

The Terror of Trauma

Years after their occurrence, terrorist attacks, natural disasters and accidents continue to trigger anxiety and panic attacks in many people. Those afflicted find themselves reliving the event in nightmares or flashbacks. A team of doctors and researchers at the **Max Planck Institute for Psychiatry** in Munich, headed by the institute's Director, **Florian Holsboer**, is seeking ways to prevent and treat such post-traumatic stress disorders.

TEXT **ADELHEID MÜLLER-LISSNER**

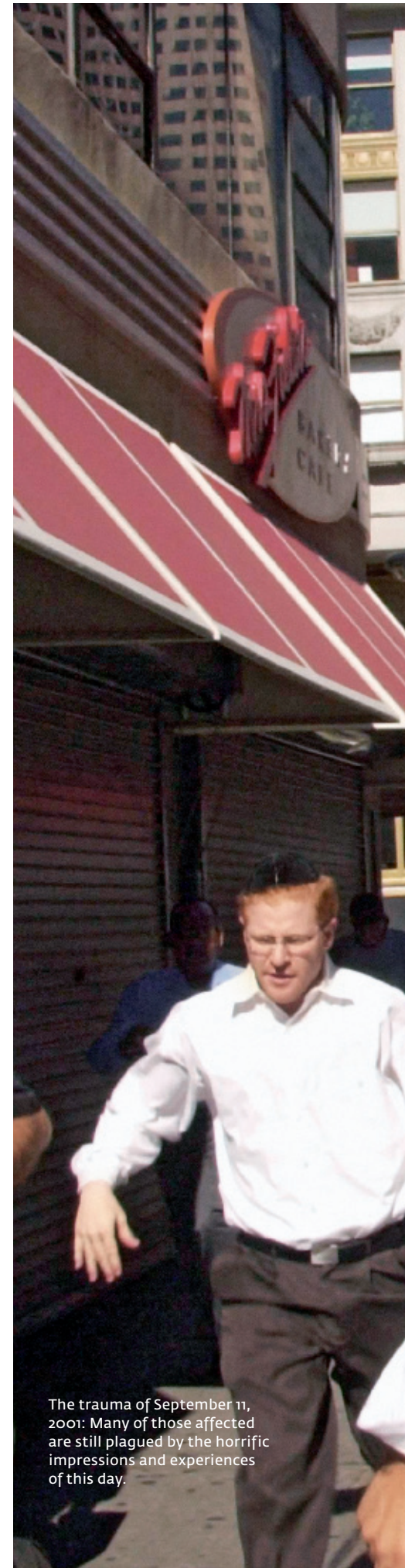
In the opinion of some of his colleagues, psychiatry's gain in attracting Florian Holsboer to its ranks was architecture's loss. Shortly after he took up the position as the new Director at the Max Planck Institute for Psychiatry in Munich in 1989, the din of construction could be heard on the institute campus, where the light-filled semi-circle of the lecture hall in the new institute building was being completed, the design of which Holsboer was closely involved in. His colleagues thus had good reason, on the occasion of his 60th birthday, to present him with a "golden book of building" inscribed with the motto – based on Descartes – "I build, therefore I am." Holsboer shows the book to visitors with the satisfaction of someone who feels that he is understood.

And, of all people, this man, whose work on the development of the institute was expressed in the functionality and aesthetic appeal of the institute's new buildings, would experience first hand the collapse of the two towers of

the World Trade Center in New York on September 11, 2001. From the window of his hotel room, Holsboer saw one of the two jets that flew over Manhattan and, in an unprecedented act of terrorism, destroyed thousands of human lives and reduced an iconic modern landmark to ash and rubble. Remaining "cool and composed," he photographed the unfolding event "as though it had nothing to do with me at all," relates the psychiatrist nearly ten years later.

