Age Touches **a Nerve**

Philipp Khaitovich works in Shanghai, a city that is developing at a pace as dramatic as his research field. At the **CAS-MPG Partner Institute for Computational Biology,** the molecular biologist is investigating how the different brain development of primates is linked to their age.

TEXT **MARTIN PAETSCH**

When Philipp Khaitovich opens the door, he is greeted by a draft of fresh air. In the small room, it is noticeably cooler than outside in the hallway that, on this beautiful spring day, is bathed in sunlight. Inside, machines are humming. The room is packed with white cabinets and deep freezers. The freezers are covered with digital displays; a temperature recorder controls the degree of coldness inside: -80°C or lower.

Inside the freezers are the treasures of his research team. There are dozens of brain samples from humans, chimpanzees and rhesus monkeys of different ages that Khaitovich has painstakingly collected. Using the pieces of tissue stored here, the scientists are seeking to discover more about the differences between humans and monkeys. By comparing the activity of genes and the concentration of various molecules in the brain samples, the team can determine how the development and aging progress in the different species on the molecular level.

The research conducted should help provide answers to some of the fundamental questions in biology: Why do *Homo sapiens* live so much longer than closely related primates? What makes our species so special? "These are, of course, major questions," says Khaitovich in his office, a bright room where he looks out of the window onto a street lined with sycamore trees.

SO WHAT IS IT THAT MAKES *HOMO SAPIENS* SO SPECIAL?

With a slightly faltering Russian accent, he explains his project, his hands describing wide arcs in the air. He gesticulates and laughs a lot. For almost seven years, the Russian has been carrying out research at the Shanghai center, at the CAS-MPG Partner Institute for Computational Biology, which has been run jointly by the Chinese Academy of Sciences and the Max Planck Society since 2005. At 40 years of age, he is currently the youngest director at the institute.

"Humans can live to be 100, in some cases even longer," explains Philipp Khaitovich. "In contrast, rhesus monkeys, for instance, live to at most 40 years, even with the best medical care." Humans do differ, even from their closest living relatives, chimpanzees, simply in the development of their intellectual capabilities. Physical development is also dissimilar in the two species. For example, sexual maturity in female chimpanzees begins at the age of 8 or 9 years, whereas in *Homo sapiens* it is more like 13 or 14.

Why there is such a dramatic difference in the development of man and apes has long been the subject of research. "For a very long time, scientists have been puzzling over this question, including big names like Konrad Lorenz and Stephen Jay Gould," says Khaitovich. "Every conceivable hypothesis has already been considered."

There is, for example, the idea of neoteny. According to this theory, which has been debated over and over again since the beginning of the 19th century, human development is considerably delayed compared to any other primates.

The basic idea is that the adult human, with its sparse hair development, on the outside resembles the small face and big head of a baby monkey. At the same time, the human brain retains its plasticity longer, which might explain the special cognitive capabilities of our species. Up to now, however, such theories have been nothing more than just that – theories – because they cannot be validated, as such. It was only a few years ago that rapid technological development made it possible to put them to the test.

In the 1990s, when Philipp Khaitovich was studying molecular biology at Moscow

View over the rooftops of Shanghai – Philipp Khaitovich enjoys the skyline of the megacity. He has been conducting research at the CAS-MPG Partner Institute for Computational Biology for the past seven years.

State University, this kind of research hadn't yet even been thought of. At that time, it took several years just to investigate the structure and function of a protein. After studying in Moscow, he went to Chicago to do his doctorate, then on to Germany where he worked at the Max Planck Institute for Evolutionary Anthropology in Leipzig.

There, in the group headed by Swedish evolutionary geneticist Svante Pääbo, he gained significant impetus for his later work. "Svante is a true pioneer. He was one of the first to use new genetic methods to investigate human evolution," says Khaitovich. "My current subject is based largely on his ideas."

To get to the bottom of these peculiar human characteristics, Khaitovich and his students are comparing the brain samples of humans, chimpanzees and rhesus monkeys – all at different ages. To be able to gain knowledge on the development of the brain, the team needs pieces of tissue both from newborns and from the very old. And from individuals in a number of different age groups in between.

NEWBORNS AND THE ELDERLY PROVIDE THE ANSWER

Finding the right pieces of tissue is a real challenge. Time and again, Khaitovich must persuade other institutes to cooperate, because the samples not only need to be from a human or animal of a certain age, but they also need to come from a specifically defined area of the brain. From the prefrontal cortex, for example – the area behind the brain where inherently human capabilities, such as rational thinking, are located.

The human samples cause Philipp Khaitovich the least problems. He orders them from "brain banks" – facilities where brain tissue from various donors is archived for research purposes. For chimpanzee samples, he is still on good terms with his former professor in Leipzig, where Svante Pääbo several years ago began to archive the brain tis-

Research in China is no different than anywhere else in the world. "Science is a universal language," says Philipp Khaitovich. "You analyze data and obtain results, then interpret them – that is exactly the same here as it is in Europe or America."

