



JARA-BRAIN – Combined Expertise

AN INITIATIVE OF

RWTHAACHEN
UNIVERSITY

 **JÜLICH**
FORSCHUNGSZENTRUM

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Welcome

When the Jülich Aachen Research Alliance (JARA) was founded on August 6, 2007, it changed the nature of the close working relationship between RWTH Aachen University and Forschungszentrum Jülich. Whereas scientists and researchers had previously decided to embark on collaborative research projects on a case-by-case basis, this new partnership created a permanent management and organizational structure to strategically coordinate work in specific subject areas. This allowed us to do away with institutional hurdles and to work together more effectively on tackling the major challenges facing our society. It has also increased our ability to attract funding and the finest researchers at an international level.

The merger focused on research fields that would effectively complement the strengths of both institutions. These are all subject areas that are of key importance in providing solutions to future challenges. JARA now comprises four sections, which focus on the issues of future energy supply (JARA-ENERGY), simulation sciences (JARA-SIM), the future of information technology (JARA-FIT) and the challenge of a foreseeable increase in psychological and neurological disorders (JARA-BRAIN).

JARA-BRAIN is effectively harnessing the opportunities offered by a combination of leading research in the field of basic neuroscientific research and the specific challenges of providing pre-



The two JARA presidents: Prof. Dr. Achim Bachem, Chairman of the Board of Directors at Forschungszentrum Jülich (right) and Prof. Dr.-Ing. Ernst Schmachtenberg, Rector of RWTH Aachen University.

mium care in a university hospital. The idea of translational research, which brings together basic research, clinical research, and clinical practice, provides the basis for successfully facing the challenges posed by the predicted increase in psychiatric and neurological disorders. This concept does not imply a one-way transfer of knowledge; rather, information flows to and from both institutions equally. JARA-BRAIN is testing this model through its “clinician scientists,” where physicians practice in a clinic while also benefiting from sufficient scope to carry out basic or

clinical research.

Today our new form of partnership is flourishing in all four sections, helping RWTH Aachen University and Forschungszentrum Jülich to grow together. The number of joint scientific publications – a clear indicator of success – has risen significantly, and the two institutions are increasingly organizing joint events for the scientific community and the general public.

We brought JARA into existence with ambitious plans, which were commended by the Excellence Initiative.

We implemented the fundamental el-

ements of this project in a short space of time. New positions were created for junior professors and new research fields were established with help from projects supported by Seed Funds. The fact that JARA is already attracting outstanding young scientists to the region shows us that the alliance is on the right path to achieving its goals.

Happy reading!

Prof. Dr. Achim Bachem,
Chairman of the Board of Directors
at Forschungszentrum Jülich

Prof. Dr.-Ing. Ernst Schmachtenberg,
Rector of RWTH Aachen University

JARA-BRAIN: Research Alliance Explores the Brain

The brain enables us to feel, think, and act. Scientists at RWTH Aachen University and Forschungszentrum Jülich explore the mysteries of the human control center in JARA-BRAIN. This unique, national brain research collaboration between a university and a major research center aims to achieve a greater understanding of the structure and functioning of the brain – and thus to help millions of people.

Psychiatric and neurological disorders are increasing around the world. Depression, anxiety, addiction, and dementia are now wide-spread mental problems. According to the World Health Organization (WHO), in Europe alone over five million people suffer from dementia and more than 1.2 million have Parkinson's disease. In addition, one in five people are expected to become mentally ill at least once in their lives. These disorders often bring about drastic changes and burdens for the individuals and their families, since patients can no longer cope with everyday life on their own. There is often a lack of understanding of these disorders in society, which

can result in patients suffering from loneliness and social isolation. Mental and neurological disorders are also a sociopolitical challenge. Demographic changes will mean that the proportion of neurodegenerative diseases like Alzheimer's and Parkinson's will increase dramatically worldwide.

Brain research is a sociopolitical challenge of the 21st century

Today, 1.2 million people suffer from dementia in Germany alone, and the number is growing. Experts estimate that it will reach around four million by 2050. The forecasts are similar in other industrialized countries. This

has huge financial implications for the health systems and economies of these countries.

Modern brain research is, in this context, one of the central sociopolitical challenges of the 21st century. New strategies for diagnosis and treatment of mental and neurological disorders must be developed to permanently stabilize the quality of life of individuals and the health systems of modern industrial societies. The JARA-BRAIN research association brings together high-caliber scientists from RWTH Aachen University and Forschungszentrum Jülich to address this pressing issue for the future. In August 2007, previous individ-



Psychiatric and neurological disorders are increasing worldwide. Depression, anxiety, addiction, and dementia are now common mental illnesses. One in five people is expected to be mentally ill at least once in their life.

ual collaborations between the two research institutes were replaced by a strategic partnership, the Jülich Aachen Research Alliance (JARA). It institutionalized and strengthened collaboration between RWTH Aachen University and Forschungszentrum Jülich (part of the Helmholtz Association) in various scientific fields under a cooperative management. Two additional areas of research were created at the same time as JARA-BRAIN: JARA-FIT, with a research focus on information technology, and JARA-SIM, with a simulation science focus. In 2008, an alliance focusing on energy was added (JARA-ENERGY).

