

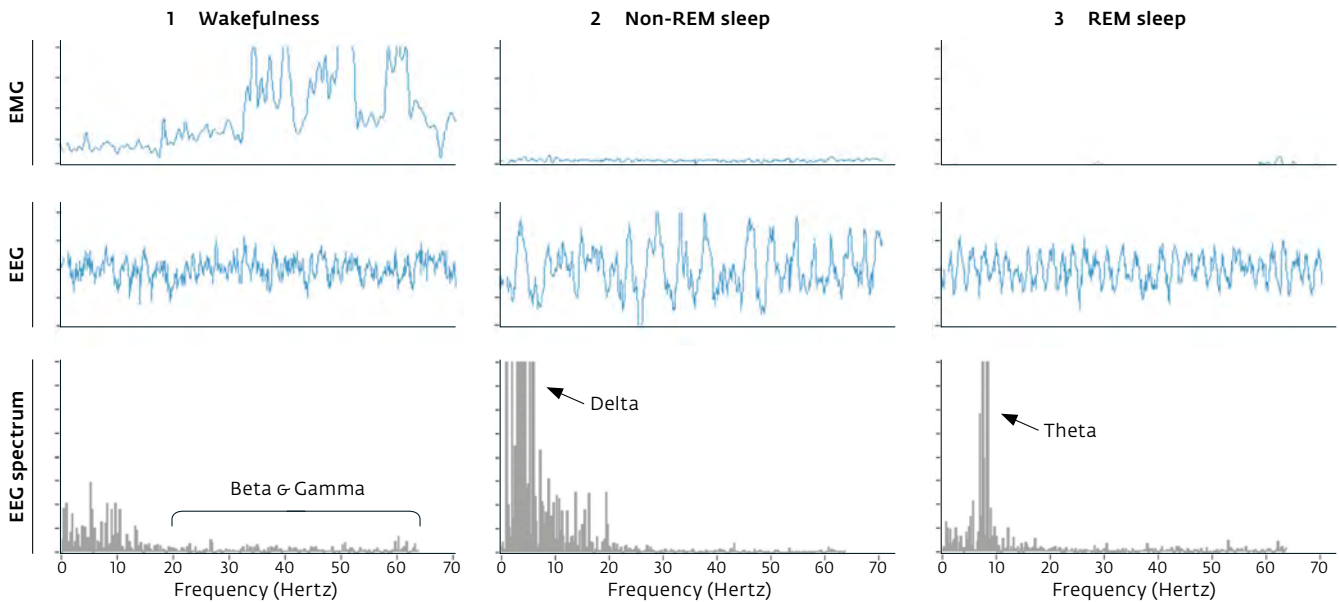
High-tech nightcap: Researchers use more than 100 electrodes to record the electrical currents on the surface of the head while a subject sleeps. This brain activity is used to generate a sleep profile.



When the Brain Switches to Standby

People who haven't gotten enough sleep often see the world as a fairly sad place. If their tiredness lasts for weeks or even months, their dark mood may become chronic and develop into depression. Conversely, depression is frequently also associated with severe sleep disorders. **Axel Steiger** and his team at the **Max Planck Institute of Psychiatry** in Munich are studying the connection between disturbed sleep and depression. To do this, they measure human brain activity in the sleep lab.

TEXT **CATARINA PIETSCHMANN**



Top Measuring mouse sleep: While awake (column 1), mice move around a lot, so their muscles are more frequently active. The graph shows the electrical signals from their neck muscles (electromyograph; top). The neurons in their brain fire in different rhythms and across a broad range of frequencies (middle and bottom). In non-REM sleep (column 2), the skeletal muscles become inactive (top). Brain activity oscillates with high amplitudes but low frequency (delta waves; middle and bottom). In REM sleep (column 3), the muscle tones are almost flat (top) and theta rhythms predominate in the brain (middle and bottom).

Opposite page In the sleep lab of the Max Planck Institute of Psychiatry, Michael Czisch records the subject's brain activity in an MRI scanner. This device makes the activity of the sleeping brain visible to scientists.

Stress at work, relationship issues or moving to another city can literally rob people of their sleep. According to the Robert Koch Institute, one out of every three German citizens has suffered from a sleep disorder at some stage in their life. In most cases, sleep patterns return to normal once the stressful event or issue has passed. However, when such symptoms persist for weeks or months, it is important to consult a doctor.

Poor sleep can have physical or mental causes. “Disturbed sleep can be both a cause and a consequence of depression – in other words, it is both a symptom and a risk factor. It leads to a huge increase in the risk of depression,” explains Axel Steiger, Senior Physician and Head of the Outpatient Clinic for

Sleep Medicine at the Max Planck Institute of Psychiatry in Munich.

