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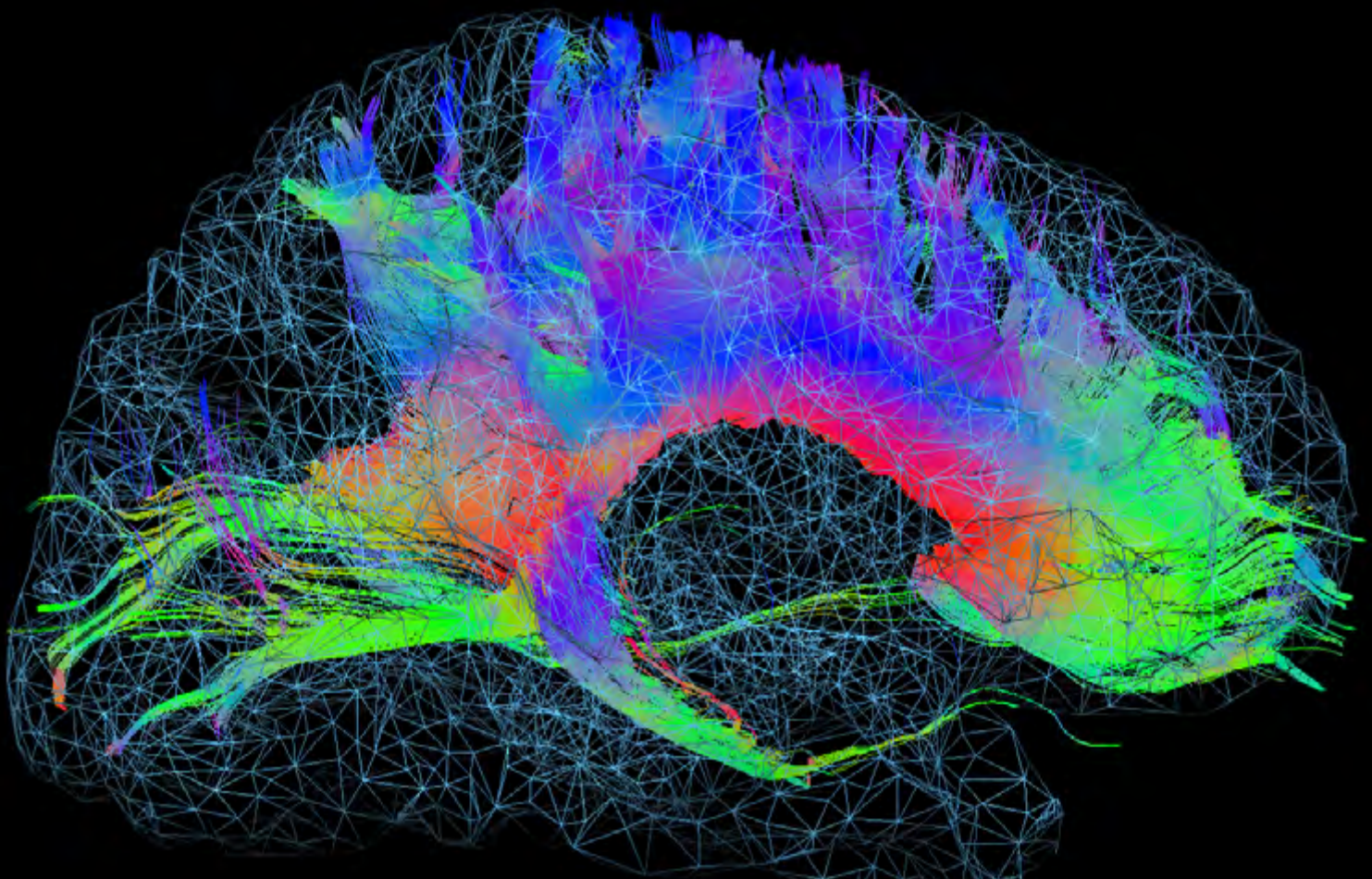


EXTINCTION LEARNING

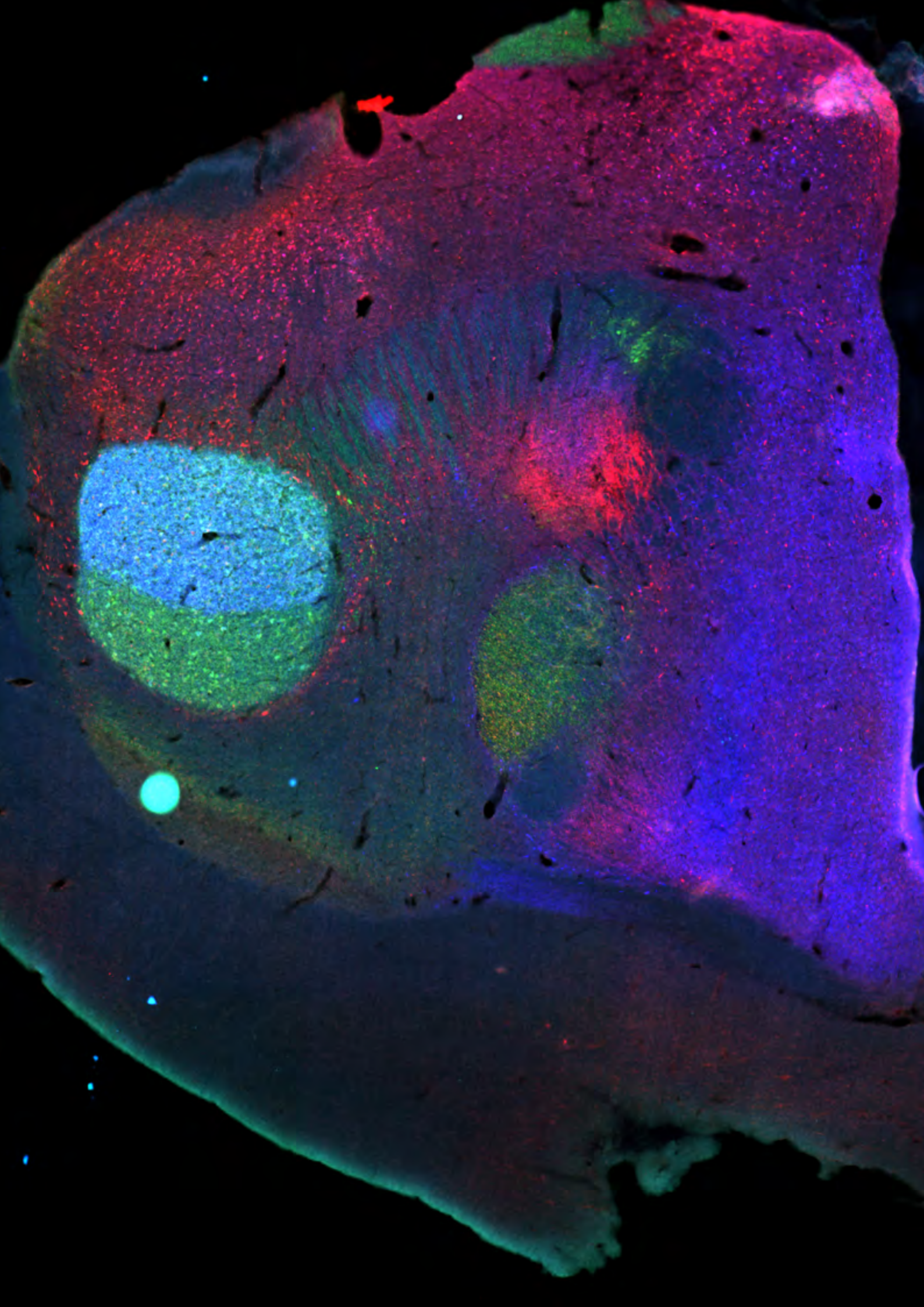
What happens in the brain during learning

Why the context of an experience is crucial in this process

And how research into extinction learning helps patients overcome pain and anxiety

#35

Special Issue 2025:
SFB 1280
Extinction Learning



EDITORIAL

photo: rs

The Greek philosopher Heraclitus wrote that no man ever steps in the same river twice. By that he meant that the uniformity of life is an illusion and, like a river, our reality is constantly changing. For example, no two journeys from our home to work are actually the same, despite them feeling monotonous. This is because our brain creates a model of an average journey over time and all the small daily trivialities melt into it.

But what happens if a child suddenly jumps onto the road in front of your car while you're driving? Squealing, you just manage to come to a halt. Thank God nothing has happened to the child! You're relieved, but your hands are shaking and your heart is beating like crazy. This journey can no longer be melted into the model of your usual commute. Suddenly, two memories of the journey to work exist in your brain in parallel to each other: an everyday one without any emotionality and a second one filled with fear. Which of these two memories will dominate your thoughts when you get into your car the next morning? Will you be relaxed, or will your hands shake because you expect another catastrophe? If it's the latter, it's possible that you'll soon be afraid of every car journey and that this fear will become more and more widespread, increasingly dominating your life. Then you will be like 260 million people worldwide who suffer from an anxiety disorder.

Let's go back to the beginning of that fateful day. When you got into the car in the morning, you naturally didn't expect a child to jump out in front of your car. When that happened, your brain thus generated a prediction error. This marks the beginning of extinction learning, in which a second memory trace – the extinction memory – is created in the brain. It inhibits the initial memory trace and can generalize, so that the fearful thoughts spread to many similar situations. But what exactly is the brain's prediction error, where does it occur, what effect does it have? How does the extinction memory manage to inhibit the other memory trace? Why is it active every time you sit behind the wheel? Why do some people shake off anxieties, while others suffer from them their whole lives? And how do we ensure that the memory enabling us to live an anxiety-free life wins the competition between the memory traces? These are questions that we want to answer in Collaborative Research Center (SFB) 1280 and about which we are reporting in this issue.

Prof. Dr. Onur Güntürkün, Spokesperson of SFB 1280

RUBIN ONLINE

All articles of this special issue:

→ **news.rub.de/rubin-extinction-learning-2025**

i ABOUT THE COLLABORATIVE RESEARCH CENTER EXTINCTION LEARNING

The Collaborative Research Center 1280 Extinction Learning (SFB 1280) is a cooperative research network of Ruhr University Bochum, University of Duisburg-Essen, Leibniz Research Centre for Working Environment and Human Factors at the Technical University of Dortmund and Philipps University Marburg. In 20 sub-projects, around 90 people are researching extinction learning in a transdisciplinary and international team. Ruhr University Bochum is coordinating the Collaborative Research Center.

The SFB 1280 Extinction Learning is funded and made possible by the German Research Foundation.

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

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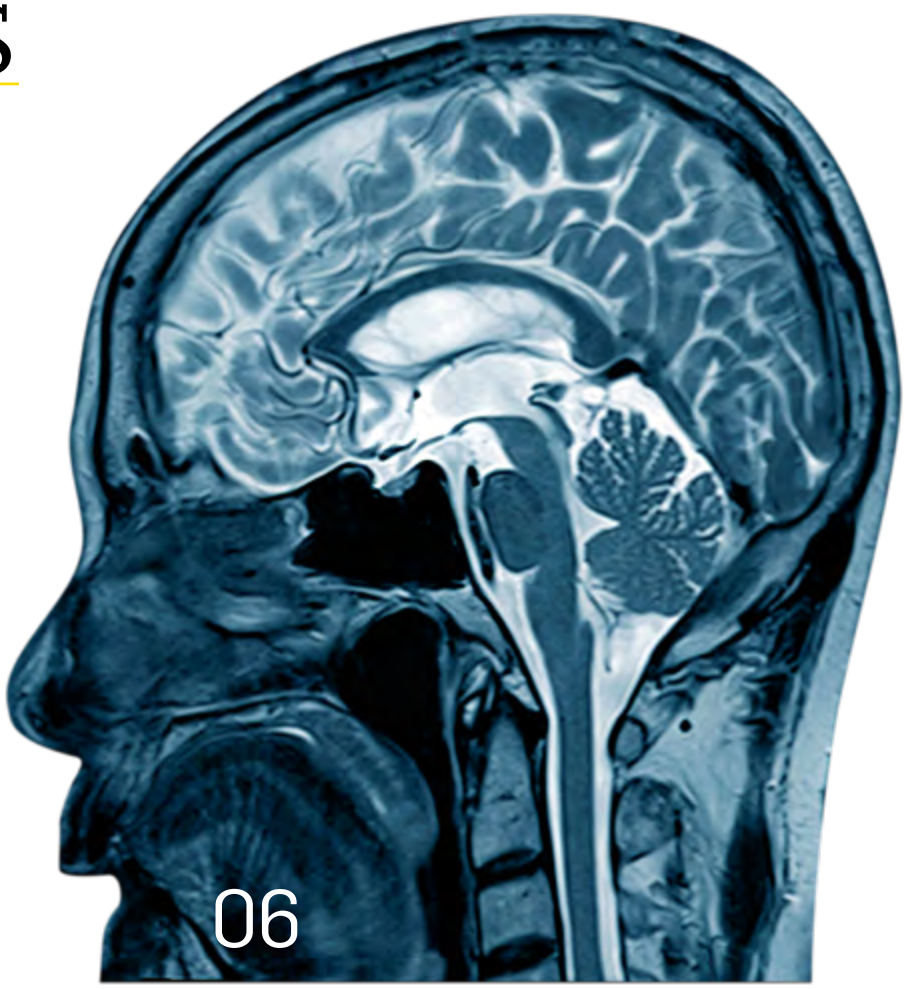

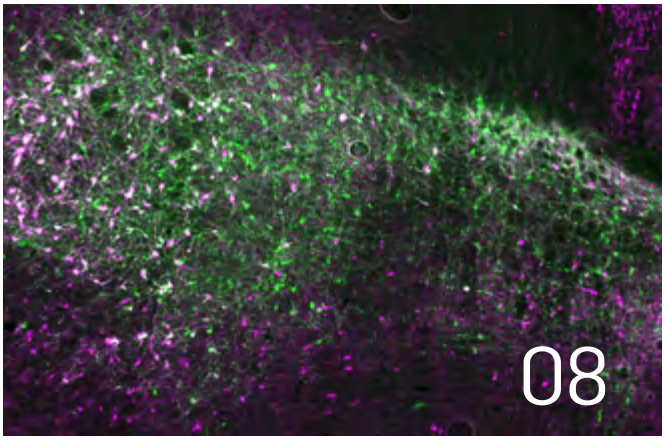

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>
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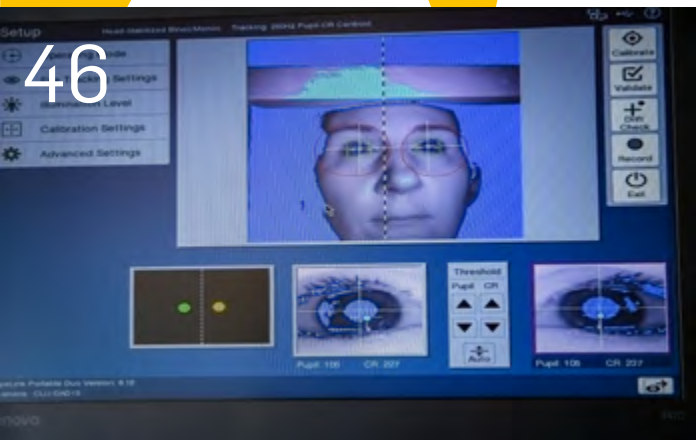


WHAT IS EXTINCTION LEARNING?

When an existing memory trace in the brain is confronted with a second memory trace, which inhibits the first one, this is referred to as extinction learning.

1.

HOW ARE MEMORIES ACTUALLY FORMED?

When we have a new experience, the information about this memory is processed by neurons in the cerebral cortex and the hippocampus. During this, special proteins strengthen the cortical synaptic connections. If an experience is strong enough or if we remember it often right after the experience, the hippocampus frequently activates the neurons of the cerebral cortex that are involved in the memory. The cortical memory trace thus becomes permanent.

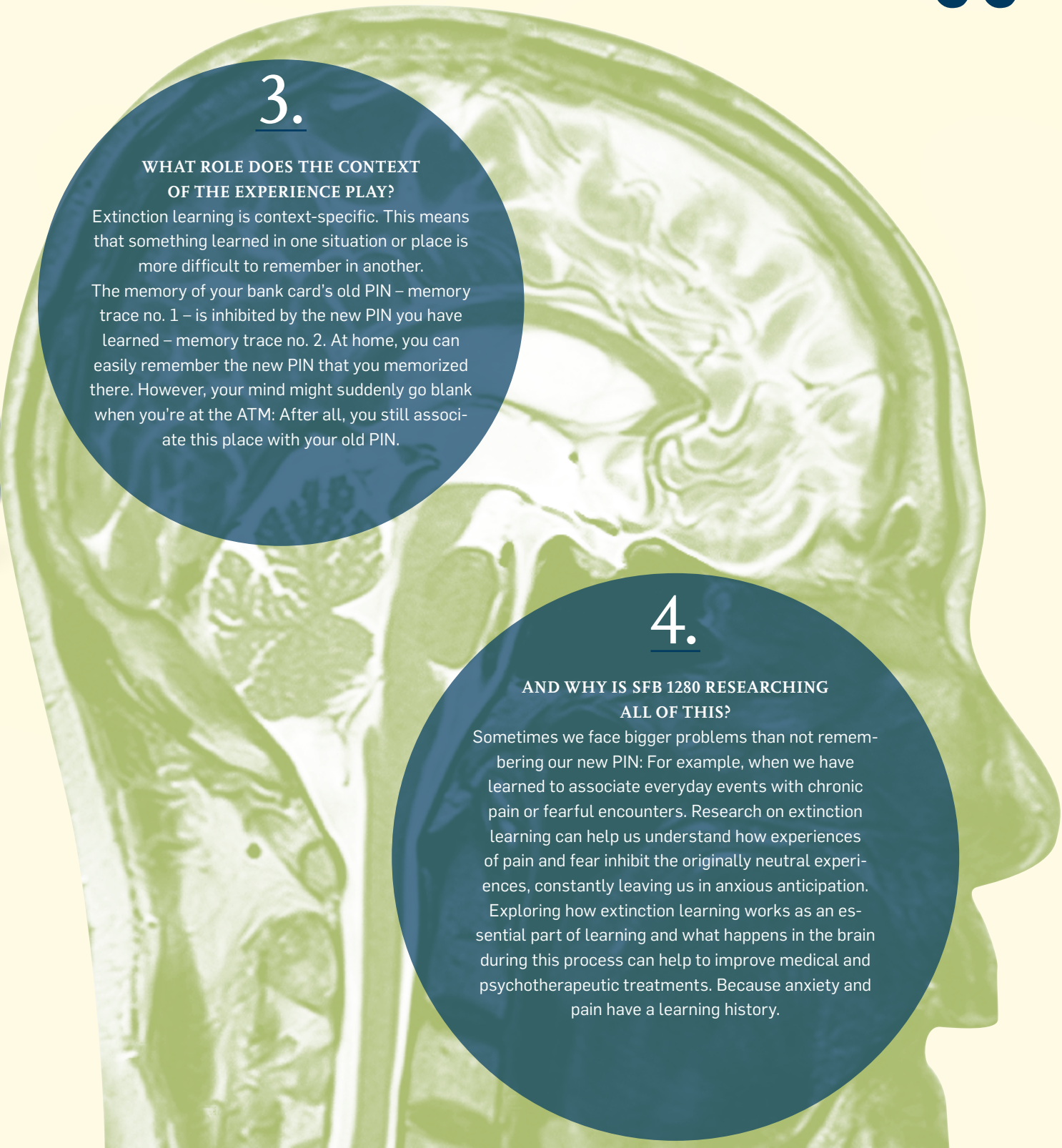
2.

WHAT HAPPENS IN OUR MEMORY DURING EXTINCTION?

If we have strong memories of something, but we have a new experience that makes an impression on us, it is possible that this new memory will inhibit the original memory. New information is then laid over the old memory trace and inhibits it to a certain extent. When this is the case, we talk about "extinction". However, extinction does not mean that the original memory is permanently removed, but instead refers to a relearning process that overlays what was previously learned, although the original trace is still present.

MOST OF WHAT WE THINK WE HAVE FORGOTTEN HAS NOT BEEN FORGOTTEN AT ALL.

Onur Güntürkün



3.

