Unpicking the Brain

For anatomist Anja Bräuer the way brain cells grow and connect with each other is a source of endless fascination. With her research she aims not just to gain a better understanding of the fundamentals of brain development but also to find ways to improve the diagnosis and treatment of diseases like Alzheimer's

A ripple goes through the audience at the University's Audimax auditorium as the children thrust their hands in the air. Prof. Dr. Anja Bräuer has just finished enthusiastically explaining to at least 450 eight to twelve-year-olds how the brain is structured and how nerve cells connect with each other. Now the children are allowed to ask questions: What happens when you suffer a concussion? Which living beings have the largest brains? This Kids' University ("KinderUniversität") lecture was definitely a challenge, Bräuer notes afterwards. "I've never done anything with that many children," she laughs.

Bräuer loves a challenge. Since March 2017 the 48-year-old academic has led the Anatomy division at the University's School of Medicine and Health Sciences and is a member of the Directorate of the Human Medicine Department. She studied biotechnology and fulfilled her dream of a career in medical research early on, when she was a doctoral candidate at the Institute of Cell- and Neurobiology at the Medical School Charité in Berlin. As Junior Professor of Molecular Neurobiology she became the acting director of the university's anatomy chair in 2006. Today, Bräuer represents the entire spectrum of anatomy in her research and teaching. Building up her own team and putting new ideas into practice is what makes her work at the young medical faculty in Oldenburg particularly exciting, she says.

The main focus of her research is the brain – and the processes that give rise to its complex structures: "We still haven't understood how this organ develops," says Bräuer. Her goal is to understand which molecular mechanisms stimulate nerve cells to grow and differentiate, in other words, take on their subsequent form and function. How does a nerve fibre, an axon, find its way to exactly the right cell in the other half of the brain? Which molecules steer this process? How do functioning neuronal networks form? In her quest for answers the neuroanatomist also wants to find out how nerves and brain tissue recover from injuries.

„We know that regeneration takes place in the brain and we want to study which molecules play a role here and how we can aid this process," she says. Bräuer and her team are interested in a broad spectrum of diseases, from dementia disorders and spinal cord injuries to rare diseases like Niemann-Pick Type C (NPC). There are only 500 to 700 known NPC cases in Germany. The disease is due to a single genetic defect, a so-called point mutation. This defect causes cholesterol and other lipids, also known as fatty acids, to build up in the body's cells and above all in certain regions of the brain. "People with this disease have dysfunctions in all their organs and die young," Bräuer explains.

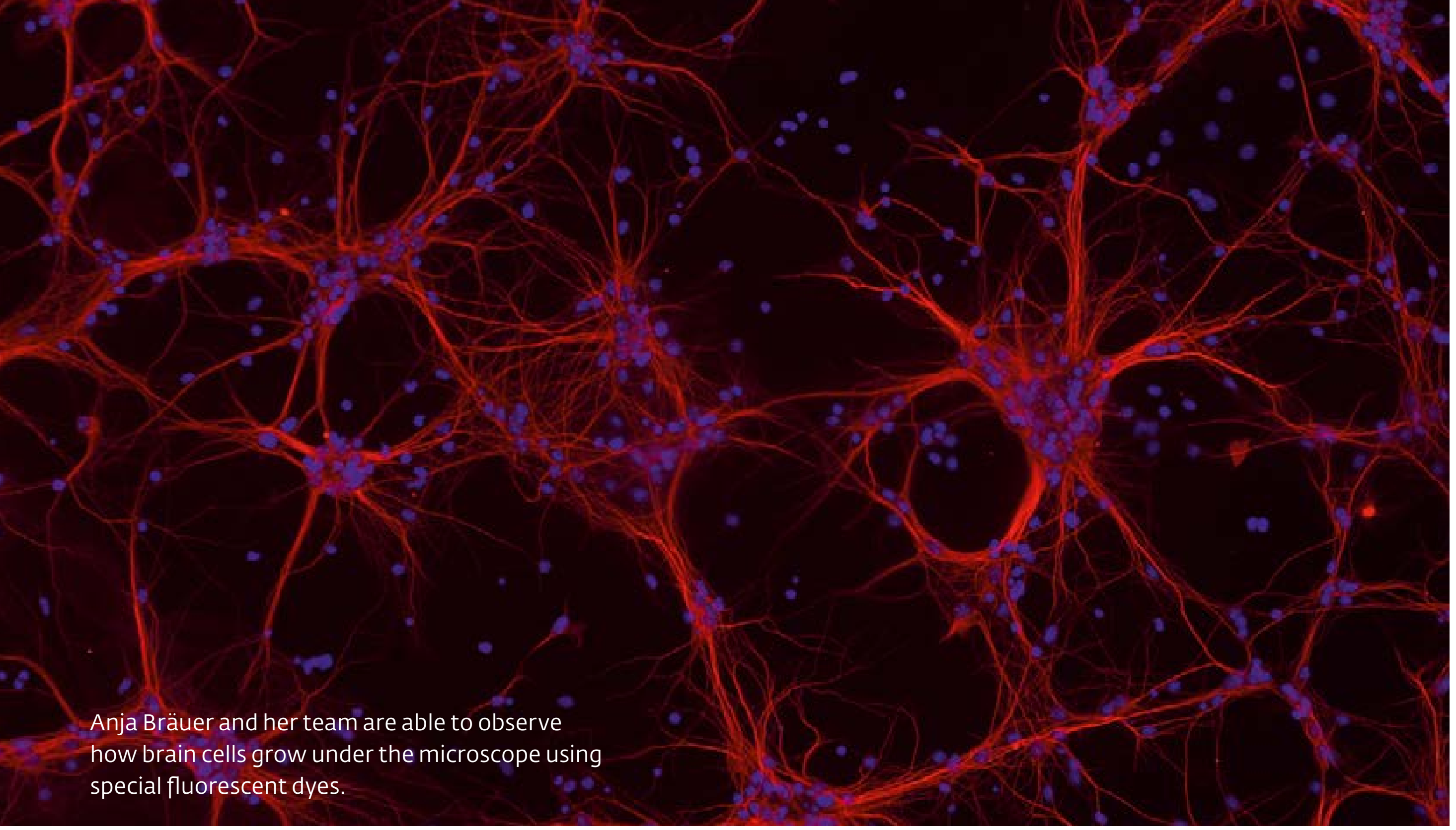
How do nerve cells develop their form and function?

