BRIEFLY SPEAKING

ACADEMIA

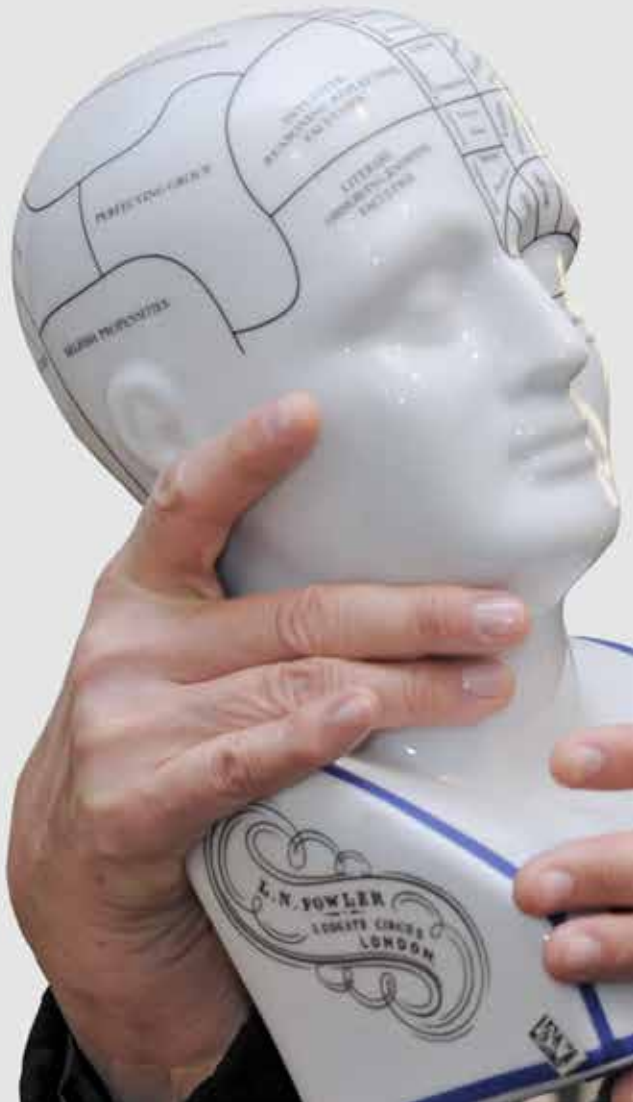
# Learning by

**Prof. Małgorzata Kossut** of the Nencki Institute of Experimental Biology talks about brain plasticity, the mechanisms of learning, and the mysteries of forgetfulness

ACADEMIA: **Is the nervous system a rigid, fixed structure that changes only as a result of damage?**