The Jülich Aachen Research Alliance (JARA)

RWTH Aachen University and Forschungszentrum Jülich are tackling the central sociopolitical challenges of the future. In August 2007, they established the strategic partnership Jülich Aachen Research Alliance (JARA). This research collaboration supersedes previous research collaborations. Whereas scientists had previously decided to embark on collaborative research projects on a case-by-case basis, this new partnership created a permanent management and organizational structure

to strategically coordinate work. JARA has institutionalized and strengthened the cooperation between RWTH Aachen University and Forschungszentrum Jülich in four scientific areas under joint management. The alliances jointly define research goals, establish scientific strategies and appoint and train academic staff. In addition to JARA-BRAIN, there are three other alliances: JARA-FIT, with a focus on information technology, JARA-SIM, with a focus on simulation science, and JARA-ENERGY.



The JARA-BRAIN research spectrum ranges from new measuring techniques and procedures to basic research and clinical brain research in primary progressive aphasia or Attention-Deficit and Hyperactivity Disorder (ADHD) in children.

Prof. Dr. Beate Herpertz-Dahlmann

“Child and adolescent psychiatry benefits greatly from JARA-BRAIN. On the one hand, from the targeted promotion of interdisciplinary exchange in the field of neuroscience, and on the other, from the technical and methodological expertise that exists at Forschungszentrum Jülich. The latter allows the development of new imaging methods for children, a process which has to work with shorter measurement times. I particularly appreciate the establishment of the junior professorship for translational brain research at the Department of Child and Adolescent Psychiatry, as this outstandingly connects clinical work and research. Our own contribution to JARA-BRAIN is the integration of the developmental aspect, which is of great importance in understanding brain function.”



Prof. Dr. Beate Herpertz-Dahlmann, head of the Department for Child and Adolescent Psychiatry

and Psychotherapy at University Hospital Aachen

JARA-BRAIN brings together scientists from more than 20 clinical departments and institutes at Aachen's elite university, and from five institutes at Forschungszentrum Jülich to perform research into how brain diseases can be better diagnosed and treated in the future. Their work covers the entire chain of scientific inquiry in neurobiological research, from basic science up to the clinically oriented development of new therapies. They ask questions such as: How is our brain structured? What neurochemical processes occur in its neurons and synapses? Which brain areas are altered in children with Attention-Deficit Hyperactivity Disorder (ADHD), or in a patient with Parkinson's disease? How do certain antipsychotics affect schizophrenia? The aim is to improve, based on new methods and findings, the prevention, diagnosis and treatment of brain disorders.

The benefits of the alliance are clear. “JARA-BRAIN combines the medical expertise of clinical neuroscience at University Hospital Aachen with the basic research, methodological expertise and out-

standing technical infrastructure at the Institute of Neuroscience and Medicine of Forschungszentrum Jülich,” explains Prof. Dr. Dr. Frank Schneider, head of the Department of Psychiatry and Psychotherapy at University Hospital Aachen.

Scientists obtain a new quality of brain images

Jülich scientists were responsible for developing the “9komma4” device, a unique hybrid system which combines the possibilities of positron emission tomography (PET) with those of magnetic resonance imaging (MRI). Scientists thus obtain a completely new quality of brain images. Prof. Dr. Karl Zilles, director of the Institute of Neuroscience and Medicine at Forschungszentrum Jülich, says, “Our common goal is to better understand the structure and function of the brain in healthy humans and in those suffering from diseases. A single institution cannot accomplish this complex research alone. Research centers, such as the one in Jülich, possess extremely elaborate, high-tech equipment and basic research competencies, but we lack the pa-

The JARA-BRAIN Aachen-Jülich leadership duo



“JARA-BRAIN combines the medical expertise of the clinical neurosciences at University Hospital Aachen with the methodological expertise and the outstanding technical infrastructure at the Institute for Neuroscience and Medicine at Forschungszentrum Jülich.”

Prof. Dr. Frank Schneider,
JARA-BRAIN director and head of the Department of Psychiatry and Psychotherapy at University Hospital Aachen

“Our common goal is to better understand the structure and function of the brain in healthy humans and in those suffering from diseases. A single institution cannot accomplish this complex research task alone.”

Prof. Dr. Karl Zilles,
JARA-BRAIN director and head of the Institute for Neuroscience and Medicine at Forschungszentrum Jülich



Attention-Deficit and Hyperactivity Disorder (ADHD). One of the aims of JARA-BRAIN is to stimulate projects that are still in a very experimental and innovative stage. JARA-BRAIN general manager Volker Backes says, “In addition to following established scientific paths, we purposefully foster new approaches. Our goal is – to stick with the metaphor – to reap the richest harvest with the funds that we sow.”

tient contact and clinical experience which is important for many research approaches.” JARA-BRAIN is therefore headed by two directors, one from Aachen and one from Jülich.

