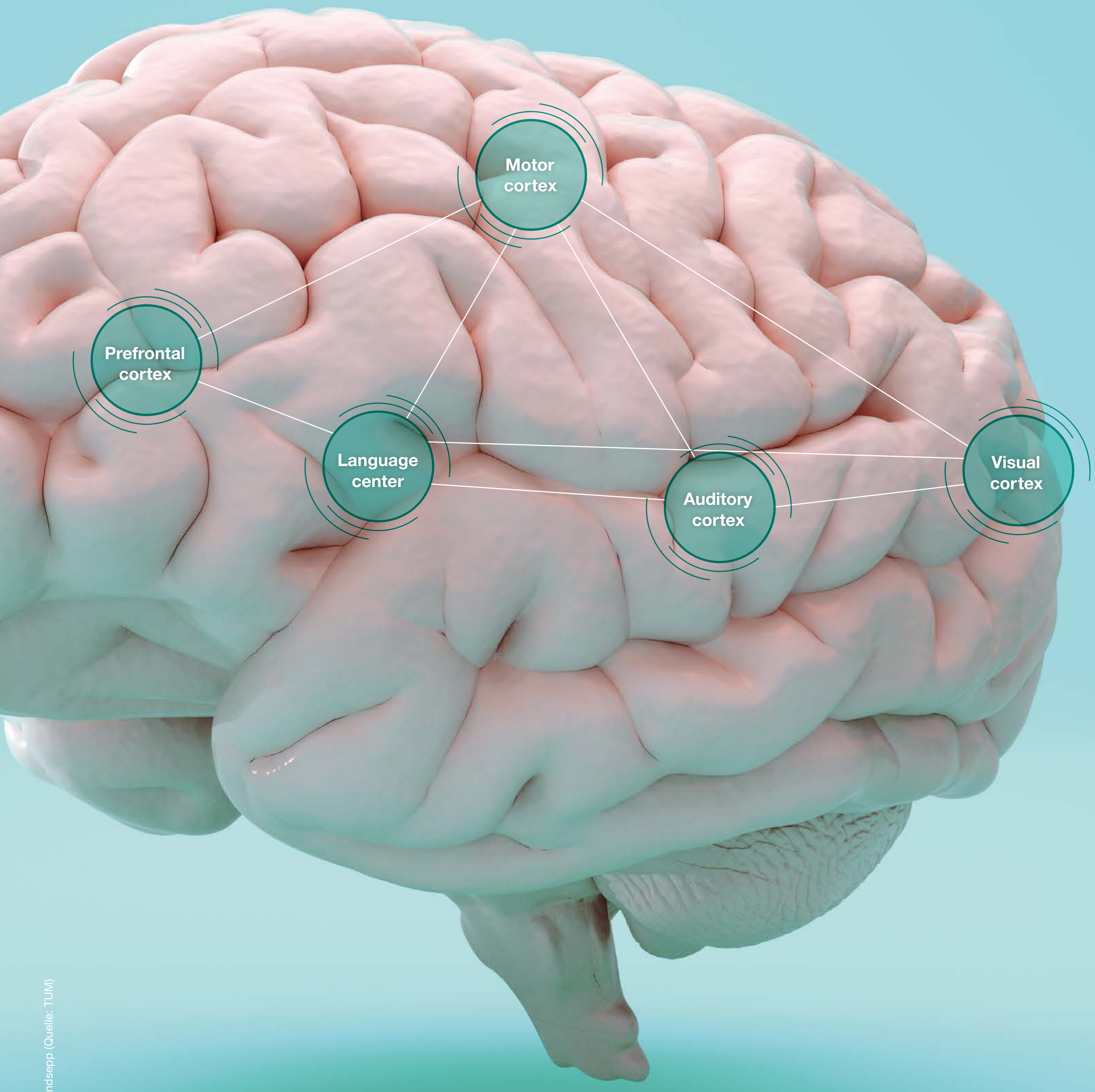
Teamwork to Regain the Power of Language

Cognitive brain functions such as language and a powerful memory are what make humans unique. But the mechanisms behind them are still poorly understood. Neurologist Prof. Simon Jacob is working closely with specialists from other disciplines to change this. Using knowledge gained from many years of research with animals and humans, his team is now embarking on a study aimed at helping stroke patients regain their ability to understand and produce speech.