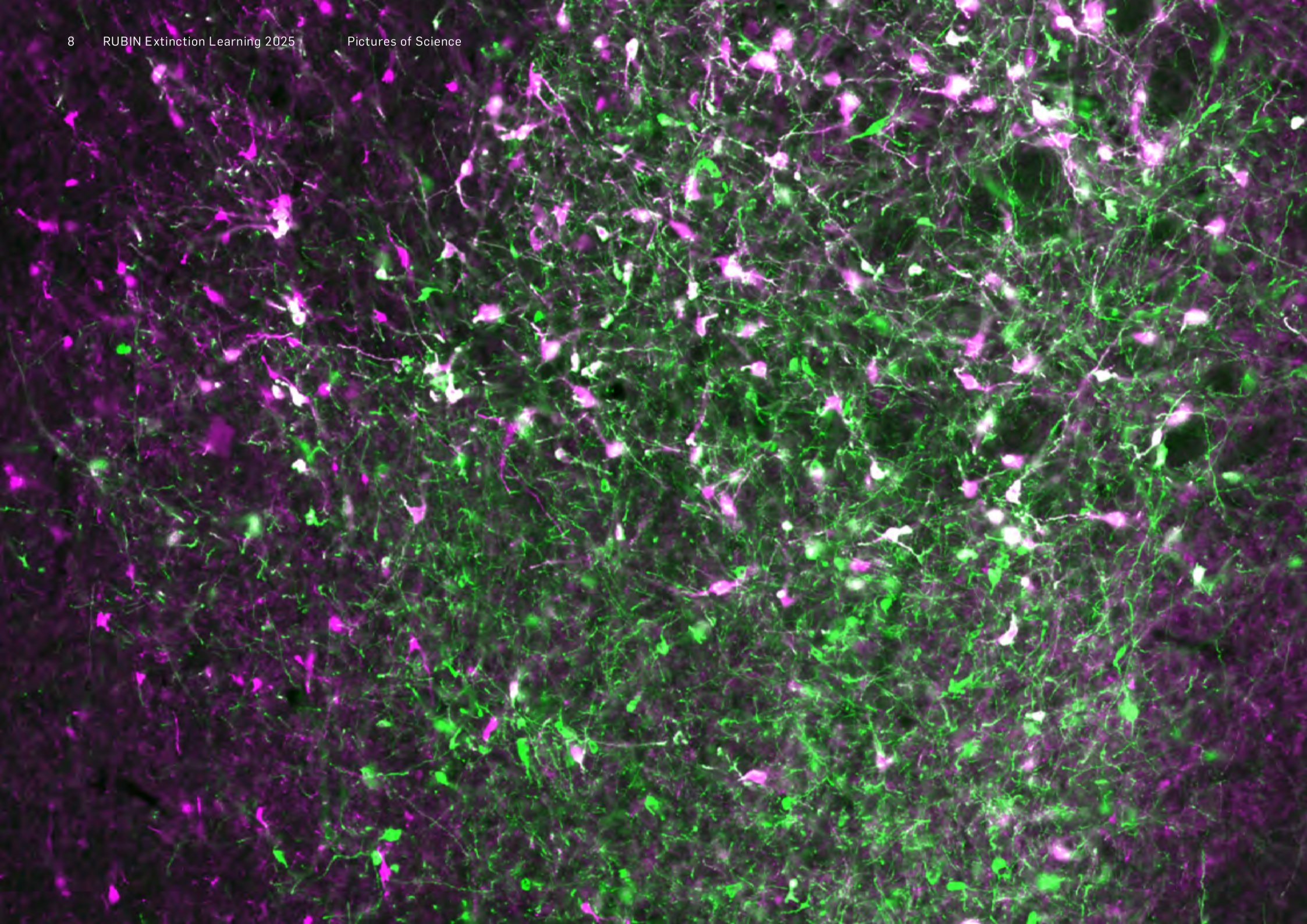
WHAT ROLE DOES THE CONTEXT OF THE EXPERIENCE PLAY?

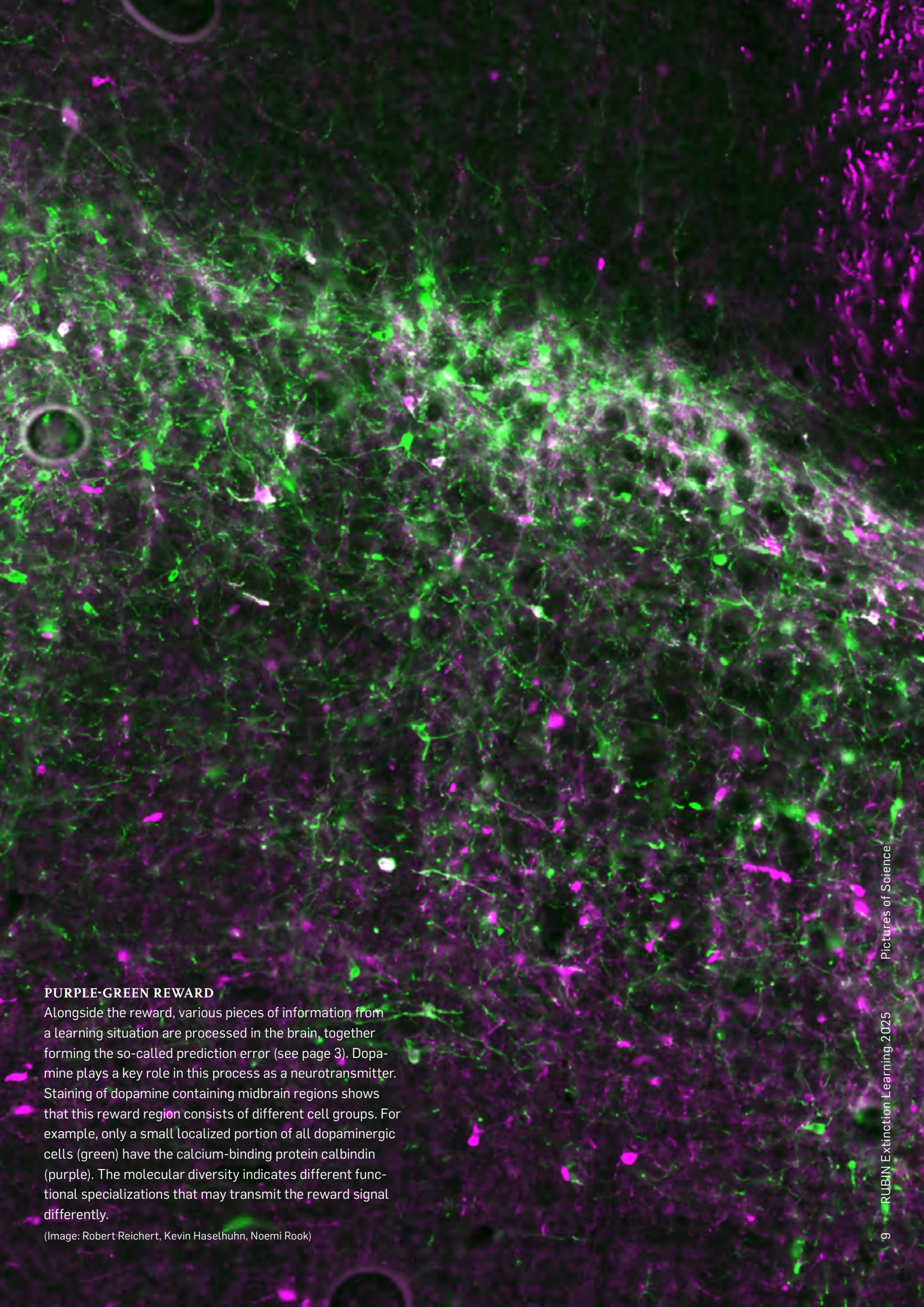
Extinction learning is context-specific. This means that something learned in one situation or place is more difficult to remember in another.
The memory of your bank card's old PIN – memory trace no. 1 – is inhibited by the new PIN you have learned – memory trace no. 2. At home, you can easily remember the new PIN that you memorized there. However, your mind might suddenly go blank when you're at the ATM: After all, you still associate this place with your old PIN.

4.

AND WHY IS SFB 1280 RESEARCHING ALL OF THIS?

Sometimes we face bigger problems than not remembering our new PIN: For example, when we have learned to associate everyday events with chronic pain or fearful encounters. Research on extinction learning can help us understand how experiences of pain and fear inhibit the originally neutral experiences, constantly leaving us in anxious anticipation. Exploring how extinction learning works as an essential part of learning and what happens in the brain during this process can help to improve medical and psychotherapeutic treatments. Because anxiety and pain have a learning history.

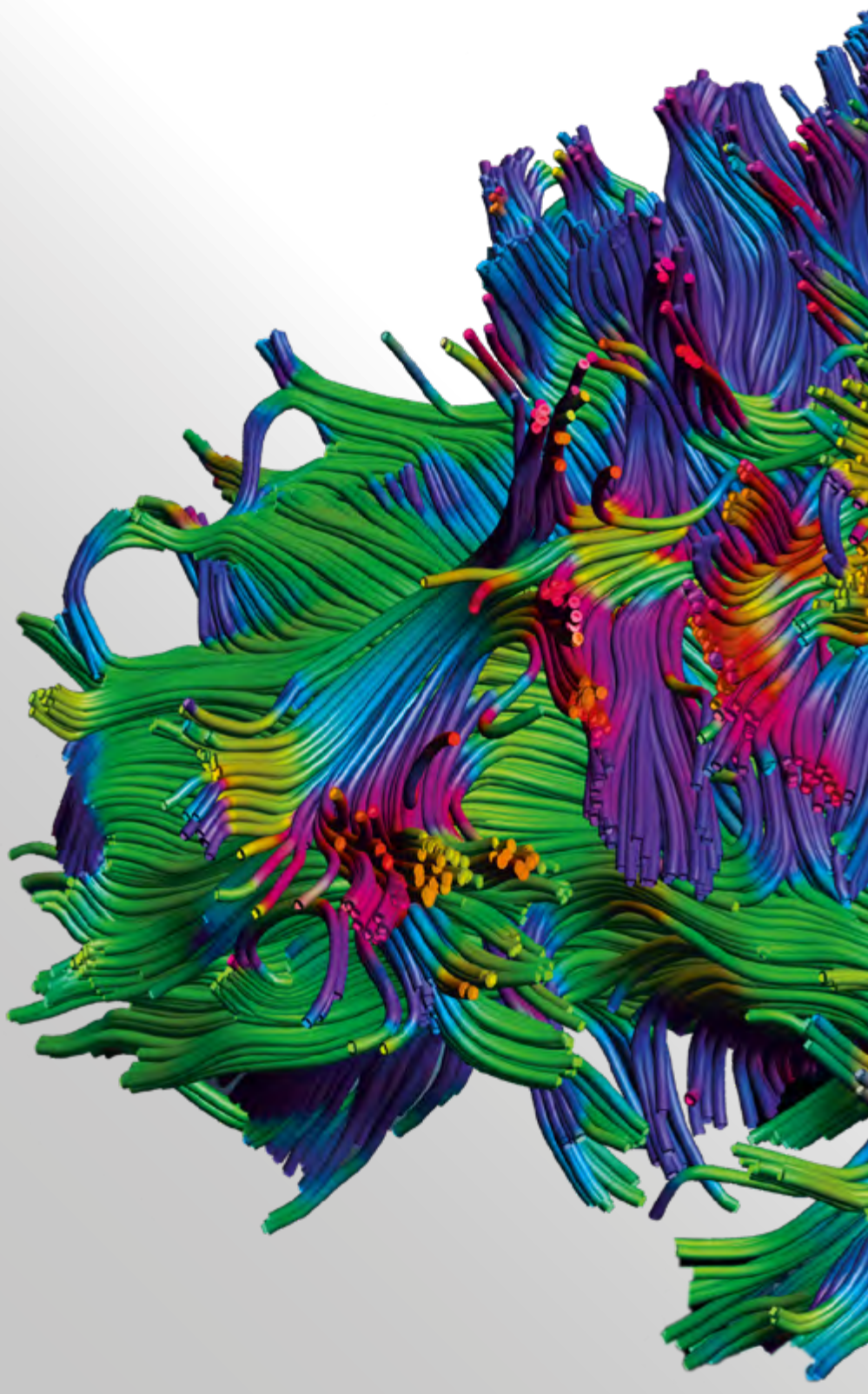




PURPLE-GREEN REWARD

Alongside the reward, various pieces of information from a learning situation are processed in the brain, together forming the so-called prediction error (see page 3). Dopamine plays a key role in this process as a neurotransmitter. Staining of dopamine containing midbrain regions shows that this reward region consists of different cell groups. For example, only a small localized portion of all dopaminergic cells (green) have the calcium-binding protein calbindin (purple). The molecular diversity indicates different functional specializations that may transmit the reward signal differently.

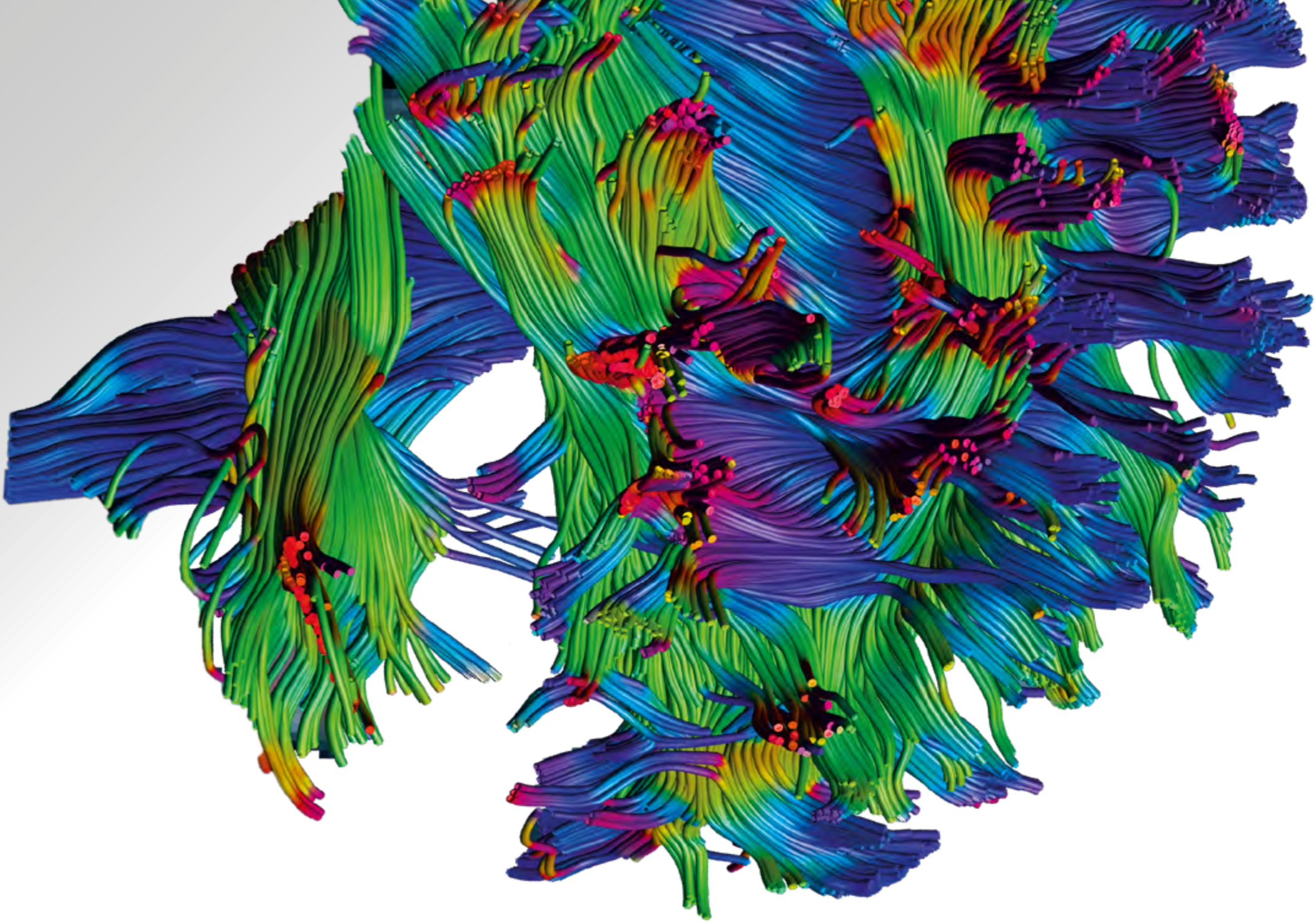
(Image: Robert Reichert, Kevin Haselhuhn, Noemi Rook)



BRAIN ART

This image looks like modern art. In reality, however, it is a highly technical representation of the human brain – a so-called diffusion tensor image (short: DTI). Using a specific sequence of radiofrequency pulses during magnetic resonance imaging (MRI), researchers have succeeded in schematically depicting the course of nerve fibers in the brain. The MRI scanner records the diffusion movement of water molecules in the brain. This is restricted by natural barriers such as cell membranes, such that the direction of diffusion of the molecules reflects the course of the nerve fibers. Each directional axis is assigned a specific color. Red for fibers that go from left to right, green for front to back, and blue for fibers that go from top to bottom.

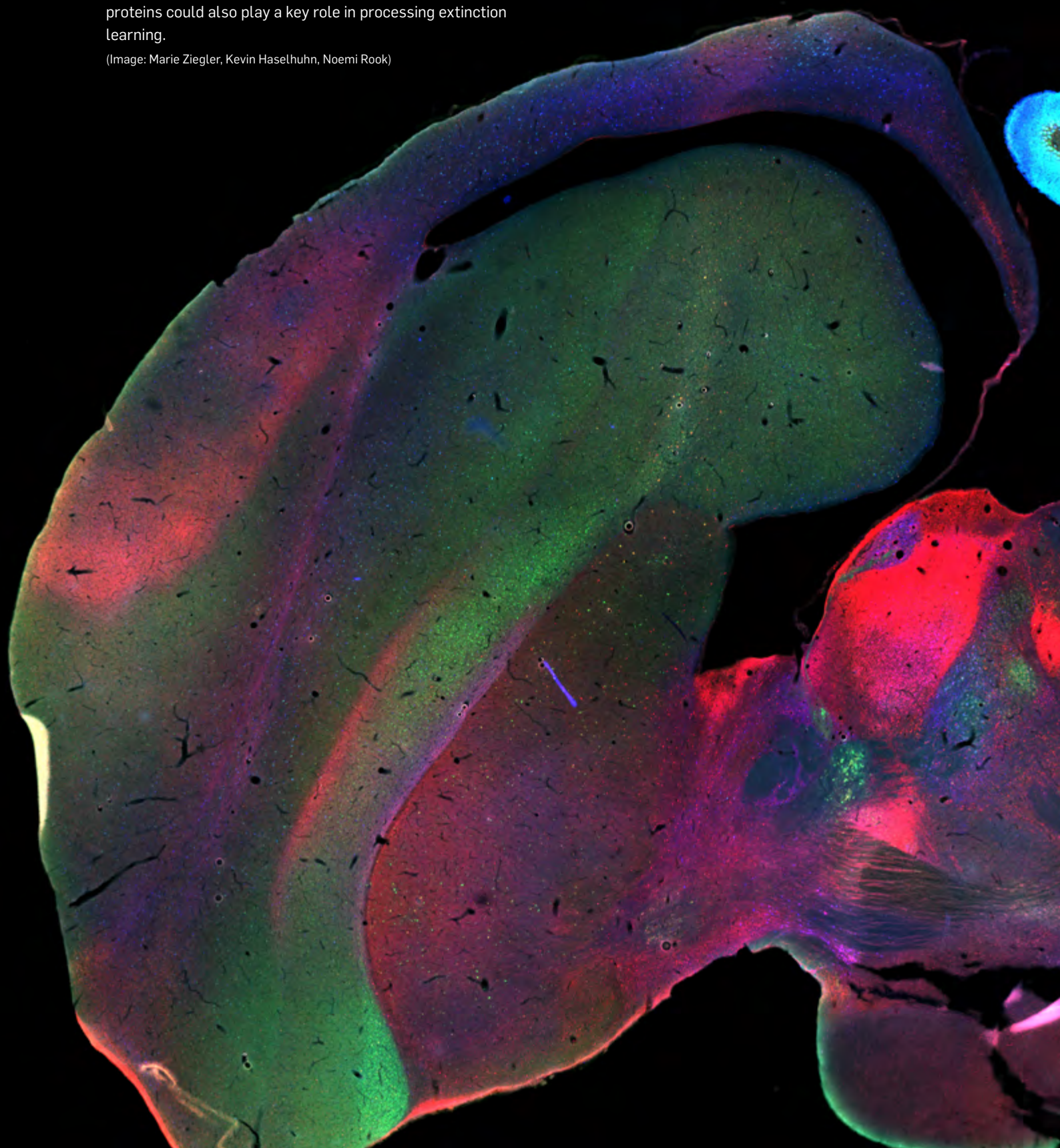
(Image: Christoph Fraenz, Erhan Genç)

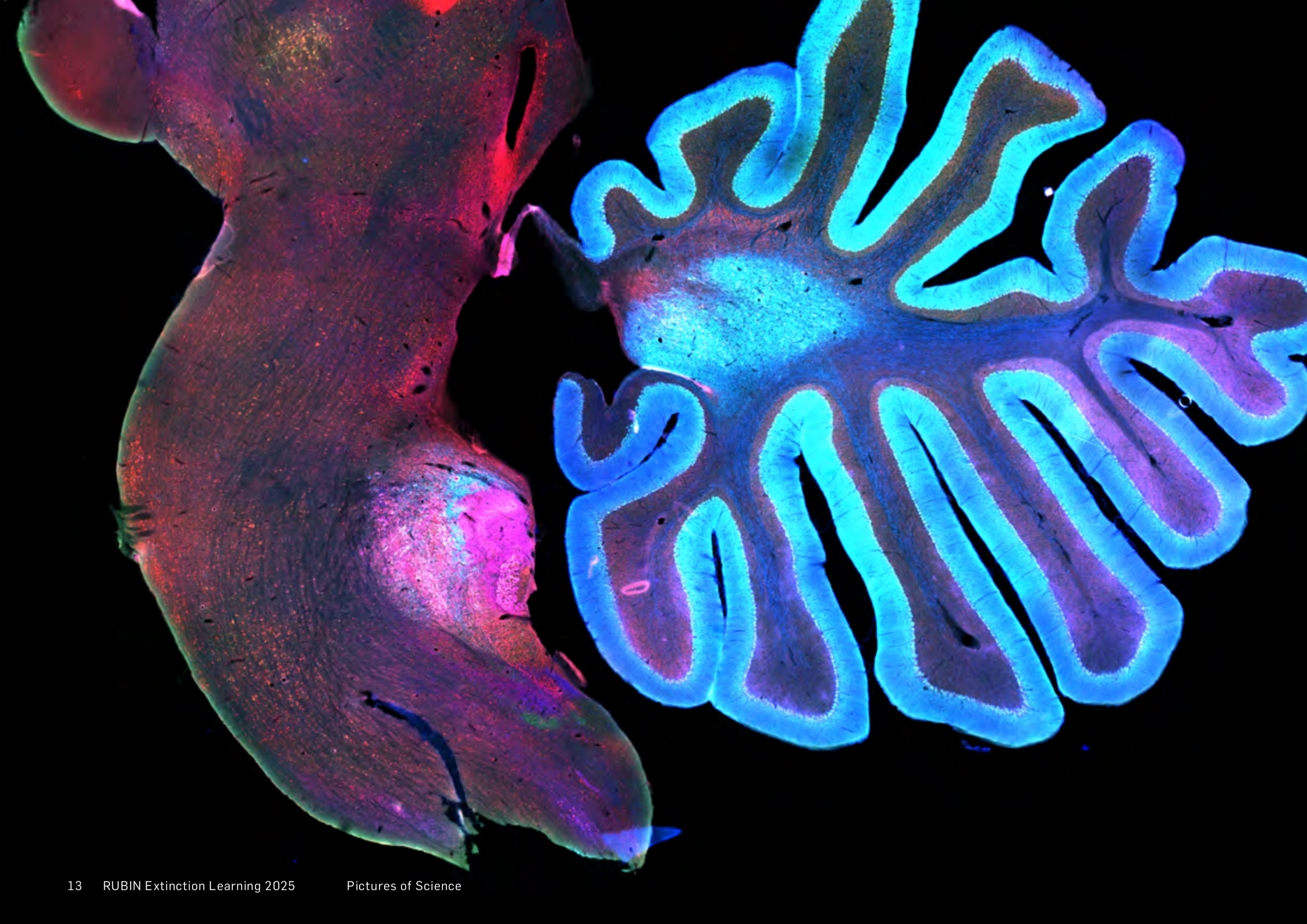


TRACING LEARNING SIGNALS

How do birds process learning signals? This is what researchers from the Extinction Learning Collaborative Research Center want to find out. Although birds do not have a prefrontal cortex, their visual system processes the corresponding stimuli in hierarchically arranged levels, similar to mammals. To identify these levels and to better understand this process in the pigeon brain, researchers stain cell groups containing involved proteins with different colors (depicted in red, green and blue). These proteins could also play a key role in processing extinction learning.

