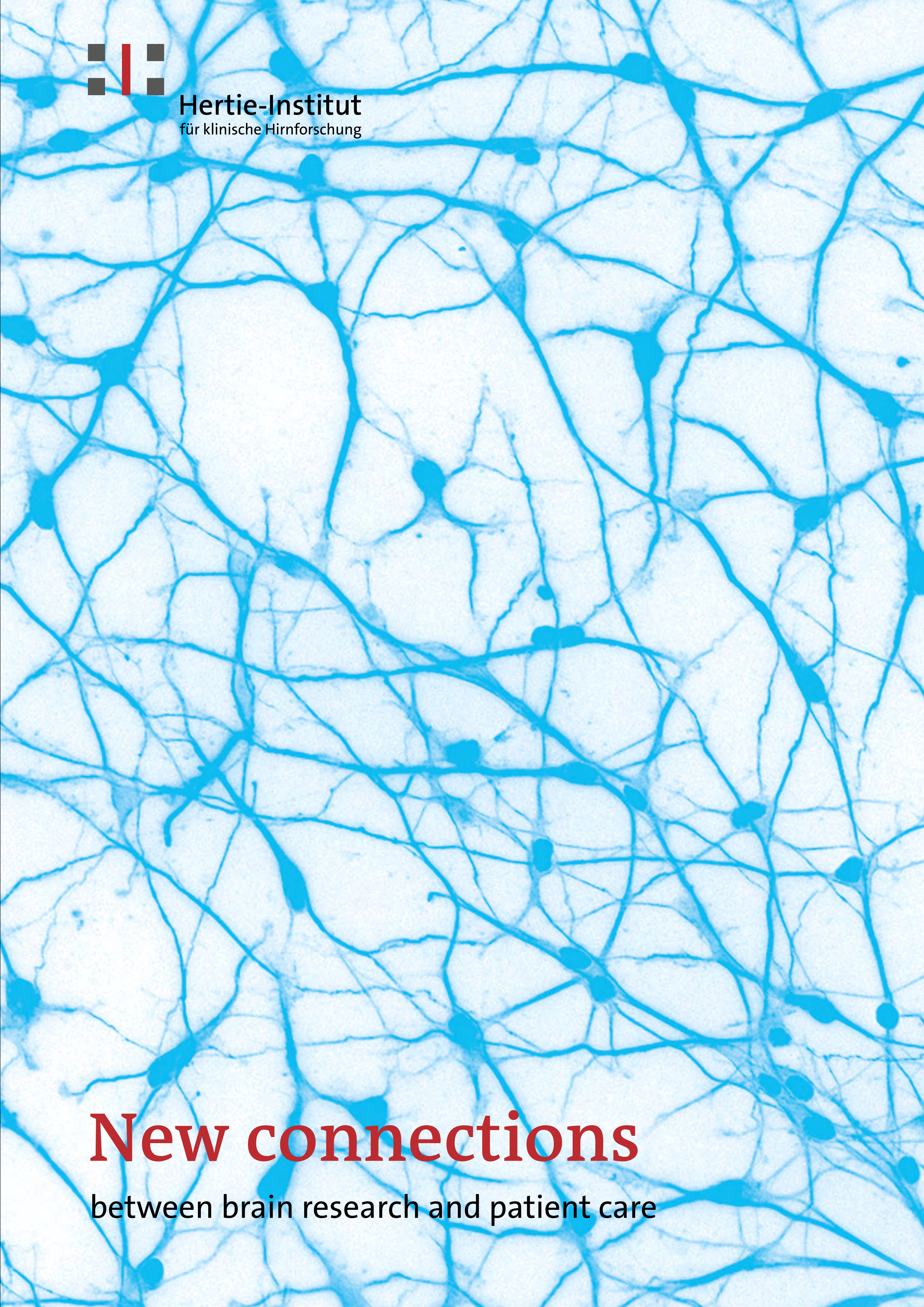
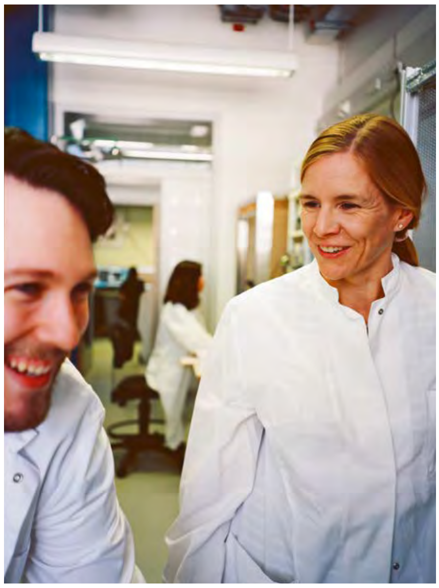


Hertie-Institut
für klinische Hirnforschung

New connections

between brain research and patient care




CTF
it's about time

The cover picture shows a neural network that was generated from a patient's skin cells using targeted methods. In this way, the researchers at the Hertie Institute obtain disease-specific nerve cells, which they can use to study the causes of the respective diseases and test possible drugs.

Editorial

The Center of Neurology, which includes the Hertie Institute for Clinical Brain Research and the Clinic of Neurology at the University Hospital Tübingen, celebrated its 20th anniversary in 2021. This milestone shows how rapidly the Center has grown since it was founded as a pioneering partnership between private and public institutions. Over the years, its number of employees has almost quadrupled, and its volume of third-party funding has increased almost sixfold. In terms of top publications, the Center of Neurology is on an equal footing with other major centers for brain research in Europe. We have come a long way from the humble beginnings of temporary laboratories and a greenfield construction site. Today, two other institutions in the immediate vicinity of the Hertie Institute highlight the importance of brain research to the excellence strategy at the University of Tübingen: the Werner Reichardt Centre for Integrative Neuroscience (CIN) and the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE), which researchers from the Hertie Institute played a significant role in founding. But there is still much to come in the years ahead and the Center of Neurology has developed an extensive strategy to address developments in digitalization, molecular medicine, systems neurobiology and robotics, while prioritizing the specific needs of neurology patients and excellence in patient care. Ensuring that our patients benefit from our research directly in terms of quality of care and best possible clinical outcomes is fundamental to our tasks at the Center of Neurology.

Professor Dr. Thomas Gasser
Chair of the Center of Neurology

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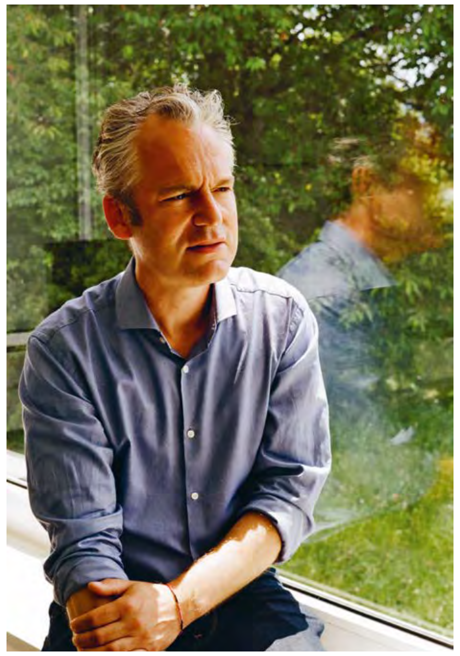

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Tomorrow's neuromedicine today

The fragility of the mind

Millions of people worldwide suffer from Alzheimer's disease and dementia – and patient numbers are climbing. Innovation in medicine and brain research offers hope to many patients who are afraid of losing their sense of identity. Professor Dr. Mathias Jucker from the Hertie Institute for Clinical Brain Research specializes in this field.

Text: Christian Jung

"I think therefore I am." In the 17th century, René Descartes, a French philosopher, mathematician and scientist, described thought and physical existence as the two inseparable halves of our being. We have learned from Alzheimer's disease that this connection can gradually dissolve and be lost. Although Alzheimer's disease remains an alarming diagnosis for patients, scientists are far from giving up hope. Researchers around the world are gradually putting together pieces of the puzzle of mechanisms that cause forgetting.

Mathias Jucker from the Hertie Institute for Clinical Brain Research and the German Center for Neurodegenerative Diseases in Tübingen is among them. He specializes in the very early changes caused by Alzheimer's disease. "By the time we are able to observe that a patient's memory performance is declining or their sense of identity is diminishing in a way typical of Alzheimer's disease, the brain has already undergone certain processes of change for fifteen to twenty years," says Mathias Jucker, co-director of the Hertie Institute. Jucker's ambition is to narrow down these early stages and better understand the origins of Alzheimer's disease. "We still have much to learn about these processes," explains the neurobiologist, who received the prestigious Gertrud Reemtsma Foundation Prize in 2020, his most recent addition to a long line of awards. "We urgently need to know more about the very early stages of the disease before the first misfolded proteins are deposited," he emphasizes. "From the precise moment when it is clear that a person will one day develop Alzheimer's disease."

An early biomarker for Alzheimer's disease

Sensitive biomarkers can play an important part in detecting Alzheimer's disease at an early stage. In the best case, they can also provide information on the course of the disease. Thanks to the commitment of researchers in Tübingen, a method is now available that measures neurofilament light in blood. This test can now predict the progression of Alzheimer's disease already at very early stages. Neurofilaments are found inside nerve cells and they provide structural support for the cytoskeleton. They are released when the cells die and can be detected in the cerebrospinal fluid and the blood, in lower concentrations – long before the first symptoms occur.

"We discovered the new biomarker when we decided not to rely solely on the amyloid protein as a potentially useful biomarker," says Jucker, "but to also look at the end of neurodegeneration, at the death of nerve cells. We found that neurofilaments can be detected in cerebrospinal fluid and even in the blood long before clinical symptoms occur. The amount of neurofilaments released also corresponded closely to the course of the disease."

Jucker and his team used these findings to accurately assess the amount of cellular filament degradation products in the blood of Alzheimer's patients. This test can be performed in two ways: It can detect the disease at a very early stage and also determine the progression of the disease from the gradual pathological changes in the body. It is a less invasive procedure as it no longer requires the removal of cerebrospinal fluid.

Alzheimer's disease can be dominantly inherited

The scientists in Tübingen have also clarified how the neurofilament light appears in the blood in time for the onset of the first clinical symptoms. They studied data and samples from around 400 people who are very likely to develop Alzheimer's disease due to genetic inheritance, specifically by mutations in the three genes APP, PSEN1 and PSEN2. People who have a dominantly inherited genetic defect pass it on to every second child on average. The first symptoms generally appear before the 60th birthday.

Patients affected with these clearly genetically induced variants of Alzheimer's disease can become part of the international DIAN network (Dominantly Inherited Alzheimer's Network). Mathias Jucker is directing the DIAN network in Germany. In a study that has been ongoing since 2012, the scientists aim to better understand dominantly inherited Alzheimer's and derive new therapies for all forms of the disease. Genetic analysis and regular physical and neuropsychological tests already allow quite precise predictions to be made as to whether and when someone will develop this form of dementia.

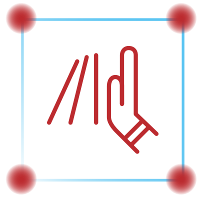
"In consultations with those affected and their family members, it is evident how stressful the knowledge of having the hereditary form of Alzheimer's disease is," says Mathias Jucker. The risk of illness often hangs over the heads of several generations – a heavy burden which can affect all areas of their lives. "Talking openly about Alzheimer's disease and dementia in general is still often taboo in our society. This makes it difficult to discuss within families let alone with other people outside the family," Jucker emphasizes. He advocates that society be more open to the massive emotional, psychological and financial burdens that those affected have to bear.

The Tübingen researchers have set standards in many respects within the DIAN initiative. "Part of the overall concept is that we organize annual meetings for families in Germany," says Jucker. This helps to get to know each other and share what they are going through and how they are dealing with their experiences and problems. Lectures on legal or social-medical issues could also provide valuable information to those affected. "Some members of the network have even become good friends over the years. We feel like one big family", says Jucker.