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simonjacob.de

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Gemeinsam gegen Sprachlosigkeit

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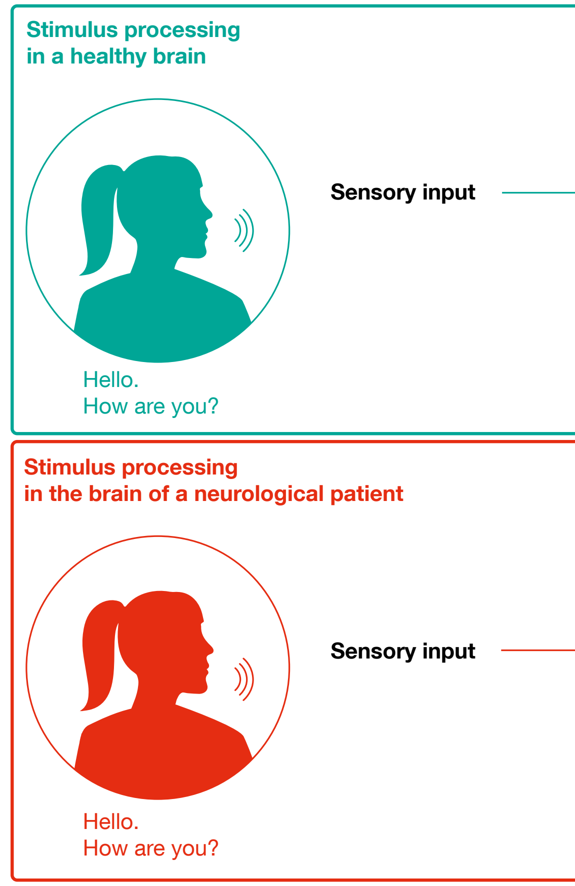
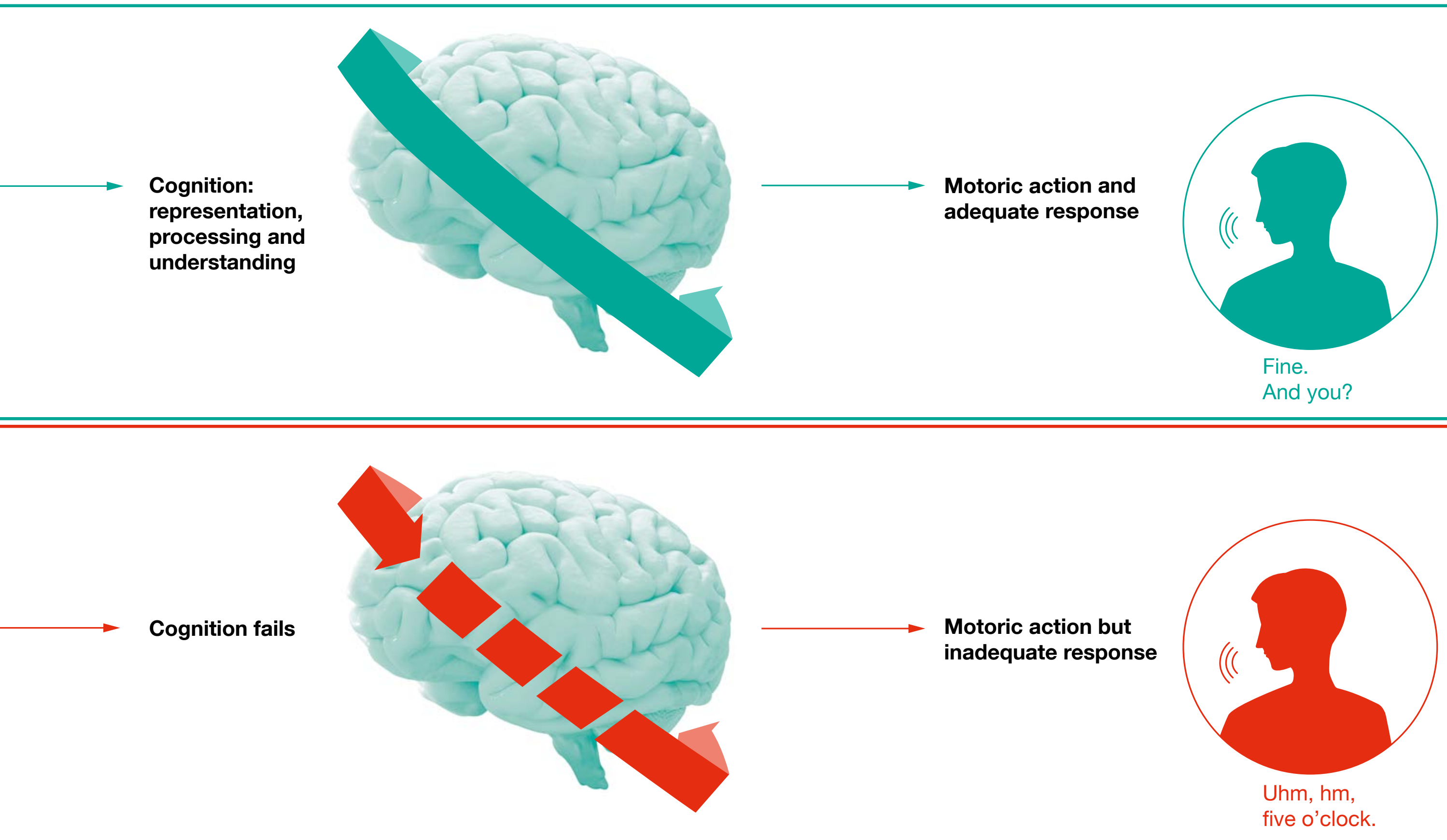
Kognitive Hirnleistungen wie Sprache und ein leistungsfähiges Gedächtnis auch für komplexe, abstrakte Informationen entstehen durch ein exakt koordiniertes Zusammenspiel verschiedener Hirnbereiche. Diese Funktionen finden sich so nicht bei anderen Tieren und prägen uns als Menschen. Sind sie infolge einer Krankheit oder Verletzung gestört, ist das für die Betroffenen sehr belastend. Damit Ärztinnen und Ärzte diesen Menschen helfen können, müssen zuerst die entsprechenden Prozesse im Gehirn genau verstanden sein. Ihre Erforschung wird jedoch dadurch erschwert, dass vielen Tiermodellen bestimmte kognitive Hirnfunktionen fehlen. Bei Menschen wiederum dürfen aus ethischen Gründen meist nur nicht-invasive Methoden eingesetzt werden, welche die neuronalen Vorgänge nur unzureichend abbilden. Der Arzt und Neurophysiologe Prof. Simon Jacob setzt deshalb auf eine Kombination aus Experimenten im Tiermodell und Untersuchungen bei Menschen, die sich aus medizinischen Gründen einer neurochirurgischen Operation am Gehirn unterziehen. In enger Zusammenarbeit mit Spezialisten mehrerer Fachrichtungen möchte er unter anderem Verfahren entwickeln, mit denen Patientinnen nach einem Schlaganfall ihre Sprachfähigkeit zurückgewinnen können. □