JARA-BRAIN junior professors work as “clinician scientists” in Aachen and Jülich

The JARA-BRAIN cooperation not only has scientific research foci, but is also based on a specific organizational and structural approach. Personnel decisions, such as appointments, are made jointly. Thus, in the context of JARA-BRAIN, a new professorship, “Neurobehavioral Gender Studies,” was set up to study gender-specific influences in patient diagnosis and therapy. In addition, four junior professors serving as “clinician scientists” were appointed. “With ‘clinical researcher’ model, we support promising young scientists in their research activities. At the same time, each of the four professors also undertakes clinical tasks,” says Frank Schneider. The junior professors welcome the combination of clinical work and research, as well as having their own equipment and staff. “The JARA-

BRAIN junior professorship allows me to do independent scientific work under excellent conditions and to gain the necessary knowledge to become a specialist in my field,” says Prof. Dr. Florian Daniel Zepf, who works as an assistant physician and junior professor at the Department of Child and Adolescent Psychiatry at University Hospital Aachen. In order to initiate innovative research projects within the Jülich Aachen Research Alliance, a total of €2.55 million was allocated from the JARA Seed Funds. Scientists from all sections submitted project proposals for this funding.

JARA Seed Funds aim to stimulate innovative projects

Eleven JARA-BRAIN projects are currently receiving support from the Seed Funds. They cover a wide range of topics, from new measuring techniques and procedures (real-time fMRI, neurofeedback platform development for JARA-BRAIN, and distortion-free diffusion tensor imaging and application) to basic research (in vivo characterization of brain networks) and clinical brain research in primary progressive aphasia or child

Prof. Dr. Jörg B. Schulz

“Because of increasing life expectancy, neurological disorders will increase dramatically in the next 10 to 20 years. In order to improve the quality of life of those affected and to maintain the stability of healthcare costs, medical research needs to work quickly to develop new diagnostic methods and therapies. JARA-BRAIN is an excellent research setting. Aachen and Jülich biologists, neurologists, psychiatrists, and psychologists conduct interdisciplinary research into the neurobiological causes of Parkinson’s disease, dementia, and other neurological disorders. We profit from the outstanding technical equipment at University Hospital Aachen and Forschungszentrum Jülich.”



Prof. Dr. Jörg B. Schulz, head of the Neurology Clinic at University Hospital Aachen



Up to now, the influence of gender in the diagnosis and treatment of patients was too often overlooked in the neurosciences. RWTH Aachen University therefore established a new research field in neuropsychological gender research.

Typical Man? - Typical Woman?

According to widespread opinion women have more empathy than men, but scientific evidence proves that both sexes experience emotional events with equal intensity. The small but subtle difference lies deeper, in the different processing mechanisms in the brain.

“Imagine you lost a valuable memento. How does it make you feel?” In an empathy study at the Department of Psychiatry and Psychotherapy at University Hospital Aachen, men and women answered questions like these by pressing a button on a scale. Instead of sitting on a desk chair, however, the subjects in the study were in an MRI scanner. It was then possible for the scientific team, led by Prof. Dr. Ute Habel, to observe the decision-making network in the subjects brains. Interestingly, they found that the men showed the same intensity of empathy as the women. However, the way their brains processed emotions differed strikingly. “The emotional exercise showed that women exhibited significantly more brain activity than men in, for example, the frontal, cingulate, and insular cortex and in the hippocampus,” says the psychologist who heads the Neuropsychological Gender Studies research group in the Department

of Psychiatry and Psychotherapy at University Hospital Aachen. In contrast, men showed no stronger activity in any regions of the brain during the exercise. Although scientists have yet to fully understand why brain activity varies by gender, it is certainly the result of an interaction of environmental and biological factors.

Socialization processes can affect brain activation

The recently established Neuropsychological Gender Studies research group extends the range of JARA-BRAIN’s work. “In the neurosciences, possible effects and influences of gender have seldom been considered in the diagnosis and treatment of patients,” says Ute Habel. However, different socialization processes or physical differences, such as hormone status, can affect brain activation and processing of information. Thus, these and other studies also

showed that women recognize emotions in the follicular phase better than in other phases of their menstrual cycle. In parallel, fMRI identified significantly increased amygdala activity during the follicular phase. “This sensitivity can be understood from an evolutionary perspective,” says Ute Habel. “The increased social attention may facilitate the choice of a partner in the fertile phase.” What positive effects do these gender differences bring to the treatment of psychiatric disorders today? “We conduct basic research. In most psychiatric disorders gender ratios are unequal. Hence, the more we know about the processes in the brain, the easier it will be to develop more individualized and successful new therapies,” says Ute Habel.



IRTG scientists use modern imaging techniques.