Pathogenic protein seeds

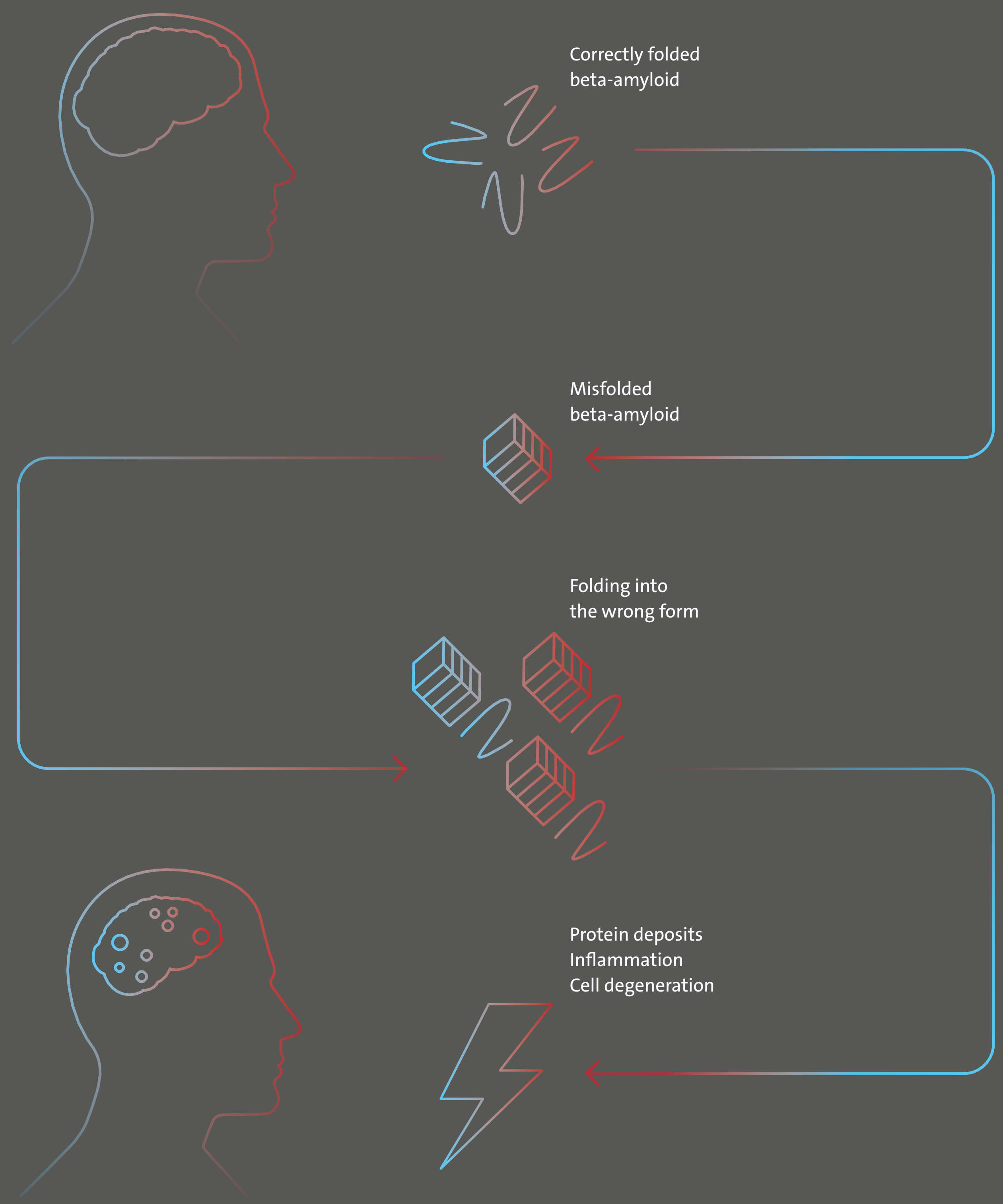
Meanwhile, Jucker's team are moving ever closer to narrowing down the earliest stages of forgetting. With the occurrence of seeds, they have defined by far the earliest stage in which Alzheimer's disease is already in full swing. At present, however, seeds can only be defined by their role in the fatal chain reaction forming Alzheimer's plaques – because no one has ever seen them.

Scientists have worked to detect seeds at least indirectly by testing six antibodies on the brain tissue of mouse models before they showed any typical protein damage. One of the antibodies proved effective. It recognizes protein aggregates rather than individual beta-amyloid proteins. "The short treatment lasting just five days has obviously been sufficient in eliminating the pathogenic seeds to a large extent," explains Jucker. "Fewer deposits form in the weeks and months after antibody treatment as new pathogenic seeds take time to develop." Jucker and his team are currently trying to isolate the seeds in order to better describe them in the next stage of their research. "Looking forward, we also need further



Alzheimer's disease tends to develop slowly and worsens gradually. As the disease progresses, plaques are formed from tiny pathogenic seeds. The earlier this chain reaction is prevented, the greater the success of the treatment could be.

The long road to Alzheimer's disease



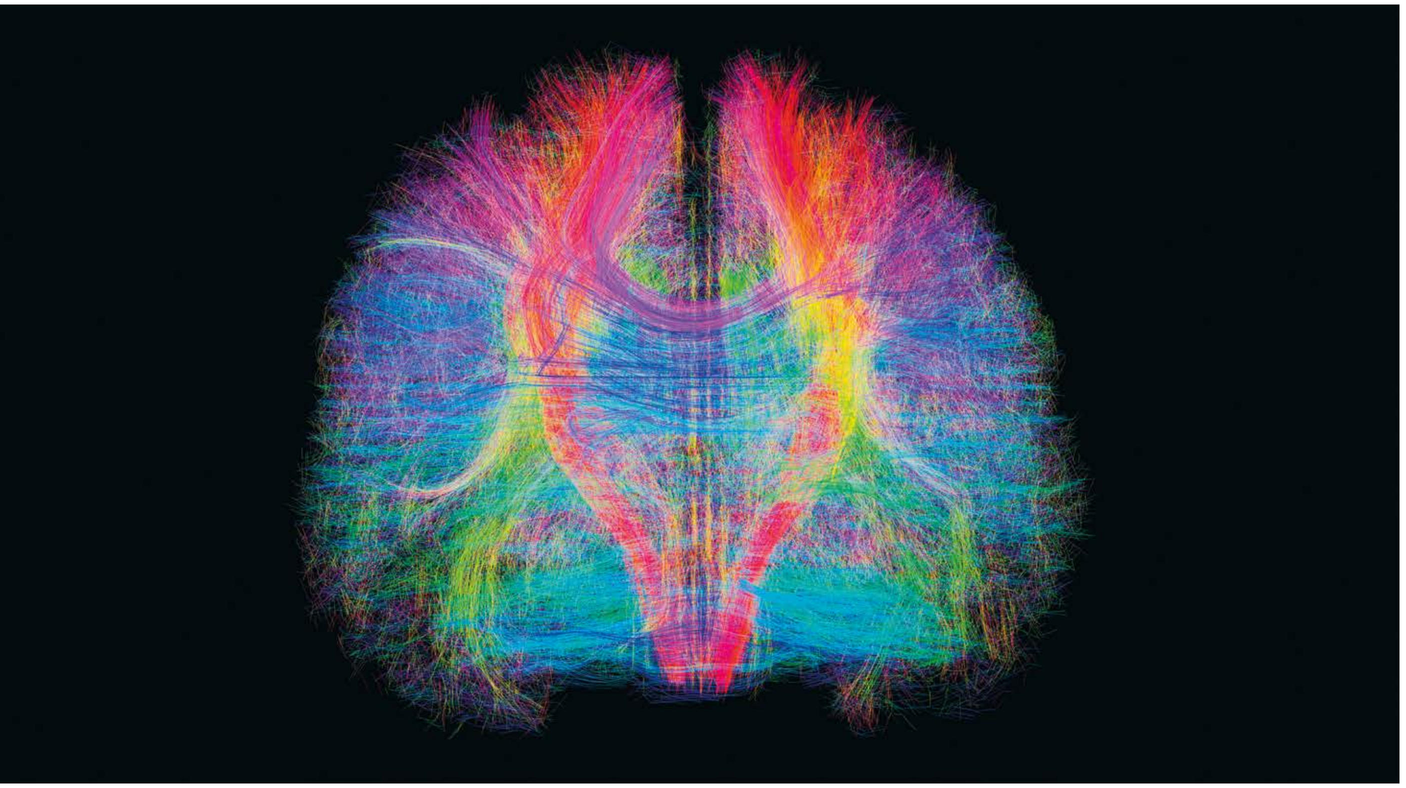
Bad influence: Misfolded beta-amyloid imposes its pathogenic form on correctly folded beta-amyloid. This results in a fatal chain reaction that damages the brain and leads to Alzheimer's disease.

antibodies that recognize different types of seeds and help us to understand how they trigger the fatal chain reaction and how the antibodies can be used in therapy," says Jucker.

At least in mice, the new findings redefine the early stage of Alzheimer's disease. Previously, scientists defined the stage where protein deposits are formed without symptoms of dementia as premature. However, new findings indicate that there is an even earlier stage of the disease before plaques are formed or symptoms occur. This suggests that treatment of Alzheimer's based on the causes of the disease must begin much earlier than previously assumed.

"Research on aging will also become increasingly important for our society – and not just because more people are living for 100 years and beyond," says the renowned neurobiologist, who began his career in gerontology and sees himself returning to this field. He hopes for a society that will become interested again in science and scientific contexts – the fascination sparkles in his eyes when he describes how fundamentally genetic and molecular biological research has changed the understanding of the biology of aging in recent decades. Mathias Jucker is deeply confident that somewhere in all these biological processes there is a switch that can be flipped that will prove effective against Alzheimer's disease.

Recognition from the scientific community in the many awards Jucker and his team have received in recent years indicate that Jucker's scientific intuition and expertise, his laboratory and outlook on life are certainly on the right track: He personally attributes this to something very important: "It is imperative to pause and think during the most decisive moments in life. And sometimes we even need to take a break from thinking." Jucker is a keen mountaineer and follows this advice by joining his employees regularly on climbing and hiking trips in the mountains.



Medicine of the future

Excellent research and a strategic organizational and management structure have made the Hertie Institute for Clinical Brain Research an internationally leading institution – with far-reaching plans for the future.

It all started with a vision, a public-private partnership and a foundation agreement. On December 19, 2000, the Hertie Foundation, the State of Baden-Württemberg, the University of Tübingen and its Faculty of Medicine and the University Hospital, signed an agreement to establish an institute for research into brain diseases. To ensure that patients with brain diseases could benefit as soon as possible from its findings, the Hertie Institute for Clinical Brain Research, which was founded on January 1, 2001, merged with the Clinic of Neurology of the University Hospital to form the Center of Neurology. Since then, research, teaching and patient care have been reinforced in a unified approach, which has surpassed the funding and organizational hurdles often faced in university medicine. Fifteen years later, the Center of Neurology was rated by the German Council of Science and Humanities as excellent and exemplary for university medicine in Germany.

The merger of the Hertie Institute and the Clinic of Neurology required a profound structural change, as the Center for Neurology shoulders three tasks: comprehensive care for neurology

patients including all therapies in neurology that are medically and economically possible, education and training in neurology and the neurosciences, as well as basic and clinical research at the Hertie Institute.

This balancing act is mastered by six departments that share tasks and responsibilities in research, clinical care and overall economic performance – in partnership, cooperatively and on an equal footing, without a classical Ordinariate structure, but with equal-size departments and a comparable and reliable funding in the background. The departmental model has introduced a new governance structure that is a catalyst for advancing neuroscience research at the University of Tübingen – and far beyond.

Networking at all levels

How does this innovative model work? The Center of Neurology is based on a matrix structure in which departments network both horizontally and vertically. This ensures that the departments work together closely in diagnosis and treatment, despite their priorities, and also cooperate closely in research and rapid translation of findings into clinical practice. This matrix structure creates an environment that promotes mutual exchange beyond individual specialization, favors cooperation and in which projects are repeatedly scrutinized - a win-win situation for everyone – including patients at the Clinic of Neurology at the University Hospital.

Academically and under corporation law, the six department heads are placed on an equal footing and form the Board of Directors together with the administrative director and three elected representatives of the research groups. The Board of Directors elects a chair and a managing clinical director from its members to the Executive Board for a fixed term. The administrative director supports the chair and managing clinical director in operational areas. The Board of Directors is also assisted by a Board of Trustees and a Supervisory Board. The Board of Trustees advises the Board of Directors on scientific and strategic issues, while the Supervisory Board oversees the expenditure of funds from the Hertie Foundation, which has financed the Hertie Institute with more than 55 million euros since its foundation.

How is patient care, research and education organized within the framework of this departmental and governance structure? Four of the six departments have hospital beds and the remaining departments operate special outpatient

> “We treat patients in all areas of Neurology at the Center and our patients can expect a united team with an agile organizational structure.”
>
> Prof. Dr. Holger Lerche, Managing clinical director

clinics. In-patient beds are managed by the Department of Neurology with Neurovascular Medicine (Professor Ulf Ziemann), the Department of Neurodegenerative Diseases (Professor Thomas Gasser), the Department of Neurology and Epileptology (Professor Holger Lerche) and the Department of Neurology and Interdisciplinary Neuro-Oncology (Professor Ghazaleh Tabatabai). Patients with illnesses that do not correspond to any of the above-mentioned priorities receive comprehensive inpatient and outpatient care at the Clinic of Neurology. The Department of Cellular Neurology (Professor Mathias Jucker) and the Department of Neural Dynamics and Magnetoencephalography (Professor Markus Siegel) operate special outpatient clinics. Research is carried out in departmental research groups and independent research groups. National and international clinical studies initiated by the Hertie Institute have an important role in connecting research groups.