(Image: Marie Ziegler, Kevin Haselhuhn, Noemi Rook)





WHY CAN YOU LEARN ABOUT THE HUMAN BRAIN WITH **PIGEONS?**

The birds are an integral part of research. They provide many insights into how learning and memory work.

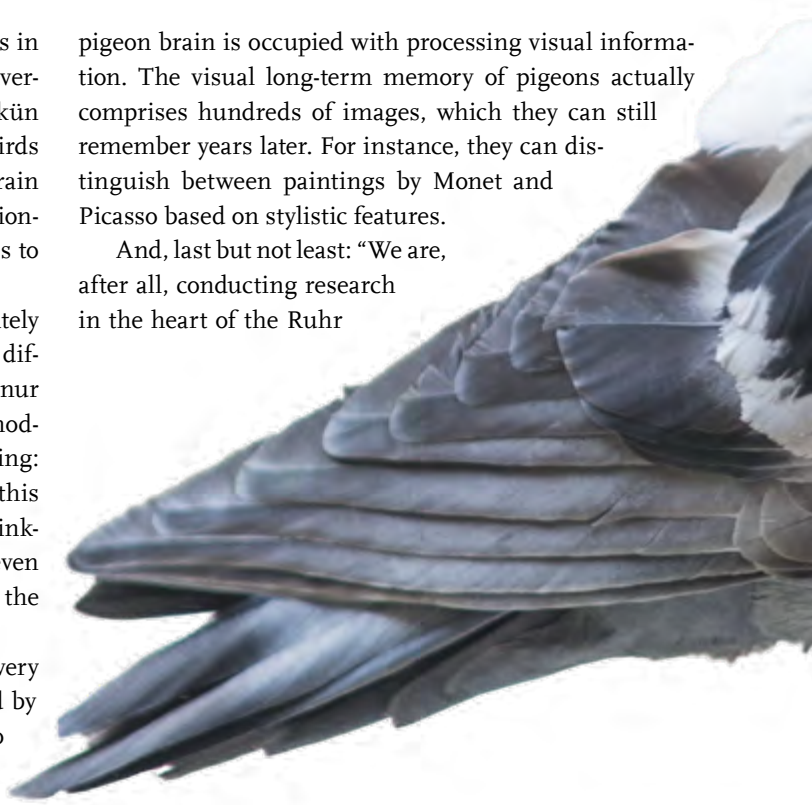
They are among the most important employees in the Department of Biopsychology at Ruhr University Bochum: Pigeons! Professor Onur Güntürkün and his human colleagues have been using birds for decades to find out how memory, learning, and the brain generally work. But why them? As birds, aren't they evolutionary far too distant from mammals and thus from humans to be able to draw conclusions about our behavior?

"The fact that birds have undergone evolution separately for over 300 million years, that they have a completely differently structured brain, is of benefit to us," explains Onur Güntürkün. "It is even a strategy in science to take a model that is completely different to humans. We are studying: Where are the similarities? Where are the differences? In this way, we can identify core mechanisms of learning and thinking that correspond to both species. And then we'll look even further: Do they also exist in octopuses and bees?" says the biopsychologist.

Pigeons also offer many other advantages. They are very tame, rarely react aggressively, and can easily be touched by trusted people. Pigeons also have a tremendous ability to learn and an unusual tolerance to frustration. They can reliably work on a cognitively demanding task for several hours uninterrupted and are not offended if it doesn't work for a while.

And there's another thing that sets them apart: "Like most birds, pigeons have a highly developed visual system. Their retina sends information to other regions of the brain via two to three million nerve fibers," explains Onur Güntürkün. As a comparison: Humans only have around one million nerve fibers per eye. Consequently, a very large proportion of the pigeon brain is occupied with processing visual information. The visual long-term memory of pigeons actually comprises hundreds of images, which they can still remember years later. For instance, they can distinguish between paintings by Monet and Picasso based on stylistic features.

And, last but not least: "We are, after all, conducting research in the heart of the Ruhr area," says Onur Güntürkün with a wink. What animal represents this region better than the pigeon? It used to be the poor man's racehorse. And, like the Ruhr area has undergone a structural transformation, pigeons now work at the university. That makes sense, right?



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HUMAN
1.3 to 1.5 kilos
PIGEON
2.3 grams
=
WALNUT
ELEPHANT
5 kilos
SHREW
0.1 gram
SPERM WHALE
8.5 kilos

Biopsychology

A SMALL BUT **POWERFUL BRAIN**

Pigeons are intelligent, hard-working and evolutionarily far removed from humans. This combination makes them particularly interesting for the Bochum team's research. (photo: rs)

Pigeons are hard-working learners. And quite clever. A stroke of luck for the Bochum biopsychologists, who, thanks to them, are making advances into the fundamental mechanisms of extinction learning.

A yellow square lights up. Peck! The pigeon hits the glowing square with its beak. Shortly after, a flap at its feet opens up and releases a food pellet, which disappears into its beak in an instant. With the aid of rewards of this kind, pigeons quickly learn to associate the reaction to an actually neutral stimulus such as the illuminated square with a positive outcome. The Biopsychology research group at Ruhr University Bochum, however, is above all interested in what happens when the birds have to relearn, i.e. if the yellow square suddenly no longer results in a reward. The mechanisms of this extinction learning are the focus of Collaborative Research Center 1280.

Unlike in many other experiments, Bochum biopsychologists Dr. Roland Pusch and Professor Onur Güntürkün work with birds instead of mice, rats, or humans. "We are studying an animal whose last shared ancestor with these three species lived 324 million years ago: the pigeon," explains Onur Güntürkün. The reason for this is simple: Pusch and Güntürkün are searching for the fundamental components of extinction learning that should even be the same in species far distant from humans from an evolutionary perspective.

"Fear conditioning has been used for many studies with humans, rats, and mice," explains Roland Pusch. In these studies, animals and humans learn to associate a neutral stimulus with unpleasant consequences, such as a mild electric shock – and then to unlearn this association again. Such experiments are obvious, as reduced extinction learning ability following unpleasant experiences is central to anxiety disorders. But do studies of fear conditioning provide general information about extinction learning? Or are the results only specific to learning fear? Or possibly specific to the studied species? From reward-based studies with pigeons and comparisons with earlier work on other species, the Biopsychology team is hoping to gain general insights into extinction learning. ▸

Roland Pusch and Onur Güntürkün are looking into the general principles of extinction learning in Collaborative Research Center 1280. (photo: rs)

"There are pigeons wherever you find humans. They live right alongside us and no one would think that the perfect adaptation to identical habitats is possible with a brain that is organized completely differently," says Güntürkün. As a comparative cognitive neuroscientist, he is interested in the cognition of various animal species. "Birds have taken a different path to mammals in the evolution of their brains," he explains.

Comparable learning processes in pigeons and humans

The cerebral cortex, which makes up the majority of the human forebrain, developed in pigeons independently of mammals and is limited to areas that process sensory information. Most other areas are organized in an as yet unknown fashion and appear under the microscope to be a disorganized gray mass – i.e. completely different to the six-layered cerebral cortex of the mammalian brain. Despite these major differences, birds, and thus also pigeons, display comparable learning processes and functionality of extinction learning, as Pusch and Güntürkün showed in a series of experiments.

To do this, they taught the birds to peck at colored squares for a food reward. These experiments took place in behavioral boxes in which the animals were presented with various stimuli. Not all stimuli were linked to a food reward. By specifically switching off individual areas of the brain pharmacologically, the researchers were able to uncover their contribution to extinction learning. The comparative results were mixed: Some brain structures appeared to do exactly the same as is known in mammals, while other regions displayed altered functions. For example, the hippocampus in mammals learns the context, i.e. the surrounding stimuli, in which the extinction learning takes place. This is similar in birds, but the visual system is also specialized in this. "A large proportion of the principles is thus the same and has a long evolutionary history," summarizes Roland Pusch. "However, on the long evolutionary path that birds and mammals have taken separately, changes have also occurred. Nevertheless, it is astounding how similar the mechanisms still are after 324 million years."

Prediction error triggers new learning process

In a further experiment, the two researchers looked at the activity of individual neurons during learning. "For this experiment, the pigeons had to work extremely hard," says Roland Pusch. The animals first learned that pecking a certain visual stimulus results in a food reward. As soon as they achieved their learning criterion, the color of the context, i.e. the ambient lighting, changed from white to red. From that moment on, pecking on the previously rewarded visual stimulus no longer led to a food reward. The pigeons repeatedly pecked at the pattern in annoyance, but nothing happened. They gradually stopped reacting: Extinction learning took place.

Güntürkün and Pusch wanted to find out what happens in the brain in the moment in which the previously learned pattern of behavior no longer worked. The absence of reward after a previously correct action leads to what is known as a prediction error in the brain. This event signals to the brain that an expectation was not fulfilled and a new learning process should begin. The experiments showed that the prediction error changes various components of the previously learned behavior.

The researchers expanded their experiment. After the extinction learning was completed, they changed the ambient lighting back to the original color. The pigeons immediately displayed the learned pecking behavior again, although it was also not followed by a reward in this phase. The learned behavior was not forgotten and its reappearance took place exclusively in expectation of a reward. The analysis of neuron activity showed: Information about the context – i.e. the environment in which the learning took place – is mainly stored in a region of the brain called the hippocampus. This information is provided in a region in the frontal area of the pigeon brain. There, decisions are prepared and made depending on the expectation of reward in the respective test environment.

Evaluating individual neurons in the brain produces a detailed picture of the thought machinery, but remains restricted to small regions of the brain. To study the entire brain at work, Onur Güntürkün, together with Dr. Mehdi Behroozi, developed a system in which pigeons can carry out extinction learning in an MRI scanner. For the first time, they were able to visualize the process of extinction learning in the entire brain in a non-human animal with high spatial resolution. ▸

Always hard at work: In behavioral boxes like this, the animals learn that reactions to certain visual stimuli are associated with food rewards. (photo: RUB, Marquard)

Roland Pusch originally investigated the sensory systems of fish. He is now fascinated by pigeons as a research animal. (photo: RUB, Marquard)

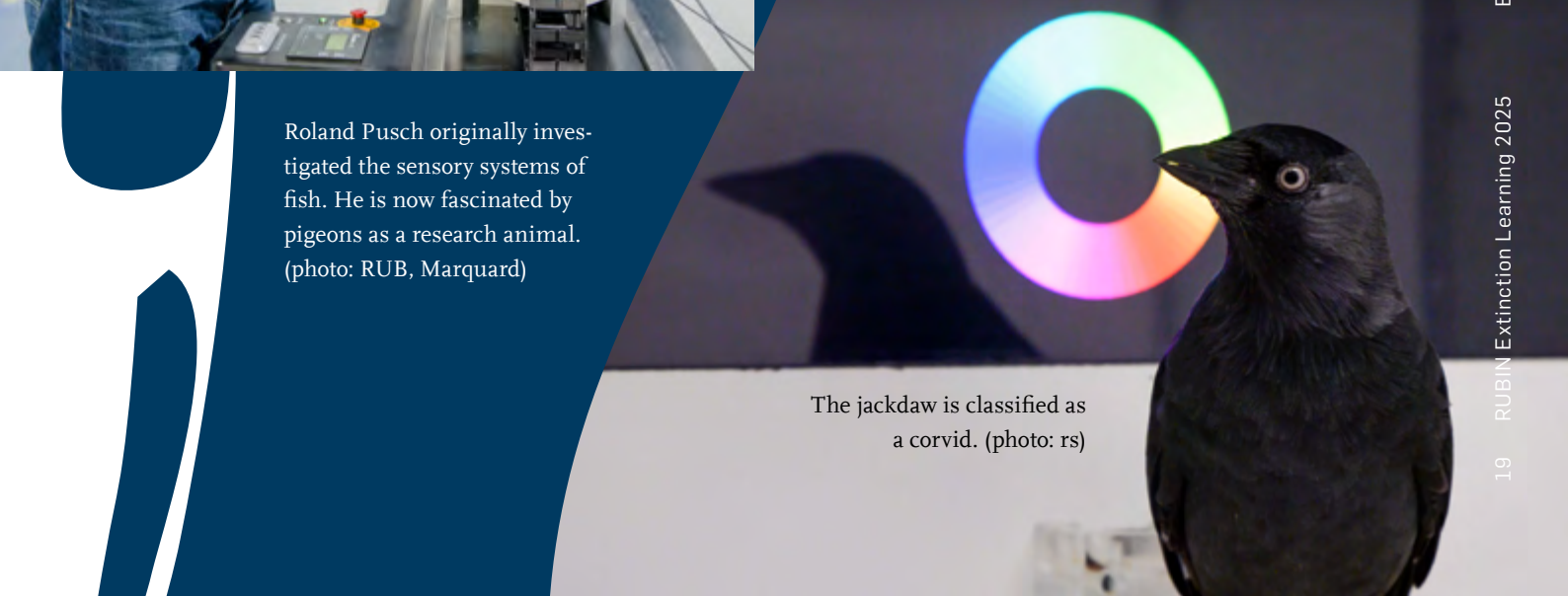
IT ALL DEPENDS ON THE CONTEXT

Appropriate behavior depends on the context. What is appropriate in one situation may be completely inappropriate in another. But what exactly is context? Professor Jonas Rose and his team are investigating context with pigeons, crows and jackdaws in another sub-project of the Collaborative Research Center 1280. The group "Neural Basis of Learning" teaches pigeons certain behaviors that the animals later learn to abandon. This extinction learning depends on the context. In other words, the behavior is stopped only in the context of extinction, while in other contexts, the behavior occurs again – a phenomenon that is referred to as renewal.

"A context is intuitively understood as the surrounding of learning, for example a room or a certain background," says Jonas Rose. "However, our experiments have shown that any stimulus can become a context – even a small visual stimulus that is present during extinction learning." However, if this stimulus was minimally changed – for example, if it lit up a second later – the rules of learning change and the animals no longer perceive it as the context. This shows that context is learned and independent of the physical stimulus properties.

In further studies, Jonas Rose's team would like to find out more about context dependency, for example whether the social context also influences extinction learning. The group has been researching social communication and attention in jackdaws for some time. "These birds are very clever animals whose intelligence is comparable to that of higher mammals," says Rose.

jwe



The jackdaw is classified as a corvid. (photo: rs)

As soon as extinction learning begins, activity is shut down in regions of the brain that process visual stimuli, which are important for the experiment. “The animal continues to perceive everything,” explains Güntürkün. “However, the processing pays less attention to these stimuli.” At the same time, limbic regions of the brain, which regulate emotional processes and are possibly connected to the animal’s surprise at not receiving a reward, despite believing it has done everything right, become active. In addition, the pigeon brain appears to go through a phase of restructuring its action program so that motor regions are activated. This makes sense, as the animal no longer has to react to the previously rewarded stimulus.

Common core of extinction learning

“Our studies show that there is a core of extinction learning that extends from humans to pigeons,” deduces Onur Güntürkün. “The most important trigger for extinction learning is the prediction error. It occurred in all species that have been studied so far. It is a wake-up signal that plows through most areas of the brain and gradually changes the way that the neurons react to changing conditions.” The regions that are changed in their coding processes are partly identical in birds and mammals. The prefrontal cortex for decision-making, the hippocampus for context memory, and the amygdala for emotion coding appear to be an indispensable trias that occurs in a similar way in these distant relatives.

“With functional MRI, it is now possible to study extinction learning in the entire brain of a non-human animal,” says Güntürkün. “Our results show that focusing on individual regions is not effective, as it only covers a small proportion of the processes in the brain. It is just as important to concentrate on how the processing changes in sensory areas, how the entire action processes are reconstructed, and how these changes are coordinated across large parts of the brain.”

Extinction learning comprises the largest part of the brain, and the prediction error leads to a massive change in the interaction between different areas. These insights are opening up approaches to developing therapeutic processes in many different areas for humans who are unable to find a way out of their anxiety because extinction learning is not functioning correctly for them. The Bochum pigeons will continue to help understand these processes – and earn even more delicious food pellets as they do so.

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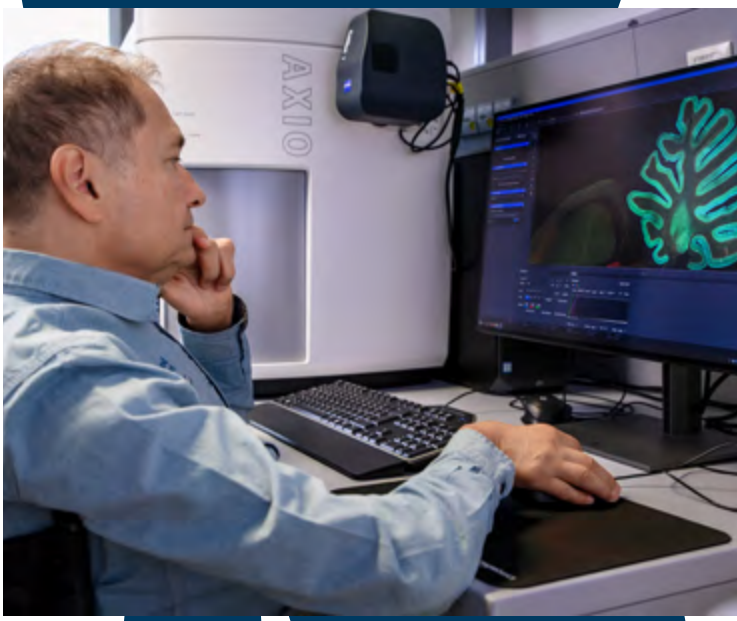
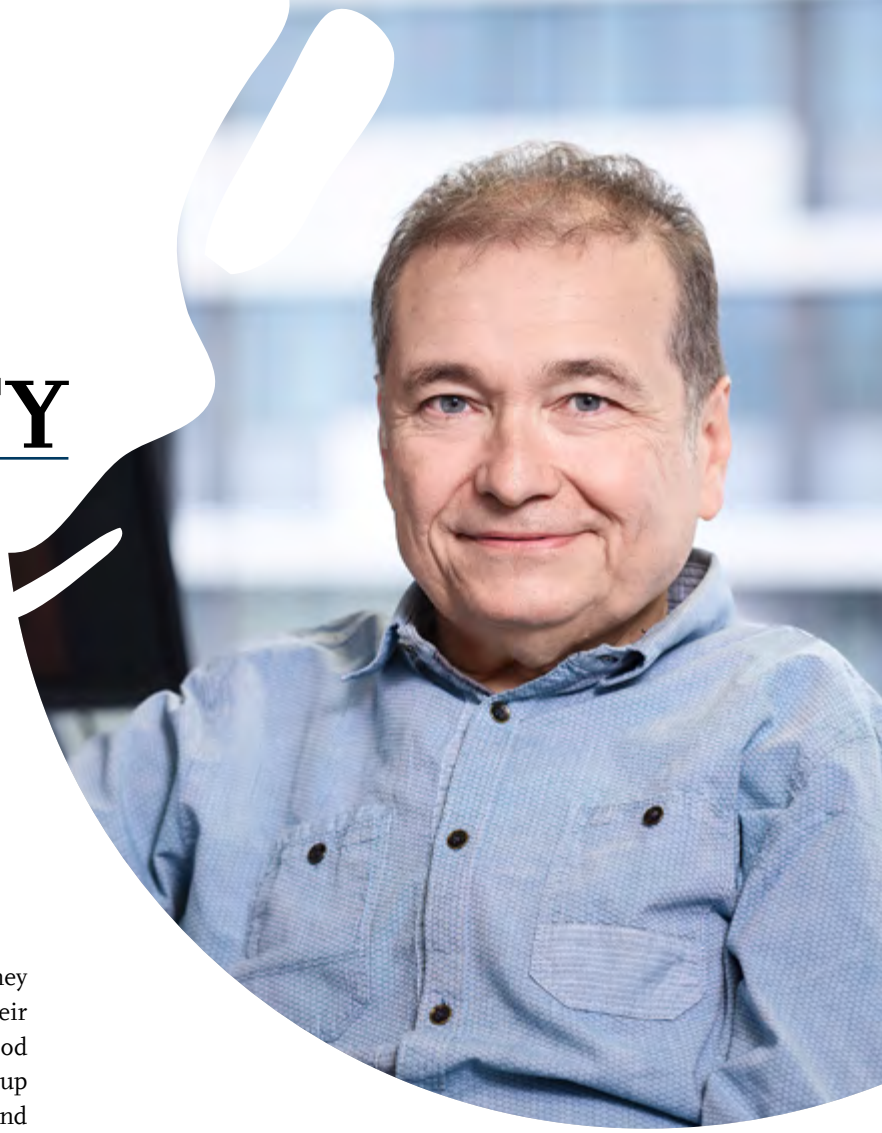
> ”OUR STUDIES SHOW THAT THERE IS A CORE OF EXTINCTION LEARNING THAT EXTENDS FROM HUMANS TO PIGEONS.“
>
> Onur Güntürkün



A special feature of the Collaborative Research Center 1280 is that extinction learning is studied at all levels, from individual cells to behavior. (photo: rs)

Point of View

THE VALUE OF CURIOSITY



Fundamental research: Many people in academia are concerned with the pursuit of knowledge, without an explicit application in mind. Is that a good thing? A commentary by Onur Güntürkün.