NORMALITY IN AN EMERGENCY

Holsboer's amazement at how he was able to get something to eat and then go for a haircut just a few hours after the disaster is still palpable. Everyday actions in an emergency situation – everyday actions that he will remember, right down to the very last detail, for the rest of his life. "I ordered poached eggs on a bed of spinach, a dish called eggs benedict." But he probably left the hotel that day only so he could engage in normal conversation with people. >



The trauma of September 11, 2001: Many of those affected are still plagued by the horrific impressions and experiences of this day.





Many people who managed to reach safety that day or who lost relatives in the rubble of the Twin Towers were so shocked by these events that they became mentally ill. Post-traumatic stress disorder is the psychiatrists' diagnosis. It is also made several times a day at the trauma outpatient department of the Max Planck Institute for Psychiatry: in women and girls who have been raped, people who have been involved in serious car accidents and were sitting beside another passenger who was killed, and soldiers who have been traumatized through their involvement in dangerous military interventions.

According to the internationally recognized DSM-IV diagnosis manual of the American Psychiatric Association, the ability to identify a clear trigger for the disease is a feature of post-traumatic stress disorder (PTSD). "By the time the patients come to us, many

of the events that trigger the disease go back several years," says psychiatrist Ulrike Schmidt, head of the outpatient trauma clinic at the Max Planck Institute in Munich. Her patients come to her because they have long been unable to sleep properly, because they are tortured by nightmares or because their memory has been permanently altered by the traumatic experience. They come when they are plagued by memories in the form of flashbacks, when they find themselves forced to avoid vital everyday situations, when they have become extremely jumpy and anxious.

Tests carried out on, for example, former American soldiers would suggest that around one-tenth of those who have experienced a particularly stressful situation go on to develop a mental disorder. Not all display the typical symptoms of PTSD but, at the very least, they experience adjustment dis-

orders or show character changes. Women become ill after bad experiences more frequently than men; it is thus likely that sex hormones also play a role in these conditions.

BETTER SOONER THAN LATER WITH TREATMENT

"The longer you wait with such symptoms, the more difficult and longer the therapy required," says senior physician Ulrike Schmidt. In some cases, it is unlikely that the patient will make a complete recovery, "but we can always make an improvement." The aims of the therapy are defined in consultation with the patient at the beginning of the therapy. Transparency is an important principle here – particularly when the psychiatrists consider the patient's condition as being so acute and dangerous that they advise inpatient treatment.



Creative activity can help patients express their moods and deal with stressful feelings. These paintings are the work of the patient G.B., who has been receiving treatment at the Max Planck Institute for Psychiatry for a long time. She experienced certain effects of her illness as traumatizing. These include the compulsion to harm herself. She expressed her perceptions during the different stages of her illness in visual images.

left: "Self harm" – "This painting emerged from the impulse to harm myself. However, I was able to deflect the impulse onto the canvas."

right: "I was in complete despair about my condition and the many drugs, but I filled the empty drug containers with paint as a sign that there was still hope that I would emerge from my illness with the help of the drugs."

This is the case with every fifth patient who comes to the institute with a stress disorder of this kind. "Some have serious suicidal thoughts, while others are detached and unapproachable and ward off the serious stresses in this way," explains Ulrike Schmidt. A group of victims is occasionally monitored at the institute's day clinic.

But the treatment of post-traumatic stress disorder need not always be a lengthy affair: "In some patients, ten two-hour sessions followed, perhaps, by a concluding session six months later is sufficient." Different therapeutic methods are combined in an undogmatic way for the psychotherapy. "We don't follow a strict plan, but rather take direction from the patient's individual needs," explains Schmidt. One thing is always ensured, however: before the patients are directly confronted with the bad event at the root of their condition, they must

be safe from a possible perpetrator and must have learned how to curb their stressful thoughts using such methods as the "thought stop" technique. Therapy is also accompanied by the administration of various drugs, for example to counteract sleep disorders. However, there are no drugs available that are specifically effective against PTSD, and this represents a challenge for a research institute whose Director embarked on his academic career as a chemist.