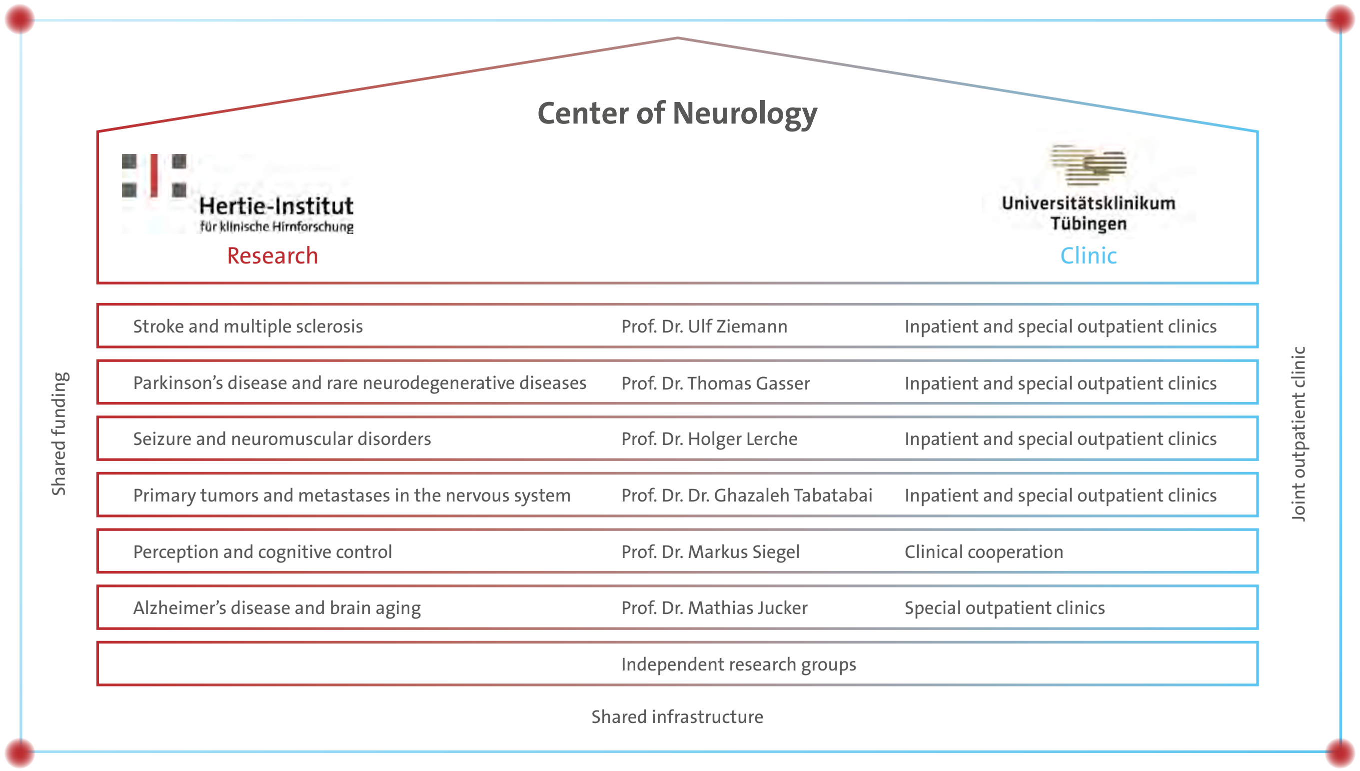
Unity and diversity

The departments meet the challenges of caring for neurological patients through shared infrastructure, forming a single unit with the Center of Neurology across its six departments, with central patient admission, diagnostics, bed and care management. The departments are also jointly responsible for clinical training across the entire spectrum of neurology. In research at the Hertie Institute, the departments share scientific infrastructure and pool funding flexibly for further development.

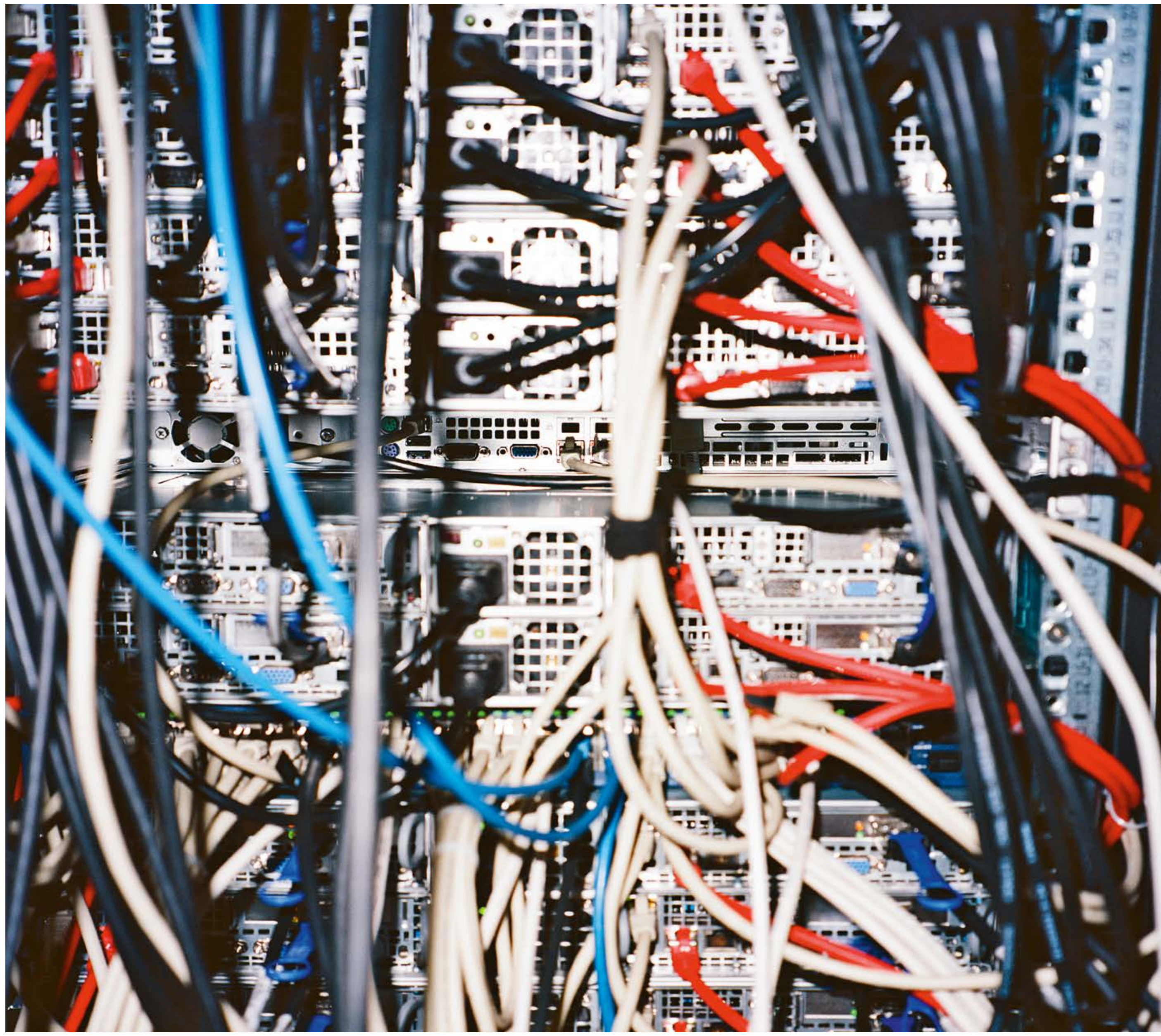
The Center of Neurology also sets standards in the training and promotion of junior researchers with structured training for physicians in clinical research. During further training, physicians are released from their clinical obligations for a period of time or train as a Clinician Scientist. Clinician Scientists specialize in patient care and laboratory research. At the Hertie Institute, natural scientists are directly involved in the translation of their findings in applied and patient-oriented research. Excellent graduate programs are offered in a partnership between the University of Tübingen and the Max Planck Institutes in Tübingen. Postdoctoral researchers apply to the Hertie Institute from all over the world. After completing training at the Hertie Institute, scientists can expect excellent career opportunities.

Brain diseases affect people more than anything else in their innermost self, consciousness and personality. Progress in neuroscience can therefore literally extend the boundaries of what is humanly possible. The Hertie Institute has an internationally leading role in this dynamic field of medicine and researches widespread diseases such as Alzheimer's disease, epilepsy, Parkinson's disease and stroke, but also tumors in the nervous system and rare neurological conditions that affect only a few hundred people worldwide. In the coming years, the Hertie Institute will focus on early detection and prevention, personalized medicine and neurorehabilitation, systems neuroscience and artificial intelligence. There is much work to be done at the Center of Neurology. We are ready to face it head on.

Many of the Center's publications are among top-cited research.



Innovative structure: At the Center of Neurology, six departments work together toward unified patient care and interdisciplinary clinical research. We care for patients across the entire spectrum of neurology.



Cooperation on an equal footing

At the Center of Neurology, six departments and many research groups are working on the rapid transfer of scientific findings into clinical care. Research priorities and perspectives.

The Hertie Institute currently consists of six departments, four of which are involved in inpatient care at the Clinic of Neurology at the University Hospital. The other two departments are involved in patient care through special outpatient clinics and clinical cooperation. The departments represent priorities in clinical research and patient care, reflecting the entire spectrum of clinical neurology.

Independent research groups deal with research from all perspectives in the neurosciences. Research groups are led either by professors or junior researchers. Several groups investigate cognitive brain performance using psychological or electrophysiological methods. Others work in the field of theoretical neurosciences and use computer models and simulations to better understand the brain. Further research teams investigate the genetic and molecular basis of brain development and neurodegenerative diseases.

Brain diseases often affect people in their innermost selves.

Department profiles

Neurodegenerative Diseases

Early detection, personalized medicine and prevention are strategic topics in the future of medicine for Professor Dr. Thomas Gasser and his team at the Department of Neurodegenerative Diseases. The department investigates the genetic causes of Parkinson's disease and other movement disorders. With great success: scientists at the department have succeeded in identifying a gene as the most currently known trigger of the hereditary form of Parkinson's disease. They were also able to pinpoint an entire range of gene mutations that lead to rare neurodegenerative diseases, such as certain forms of gait disorders. The biobank has been an important basis of the department's research over the last 10 years. It now includes almost 450,000 samples from around 25,000 patients, providing important records of the progress of many illnesses. Many samples originated from the Tübingen survey of risk factors for the detection of neurodegeneration (TREND). Deep brain stimulation (DBS) is also an important priority in the department's clinical research. Around 600 patients have been treated with DBS in Tübingen since 1999, enabling them to return to a largely normal everyday life. The department is based at the Hertie Institute and the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE), connecting both institutions.

Cellular Neurology

Deciphering the cellular and molecular mechanisms of brain aging and age-related neurodegenerative diseases is the mission of Professor Dr. Mathias Jucker and his team of scientists at the Department of Cellular Neurology, which deals mostly with research into the development of Alzheimer's disease. Scientists in the department have yielded groundbreaking findings in basic research on several occasions that have received significant international recognition. For example, they showed that Alzheimer's disease is triggered by a prion-like mechanism: Tiny pathogenic seeds of misfolded and defective proteins impose their abnormal form on properly folded proteins, triggering a fatal chain reaction in the brain. A little later – but still years before the onset of the disease – early indicators of the disease can be detected in the blood, as the scientists have demonstrated. Jucker and his team recommend that the treatment of the disease must therefore start as early as possible. Recently, they also succeeded in identifying the first antibodies that could enable the causes of Alzheimer's disease to be treated. Working closely with clinical partners ensures that their findings can be transferred to clinical studies at the earliest possible opportunity. As part of this collaboration, the department has set up a section for dementia research which also offers a memory consultation service for patients. Jucker and his team are also associated with the Tübingen site of the DZNE.

Neurology and Epileptology

Developing targeted therapies for epilepsy, migraine and related illnesses is the mission of Professor Dr. Holger Lerche and the Department of Neurology and Epileptology. Researchers at the department investigate which gene mutations and cellular mechanisms lead to these illnesses. Changes in ion channels play the most important role as they serve as a point of attack for targeted drugs. The team found that a certain form of early childhood epilepsy is triggered by the mutation of a potassium channel gene. This causes the channel to become overactive, resulting in epileptic seizures. A potassium channel blocker which was initially approved for multiple sclerosis can be used to inhibit this activity. Children who receive this treatment are doing remarkably well. The department now treats different forms of epilepsy in this individualized way. In the long term, Lerche and his team see an enormous potential in gene therapy. The department is also working on developing the use of ultrasound imaging in peripheral neuropathy and related diseases. Dynamic assessment of structure and composition of tissue enables physicians to reach a correct diagnosis more quickly and forecast clinical outcomes accurately while avoiding unnecessary treatment.

Neural Dynamics and Magnetoencephalography

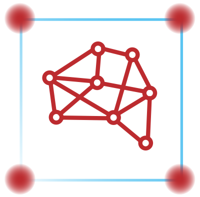
How does the interaction of widely distributed nerve cells in the brain create our perception, our thinking and our actions? What mechanisms are conducting this neural orchestra? How are they disturbed by brain diseases? Professor Dr. Markus Siegel and his team at the Department of Neural Dynamics and Magnetoencephalography are searching for answers to these questions. They are particularly hoping to make progress by combining insights into how the brain functions at various levels – nerve cells, networks, and the entire organ. Scientists at the department investigate how sensory, cognitive and motor information flow through the brain and are related to the measurable brainwaves, activity patterns and neuronal interactions. Their methods combine state-of-the-art data analysis with a broad range of electrophysiological methods. Magnetoencephalography (MEG) is an important part of this research. At the MEG Center the department operates one of the few systems in Germany for measuring human brain activity in a non-invasive manner and with the best temporal resolution and signal quality. The department ensures that its research is transferred to clinical applications through several partnerships.

Neurology and Neuro-Oncology

Patient-centered neuro-oncology is the mission of the Department of Neurology and Interdisciplinary Neuro-Oncology led by Professor Ghazaleh Tabatabai. Professor Tabatabai and her team work towards improving the lives of patients with tumors in the nervous system. Such tumors are both complex and heterogeneous and the team need to combat them at very different points. For a particularly aggressive form, glioblastoma, the scientists focus on the immune system: They have developed an active ingredient that is intended to activate T cells that can attack and destroy the tumor cells. This immunomodulator is currently being used and tested in a phase one trial. This ensures that the latest research is considered in improving diagnostics and therapy. Research priorities at the department connect the research areas of oncology, immunology and neuroscience and the department is also a founding member of the Cluster of Excellence 2180 "Image-guided and Functionally Instructed Tumor Therapies" (iFIT). Patient care at the department also involves interdisciplinary networking and the team works closely with the clinics for neurosurgery and radiation oncology. This department is a member of the Center for Neuro-Oncology within the the Comprehensive Cancer Center Tübingen-Stuttgart and integrated in the National Center for Tumor Diseases (NCT) in Tübingen, which, together with Ulm and Stuttgart, forms the NCT Southwest.

In statistics on the global burden of disease and premature deaths, five of the ten most common diseases are neurological disorders.