The long-standing clinic, which focuses on stress-related complaints such as depression, sleep disorders and anxiety, was founded by Emil Kraepelin in 1917 as the German Research Institute for Psychiatry, and became a member of the Kaiser Wilhelm Society in 1924. It contains five wards with a total of 120 beds, a day clinic, a number of special outpatient clinics and several research institutions, all under one roof.

SNOOZING IN THE NAME OF SCIENCE

Patients can voluntarily choose to take part in scientific studies – for Steiger, who has led the Sleep Endocrinology Research Group since 1991, it is an ide-

al environment for his research. He and his team study the connection between sleep patterns and nocturnal hormone release in depression. While the volunteers spend a night in the sleep lab, the scientists measure the electrical impulses of their brain and muscles, record their eye movements and regularly take small blood samples to assess the levels of certain hormones.

The researchers then use the wave patterns from the electroencephalogram (EEG) along with the other measurements to extrapolate the sequence of the different sleep stages, also known as the sleep profile, or hypnogram. This is a step-like diagram consisting of several phases: At the start of the night, the subject gradually falls into a deeper sleep, and the amplitude of the EEG waves increases as this oc-



curs. The EEG amplitude is low when the subject is awake or in REM sleep, and high during deep sleep, the lowest rung on the ladder.

The Institute also uses high-density EEG (HD-EEG), the newest technology in this area, to evaluate brain activity. Subjects wear a kind of “nightcap” fitted to the head with 118 fine electrodes – normally there are ten. While they slumber in the soundproof room, their brain, facial muscles and heart send a

continual stream of data down the wires to a computer. This allows the researchers to look into the cerebral cortex and even deeper parts, such as the limbic system, the seat of the emotions.

Schematic representations of the hypnogram show clear differences between REM (rapid eye movement) sleep, when dreaming typically occurs, and non-REM sleep. REM sleep appears as a stage below the waking state but clearly above that of deep sleep. It is

characterized by increased blood pressure and pulse, while the skeletal muscles remain fully relaxed. Four, five or sometimes even six or more cycles of deep sleep and REM sleep per night are typical. Deep sleep is a component of non-REM sleep. In healthy young people, it is most pronounced at the start of the night and occurs only rarely or not at all in the early morning.

Directly after falling asleep, most people sleep especially deeply for about

LEARNING WHILE ASLEEP

While asleep, the body is at rest only on the outside, because sleep is an active process: metabolism is running at full speed, particularly in terms of growth and regeneration, detoxification and tissue repair. Some parts of the brain are also highly active, processing the stimuli that the brain absorbed during the day, separating important information from irrelevant details, and moving memories from short-term to long-term storage. That’s why good sleep promotes good memory.

The need for sleep decreases continuously during the course of a lifetime. In the first three months of life, infants

sleep for up to 17 hours a day. This is due to the enormous growth and maturing processes that occur in the brain during this time. Never again do humans learn so much as in the first weeks and months of life. Three- to five-year-olds can manage on 10 to 13 hours, while seven to eight hours is generally enough for 18- to 78-year-olds. The sleep-wake cycle also changes. Adults generally sleep only at night and for a single stretch, while newborns take a number of shorter sleeps over the course of a day. By the age of one, most children already sleep through the night, and their daytime sleep decreases noticeably.



Axel Steiger has devoted nearly his entire research life to sleep. Among other things, he is Head of the Outpatient Clinic for Sleep Medicine at the Max Planck Institute of Psychiatry. There, various disorders are diagnosed and treated, such as nighttime sleep and movement disorders, unusual sleep behaviors (such as sleepwalking), and night terrors and nightmares.

90 minutes. This is followed by the first REM period. “Depressed patients, on the other hand, progress to REM sleep faster, sometimes after just ten minutes,” says Steiger. In addition, the first REM period is generally longer in these patients.

If we compare patterns of hormone secretion with sleep profiles, it is notable that less growth hormone is released in depressed patients than in healthy subjects. The cortisol values are also different, climbing much higher in many patients, especially in the second half of the night.

Cortisol is an important stress hormone. Its production is regulated by the brain by means of corticotropin-re-

leasing hormone (CRH). In the event of an infection, for example, CRH indirectly stimulates the release of cortisol in the adrenal glands. The cortisol then activates the immune system. The same thing happens in the event of exam stress or a heated argument. Once the situation has passed, the stress hormones come back into balance. At this stage, the cortisol already circulating slows CRH release and hence its own production.