In all cases, treatment is preceded by a detailed diagnosis. In addition to structured interviews, this also involves the determination of biological parameters. To this end, blood is taken from the patient several times over the course of the treatment. Schmidt and her colleagues from the Molecular Psychotraumatology research group analyze the blood for markers that show the biological effects of the traumatic

event, for example how it alters the programming of gene and protein activities. The biomarkers are biological informants that later also provide pointers as to how the epigenetic and biochemical changes can be reversed, in part, through successful therapy.

The scientists at the institute would now like to research this process in a major clinical study on post-traumatic stress disorder involving around 800 patients. A cooperation with the German armed forces is planned. "We would also like to be able to include a group of people who have experienced traumatic situations without developing psychological problems," says Schmidt. This is one of the great conundrums that puzzle the researchers at the Max Planck Institute for Psychiatry: Why do some people become ill after a bad experience, while others remain unaffected? What are the risk factors



"This painting expresses the desire for beauty, but it also shows bars – a symbol of the experience of being locked up in the closed psychiatric unit. The bars block the view of the beauty, but they also link the light and the darkness."

for predisposition to a stress disorder? These are questions that lead the researchers from humans to mice. "In our work, the topics for examination in basic research come from the clinic," stresses institute Director Florian Holsboer. Whereas the principle "from bench to bedside" is frequently cited in other research contexts, he consciously expresses the philosophy of his institute the opposite way around: "From bed to bench – and back!"

Biologist Carsten Wotjak, head of the Neuronal Plasticity research group, may be the institute's "lord of the mice." But when he subjects the rodents to different stressors, it is subway drivers, emergency medical technicians and soldiers that are foremost on his mind. "The ultimate aim is to predict the individual predisposition to strong or weak traumatization, and to be able

to intervene at an early stage after a traumatic event." A very well received study that was published in November 2009, and whose authors include Holsboer and Wotjak, showed that baby mice that are separated from their mothers at an early stage display increased activity of the vasopressin gene and altered methylation patterns in their DNA. As the biologist points out, however, rats and mice also display significant differences in terms of their vulnerability to stress.

The researchers are largely dependent on the interpretation of the laboratory animals' behavior for their studies – when they recognize brain activity characteristic of fear from the brainwaves in an electroencephalogram, they can't ask the mouse whether it remembers the unpleasant electric shock it felt against its foot. Therefore, wheth-

er or not undesired memory content constantly arises in the mouse's mind, as is the case with humans with post-traumatic stress disorders, remains purely a matter of conjecture. The fact that a mouse is traumatized is most likely to manifest itself at the behavioral level through altered mobility patterns, for example through increased agitation shortly after the traumatic event. The animals will also tend to avoid situations that they know to be unpleasant for a long time after the initial experience.

With a view to answering the question as to what makes mice particularly vulnerable to symptoms reminiscent of a post-traumatic stress disorder, the scientists anaesthetized the small rodents and placed them in a magnetic resonance imaging (MRI) scanner. These tests showed that animals that

» The number of people who develop a post-traumatic stress disorder after a traumatic experience has remained constant since time immemorial.

have particularly high concentrations of N-acetylaspartate – a metabolic product of nerve cells – in a particular region of the hippocampus later react particularly robustly to stress. “Our findings suggest that this is a biomarker that could also help identify people who are at risk from PTSD in advance of a traumatic experience,” explains Wotjak.

The Max Planck scientists hope to achieve similar results from the measurement of sleep quality. Michael Czisch and his research group influenced the fear memory of healthy young test subjects using mild electrical impulses before they allowed them to take a long afternoon nap. The test participants who did not have any REM sleep phase displayed the strongest fear reactions.