Neurology with Neurovascular Medicine
The Department of Neurology with Neurovascular Medicine emerged from the vision and research of Professor Ulf Ziemann, one of the world's leading scientists in the development of non-invasive therapeutic brain stimulation through transcranial magnetic stimulation (TMS). The team's approach to stimulating the brain in synchronization with the brain state is fundamentally new. A technology developed by the researchers enables them to evaluate EEG data in real time and set magnetic pulses at the optimum time. This closed-loop method has been particularly successful in the rehabilitative treatment of individual stroke patients with hand or arm paralysis and is currently undergoing clinical translation. It will be tested in larger studies and extended to other network diseases of the brain, such as depression. At the TMS outpatient clinic which opened in 2018, the department has access to an infrastructure that is unique in Germany. Ziemann and his team expect a paradigm shift toward highly personalized therapeutic brain stimulation. Their long-term goal is therefore to develop a helmet with an integrated EEG cap and 50 magnetic coils, which enables high-resolution spatial and temporal stimulation.



The brain is an electrical organ that transmits its impulses via a gigantic network of nerve cells.

Not a side job

Strategic management and systematic development have been core values at the Hertie Institute since its foundation and this is overseen by professional administrative structures.

It was clear to the Hertie Foundation from the outset that an institution that combines clinical care and research at the highest level and in which the department heads are equal in terms of academic and corporate law cannot simply be managed on the side. This task must be solved professionally and with a clear division of roles and responsibilities. The Board of Directors and the Board of Trustees are responsible for the institute's clinical research profile. The administrative director sets requirements and strategies for achieving them, monitors organizational developments and programs and supports the leadership of the Center of Neurology. She also has a veto right on major financial expenditure which could restrict the Center's agility.

Dr. Astrid Proksch has been administrative director of the Hertie Institute since 2011 and has also been managing director of the "Brain Research" program of the Hertie Foundation since 2017. She handed over the coordination of the DZNE site in Tübingen when she accepted her current position. Dr. Proksch is a biochemist who also holds a Master's degree in Management, demonstrating her scientific expertise and leadership knowledge. Before joining the Hertie Institute she headed the department of the Scientific Board of the German Cancer Research Center. Astrid Proksch has advanced the Center of Neurology in many ways: with new governance structures, initiatives for sustainable financing, strategic accounting and central investment management for major instrumentation, networking initiatives, programs for career advancement and the recruitment of junior researchers and, last but not least, through consistent external and internal communication. "I see my strengths in strategy development, but I also ensure strategy becomes reality," says Astrid Proksch. "That everything we design and implement actually serves our ambitious goals. We have achieved a lot, but we still have a lot on our minds."

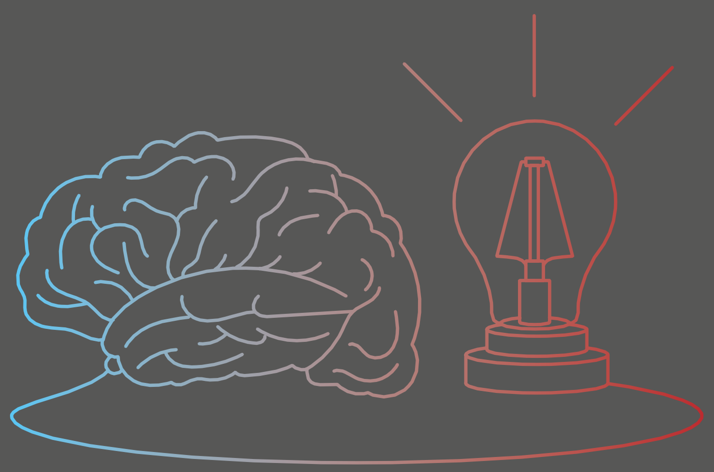
The Hertie Foundation has invested more than 55 million euros in the Hertie Institute to date and also supports its strategic development and networking initiatives.

True or False?

1. The brain cannot feel pain. If you made an incision to the brain while a person is still conscious they would not feel it.

2. To power a light bulb, you would need electric current from many human brains.

3. The number of nerve cells in our brain is about the same as the number of stars in the Milky Way.



4. The building blocks for forming and regulating the brain are relatively simple. The brain only needs one-third of our genetic material to get started.

5. The brain constantly disposes of waste and has a complex cleaning system.

6. Epilepsy is the fourth most common neurological disease and causes suffering to many.

Answers

1. True. Although the brain perceives pain signals from the body, it does not have any pain receptors. Headaches are caused by pain receptors in the cerebral membranes, which separate the brain and skull from each other.

2. False. A human brain has a total electrical power of 25 watts. So it would only theoretically take one brain to power a light bulb.

3. True. Our brain has about 100 billion nerve cells. This corresponds to the number of stars in our galaxy. The brain also connects its nerve cells via hundreds of trillions of neural circuits forming an unimaginably powerful network for thinking, feeling and acting.

4. False. The brain is so complex that it needs around half of our genome, but at barely 3 pounds it makes up only 2 percent of our body weight. The remaining half of the human genome is used by all other organs and structures in the body.

5. True. The brain disposes of its waste either through the blood, through cerebrospinal fluids or through a special drainage system. Failure of this cleaning system can cause neurological diseases.

6. True. Epilepsy is the fourth most common neurological disease. One in 100 people suffer from epilepsy and one in 26 will have an epileptic seizure at some point in their lives. Most new cases affect children under 5 years of age and adults over 60 years of age.

Rethinking brain tumors

Tübingen neurologist and physician scientist Professor Dr. Ghazaleh Tabatabai has taken on a special challenge: She wants to cure malignant brain tumors.

Text: Claudia Eberhard-Metzger

Our brain weighs barely more than three pounds. But it's an incredibly powerful organ. 100 billion nerve cells are linked to a gigantic communication network through over 280 trillion connections, the synapses that makes us think, talk, feel, remember, smell, see, taste and walk. The control center in our minds is considered the most complex structure in the universe and has always been a challenge to science. "Dark are the building blocks of the brain," wrote Giovanni Fantoni, professor at the University of Turin, around 1700, who spent his life trying to understand this magnificent organ, "even darker are the diseases, darkest are the processes in them."

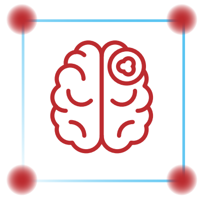
In the meantime, scientists have brought more light into the darkness, but many pathological processes remain out of reach, for example in malignant brain tumors such as glioblastoma. Surgeons cannot completely remove the tumor and its many dispersed cells, which grow diffusely into healthy brain tissue. Despite surgery, radiotherapy and chemotherapy, glioblastoma often returns quickly because its uncontrollably growing cells are extremely resistant and multiform. Glioblastoma is not curable with current scientific knowledge. Finding a breakthrough treatment is a major scientific and medical challenge. Ghazaleh Tabatabai, professor of neurology at the University of Tübingen and co-director at the Hertie Institute, has taken up this challenge because she is fascinated by the complexity of the brain and because she wants to do something "with others for the benefit of others" When something is particularly difficult and much is unknown, the effort is especially worthwhile, she emphasizes. Ghazaleh Tabatabai is equipped for this task in two ways: as a physician, who has daily contact with patients seeking treatment in the Clinic of Neurology at the University Hospital, and as a neuroscientist in the laboratories of the Hertie Institute for Clinical Brain Research. Linking roles in the clinic and basic research is intended to ensure that scientific knowledge gained in the laboratory benefits patients as soon as possible. The Hertie Foundation, together with the Hertie Institute for Clinical Brain Research, provides a structural and organizational bridge for a faster transition, a better translation of research results into practice. Tübingen is also a partner location in the German Consortium for Translational Cancer Research. "There is still a long road ahead," admits Ghazaleh Tabatabai. However, progress has been made in the diagnosis and therapy of tumors such as glioblastoma that improve conditions for patients that were previously unsatisfactory. "Even if they are only small steps, we are gaining ground," says Ghazaleh Tabatabai.

The reason for this brighter view of the future are advances in cancer research, which can now describe tumors at the molecular level. "Every tumor is as unique as humans are," explains Tabatabai. Modern imaging methods cannot yet represent this uniqueness in the detail required. Highly complex molecular biological methods, on the other hand, are increasingly showing when and how genes can be altered and cells can turn on

the body and grow destructively. “Greater knowledge opens up new concepts in therapy,” says Tabatabai. Patients can already be categorized into molecularly defined groups that may soon have better and targeted therapies. Knowing exactly which changes turn normal functioning cells into malignant cancer cells gives physicians and patients hope for new, targeted medications.

Personalized medicine

The fundamental idea that has emerged from the findings of molecular biological research is personalized medicine, treatment that incorporates individual molecular tumor characteristics, biomarkers, rather than treating all patients as if there were no differences between them. Ghazaleh Tabatabai and her team intend to identify these biomarkers, which belong to two groups: Tumor-specific molecular alterations ideally characterize tumor cells unambiguously, making them a potential target for precision medicine. Prognostic biomarkers can be used to better estimate how the disease will develop over time. In a recent study, scientists from Tübingen tested a prognostic biomarker for meningiomas. While some of these tumors that originate from the brain’s membranes grow slowly and do not recur after the operation, others behave aggressively and return. Previously, the course of the disease could not be predicted. The scientists in Tübingen led by Ghazaleh Tabatabai were able to show in their study that a biomarker can help to improve prognosis.



Malignant brain tumors account for only two percent of adult cancers. However, they are particularly aggressive and heterogeneous.

> “Brain tumor diagnoses are representative of many individual molecular diseases. We need to decode, understand and use this molecular uniqueness therapeutically.”
>
> Professor Ghazaleh Tabatabai

A further example of the team’s steady but groundbreaking research are new cell-based strategies for improving targeted drug delivery into the brain. The brain is protected naturally from molecules that could potentially cause damage by the blood-brain barrier. Selectively opening this biological barrier so that targeted drugs can reach the tumor unhindered and act on site could optimize treatment. Another fatal feature of the glioblastoma cells is on the research agenda in Tübingen: How do degenerate cells become resistant to treatment? Today, it is known that the tumor cells open up escape routes by switching certain molecular signal chains on or off. With knowledge of these escape routes and their molecular mechanisms, Ghazaleh Tabatabai explains that this fatal resistance could possibly be broken.

Activating the body’s precision weapon

High hopes rest on immunotherapies that use the body’s defenses in the fight against cancer. The immune system can be a highly effective weapon against cancer cells – but it is too tolerant of dangerously altered cells for too long. To make matters worse, cancer cells can camouflage themselves perfidiously and undermine defense mechanisms. Communicating the life-threatening threat to the immune system from its own ranks so unambiguously that it abandons its fatal tolerance and uses all its means against cancer cells in a targeted manner is a potential therapeutic route may be an important weapon in fighting cancer. This goal could be achieved with an activating vaccination by delivering a protein to the immune system that can identify cancer cells and trigger an immune response. A vaccination with multiple proteins (multipeptide vaccination) and a separate immunostimulator developed in Tübingen is currently being tested in a phase one clinical trial, led by Ghazaleh Tabatabai at the University Hospital, in glioblastoma patients who belong to a specific, molecularly defined subgroup.

"It's a very exciting time to be researching in this field, there is so much happening," says Ghazaleh Tabatabai. For ten years, hardly anything has changed in the medical guidelines for the diagnosis and treatment of malignant brain tumors, but personalized medicine offers new perspectives; some of which have already arrived in the clinic. This afternoon, for example, Professor Tabatabai will take part in the Molecular Tumor Board, an interdisciplinary conference with colleagues from internal medicine, neurology, neurosurgery, radiology, pathology, neuropathology, nuclear medicine, pharmacology, molecular biology, genetics and bioinformatics, which was established in Tübingen in 2016. In addition to the Neuro-oncological Tumor Board which is a central communication platform in the clinic, the Molecular Tumor Board meets to discuss the individual molecular profile of the tumor and consider whether and how the patient could be treated with a personalized therapy concept.

No room for nihilism

In the short-term, Professor Tabatabai modestly hopes that "we soon have a widespread consensus that nihilism is not effective in treating neuro-oncological diseases." She also feels that willingness to work together on a solution rather than compete could also grow a little. Given five to ten years "we might even have effective biomarker-based therapies that we can combine," says Tabatabai. Combined treatments could target cancer cells with different weapons and from different sides. In this way, a deadly threat such as glioblastoma could become a chronic disease that can be controlled in the long term, offering patients the prospect of an improved outcome.

Prospects that the 47-year-old physician would like to see helping as many patients as possible: "I would like our research results and clinical studies to be effective not only in rich nations, but also to reach poorer countries." She recalls hearing about a study that found that less than 10 percent of the world's population benefited from new scientific findings. Ghazaleh Tabatabai emphasizes the need to bridge this gap.

Tomorrow's neuromedicine today: New perspectives at the Center of Neurology

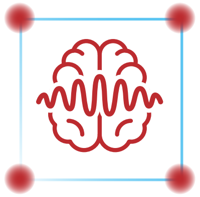
Tomorrow's neuromedicine will emerge from a better understanding of the molecular and electrophysiological processes at cellular level and in the brain as a whole. We are setting the course to make this happen.

The Center of Neurology, consisting of the Hertie Institute for Clinical Brain Research and the Clinic of Neurology at the University Hospital Tübingen prioritizes a profound connection in research and patient care across the entire spectrum of clinical neurology and excellence in training junior researchers. Its mission of ensuring that findings can be translated from basic research in neurology and neuroscience to benefit patients as quickly as possible and to the highest standards is anchored throughout its activities.

Looking ahead, the Center will continue to explore new strategies for the early detection, prevention and rehabilitation of neurological diseases, focusing on two strategic fields in research and patient care: systems-based neuromedicine and molecular therapies that address the individual causes of diseases. New working groups and structures will be established for this purpose.

