

Construction in the Head

Not many Max Planck institutes can claim to have a fitness room – and that for research purposes, no less. But **Arno Villringer** at the **Max Planck Institute for Human Cognitive and Brain Sciences** in Leipzig isn't interested in hardening muscles. He wants to use the training equipment to study how training motion sequences changes the brain.

TEXT **FELICITAS WITTE**

The seesaw actually looks very stable – but anyone who tries to stand on it for the first time loses their balance within seconds. Patrick Ragert, who has been working in the Neurology Department at the Max Planck Institute for Human Cognitive and Brain Sciences since 2008, invites his visitor to perform a balancing act on the seesaw. After a few seconds, she is forced to step down, and gratefully reaches for the scientist's hands. "Everyone has that experience at the beginning, but our brain learns quickly," says Ragert. In the neurobiologist's studies, at least, subjects who have trained for some time can stay on the device for almost half a minute.

Arno Villringer is the Director of the Neurology Department at the institute in Leipzig. His area of specialty is the adaptability of the gray matter of the human brain – those regions of the nervous tissue in which the cell bodies are located. It was long assumed that, in the brain, new connections between

neurons were created and new neurons formed only during development in the womb. In fact, however, the brain is modified throughout life. The technical term for this ability that the human brain possesses is neural plasticity.

THE HARDWARE ADAPTS TO THE USER

And the brain regions that are used extensively are the ones that change the most. Back in the early 1990s, scientists in California showed that, in monkeys, brain areas for sensory stimuli from the fingers become enlarged when the animals previously had to use their fingers extensively to feel objects. In humans, too, repeated movement of the fingers causes the associated brain regions to grow. "It's like the hardware of a computer adapting to the wishes of its user," explains Villringer. "For a German journalist, for example, the E key on the keyboard would enlarge, since this letter occurs very frequently in German.

For a graphic designer, on the other hand, the monitor and mouse would grow, because they are used often."

So the brain grows with its tasks – at least parts of it. Villringer and his team concentrate on how it reacts to the training of motion sequences. To this end, they give volunteers learning tests in which they have to navigate back and forth between multiple objects on a computer screen without overshooting the goal. Electrodes on their arms record the activity of the finger and hand muscles.

A mere six half-hour training units were enough to improve the subjects' motor skills considerably. "Next, we wanted to know whether these test results could be further improved if we additionally stimulated the brain," says Ragert. Using a method known as transcranial magnetic stimulation, the scientist can activate neurons in certain

Balancing act: Repeated training on the seesaw trains the sense of balance – and changes the brain structure.



brain regions before and after training, and thus measure the brain activity. To do this, he holds the stimulation device, which resembles a shower hose, above the subject's head, stimulating cells in the motor cortex – a region that transmits motion commands to the muscles of the hands and fingers. "Most people hardly feel it."

And sure enough: When this area of the brain is externally stimulated using direct-current stimulation, the study

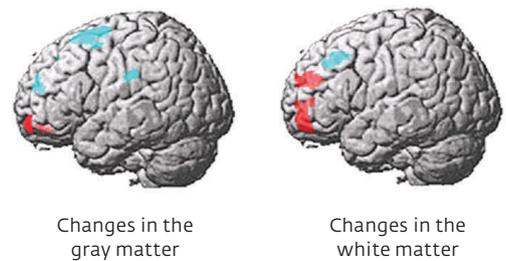
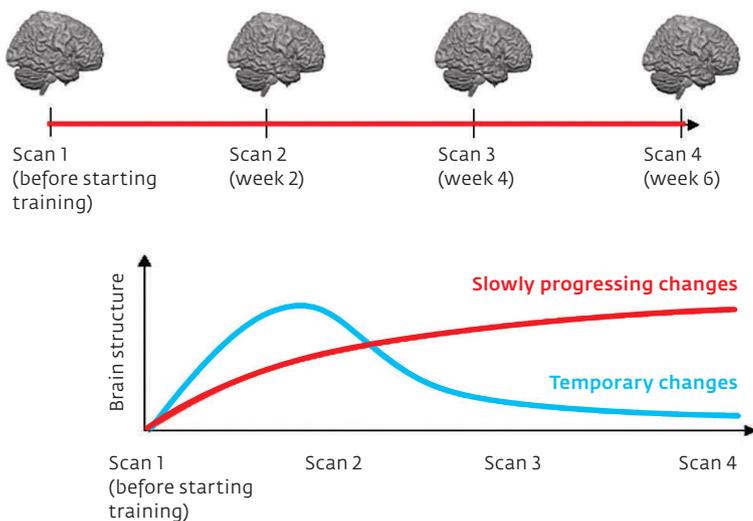
participants complete the test even faster and with greater precision. This brain stimulation thus influences the learning of motion sequences. But does it also change the brain's wiring?