Humans are the only animals able to reflect on their position in the animal kingdom. We are able to do so because of complex brain functions such as active perception, memory, and language. The umbrella term for these functions is cognition. "Cognitive processes translate sensory stimuli in our environment into purposeful, planned action and enable us to, for example, respond in completely different ways to a repeating situation. The key brain region for these processes is the frontal lobe," explains Simon Jacob, who, as TUM Professor of Translational Neurotechnology, researches cognitive functions at TUM. As a neurologist and neurophysiologist, he has the perfect qualifications for the post. "Translational" means turning scientific insights into treatments, and Jacob is one of those rare basic researchers who – as a qualified doctor – is actually familiar with medicine in practice. "Medicine is and remains the inspiration behind and the motivation for our research," stresses Jacob. "We hope that our results will be translated into practical applications."

Cognitive impairment is a feature of a number of psychiatric and neurological disorders, ranging from depression, schizophrenia, and dementia to stroke and head injury. From his interactions with patients, Jacob knows how difficult this can be for sufferers and their relatives. "When our cognitive functions are impaired, we are no longer ourselves," he explains, noting that there are still no effective treatments for many of these conditions, as we still do not understand exactly what's going on in the brain in these disorders. "We have a very good understanding of how individual nerve cells or neurons work, but we don't yet understand how exactly they work together in networks."



Cognitive processes translate sensory stimuli into purposeful, planned action. There are still no effective treatments for persons suffering from impaired cognitive functions, such as after a stroke.

Understanding cognitive processes in monkeys

One reason for this is that reproducing the complexity of cognition – which arises from interactions between different brain regions – in a cell culture dish is simply not possible. In addition, because few animals have cognitive abilities comparable to humans, there are few animals capable of serving as animal models for research. Ethical considerations rule out using invasive methods to measure the activity of individual neurons in humans. "In healthy people, we are limited to measuring brain waves or using MRI to map the activity of specific brain regions," explains Jacob. "But these methods don't have very good spatial resolution." In other words, you can see which brain regions are at work, but not what's happening at the level of individual brain cells. But to understand disease processes with enough precision to be able to help people who are ill, you need to do exactly that.

That's why, before coming to Munich, Jacob worked with non-human primates, where invasive techniques are permitted. "Research using non-human primates as an animal model is incredibly important for medicine. It goes without saying that all experiments must be licensed by the relevant supervisory authority and are monitored very closely," says the researcher. "We anesthetize and prepare the animals for neuronal measurements in the same way as we would humans." Rhesus monkeys can be trained so that in some domains they exhibit cognitive abilities approaching those of humans. Through research like this, Jacob has gained important insights into a key cognitive function – working memory. Working memory stores information online for a few seconds before having to decide which items need to be acted on and which do not. ▷