Engaged in transatlantic cooperation: IRTG coordinator Prof. Dr. Ute Habel.

Transatlantic Alliance

Scientific progress thrives on well-trained talent. The International Research Training Group 1328 “Schizophrenia and Autism” is an excellent example of this. JARA-BRAIN scientists from Aachen and Jülich conduct joint research with colleagues from the prestigious University of Pennsylvania in the U.S. IRTG coordinator, Prof. Dr. Ute Habel, introduces the top-class training program.

What are the outstanding features of the IRTG training program?

Prof. Habel: First and foremost, the IRTG training program is characterized by its strong structure, something which is still rather rare in doctoral training in Germany. It also offers an interdisciplinary and international focus. As an international graduate school, it offers students the opportunity to research for about half a year at a prestigious American university. We cooperate with the University of Pennsylvania, which is one of eight Ivy League universities. This close collaboration is also reflected in our dual staff leadership. We have two IRTG spokesmen: Prof. Dr. Frank Schneider from the RWTH side, and Prof. Dr. Ruben C. Gur of the University of Pennsylvania. Finally, the IRTG is the only German graduate school using imaging techniques to investigate schizophrenia, autism, and their neurological basis.

What are the main structural elements of the training?

Prof. Habel: The students have both an American and a German supervisor, who closely and regularly oversee their doctoral thesis. One way in which this happens is through our annual winter school, which is jointly organized by the two universities and alternates between the U.S. and Germany. We also have a number of other joint events, such as our visiting professor program. We invite national and international experts to participate, allowing the fellows to build an international network early in their research career. Furthermore, we have developed a supervision agreement that specifies the details of the doctoral training. Regular student presentations of projects, a series of methodological and clinical workshops, and transferable skills training complete the training concept.

Professor Habel, what disciplines does IRTG represent?

Prof. Habel: The IRTG is largely interdisciplinary. It includes physicians, psychologists, biologists, physicists, computer scientists, neuroscientists, lawyers, and linguists. Most of them work in the narrow thematic area of the IRTG – emotions, schizophrenia, autism, and modern imaging techniques. The scientists in Germany cooperate very closely with those across the Atlantic. At the Institute for Computer Science, for example, American students work with RWTH students to develop shared computerized test material for our studies in functional magnetic resonance imaging (fMRI). Not only do IRTG students benefit from the program, but so do other students and staff of RWTH Aachen University and the University of Pennsylvania.

Ambitious Young Academics

Freedom of research, and clinical training and activities all rolled into one: For four promising young scientists, this is not wishful thinking but reality. The JARA-BRAIN junior professors conduct research and work in parallel at University Hospital Aachen and Forschungszentrum Jülich.

Prof. Dr. Kathrin Reetz

JARA-BRAIN junior professor at the Department of Neurology, University Hospital Aachen and Forschungszentrum Jülich (Institute of Neuroscience and Medicine)

“The Jülich Aachen Research Alliance offers me, as a clinician scientist, a unique combination of clinical practice, research, and the highest technical and methodological expertise.”

Professional background

Studies

1997 - 2004

Medicine, University of Cologne, Germany

Scientific Employment

February 2009 - present

JARA-BRAIN junior professor at the Department of Neurology, RWTH Aachen and Forschungszentrum Jülich, Germany

October 2007 - January 2009

Research fellow at the Center for Neurosciences, Feinstein Institute for Medical Research, USA (Prof. Dr. D. Eidelberg)

January - December 2006

Research fellow at the Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany (Prof. Dr. C. Büchel; principal investigators: Prof. Dr. F. Binkofski and Prof. Dr. H. R. Siebner)

October 2004 - September 2007

Member of the research association Neurolmage Nord, University of Lübeck, Germany (Prof. Dr. F. Binkofski)

Scholarships

January 2008 - February 2009

Research grant (FUL) from the Medical Faculty, University of Lübeck, Germany

January 2008 - February 2009

Research grant from the German Research Foundation (DFG), Germany

August 2005 - December 2006

Research grant (FUL) from the Medical Faculty, University of Lübeck, Germany

Clinical Employment

February 2009 - present

Assistant physician at the Department of Neurology, University Hospital Aachen, Germany (Prof. Dr. J. B. Schulz)

July 2004 - September 2007

Assistant physician at the Department of Neurology, University of Lübeck, Germany (Prof. Dr. D. Kömpf)

The research focus of Kathrin Reetz's JARA-BRAIN working group is to identify specific imaging markers for neurodegenerative diseases through innovative imaging techniques, and to evaluate them clinically in the context of



neuropsychiatric and genetic/chemical laboratory parameters. The polymodal approach may offer new opportunities for a better pathophysiological understanding and prediction of the risks and courses of individual diseases. The research group has a particular interest in presymptomatic and early stages of neurodegenerative diseases. Current research interests mainly include neurodegenerative disorders such as Parkinson's disease, Huntington's disease, spinocerebellar ataxias, and dementia.