The question that arises here is whether it will one day be possible to say who should not join the police force or fire department on the basis of sleep tests and biomarkers. Ulrike Schmidt is convinced that the number of people who develop a post-traumatic stress disorder after a traumatic experience has remained constant since time immemorial. What is certain is that there can be no blanket prophylax-

is against this kind of disorder; we can all fall victim to a tsunami or terrorist attack. Furthermore, the well intentioned attempt to provide “debriefing” for all those affected in the aftermath of a catastrophe is now viewed by experts as harmful. According to Holsboer, the “cellular turmoil” in people at particular risk from PTSD is far too great. The most effective measure would be to recognize this fact immediately and proceed with targeted therapeutic intervention.

THE PSYCHOLOGICAL IMPACTS OF SEPTEMBER 11TH

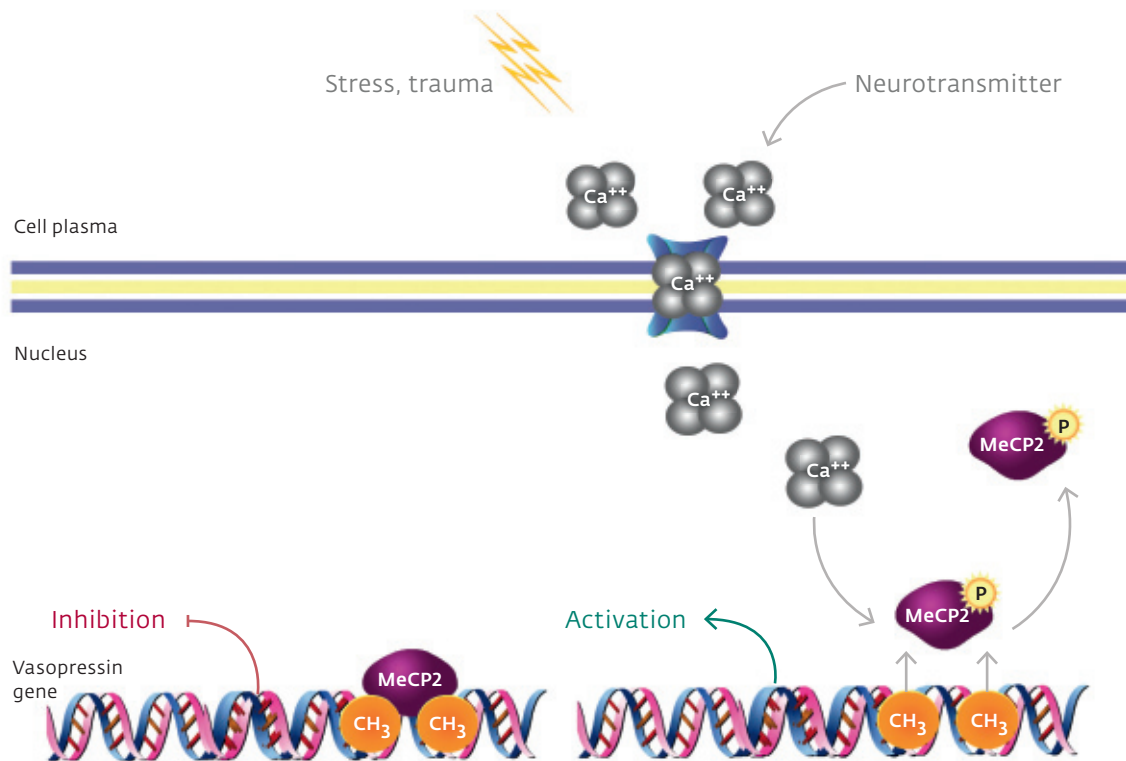
This brings us back to the key traumatic event of September 11, 2001. “As horrendous as this event was, it offered favorable conditions for our research,” says Marcus Ising, who works in the fascinating area of molecular psychology. “Nine eleven” ultimately affected people from all walks of life and thus provided the researchers with a valuable representative sample. The researchers from the Max Planck Institute for Psychiatry did not develop an interest in those affected by this event solely because their boss was in New York on the

day of the attack; they also saw it as a challenge that they should rise to, since the stress hormone system had long been one of the institute’s main research topics. And if you are involved in research on stress and the psyche, there is hardly any way around post-traumatic stress disorder.