The brain is the most complex organ in humans that controls the entire body through the electrical activity of its neural networks. Part of this electrical activity is caused by the concurrence of genes and proteins at the cellular level but it is also generated by the interaction of nerve cells at the network level. In setting the course for tomorrow's neuromedicine, the Center of Neurology will focus on both the electrical activity of the brain as a whole and molecular activity in the cell, seeking personalized interventions on both levels: Neuromodulation, neurorehabilitation or neuroprosthetics that target the brain activity of individual patients and molecular therapies that compensate or correct the pathogenic effect of genetic changes or disturbed protein functions. As part of this strategy, the Center of Neurology will bring together technological knowledge, brain research, healthcare and digitalization.

New professorships and junior research groups are planned to complement and expand existing research priorities. Further national and international partnerships will also underpin the Center's leading position. Innovative scientific studies expedite the route to initial clinical trials. Strategic partnerships with companies are planned to secure research results in the long term and transfer them into patient care. Ensuring excellence in training junior researchers is integral to sustaining this vision. In the coming years, the Center will also increasingly seek partnerships with independent physicians to rapidly extend the availability of new diagnostics and therapies.



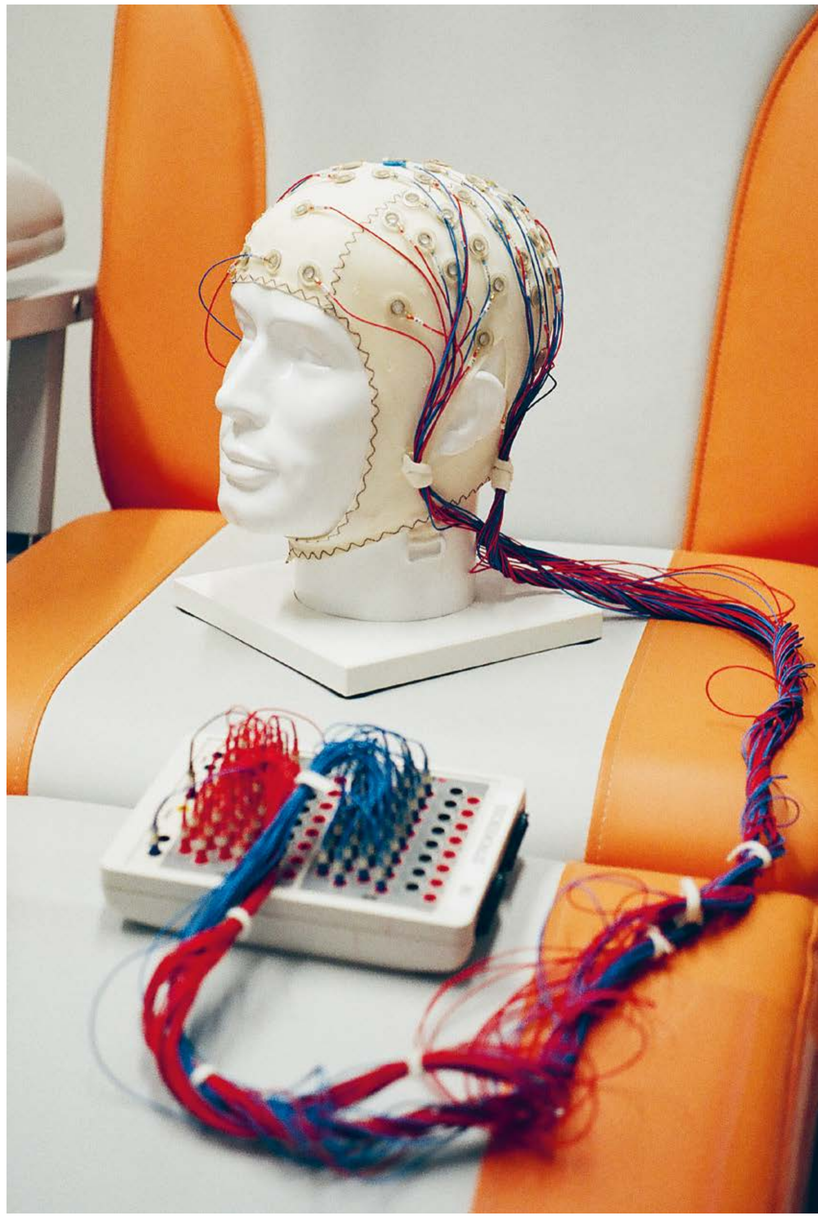
Scientists observe countless neurons and analyze the networks with artificial intelligence.

Advances in research and patient care are also based on ever-increasing amounts of data and digital transformation and the Center of Neurology will strengthen its digitalization priorities and incorporate methods from machine learning and artificial intelligence. The Center's strategy prioritizes the fundamental expansion of symptom-related therapy through personalized medicine and rehabilitation that address the molecular causes of diseases and through targeted early detection and prevention. This bold step from curative to preventive medicine is the most radical answer to the enormous challenges posed by age-related brain diseases. Tomorrow's medicine will serve people even better if we can stop them from falling ill in the first place.

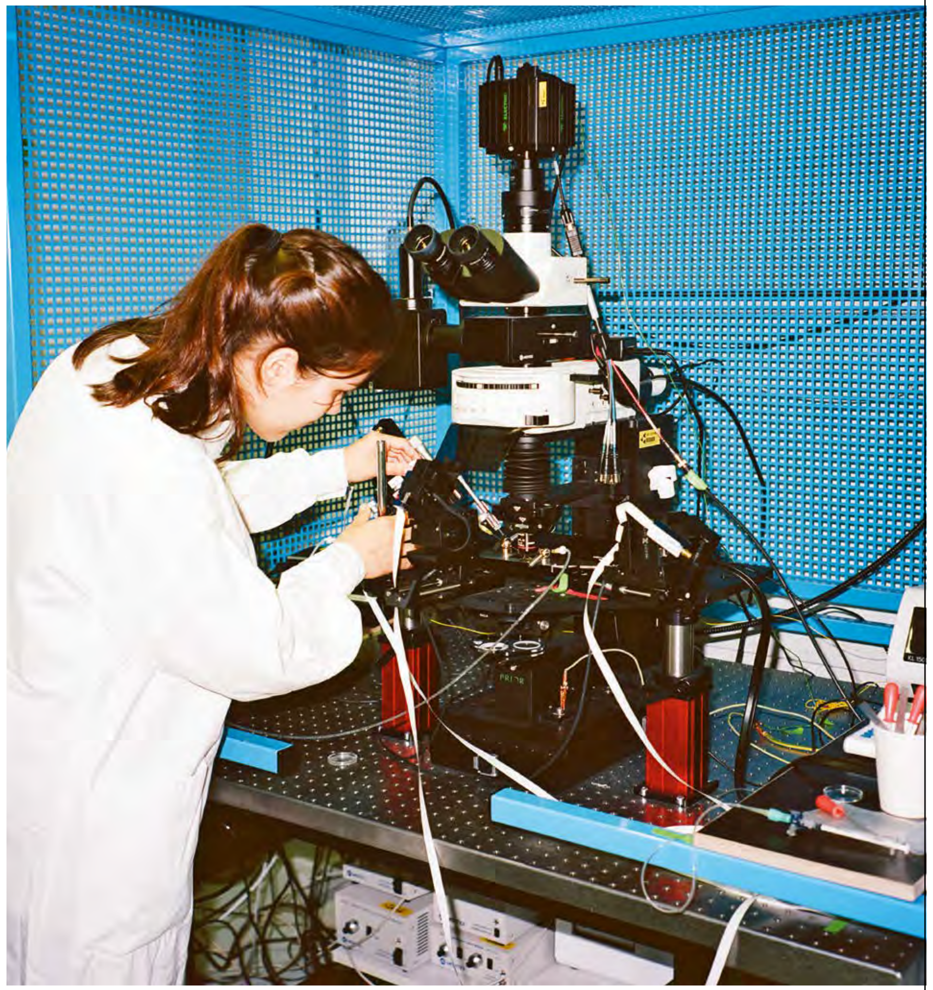
Why are these research priorities so significant?

"Systems neuroscience has enabled us to gain a better understanding of the brain as a whole," says Professor Markus Siegel, head of the Department of Neural Dynamics and Magnetic Encephalography. "We are learning how the brain encodes information in the neural networks, how various neural activities are coordinated, and how networks are flexibly modulated. We also need to determine what the relevant states are for the plasticity of the brain and which networks need to be strengthened or weakened in certain situations. This gives us an idea of what we can achieve and important starting points for innovative neurotechnologies."

Neurological clinics already use increasingly accurate information about the individual and local activities of the brain in transcranial magnetic stimulation and deep brain stimulation, analyzed by location and time. "However, our strategy is much more ambitious," says Professor Dr. Ulf Ziemann, head of the Department of Neurology with Neurovascular Diseases. "We want to give patients back a piece of their independence on the basis of their individual brain activity in real time, by means of much more targeted neuromodulation or innovative neuroprostheses that are controlled via brain activity. The Center of Neurology already has a high degree of expertise in this groundbreaking field and is well equipped for future developments."



Beyond treatment, the Center of Neurology will increasingly focus on the early detection, rehabilitation and prevention of neurological diseases.



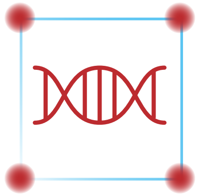
Today, medicine – and neurology is no exception – is strongly influenced by the rapidly growing knowledge of relevant genes, their functions and interactions, and disruption caused by mutations. Many known neurological diseases appear to have little in common, they frequently neither have the same causes nor the same course. In expanding its spectrum in research and patient care, the Center of Neurology will explore the influence of genetic changes on disease progression intensively. Physicians and scientists need to truly understand which molecular processes are disturbed in diseases such as Parkinson's, Alzheimer's, brain tumors or epilepsy before they can intervene in a targeted manner. The Center of Neurology will intensify the search for biomarkers that shed light on the courses of diseases and are suitable for diagnosis and examine specific target molecules that could be used in therapy.

It will also pursue a new research priority in the development of molecular and gene therapies. "We are working to balance pathologically altered functional consequences of hereditary genetic changes in individual forms of epilepsy with known or novel drugs or antisense oligonucleotides," says Professor Holger Lerche, head of the Department of Neurology and Epileptology. "However, gene therapy can also involve injecting a correct version of the mutated gene via viral vectors or repairing the defective copy using gene scissors. The Center of Neurology will intensify its efforts to find molecular and gene therapies at all levels."

Strengthening neuroimmunology

However, therapies that focus on molecular mechanisms do not necessarily have to start at the gene level. In many neurological diseases, the immune system also plays a crucial role, either because it overreacts and causes inflammation or because it fails to trigger an immune response. For this reason, the Hertie Institute recognizes the importance of neuroimmunology and neuroinflammatory research as part of its institutional strategy. An innovative form of immunotherapy is cancer vaccination. "In cancer vaccination, the immune cells are very specifically confronted with tumor antigens," says Professor Ghazaleh Tabatabai, head of the Department of Neurology and Interdisciplinary Neuro-Oncology. "The immune cells should learn to target tumor cells carrying these special antigens. We have just started a phase one study with a therapeutic cancer vaccination in glioblastoma together with cooperation partners in Tübingen". The institutional strategy of the Hertie Institute also addresses the search for cancer vaccinations for primary brain tumors.

Expanding and developing the research and care spectrum at the Hertie Institute means that a greater number of scientific clinical studies will be needed to evaluate the latest developments in neurology and neuroscience. "Because we have recruited many patients for clinical studies through the Clinic of Neurology and our special outpatient clinics in recent years, the Center of Neurology is well prepared for it," says Professor Dr. Thomas Gasser, head of the Department of Neurodegenerative Diseases. "And this is true even in the case of rare neurological diseases with only a few people affected worldwide. In the future, we will also explicitly seek cooperation with independent physicians and develop cross-sector care networks. Ultimately, anyone affected should benefit from the developments, not just those we treat personally."



The human genome consists of 3.1 billion base pairs and about 23,000 genes.

Understanding healthy aging

Prevention and early detection are prioritized in the institutional strategy of the Hertie Institute for several important reasons. Most diseases of the brain cannot be cured. However, social and economic costs of these diseases far exceed those caused by cancer and cardiovascular diseases. The urgency to prevent brain diseases for social and economic reasons is therefore considerable. Many neurological diseases also have a long prodromal phase. They develop very slowly and without noticeable signs over several years, as the brain can often compensate for slowly developing damage over a long period of time. It is often too late for early intervention or even prevention when symptoms are finally recognized. "We need to find biomarkers for detecting diseases during early stages that can help us to understand resilience and healthy aging," says Professor Dr. Mathias Jucker, head of the Department of Cellular Neurology. "We also need to identify molecules for targeted prevention. In the case of Alzheimer's disease, we have a promising starting point with pathogenic seeds that later form beta-amyloid deposits. "But that's just scratching the surface. At the Center of Neurology, we will deepen our focus on the conditions of healthy aging and strengthening preventive medicine."

Looking for a career?

A sound scientific education, early independence and excellent infrastructure at the Hertie Institute offer the best prospects for a wide range of career paths in research and clinical settings.

Supporting junior researchers in developing their careers is an investment in the future and of utmost priority at the Center of Neurology. All interdepartmental programs at the Center of Neurology are based on the highest international and academic standards. Funding programs provide early independence and offer junior researchers the opportunity to contribute to the development of the Hertie Institute.

Talented employees also have the opportunity to conduct independent research within their department at an early career stage. Through flexibility, secure prospects and transparency, young talents are given the best possible foundation for taking their career to the next level.

