
Picture credit: Bauer

A Network View of the Brain

The TUM-Neuroimaging Center is an interdisciplinary platform, bringing scientists together from a range of fields to advance neuroimaging research.

Karoline Stürmer

Eine Netzwerkperspektive auf das Gehirn

Das Neuroimaging Center (TUM-NIC) der TUM ist eine interdisziplinäre Plattform. Hier arbeiten Forscher aus unterschiedlichen Disziplinen wie beispielsweise der Neurologie, Neuroradiologie und Psychiatrie zusammen, um die Forschung im Bereich des Neuroimaging voranzutreiben. Der Brückenschlag, wie er hier mit gebündelter Kompetenz über viele neurologische und psychiatrische Erkrankungen möglich ist, eröffnet dabei völlig neue Perspektiven. Die Forscher untersuchen dazu beispielsweise mit Methoden wie der Diffusions-Tensor-Bildgebung (DTI), der funktionellen Magnetresonanztomographie (fMRT), der Elektroenzephalographie (EEG) und der Positronen-Emissions-Tomographie (PET), wie sich Netzwerke des menschlichen Gehirns bei bestimmten Krankheiten verändern, etwa beim chronischen Schmerz. Millionen von Menschen leiden in Deutschland an dieser Störung, für die sich oft keine Ursache finden lässt. Die Erkenntnis, dass solche Schmerzempfindungen auf Veränderungen von Netzwerken im Gehirn basieren, ist noch wenig verbreitet. Die Forscher am TUM-NIC konnten zeigen, dass dauerhafter Schmerz mit Veränderungen der Hirnaktivität in Teilen des „Motivations- und Evaluations-Netzwerks“ einhergeht. Dieses Netzwerk bewertet Reize und übersetzt sie in Verhalten. Dabei geht es um grundlegende Gefühle von Angst. Bei einer Fehlfunktion kann es zu Fehl- und Überbewertungen von Situationen und Sinnesreizen kommen, die dann als bedrohlicher und schmerzhafter eingeschätzt werden, als sie eigentlich sind. Das könnte nicht nur chronische Schmerzen, sondern auch Depression fördern. Demnächst wollen die Forscher nun untersuchen, ob Patienten mit Depressionen ähnliche Veränderungen dieses Netzwerkes zeigen wie Patienten mit chronischen Schmerzen. Von der Beobachtung des Zusammenspiels der unterschiedlichen Gehirnareale erhoffen sich die Forscher, das Gehirn und seine Erkrankungen besser zu verstehen, um Ansätze für neue Therapiemöglichkeiten zu entwickeln. Daneben geht es auch um die Weiterentwicklung diagnostischer Möglichkeiten. □