In a further experiment, the subjects were to learn a movement involving difficult coordination: spreading the thumb out and simultaneously tensing the deltoid in the upper arm. They were asked to do this three times per minute for 40 minutes. MRI images tak-

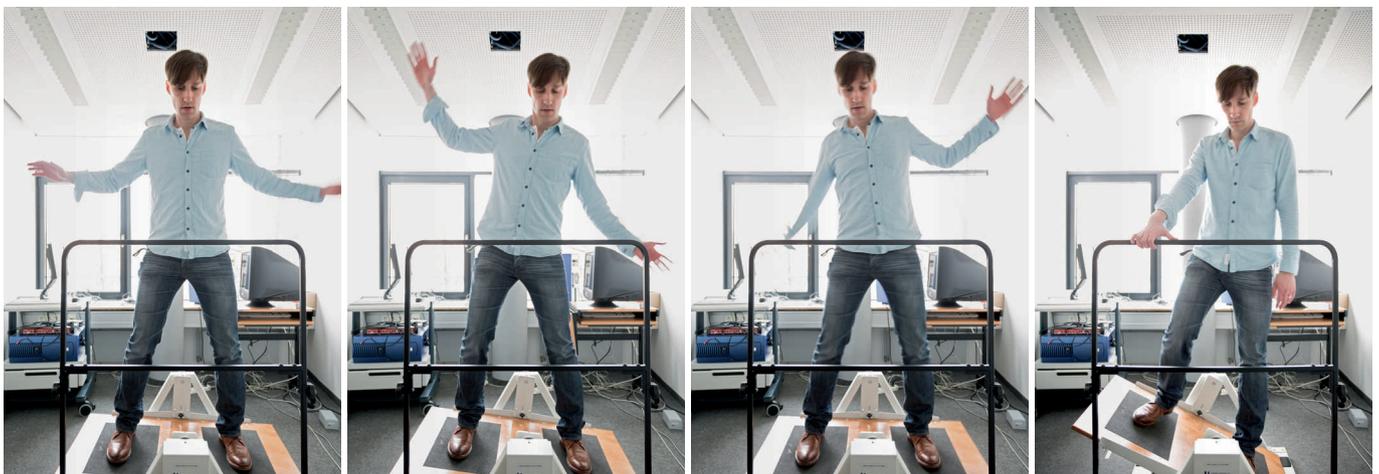
en subsequently showed that learning this movement caused the relevant regions in the motor cortex to communicate more with each other.

From previous studies, it is known that the learning-induced increase in gray matter correlates with a certain parameter of nuclear magnetic resonance, the so-called T1 time: the shorter the T1 time, the more gray matter. "From our measurements of the T1 time, we can conclude that more gray matter is

Six-week balance training



Unsteady on the seesaw. Below: In the beginning, the subject – here Patrick Ragert – manages to keep his balance for only a few seconds. Six weeks later, he is able to keep it around 20 seconds longer. Above: The training changes both brain regions in which nerve cell bodies (gray matter) are located and regions through which nerve fibers extend (white matter). Left: During the experiment, the researchers took images of the brain at two-week intervals and observed both temporary and progressive changes.





Transcranial magnetic stimulation can be used to activate the neurons in the motor cortex. This method allows the researchers to directly measure learning-induced brain changes.

created,” says Villringer. Accordingly, the brain begins with the reorganization very quickly. “The first changes in the brain structure appeared after just under an hour. We practically watched the brain learn.”

JUST AN HOUR OF TRAINING CHANGES THE BRAIN STRUCTURE

Unfortunately, the scientists can’t tell from the MRI how the brain changes in detail. That would require an MRI resolution approximately one million times greater. So they know only that more gray matter is created, but not what exactly happens to individual brain cells. It is unlikely that new neurons are formed, since, according to the current knowledge, this happens in the adult brain only in a very few regions: in the hippocampus and the so-called subventricular zone. Villringer explains the fact that the gray matter increases anyway

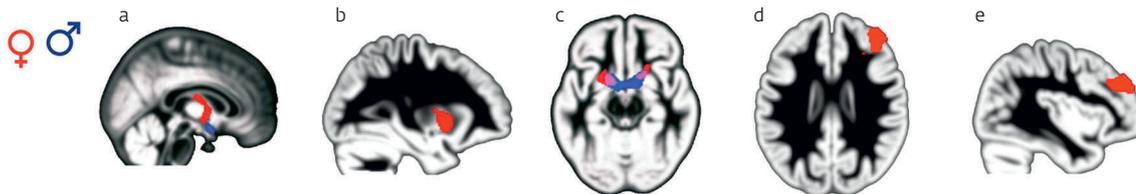
with the formation of new connections between neurons, or what are known as synapses. Moreover, the cell bodies of the neurons apparently grow, as well.