Research and patient care are closely connected throughout the Center of Neurology, opening up a wide number of career opportunities. Medical students benefit from in-depth scientific training and enter clinical research at an early stage, ensuring the modern approach to the study of medicine that is promoted by the Center of Neurology. The Johannes Dichgans scholarship supports particularly motivated students in pursuing a challenging doctoral degree in medicine. Beyond specialist training, medical students can choose the career pathway of Clinician Scientist which qualifies them to treat patients as a specialist physician while conducting research at an internationally competitive level.

The Hertie Institute also offers natural scientists excellent opportunities to advance their careers. The institute is a leading international center of excellence, with a welcoming and open culture and prospering networks. Its partnership with the Graduate Training Centre of Neuroscience ensures robust academic standards. The Graduate Training Centre is a collaboration between the Max Planck Institutes and the University of Tübingen, which offers Master's and doctoral programs with an international outlook. In education, the Hertie Institute also works closely with the Faculty of Science and contributes to medical engineering and molecular medicine programs.

"After finishing my Master's program in Translational Neuroscience at the University of Sheffield, England, the Hertie Institute was the right place for me to do top-level research close to patients. Training here opens doors to laboratories around the world."

Jorge Garcia Morato, doctoral candidate

"The Center of Neurology offers the entire spectrum of clinical neurology and cutting-edge research opportunities that are one of a kind. Sound scientific training is extremely valuable for clinical work."

Jordana Maas, doctoral candidate and Johannes Dichgans Fellow 2020/2021

"At the Hertie Institute, research takes place on an equal footing with top international research institutions. The excellent technical infrastructure and the reputation of the research group persuaded me to relocate from China to join the Hertie Institute."

Dr. Yang Bai, Humboldt Postdoctoral Fellow

"I want to be able to offer treatments that address the causes of Parkinson's disease one day. With the help of the excellent biobank at the Center of Neurology, I can investigate these causes extensively and quickly introduce the new findings into clinical treatment, ensuring that patients benefit from the highest level of care."

PD Dr. Kathrin Brockmann, senior physician and head of junior research group

"My goal is to improve the lives of Parkinson's patients with deep brain stimulation. The close link between clinic and research offers me the optimal resources for this. I can research the neural basis of gait disorders as a scientist and clinician and transfer the findings directly to therapy."

Professor Dr. Daniel Weiß, senior physician and head of junior research group

"With my Emmy Noether funding, I have returned from UC Berkeley to the Hertie Institute, as this is the best place to combine my clinical and scientific profile throughout Germany. New methods can be transferred directly into clinical diagnostics."

Dr. Dr. Randolph Helfrich, clinician scientist and head of independent research group leader

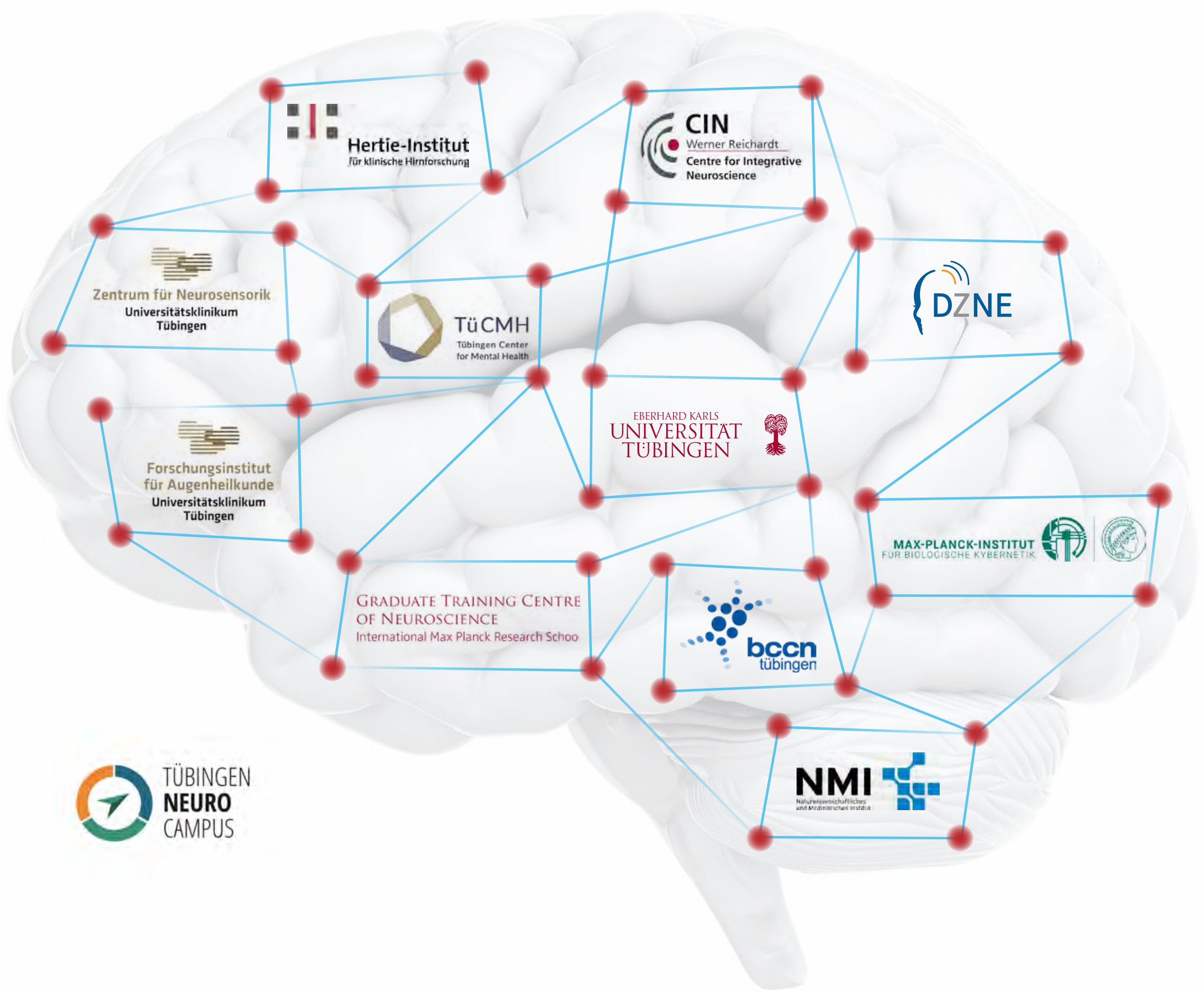
"Independent research group leaders are unheard of at German faculties. The Hertie Institute for Clinical Brain Research, however, has an innovative organizational strategy that gives scientists the freedom to independently develop their research program at an early stage."

Dr. Simone Mayer, head of independent research group

Connected brain research

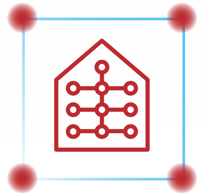
Top research institutes need first-class networks and many clever minds. The Hertie Institute is privileged with both of these assets and welcomes talented partners and ambitious collaborations.

On the eastern flank of the Schnarrenberg, three research buildings mark the importance of brain research at the University of Tübingen: the Hertie Institute for Clinical Brain Research, the Werner Reichardt Centre for Integrative Neuroscience (CIN) and the German Center for Neurodegenerative Diseases (DZNE) in Tübingen. The CIN was founded in 2007 as a Cluster of Excellence and is now an interdisciplinary center at the University of Tübingen. Numerous research groups at the Hertie Institute have been actively and successfully involved in this field of systems neuroscience since the CIN was founded, contributing to a better understanding of brain functions such as perception, memory, communication and action. The DZNE in Tübingen, which also funds Professor Gasser's and Professor Jucker's departments at the Hertie Institute, is one of the German Centers for Health Research. All three institutions work closely together. The CIN is also linked to the Faculty of Medicine, the Faculty of Science, the Max



Planck Institutes for Biological Cybernetics and Intelligent Systems, and other institutions dealing with brain research, neurobiology, artificial intelligence, and machine learning. As a University of Excellence and a partner location for three other centers of health research the University of Tübingen is a respected think tank for neuroscience.

In 2018, the Tübingen Neuro Campus (TNC) was founded in association with the Hertie Institute to make the most of this potential. Professor Thomas Gasser is the speaker of the TNC and also chair of the Hertie Institute. The TNC is a communication and networking platform for over 100 working groups in fields related to neurology and neuroscience from ten institutes. Partners in the TNC set their own priorities from their projects and initiatives. Regular events promote interdisciplinary exchange and ensure that partners discover and benefit from synergies. The TNC is also an effective vehicle for identifying and establishing new scientific and technological developments. Collaboration between the working groups in neuroscience through a shared platform also boosts external visibility and attracts top scientists from all over the world. After all, excellence attracts excellent minds. The TNC is also responsible for developing and standardizing graduate training. More than 27,600 students from all over the world are currently enrolled at the University of Tübingen. In addition to five other locations in Germany, the Hertie Institute is also part of the research and career network of the Hertie Foundation, the Hertie Network of Excellence in Clinical Neuroscience.



The Tübingen Neuro Campus includes over 100 working groups in the field of neurology and neuroscience from ten institutes.

Activating networks

With a new type of brain stimulation, Professor Dr. Ulf Ziemann wants to revolutionize the rehabilitation of stroke patients.

Text: Claudia Eberhard-Metzger

"It happened on April 13, 1737, when the whole house shook with a dull thud. Something massive and heavy must have crashed into the floor upstairs." Alarmed, a servant raced up the stairs to find his master, Georg Friedrich Händel, groaning on the floor. Shortly before, the composer had "come home from rehearsal in rage, his face bright red, the veins standing out like thick cords at his temples." The doctor was summoned. Dr. Jenkins raised Händel's right arm and it fell back as if dead. Then he raised the left arm and it stayed in its new position. He saw that one eye, the right eye, was staring while the other looked livelier. Now Dr. Jenkins knew enough. "Apoplexy. His right side is paralyzed." And when asked whether Händel will recover, he replies evasively: "Perhaps. Anything is possible."

In the Resurrection of Georg Friedrich Händel, Stefan Zweig impressively described stroke – clinical apoplexy, a sudden lack of blood flow to the brain. Reading further into Zweig's novel we learn that the right half of Händel's huge body remained as if dead for four months. Then the composer recovers, slowly regaining his agility through a miracle and his irrepressible will, the primordial power of his life, rather than through medicine.

Most strokes are caused by a blood clot (thrombus) impeding blood flow in the brain. Today, strokes can be treated with positive outcomes. There are stroke units, special units for stroke patients; physicians have drugs that dissolve clots (lysis therapy) and interventional neuroradiologists can remove the thrombus using a catheter (thrombectomy). We now also know how much time is of the essence in treating stroke patients, the faster the supply to the brain is restored, the less brain damage and permanent disabilities such as paralysis or speech disorders are to be feared. Despite these advances, stroke – one of the largest widespread diseases in Germany with 270,000 patients a year – still causes the most permanent disabilities in adulthood. Neurorehabilitation is important for helping these patients to live largely independently with the highest possible quality of life through measures such as physiotherapy or occupational therapy.

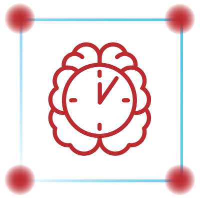
One of the leading experts in neurorehabilitation is Professor Dr. Ulf Ziemann, head of the Department of Neurology with Neurovascular Medicine at the University Hospital Tübingen and co-director of the Hertie Institute for Clinical Brain Research. Ziemann, a physician and scientist, has consistently implemented the findings of advanced systems neurobiology and developed a method that promises to revolutionize the rehabilitation of stroke patients: transcranial magnetic stimulation, or TMS for short, a targeted activation of the brain to awaken remaining potential.

The amazing plasticity of the brain

Ulf Ziemann compares his method and what is happening in the brain with an orchestra: When a piece of music is performed, every musician must play the right notes at the right time and in the right place. The billions of neurons in our brain must work together just as precisely. Like the musicians in the orchestra, nerve cells do not act independently but in dynamic networks that extend over the entire brain. Precisely this interaction allows the brain to perform its masterpiece. A stroke causes damage that affects these networks. "This is why we need to treat losses in function that occur after a stroke as network diseases," Ziemann emphasizes. He has developed a new perspective in neurorehabilitation from this approach, proposing that the residual network – the remaining nerve cells not destroyed by the stroke – can be induced to recover lost functions by repeated electrical impulses. Modern neurobiology has meanwhile demonstrated that the brain has great plasticity – the lifelong ability to regenerate and restructure itself. Returning to the orchestra, we can see how the brain can also recover: "There may have been ten violins, but the orchestra as a network can still continue to play the piece – but perhaps now with a stronger emphasis on the violas."

Transcranial magnetic stimulation was first proposed in 1985 by the English scientist Anthony Barker at the University of Sheffield. Ulf Ziemann heard about the method as a young physician in neuroscience research in the early 1990s and was immediately enthusiastic about the potential of reaching the brain from the outside without pain (transcranial means through the skull). Ziemann has steadily developed the process ever since.

"The brain is an electrical organ," he says, explaining how TMS works. Therefore, it is sensitive to the physical principle of electromagnetic stimulation: A magnetic coil applied to the skull generates a short magnetic field, changing (depolarizing) the electrical state of the nerve and creating an action potential. In other words, information is transmitted in the form of electrical excitation in the nerve cell networks. Initial studies on the effects of TMS have shown that repeated stimulation can improve network structures of the brain and physical functions, particularly if the TMS treatment is carried out immediately before physiotherapy or occupational therapy. TMS effectively exercises the brain so it can learn better and the patient can achieve faster and greater progress in rehabilitation. "This has worked quite well for some patients," Ziemann summarizes



Time is brain: Every second counts when responding to a stroke. Patients who are treated more quickly face a better outcome

> "Like the musicians in the orchestra, nerve cells do not act independently, but in dynamic networks. Precisely this interaction allows the brain to perform its masterpiece."
>
> Prof. Dr. Ulf Ziemann

the previous experience with TMS – and also acknowledges its limitations. "But many others showed no benefit." His aim is to ensure that the benefits of neurostimulation are available to all those affected.