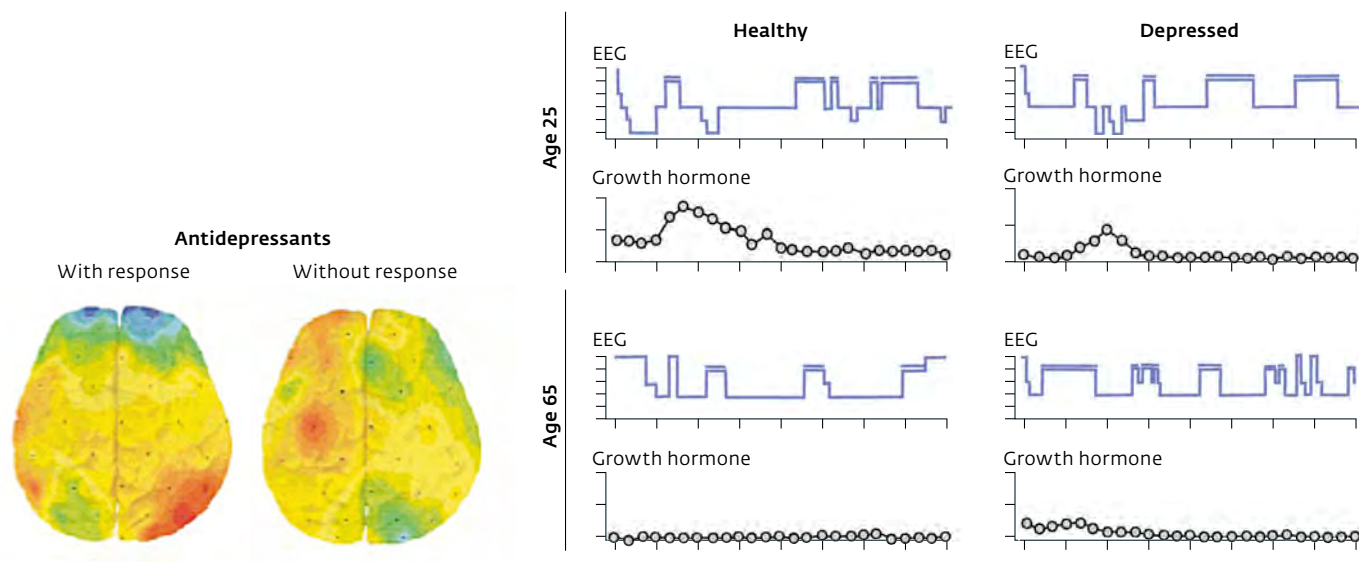
HORMONE INTERACTION AS A FOCUS OF RESEARCH

“We believe that this feedback mechanism is dysfunctional in patients with depression, probably because the cortisol receptors in the brain that stop the release of the hormone in healthy individuals are faulty,” explains Steiger. When depression subsides, the cortisol levels initially fall, while the sleep pattern remains disturbed for a time.

This interaction between CRH and cortisol also occurs in mice. Mayumi

Kimura, head of the Sleep and Telemetry Core Unit in the Institute, used rodent models in which specific genes were intentionally switched off or activated in order to study their exact function. Animals that have been stressed for extended periods, as well as those that have been genetically modified so that their brains produce more CRH than usual, fell faster and more frequently into a REM episode when asleep. This makes them the ideal animal models for depression.

But are there really depressed mice? “Of course we don’t know whether they really feel like human patients, but their sleep phenotype is certainly similar to that of depressed patients,” says Kimura. In the “forced swim” test, for example, whereas healthy mice swim around and try to struggle through longer, “depressed” mice give up sooner. And although mice generally wake more frequently and seldom sleep for longer than ten minutes at a time, the REM sleep profile of mice with elevated CRH production bears a



Left Differences in “cordance”: Following treatment with the antidepressants fluoxetine or venlafaxine, depressed patients show different patterns of brain activity. After one week of treatment, the theta-wave activity in the prefrontal cortex is lower in patients who respond to treatment (left, blue) than in patients for whom these drugs have no effect (right).

Right Sleep profile and hormone production change with age: While 25-year-olds slip quickly into deep sleep (top left, EEG), 65-year-olds take longer. When young people fall asleep, growth hormones are produced (left, top light-blue curve), but this doesn’t occur with older people (bottom left). Young people with depression (top right) take as long as elderly people to fall into deep sleep (EEG), and their brains release less growth hormone (right, top light-blue curve).

striking resemblance to that of depressed patients.

