



32

Under pressure to perform: taking an exam is a source of stress for most people. But stress can also have a positive effect. You become more awake and focused, and your attention and reactivity levels increase.

# DON'T STRESS YOURSELF

TEXT: JAN SCHWENKENBECHER



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When the human body is exposed to stress, it goes into the very same emergency mode that it used in the Stone Age. However, that reaction is not nearly as well suited to our way of life today. Scientists at the Max Planck Institute of Psychiatry and the Max Planck Institute for Human Cognitive and Brain Sciences are studying what happens in the body during stress, who is particularly susceptible to stress, as well as when it is an especially bad time to have to deal with a large amount of stress.

Stress in the cell culture: researchers are using brain organoids to study the impact of stress hormones on brain development. These organoids consist of neuronal precursor cells (green) and newly created neurons (gray).

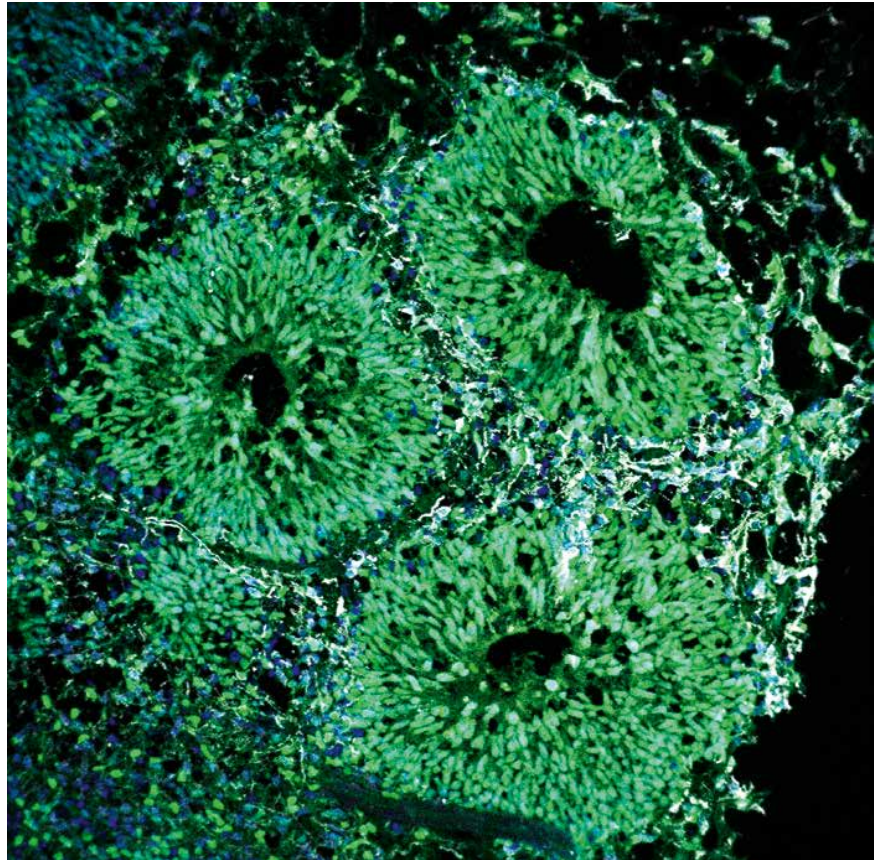
Just imagine: you have just ten minutes to prepare. And then you need to give a five-minute presentation about why you're the best candidate for a job. Without notes. And to make things worse, you have to do this in front of two psychologists in white coats, who are both experts in non-verbal behavior, who will sit motionless and impassive, just watching you. Audio and video recordings of your presentation will also be made and analyzed. And then there will be five minutes left in which you have to solve mathematical problems of medium-level difficulty. Holy moly! This doesn't exactly sound like a leisurely walk in the park – more like maximum stress!