Grafiken: ediundsepp (Quelle: TUM)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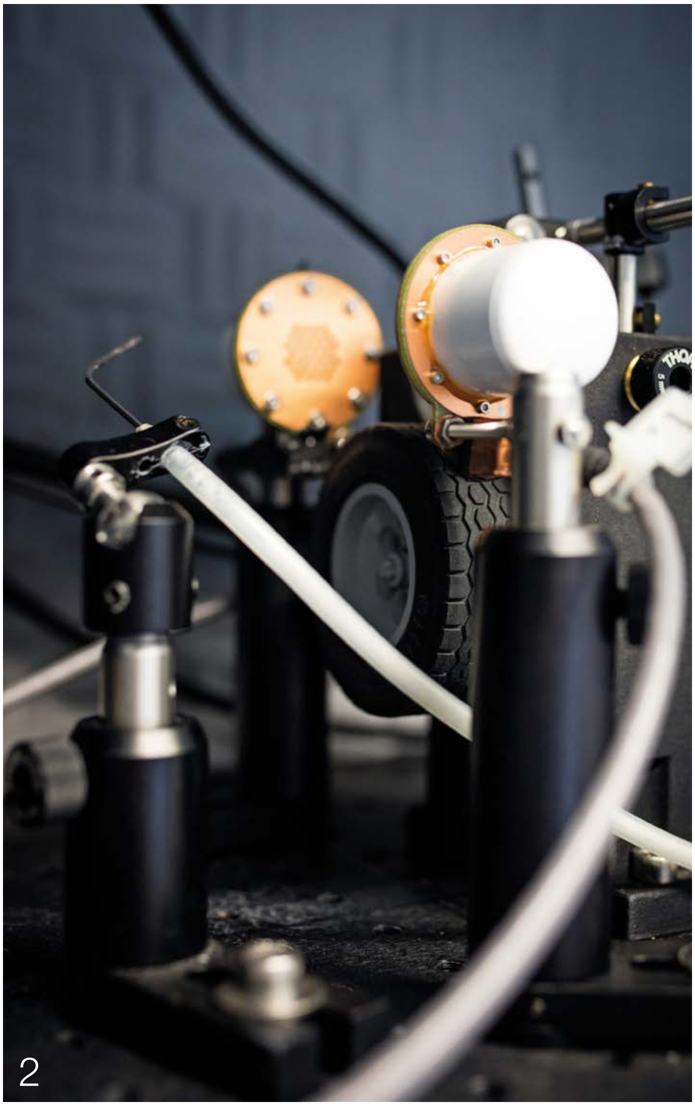
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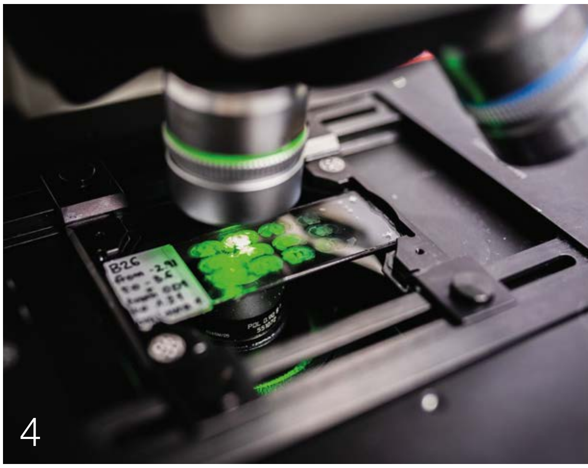
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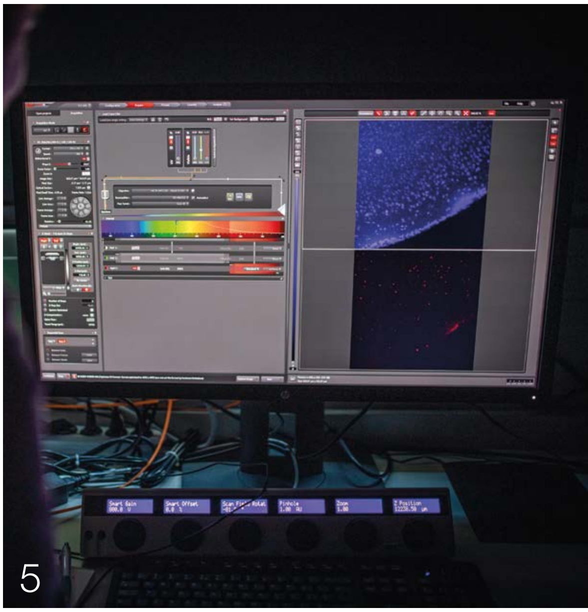
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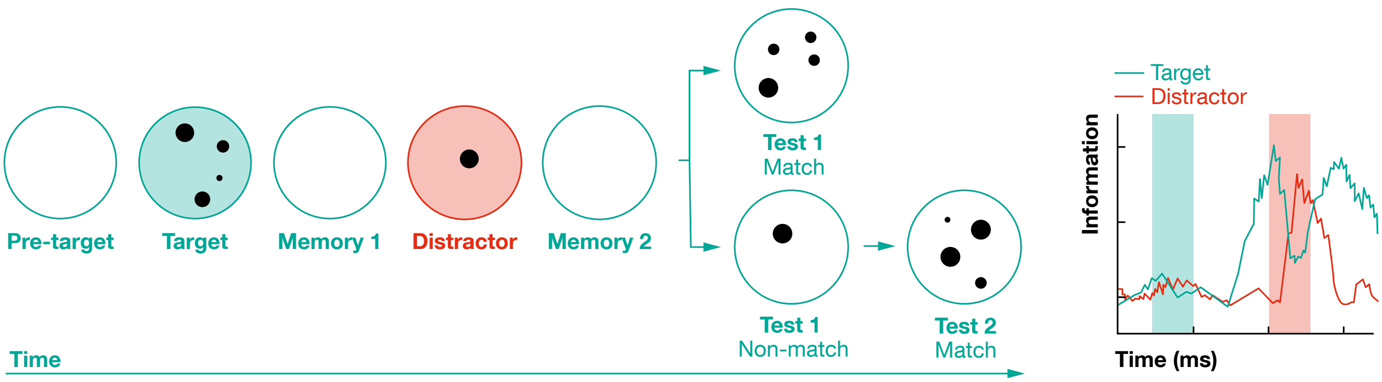
Distracting inputs are not suppressed in working memory. Instead, the prefrontal cortex registers them along with relevant inputs and selects the correct answer later on. In this experiment, animals were trained to memorize the number of dots in the target visual display and resist the distracting numerosity. Electrical activity in a typical neuron shows that both pieces of information are represented.