Prof. Dr. Ingo Vernaleken

JARA-BRAIN junior professor at the Department of Psychiatry and Psychotherapy, University Hospital Aachen and Forschungszentrum Jülich (Institute of Neuroscience and Medicine)

“As a clinician scientist, I have enough resources at JARA-BRAIN to link clinical and research practices and can thereby carry out methodologically complex studies in direct contact with patients.”

Professional Background

Studies

1990 - 1997

Human Medicine, Saarland University, Homburg (Saar), Germany

Scientific Employment

January 2009 - present

JARA-BRAIN junior professor at the Department of Psychiatry and Psychotherapy, RWTH Aachen and Forschungszentrum Jülich, Germany

1998 - 2005

Research fellow at the Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Germany

Clinical Employment

February 2005 - present

Senior physician at the Department of Psychiatry and Psychotherapy, University Hospital Aachen, Germany (Prof. Dr. Dr. Frank Schneider)

2001 - 2002

Assistant physician at the Department of Neurology, University Medical Center Mainz, Germany (Prof. Dr. Otto Benkert and Prof. Dr. Lutz G. Schmidt)

Awards

Emanuela Dalla Vecchia Award, 2009, for research into depression in mental illness

Bursary Young Scientist Award at the meeting “Neuroreceptor Mapping 2009”

Organon Poster Prize, 1999

Beneath mental illnesses, healthy behaviors, thoughts, and experiences, lie highly complex neurobiological processes. These cannot be understood without a basic knowledge of the processes in biological information transfer. The aim of Ingo Vernaleken’s working group is to understand, with the help of molecular imaging, these processes, and to make the findings available for improved diagnosis and treatment of mental disorders. Positron emission tomography (PET) makes brain structures and their changes visible. Targets can be receptors for neurotransmitters, their transporters or synthetic enzymes. Some of the research areas that the working group focus on are: disturbance of dopaminergic transmis-



sion in the context of schizophrenia and mood disorders, early detection of psychotic disorders using PET, effects of antipsychotics or antidepressants on the dopamine system, influence of dependence-producing substances on the dopamine system, genetic polymorphisms and their relationship with the neurotransmitter systems, and the analysis of neurobiological processes in the context of deep brain stimulation for treatment-resistant mental disorders (e.g. Tourette’s syndrome).

Prof. Dr. Simon Eickhoff

JARA-BRAIN junior professor at the Department of Psychiatry and Psychotherapy, University Hospital Aachen and Forschungszentrum Jülich (Institute of Neuroscience and Medicine)

“By combining modern imaging techniques with mathematical models of effective connectivity, we can, in the context of JARA-BRAIN, track and analyze changes in network functions, such as schizophrenia or depression.”

Professional Background

Studies

1999 - 2006

Human Medicine at the RWTH Aachen, Germany

Studied abroad in Sydney (Australia), and Sheffield and London (U.K.)

Scientific Employment

January 2009 - present

JARA-BRAIN junior professor at the Department of Psychiatry and Psychotherapy, RWTH Aachen and Forschungszentrum Jülich, Germany

May 2006 - December 2008

Research fellow at the Department of Neuroscience and Medicine, Forschungszentrum Jülich, Germany (Prof. Dr. Karl Zilles)

Clinical Employment

January 2009 - present

Assistant physician at the Department of Psychiatry and Psychotherapy, University Hospital Aachen (Prof. Dr. Dr. Frank Schneider)

December 2007 - present

Visiting lecturer, Academic Department of Psychiatry, University of Sheffield, U.K. (Prof. Dr. Peter Woodruff)

Awards

Forschungsförderpreis for “Imaging in Psychiatry and Psychotherapy”, November 2009

Promotionspreis, July 2008, from the Heinrich Heine University, Düsseldorf, Germany, for the best medical dissertation of the year 2006/2007

Scholarship from the German National Academic Foundation, 2000 - 2006

A detailed understanding of the principles of the organization of the human brain is necessary to better treat and diagnose psychiatric disorders such as schizophrenia, depression, and dementia. The aim of the working group “Translational Research on the brain: Neuropsychiatric Systems Biology” is to contribute towards such an understanding by combining basic neuroscientific research with clinical questions. How are the processes that underlie motor, cognitive, and emotional capabilities organized in the brain? How do the brain regions involved interact with one another to form functional networks? How are regional functions, or the in-



tegration of various partial functions, affected in patients with psychiatric or neurological disorders? Current externally funded projects are examining the basics of action control in the human brain at a systems level. In addition, procedures for the implementation of quantitative meta-analysis of functional imaging studies are being developed and implemented in cooperation with the University of Texas. The aim is to integrate the diverse, objectified results of functional imaging studies to obtain valid statements about physiological and pathological activity.

Junior Professors at JARA-BRAIN

Prof. Dr. Florian Daniel Zepf



and young people with ADHD are treated with the help of EEG-based neurofeedback. Through EEG neurofeedback patients learn to positively influence their own brain activity to help reduce their symptoms, such as concentration problems. Furthermore, the group examines neurochemical correlates of various processes in the brain of patients with disorders like ADHD.