Returning to humans: it is striking that the sleep pattern of depressed patients resembles that of healthy elderly people. “Some depressions are actually like premature aging,” affirms Steiger. In old age, there is less deep sleep each night, and subjects wake more often and sleep less overall.

The fact that more women are affected by depression than men is apparently no coincidence. Hormonal fluctuations during their cycle, pregnancy and as a result of menopause contribute to women of fertile age being two to three times more likely to suffer from depression than men. The risk also remains higher during menopause. Conversely, female sex hormones provide protection against psychosis, which may explain why men develop schizophrenia earlier in life than women.

In addition to stress, age and gender, certain genes can increase the risk of depression in healthy individuals. In an earlier study, researchers at the Max

Planck Institute observed that the children and siblings of depressed patients had a higher rate of rapid eye movements in the first REM period, even though they themselves were healthy. “We also discovered that healthy subjects can have conspicuous sleep patterns if they possess certain risk genes for depression,” explains Axel Steiger. Previous investigations at the Institute found that one of these genes, P2RX7, is associated with unipolar depression.

MICE WITH A HUMAN DEPRESSION GENE

The influence of depression risk genes on sleep has also been observed in mice. Having provided the animals with the human version of the P2RX7 variant, Mayumi Kimura and her colleagues recorded their sleep patterns and discovered marked changes in their EEG patterns, similar to those of depressed patients. Kimura now hopes to use the genetically modified mice to study the effect of new antidepressants.

Genes also influence how well an antidepressant works in a patient. The gene ABCB1 exists in two variants that determine how efficiently certain drugs cross the blood-brain barrier. A DNA test has now been developed, enabling doctors to test which class of drugs is most suitable for their patient before starting treatment.

So there are different genes that increase the risk of depression. This leads the researchers to believe that there are also different forms of depression, depending on the gene. To date, the psychiatric classification of depression is based on the symptoms. However, different diseases can trigger the same symptoms. “Sleep profiles could help to distinguish between different types of depression. But we don’t yet know the exact connection between sleep patterns and genes,” says Steiger.

But sleep can not only aid in diagnosis, it can also play a role in treatment. Short-term sleep deprivation, especially in the second half of the night, has turned out to be a blessing



Tommi Bauer assesses the blood samples of subjects and patients. The levels of different hormones in the blood provide him with clues about the processes that occur in the human body while we sleep.

in psychiatry, as it has a very fast-working antidepressant effect. “We use it with patient groups twice a week at the clinic. The participants get up at two thirty in the morning and go for a walk with students. They chat together or pass the time until morning playing board games,” explains Steiger. The following evening, they go to bed as usual.

During a sleepless night, the body produces more mood-lifting substances, such as serotonin and tryptophan, than it would while sleeping. Sleep disturbance is thus a double-edged sword: on the one hand, it is a risk factor for depression, but on the other hand, sleep deprivation has an antidepressant effect. “However, this is a ray of hope for patients, because it allows us to show them that their situation is not nearly as hopeless as they think,” says Steiger. “They sense that their brain is not irrevocably flawed.”

Sleep profiles thus provide clues to depression and other mental disorders. Steiger hopes that they will also enable doctors to detect early on whether patients will respond to antidepressants. “In the past, it has always taken four to five weeks before we knew whether a patient was responding to a drug or

not. Now, after just one week of treatment, we can use REM sleep data to extract a parameter for local brain activity (cordance) and see whether it’s working,” says Steiger.

For the last 30 years, there have been no new breakthroughs in treating

depression with medication. However, a precise classification of the different forms of depression may one day enable doctors to more rapidly identify the most suitable drugs for their patients. One of the keys to making this a reality lies in sleep. ◀

TO THE POINT

- Disturbed sleep can be both a cause and a consequence of depression. Conspicuous sleep profiles can thus indicate depression.
- Scientists want to draw on sleep profiles to classify different forms of depression.
- Hormone production during sleep is different in healthy and depressed subjects. In depression, cortisol values are more elevated during the second half of the night – presumably due to a defect in the receptor molecules that suppress cortisol production in healthy individuals.

GLOSSARY

ABCB1 gene: This gene is active in cells on the inside of small blood vessels in the brain. It actively transports certain substances back to the blood, thus preventing them from reaching the brain. This includes a number of antidepressants. The two variants of the ABCB1 gene carry out this task with different degrees of effectiveness. A test can determine which variant a given patient possesses and predict how that patient would respond to an antidepressant.

P2RX7 gene: This gene contains the information for a calcium channel in the membranes of neurons and glial cells in different regions of the brain. It influences signal transmission between cells and in the brain. There are indications that both unipolar and bipolar depression are caused in part by changes in this gene.