Jacob's experimental animals learned to memorize and later recognize stimuli consisting of varying numbers of dots. During the task, the monkeys were also presented with distracting stimuli, which they needed to ignore. Using electrodes implanted in the monkeys' brains, the researchers were able to measure what was happening in brain cells during this task. "The measurements don't cause the animals any pain, as the brain has no pain receptors. This is why neurosurgeons are able to perform awake brain surgery," explains Jacob.

The researchers had hypothesized that the brain directly filters out distracting stimuli, but it turned out that these irrelevant stimuli were encoded in the frontal lobe in the same way as relevant stimuli, albeit in distinct groups of cells. While it remains unclear for now how the brain subsequently selects relevant information, Jacob is confident that, "Cognitive performance is not based on blindly blocking irrelevant information, but on purposefully selecting relevant information."

1 Jacob works with mice to understand the functions of individual brain cells and their networks. **2 Animal training setup** with ultrasound speakers. **3 Miniature fluorescence microscopes** register neuronal activity. **4 + 5 Microscopic examination** of brain networks after termination of the neuronal recordings.

In addition, his team was able to show that the neurotransmitter dopamine improves working memory. This is reflected in the symptoms experienced by patients with altered dopamine signaling. "We tend to think of Parkinson's disease, which is characterized by dopamine deficiency, as being primarily a motor disorder, but patients with Parkinson's often also have memory problems and other cognitive anomalies. Significant cognitive problems are also a feature of schizophrenia, and this condition is also treated with medication that affects dopamine metabolism."

From mouse to human

To gain a deeper understanding of brain cell function and neuronal networks, Jacob has also begun to work with mice. "Today we have the technology to record from hundreds of neurons simultaneously and process the large volumes of data produced," explains Jacob. "In mice, we can look at how different brain regions interact by, for example, interrupting the connection between these regions with very high anatomical and temporal precision." In addition, many expedient molecular biology techniques have been developed for use in mice. It is, for example, possible to genetically modify neurons so that their activity can be up- or downregulated by light impulses, so that only certain groups of neurons are visible under a microscope, or so that neurotransmitters can be measured optically. This offers significant potential. "It means that, for example, we can directly observe the role dopamine plays in cognitive processes in the brain," explains Jacob. ▷

Basic research to the benefit of us all

An important step for the neurophysiologist was transferring his findings from animal models into humans. The key to doing so was to take advantage of neurosurgical operations in which, in order to improve the accuracy and safety of the operation, patients choose to remain awake. Awake brain surgery is used, for example, when removing brain tumors close to the language centers in the left-brain hemisphere. "By having the patient awake during the operation, the neurosurgeon can use electrical stimulation to identify areas involved in speech production and comprehension, enabling the surgeon to take extra care when operating in those areas," explains Jacob. Many patients also consent to take part in behavioral experiments during the operation – they are happy to support research, and they know that the results will benefit other patients. Jacob and his team are extremely grateful: "We are unfailingly impressed by the dedication shown by our patients."

By way of tiny electrodes introduced into the tissue around the tumor, the researchers can measure what's going on in the human brain during cognitive processes. Their measurements are as accurate, both temporally and spatially, as in their animal model. The TUM University Hospital is the perfect place for these studies. As a major national cancer center, dozens of awake brain surgeries are performed there every year. The fact that Jacob, as a physician, is familiar with the ins and outs of day-to-day clinical practice, with its last minute changes of plan and short lead times, and speaks the language of the neurosurgeons carrying out the operations, has proved invaluable. "This interdisciplinary approach is enabling me to bridge the gap from laboratory animals to humans," notes Jacob, before adding, "Also in my role as basic and blue skies researcher, my aim has always been about working with and for people." Bringing research and medicine closer together is very much the trend right now, says Jacob.