JARA-BRAIN junior professor at the Department of Child and Adolescent Psychiatry, University Hospital Aachen and Forschungszentrum Jülich (Institute of Neuroscience and Medicine)

„The JARA-BRAIN junior professorship allows me to do independent scientific work under excellent conditions. At the same time, I can continue my training as a specialist.”

Professional Background

Studies

1999 - 2006

Human Medicine at J.W. Goethe University, Frankfurt, Germany

Studied abroad at the University of Sydney, Australia

Scientific Employment

April 2009 - present

JARA-BRAIN junior professor at the Department of Child and Adolescent Psychiatry and Psychotherapy, RWTH Aachen and Forschungszentrum Jülich, Germany

Clinical Employment

April 2009 - present

Assistant physician at the Department of Child and Adolescent Psychiatry and Psychotherapy at the University Hospital Aachen, Germany

2006 - 2009

Assistant physician at the Department of Child and Adolescent Psychiatry and Psychotherapy, J.W. Goethe University, Frankfurt, Germany (Prof. Dr. F. Poustka)

Awards

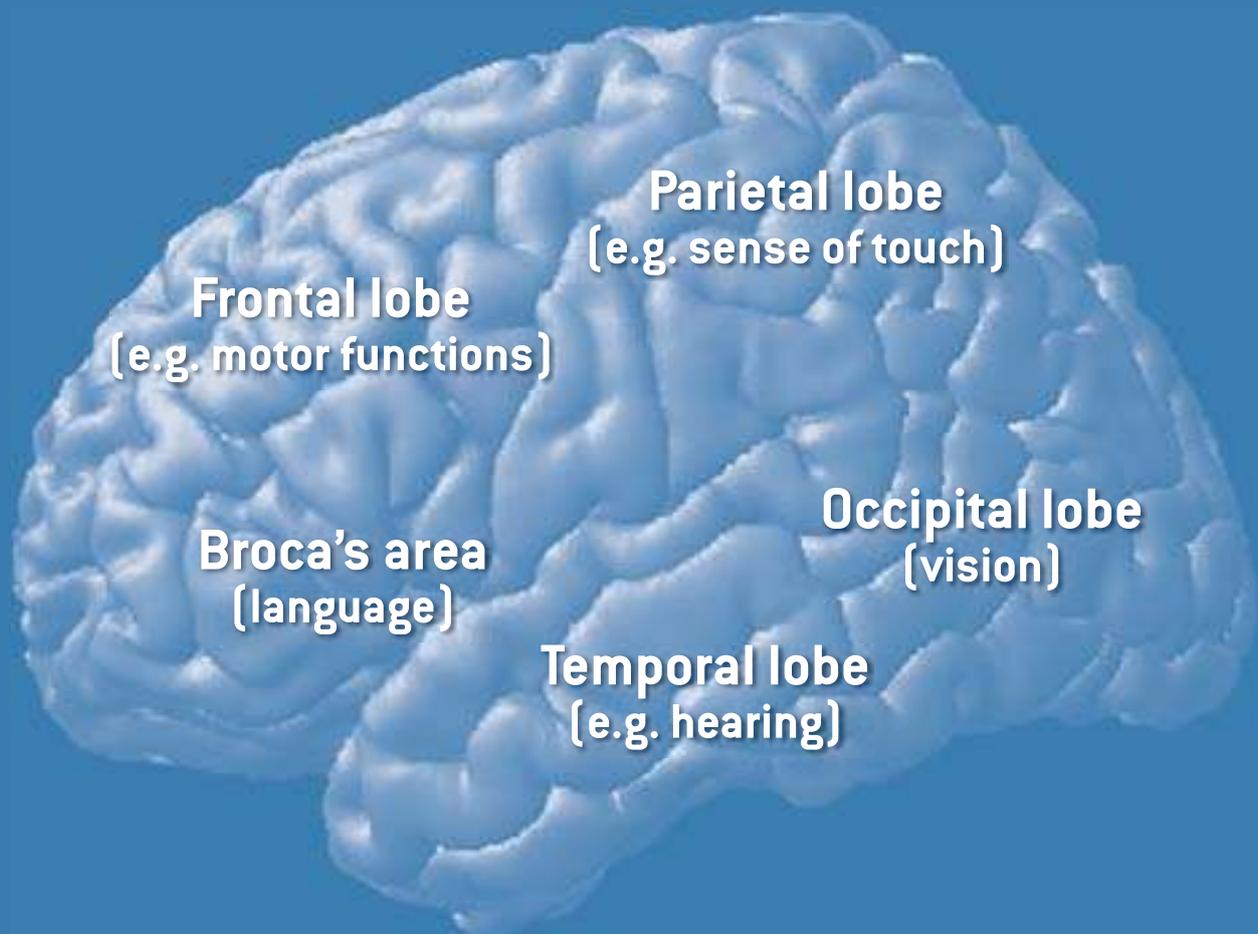
Young Minds in Psychiatry Award, 2007, from the American Psychiatric Association (APA/APIRE)