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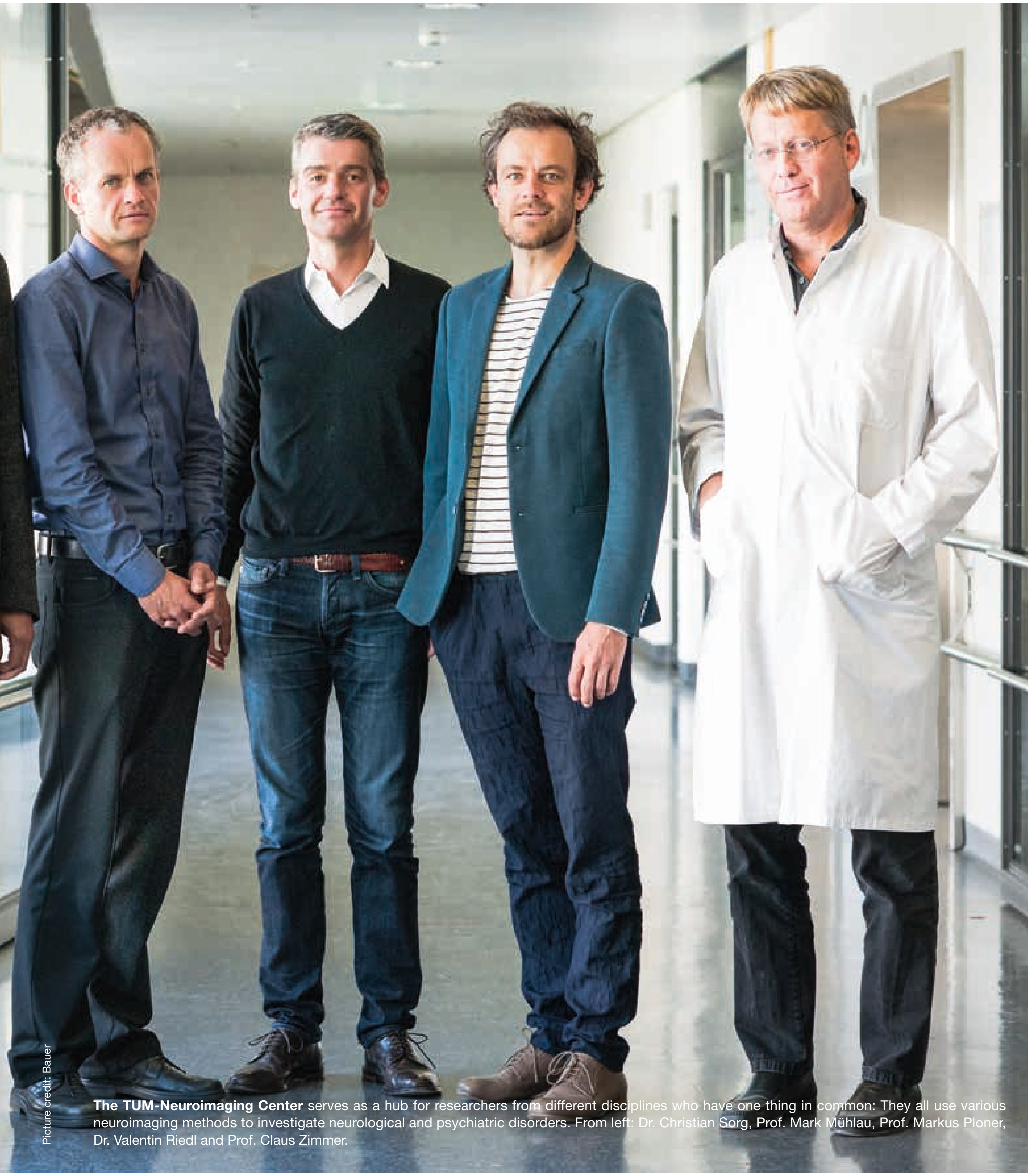

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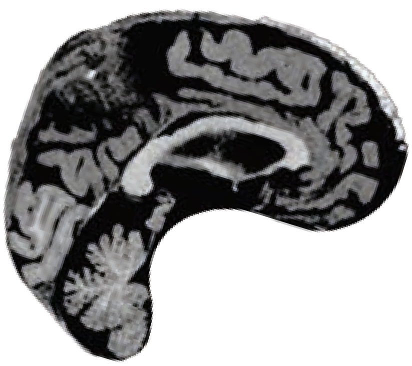
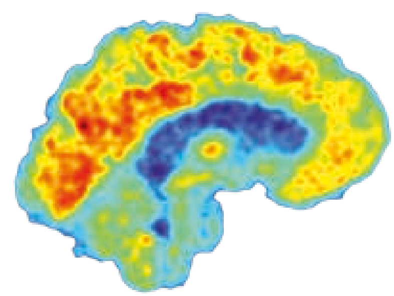
The TUM-Neuroimaging Center serves as a hub for researchers from different disciplines who have one thing in common: They all use various neuroimaging methods to investigate neurological and psychiatric disorders. From left: Dr. Christian Sorg, Prof. Mark Mühlau, Prof. Markus Ploner, Dr. Valentin Riedl and Prof. Claus Zimmer.





MRI
Magnetic resonance imaging

A strong magnetic field and additional radio waves are used to visualize the distribution of hydrogen atoms. Since hydrogen atoms occur most frequently in both blood and tissue, radio waves in different frequency bands can be used to reveal a range of information about the brain.

fMRI
Functional magnetic resonance imaging

fMRI provides an indirect way of visualizing the neuronal activity of nerve cell clusters in gray matter. Oxygen and glucose are the main sources of energy for neuronal activity. fMRI measures changes in blood oxygen levels and so detects local changes in brain activity.

PET
Positron emission tomography

PET measures metabolic processes. A radioactive tracer is attached to a molecule which is processed by the body. Here, glucose labeled with fluorine makes the local neuronal activity visible.