Many researchers are familiar with this situation: They are asked what they are working on, talk about their project and then hear the question: What is it good for? I too am familiar with this situation. My research group is interested in how the brains of birds and humans work and how behavior arises. Like many other basic researchers, we cannot answer the question about the meaning of our work by claiming that we want to cure a disease, stop climate change or develop a new product for industry. We do research to gain knowledge. Does that make sense? Yes, it does.

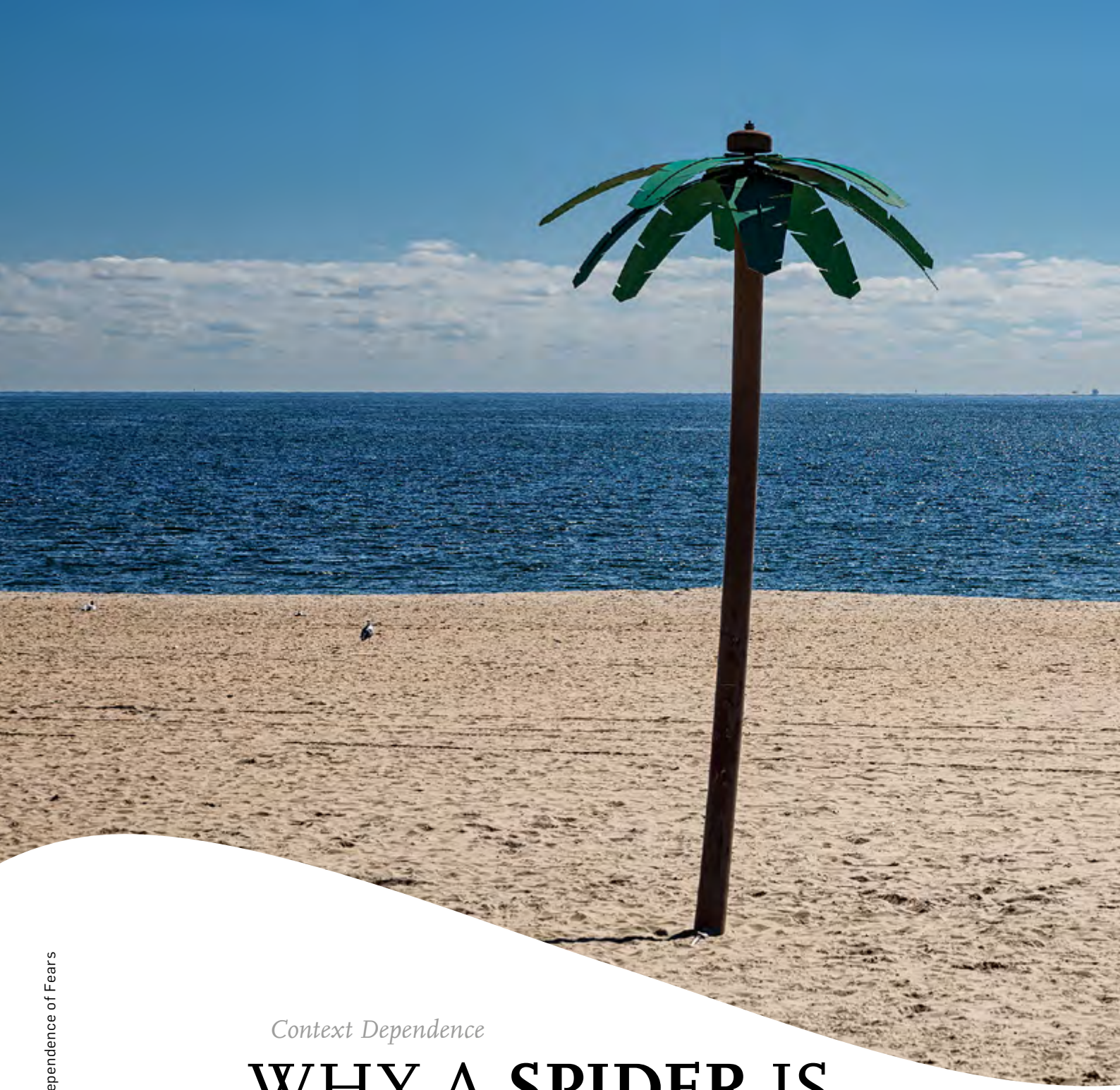
Decades ago, there was a small group of people interested in how to create a single-stranded ribonucleic acid (RNA) that could be used to transfer the genetic code for a protein. When asked with a mocking smile what this was supposed to achieve, they spoke of vague possibilities that it could cure diseases. They didn't really know. But they didn't dare to say that they were just curious to see if RNA could be artificially produced. So curious that one of them accepted the risk of leaving her home country to do research in another country. There she was later demoted by her university because of the uselessness of her research, found asylum in another laboratory and continued her research under the most difficult conditions and without financial support. In 2023, Katalin Karikó, together with her colleague Drew Weissman, received the Nobel Prize for her fundamental research on mRNA technology. This research enabled the COVID-19 vaccine and thus saved millions of lives. Most of these saved people do not know that they owe their lives to Katalin Karikó's curiosity and thus to basic research.

Basic research creates the basis for later applications. Without it, we would not have the modern world in which people in Germany live to be 80 years old on average, listen to music while jogging and turn on the light at home in the evening with a simple push of a button. Speaking of light: When Michael Faraday was working on the first electric motor, the British Prime Minister is said to have asked him who would need such a thing. He probably smiled mockingly. Faraday is said to have replied: "There is a chance that you will soon be able to tax it."

Even if basic researchers definitely don't want their research to be applied in any way, their curiosity can prove extremely useful. The mathematician Godfrey Harold Hardy was interested in number theory and was convinced that it was useless. He was wrong: His research became the basis for the cryptography currently used by your bank to protect your savings from online access by criminals.

I am interested in why birds can be so smart even though they have such a small brain that is so different from ours. Crazy, isn't it? I'm just very curious.

text: Onur Güntürkün, photo: rs



Context Dependence

WHY A **SPIDER** IS SCARIER IN THE CELLAR THAN IN THE THERAPY ROOM

Letting go of learned fears is difficult. New research findings reveal that the environment in which we learn the fear could also play a crucial role in unlearning it.

In the experiment, various holiday landscapes form a so-called context in the experiment.

At home, Nikolai Axmacher learned that it is bad manners to slurp when eating soup. The professor of neuropsychology at Ruhr University Bochum now often travels to China, where not slurping soup is considered impolite. This is just one example of the importance of context, which Axmacher is researching in the Extinction Learning Collaborative Research Center.

"Normally, what we learn tends to be generalized," he explains. "This means that we can also apply what we have learned in other contexts. For instance, if someone passes their driving test in France, they can also drive a car in Germany." Only when the context is no longer valid, such as when eating soup in China, do we become aware of it and its importance. We normally cope with this by adapting our behavior. However, the context plays a bigger role when it comes to getting rid of something we have learned, such as a phobic fear. "Someone with a fear of spiders is afraid of them no matter where they encounter them," explains Nikolai Axmacher. If this fear is very restrictive for the person, they may perhaps visit a psychotherapist and undergo exposure therapy. Accompanied by the expert, the patient gradually learns that the spiders in this country are harmless and there is no need to be afraid of them. Eventually, the patient remains completely calm when encountering a spider – at least in the psychotherapist's practice. "However, when they go home and encounter a spider in the cellar, the fear is often present again," says Nikolai Axmacher. "It clearly depends on the context in which the unlearning took place."

Axmacher aims to investigate this context dependence more closely in the Collaborative Research Center. What ▶

happens in the brain when we learn or unlearn something? Researchers are investigating these questions using functional magnetic resonance imaging on healthy participants. However, Axmacher gains a higher time resolution and more direct insights with intracranial EEG recordings, where electrical signals from the neurons in the brain are measured directly by electrodes, while the participant – in this case an epilepsy patient – takes part in an experiment.

To apply this method, Axmacher's team is cooperating with Ruhr Epileptology at Knappschaftskrankenhaus Bochum led by Professor Jörg Wellmer. The neurologist treats patients whose epilepsy cannot be controlled with medication. To plan the surgical procedure precisely, the specialists must first find out exactly where the point of origin of the patient's epileptic seizures is located. To do this, they insert electrodes into the suspected areas of the brain and measure the electrical activity in these areas. They then have to wait for an epileptic seizure to occur under observation. During this waiting period in the hospital, the Collaborative Research Center team invites suitable patients to take part in a learning experiment. To investigate the context dependence of learning and unlearning, the research team came up with the following story: Backpacker Nina is visiting various countries. As she has little money, she has to spend the night in cheap accommodation where the electrical appliances do not work very reliably. Some appliances, such as the hairdryer, washing machine, dryer, toaster and fan, are broken and give Nina an electric shock, causing her to let out a loud scream. The scream represents an aversive stimulus for the participants. The sequence of one of four typical holiday landscapes, the electrical appliances and Nina's reaction is shown 16 times in the learning phase of the experiment so that the participants quickly learn which of the appliances are faulty and cause an electric shock.

In the second phase of the experiment, the extinction phase, some of the appliances that were previously unsafe are now safe: Two out of three electrical appliances do not give Nina an electric shock. The participants are once again shown the landscape and electrical appliance 16 times and are asked whether they expect the appliance to be safe or unsafe. This causes them to relearn and finally know which of the appliances is safe. In

Elias Rau-Thalheimer works with epilepsy patients at Knappschaftskrankenhaus Bochum.

The researchers can directly measure nerve cell activity in patients who have electrodes implanted in their brains due to epilepsy.

Nikolai Axmacher is Professor of Neuropsychology at the Ruhr University Bochum and is involved in several sub-projects of the Collaborative Research Center Extinction Learning.

the third phase, new contexts are shown and the participants are once again asked whether or not they expect an appliance to be faulty. "If the hairdryer was always broken during the initial learning, but always safe during extinction learning, people were uncertain whether it would be broken during this phase," says Nikolai Axmacher about the observations so far. As a result, there remained uncertainty regarding hairdryers, which the researchers wanted to better understand using the measurements in the brain.

During the three phases of the experiment, the researchers observed which areas of the brain show changes in electric activity. "We have now been able to include 50 participants in the study," reports Nikolai Axmacher. "Two regions of the brain, the amygdala and the hippocampus, are of particular interest to us because they are significantly involved in storing memory content. This is why we have primarily included people in the study whose electrodes are implanted in these areas of the brain." Although the results have not yet been evaluated in full and are thus still provisional, the research team was surprised that the amygdala did not show increased activity during the initial learning. This conflicts with similar experiments in animals in which increased activity in the amygdala was observed.

Given the importance of context, the researchers are evaluating activity patterns while various travel landscapes are being viewed. "Our hypothesis is that it depends on the similarity of the contexts," explains Axmacher. "If the landscape viewed is similar to one in which the hairdryer was always broken, you also expect it to be broken now. If the landscape is similar to one in which the dryer was in working order, you expect that now too."

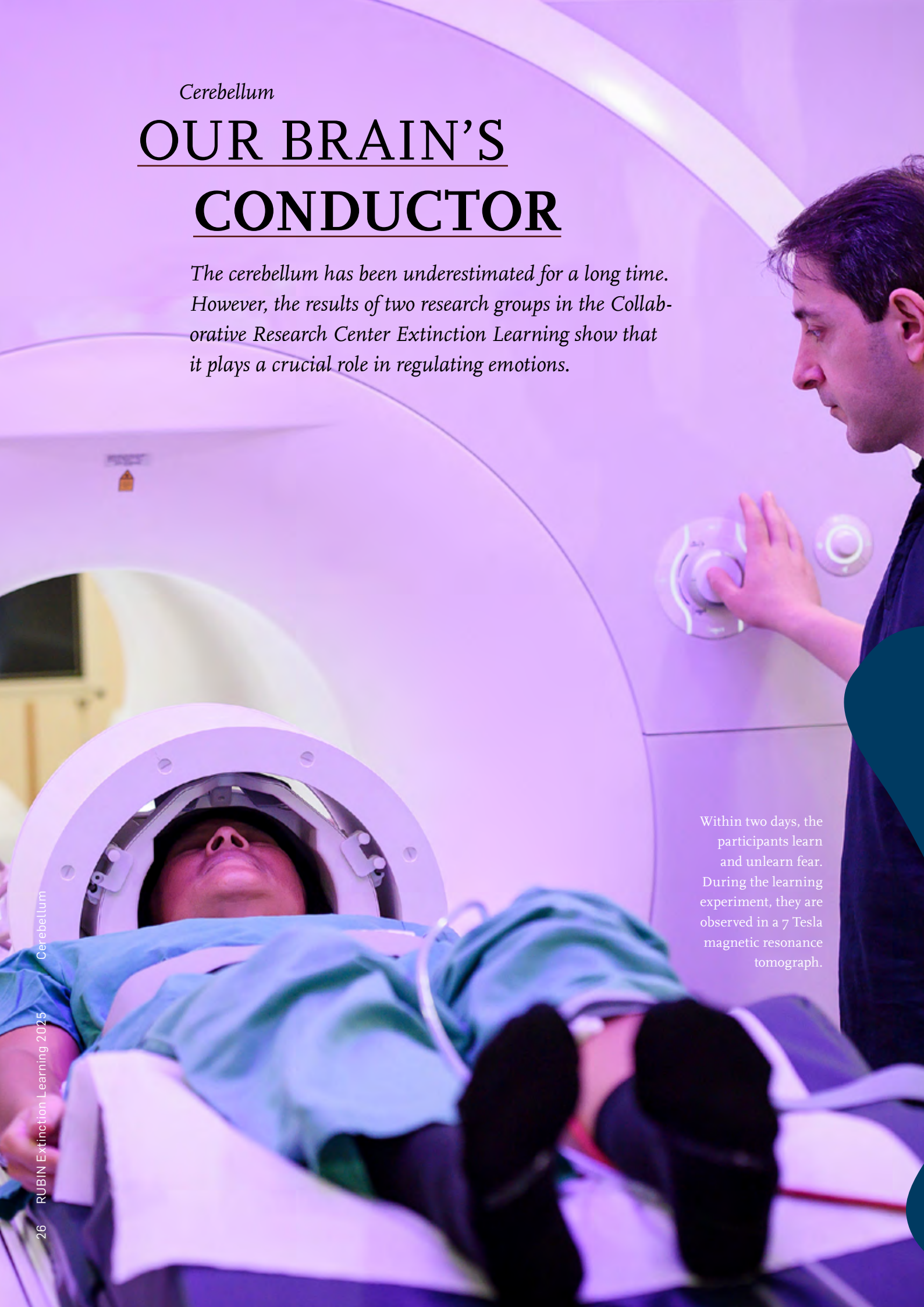
If this hypothesis were to be confirmed, it would mean that as many contexts as possible should be taken into account when treating phobias. If the patient learns in the cellar with the therapist that a spider is harmless, they can perhaps also encounter it in the garage without being afraid.

text: md, photos: rs

Cerebellum

OUR BRAIN'S CONDUCTOR

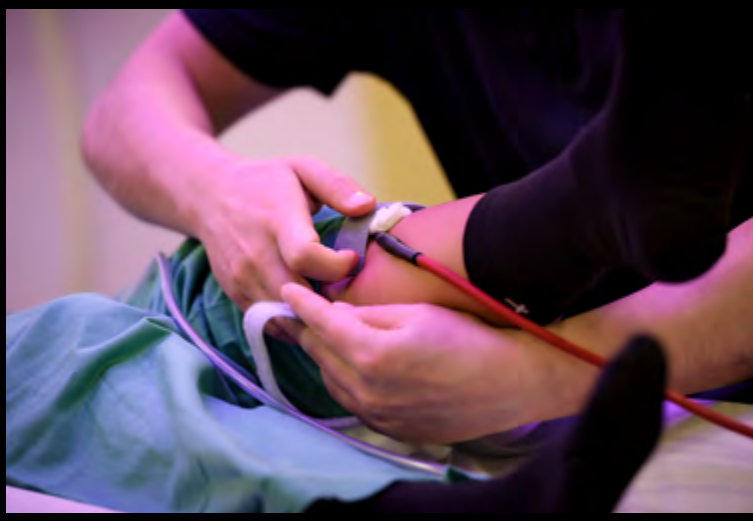
The cerebellum has been underestimated for a long time. However, the results of two research groups in the Collaborative Research Center Extinction Learning show that it plays a crucial role in regulating emotions.



Within two days, the participants learn and unlearn fear. During the learning experiment, they are observed in a 7 Tesla magnetic resonance tomograph.

Brushing your teeth, riding a bike, eating an apple: We are only able to perform these everyday actions thanks to an often-overlooked region of the brain known as the cerebellum. It weighs just 150 grams, but contains 80 per cent of our neurons. As a motor control center, it controls key motion sequences in the body and is responsible for our balance and coordination. It has been known for several years that the cerebellum also controls cognitive processes such as problem solving. And not only that. For a long time, the fact that the cerebellum also plays an important role in regulating our emotions – such as when processing fear – has been ignored. Professor Melanie Mark from Ruhr University Bochum and Professor Dagmar Timmann from the University of Duisburg-Essen are two of the first researchers to provide experimental evidence that the cerebellum contributes towards both the learning and the extinction of conditioned fear responses.

To investigate the role that the cerebellum plays in fear learning, the two neuroscientists conducted learning experiments – the neurologist with humans and the neurobiologist with mice. "In our studies, we draw on classic fear-conditioning experiments and compare healthy humans and mice with those that have a cerebellar disease, ataxia," says Timmann, summarizing the shared study design.



To trigger fear in the learning experiment, the participants feel an unpleasant electric shock on their shin when they see a certain image on the monitor. They quickly learn to associate the image with the electric shock.

In her latest study, the clinical neuroscientist selected 20 participants who suffer from rare cerebellar diseases such as spinocerebellar ataxia type 6 (SCA6), in addition to 20 healthy people. "The movement disorder SCA6 is triggered by a genetic defect similar to Huntington's disease and only affects a very small number of people in Germany," explains Timmann, who has been offering ataxia consultations at Essen University Hospital for many years. "SCA6 is associated with a loss of a specific type of neuron in the cerebellum, the Purkinje cells. The Purkinje cells are important as intermediaries between the cerebellum and the rest of the brain. For instance, the cerebellum helps the cerebrum to optimize motion sequences," says the researcher.

In their study, Timmann and her team had patients and participants learn and then unlearn fear within two days while observing them in the 7 tesla MRI scanner. ▸

i ATAXIA

The term "ataxia" is ambiguous. Ataxia generally describes motion sequence impairments. There can be many different causes of coordination problems. For instance, they can be due to malfunctions in the peripheral nervous system, in the spinal cord or in the brain. Someone who displays ataxic symptoms thus does not necessarily suffer from a cerebellar disease, i.e. cerebellar ataxia, but, for instance, may have severe polyneuropathy and thus sensory ataxia. Ataxia, however, describes a group of illnesses in which the cerebellum is always involved. A distinction is made between acquired and hereditary forms of ataxia.

7 TESLA MRI SYSTEM

Within their research project, the researchers benefit from the new Terra 7 tesla MRI system at the Erwin L. Hahn Institute in Essen. The full-body MRI scanner works with a magnetic field strength of 7 tesla and enables detailed high-resolution images of the brain. In comparison to the 1.5 tesla and 3 tesla scanners, which are often used in clinical imaging, the 7 tesla system offers much higher accuracy for the measurements. The stronger the magnetic field, the more precisely the functional structure of our brain can be identified in the images.

> "THE CEREBELLUM IS WHICH CONTROLS THE AND EMOTIONS."
>
> Melanie Mark

Neurologist Professor Dagmar Timmann from the University of Duisburg-Essen (left) and neuroscientist Professor Melanie Mark from Ruhr University Bochum are working closely together on understanding the cerebellum.