In fact, that's the whole idea. The situation described is part of the script for the Trier Social Stress Test, or TSST. The test is designed with just one aim in mind: to trigger stress. It is particularly effective at doing just that, since the test situation combines three central components of psychosocial stress: unfamiliarity with a new situation, lack of control and a threat to the ego – in other words, something happens that has a negative impact on your own self-image or sense of self-worth. Psychologists and stress researchers use the TSST to simulate stress in scientific studies. One of these researchers is Veronika Engert from the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig. Engert is a psychologist and a professor of social neurosciences at the University Hospital in Jena. At the Max Planck Institute, she is the leader of the Social Stress and Family Health Research Group. Together with her team, she is studying when people experience stress in social contexts, how this occurs, and what they can do to protect themselves.

The human stress system originally evolved as a kind of emergency response system that floods the body with energy within a matter of seconds, making us better able to overcome a potentially life-threatening situation. Our senses become more alert, our muscles get stronger, and our regenerative capacity increases. At one time, our physical stress response often saved lives. Today, however, the World Health Organization has declared stress to be one of the greatest health risks of the 21<sup>st</sup> century.

“Life-threatening stressors have become relatively rare in our modern, western society,” says Veronika Engert. “The things that stress us are mainly of a psychological

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nature.” These things can range from a meeting with your boss, to the growing stack of unpaid bills on your desk, to having a phone conversation about work while you're picking up the kids from daycare, to getting stuck in traffic. “There are countless small incidents that occur in everyday life that make us feel stressed. The interesting thing is that our bodies respond in the very same way as if we were being threatened by a bear,” she explains. The body releases a vast amount of hormones, ratchets up our blood pressure and accelerates our breathing. “But we often don't need that added energy – for example, when we're only sitting in the car stuck in a traffic jam. It just makes us even more agitated.” Another problem is that people today feel stress

**“But we generally don't need that added energy at all.”**

VERONIKA ENGERT

far more frequently than they used to. “The way we live our lives means that most of us are exposed to low-threshold stress too often,” Engert says. In other words, it might be just minor incidents that bother us, but there are far too many of them, in too quick succession. “The next stressor usually rears its head before our body can recover from the last. As a result, we’re constantly in a state of increased stress and stewing in toxic stress hormones.”

Being in a state of stress is first and foremost bad for the health of the person who is experiencing it. However, that’s not all. Together with her group, Veronika Engert has demonstrated multiple times that we not only feel stressed when we are personally exposed to time pressure, arguments, traffic jams or aggravation. We also experience it when we see that other people are feeling stressed. A few years ago, Engert and her colleagues published the results of a study of 211 couples who were either life partners or two people who didn’t know each other. In the laboratory, one person in each dyad underwent the TSST and became increasingly stressed, while the other half of the dyad watched, either via video recording or through a panel that appeared as a mirror on the other side. Engert and her team took saliva samples from both participants before and after the TSST and examined them for cortisol levels. Created by the body in the adrenal cortex, this hormone is primarily released when we are under stress, and acts as a biological marker for researchers studying the stress that a person has recently experienced. As Engert and her team discovered, the levels of cortisol among the observers increased to the same extent as those of their actively stressed partners. Simply knowing how stressful the situation must be for the other person was sufficient to cause the observers to experience stress themselves. After their visit to the laboratory, the test subjects who were partners in real life were asked to collect six saliva samples each over the course of two more days, and to send them to the team. It emerged that in everyday life, too, if one partner was stressed, the other person felt stressed in response.

“The stress felt by others activates my own stress axis,” Engert explains. This phenomenon is known among researchers as ‘empathic stress’. “This effect even occurs when the person who is stressed is someone I don’t know,” Engert says. “However, the closer my relationship is to the stressed person, the more strongly I experience the stress myself.” The question is: what’s the point in encumbering myself with the stress felt by others on top of the stress I’m feeling myself? “Empathic stress does indeed have a useful function,” Engert explains. “For example, as a mother, if I can see that my child is experiencing stress right now, that gives me the energy to help.” Or conversely: if a mother

and child are crossing the road and a car approaches at high speed, the child might not yet be able to assess the situation correctly. However, because the child feels the mother’s stress, he or she gains the energy and insight needed to quickly jump to one side.