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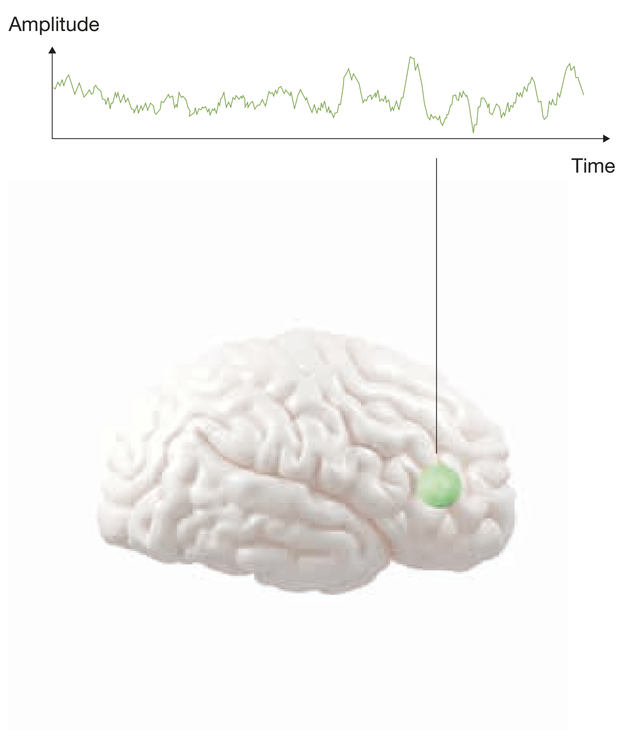
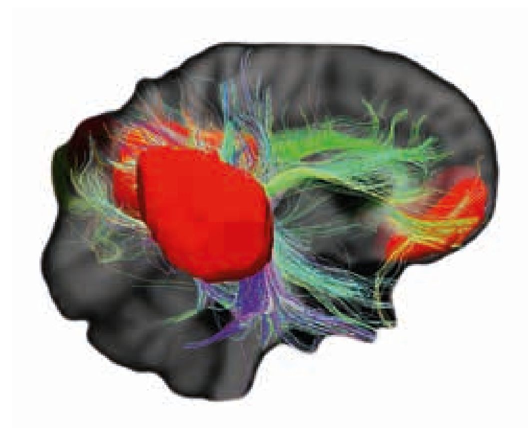




EEG
Electroencephalography

EEG measures brain activity by means of electrodes placed on the head of patients or healthy subjects. EEG directly measures the currents resulting from the activity of nerve cells in the brain. This method of measuring brain activity has a high temporal resolution in the millisecond range.

DTI
Diffusion tensor imaging

DTI is used to map the large bundles of fibers in the white matter of the brain. DTI is an MRI process that detects the diffusion patterns of water molecules along the white matter fiber tracts.

Preparation of MRI assessment to generate images of brain structures (structural MRI), of brain activity (fMRI) or of white matter fiber tracts (DTI).

Picture credit: Bauer

View of the brain of one patient based on distinct MRI assessment techniques, which visualize different aspects of brain tissue.