ConnectToBrain

TMS therapy so far has used individual magnetic coils that can stimulate only one point in the brain. Researchers from Tübingen and their partners in Finland and Italy in the ConnectToBrain project are developing a user-friendly helmet, which uses approximately 50 magnetic coils. "This stimulates several nodes of a network distributed over the entire brain rather than a single point," Ziemann explains. The European Research Council is funding the ConnectToBrain project with ten million euros until 2026, when the first helmet should be ready to use in a clinical setting. The new design is already being tested in clinical pilot studies on healthy people and stroke patients and is far from the only innovation made by scientists in Tübingen.

Ulf Ziemann and his team have also personalized the TMS, equipping it with additional technology that adapts the stimulation to individual requirements and to the brain's current state of activity. "With the first TMS system, all patients received the same treatment, regardless of losses in physical function or severity level," explains Ziemann. "Earlier methods also did not account for current brain activity". In Tübingen, physicians first determine the immediate electrical state of the brain, known as the brain state, before placing the helmet onto their patients. From this they determine when and where the TMS pulses should be applied to achieve a certain effect. The researchers use electroencephalography (EEG) to detect and record the electrical activity of the brain via electrodes on the scalp. Equipped with computers that can analyze large amounts of data in milliseconds and special evaluation algorithms, the physicians use EEG to determine the electrophysiological status of the brain in real time. This knowledge is an important prerequisite for the therapeutic success of the TMS, since it is known from brain research that different electrical states of the brain are susceptible to stimulation in different ways and it is important to find exactly the right time for stimulation in constantly changing brain activities. "Every patient receives an optimized stimulation pattern that matches their needs," Ziemann emphasizes. This personalized therapeutic approach is groundbreaking and promises far greater therapeutic effects than early TMS – not only in stroke patients.

Network disorders cover much more than stroke. Conditions that might not seem related at first glance such as Alzheimer's and Parkinson's disease, tinnitus and epilepsy, schizophrenia, depression or pain are now all considered as network disorders. "All these disorders are based on dysfunctional networks of the brain," explains Ziemann. He hopes that personalized TMS therapy applied in real-time will therefore be able to treat all of these disorders in time. However, to achieve this goal the technology needs to be developed – the Hertie Foundation provides the necessary structures and closely links basic research with clinical application for transferring research findings. Ulf Ziemann hopes that TMS will soon be able to benefit many patients: "This would also mark the achievement of my personal vision of combining brain research with neurological practice."

Different from the start

Professors Johannes Dichgans and Hans-Jochen Heinze discuss the foundation of the Center of Neurology in Tübingen, its model character for university medicine in Germany and what German Centers of Excellence can learn from American institutions.

Professor Dichgans, you are the founding director of the Center of Neurology. What motivated you to launch this model project twenty years ago?

Dichgans: The main reason was the lack of quality of clinical research in Germany at the end of the 1990s. There were clear shortcomings in the number of publications in first-rate journals, the number of international clinical studies conducted under German supervision and the number of clinical studies from Germany cited in international research. This led to the publication of the research memorandum “Clinical Research”, in which I was involved as Vice President of the German Research Foundation (DFG). The memorandum showed unequivocally that clinical research in Germany was not institutionalized, that dedicated funds were missing for the financing of research and that research facilities were not allocated according to performance. There was also a lack of profound scientific training for competitive research at German university hospitals and career options for full-time researchers in medicine. It was clear that research and patient care must be linked more closely so that patients can benefit more quickly from the findings. This ruthless analysis left no doubt that clinical research in Germany needed a profound structural change. What was needed were flatter hierarchies with many specialized research groups that work and publish independently.

It was a long journey from identifying the problem to establishing a model center of neurology. It also needed a lot of money. How did the Hertie Foundation fund this transformation?

Dichgans: The support and commitment of the Hertie Foundation came at the right place at the right time. We could not say otherwise. I was determined to drive structural change within my own sphere of influence. When I spoke to the Hertie Foundation about another matter, I had the opportunity to talk to the then CEO Dr. Michael Endres about the urgently needed structural change for clinical research in Germany. The foundation was very quickly prepared to finance this structural change at the Clinic of Neurology at the University Hospital in Tübingen by establishing its own research institute and the initial investment of 43 million DM in seed capital over a period of ten years. However, I had underestimated the resistance that this offer triggered among the ranks of the Faculty of Medicine. Many colleagues feared at the time that the planned Center of Neurology would shift the balance between the subjects and could command higher budgets at their expense. Indeed, the project was on the verge of collapse on several occasions. Support from the Ministry of Science, Research and the Arts of Baden-Württemberg and the President’s Office at the University of Tübingen were decisive for this success. Both institutions recognized that the center would have a model character for university medicine in Germany and would serve the excellence status of the University of Tübingen.

Vision, the right place and the right time: The foundation of the Hertie Institute is the result of strategic vision and the right moment.

"The Center of Neurology in Tübingen is an important role model across Germany, which was clearly acknowledged in a report by the German Council of Science and Humanities in 2015."

Prof. Dr. Hans-Jochen Heinze,
University Hospital Magdeburg

Professor Heinze, you are director and chairman of the Board of Directors of the University Hospital Magdeburg and chairman of the Board of Trustees at the Center of Neurology in Tübingen. Would you like to see a similar center of neurology in Magdeburg?

Heinze: The Center of Neurology in Tübingen is an important role model across Germany, which was clearly acknowledged in a report by the German Council of Science and Humanities in 2015. In many ways, I am guided by the ideas behind the Center of Neurology in Tübingen. As Director of Neurology in Magdeburg, I have already set up various departments in this clinic that are similar to the departments in Tübingen with the goal of ensuring that heads and directors can organize their departments independently. The Board of Directors at the University Hospital in Magdeburg also attaches great importance to sound clinical and scientific further training for our employees. An essential prerequisite for employees to take on the challenging dual role of patient care and research is a high level of self-motivation – and this means that successful independent research and development must be anchored in their career profile. Nobody wants to work just for the reputation of their boss.

The Center of Neurology shows that comprehensive care and competitive research are also possible with a flat hierarchy. Why does it seem that the old hierarchical thinking still dominates in many places in German university medicine?

Heinze: New structures and organizational forms are only part of a research-oriented, translation-oriented university medicine. They also need to be accepted and practiced – as in the Center of Neurology in Tübingen. However, this needs a cultural change at management level, which in many places remains painfully slow. Many are still clinging to the old role models and titles, much to the detriment of junior researchers. There is a need for many role models who are living this change, and in particular for institutions such as the Hertie Institute for Clinical Brain Research, which show what examples of excellence are possible with flat hierarchies and without a classical Ordinariate structure.

What can German Centers of Excellence learn from comparable institutions abroad?

Heinze: Institutions in the USA have firmly established the principle of merit at management level. Put simply, they conduct an intensive assessment during professorial appointments and a fixed-term employment contract, which is extended after a positive evaluation. That way, everyone is on an equal footing from the start. In such a situation, everyone in the department has a strong interest in ensuring that the entire department is successful. I firmly believe that there would also be a strong boost in performance in German institutions if competition was anchored at the management level and encouraged as a cultural value throughout the entire institution. However this would require radical administrative reform and a shift to leaner structures. As they stand, administrative procedures are often incredibly complex and cumbersome. Many things get lost in the system. On an administrative level, the Hertie Institute for Clinical Brain Research is also an example of excellence. It was already clear at the time of its founding that it must have a separate management team with its finger on the pulse.

Dichgans: Rewards and incentives are also firmly anchored in the United States. Not everyone can be treated equally in a center of excellence. Incentives and rewards are the breeding ground on which motivation thrives. For example, early self-employment, performance-based allocation of facilities, but also other research funds or even performance bonuses might be considered.

The Center of Neurology is focusing on systems-based neuromedicine and molecular therapies as well as on early detection, prevention and rehabilitation in research and patient care in its expansion and throughout its institutional strategy. Is this the basis for the neuromedicine of the future?

Heinze: By focusing on these topics, the Center of Neurology is staking its claim to a leading international position and effectively balancing these important strategic fields together in a single institution via its six departments. With neuroprosthetics and systems neuroscience, the center is building on the strength of computational neuroscience in Tübingen and the surrounding area. Molecular therapies and gene therapy are already essential today. Personally, however, I always point out that the mind is far more than the brain. Neuroreduction is not the way forward – but everyone in Tübingen knows that.

Dichgans: I also see the Center of Neurology on a firm footing in these fields. The strategic priorities that we have set mean that we can continue to deliver excellence and success. However, we will always need to ensure that basic research is always oriented toward the clinic. The decision on new appointments and the establishment of research groups requires extensive verification by the Board of Trustees which is an important governance mechanism in quality assurance.

"Twenty years ago, a ruthless analysis left no doubt that clinical research in Germany needed a profound structural change."

Prof. Dr. Johannes Dichgans, founding director of the Center of Neurology

Brain research at the highest level

The Hertie Foundation creates incentives for change, calls people and institutions to action, promotes awareness and self-initiative in a sustainable way. The Center of Neurology in Tübingen is one of its most important funding projects.

The Hertie Foundation is one of the largest private foundations in Germany and acknowledges its role in setting standards for transformation in society. In its two key issues – strengthening democracy and brain research – the Hertie Foundation is searching for new, intelligent solutions to the pressing problems of our time and pushing ahead with their implementation within its own operations and funded projects.

In its "Brain Research" program, the Hertie Foundation focuses on the functioning of the brain and combating neurological disorders. How can brain research prevent and treat the increase in age-related brain diseases? Can scientists and physicians unravel pathogenic processes in brain cells and intervene therapeutically? What is the connection between neurological disorders and natural aging? Can digital applications help us to solve these questions? What significance do findings in neurology and neuroscience have for social discussions and decisions?

Providing structures that contribute to the growth and efficiency of scientific research is an important funding objective. But what are optimal structures for cutting-edge research in clinical brain research? How can patient care and research be linked effectively? With its flagship initiative in the field of brain research, the Hertie Institute for Clinical Brain Research as an example for reforming university institutes, the Hertie Foundation has shown this can be achieved. Through the foundation and long-standing funding of the Hertie Institute, which together with

The Hertie Foundation is one of the largest private sponsors of brain research in Germany.

"Our initiatives in "Brain Research" pursue three objectives that are closely connected: Creating structures, promoting talent and reaching people. Through structural innovation in clinical brain research, we intend to optimize the conditions for cutting-edge research. And we need the best minds for the job. The Hertie Institute is our priority project in the field of brain research."

Dr. h .c. Frank – J. Weise, Chairman of the Hertie Foundation

the Clinic of Neurology at the University Hospital Tübingen forms the Center of Neurology, the public-private partnership makes the Foundation today one of the largest private sponsors of brain research in Germany and Europe. So far, more than 55 million euros have been invested in the Center of Neurology in Tübingen. The Hertie Foundation continues to support the development and networking of the center. The Hertie Institute's role in training junior researchers in basic research and physicians who are also active in clinical research is particularly important.

As a foundation for reform, the Hertie Foundation pursues approaches to change and transformation. At the Center of Neurology in Tübingen, this strategy focuses specifically on the rapid transfer of scientific knowledge from basic research to patient care. This is achieved through flat hierarchies and innovative strategies, through early independence of junior researchers and diverse career opportunities. The German Council of Science and Humanities has acknowledged that the Center of Neurology is a model for university medicine in Germany.

In addition, Hertie Foundation is a catalyst for strategic partnerships and career development beyond Tübingen. In 2019, the Hertie Foundation founded the Hertie Network of Excellence in Clinical Neuroscience. This foundation network also supports five other university research locations in Germany. Promoting research and careers in a network of excellence is unparalleled in the German research landscape. The Hertie Foundation is serious about investing in the future of brain research.

Promoting transformation

Dr. Michael Endres is one of the co-founders of the Center of Neurology. As long-standing chairman of the board of the Hertie Foundation and today honorary chairman of the foundation's Board of Trustees, he has continued to accompany the development of the institution that he co-founded.

Dr. Endres, why did the Hertie Foundation support the reform of clinical research in Germany with a new Center of Neurology?

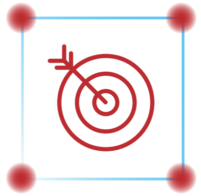
Endres: The Hertie Foundation sees its role as a reform foundation that finances projects that are new and of national benefit. The vision that Johannes Dichgans brought to us for reforming clinical research was such a project: A center with a departmental structure instead of academic hierarchies, with competitive research instead of research after work and excellent patient care that quickly benefits from the results of the research. In addition, this project was in line with the wishes of the Karg family, who are very committed to promoting brain research. With the foundation of the Hertie Institute and the establishment of the Center of Neurology, we achieved both – promoting transformation and the fulfillment of our sponsor's objectives.

Why was the center set up in Tübingen?

Endres: At that time, we thought briefly about other locations, but quickly agreed that Tübingen offers the best conditions. Johannes Dichgans, director of the Clinic of Neurology at the University Hospital Tübingen and the University of Tübingen and Ministry of Science, Research and the Arts in the Baden-Württemberg had agreed to support such an institute. The support from the ministry confirmed that Tübingen is an ideal location. Today, Tübingen and the Stuttgart metropolitan area are a top region for brain research, systems neuroscience, robotics and digitalization.

How would you summarize the achievements of the Hertie Foundation?

Endres: The Center of Neurology is a success story and a model of excellence for other institutions. At the time, the Hertie Foundation initiated two other major projects: the Hertie School – formerly the Hertie School of Governance – and the Start Foundation. Both are also very successful. It has always been important to us to promote projects that have a broad impact and that promise improvements that benefit target groups such as patients, training physicians and students. We have generally succeeded in doing this in all our projects.