Such changes take place with various forms of learning, and should therefore be detectable also in other regions of the brain. Hence the experiment with the seesaw: “Balancing requires, for one thing, the muscles of the feet and, for another, the sense of balance. The question is whether the training also changes the brain regions that are responsible for this, the prefrontal and the temporal cerebral cortex.”

The balance training was successful: the training participants were able to balance longer on the seesaw, an average of 20 seconds after six weeks of training once per week. This learning achievement was also reflected in the MRI: “In the balancing region, the gray matter already begins to increase after an hour,” says Villringer.

Similar training programs could also help Parkinson’s patients, hopes the neurologist. In this progressive disease, neurons decay in a brain region that is needed for planning and executing movements. The result is stiff muscles and trembling. Moreover, those affected can no longer keep their body in a stable, upright position and are constantly in danger of losing their balance.

That is why Villringer wants to use balance exercises on the seesaw to bolster the patients’ sense of balance. The researchers secure the study patients, who are, on average, 64 years old, with safety harnesses in case the seesaw throws them off balance. If the patients can initially maintain their balance for just 8 seconds, after six weeks they manage about 13 seconds. At the end of the training, the patients even maintained their balance longer than healthy, untrained peers. And in the brains of the Parkinson’s patients, too, the previous-



Weight problems are also evidenced in the brain, especially in regions belonging to the reward system. And there are gender-specific differences: in both sexes, the posterior medial orbitofrontal cortex (c), the nucleus accumbens (c) and the hypothalamus (a) are enlarged, and in women, additionally the putamen (b) and fornix (a). Furthermore, regions of reduced nerve cell density are found in the right lateral prefrontal cortex (d, e) in women.

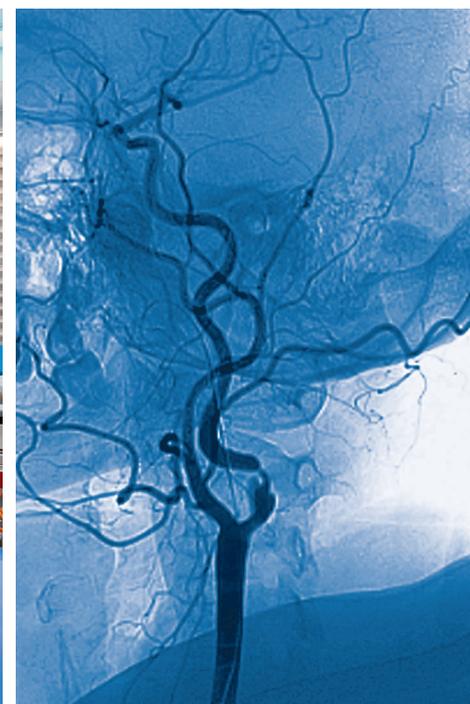
ly seen increase in gray matter was evident in the MRI. “Our balance training could become an important component in the treatment of Parkinson’s symptoms,” concludes the neurologist.

People with weight problems, too, could benefit from physical exercises in as yet unforeseen ways. After all, movement not only burns calories,

thus promoting weight loss, but it also impacts the brain. Villringer and his colleagues discovered, for example, that the orbitofrontal cortex and the nucleus accumbens – regions that belong to the brain’s reward system – are larger in overweight patients. The heavier the person, the more gray matter is found in these brain regions. “People

who regularly give in to the desire to eat thus subconsciously train the brain’s reward system,” explains Villringer. “If these people lose weight with the aid of training programs, we postulate that their reward centers will shrink. It is still unclear which programs are best for this and whether exercise or weight loss alone are relevant. But if the re-

Pre-empting stroke: Physicians can use angiography to visualize the blood vessels in the body on a screen. This allows them to detect dangerous constrictions early on, such as the one here in the carotid artery of a 56-year-old patient (right).





Arno Villringer (right) and his fellow scientist Patrick Ragert discuss the results of their tests. They want to use practical exercises and transcranial magnetic stimulation to help stroke patients.

structuring of the reward centers can be successfully reversed through training, this might be the key to permanent weight loss.”