“Empathic stress therefore has an important, positive function,” says Engert. However, as is so often the case with stress, there is also another side to the coin. “When I think of a child living in a home with chronically stressed parents, who is constantly exposed to their stress, then it’s easy to imagine that this situation isn’t exactly healthy for that child.” Just how bad stress is for our health, and who is particularly affected by it, is demonstrated by the research being conducted by Mathias Schmidt at the Max Planck Institute of Psychiatry in Munich. “There is a whole range of diseases that are either caused or exacerbated by stress,” Schmidt explains. “Anxiety disorders and depression are just two examples.”

Schmidt is the leader of the Neurobiology of Stress Resilience Research Group. Together with his team, he is studying the influence of acute and chronic stress on the human body during different stages of development. One of his key questions is: when and why does one person tend to be resistant to stress; and when and why is someone else particularly susceptible to it?

## Biomarkers are an indication of susceptibility

As Schmidt already knows: “On the one hand, our genes play an important role. We have observed in mice that they react differently to stress, depending on their genetic predisposition.” However, genes are not the only triggers for that response. “We also know that environmental factors play a very important role,” Schmidt says. “It’s not necessarily the case that someone with a certain genetic background will inevitably be sensitive to stress. Genes are a risk factor, but there are several other factors that also play a role.” It’s never about one single stress gene. When stress researchers like Schmidt talk about “genetic influence”, they mean a large number of different genes, each of which increases the likelihood that someone responds more sensitively to stress, at least to a small degree.

To find answers to his questions, Mathias Schmidt conducts experiments on mice. For him, this has several advantages. For one thing, pregnancy in mice lasts for just three weeks, and mice are already teenagers just a few weeks after birth. As a result, the researchers are often able to study the longer-term consequences of stress without having to wait years to do so. “In this



way, we want to find out which genes and which circuits in the brain cause mouse one to be more vulnerable during stress exposure, but do not have that effect in mouse two,” Schmidt explains. “To do that, we look for biomarkers – physical signs that can predict what will happen without us having to put the mouse under stress.” There are various things that can be used as biomarkers: brain structures or entire circuits, as well as individual genes or certain combinations of several genes. “Meanwhile we’ve found several indicators for such biomarkers, which let us know that by manipulating them, we can increase or reduce the sensitivity to stress,” says Schmidt. One example is the protein FKBP51. It performs several tasks in the body, but one of them is of particular interest to researchers: it influences the sensitivity of stress hormone receptors. In so doing, it also has an effect on the processes in the cell that are triggered when the stress hormones bond with them after the body has released them as a response to stress. “Here, FKBP51 appears to play a very important role,” Schmidt says. “And we now also know from studies on humans that changes in the genetic structure of the FKBP gene, known as polymorphisms, influence how sensitive someone is to stress, and even affect the risk of their susceptibility to depression.”

Research in Psychiatry Department. According to a study published by Cruceanu in the fall of last year, one of these cases of bad timing occurs even before a baby is born. Cruceanu uses brain organoids to conduct her research. These are three-dimensional models which, starting from stem cells, create a model of human brain growth in a petri dish. “Of course, it’s not a real brain,” explains Cruceanu. “But it does have many features of a brain, and we can monitor its development over a period of time that corresponds to the development of a baby in the womb during pregnancy.” Naturally, it’s not possible, she says, to exactly compare the petri-dish brain with a real-life brain. However, if you know which questions it’s worth asking and which are not, brain organoids can be of huge benefit.