D.J. Cohen Fellowship Award, 2006, from the International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP)

Young Scientist Award, 2005, from the World Federation of Societies of Biological Psychiatry (WFSBP)

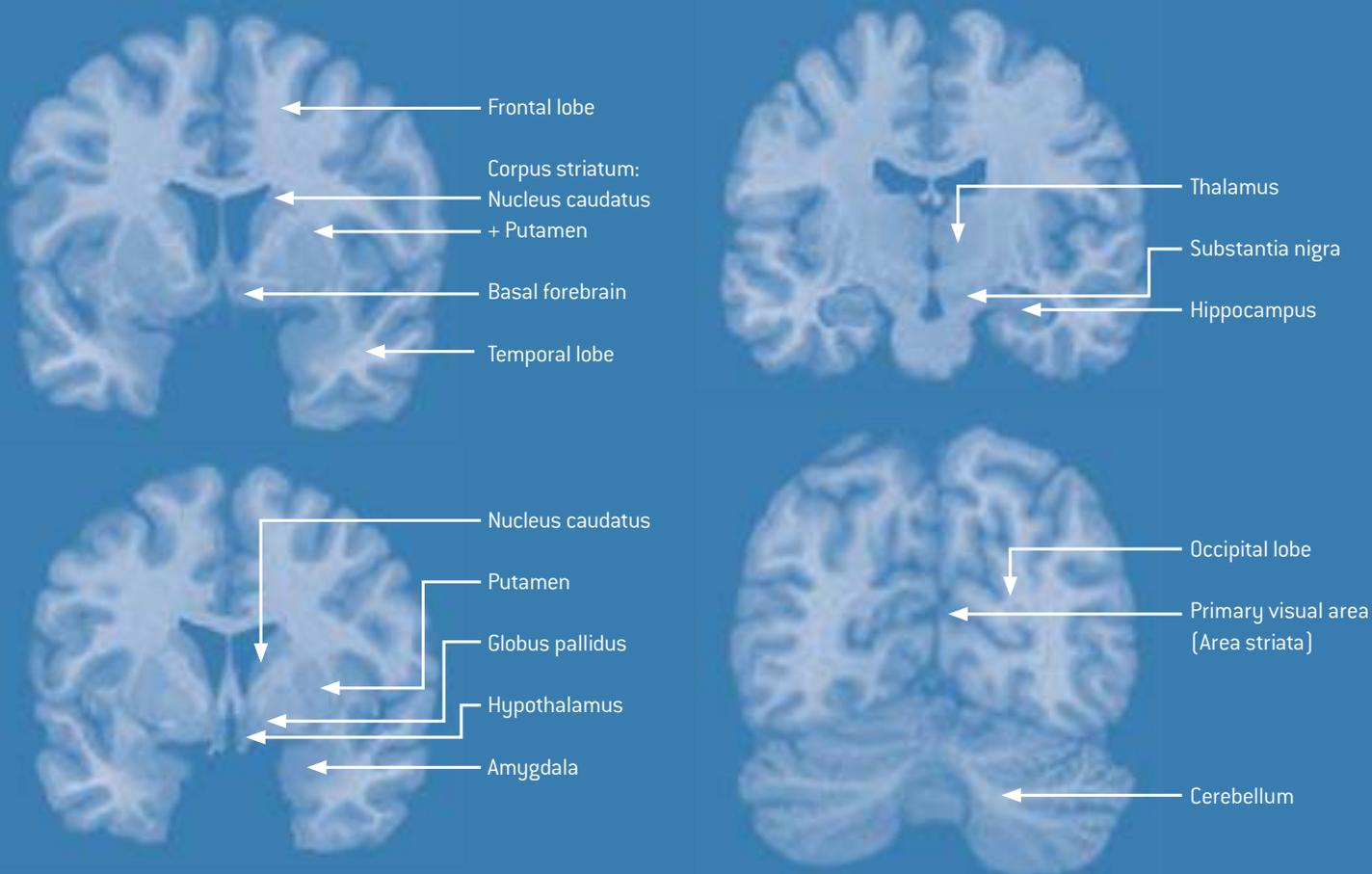
Florian Zepf's working group investigates the developmental aspects of psychiatric disorders in children and young people. Methods used include structural and functional imaging, neurochemistry and electrophysiology, and molecular genetics. Cognitive and emotional processes are a particular focus, as are their normal and altered development in the context of mental disorders such as Attention-Deficit Hyperactivity Disorder (ADHD).