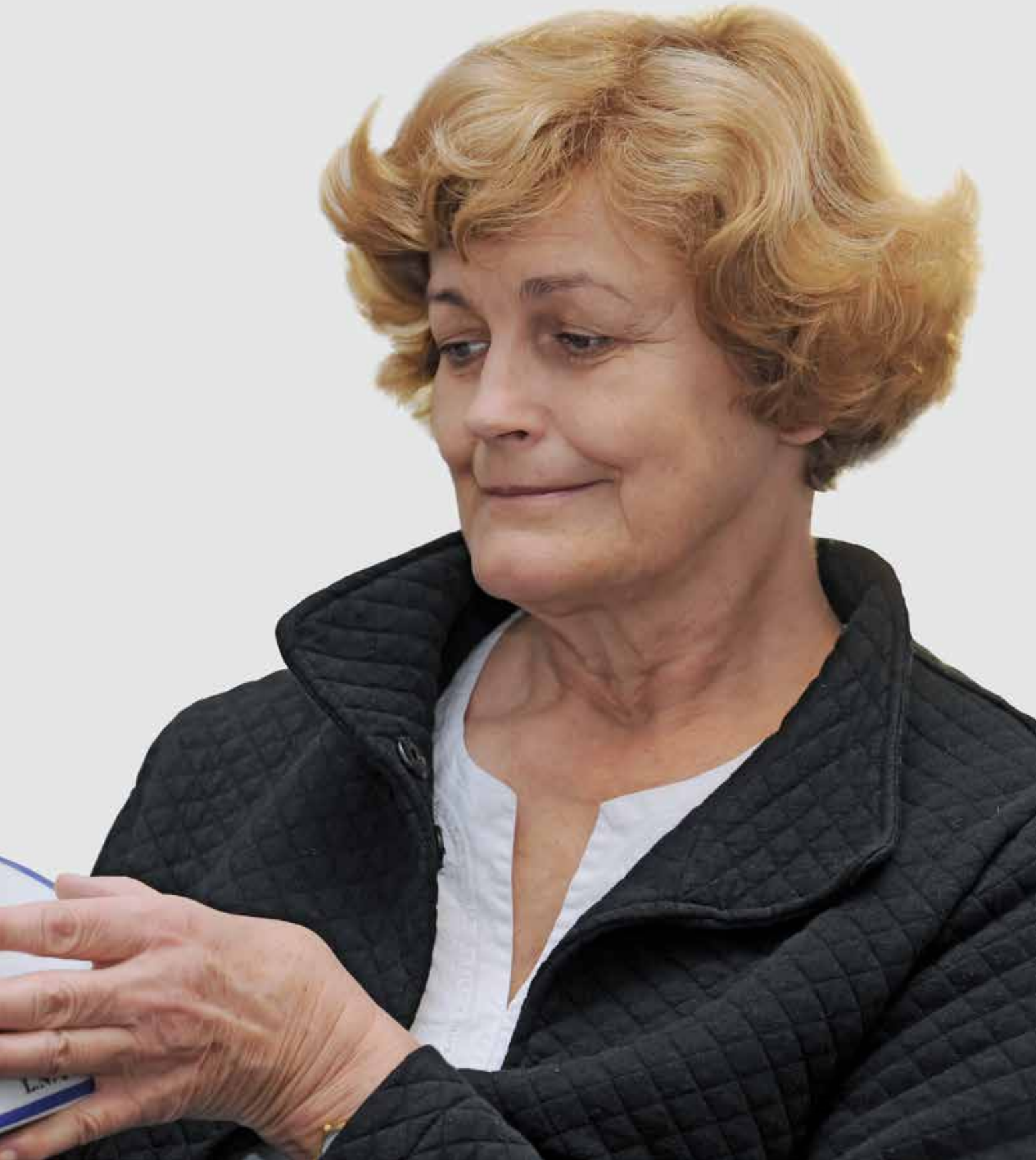
MAŁGORZATA KOSSUT: Such was the belief in medicine for nearly a hundred years, because the renowned nineteenth-century neuroanatomist Santiago Ramon y Cajal claimed that once something was created in the brain, it could not change. He was also convinced that if the brain is damaged, it does not regenerate, and that nothing new can appear in the developed nervous system, such as neurons or synapses. This turned out not to be true. We now know that the brain is "plastic," in the technical sense of being malleable – in other words neurons do undergo constant change under the influence of incoming stimuli. Firstly, in the adult, even old human brain, new neurons are still being created in specific areas. Secondly, the brain has a great capacity for self-healing, and a damaged brain can demonstrate various self-repair strategies. Although the axons in the brain do not regenerate, sprouting can occur instead, where new sprouts from healthy axons take the place in the brain that has been vacated by the dying sprouts of damaged neurons. Neuroplasticity involves a whole range of phenomena, from developmental to pathological plasticity, which occurs during neuropathic pain or addiction. The molecular mechanisms of these phenomena have many similarities. Therefore, we have a broad definition of plasticity, which includes learning and memory. Humans are able to continue learning practically until their death, and have a good short-term memory, if they are lucky enough to die without dementia.

We also know that a damaged brain can create new "action strategies" that allow it to recover lost functions. New cells may be created within the brain that in some way will aid this process, and new axons may grow as well. A good example of this can be found in patients with brain injuries who have been in a coma



PROF. MAŁGORZATA KOSSUT

# A WHISKER



for many years, and whose brains were considered permanently damaged, but who nevertheless were able to wake up. In some of them, we observed how a new nervous path can grow in an amazing way.