Cruceanu and her colleagues asked the following question in their study: what happens when a developing brain is confronted with an increased level of the stress hormone cortisol? “We know that this hormone plays an important role in development,” Cruceanu says. “We also know that the increased level of cortisol in mothers who are suffering from extreme stress – perhaps because they are suffering from a psychological disorder, are experiencing war or forms of abuse in their daily lives – is in part transferred to the unborn child. We wanted to find out whether this increase in cortisol has an impact on the baby’s development, and if so, how.” The researchers found the brain does indeed develop differently: it develops a significantly higher number of nerve cells. What does that mean? “It could be beneficial that leads to a higher tolerance for stress in later life,” Cruceanu explains. “However, there are also indications that it is a disadvantage.” Here, the limits of the brain model have been reached; the question will need to be answered in other studies, using other methods. But some studies have already been conducted that shed light on this topic, Cruceanu says. “We know from earlier research that in households in which the mothers were exposed to stress, the children more frequently suffer from depression, autism spectrum disorders or other neurological development dis-

36

## Children in their mother’s womb are also at risk

Schmidt’s research is directly linked to the field of psychiatry. It is application-oriented, preventive research. “We do the same for other diseases,” he explains. “When a doctor ascertains that I have an increased blood sugar level, I know that I need to be careful and to adapt my way of life. Because if I continue my behaviors, I might develop diabetes in two years’ time.” A very similar approach could be taken in psychiatry in the future: if there is an awareness of a susceptibility to stress in a person’s individual risk profile, those who are more at risk could be advised to reduce the level of stress in their everyday lives. This could prevent certain psychological disorders from developing.

Once again: stress isn’t a bad thing in itself. The body’s stress response helps us become more capable of taking effective action within seconds. However, what matters is the amount of stress, and the point in time at which it occurs. Constantly living with time pressure, daily agitation and upsets among work colleagues, or exposure to incessant city noise, means that stress becomes a permanent situation that can lead to problems in the long term. The same is true if stress occurs at the wrong time. Cristiana Cruceanu knows all about that. She is a postdoc who also works at the Max Planck Institute of Psychiatry in Munich, in the Translational

**“Mice respond differently to stress depending on their genetic disposition.”**

MATHIAS SCHMIDT



Stress test: for the Trier Social Stress Test, a test subject is made to face a grueling job application situation. Using this simulation, researchers aim to obtain new insights into how social stress is created and what its consequences are.

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## SUMMARY

Researchers are looking for physical signs that provide early indicators of whether stress can lead to psychiatric disorders.

Stress in expectant mothers influences the brain development of the embryo.

The phenomenon of “empathic stress” causes individuals who are exposed to people who are stressed to experience stress themselves.

If someone feels compassion for a stressed person instead of empathy, they may be less likely to take on that person’s stress.

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orders.” Therefore, too much stress harms more than the stressed individuals themselves. Expectant mothers who are constantly or severely stressed during pregnancy are probably increasing the risk of their child becoming more susceptible to stress later on.

And Veronika Engert’s research on empathic stress shows that parents transmit their stress to their children, even after they’re born. But, thanks to the latest research by Engert and her team, help may be on the way, particularly with regard to the transmission of stress. Engert’s team is currently studying the extent to which it makes a difference if an individual who witnesses someone close to them feeling stress responds with empathy or compassion. “In science, we differentiate between empathy and compassion,” Engert says. “Empathy is purely sharing the other person’s distress: ‘I feel your suffering.’ Compassion goes beyond this to: ‘I want to relieve your suffering.’ A person who feels compassion always wants the other person to be in a good situation, to experience mercy, in spite of their suffering.” Engert and her team are now investigating whether children are protected against that stress reaction if they tend to feel more compassion than empathy.

“We have a few interim results which indicate that children who feel a particularly high level of empathy experience the stress reaction of their mother more profoundly,” Engert says. “In contrast, children who primarily show compassion and who wish to help their mother don’t experience the stress themselves to nearly the same degree.” If these results are confirmed, this would be an approach that could help define methods of stress prevention. After all, feeling compassion instead of empathy is something that we can learn. This kind of training is already available, particularly for people who work in the care sector, such as doctors, therapists and caregivers. Perhaps similar programs could also be developed for families.

In any case, Veronika Engert’s research on empathic stress comes to the same conclusion as Mathias Schmidt’s and Cristina Cruceanu’s findings: the stress response helps humans react to unusual situations in an unusual way. For this reason, it’s important that these situations remain unusual, and that they by no means become the rule. The best way to tackle stress is not to let yourself be influenced by it in the first place.

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