To trigger fear, the participants were given an unpleasant electric shock on their shin whenever they saw a certain image on the monitor on day 1. They soon learned that an electric shock was imminent whenever this image was shown. The skin conductance and pupil size of the participants were measured during the experiment. "Our participants' pupils dilated and their skin conductance increased when the shock took place. And, as shown over the course of the experiment, also when pain was expected," says Timmann. The observation corresponds to the answers that the participants gave in the questionnaires at the end of the experiment. While the image triggered neutral feelings at the start of the experiment, the people stated at the end that the image triggered fear in them.

The image was shown again on day 2, but this time it was not followed by a shock. "The participants unlearned the fear response, which is called extinction," explains Timmann. And the result? The direct comparison of healthy participants and people with ataxia confirmed the assumption that people with ataxia have deficits when learning and unlearning fear. Not only did the acquisition and consolidation of the learned fear response take longer than in the healthy control group, but unlearning the fear was also more prolonged. However, the deficits were much lower than expected: "Beforehand, we assumed that our ataxia patients would be much more significantly impaired during the fear conditioning and that this, in turn, would be associated with clearly visible changes in the cerebellum," says Timmann. However, in the 7 tesla MRI, the activation pattern in the ataxia patients was also reasonably well preserved and only showed minor deviations from the healthy participants.

To confirm the Essen clinician's observations, her research colleague in Bochum, neurobiologist Melanie Mark, conducted the fear conditioning study with healthy mice and mice suffering from SCA6. Mark used SCA6 mouse models that she had already developed for previous studies.

"We wanted to find out whether our degenerative cerebellum mouse model shows similar deficits in fear conditioning," says Mark. During the learning experiment, the healthy and sick mice were conditioned on day 1 by giving them a shock whenever they heard a certain tone, causing them to learn to associate the tone with the unpleasant shock from then on. Whenever they heard the tone after that, both the healthy and the sick mice froze in fear of the electric shock.

One day later, only the tone sounded, but there was no shock. The healthy mice nevertheless froze in fear as they expected the shock. In contrast to this, the SCA6 mice showed much less fear on day 2. "Our SCA6 mice were able to learn the fear response exactly like the people with ataxia, but they did not consolidate what they had learned. Their memory of the learned association task did not last until the next day," explains Mark. The researcher was thus able to show that the fear memory in

THE MOUSE MODEL

Melanie Mark and her team have established a mouse model for the human illness SCA6 in order to understand how the cerebellar disease arises and to develop possible treatments. It is known that SCA6 is among what are known as the polyglutamine diseases, along with Huntington's disease. In these diseases, proteins contain too many repeats of the amino acid glutamine in certain areas. Melanie Mark's team uses a human calcium channel fragment, which carries the same glutamine repeats as in SCA6 patients, and introduces it into the Purkinje cells of mice. This fragment is sufficient to trigger SCA6-like symptoms.

OUR BRAIN'S CONDUCTOR, SYMPHONIES OF OUR THOUGHTS

the SCA6 mice was disrupted in comparison to the healthy mice. The cerebellar disease prevented the mice from consolidating what they had learned and, based on this, from being able to make a learned prediction.

Mark thus came to the same conclusion as Timmann: The cerebellum plays a role in learning fear responses. However, the deficits were also much lower than expected in the mouse model. "In this chronic illness, other regions of the brain have possibly learned to compensate for the cerebellar deficit. This is desirable from an evolutionary perspective. If a region fails, the whole neuronal circuit does not immediately collapse. This does not mean that the cerebellum is not involved," explain Mark and Timmann.

Melanie Mark's team is now working hard on rectifying the learning deficits in SCA6 mice using various methods. "The special thing about our mouse model is that we can specifically control and stimulate individual cells and cell populations in the cerebellum to see what role they play in learning and forgetting fear," explains Mark. In the long term, Mark and Timmann hope to better understand the precise contribution made by the cerebellum in these learning processes. The special cooperation between neurology and neurobiology, which the Collaborative Research Center 1280 makes possible, is indispensable here.

With their research, Mark and Timmann are paying a region of the brain the attention it has long deserved. Their results confirm that the cerebellum plays an important role in fine-tuning our fear responses. "The cerebellum is our brain's conductor, which controls the symphonies of our thoughts and emotions," describes Mark. "It collects and organizes all of the information and then passes on the knowledge to other regions of the brain and makes a prediction."

text: lb, photos: rs

The fear conditioning is investigated in healthy mice and mice suffering from SCA6.

The researchers carefully observe and study the movement patterns of mice during fear conditioning.

SWITCHING OFF **FEAR**

The extended amygdala plays a major role in assessing diffuse threats and in persistent fear reactions. Studies show that it is also involved in learning and unlearning specific fear stimuli.

If a neighbor's dog dislikes children and jumps up at them, barking loudly, the children might give all dogs a wide berth for a while. A sensible learning effect – as who knows whether all dogs are so aggressive? You can also free yourself of a fear learned in this way: If the children have better experiences with friendlier dogs, they can lose their fear again. "For some conditions, however, this unlearning of the fear response doesn't work correctly," says Dr. Katharina Spoida from the Department of General Zoology and Neurobiology at Ruhr University Bochum. Following a traumatic experience, those affected are unable to break the link between a neutral stimulus and fear. They become overwhelmed by overpowering anxiety in everyday life – signs of post-traumatic stress disorder.

Katharina Spoida wants to know what happens in the brain when a fear memory is formed and how this fear is later extinguished. The focus lies on an area of the brain that we know plays an important role in the development and rejection of fear: the amygdala. The neurotransmitter serotonin and, with it, the receptors via which it can transmit signals to neurons also play a key role.

To find out which processes take place in the brain during the learning and unlearning of fear, the researchers are using various mouse models. "There are genetically modified mice that lack a certain serotonin receptor called 5-HT2C," reports Katharina Spoida. These "knock-out mice" are known to differ from wild mice in that, among other things, they are less anxious. Spoida's team is investigating how fear is learned and unlearned in the mice in comparative experiments.

They presented the various mice with a 30-second tone as a neutral stimulus and followed this with an unpleasant but painless electrical stimulus. "It only takes five repetitions for the mice to learn this link," reports the researcher. "We can tell this because the mice display a behavior that we call freezing, a motionless pause, after the tone is played. In a threatening situation, freezing represents an important survival strategy, as it makes the mice less visible to the predator. ▸

The mice used by the researchers are derived from genetically modified mouse lines.

On the following day, the researchers played the corresponding tone to the animals several times without it being followed by the unpleasant stimulus. "The remarkable thing was that the knock-out mice learned to no longer fear the tone much faster than mice without the genetic modification," says Katharina Spoida. The absence of the serotonin receptor, therefore, appears to be an advantage for extinction learning.

Gender-dependent results

The researchers investigated this phenomenon further and found that the knock-out mice display changes in their neuronal activity in two different areas of the brain. This includes a specific sub-region of the dorsal raphe nucleus (DRN), which is generally the main location for serotonin production in our brain. The researchers also discovered deviating neuronal activity in the bed nucleus of the stria terminalis (BNST), which is part of the extended amygdala. The research results also show a connection between both regions of the brain, suggesting that an interaction could be important for improved extinction learning.

"The interesting thing about this experiment is that the results look completely different when carried out with females," reports Katharina Spoida. "We do not see the altered learning affects in them." This finding is of particular importance, as twice as many women as men suffer from post-traumatic stress disorder. However, up to now, everyone receives the same treatment.

To uncover the reasons for the change in learning in male knock-out mice and gain general insights into signal processing during the learning of fear, the researchers at the Department of General Zoology and Neurobiology are using targeted measures to trigger neuron activity themselves. This can be achieved using light or chemical stimuli.

"This approach enables us to activate or inhibit cells in a targeted manner and see what effect this has on the animal's learning of fear," explains Katharina Spoida. If they inhibit a subset of corticotropin-releasing factor (CRF) neurons in knock-out mice in the BNST, these mice unlearn the fear more slowly. If they activate them in wildtype mice, the unlearning effect is accelerated. The research team was thus able to confirm which regions of the brain contain the crucial structures for learning and unlearning fear in their mouse model. "The bed nucleus of the stria terminalis is split into areas that tend to promote fear and those that tend to reduce fear," says the researcher. In male knock-out mice, activity in the fear-reducing area is increased compared to their wild counterparts, and lower in the fear-promoting areas. The absence of the 5-HT2C receptor appears to push neuronal activity in the BNST in an extinction-supporting direction, and the CRF neurons play an important role in this.

In view of the medicinal treatment of patients with post-traumatic stress disorder, the findings from fundamental research explain why symptoms often tend to worsen rather than improve in the beginning: By using what are known as selective serotonin reuptake inhibitors (SSRIs), more serotonin is freely available in the brain and can activate the various fear-promoting serotonin receptors. Only after several weeks do the symptoms improve, as the cells withdraw the receptors due to the constant overstimulation. "These initial effects could be minimized by combining medications to block the receptors," says Katharina Spoida. In general, she hopes to help make the treatment more specific in the future. "In the future, we should take greater account of gender-specific differences when researching and treating mental illnesses," she says with certainty.

text: md, photos: RUB, Marquard

i OPTOGENETICS

The optogenetics technique was significantly co-developed and refined in the research group of Professor Stefan Herlitze at Ruhr University Bochum. "We have lines of genetically modified mice that produce the Cre enzyme (a recombinase) in certain neurons of the brain. These neurons differ, for example, in the neurotransmitters they release", explains Katharina Spoida. The researchers introduce a receptor into these cells, which they later want to switch on and off optically or chemically. The blueprint for the receptor lies in the DNA of specially tailored viruses. The researchers use a tiny pipette to inject small quantities of the virus into the corresponding areas of the brain. "The viruses infiltrate all of the neurons," explains Katharina Spoida, "but the enzyme that is exclusively present in the Cre-expressing neurons is essential in order for the receptor blueprint to be read and implemented." The receptor is thus only produced in these cells. Some receptors can be switched on and off chemically – using a drug administered to the mouse – others optically. "We have to implant optical fibers for the optical method, which is naturally complex," says Katharina Spoida. "However, this method enables us to time the switching operations very precisely." The chemical method is less complex, but less precise in terms of time. Both procedures are spatially precise.

Katharina Spoida, Sandra Süß and their team can directly activate and inhibit cells. This enables extremely detailed research into learning phenomena at cellular level.

Katharina Spoida is a researcher at the Department of General Zoology and Neurobiology at Ruhr University Bochum.

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IN THE FUTURE, WE SHOULD TAKE GREATER ACCOUNT OF GENDER-SPECIFIC DIFFERENCES WHEN RESEARCHING AND TREATING MENTAL ILLNESSES.

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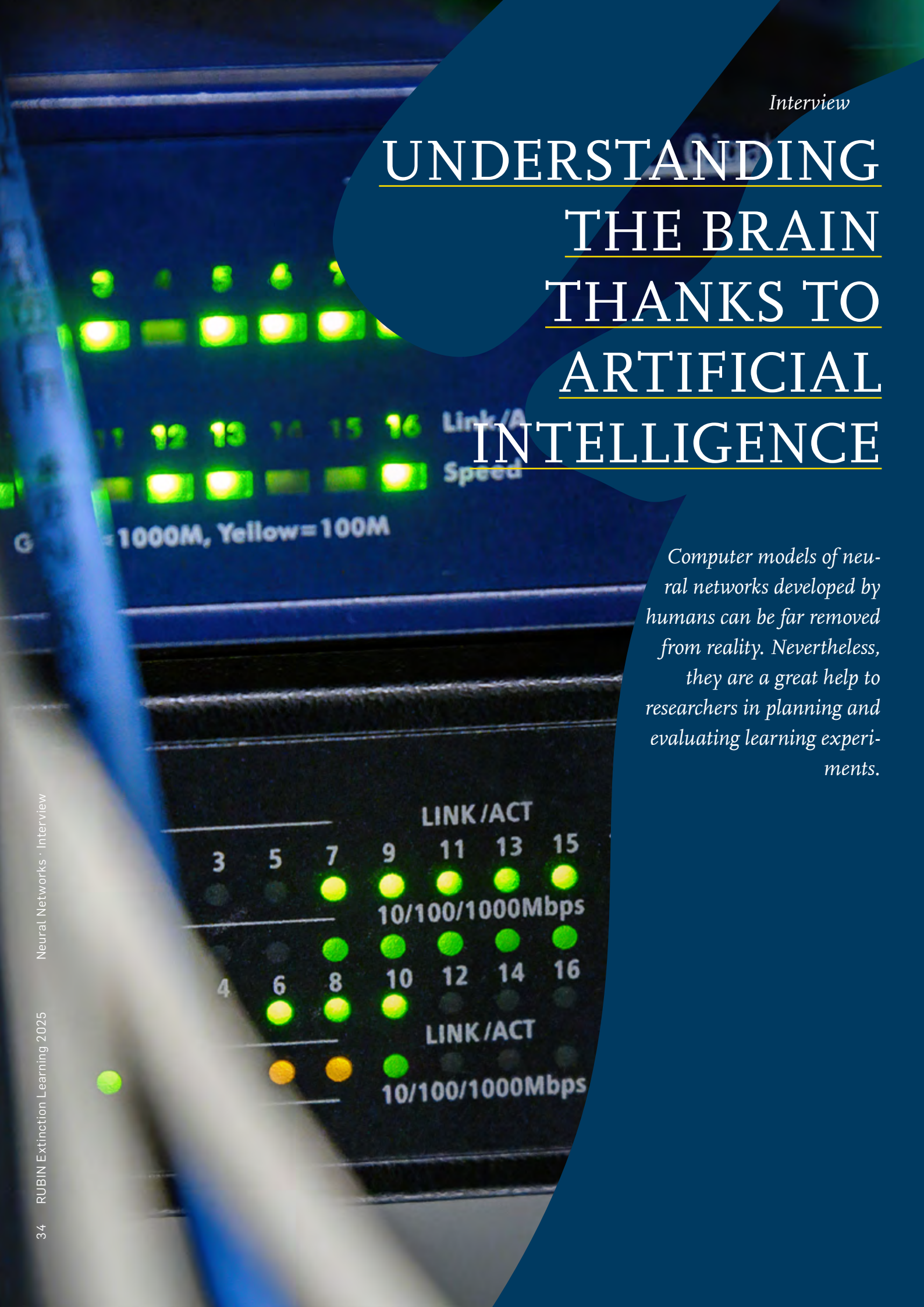
Katharina Spoida



Interview

UNDERSTANDING THE BRAIN THANKS TO ARTIFICIAL INTELLIGENCE

Computer models of neural networks developed by humans can be far removed from reality. Nevertheless, they are a great help to researchers in planning and evaluating learning experiments.

Sen Cheng heads the Computational Neuroscience Group at the Institute of Neuroinformatics at Ruhr University Bochum.

Why is it so difficult to let go of learned behaviors? How do computer models based on artificial intelligence (AI) help to understand this better? Computational neuroscientist Professor Sen Cheng from Ruhr University Bochum and psychologist Professor Metin Üngör from Philipps University Marburg explain in a joint interview. They work together in the Collaborative Research Center Extinction Learning.

Professor Üngör, what is extinction learning?
Metin Üngör: It comprises everything that ensures that learned behavior diminishes and is no longer displayed: It is extinguished.

Why is it so difficult to change existing behaviors?
Üngör: This is actually a good evolutionary adaption mechanism. I probably save energy if I don't throw something that took effort to learn overboard as soon as the situation changes. That way it remains ready to be accessed if it changes again.

Sen Cheng: Our brain also doesn't work like a hard drive. We cannot find and delete files on it. The brain stores information by neural networks changing their connections. The information is then distributed across these networks. This is why it probably isn't possible to completely extinguish something that has been learned.

What tasks has AI taken over in your research?
Cheng: It is able to generate meaningful information from huge quantities of data. If a neuron is activated in the brain, it sends out an electrical signal, an action potential. If I detect these signals from a thousand individual neurons, I get a thousand lines.

On each of them I see the individual action potentials of a neuron as an upward swing. I then have to find meaning in it. AI can visualize how the entire population of a thousand neurons behaved in the experiment.

You can also view AI as a model system that is capable of solving complex problems. I conduct a lot of research in the field of spatial navigation. If my artificial system learns to navigate in an environment, I can see precisely what is happening in its replicated neural networks.

Isn't it better to see this with experimental methods with which brain activity can be measured directly?
Cheng: We compare the AI data with the neural activity that we record from the brains of rats and mice when they learn spatial navigation. However, the AI offers much better access to what is happening. Because I know what algorithm it is using and can measure the activity in all units of its network simultaneously.

This allows ideas to be tested and mechanisms to be researched very quickly. If I better understand the artificial sys- ▸

> "IF I BETTER UNDERSTAND THE ARTIFICIAL SYSTEM, I HOPE TO ALSO BETTER COMPREHEND THE BIOLOGICAL ONE."
>
> Sen Cheng

tem, I hope to also better comprehend the biological one. We naturally also use AI to analyze this synthetic data. We develop analysis methods and strategies that can then be applied to experimental data.

What insights do you gain when you test an assumption using AI?

Cheng: Our AI models are invented by humans and can be arbitrarily far removed from reality. Either I have to discard my assumption or I can say that there is probably something to it. We now have a rough idea of which area of the brain does what. But how exactly the activity of the different neurons causes a certain behavior to happen is still not well understood.

In my AI model, I have different types of neurons and can test whether the model behaves as expected when I activate a certain population of them. This enables me to try things out and get an idea of what I should look at more closely.

In which research topic are you currently using AI?

Cheng: In learning. It's standard to look at behavior before and after learning. However, this gives you a view that perhaps has very little to do with reality. Learning curves are a good example of this.

If an individual learns quickly, their learning curve climbs quickly; if they learn slowly, it climbs slowly. If you average the learning curves of many people, the result no longer says anything about how an individual learns. Then it looks as though you're always learning a little bit at a time, until you eventually don't get any better.

But that's not how learning really works?

Cheng: Apparently, learning does not take place gradually but instead in spurts. At some point, you go from zero to a hundred. This has nothing to do with intelligence. We see this in our models, which have very simple learning rules.

If you connect enough units together in a network, the network suddenly behaves very unexpectedly. It learns things in just one attempt. Although the individual parts only learn associations and change very little locally, this can add up in a non-linear way throughout the system and lead to sudden changes in behavior.

We also observe these spurts, after which behavior changes abruptly, and extreme differences between individuals in humans, rats and pigeons. But when you look in textbooks, you always see averaged gradual learning curves.

Do other scientists also use your AI models?

Cheng: There are some who would perhaps like to use them, but we first have to show to what extent they work and deliver insights that we would not otherwise have.

Üngör: In our Collaborative Research Center, many researchers already use experimental designs that we have developed with support from AI. These can then be implemented in human experiments with relatively simple experimental arrangements, such as predictive learning tasks. Predictive learning tasks are special categorization tasks that have been used in experiments for decades.

For example, the participants in our experiment take on the role of a doctor whose patient is suffering from abdominal pain. The doctor now needs to find out which foods the patient has an allergic reaction to and which are harmless to

Metin Üngör is a professor in the Department of Psychology at Philipps University Marburg, specializing in learning theory.

> "THESE PREDICTIVE LEARNING EXPERIMENTS IN HUMAN RESEARCH ARE INCREASINGLY REPLACING ANIMAL TESTING."
>
> Metin Üngör

Using the artificial networks, the researchers can see that learning is often not gradual, but takes place in leaps and bounds.

them. In the experiment, the doctor gives the patient various things to eat and can directly observe how they react to them. Tasks such as this can be adapted to many research questions and thus very quickly create specific learning experiences for the participants, which can then be changed over the course of the experiment.

What role does AI play in this?

Üngör: In an experiment, we often want to test two competing theories against each other that explain something via different mechanisms. To do this, we create situations in which both theories lead to different predictions on how a participant will behave. Simulations can help to reduce the number of experiments necessary.

Do you still need animals for these experiments?

Üngör: These predictive learning experiments in human research are increasingly replacing animal testing. There are more and more research groups that used to work purely with animal testing that have since either switched completely to human research or use human experiments alongside animal testing.

Cheng: This may reduce the need for experiments on animals that would otherwise be carried out to find out which areas of the brain are important and which are not. I can also try out in advance how many neural derivations are needed to get a meaningful result in the experiment.

Will it eventually be possible to understand the function of the entire human brain?

Cheng: I believe that we will one day be able to do this, but presumably in the distant future. There are many things that my brain does not comprehend, but I can program these things and run them as a simulation. I then draw my conclusions from this. Viewed in this way, AI can perhaps even help me to understand my brain by preparing the data in a way that I can understand.

text: ch, portrait Üngör: private, other photos: rs

The simulations require a lot of computing power.

Immune System

THE SIXTH SENSE

Immune responses can affect our mood and interfere with learning. Conversely, learning processes can influence immune responses.

Sick in bed – everyone knows this feeling. While the immune system is fighting an infection, it is constantly exchanging information with the brain.

The nose is running, the next pack of tissues is empty, and there is that nagging cough. As if that wasn't bad enough, your head is pounding and you can't get anything done. Lack of appetite, fatigue and a bad mood perfectly round out the feeling of having an infection. Surely, everyone has experienced situations like this. When we feel physically ill, this also depresses our mood.

"That sounds negative, but it's actually an adaptive response by our body to protect us and others: You take it easy, avoid contact and stay at home," explains Professor Harald Engler. He is an expert in behavioral immunobiology at University Hospital Essen, which is part of the University of Duisburg-Essen and cooperates with Ruhr University Bochum within the University Alliance Ruhr.

Engler is interested in how the immune system affects the nervous system. "Our immune system serves as our sixth sense," he says. "It detects things that we are unable to see, hear or smell because they are too small – such as pathogens and inflammatory processes – but which nevertheless pose a threat to our body." If the immune system impacts on our mood and behavior, it is a protective mechanism. "Things get problematic when people suffer from chronic inflammation, as in the case of arthritis or inflammatory bowel disease," says Engler. "As a result of this, they can develop clinical depression, the cause of which does not primarily lie in brain metabolism but in inflammation."