**You are the head of the neuroplasticity lab. Have you devoted your career to researching this very topic?**

The vast majority of it, yes. I studied biology in order to work in neurobiology. I was interested in learning and memory, especially the neurochemical phenomena occurring in the process of memorizing. I wanted to work with Prof. Stella Niemierko, whose lab was working in this area. In the end, I did not get to work with her, but I worked for Prof. Żernicki, who studied the development of visual perception and plasticity of the visual system. This brought me closer to studying the plasticity associated with the learning process.

> A damaged brain can create new "action strategies" that allow it to recover lost functions

**How does the brain learn?**

The most interesting thing I discovered as a post-doc at the University of Pennsylvania was the plasticity of the adult cerebral cortex, something that had been thought to be non-existent. While there, I learned to work on part of the tactile sensory system in mice and rats, which had been discovered just a few years earlier. I am referring to the vibrissae – the long whiskers on their muzzles. These are important sensory organs. A large area of their brain is devoted to the analysis of information from the vibrissae. Each vibrissa corresponds to a tiny structure in the fourth layer of the cerebral cortex, which looks like a small barrel. These barrels are stacked side by side in the cortex in a manner that corresponds to the position on the vibrissae on the muzzle. The whiskers grow in five rows, and there are five rows of barrels in the cortex, so I know that when I move the vibrissa in $C_3$, I should get a response in the barrel of $C_3$. If the vibrissa registers stimuli vital in the learning process, I will know where to look for changes. The big challenge in the early studies of learning and memory processes was locating the place where neuron changes occurred as a result of learning. Common sense told us to look in the cortex and in the hippocampus, but these are large structures. If we were studying the entire cerebral cortex after a rat learned to walk in the direction of a red light, for instance, or to run through a maze, we may miss the specific change that occurs in a certain nerve circuit. The vibrissae sensory system helped us hone in on the location. I studying the system by means of autoradiography, using the same kind of tracer compound that is used to image the activity of the human brain in positron emission tomography. I used deoxyglucose labeled with radioactive carbon, or modified glucose. This helps to map the brain with greater accuracy than in clinical scanners, because in autoradiography brain specimens are placed on the film. You can see details on them which are not yet available in PET or fMRI imaging studies. I showed that if we left only one vibrissa on the rat's muzzle, its cortical representation would greatly increase. This is because it must try to stand in for all the other, twenty-something removed vibrissae in order to sense what is happening in the animal's surroundings. If all other vibrissae are removed, the one left is surrounded with an inactive cerebral cortex, but quickly colonizes the area. This is clear evidence of cerebral cortex plasticity in adult animals. My lab continues to work on this system.

**Do different parts of the brain correspond to the regular way of learning, as opposed to conditioned learning?**

Yes, conditioning is a very simple form of learning and in classic form it does not require the participation of complex cortical brain structures. Here, the amygdala or cerebellum are enough. The ideal situation is when both conditional and unconditional stimuli briefly act together, because the brain has numerous mechanisms to capture such conjunctions of stimuli. If they do not occur simultaneously, but consecutively, this is more difficult and requires more sophisticated structures of the brain.

A certain classification system of the mechanisms of memory, and thus learning, was developed in the 1980s. Declarative, conscious memory was distinguished from nondeclarative, unconscious memory, and thorough neuroanatomy work was done in this respect. So we know more or less which brain regions are more associated with which form of memory, where human autobiographical memory (memory of events) is stored, and where semantic memory (factual memory) is located. The extraordinary imaging studies using new methods of signal analysis also showed how the lexicon is arranged inside the brain. The cortical representation of words is grouped around different categories, such as animals, plants, emotions, etc.

**And organized like in drawers?**

Yes. We also know that these categories are also plastic. For example, experiments were carried out on monkeys, which looked at synthetic images on

a computer where figures of animals were gradually morphed, such as a dog into a cat, for instance. The monkey was rewarded for choosing a dog, for example, and thus learned to sense the differences between dog and cat features. When the pattern was changed and the monkey was rewarded for showing a cat, it relearned and the neurons that previously reacted to the sight of a dog now responded to the cat. It turned out that more neurons responded to the rewarded stimulus. What is significant is that these were laboratory monkeys that had never before seen a dog or a cat.