Prof. Simon Jacob

is a neurophysiologist and board-certified neurologist. He studied medicine on a scholarship from the Studienstiftung des deutschen Volkes at the Universities of Freiburg and Heidelberg, at University College London (UK), and at Harvard University (USA). In the course of his experimental doctoral thesis at Yale University (USA), he became strongly attracted to scientific work. He subsequently trained as a neurologist and systems neuroscientist at University Hospital Tübingen and the Charité in Berlin. Jacob joined TUM in 2015, and in 2019 was appointed Professor of Translational Neurotechnology. He has received numerous awards for his work, which is currently funded by a prestigious ERC Starting Grant.

"Being physically close to other specialists, as we are at TUM's Center for Neuromedicine, is hugely important."

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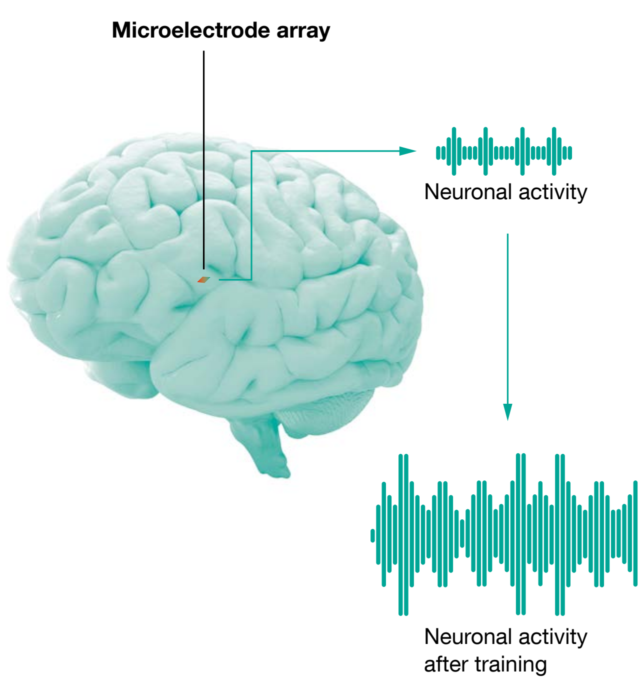
Helping stroke patients with language disorders

The excellent conditions at TUM are now enabling Jacob to carry out a study which will, for the first time, examine whether this invasive procedure can be used to treat language disorders (aphasia). In this study, electrodes will be implanted into the brains of patients who have had a stroke which has affected their ability to understand and, in particular, produce speech. The electrodes record neuronal activity when the patient speaks, which the researchers can also translate into audible and visible cues. These cues can be used to help study participants. “Language is the noblest, most human cognitive function. In common with all other cognitive functions, it is about processing sensory stimuli and responding appropriately to this information,” explains Jacob. “As a physician, I find the suffering of people with aphasia, who find themselves unable to communicate with those around them after a stroke, very affecting. We hope that participants in our biofeedback treatment study will learn to steer their brain activity so that they can learn to once again speak more fluently.” ▷



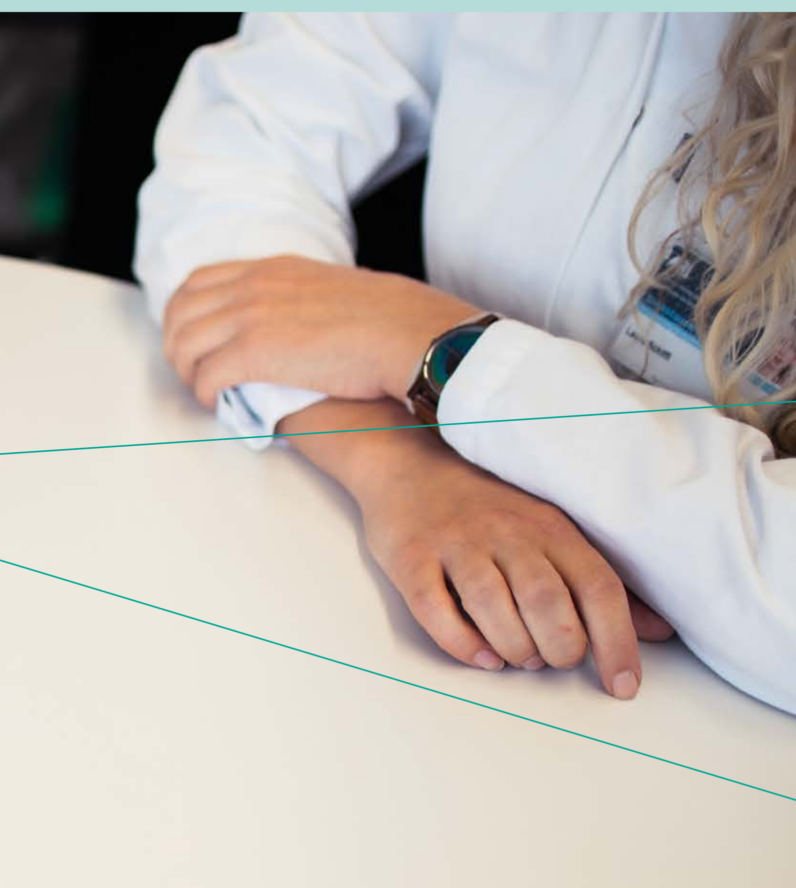
Biofeedback could help study participants improve speech production. Neuronal measurements from the implanted Utah array can be translated into audiovisual signals that are presented to the patient. In multiple training sessions, patients learn to use the feedback signals to specifically control their brain activity.