So the Munich-based psychiatrists cooperated with the New York Academy of Medicine and the Mount Sinai School of Medicine, from where Rachel Yehuda came to Munich to take up the Kraepelin Professorship at the Max Planck Institute for Psychiatry in 2004. The work carried out in this context included the examination of blood samples taken from 40 people directly affected by the attack. According to these analyses, half of the study participants developed a stress disorder and, despite being exposed to the same conditions, the other half remained mentally healthy. All of the participants shared a similar genetic background. >

left: Soldiers deployed in war are often traumatized. The earlier a post-traumatic stress disorder is treated, the greater the chance that treatment will succeed.
right: Ulrike Schmidt with a patient





above: Epigenetic trauma memory in the brain: Chemical appendages, known as methylations (CH₃), inhibit the production of the stress hormone vasopressin (bottom left). In the event of stress or trauma, excess calcium flows into the neurons of the midbrain. The molecule MeCP2 gains phosphate (P) as a result and is no longer able to bind to the control region of the vasopressin gene. The gene then becomes overactive (bottom right). But MeCP2 has another function: it provides a docking site for proteins that give the DNA the epigenetic markers. Missing methylations can no longer be completed and are gradually lost. The formation of vasopressin can't be controlled, and life-long overproduction occurs.

below: Florian Holsboer, Director of the Max Planck Institute for Psychiatry



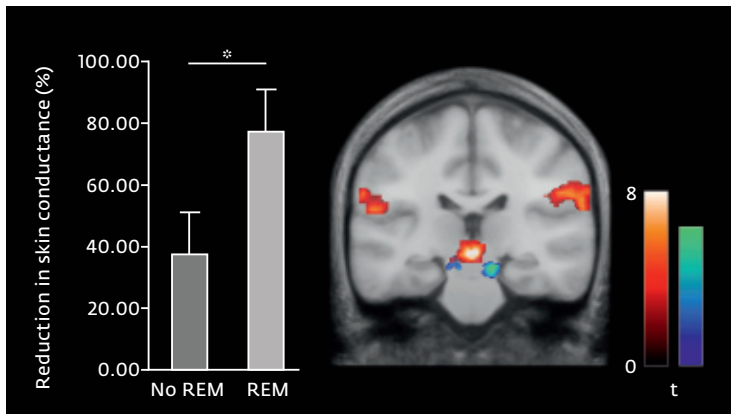
The question that interested the scientists here concerned the differences displayed by the gene activity in their cells. "We tested over 3,000 pieces of data and an old acquaintance eventually came to light," reports Ising. The old acquaintance was the FKBP5 gene. In their work on depression, the researchers had previously observed that minor variations, or polymorphisms, in this gene could have a crucial influence on the disease. Indeed, depression is the field for which the Munich-based institute and its Director Florian Holsboer, who treated the prominent German soccer player Sebastian Deisler for the condition, has been renowned for many years.

EXAGGERATED EFFECT OF CORTISOL

In cells, the FKBP5 gene modulates the glucocorticoid receptor, a docking site for cortisol, which plays a crucial role in the regulation of the stress hormone axis. Whereas, typically, the gene is particularly active in patients with depression, at initial glance, the opposite appeared to be the case in patients suffering from post-traumatic stress disorders: the gene displayed a particularly low level of activity in these patients.

The interactions here, as Ising explains, are complicated: "The gene plays a crucial role in the sensitivity of the receptor. If it is turned down, as in the case of patients with a PTSD, the receptor is able to do its job particularly well."