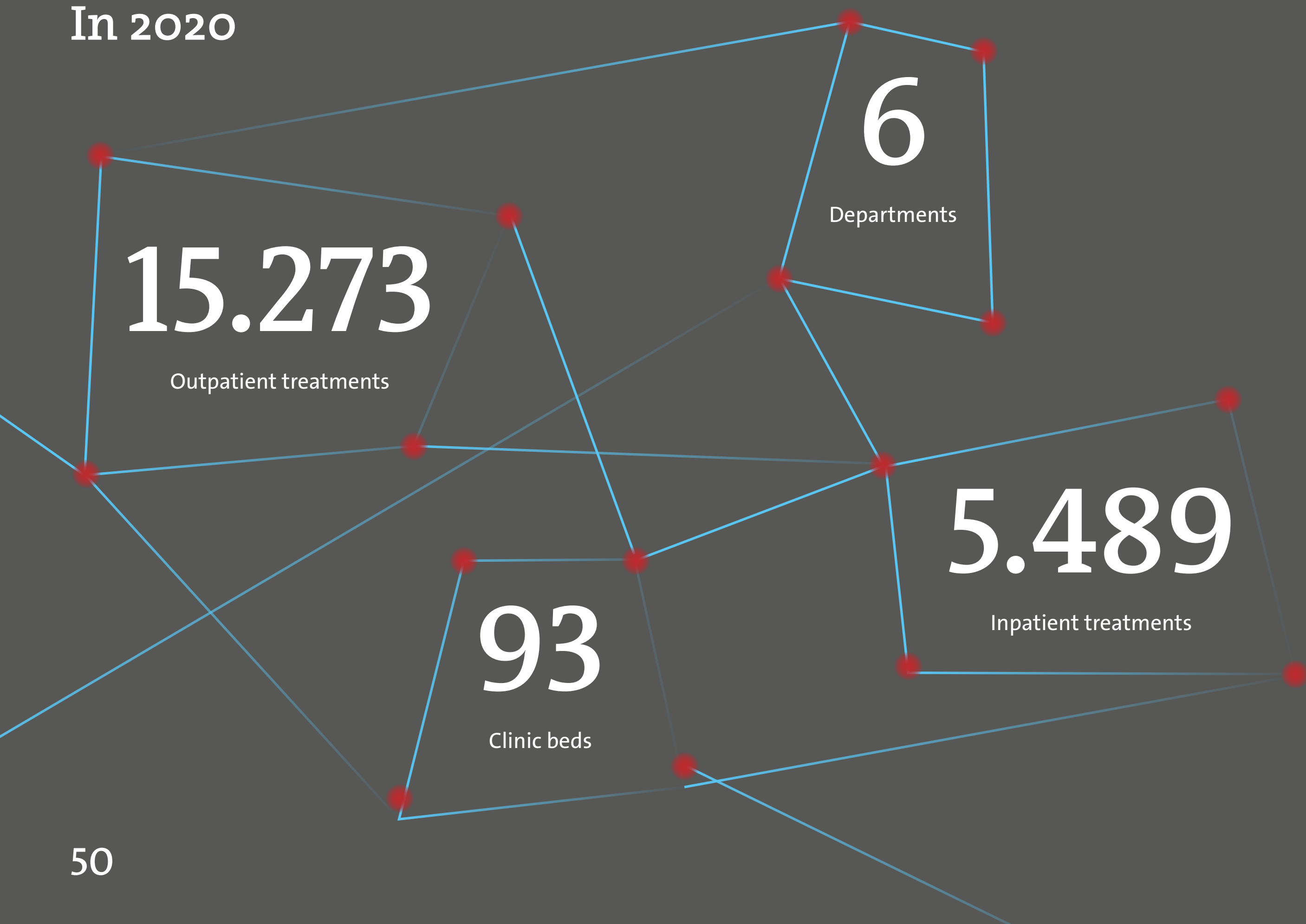
As a foundation for reform, the Hertie Foundation pursues approaches to change and transformation.

The Center of Neurology in figures

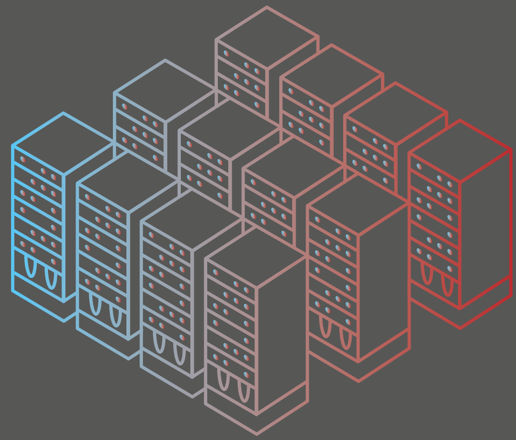
Performance indicators in 2020 and 2001

	2020	2001
Employees	427	120
Professors	21	5
Number of publications (with impact factor over 10)	255 (37)	123 (not comparable)
Total publications with high impact factors	1724.5	not comparable
Income from third-party funding in million euros	10	1.7

In 2020



Astounding facts

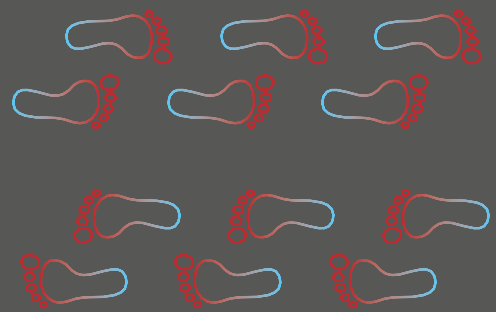


1. Around 400 terabytes of data is stored on the Hertie Institute's servers

2. Every week, around 1000 m³ of liquid nitrogen are delivered to the Hertie Institute for freezing biological and medical material at -180°C.

3. Since 1999, 600 patients at the Clinic of Neurology have been treated with a brain pacemaker.

4. The biobank of the Center of Neurology contains almost 450,000 samples from around 25,000 patients.



5. A nurse takes an average of 8,000 to 10,000 steps during an 8-hour shift.

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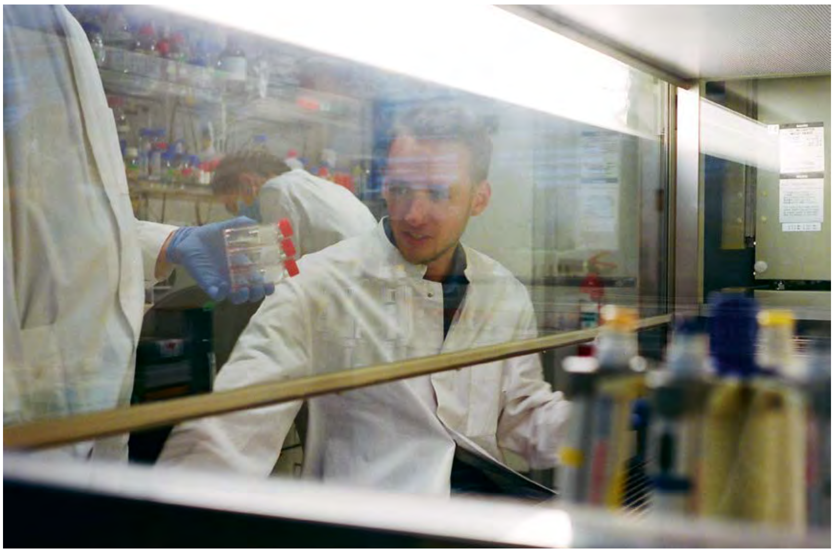

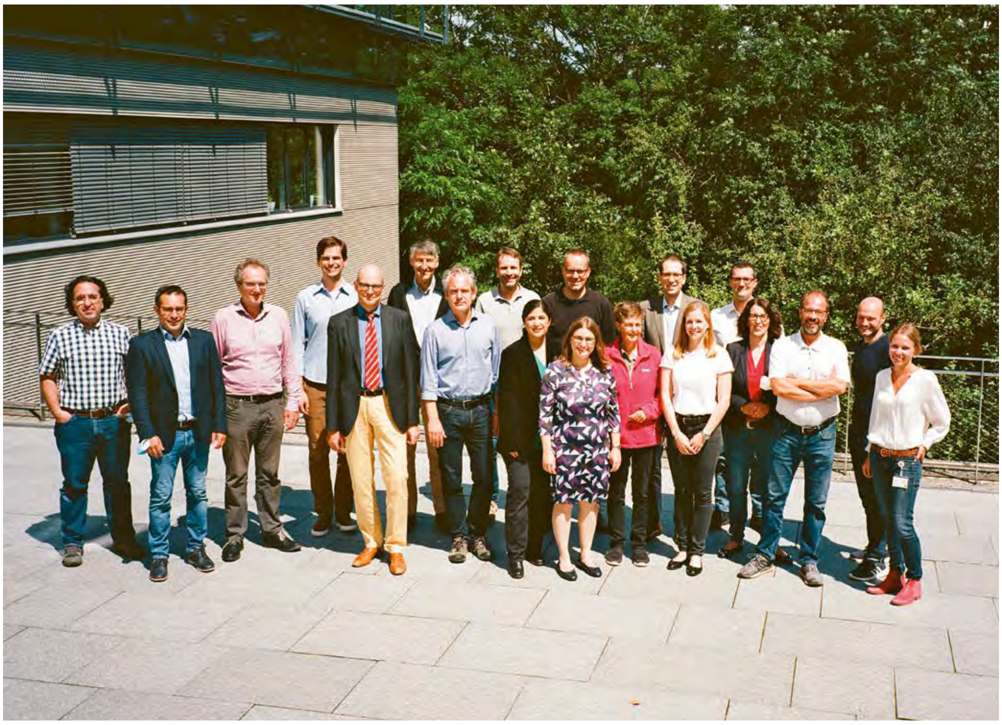

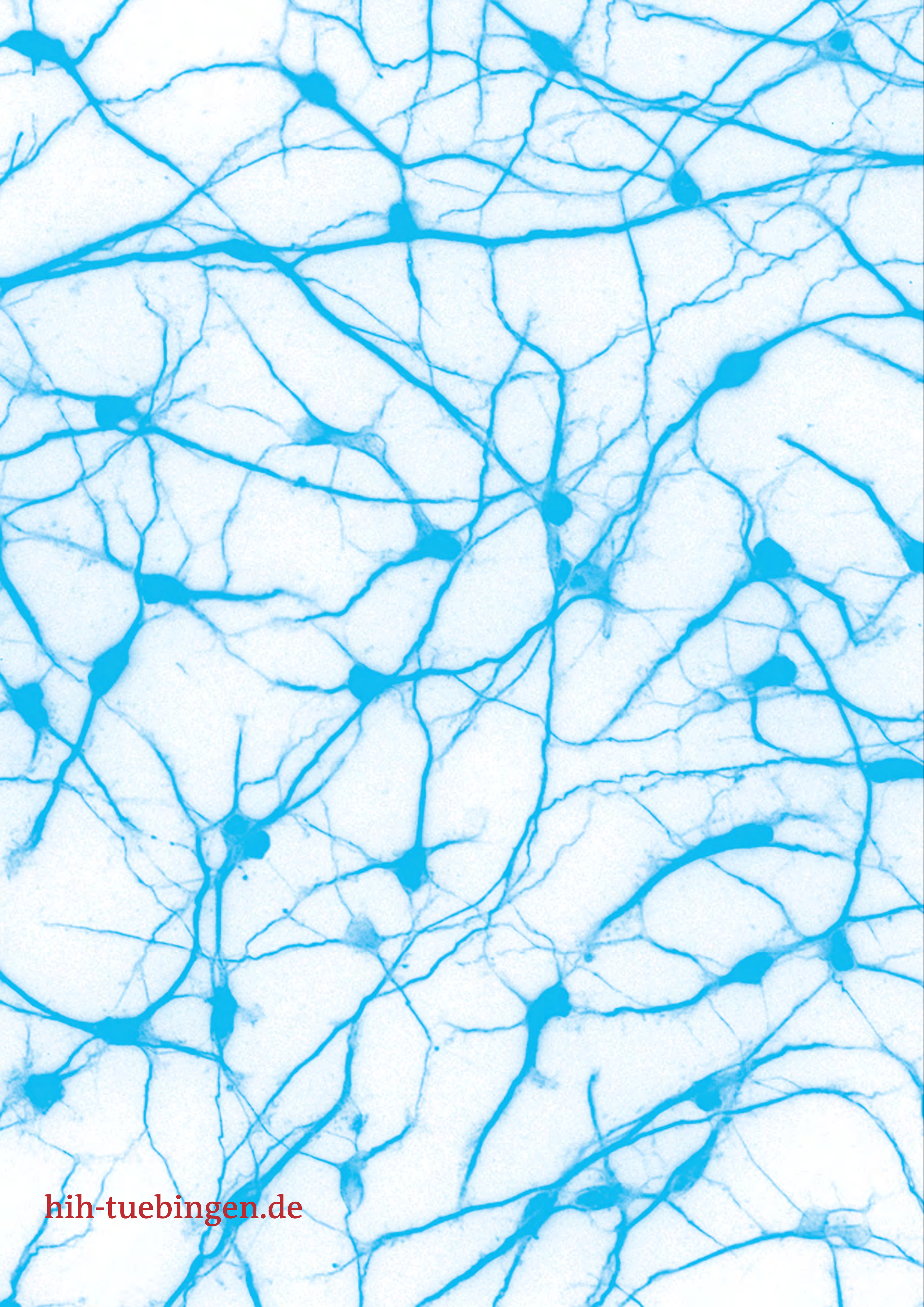

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