**What impact do humans have on what and how we learn?**

The learning process is closely linked with the attention process. We mostly remember things we pay attention to. The second thing that enhances learning is emotion. Prof. Jerzy Vetulani gives a good example of this, saying that we remember a short film about pulling teeth much better that a short film about brushing teeth. It is also easier to memorize things that we can associate with what is already stored in our brain. We "like the songs that we already know." If there is a trace in our memory, an internal representation of an external phenomenon, which new, incoming knowledge can mesh with then we have a better chance of remembering it. But in order for such memory trace to form, the brain needs to make an effort. This is not an easy task, so anything that makes the process easier helps a lot.

**What about forgetfulness?**

This is a bit more complicated. The first to study this process was the German scientist Hermann von Ebbinghaus in the early nineteenth century. To make it totally objective, he decided to memorize sets of nonsense syllables, and then observed how quickly he forgot them. It turned out he forgot them very quickly. Within a few hours he remembered only 30–40 percent of what he originally memorized, and the next day this number went down to about 25 percent. Of course it is easier to remember things that makes sense, but memory is unreliable. Every judge knows this when he asks eyewitnesses of an event about what they actually saw. In general, their statements differ in details because our brains don't retain them. Our body is besieged by such a huge number of stimuli per second, that only a tiny fraction reaches the brain allowing for conscious recognition. We do not have such processing power. The system that controls our perception and consciousness has certain "bottlenecks" which only allow the strongest of stimuli, such as loud noises or a great tragedy, to pass through.

**So there is no separate process responsible for forgetfulness?**

There may be, but we don't know much about it. Even among psychologists, forgetfulness is a very mysterious phenomenon. Perhaps some things disappear from the mind, or maybe we are just not able to extract them from it, because their traces are no longer visible.

**Can forgetfulness be caused by brain damage as a result of a stroke, for example?**

The British scientist Elizabeth Warrington described a patient (a professor friend of hers), who suddenly realized that he could not recognize or remember the names of animals. It turned out that a minor stroke had damaged the part of his cortex that stores knowledge about animals. There have been cases of stroke patients who no longer recognized frequently used tools, their own homes, or human faces.

But forgetfulness is also caused by the disappearance of synapses in old age, the death of cells, and the weakening of unused connections. We imagine that a memory trace is a circuit of many neurons, the synapses between which are more strongly linked than before it was formed. We know how this combination is formed, but we have no idea how it persists for years, or what factors weaken communication between the cells of this chain of neurons. There is a lot more work to be done in this area.

> People with higher education and with greater mental activity have a chance of contracting Alzheimer's at a later point in life

**What exactly happens inside the brains of people who don't recognize anyone after a stroke?**

Simply put, during a stroke certain areas of the brain do not receive oxygen for some time. Neurons cannot tolerate this. Neurotransmitters spill out of them and this excess stimulates their receptors, which causes an inappropriate flow of ions resulting in the neurons swelling and finally dying. They never grow back in the original amount. The effect depends on which vessel clogs up or breaks, and which area will be damaged. If the damage is quite dramatic – everything stops functioning.

Two types of death processes are activated – one is necrosis, or cell death from injury, the other apoptosis, or programmed cell death. Protein synthesis stops,

neuron electrical activity fades, and inhibition waves go through the brain, which we call rampant depression. So everything goes wrong, resulting in swelling and inflammation.

This was the subject of my second interesting discovery. My colleague from Germany, Professor Otto Witte, had a theory that a stroke opens a window of plasticity for the brain, and that there are some endogenous mechanisms that allow the brain to be repaired soon after a stroke, or that it can at least be aided in recovery. Such thinking was a major breakthrough in neuroscience. A stroke was treated as a cardiovascular disease, and hospitals had no special stroke units. The fact that they began to appear in Poland was thanks to Prof. Anna Członkowska [an interview with her was included in Issue 1/2016 – ed.]. The younger generation of neurologists at some point simply began to insist that rehabilitation begins the very next day after a stroke, not two months later. There was some controversy as to how early it should begin, because animal studies showed that very early intervention leads the worsening of the post-stroke damaged area. Prof. Witte turned to me because I had success in inducing plasticity in the vibrissae system, and asked me to look into this issue, as there were reasons to believe that plasticity improves after a stroke, but there was no hard evidence for this. We did an experiment together and it turned out that plasticity after a stroke is actually worse than normal, and this is due to post-stroke inflammation. If you want to start rehabilitation right away you need to immediately administer anti-inflammatory agents, because inflammation impairs the neuroplastic potential of the brain.