By gaining a better understanding of how NPC develops and how it can be treated Bräuer and her team hope to acquire fundamental insights into other neurodegenerative diseases. Because as with NPC, in Alzheimer's too, for example, cholesterol accumulates inside cells in vesicles called lysosomes. With Alzheimer's, it is not just a single gene that is responsible for this symptom. Yet the consequences are similar: instead of helping neurons to grow and regenerate the cholesterol in the cells eventually causes them to burst. "We want to find out how a cell regulates its lipid content in order to function properly – and in this way discover new therapy options," Bräuer explains.

For a long time scientists were unaware of the key role lipids play in nerve growth. Fatty acids such as phospholipids are a major component of all cell membranes – the layers surrounding the cell and its subunits. They have a barrier function here. In 1996, however, scientists discovered that lipids also have another important function: they transmit messages between cells. Phospholipids bind to certain molecules called, for example, LPA receptors which are attached to the outside of a cell and transmit signals to the inside. "Ever since then we have known that these molecules regulate and influence cellular processes," Bräuer says. This is one of the reasons why research is now focussing on the role of lipids in nerve cell growth and diseases of the brain.

As is often the case in science, it was quite by chance that Bräuer came upon this topic which she has been researching for several years. In 2003 she and a group of colleagues at the Charité found through experiments on rats a group of molecules that belong to the phosphatase groups of enzymes. The researchers were able to demonstrate that these proteins can modify certain phospholipids in brain tissue. These lipids, in turn, inhibited nerve fibre growth. Bräuer and her colleagues were also able to identify a previously unknown gene that contains the blueprint for one of the proteins. They called it the "plasticity related gene" (PRG) because it is mainly active in the phase during which the brain forms and matures, or when brain tissue is injured. With this discovery the scientists had found important information about the influence of lipids and the interactions between the various molecules.

„We had discovered something entirely new that had not even occurred to anyone before then," says Bräuer. "We did know there are attracting and repelling factors that regulate nerve growth." But they hadn't been looking for lipids, Bräuer explains – so this opened up a whole new field of research. One problem the scientists encountered at the time was that very few laboratory methods had been designed for examining the role of phospholipids. "Lipids are not easy to work with. They clog the membranes of analytical instruments for instance," says Bauer: "This meant that scientists and the



laboratory industry first had to develop new methods."

Today Bräuer's labs on the University's Wechloy Campus are equipped with all the devices she needs for her research. In addition to the PRG1 discovered years ago, she and other scientists have now identified several other PRGs. To gain further insights into their role in brain development, nerve fibre growth and repair mechanisms, the researchers are carrying out various experiments, some of them on mice. Through the microscope they monitor changes in brain tissue. They are also investigating the role played by PRGs in the development of dendritic spines in brain cells. These small protrusions are vital for communication between nerve cells via the synapses. Experts even believe abnormalities in spine development are associated with diseases such as autism or schizophrenia. Bräuer also sees potential for PRGs to be used in the treatment of long-term quadriplegia. Spinal cord injuries leave a scar that nerve fibres are unable to repair, she explains. "Our idea is to build small bridges into which we could insert factors such as PRGs so that axons would be able to grow again."

But the neuroanatomist's research doesn't end in the laboratory: "For me, working with clinical practitioners is immensely important," Bräuer stresses. Together with Prof. Dr. Stefan Teipel of the German Center for Neurodegenerative Diseases (DZNE) in Rostock she is investigating whether it may be possible to detect certain degenerative processes or inflammation in the brain on the basis of the presence of phospholipids in a patient's blood, for example. These molecules could potentially help to diagnose diseases like Alzheimer's at an early stage. This is because whenever something in the brain degenerates, or in other words is destroyed, the lipid membranes are also destroyed. The researchers hope to track down the fragments of these membranes.

Digital learning as an important task for the future

One aspect Bräuer values about her work at the University's medical faculty is the freedom to develop new research focuses. She wants to work with the neurologists to gain a better understanding of the underlying cellular processes in chronic diseases like multiple sclerosis. And she is pursuing yet another idea with colleagues from the natural sciences faculty. Physical chemists there are developing a 3D printer which they hope will be able to print live cells – a distant goal that will require close collaboration between physicians, chemists, psychologists, computer scientists and engineers, the researcher notes.

Bräuer is also an enthusiastic lecturer and is passionate about teaching: "When I stand in front of the students I can explain how fascinating the brain and the entire human body is – how it develops and has the potential to defend itself against stress or diseases." Bräuer sees the digitalisation of teaching as an important task for the future. She believes that although digital dissection labs or operating theatres cannot replace classic anatomy training, they can be a useful supplement – for instance in training paediatricians. For this reason Bräuer and her colleague Prof. Dr. Janniko Georgiadis of the University Medical Center Groningen are planning to set up an Anatomy and Surgical Academy. Their goal is to establish a European training centre where physicians can practice surgical operations on donated body parts in the traditional way, but also using the latest 3D technologies such as augmented and virtual Reality. (cb)