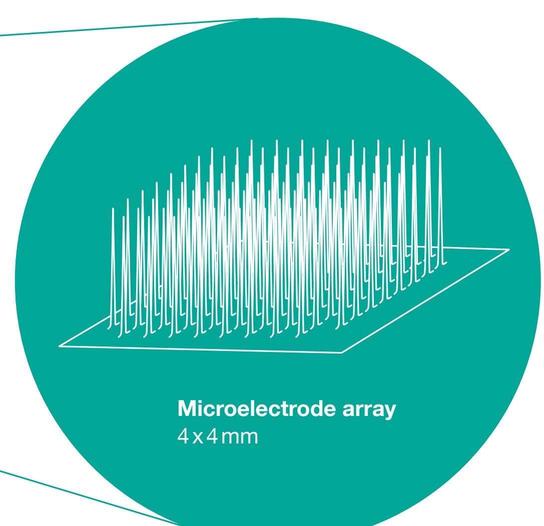
This project too has a strongly interdisciplinary flavor. “We will not make any further progress in aphasia using conventional methods,” believes Jacob. “We have to now trust ourselves to put our insights from basic research into practice and work together across different disciplines.” Consequently, as well as neurophysiologists, with their understanding of the processes in the brain, and the neurosurgeons who carry out the surgery, the work also involves computer scientists who are analyzing the data produced, engineers who are designing new probes, and technicians who are developing measuring devices able to communicate with the electrodes wirelessly and non-invasively. Jacob is confident that the future will see better technologies for treating cognitive disorders. “There are a lot of technical issues to be resolved, but we now have a new generation of physicians who have learned to think along interdisciplinary lines,” he explains. ▷

Bildquellen: Juli Eberle; Grafiken: ediundsepp (Quelle: TUM)

△ **Being both a basic researcher and a clinician** enables Jacob to build bridges between lab bench and bedside and to transfer his scientific findings from animals to humans.

◁ **A study designed to help stroke patients** regain their ability to produce speech: a microelectrode array (Utah array) implanted into participants' brains records neuronal activity while the patients speak.





Scientific thinking and interdisciplinary collaboration

His own team is a broad mix of physicians and scientists, including biologists, psychologists, neuroscientists, and computer scientists. There is also a special doctoral program which enables interested medical students to dive deeper into scientific methods. Jacob is confident this will help change the perspective of aspiring neurologists, neurosurgeons, and psychiatrists. “By recognizing the value of neuroscience and building our medical practice on a solid foundation of neurophysiology and neurobiology, we are able to achieve more for our patients.” The newly founded TUM Innovation Network for Neurotechnology in Mental Health, which Jacob is coordinating, is also aimed at facilitating interactions between disciplines. “Our network will be leading the way as a flagship project internationally,” says Jacob. As a technical university, TUM is perfectly positioned for this approach, as it can involve researchers from the engineering, artificial intelligence, data modeling, ethics, and social sciences fields. “When such different cultures talk to each other, there can sometimes be a little friction,” admits Jacob. “But it is very enriching and I find it a constant inspiration.”