**Is there anything else that makes you say to yourself: I really did it!**

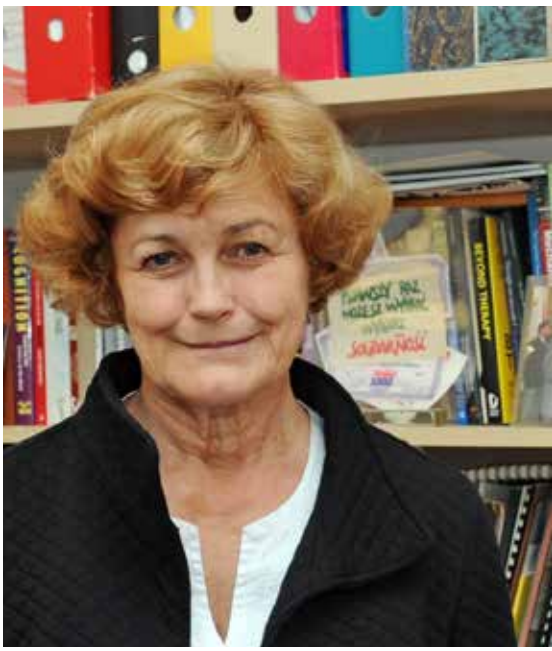
I really enjoy what we are doing now, which is studying the different aspects of cerebral cortex plasticity in mice induced by learning. It is evoked by stroking the whiskers and providing a pleasant or unpleasant incentive. In either case the area of the cerebral cortex that is activated by stimulating the vibrassae grows by one half of its size and the cortical representation increases. We observe how various neurotransmitters and their receptors change within it. To our surprise, we observed an increase in various indicators related to inhibitory neurotransmission, a key process, which causes epilepsy, schizophrenia, and depression. It was thought, and many people still believe it today, that the inhibitory neurons that control the activity of excitatory neurons, which make up 20 percent of all neurons, are not plastic. That they play a significant role in the precise synchronization of cortical oscillations or time intervals, where they can block the path of a traveling impulse, but they themselves do not change. Meanwhile, we see that they do change. We observe changes in the levels of the neurotransmitter, synthesizing enzyme and its mRNA, and the cellular response. We also see more inhibitory synapses in the cerebral cortex.

We tried to identify what type of interneurons take part in this process and we were able to find evidence of this. Without going into detail, we can say that interneurons are present in many forms. There are some that choke the cell by the throat or head, and some that block the cell's entry or exit. We also found some that are specifically modified in the course of learning. We already have a theory on how such a circuit works. Using

**Dr. Małgorzata Kossut**

- MS: 1973
- PhD: 1976
- DSc (*habilitation*): 1988
- Professorship: 1994

A neuroscientist, she held post-doctoral fellowships at the University of Pennsylvania and at Oxford University and has received scholarships from the Alfred P. Sloane Foundation, Fulbright Foundation, McDonnel Foundation for Cognitive Neuroscience, and Howard Hughes Medical Institute. Since 1989 she has been the head of the Laboratory of Neuroplasticity at the Nencki Institute. Her research focuses on the cellular and molecular mechanisms of learning and memory. She introduced the methods for autoradiography mapping of the functional activity of the brain and image analysis to Polish neuroscience. In 1991 she co-founded the Polish Society for Neuroscience. Board member of the European DANA Alliance for the Brain. She is a member of the Polish Academy of Learning (PAU) and the Polish Academy of Sciences (as an Ordinary Member since 1 December 2016).
Her team at the Nencki Institute focuses on the visualization of neuronal mechanisms of the learning process, and post-stroke plasticity in the adult and aging brain. The techniques for inducing model changes in plasticity developed in this laboratory are used for determining the effect of genetic modification and diseases on the functioning of the cerebral cortex.



the new chemogenetic method, by which one can turn any neural system on or off, we want to turn off these neurons during the learning process. This will tell us whether they are a key element of plasticity induced by learning. This is what we are working on at the moment.