Accordingly, the changes in the gene regulation in the two conditions are mirror images of each other: in the case of PTSD, the reaction of the receptor to the stress hormone cortisol is excessive, and in the case of depression, it is extremely attenuated. "Both reactions appear to be harmful," explains Ising. He and his colleagues are unanimous in their assumption that the conditions involved here are not opposites. "We believe that the reaction is initially the same in both cases. The reduced activity of the FKBP5 gene in the case of a post-traumatic stress disorder is probably not the cause, but the consequence of the illness." It is likely to be the outcome of an incorrect biological strategy, a desperate self-defense measure by cells that find themselves in turmoil in the face of extreme stress. This idea is also supported by studies carried out in the US in which Ising's colleague Elisabeth Binder was also involved: "As we now know today, the genetic variants that promote the development of



Sleep tells us a lot about the predisposition for post-traumatic stress disorder (above). Test subjects with REM sleep phases react less anxiously to light electrical impulses when awake: their fear-sweat production declines more than that of test subjects who don't experience REM sleep phases (bottom left). In the red brain regions, the brain activity rises after the electrical impulses (bottom right). The cool colors show areas near the possible REM sleep center that are more active in people without REM phases than in people with REM. The hyperactivity of these areas probably causes the absence of REM phases.

depression can also lead to post-traumatic stress disorders."

The possibility of a relationship between depression and PTSD is also supported by the observations that the two conditions frequently arise in combination and that antidepressants can help prevent the development of a post-traumatic stress disorder in the immediate aftermath of a bad experience. Ising refers to the "multiple ties between the two illnesses." And this includes anxiety disorders.

Like the psychiatric disorders they research, the scientists at the Max Planck Institute for Psychiatry are also inextricably linked. When the psychiatrists, psychologists and biologists

visit each other, they frequently pass by Emil Kraepelin, who founded the "German Research Institute for Psychiatry" in 1917 and whose bust is prominently displayed near the institute's lecture hall. The systems currently used for the classification of mental illnesses have their roots in Kraepelin's work. And the very man who today advocates "breaking down diagnostic restrictions in favor of a causal understanding" of mental illnesses is Kraepelin's seventh successor at the institute in Munich. Florian Holsboer might also be able to persuade Kraepelin that psychiatry must find personalized treatment paths. "After all, we are all proud to be individuals," he

notes. "Only when we become ill are we happy to take cover under the general umbrella of a diagnosis."

It is unlikely that Kraepelin would be able to follow his colleagues today when they speak of "genetic switches" that "are reset by a trauma," or "drawing-board-design molecules that accumulate specifically at receptors." He would note, however, that building and development work is still under way at the Max Planck Institute for Psychiatry in Munich's Schwabing district. And what's more, defenses are also being erected there that are strong enough to protect the human soul against mental illness in the aftermath of a traumatic experience. ◀

GLOSSARY

REM sleep (REM: "rapid eye movement")

The phase of sleep characterized by rapid movement of the eyes, increased heart and breathing frequency, and dream phases. It appears that people who react particularly strongly to fear stimuli do not attain the REM phase of sleep. Permanent activity of the brainstem may play an important role in these people. The brainstem is located next to the brain's REM sleep center. Its overreaction probably results in the complete omission of this sleep phase. Brain processes that depend on REM sleep phases can be impaired as a result, and this can explain the fear reactions.

Stress hormones

The stress hormones include cortisol, cortisone and corticosterone. These hormones, which are also known as glucocorticoids, are produced in the adrenal cortex. They bind to receptors in the cell membrane and regulate the cell's gene activity via signaling chains. The effects of stress hormones include analgesia and immune inhibition, and they also influence the body's water and mineral balance. Stress hormones and their receptors clearly play a role in mental illness.

Epigenetics

Epigenetic changes are molecular appendages, e.g. methylations, that facilitate or hinder the reading of genes. An organism's living conditions can influence its genes in this way. Mental illnesses caused by stress can also be based on epigenetic changes. For example, the genes of baby mice that are separated from their mothers shortly after birth undergo epigenetic modifications. The animals produce increased levels of stress hormones as a result, and have problems dealing with stressful situations. Such acquired genetic changes can be passed on to subsequent generations.