Picture credit: Bauer

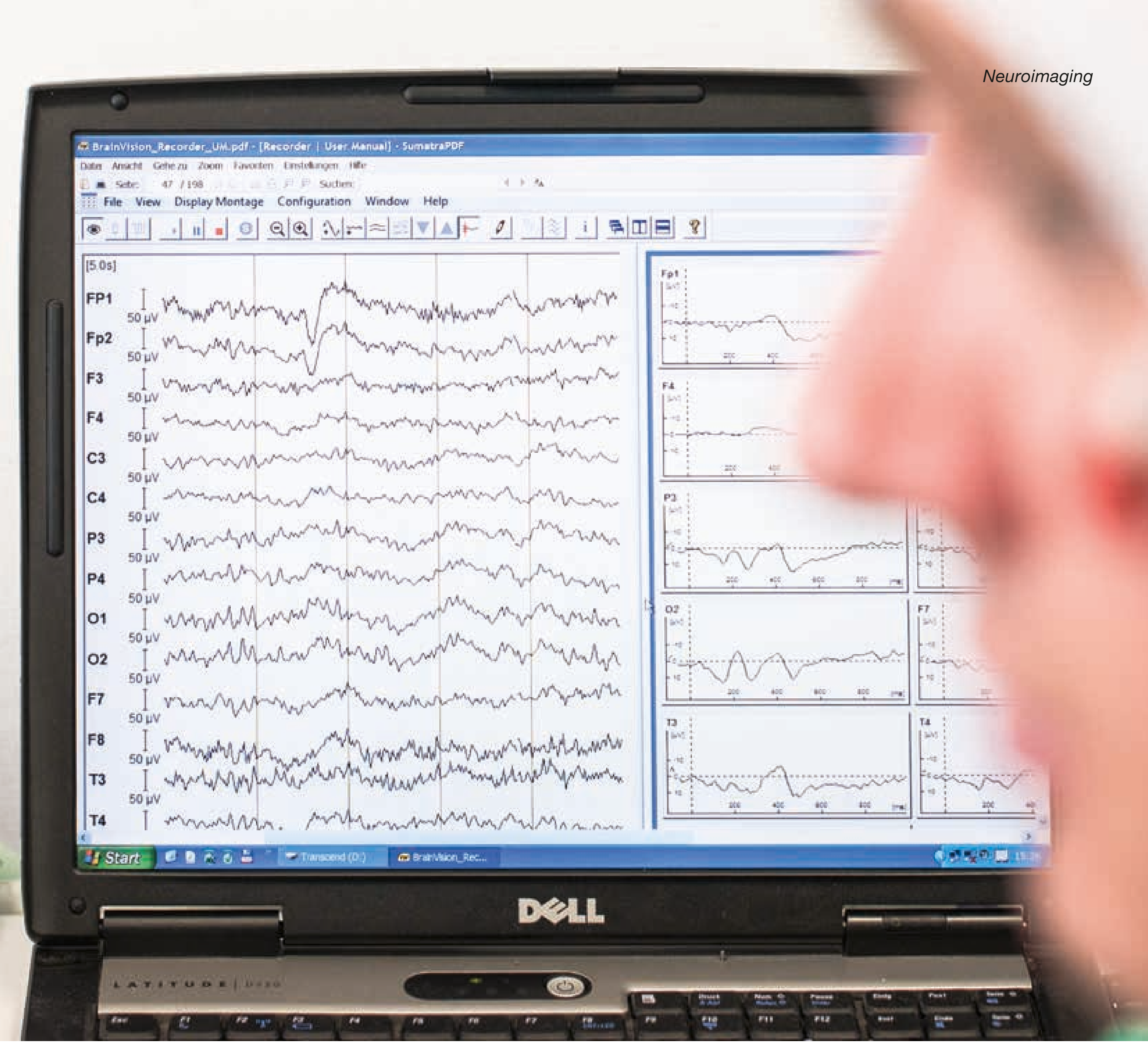
Markus Ploner and a colleague prepare an EEG recording. They use EEG to investigate how pain is processed in the human brain.

Researchers at the TUM-Neuroimaging Center (TUM-NIC) come from a variety of research groups and departments and specialize in very different areas. But they all have one thing in common: they use neuroimaging methods to investigate the structure and function of the brain in neurological and psychiatric disorders. These conditions include chronic pain, Alzheimer's disease, depression, obsessive-compulsive disorder, schizophrenia and multiple sclerosis. The researchers' aim is to learn from one another and put their bundled expertise to the best possible use, both within their research projects and in clinical practice. TUM-NIC was founded four years ago as an interdisciplinary platform to facilitate this aim.

The roughly 100 billion neurons of the human brain form complex, interconnected networks. Researchers at TUM-NIC are seeking to understand how these networks change in certain disorders. While chronic pain and depression might have quite different causes, for instance, various mechanisms at brain network level are similar. "With experts in neurology, neuroradiology and psychiatry, TUM-NIC is able to bridge many different neurological conditions and explore entirely new horizons in this area," states Prof. Mark Mühlau from TUM's Department of Neurology. The researchers hope that this will enable them to gain a better understanding of the causes and mechanisms of disease, as well as of the hugely complex workings of the brain.

Neuroradiology lies at the core of TUM-NIC. In addition to powerful equipment used to examine patients, "Our physicists are continually refining and developing new methods to further advance clinical diagnostic and treatment options, as well as basic research endeavors," outlines Prof. Claus Zimmer, Director of TUM's Department of Diagnostic and Interventional Neuroradiology. Scientists from various departments process the data collected in this area and perform statistical analyses. With the aid of special tests, doctors and psychologists are then able to link the imaging results to cognitive changes in patients.