Photo: MPS/Patrick Wack

sue of apes of various ages; however, it is difficult to get hold of viable brain samples from old macaques. "Rhesus monkeys can live to about 35 years of age, but there are perhaps only a few dozen animals of this age throughout the world."

The scientists then send the samples from the various elderly humans and monkeys for analysis in partner laboratories to determine gene expressions and other data. For this, they ignore the complicated structure of the brain tissue – the samples contain different types of neurons, glia cells and gray matter. "It's as if two ecosystems, together with all the animals and plants living in them, are being compared with one another."

Khaitovich is the first to admit that there are weaknesses in this procedure. "This is all still very primitive," he admits. And at the moment, the technology to investigate the brain comprehensively and look at all the different cell types separately simply doesn't exist. Nevertheless, Philipp Khaitovich is proud of exploring new avenues: "At least I can say that we're working at the cutting edge of research."

FEELING AN ELEPHANT WITH YOUR HANDS

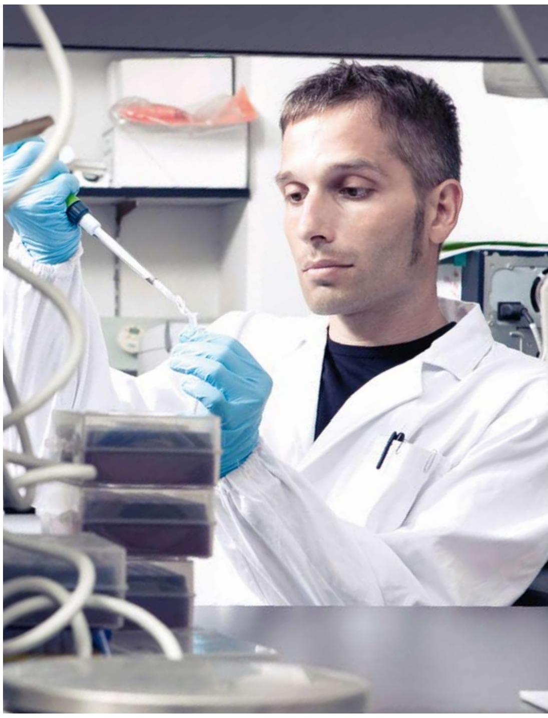
For the scientist, the technical development of biology can't advance fast enough. Sometimes he feels like a blind man trying to feel an elephant with his hands – and instead of the trunk, thinks he has found a snake; instead of a leg, a tree. All the same, he has at his disposal the most state-of-the-art measuring methods to answer his questions on the development of the human brain. "It's like looking at things for the first time under a microscope that you've previously been able to examine only with a magnifying glass," enthuses the researcher. He also takes rather unusual routes in some of his analyses. For example, he is working with a research facility that, at first glance, has nothing to do with the human brain – the Max Planck Institute of Molecular Plant Physiology in Golm, where a new measuring method has been developed to determine how much oil and other metabolic products different plants produce – a method that can also be used just as effectively to measure the different molecules in brain samples, such as neurotransmitters and lipids.

Khaitovich receives vast amounts of data from the partner institutes, which must then be evaluated. Among the wealth of information, the scientists attempt to recognize biological signals – certain patterns in the data that indicate peculiarities in the development of the various species. "Sometimes we fail miserably," Khaitovich admits. "And quite simply because there is no established procedure to point us in the right direction."

The first results, however, are encouraging, although the data hasn't yet been fully evaluated. "We can already see very clear molecular differences between the brains of humans and apes." One of the results confirms the old idea of neoteny – but only to some extent. According to this theory, the gene expression in the brain of a juvenile human is roughly equal to that of a chimpanzee a few years old. For several hereditary features, this is actually the case. "But for other genes, the picture is completely different," says Khaitovich. His interim assessment: "The reality is much more complicated than we previously imagined."

Differences in the speed of brain maturation between humans and apes have practical implications. Recent work done by the Khaitovich lab in collaboration with the lab of Schahram Akbarian at the Mount Sinai Hospital show links between human neoteny and autism – a cognitive disorder affecting up to 2 percent of humans. While, in healthy human brains, connections between neurons take five to ten years to develop, this process loses its neotenic pattern in autistic brains. As a result, neuron connections in an autistic brain are formed at a much faster pace, resulting in aberrant synaptic connectivity patterns.

The young researchers can get closer to an answer only step by step, theory by theory. This is sometimes frustrating, not only for the scientist, but also for his mother in Moscow, who, says Philipp Khaitovich, is very interested in his research. So far, though, she has not been disappointed by the progress: "She believes that there are so many interesting things to find out about the brain and the longevity of humans," says Khaitovich with a wide grin: "And she says that we are concentrating on far too small an area. But we're really just a very small research group." ◂



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The **CAS-MPG Partner Institute for Computational Biology** was founded in May 2005. It was jointly established by the Chinese Academy of Sciences (CAS) and the German Max Planck Society (MPS) and focuses its research on the interface between theoretical and experimental molecular and cell biology. http://www.picb.ac.cn