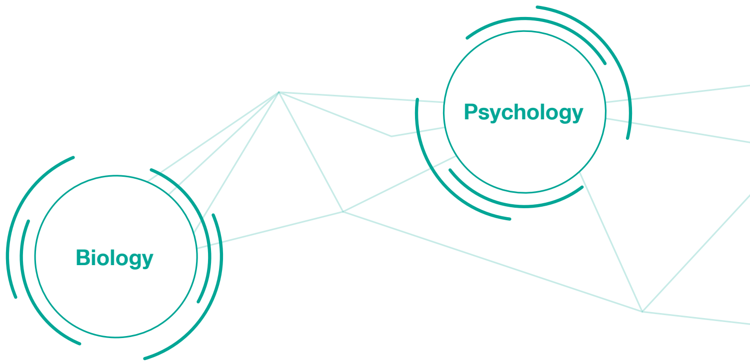
Larissa Tetsch

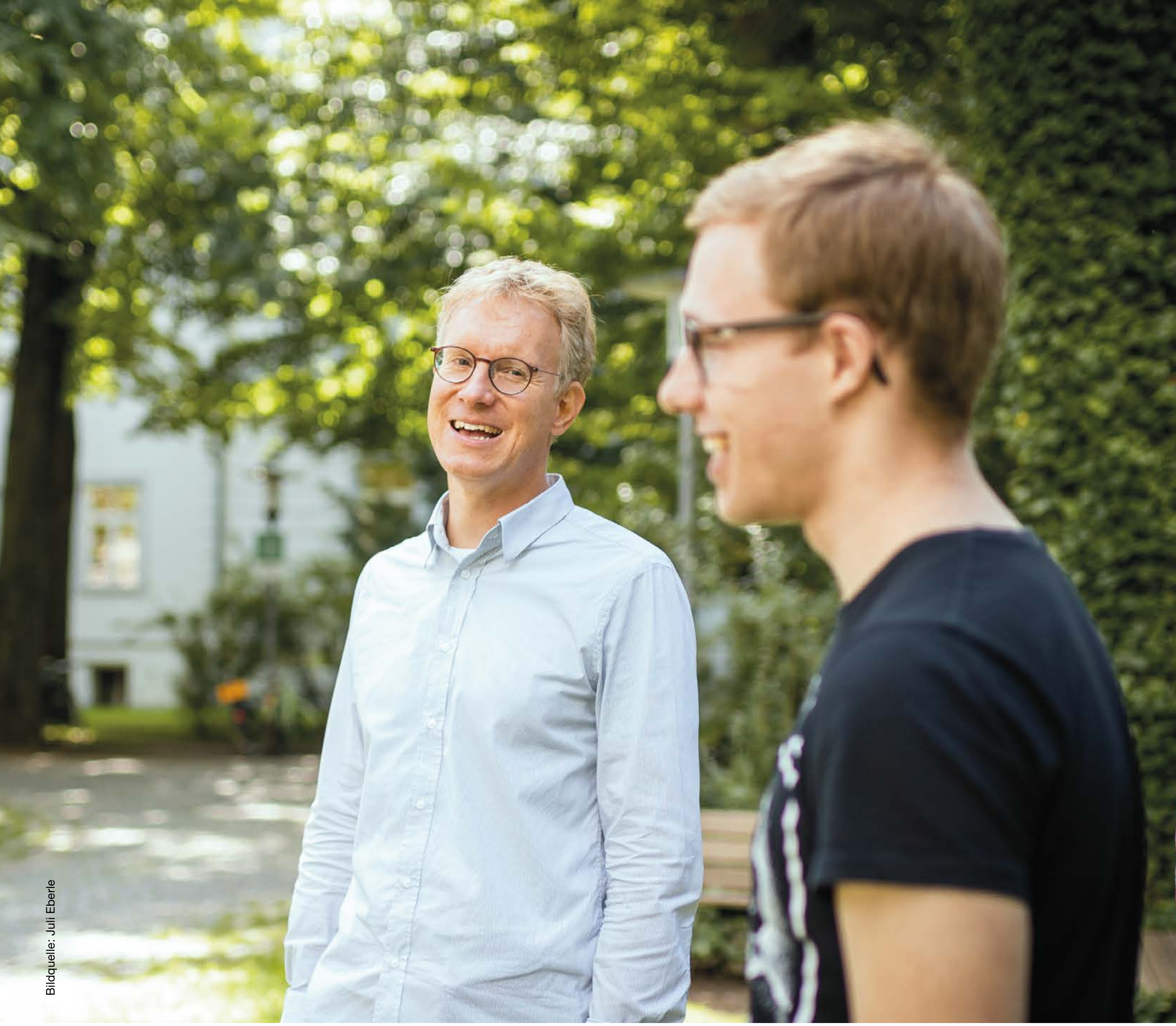
TUM Innovation Network for Neurotechnology in Mental Health (NEUROTECH)

Part of the TUM Excellence Initiative, TUM Innovation Networks are intended to nurture innovative research fields straddling multiple disciplines. The interdisciplinary teams are made up of seven to ten principal investigators and up to ten PhD students and postdocs. Each network is granted around €3 million in funding over a four-year period.

NEUROTECH, the transdisciplinary Network for Mental Health, was selected from 32 applications as one of the first three networks to receive funding. Led by Professor Simon Jacob, it started work on April 1, 2021. The aim of the researchers is to improve our understanding of psychiatric and neurological disorders to enable more reliable diagnoses and individualized treatments.

Simon Jacob is convinced that progress in treating brain disorders requires working across many disciplines. Consequently, his team is made up of scientists and clinicians with expertise in various fields.





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