Take chronic pain, for instance. Millions of people in Germany are affected by this condition, with patients frequently experiencing sensations for years without any evident physical cause. "Recognition that these pain sensations stem from changes in the brain networks is not yet widespread," explains Markus Ploner, Heisenberg Professor of Human Pain Research at TUM's Department of Neurology. However, increasing



EEG recordings show brain activity with high temporal resolution. The traces show brain activity recorded at different EEG electrodes (FP1, Fp2, F3, …) over a period of 5 seconds.

awareness of the causes of this type of pain changes the general perception of these patients, who are not always taken seriously. Together with his colleagues at TUM-NIC, Ploner conducted a more rigorous examination of the brain during ongoing pain and made a surprising discovery: chronic pain is associated with rhythmic nerve cell activity, known as gamma oscillations, in the prefrontal cortex. Nerve fibers closely link this brain area to the nucleus accumbens, with the two regions forming what can be referred to as the valuation or motivation network.

Strictly speaking, the brain is a huge network, which is divided into numerous subnetworks. Each network or subnetwork comprises several interconnected areas. Networks can be observed both in active and resting states – our brains are always on. One of the best known resting state networks is the default mode network, which is active when the brain is mainly occupied with itself and the mind is wandering.

The valuation or motivation network is a resting state network that exhibits changes not only during chronic pain but also in other neurological and psychiatric disorders, as well as warning us of danger. The TUM-NIC researchers are investigating the interaction between nerve cells in this and other networks on three levels: ▷

Picture credits: Bauer

The neurons of the human brain form complex, interconnected networks. Researchers at TUM-NIC are seeking to understand how these networks change in certain disorders.

1. How are the different areas of brain network structurally connected to each other?
2. Do the areas communicate with one another?
3. Is the communication on an equal footing or does one of them dominate?

The first question can be tackled with the aid of diffusion tensor imaging (DTI). The connections between the brain areas involved in the valuation or motivation network are made up of nerve fibers – the threadlike extensions of nerve cells, also termed the brain's white matter. DTI uses magnetic resonance imaging (MRI) to measure and map the diffusion patterns of water molecules in body tissue. Since water molecules diffuse better along the nerve fibers than in other directions, large bundles of fibers can be identified particularly well with this method. "Patients with chronic pain do indeed exhibit reduced integrity of nerve fiber bundles in comparison with healthy subjects," Ploner confirms. However, the mere presence of nerve fiber bundles between different areas is not sufficient to answer the second question – whether and how intensively the areas communicate with one another. The degree to which their activity is synchronized reflects the extent of their collaboration – the more closely they work together, the more frequently they are active at the same time. Alongside his colleagues, Dr. Christian Sorg, psychiatrist at TUM's Department of Diagnostic and Interventional Neuroradiology, investigated this aspect of the valuation or motivation network by using functional magnetic resonance imaging (fMRI). This imaging method visualizes changes associated with blood flow in active brain areas. It is based on differences between oxygen-rich and oxygen-poor blood and allows high spatial resolution. To increase the temporal resolution, researchers also monitored the changes using electroencephalography (EEG). This records the brain's electrical activity by measuring voltage fluctuations on the surface of the scalp. "In both methods, synchronized activity in the monitored area was altered in chronic pain patients as opposed to healthy volunteers," reports Ploner.

The valuation or motivation network is a network of brain regions found in many species that evaluates stimuli and translates them into behavioral responses. This process involves basic feelings: am I safe or in danger; should I be afraid; should I run away? "A malfunction here can result in erroneous or exaggerated assessment of situations and sensory input, which are then deemed more threatening or painful than they actually are," explains Sorg. This might lead not only to chronic pain, but also to depression. So in a subsequent step, the researchers intend to investigate whether patients with depressive disorders also show similar changes in this network to those with chronic pain. ▷