**Can you explain to a layman how this experiment works?**

Chemogenetics works by introducing artificially derived excitatory or inhibitory receptors, which were never there, to a chosen type of cells in the brain. Then a synthetic activator of these receptors is introduced. It can be injected or the animal can drink it with water. It is important that we put these receptors where we want them, inside the chosen type of neuron. And this is what makes biotechnology so appealing. We already have the ability to target a tiny selected piece of the brain. We can excite it, inhibit it, and observe how it affects the studied process.

**Do you also conduct experiments on people?**

Since the Institute has the ability to do resonance scans, we have been able to show the tremendous plasticity of the adult brain. We had normally sighted people learn to read Braille, and they did fairly well: areas of their associative visual cortex and areas associated with the tongue responded when they touched Braille letters with one finger. In blind people, substantial brain remapping occurs as the unused visual cortex responds to both auditory and tactile stimuli. In the case of normally sighted people it turned out that tactile learning to read quickly remaps the brain and tactile stimuli, but interpreted as letters they stimulate a place called the Visual Word Form Area, a place in the brain that responds to the shape of letters. This is a very interesting place, because reading is a new process in human development, so it's difficult to suspect that it was created by evolution.

**The brains of the elderly is another topic you are interested in researching.**

My younger colleague Monika Liguz-Lęcznar is primarily concerned with this area. It is generally a sad problem. People are living longer, but not necessarily better. We sometimes hear the slogan "healthy aging," but it actually applies to only 5–10 percent of the population, whereas for the rest this stage of life is cruel, unhealthy, humiliating and depressing. We are trying to see what elements of synapse function get disrupted in the aging process, and again we are using the vibrissae system, or the barrels, because we saw that in our experimental models aging disrupts brain plasticity in different ways. We have studied it in young, middle-aged, and elderly mice. It turned out that plasticity induced by learning is already significantly impaired in middle-aged mice. We believe this is because the inhibitory transmission system operates less efficiently and needs longer stimulation to help reorganize the cerebral cortex, so that the representation of the whisker, so important to the animal, increases inside the cortex.

**Maybe at some point something will be discovered that will help improve brain function in the elderly?**

I hope so. It would be nice to have the same agility that Prof. Bartoszewski showed in old age, but that is not the case for most people. Not only their brain, but also the rest of their body deteriorates. Very soon we begin experiencing impaired movement, vision, hearing, etc. This is why a few years ago we were excited to see an experiment with young blood. A young mouse and old mouse were joined vascularly (via parabiosis) and the elder mouse became younger. Of course, soon they began doing blood transfusions from young to old mice. There are also experiments on humans. Companies have sprung up, as this is a medical procedure which any doctor can perform without asking an ethics committee for permission.

**So recommendations to exercise the brain by doing crosswords, for example, are questionable?**

Epidemiological studies show that people with higher education and with greater mental activity have a chance of contracting Alzheimer's at a later point in life. Let's stick to this theory. But can mental activity initiated in old age actually help? That we do not know. But one thing is certain: physical activity, even when started in old age, improves blood supply to the brain. It also has a magical effect as it affects the secretion of trophic factors, which generate new neurons in the hippocampus. There was also a theory that the substances produced in the muscles of runners penetrate the blood-brain barrier and have a positive impact on cognitive abilities. But I am not sure if this has been confirmed.

**I feel that running or fast-paced walking does have some benefits.**

We know that walking at a fast pace is good for us. Prof. Maria Barcikowska from the PAS Institute of Experimental and Clinical Medicine concluded that this rhythmic rocking of the body causes the pulsating blood vessels to press on the hippocampus, which would cause the neurons, which are formed in the hippocampus until old age, to form in larger quantities.

**What do you love to do, outside of work?**

I love to read. This is why I take care of my eyes the most. I mostly enjoy reading novels and periodicals, the kind that intellectuals buy for themselves. But I also love reading on my Kindle.

Interview by **Anna Zawadzka**
Photography by **Jakub Ostałowski**