As part of the Collaborative Research Center on Extinction Learning, Engler and his colleagues are investigating when the protective mechanism becomes a problem. "Somewhere a switch gets flipped. Then the immune mechanism that affects our mood and behavior is no longer adaptive, but harmful", he explains. The relationships are complex. This is why Engler's work covers the entire spectrum – from animal experiments to studies in healthy people and patients. From the many pieces of the puzzle, the researchers hope to one day gain a better understanding of the interactions between inflammation, learning processes, and the mind.

Extinction learning seems to play an important role. The term is related to classical conditioning, which became famous through Pavlov's dog experiments. Pavlov repeatedly combined a neutral stimulus, the ringing of a bell, with a second stimulus: the provision of food. Over time, the dog learned that the bell signaled the presentation of food, and responded solely to the sound by salivating. However, when the presentation of food stops, the connection between the bell and the food is unlearned, a process called extinction. Harald Engler's team is pursuing the hypothesis that some ▸

The work of the researchers in Essen covers the entire spectrum – from animal experiments to studies in patients.

In order to investigate the role of individual brain regions in the interaction with the immune system, the researchers manipulate neuronal activity in certain brain areas of experimental animals with the help of chemogenetic techniques.

disorders are associated with altered extinction learning and that inflammatory processes can disrupt successful extinction. Together with the team of Bochum researcher Professor Sigrid Elsenbruch, his group demonstrated such an effect in healthy volunteers. The study participants first learned to associate geometric symbols with pain. They repeatedly saw images of triangles, circles and squares, for example. Some of these symbols, e.g. the triangle, were paired with a brief pain stimulus. Thus, after the learning phase, the participants rated the triangle more unpleasant than the other geometric symbols. On the following day, extinction learning took place: Now none of the geometric symbols was associated with pain. After the extinction phase, the participants had to rate again how unpleasant they perceived the different symbols. At the same time, the researchers recorded their brain activity with functional magnetic resonance imaging.

Inflammation slows down extinction learning

The results were dependent on whether or not the participants had experienced an inflammatory response during the learning on the first day. "By administering a very low dose of a bacterial component, we can safely induce an inflammatory response along with depressive mood in healthy people over a period of several hours," explains Harald Engler. "After 24 hours, the effects are completely gone."

If the participants learned the association between the geometric symbol and the pain stimulus under the influence of this experimental inflammation, the researchers observed increased neural activation in what is known as the brain's fear network when the geometric symbol was presented during extinction learning. In addition, the participants also rated unannounced pain stimuli as much more unpleasant than people who had only been given a placebo on the first day. This indicates that inflammatory processes strengthen the memory trace for pain-associated stimuli.

"We assume that this mechanism could foster the development of chronic pain," concludes Harald Engler. The researchers now want to further investigate this theory and the underlying mechanisms in an animal model and in patients with chronic inflammatory disease.

While Harald Engler is trying to promote extinction learning and to erase pain associations, Professor Martin Hadamitzky's research aims towards the opposite direction: He also works in the field of behavioral immunobiology at University Hospital Essen, but he wants to prevent the extinction of learned associations. Hadamitzky investigates how learning processes influence immune responses. "The brain and immune system communicate through complex bidirectional pathways," emphasizes Hadamitzky.

In animal studies, Hadamitzky's team pairs neutral stimuli such as sugar water with the administration of an immunomodulatory drug. For example, the researchers are working with rapamycin, a compound which inhibits the growth of tumors. They showed that rats were able to learn an association between the taste of the sugar water and the immunological changes induced by rapamycin: If the animals repeatedly received a combination of sugar water and the drug, the administration of sugar water alone ultimately led to substantial effects on the rats' immune system.

"However, these effects eventually disappear at some point due to extinction learning," says Hadamitzky. Together with his colleagues, he is thus looking for ways to prevent conditioned responses from being extinguished or relearned. "Our idea is to give the immune system a reminder," explains the neurobiologist. For the initial learning phase in the conditioning experiments, the researchers administer a clinically

Behavioral immunobiologists Harald Engler (back) and Martin Hadamitzky (front) from the University Hospital Essen work closely with teams from Ruhr University Bochum in the Collaborative Research Center Extinction Learning.

relevant dose of rapamycin, i.e. an amount of active ingredient that has been shown to efficiently prevent tumor growth. After the animals have learned the association between the sugar water and the immunological action of rapamycin, the researchers did not stop administering the drug completely, but continued to pair the sugar water with only ten percent of the original drug dose.

"This is a subeffective dose," explains Martin Hadamitzky. "If we only work with this ten percent dose right from the start, it has no effect on tumor growth at all." Things look different if the animals have previously learned an association between sugar water and the full rapamycin dose. In this case, the ten percent dose is sufficient to attenuate tumor growth just as much as if animals were treated with the full dose and without associative learning. The subeffective dose thus acts like a reminder cue for the immune system and slows down or even prevents extinction learning.

In further studies, Martin Hadamitzky wants to find out what exactly happens in the brain. The underlying mechanisms have to be well understood in order to potentially transfer their findings to humans. After all, the researchers cannot simply experiment on patients whose survival depends on a drug. Following extensive animal studies, investigations are therefore initially planned with healthy volunteers and patients with less severe disease conditions, such as inflammatory skin reactions.

However, Martin Hadamitzky and Harald Engler envision that their work will one day offer patients better quality of life. "Many people, such as cancer patients or patients who have received an organ transplant, have to take drugs with severe side effects on a daily basis," explains Harald Engler. "It will never be possible to go without medication completely, that would be an illusion," adds Martin Hadamitzky. "But if we could reduce the dose while maintaining the therapeutic efficacy, that would be a huge win." As if it were possible to prevent harmless inflammation from triggering depression.

text: jwe, photos: rs

"SOMEWHERE A SWITCH GETS FLIPPED. THEN THE IMMUNE MECHANISM THAT AFFECTS OUR MOOD AND BEHAVIOR IS NO LONGER ADAPTIVE, BUT HARMFUL."

Harald Engler

Interview

THE SECOND BRAIN IN OUR GUT

There are more than 100 million neurons in our gut. That is why it is also known as the second brain. Researchers from Bochum are uncovering the role of the brain-gut connection in learning and unlearning pain.

Butterflies in your tummy, nervous stomach rumblings, hunger: Our brain and gut are in constant communication with each other. This communication is particularly intense when we experience pain arising from the gastrointestinal tract. When fear of such pain becomes worse than the pain itself, this is often the result of learning processes. Professor Adriane Icenhour and Dr. Franziska Labrenz from Collaborative Research Center 1280 are investigating how people could be helped to overcome the vicious circle of fear and pain.

Professor Icenhour, what does pain have to do with learning processes?

Icenhour: We are all familiar with this: When we are in pain, we start to worry and wonder what is wrong and what we can do about it. Go to the doctor? Take a tablet? Rest and regenerate? Pain is one of the most important warning signals and a high motivation for the body – and therefore particularly powerful to stimulate learning processes so that we can adapt to the unpleasant situation or, more importantly, avoid experiencing it again in the future. What can we do to prevent pain from arising in the first place? Which signals from outside or inside the body should we regard as warning signals in the future so that the pain will not occur at all?

In your research projects, you are looking at a very specific type of pain, visceral pain. What characterizes it?

Icenhour: Visceral pain can be translated as pain arising from our internal organs and encompasses all aversive sensations from our gastrointestinal tract, from painful belching to abdominal pain. This type of pain from the inside of our body is special in that it is perceived as much more frightening than pain from the outside of the body. We can't escape it – not in the same way that we quickly pull our hand away from a hot hob, for example. And: We are often unable to say exactly what hurts. We have a diffuse discomfort that is difficult to localize and we are unable to do anything about it. ▸

Adriane Icenhour (left) and Franziska Labrenz are investigating the role of the brain-gut connection in learning and unlearning pain.

Discomfort, stomach rumbling, abdominal pain: The pain from inside the body is often experienced as diffuse, difficult to localize – and terrifying.

> YOU CAN HARDLY DISTINGUISH BETWEEN THE CLUSTER OF NERVES IN THE GUT AND THAT IN THE BRAIN.

Franziska Labrenz

The term "brain-gut axis" is often used in this context. What does this mean?

Icenhour: Wetting your pants from anxiety or stress that upsets your stomach: In our everyday language, the connection between the brain and the gastrointestinal tract is intuitively understandable. It has been scientifically shown that signals from inside the body are communicated along the brain-gut axis via various messenger substances. And this happens constantly and often unnoticed. This communication is bidirectional: Our brain, including our emotions, influences gastrointestinal processes and vice versa.

Franziska Labrenz: Our intestines are not just one organ, but one of three nervous systems. In addition to our central and peripheral nervous system, there is also the so-called enteric nervous system, which runs through our gastrointestinal tract. Just as we have nerve cells in our brain, we also have nerve cells in our intestines – around 100 million of them. And this second brain has a very similar structure. You can hardly distinguish between the cluster of nerves in the gut and that in the brain.

In your research projects, you are trying to find out how visceral pain is communicated along this axis, how it is learned and unlearned. What do the learning experiments look like?

Icenhour: We have a range of experimental studies that we carry out both with patients and healthy participants. In our conditioning studies, we often use unpleasant stimuli to produce either visceral pain, such as abdominal pain caused by pressure, or external, somatic pain, such as heat stimuli on the surface of the skin.

This is known as conditioning. Like the famous Pavlovian dog?

Icenhour: Yes, ultimately exactly the same. Incidentally, Pavlov's dog is also an example of conditioning in the visceral domain. Whenever the dog hears a sound, it gets something to eat. At some point, the sound is sufficient for the dog to salivate. And this appetitive conditioning can be transferred to aversive learning processes. We usually work with visual stimuli, i.e. images of simple geometric shapes. A triangle, for example, is paired with a pain stimulus and can thus predict it. A circle cannot. It then serves as a safety signal.

Labrenz: We then use functional magnetic resonance imaging (fMRI) to observe what happens when the participants see a triangle at the beginning of the experiment and what happens when they see this triangle after they have repeatedly experienced that this triangle is followed by pain. The MRI allows us to observe which brain regions become active or communicate with each other. We also work, for instance, with questionnaires and assessments. Before and after the experiment, we ask participants how they rate the stimuli on a scale from very pleasant to very unpleasant and observe learning-induced differences.

What have you observed? How is pain from the inside of the body perceived?

Icenhour: It is possible, for example, to condition participants with two different stimuli, one from the inside and one from the outside of the body, at the same time in order to make comparative statements. Prior to conditioning, our participants rated the intensity of the two stimuli as equally strong, with the visceral stimulus being perceived as more unpleasant overall. This aversion to visceral pain increased sharply after conditioning. While the externally administered stimulus was rated as neutral, the visceral stimulus from the inside of the body was rated at over 75 on a scale from zero to 100, i.e. it was perceived as significantly more unpleasant after conditioning. A similar pattern applies to fear of pain.

Labrenz: Our participants were able to completely ignore the external stimulus. So no significant learning process took place here. Instead, they focused more strongly on the visceral stimulus, memorized it and experienced it as much more frightening.

You keep talking about pain-related fear. So, pain memory and fear are closely intertwined?

Icenhour: Psychological factors play a central role. Many of our patients have so-called comorbidities. In addition to abdominal pain, they suffer from anxiety disorders and depression, for example. For many, fear of pain is also a major factor and prevents them from going about their daily lives.

Labrenz: So it's not the visceral pain that's so bad, but the fear. What do I do if I get diarrhea and there is no toilet? People then stop travelling by train, switch to the car or end up staying at home altogether. Others know that they have a stressful day ahead of them and take stomach pills even though they have no symptoms.

Icenhour: So they take measures that keep the fear alive. They catastrophize, they pay increased attention to any internal signal. We want to break this vicious circle, better understand pain-related fear and, based on this, develop new forms of therapy and improve existing ones.

What could such therapies look like?

Icenhour: Psychotherapies based on the extinction of fear are also effective in chronic pain. The logical next step is now to look at the mechanisms by which these exposure therapies work in patients with chronic abdominal pain.

Labrenz: We know from anxiety research, for example, that fear avoidance behavior maintains fear and prevents extinction. We recently simulated this avoidance behavior in a pain experiment and were able to show impressively that avoidance also maintains pain-related fear.

Icenhour: Similar to the treatment of anxiety disorders, you can also confront pain patients with their fear, for example by having them do specific sports exercises under supervision that involve tensing their stomach or asking them to eat foods that they have avoided for years. In this way, by confronting their fears, they learn that nothing bad will happen, or that even if they experience symptoms, they are able to manage them. Once we have the fear under control – patients feel more confident again, have positive experiences and their quality of life improves – then the way they deal with their pain also becomes more adaptive and it subsides. The subjective assessment of the pain is then different – even if it may not be completely cured.

text: lb, photos: rs

The participants are observed during the learning experiment using functional magnetic resonance imaging (fMRI).

The researchers track what happens during the experiment, for example, when the participants experience that a stimulus is followed by pain.

A Day With a Stress Researcher

ELECTRIC **SHOCKS**, COLD **SWEATS**, AND A TREADMILL **FIASCO**

Contrary to popular opinion, stress can have a positive effect on learning. What is crucial is the time at which we experience it.

My calf twitches – an electric shock. I could see it coming and was already afraid. I can't escape, my calf and my hand are wired up, my chin and forehead lie in a head rest, my eyes can only look at a monitor. What have I got myself into?

When the topics for this issue of the science magazine Rubin were shared among the members of the editorial team, I impulsively called out "Here!" when it came to who wanted to report on the research project by Dr. Valerie Jentsch and her PhD student Lianne Wolsink. And then also offered myself as a guinea pig to experience up close what awaits the participants during the experiment.

Valerie Jentsch is a stress researcher at the Department of Cognitive Psychology at Ruhr University Bochum and project manager in the Collaborative Research Center 1280. In her current project, she is investigating how stress affects extinction learning. What we already know: Stress impairs memory retrieval. However, contrary to what you might think, the effect of stress on memory isn't purely negative.

What Jentsch and other researchers have discovered: "It very much depends on at what time we experience the stress. If we experience stress before an exam, for example, this tends to impair our performance in the exam, some of us even have the typical blackout. But if we experience stress shortly after the initial learning experience, it can even strengthen the memory trace of what has already been learned, enabling us to better retrieve this newly acquired knowledge at a later point in time," explains Jentsch.

In her current research project, the researcher, together with her PhD student, is investigating whether intensive exercise – during which the stress hormone cortisol is released – has the same effect on extinction learning as stress. "This would be very helpful, especially in view of a subsequent clinical application within behavior therapy," says Jentsch. Instead of subjecting patients, who are already not doing well, to an additional psychologically stressful situation, the same physiological effect could be achieved through a much more positively accepted exercise session.

I'll also have to exercise in a bit, Valerie Jentsch has already told me. OK, sport is fundamentally healthy and I do too little of it anyway. I'll see later on: This is precisely what will be my undoing. When I entered the simply furnished laboratory earlier with our photographer, I was not fully aware of what would await me. Valerie Jentsch had asked me to sit at the table at the front, and explained the procedure to me while she attached electrodes to my left calf and my left hand.

Classical fear conditioning

Lianne Wolsink now measures my skin conductance via the electrode on my hand. In plain language: She sees in black and white how I break out in a cold sweat. This is actually caused by the electrodes on my leg: They deliver brief electric shocks to me. My task: While my head is fixed in place with chin and forehead supports, I look straight ahead at the monitor. My pupils are filmed and Lianne can see on her monitor how they dilate or constrict during the experiment. This, too, is a response by the body to fear.

On my monitor, I am shown an image of an office in which there is a desk lamp. This is the neutral stimulus. Sometimes the lamp lights up yellow, sometimes blue. The catch: Yellow is sometimes followed by a short, harmless electric shock (we determined my pain threshold beforehand – after all, no one should leave the laboratory with a barbecued leg).

What I experience here is classical fear conditioning. And it works incredibly well. After just a short time, everything in me tenses up when the lamp lights up yellow. Will the light ▸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once again be followed by the nasty electric shock? I notice myself that my hand is getting sweaty, I don't have to look at the curve on Lianne's monitor to see that.

As we know, you should always get out while the going's good. And I think this experience is now enough for me to get an initial impression. Valerie Jentsch takes pity on me and we agree to move on to the next section. One thing first: I'm not running through the whole experiment like the participants usually do, but only experiencing two excerpts. The participants actually have to come to the laboratory for three days.

The second section takes me into another room. There is a treadmill. Before doing my sports session on it, I provide a saliva sample. This is used to measure the level of the stress hormone cortisol. "Exercise can relieve chronic stress. Exercise itself is also a stressor, namely a physical one. When I exercise at a certain intensity, my stress hormones increase. My sympathetic nervous system is activated, my heart beats faster, my bronchia expand, and cortisol is released," explains Valerie Jentsch.

The hormone can directly pass through the blood-brain barrier and bind to receptors in the brain, whereby the excitability of the brain cells is changed. Among other places, in regions of the brain that are particularly important for our memory. This is why stress has an influence on learning and memory.

Stress through sport

We get started on the treadmill. Without vanity, I can say: Based on my outward appearance, most people tend to think I look quite sporty. But how wrong they are! I have approximately zero fitness. I've never liked jogging. Valerie Jentsch quickly increases the speed. I'm supposed to run fast for 15 minutes. Seriously? After five minutes I'm reaching my limits. After seven minutes I stop. Judging by my breathing, I've covered 42 kilometers. OK, let's not talk about it.

"When it comes to the real participants, we don't test anyone who doesn't exercise at all," explains Valerie Jentsch, smirking. I would say that's a wise decision. Once I've got my breath back, we go to the scientist's office, and she tells me more about the links between stress, sport, and extinction memory.

What particularly interests the researcher is how extinction learning can be strengthened and also how it can be made more independent from the context. "Extinction learning is extremely context-dependent. This means that a patient who has learned, for instance, to no longer be afraid of dogs during behavior therapy in a practice is quite likely to still experience their old fear outside of the practice premises, i.e., in a different context. We want to find out what we can do to increase the persistence of the extinction memory and how we can disconnect it from the context of the learning situation," explains Valerie Jentsch.

i EXPERIMENT PROCEDURE

Day 1: Fear conditioning: A neutral stimulus (yellow lamp) is linked to electrical stimulation, whereas electrical stimulation never follows another neutral stimulus (for example, blue lamp).
Day 2: Extinction learning: Both stimuli (yellow and blue lamp) are presented, but both without electrical stimulation. The participant now learns: The yellow lamp (which, after day one, was not neutral but instead a fear-inducing stimulus) is no longer dangerous.
Day 3: Memory retrieval test. How do the participants now react to the different lamp colors? Results show: Participants who were exposed to stress before extinction learning are more likely to retrieve the second memory trace – the extinction memory (yellow lamp = no pain) learned on day 2 – than the first one (yellow lamp = pain) learned on day 1.

The results of her research show: "If we stress the participant after extinction learning, it helps them to better retrieve the extinction memory, but only in the context in which they learned it. However, if we stress the participants before extinction learning, it leads to better extinction retrieval independent of the context. That's what we want." It thus crucially depends on at what time the participants, or later the patients, are exposed to the stressor.

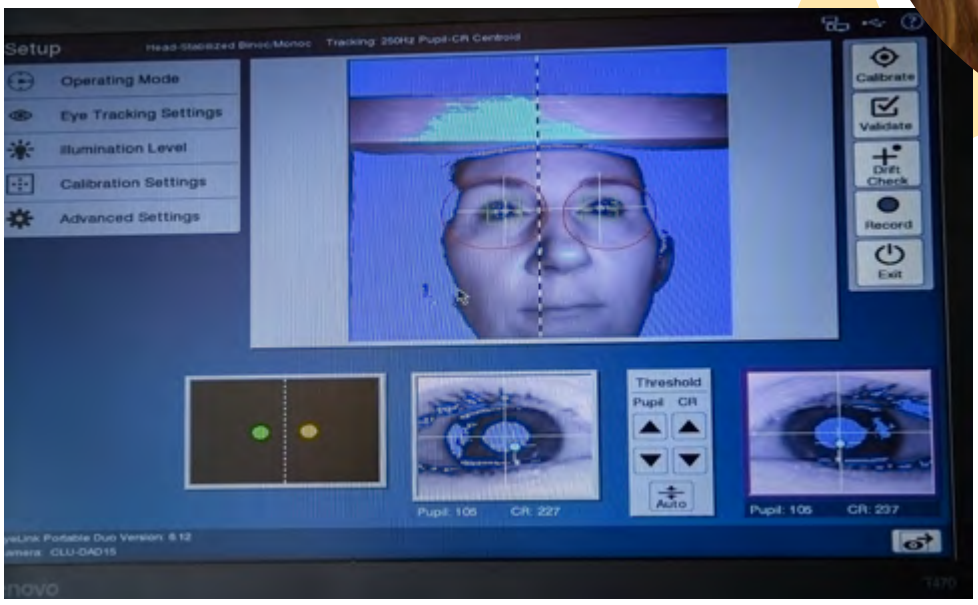
The results from the current project also show that exercise can bring about the same effects on extinction learning as psychosocial stress. However, unlike stress, which is usually associated with negative emotions, exercise tends to be associated with positive emotions. This is important if you want to translate the findings that you have obtained in the lab to the clinic.