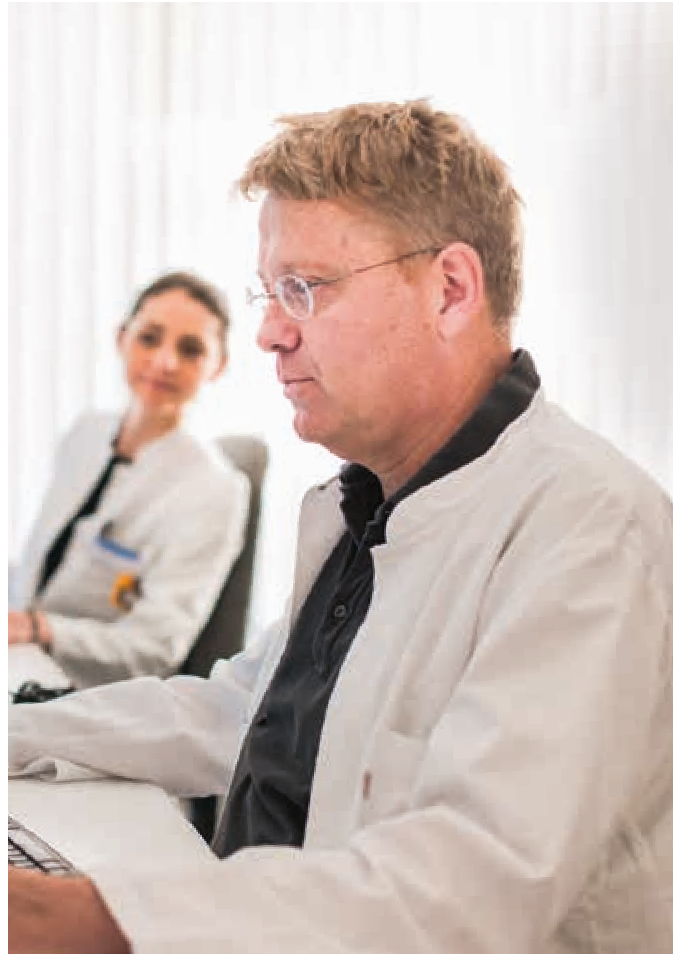
Picture credits: Bauer; Graphics: TUM

"The last few years in neuroscience have seen an increasing tendency to consider malfunctions across multiple diseases."

Markus Ploner

That leaves us with the third question: in which direction does the information flow within the network? This is next on the researchers' agenda. Dr. Valentin Riedl, doctor and neuroscientist at TUM's Department of Diagnostic and Interventional Neuroradiology, has developed a completely new method to this end, which he has already tested on healthy subjects. It involves a combination of fMRI and positron emission tomography (PET) – a technique used to visualize the distribution of a mildly radioactive tracer substance. Patients are injected with radioactively tagged glucose for this purpose. However, simultaneous use of fMRI and PET is only possible at a few locations worldwide – TUM's Department of Nuclear Medicine being one of them. Summarizing his method, Riedl explains: "Since active brain areas require substantial energy, which the body provides in the form of glucose, we can indirectly detect their activity in this way." Use of fMRI enables significantly greater spatial resolution than PET, thus also allowing focused imaging of the processes between the brain areas. "We know that the most energy is consumed at the synapses – the contact structures between the neurons – by the receptors," describes Riedl. The researchers are applying this cellular model of energy consumption at the macroscopic scale here, using fMRI and PET scans to observe not single cells but millions of neurons simultaneously. "Based on the distribution pattern of energy consumption within a network, we can thus determine the direction of information flow in the human brain," Riedl concludes.

By studying interaction between the various brain areas, the researchers hope to gain new insights. Ultimately, their aim is to improve their understanding of the brain and its disorders in order to develop new therapeutic strategies. Alzheimer's disease is a case in point. The TUM-NIC researchers now know how the amyloid and tau protein deposits typical of Alzheimer's spread out along different networks. "We are currently investigating how this type of pathological deposit modifies the activity and structure of the network areas affected," reveals Sorg. "Our expectation is that this focus on brain network changes will greatly improve our therapeutic options, for instance by enabling us to identify disease mechanisms more precisely and target treatment accordingly."



Improving diagnostic capabilities and quantifying structural changes in the brain are also key focus areas for the researchers. Prof. Mühlau, for instance, has succeeded in automating – and thus greatly simplifying – evaluation of MRI scans of diseased brain areas in patients with multiple sclerosis (MS). These images display areas of damage, or lesions, which previously had to be measured by hand to track their growth. The algorithm developed by Mühlau and his team is particularly well suited to analyzing large volumes of data. This enables large-scale comparison of MRI scan measurements with