The brain also proves its ability to adapt after a stroke. In such a cerebral infarction, a blood vessel is blocked by a clot, and parts of the brain no longer receive sufficient blood supply. As a result, the cells in the affected areas die off. Neurologists can at least partially reverse the impairments triggered by these cell deaths, such as paralysis and loss of speech, through physiotherapy and systematic speech training.

When they do so, neighboring areas, or mirror-inverted areas that lie in the other brain hemisphere, take over the tasks of the dead regions. Thus, a stroke in the region of the frontal cortex, which controls the arm muscles,

usually results in paralysis of the arms. In the course of recovery, nerve processes can sprout out of the adjacent area, which actually sends movement signals to the legs, and form a network with the former partners of the dead neurons. In this way, a paralyzed arm can, in time, regain some of its mobility.

YOUNG BRAINS REGENERATE FASTER

This doesn't hold true if an area has already been previously affected by a stroke. The ability to regenerate is then considerably lower. Also, not all regions can regenerate as well as the cerebral cortex. The pyramidal tract, for example – a part of the locomotor system that extends from the cerebral cortex across the brain stem and into the spi-

nal cord – can hardly reverse severe damage. Age likewise influences regeneration. “It's similar to tissue repair: in older people, wounds heal more slowly than in younger people.”

Villringer wants to help the brain compensate for the damage caused by strokes. Again, he relies on transcranial magnetic stimulation and practical exercises. His studies have shown that this helps improve mobility and word-finding problems after a stroke. According to Villringer, the training supports the reconstruction of the brain areas affected by the stroke.

What is even more effective than repairing the damage after a stroke is, of course, preventing the infarction in the first place. Controlling blood pressure plays an important role here, as high blood pressure is one of the main risk



Playing football during a coffee break: Arno Villringer's and Patrick Ragert's focus on motor skills isn't restricted to their work. And just as with their subjects on the seesaw, training pays off in table soccer, too. This time, the point goes to the boss.

factors for stroke. Villringer suspects that high blood pressure leaves its mark on the brain, specifically in the amygdala. This small area in the cerebral cortex is involved in the formation of emotions such as fear and stress.

WAVES ON THE SCREEN LOWER BLOOD PRESSURE

Villringer's team suspects that, in people with stress-related high blood pressure, the amygdala reacts too strongly to stress and subsequently shrinks. The researchers want to put this finding to therapeutic use and develop a training program that, in the early stages, makes the amygdala less sensitive to stress, and later, promotes its recovery. Experiments on patients with stress-induced high blood pressure show how this might be done. When these patients think of something nice and relaxing, their brains produce special brain waves. Merely watching such "relaxation waves" on a computer screen lowers the patients' blood pressure. MRI studies are now expected to clarify whether this also causes the amygdala to grow.

Some researchers' plans to help jog the brain using drugs are likewise promising, according to Villringer, but he urges patience: "Those are interesting approaches, but it will take some time before they result in patient therapies." For example, there are no clear criteria

establishing which patients such therapies are suitable for, or what side effects can occur.

"We simply don't know enough about what the brain looks like when it changes back into its healthy state." ◀

TO THE POINT

- Learning new motion sequences changes not only how the brain functions, but also how it is structured.
- External stimulation of the brain helps in learning motion sequences. This could benefit Parkinson's and stroke patients.
- Excess weight causes the reward systems in the orbitofrontal cortex and in the nucleus accumbens to grow. Training programs could reverse these changes.
- In people with stress-induced high blood pressure, the amygdala reacts too strongly and subsequently shrinks. It is hoped that relaxation training can reverse these processes.

GLOSSARY

Nuclear magnetic resonance: Nuclear magnetic resonance imaging, also called magnetic resonance tomography, is a medical technique that makes tissues and organs visible. It involves producing images from different levels. The method works with strong magnetic fields that align the hydrogen atoms in the tissues. Another, high-frequency magnetic field briefly realigns the atoms. Afterward they fall back into their original state according to tissue type, releasing an electromagnetic impulse in the process. This impulse is dependent on the composition of the tissue and can be measured by the scanning device.

Transcranial magnetic stimulation: A method of brain stimulation. A strong current flow in a coil produces a magnetic field that, through induction, can generate currents in nerve fibers in the brain. The magnetic field produced depends on the shape of the coil used and its position and orientation. It therefore also influences which brain regions are stimulated. This technology can be used, for example, to treat Parkinson's, depression and schizophrenia.

T1 time: An MRI method for imaging tissue structure with particularly high contrast. Conversely, T2 time is suitable primarily for imaging pathological processes, such as tumors. The T1 time is the time it takes the hydrogen atoms that are realigned by the alternating magnetic field to regain 63 percent of their original orientation (relaxation time).