However, it is uncertain when exercise interventions will in fact be implemented in clinical setting. "We have to be clear that we are doing basic research here," says Valerie Jentsch. "However, the step towards clinical applications is not infinitely large." And it is particularly the fact that her work once could also benefit patients suffering from anxiety disorders that motivates the scientist in her research every day.

text: rr, photos: rs

Fear makes your hands sweaty: This reaction is recorded with sensors.

Stress researcher Dr. Valerie Jentsch (left) and PhD student Lianne Wolsink investigate how extinction learning can be improved.



Like skin conductance, pupil dilation also provides information on whether the participants experience fear.

No chance of escape: The participant's pupil diameter is filmed using a camera. They, too, reveal something about the learned fear.

> "IT VERY MUCH DEPENDS ON AT WHICH TIMEPOINT WE EXPERIENCE THE STRESS."
>
> Valerie Jentsch

Psychotherapy

LOOKING FEAR IN THE EYE

Phobias arise through learning processes, so it is also possible to unlearn them. Bochum psychologists are using various interventions to help those affected conquer their fears.

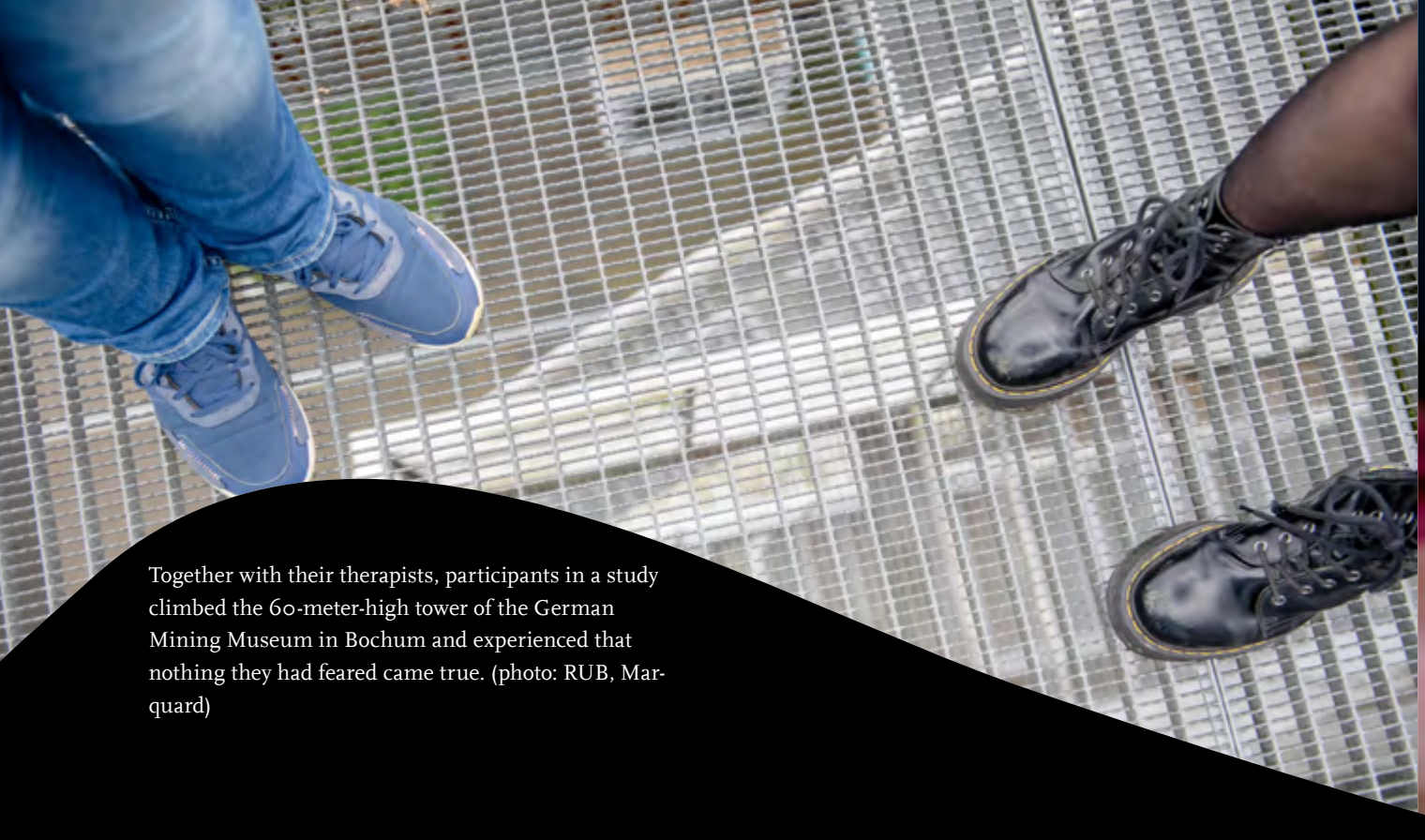
Professor Armin Zlomuzica doesn't have it. Instead, his Department of Behavioral and Clinical Neuroscience at the Mental Health Research and Treatment Center at Ruhr University Bochum is home to some impressive spider specimens, including tarantulas, which are lovingly cared for by his team. They perform an important job in treating patients with arachnophobia. "The proven most successful therapy for anxiety disorders and phobias such as a fear of spiders or heights is exposure therapy," says the psychologist. "This means you are exposed to the anxiety-inducing stimulus in the company of a therapist and learn that the catastrophe you are expecting doesn't actually happen, i.e., the spider doesn't bite you or jump on you and crawl inside somewhere." Those affected may only bring themselves to look at the box with the tarantula from a distance at the beginning of the therapy. However, they eventually manage to get closer to it and even touch the container. This strategy helps the majority of patients.

"There is, however, still room for improvement," says Zlomuzica. There are some patients who, for unknown reasons, do not benefit from exposure therapy. Others conquer their fear during therapy, but are still afraid when they encounter a spider in their own basement. Or the fear appears to have been overcome, but returns at some point.

"We therefore want to better understand which learning mechanisms underlie these anxiety disorders and find out whether there are additional strategies that support the effect and sustainability of the therapy," explains Zlomuzica. Learning and memory are aspects that interest the researchers be- ▸

Armin Zlomuzica keeps extra spiders in his premises for the therapy of people with arachnophobia. (photo: FBZ)

One of the tarantulas that patiently help with exposure therapy in the laboratory. (photo: rs)



Together with their therapists, participants in a study climbed the 60-meter-high tower of the German Mining Museum in Bochum and experienced that nothing they had feared came true. (photo: RUB, Marquard)

cause, in anxiety disorders, what has been learned appears to be difficult to unlearn: An originally neutral stimulus – the spider or even the height – is linked to something negative that never happens. However, this learned link is not extinguished by the experience that the spider didn't bite or that you didn't pass out when you climbed a high tower. "Relearning appears to be deficient in anxiety patients," reports Armin Zlomuzica from his studies. "This seems to be a general, characteristic feature of anxiety disorders."

To make therapy more successful and sustainable, the researchers are investigating the effects of various accompanying measures in the Extinction Learning Collaborative Research Center. One starting point for this is self-efficacy. "It feels good when we realize we have mastered a task independently," explains Zlomuzica. "We can use this feeling to make the interventions in exposure therapy more effective."

The effect of boosting self-efficacy

The trick: When anxiety patients realize during therapy that they survived their confrontation with the spider or the height without anything bad happening, their expectation is violated and they learn that they can master the situation. After all, they had seen the catastrophe approaching. When the therapy team reinforces this unexpected experience of self-efficacy, and promotes and activates the good feeling of having mastered the situation on one's own, patients do better in their next confrontation with the anxiety-inducing stimulus than they do without this self-efficacy activation.

"We have also been able to demonstrate the effect of boosting self-efficacy in related experiments," reports Armin Zlomuzica. The researchers increased self-efficacy in a group of participants by giving them a false positive feedback during a task. "For example, during a standardized task, we gave this group feedback that they are among the five per cent most stress-resistant people," explains the researcher. In a subsequent extinction learning experiment, which involved unlearning something that had already been learned, this group did better than the comparison group, which did not receive the feedback. As self-efficacy can be promoted via various sources – be it via an experience or via verbal confirmation – the research team believes this strategy offers great potential for therapy.

Other strategies are also based on influencing cognitive processes to improve the unlearning of fear. Professor Marcella Woud, who moved from Ruhr University Bochum to the University of Göttingen in fall 2023 as the Head of the Department of Clinical Psychology and Experimental Psychopathology, conducted a study with 80 patients suffering from fear of heights. All patients received exposure therapy, again with the goal to disconfirm their fear beliefs, i.e., the experience that the patients' threat does actually not occur once they reach a great height. During the exposure therapy, patients climbed the 60-meter-high tower of the German Mining Museum in Bochum, together with their therapists, and experienced (i.e., learned) that their feared outcome such as passing out or falling down did not occur.

To consolidate this experience, half of the participants received a cognitive bias modification interpretation training. During this computer-aided training, participants complete ambiguous, height-relevant sentences positively, and by doing so resolve the height-related ambiguity in a functional and adaptive manner. A typical training sentence could be as follows: "You are standing at the railing on the 4th floor of a shopping mall. As you look down, you realize that the railing only reaches up to your hip. You know that falling down is ... unlikely." Or: "You are dining on the roof terrace of a restaurant. To get to your table, you have to get very close to the edge of the roof. You approach the edge and feel ... relaxed." As a comparison, the other half of the participants were given a placebo training on the computer.

Marcella Woud would like to use computer-based training to help consolidate the experience gained during therapy. (photo: Heike Engelberg)

The researchers also work with virtual reality as part of the Collaborative Research Center. "The effects are similar, no matter whether you are exposed to a frightening situation in reality or in virtual reality," says Armin Zlomuzica. (photo: RUB, Marquard)

Work on the cognitive tunnel vision

Immediately after the experiment and one month later, the researchers recorded how well the therapeutic interventions, i.e., the exposure in combination with the interpretation training, had worked, via various questionnaires and tests. "Immediately after the exposure therapy, all participants reported lower levels of fear of heights than before the therapy. It was also found that immediately after the training, the group that had taken part in the active training interpreted ambiguous, height-related sentences as less threatening compared to participants from the placebo," reports Marcella Woud. Specifically, participants agreed less with typical statements such as "heights are dangerous" or "the bridge will collapse" or "my fear is uncontrollable" than the participants from the placebo group. The data from the test one month after the therapeutic interventions are currently being evaluated, and follow-up studies on this topic are planned.

"We want to find out, for instance, when the ideal timepoint is to offer this kind of training – before a confrontation with the frightening situation or afterwards? Put differently, when is the most beneficial time to try to work on the cognitive tunnel vision and to foster the cognitive change that is initiated via the exposure treatment?" explains Marcella Woud. The researchers think that it is also likely that a cognitive training of this kind could also help to encourage patients to actually confront themselves with the anxiety-provoking situation in the first place. After all, surveys from the USA and Germany have shown that only a small number of therapists actually offer exposure therapy. This has many reasons, e.g., because many patients withdraw from the exposure session at the last moment or because therapists consider this intervention too stressful for their patients.

"The cognitive component has a great influence on learning processes, and we want to learn to understand and use it better," says Armin Zlomuzica. The researchers are laying the foundations for this in the Collaborative Research Center. "Translation, i.e., the optimal transfer into therapeutic practice, however, must be researched separately", Zlomuzica and Woud are convinced. If this is successful, it could benefit not only people with a fear of spiders or heights, but also those with more complex symptoms such as panic disorder or disorder in the context of trauma.

md

Pain is learned faster and in a more lasting way than other things. Although that makes sense from an evolutionary perspective, for people with chronic pain, it's a problem.

„Since my lower back pain last year, I tense up just doing the vacuuming," reports Jürgen W. "I haven't dared to get into my car since then because it's lower down, only my son drives it now." There are many people like him. "Every day, we see patients who have experiences like this. They have learned to expect and fear pain," says Professor Ulrike Bingel. The professor of Clinical Neuroscience heads the University Center for Pain Medicine at Essen University Hospital. In various experimental studies, she and her team are investigating the connection between pain and learning processes. "Studies have been conducted on this topic for the last 20 years," she says. "But never as broadly and extensively as is possible in the Collaborative Research Center 'Extinction Learning'."

The experiments conducted concern how and which people, in particular, learn to associate a neutral stimulus with a subsequent pain stimulus, or learn that this stimulus will no longer be followed by pain. To administer experimental pain stimuli, the researchers use what is known as a thermode: a metal plate attached to the skin of the forearm that can be heated and cooled. Before each experiment, the research team determines the individual pain threshold of the participants.

The team used this approach to investigate, for example, whether the learning of pain fundamentally differs from the learning of other unpleasant stimuli. "After all, pain is a warning stimulus that tells us there may be damage to our body's tissue, or there is the risk of damage occurring that could even cost us our lives," clarifies Ulrike Bingel.

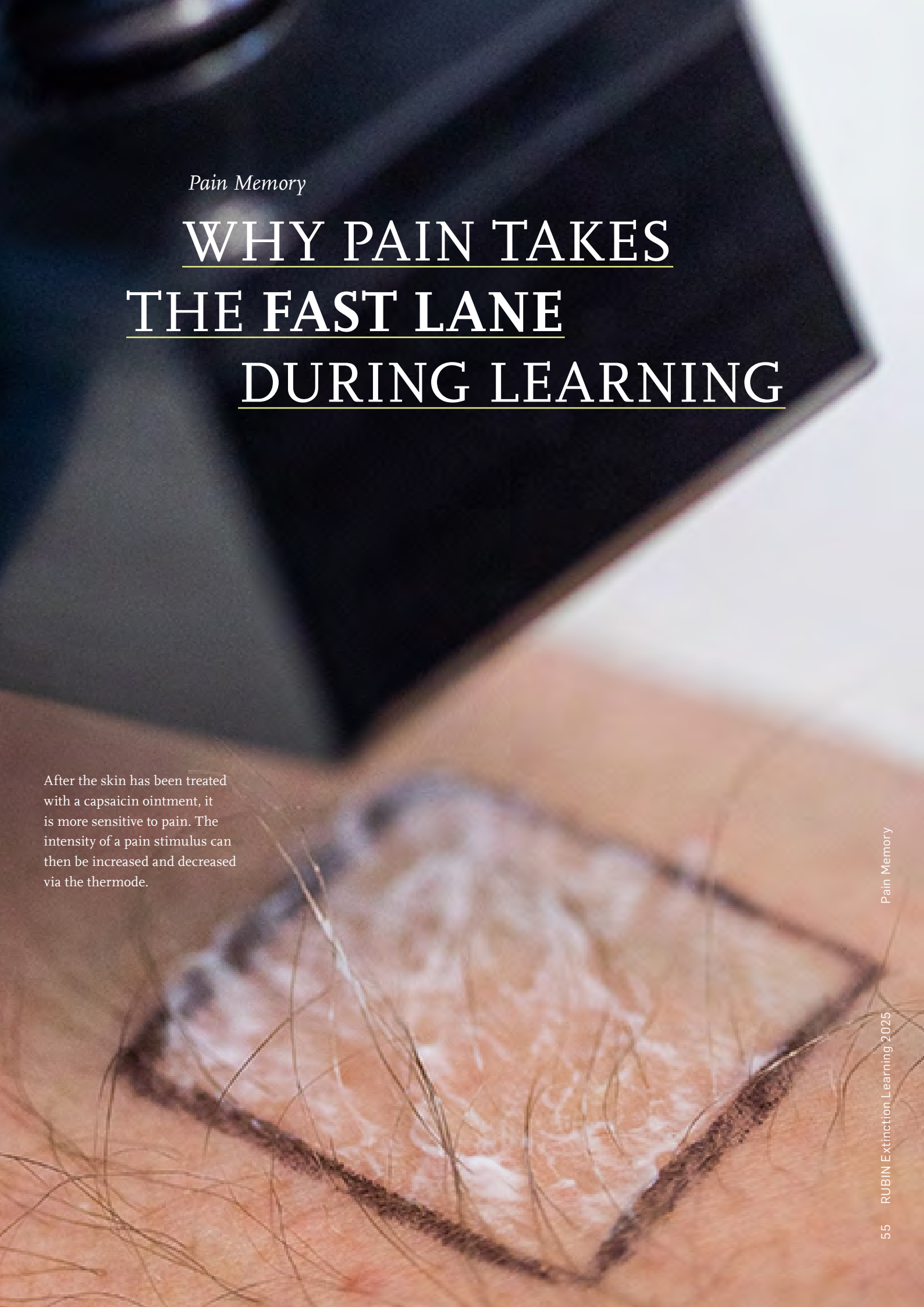
The researchers chose an unpleasant tone as a counterpart to the heat pain stimulus. They coupled the pain stimulus and the tone with neutral visual stimuli: They initially presented the participants with different geometric shapes, which were then followed with a certain likelihood by one of the unpleasant stimuli. The participants thus learned to link a shape with either pain or the tone. This link was broken again in a subsequent experimental phase, during which only the shapes were presented without the unpleasant stimuli. An established link between the geometric shape and the pain or tone was measured by the researchers using the assessed unpleasantness of the geometric shape. The researchers also measured physiological reactions such as skin conductance as a sign of stress.

Alongside the physiological measurements and surveys, the team used functional magnetic resonance imaging in ▸

Katharina Schmidt is co-project leader in the Collaborative Research Center Extinction Learning.

Pain Memory

WHY PAIN TAKES THE **FAST LANE** DURING LEARNING



After the skin has been treated with a capsaicin ointment, it is more sensitive to pain. The intensity of a pain stimulus can then be increased and decreased via the thermode.

Ulrike Bingel uses a thermode to induce experimental pain and investigates how quickly people learn the connection between a neutral stimulus and a pain stimulus.

> EVERY DAY, WE SEE PATIENTS WHO HAVE LEARNED TO EXPECT AND FEAR PAIN.

Ulrike Bingel

this study. This imaging method makes it possible to observe which areas of the brain are particularly active during a task or experiment.

"This allowed us to show that the link between the image and pain was learned more quickly and strongly than the link between the image and tone," reports Dr. Katharina Schmidt, co-project manager together with Ulrike Bingel. "The insula and amygdala areas of the brain, which are relevant for the processing of threatening stimuli, were activated more strongly during the learning of pain than of tone."

"From an evolutionary perspective, it absolutely makes sense that the learning of pain takes the fast lane, so to speak," says Ulrike Bingel. "This 'better safe than sorry' account, presumably enabled our ancestors to best protect themselves from life-threatening situations."

The group designed another experimental scenario for patients with chronic back pain and healthy control participants, this time with the possibility of changing the intensity of the pain, and once again accompanied by imaging. "Such data collections are very labor-intensive and can sometimes take several years," clarifies Katharina Schmidt. "Fortunately, our patients are very open to research and are often willing to take part in studies," says Ulrike Bingel.

In the study with over 60 healthy people and 60 patients with chronic back pain, an ointment containing the chili pepper extract capsaicin was applied to the participants' skin for a short time. Capsaicin causes the skin to be more sensitive to pain for a while. Once the ointment had been removed again, the researchers attached the thermode to this area. It was possible to slightly heat and cool the thermode to increase or decrease the pain, which was moderate at the beginning.

Does the appearance of the rhombus suggest a pain stimulus or not? The participants learn the connection between geometric figures and pain stimuli.

Using functional magnetic resonance imaging, the researchers can observe which areas of the brain are particularly active during a task.

This process was then once again linked to various geometric shapes. In this experiment, too, the participants first learned to link the increasing and decreasing of the pain stimulus to the shapes, and later to give up the link again. “This learning is very important in the context of pain,” explains Ulrike Bingel. “We learn what movements, actions or times of the day are associated with an increase in pain. However, it is also just as important to learn how we can find relief and which medications may help us.”

The researchers were able to observe that the linking of a stimulus with an increase in pain was learned much faster than with a decrease in pain. “This memory trace can also be seen for longer in the person’s behavior – a remnant of it remains,” reports Katharina Schmidt.

In a further study, the researchers investigated whether the learning of the link between the stimulus and pain differed between the healthy people and people suffering from chronic, non-specific back pain. “Chronic pain persists over at least three months,” explains Ulrike Bingel. “When we talk about non-specific pain, no specific organic cause can be found for these symptoms. They are not based on tissue being continually damaged, as would be the case, for example, with osteoarthritis.”

The researchers showed both groups of participants – each more than 60 patients with chronic back pain and healthy control people – different geometric shapes, which were sometimes followed by a pain stimulus. The link between the neutral stimulus and pain was learned first, followed by an experimental phase of breaking this link.

“The study showed that patients with chronic back pain distinguished less between the shapes shown than pain-free people,” reports Katharina Schmidt. “We can conclude from this that chronic pain is associated with altered threat and safety learning.”

The more the researchers find out about the mechanisms underlying the learning of pain, the better they hope to be able to help patients with chronic pain that significantly restricts their lives. “In the collaborative research center, we have the opportunity to work with colleagues who are dedicated to various aspects and disease patterns, such as visceral pain, in addition to back pain, which is our main focus,” says Ulrike Bingel. “There may be a general phenomenon underlying chronic pain, despite its different forms. That’s what we want to understand.”

text: md, photos: Essen University Hospital

Interview

PRESERVING THE TREASURE TROVE OF RESEARCH

At the Collaborative Research Center Extinction Learning, researchers are offered support with storing, sharing, archiving and publishing their data.

MRI scans, EEG recordings, microscope images, stress surveys – researchers produce a veritable treasure trove of research data every day. The Collaborative Research Center Extinction Learning intends to retrieve this treasure, share it with others and make it accessible to future generations of researchers. This requires trust, patience, convincing – and biscuits, according to Dr. Marlene Pacharra and Tobias Otto. They support researchers in research data management in the Information Infrastructure Project (INF) at Collaborative Research Center (SFB) 1280.

What exactly is research data management (RDM)?