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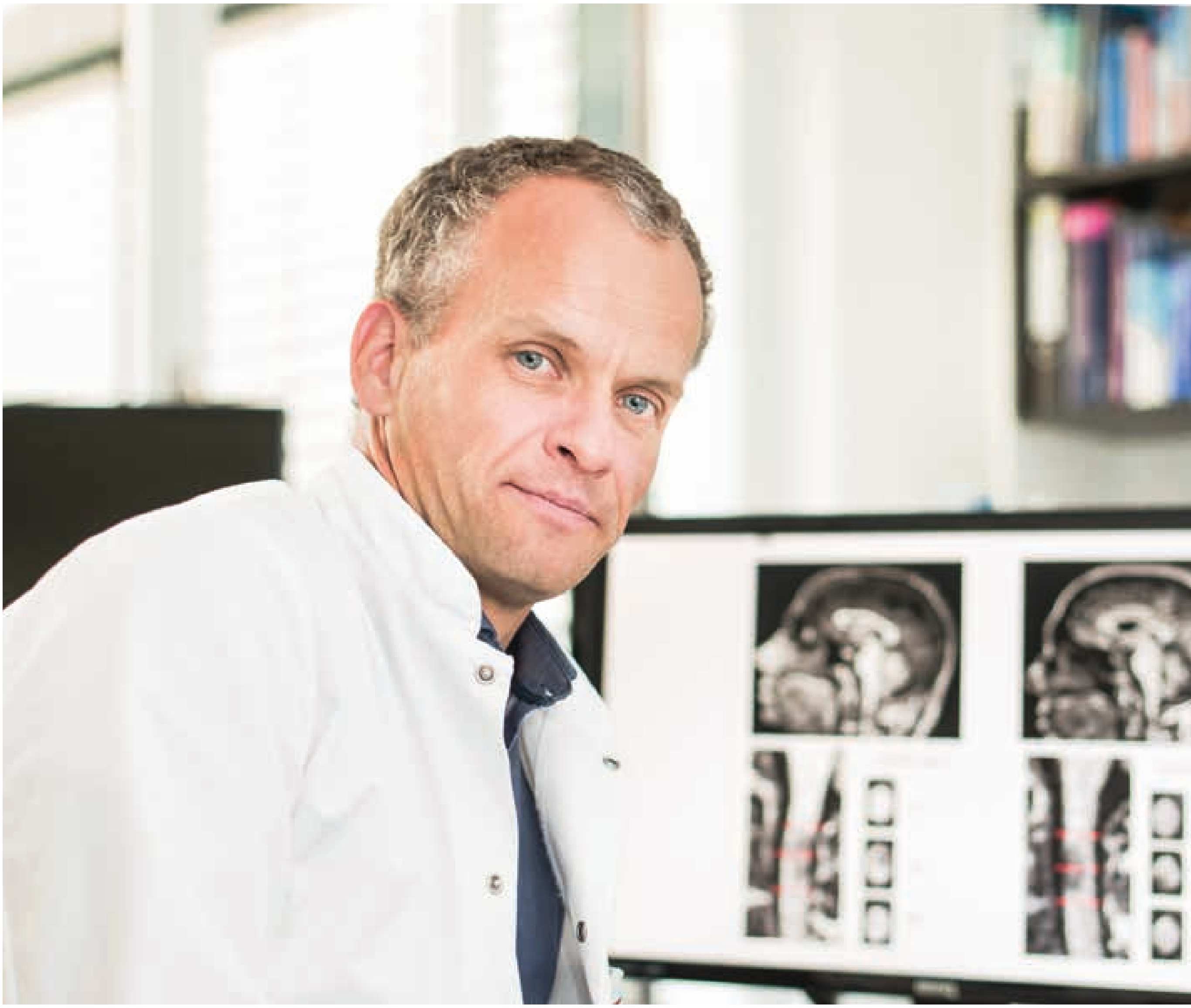

"With experts in neurology, neuroradiology and psychiatry, TUM-NIC is able to bridge many different neurological conditions and explore entirely new horizons in this area."

Mark Mühlau

values from other scientific fields such as genetics or immunology, thus yielding new insights into MS. For instance, use of this technique clarified that MS susceptibility genes – the genes associated with increased risk of developing the condition – have only a minor impact on disease progression, meaning that this is likely to be determined by other factors. Mühlau's group also developed software for reliable measurement of grey matter. This tissue compartment of the brain contains neuronal cell bodies and is also damaged in MS. Prior to this, the white matter lesions typical of MS would interfere with evaluation. Although originally developed for MS, the researchers are now also using the software for Alzheimer's patients. "The last few years in neuroscience have seen an increasing tendency to consider malfunctions across multiple diseases," Ploner confirms. And TUM-NIC's interdisciplinary research approach excels precisely in this area.

Karoline Stürmer