Depending on how strongly the cell pulls on its surroundings, the ion channel Piezo1 is more or less likely to open. Through this channel, specific ions flow into the cell, triggering a signalling cascade that influences both synapse development and the cell's electrical activity.

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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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