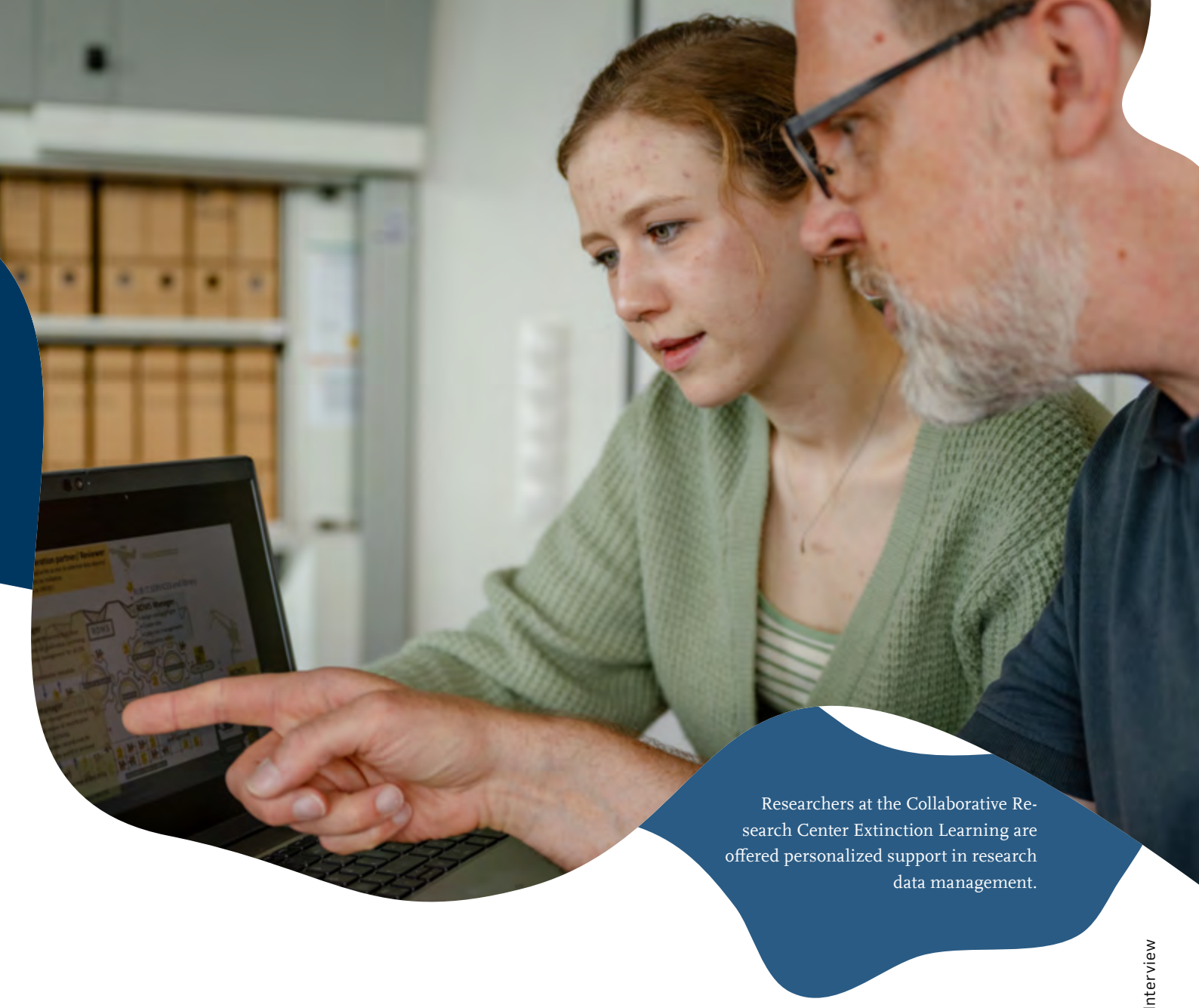
Tobias Otto: Research data management refers to the organization, storage, documentation and availability of data throughout the entire research process – all this may sound abstract at first, not at all practical and like a lot of work with no clear benefit. The problem with RDM is that it actually feels like that to begin with, but of course it's not. RDM is long-term effort that often only pays off after an experiment or project has been completed. Then, however, you immediately notice how much it was worth investing in this effort – and you will ultimately maintain this approach in the long term.

Marlene Pacharra: Ideally, researchers consider how their research data should be stored and documented even before they start their experiments. It's important to have a well-organized data and folder structure and an idea of what additional information is needed to ensure that the data will still be traceable and reusable in ten years' time. The latter is the metadata that you often hear mentioned, i.e. descriptions of the research data.

What does that mean in practice?

Pacharra: First of all, the SFB's research data managers are the researchers themselves, who, in keeping with good scientific practice, are also responsible for their own data. We assist them with advice and show them how they can improve their daily RDM routines. We are also creating sustainable infrastructures, for example, building the new research data management system ReSeeD in close cooperation with Research Data Services of Ruhr University Bochum and adapting it to the needs of the SFB. But in order for these tools to be accepted and become part of everyday research, we have to communicate with the researchers, ask them about their needs, and identify where things are going wrong.

Otto: We ask "Where are you?" and "What do you need?" We talk to researchers, build awareness of the need for good management, solve problems collaboratively, improve storage processes and so on. Accordingly, our INF project is a service project that focuses on and supports communication. Sitting down with coffee and biscuits, providing personalized sup-



Researchers at the Collaborative Research Center Extinction Learning are offered personalized support in research data management.

port – we believe this is essential to driving good research data management forward.

An important aspect of the data management strategy at the SFB is the Ruhr University's research data management system ReSeeD. Can you explain what that will look like?

Otto: At the moment, the researchers at SFB 1280 work with apps we've developed for metadata on a network drive in central IT and use a defined folder structure in order to share research data. The system has grown over the years and is still operational, stable and secure. But for publication and archiving, our researchers have to use other systems. The Ruhr University's new research data management system ReSeeD supports backup, documentation, collaboration, archiving and publication in a single system with a high level of usability for researchers, so that there's no need to switch between systems.

Pacharra: What makes this research data management system so important for us in the neurosciences is that there are no established guidelines for our field. Whereas national infrastructures do exist for other disciplines.

How long has the current system been in place?

Otto: We first started thinking about it in 2016 in the FOR 1581 Extinction Learning research group: How do we describe our different research data with metadata? What must standardized folder structures look like that can work across all areas of neuroscience, i.e. for animal data, human data, EEG recordings, MRI images and so on?

One thing was crucial right from the start: The concept doesn't have to be perfect, but it has to be right for the researchers, so that they can integrate it into their daily research routine and, ultimately, the concept ends up being applied. We want to approach researchers in their area of expertise, which is research rather than data management. We believe that this is the only way we can be successful in the long term and ensure good research data management. ▸

Ruhr University Bochum has further developed a software that is used all over the world to make it available to its researchers as ReSeeD. Have you had the chance to test the system?

Otto: We're working closely with Research Data Services at Ruhr University Bochum and have tested the beta version of the new system with other users at the university. The system is going to be excellent! It is and will remain completely open source and will be provided by our IT.Services. Everyone can and should use the system and help develop it. It's a system from the research community for the research community.

Pacharra: ReSeeD is going to be great. Our data storage is very effective. It can be specifically customized for individual Collaborative Research Centers, for example to take into account discipline-specific metadata schema requirements.

How do researchers react to research data management efforts, such as the introduction of new systems?

Pacharra: The researchers have put an insane amount of work and brainpower into their research and data collection. Researchers must have trust in the RDM structures in order to share this treasure, this data, in a way that is accessible. A cultural shift is needed in some areas for this to happen. What's more, data management eats up time. Researchers want to do research, do their experiments and file the data as soon as possible. They are busy and don't have time to laboriously organize their data. That's why it's so important that they get the support they need.

Otto: As research data management structures have been evolving over time, confidence in such systems and awareness of RDM have grown. The new generation of researchers is embracing the mindset of sharing data from the outset.

Which measures have you taken to support researchers when it comes to RDM?

Pacharra: For one, we introduced a Lab Data Cleaning Day, designed to raise awareness among researchers about managing their research data. That has to be carefully thought out in advance, because we're asking researchers to take a day off from their experiments, to review their data and clean it up. During a Lab Data Cleaning Day, we are on hand to help secure their data troves.

Otto: In order to minimize the time burden, we've agreed on fixed workflows. Awareness and commitment have now been established. Researchers keep telling us, "I need one more data cleaning day," and that's a positive development.

How do you manage to get everyone to commit and stay motivated?

Pacharra: One way is through our new research data management policy, which we agreed on with all researchers at the SFB in 2022 and which sets out binding rules. It defines responsibilities, roles, workflows and standards.

Marlene Pacharra and Tobias Otto support the researchers at the Collaborative Research Center 1280 in research data management.

> "WE HOPE FOR MORE TRANSPARENCY."
>
> Marlene Pacharra

Otto: The new policy shows our commitment. We don't conduct research data management and Open Science away from the public eye.

Pacharra: For us, it's crucial to understand where the researchers are coming from when we reach out to them and to appreciate the problems they're having with RDM. This is the only way we can provide meaningful advice and effective support with regard to RDM.

What's the greatest challenge from a professional perspective?

Pacharra: The human data, such as stress questionnaires and brain scans, represent a major challenge. A lot of effort is needed to ensure that these data are anonymized and that ethical standards are maintained. Researchers are quite rightly very cautious about this and have reservations. There's always a lingering concern that it could be possible to infer information about patients and test participants. Data protection is the top priority in this context.

> PERSONALIZED SUPPORT IS ESSENTIAL TO PROMOTE GOOD RESEARCH DATA MANAGEMENT.
>
> Tobias Otto

Otto: This is why our workflow requires three control instances. We provide tools for anonymization workflows, which we naturally also share with the research community. That, too, falls within the scope of RDM.

What do you expect of research data management going forward?

Pacharra: We want to ensure that, once compiled, valuable data don't have to be collected all over again. After all, data collection requires a lot of time, effort and brainpower, as well as a lot of money.

Otto: We hope that ReSeeD will be used sustainably and that the data will still be accessible and the experiments reproducible even a decade from now.

Pacharra: We very much hope that different disciplines will be able to access this treasure trove of data. With the standardized folder structure and the metadata, we want to create a framework in which researchers from different disciplines can easily find their way around. A psychologist could thus check out microscope data from biology and immediately understand the central aspects – and could potentially use them for further research.

That does sound very promising for research.

Pacharra: Indeed. Let's consider big data. Some research findings only come to light by collecting large amounts of data.

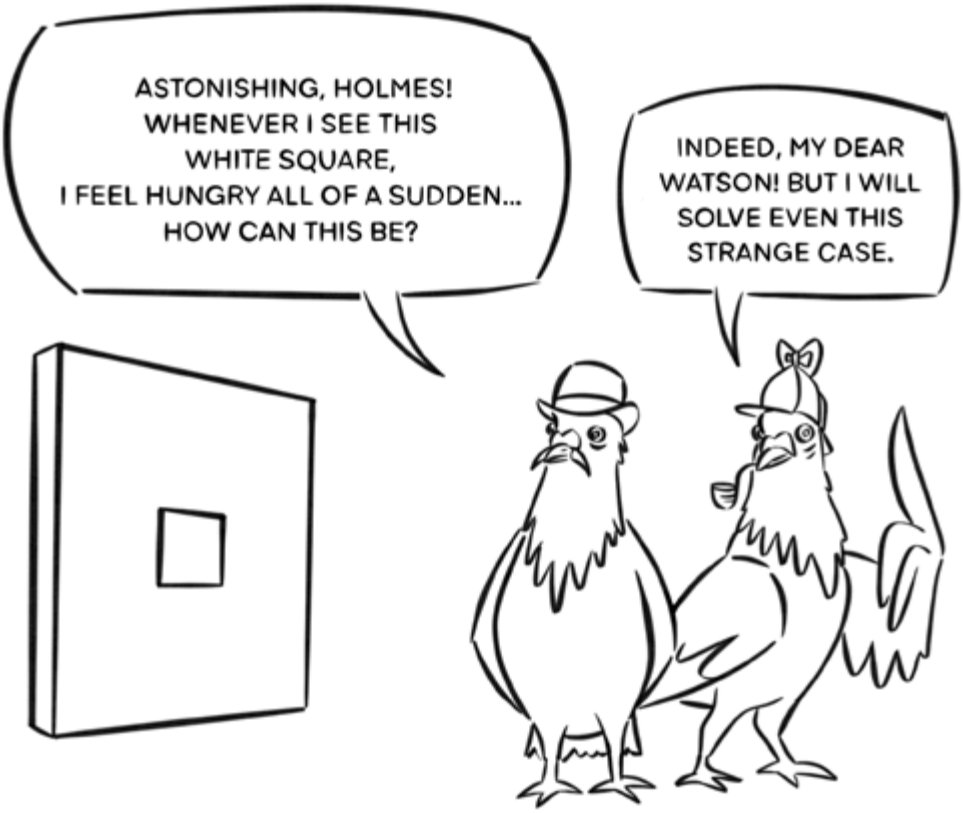
Otto: That's also the idea behind our focus groups in SFB 1280. The availability of data is essential to formulate new, overarching theories, for example by combining data from animals and humans to gain new insights or to discover mechanisms.

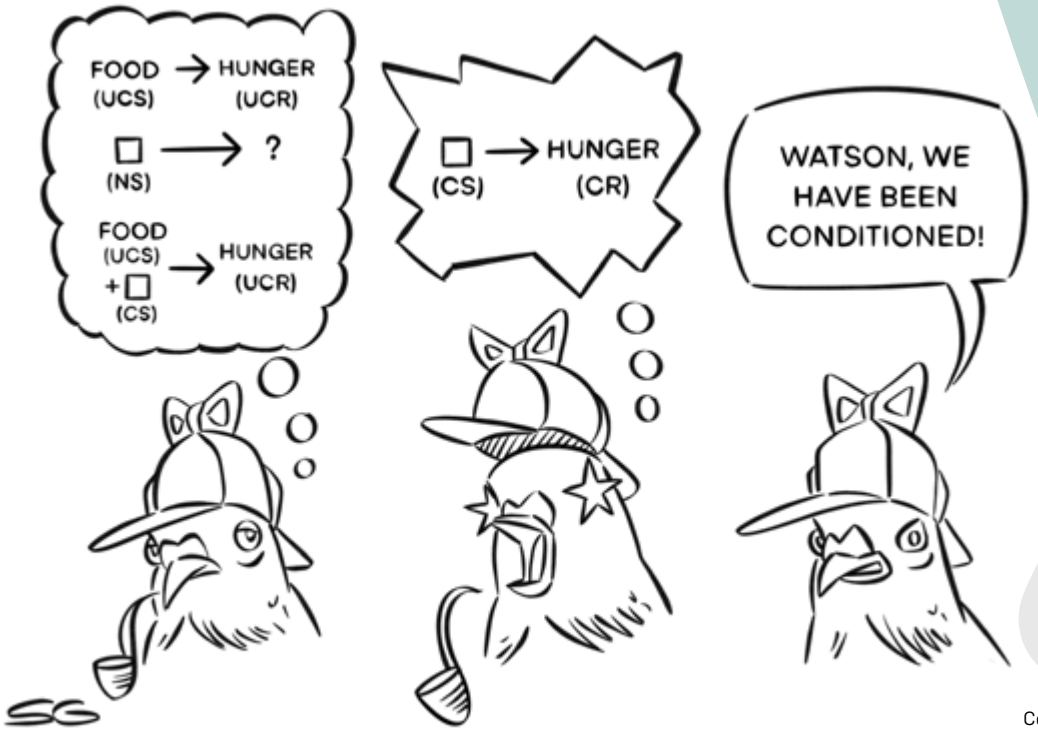
Pacharra: In the future, researchers will be able to look up whether data already exists that's relevant to their hypotheses and questions. This could speed up research processes. We also hope for more transparency overall. In psychology there's what is known as the replication crisis. But the more meta-information we have and the more we understand about the contexts of study data, the more likely we are to detect errors and manipulations in research designs. This helps to determine which studies can be reproduced and replicated – and which cannot.

text: lb, photos: RUB, Marquard

Further information on ReSeeD:
→ **datarepository.ruhr-uni-bochum.de**

EDITOR'S DEADLINE





Comic: Simon Gies

UCS: unconditioned stimulus
NS: neutral stimulus
CS: conditioned stimulus
CR: conditioned response
UCR: unconditioned response

IMPRINT

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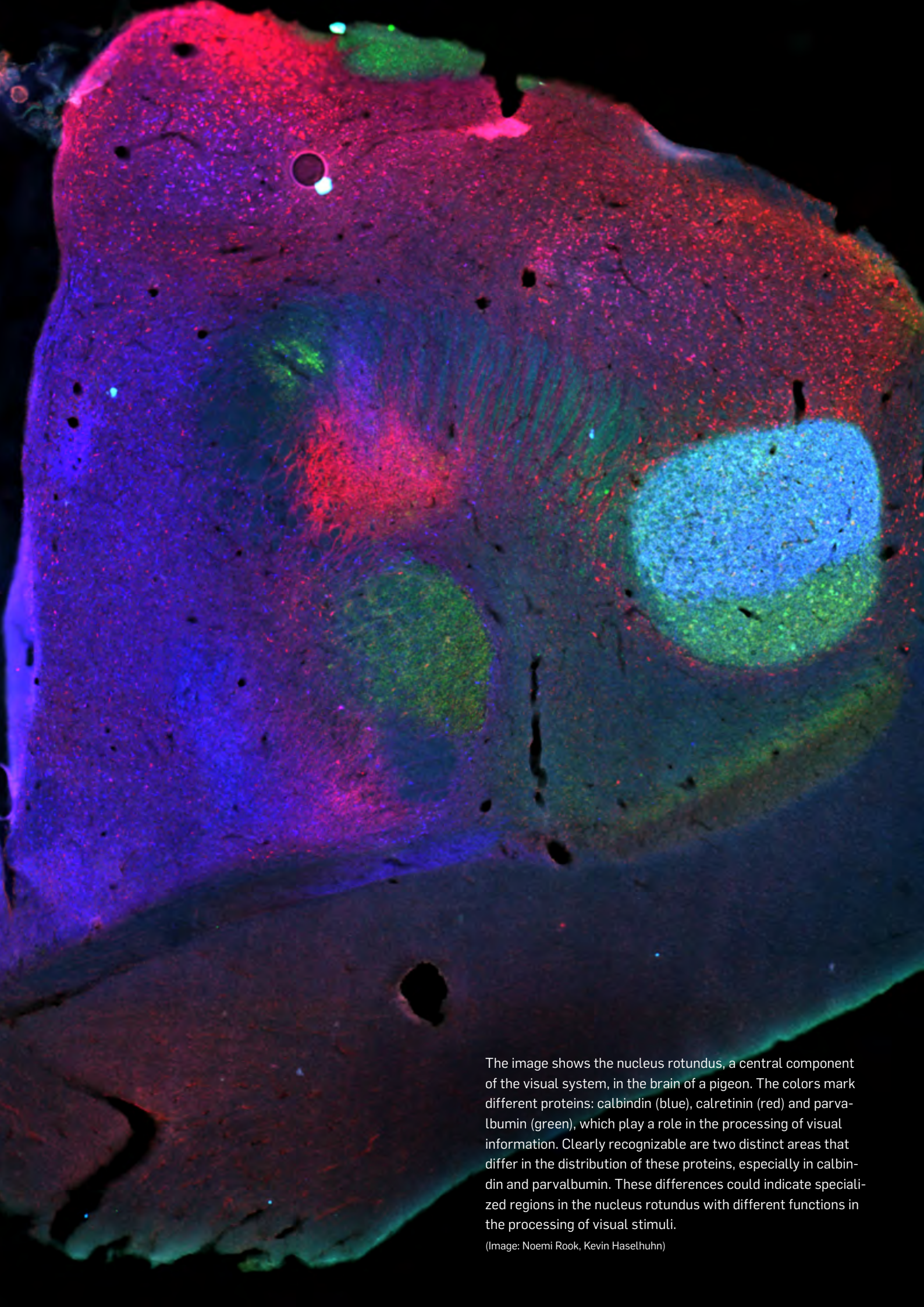

The image shows the nucleus rotundus, a central component of the visual system, in the brain of a pigeon. The colors mark different proteins: calbindin (blue), calretinin (red) and parvalbumin (green), which play a role in the processing of visual information. Clearly recognizable are two distinct areas that differ in the distribution of these proteins, especially in calbindin and parvalbumin. These differences could indicate specialized regions in the nucleus rotundus with different functions in the processing of visual stimuli.

(Image: Noemi Rook, Kevin Haselhuhn)

extinction learning | SFB 1280

KANNSTE VERGESSEN?

– Der Podcast vom Lernen, Vergessen und Erinnern

Podcast about Extinction Learning in German

Lernen ist schwer. Vergessen ist manchmal noch schwerer. Wie wird man Gelerntes wieder los? Das möchte unser Host Rainer Holl wissen und verstehen. Dazu interviewt der Autor, Slammer und Moderator Forschende des Sonderforschungsbereichs Extinktionslernen zu ihrer Arbeit, ihren Erkenntnissen und ihrer Wissenschaft.

Der Podcast gibt einen Einblick hinter die Kulissen von Psychologie, Neurowissenschaft, Medizin und angrenzenden Bereichen. »Kannste Vergessen? – Der Podcast vom Lernen, Vergessen und Erinnern« ist der Podcast des SFB 1280 und erscheint einmal im Monat – jede Folge mit der Idee, dem Gehirn ein bisschen mehr in die Karten zu gucken.

Der SFB 1280 wünscht viel Spaß beim Hören!

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