Various research projects analyze both neurochemical and electrophysiological processes in order to develop new therapies for young patients. Children



The human control center

An image of the brain and its areas

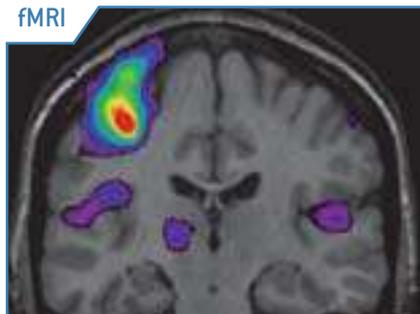


MRI



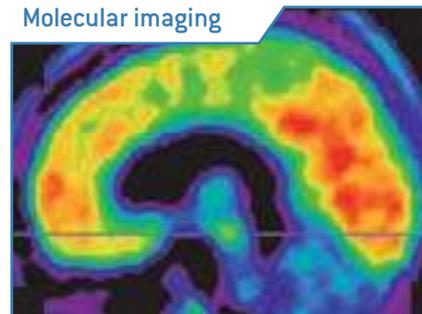
Structural magnetic resonance imaging

fMRI



Functional magnetic resonance imaging: active regions for perception of touch

Molecular imaging



Analysis of serotonin – 5HT2A receptors with positron emission tomography (PET)



Schizophrenia patients often suffer from hallucinations like hearing voices. With neurofeedback, they learn to actively influence the faulty activations in certain areas of the brain.

Training the Brain in MRI

In the future it may be possible to treat depression and hallucinations with magnetic resonance imaging exercises. Patients learn to regulate specific brain areas in order to control their symptoms.

Just as targeted strength training helps with back problems, brain training with MRI could soon help with depression, Parkinson's or schizophrenia. This is made possible with real-time functional magnetic resonance imaging (real-time fMRI), which shows the brain regions that are currently active. "Imaging techniques have evolved dramatically in recent years," says JARA-BRAIN scientist Prof. Dr. Klaus Mathiak. MRI scanners now allow scientists to actually watch the brain at work. If the subject can solve math problems by pressing a button or joystick, or assess emotions from pictures, doctors and scientists can observe the processes in the brain. It is then possible to compare brain activity in healthy and sick people and to gain further insights into mental disorders.

Real-time fMRI has opened up many new fields of research and therapeutic opportunities involving mental and neurological disorders. For instance, some patients with schizophrenia suffer from hallucinations, such as hearing voices.

Neurofeedback turns psychiatrists into "brain coaches"

"We know that one region of the brain to control language is Broca's area," explains Prof. Mathiak. "If I imagine that I am speaking with someone, I can successfully activate this part of my cerebral cortex. If the patient now learns to regulate the dysfunctional activation – that is, the processes in his or her brain that produce the voices – it could have an effect on the actual symptoms." Prof. Mathiak, a mathematician, psychiatrist and psychotherapist, co-

ordinates, among other things, a study in which patients practice this method in MRI scanners at the Department of Psychiatry and Psychotherapy at University Hospital Aachen.

Patients in this experiment are assisted by a doctor who, acting as a kind of "brain coach," provides immediate feedback (neurofeedback) and specifies what must be done to optimize the training of the affected brain areas. This is still basic research but many fields of clinical application are conceivable in the future. "Currently, patients with hallucinations and depression are treated with medication, but this affects the whole brain," says the neurobiologist. "In contrast, patients could use real-time fMRI to specifically target the affected brain areas and thus alter their symptoms." Klaus Mathiak collaborates closely with Jülich physicist Prof. Dr. N. Jon Shah and his staff



Prof. Dr. N. Jon Shah, head of the “Magnetic Resonance Physics” research group in Jülich, developed the 9.4 Tesla hybrid device in collaboration with industry partners.

to continuously improve the hardware and software in the field of imaging techniques. Supported by a JARA Seed Fund, the two scientists and their team are developing a common platform for the MRI equipment at University Hospital Aachen and Forschungszentrum Jülich. The project is currently being expanded in cooperation with the University of Pennsylvania as part of the International Research Training Group 1328 (IRTG 1328) to allow clinical trials on 3 Tesla scanners, experimental applications at 7 Tesla, and for future applications in the 9.4 PET MR hybrid system. This standardized platform allows researchers to test the latest technical developments directly in the clinical setting and to conduct larger patient studies.

Unique Worldwide:

The new 9.4 Tesla hybrid device in Jülich

Basic research and medical applications are inextricably linked with technical and methodological developments. JARA-BRAIN scientists benefit from the outstanding technical infrastructure – high-field MR equipment, hybrid scanners, and PET cameras – at University Hospital Aachen and at Forschungszentrum Jülich.

The newest Jülich technology giant weighs in at 60 tons and requires its own building. Prof. Dr. N. Jon Shah, director of the Jülich “Magnetic Resonance Physics” working group at the Institute of Neurosciences and Biophysics, and professor of brain imaging physics at the Department of Neurology at University Hospital Aachen, developed the MRI scanner in cooperation with industry partners. The 9.4

Tesla device builds up a magnetic field that is 200,000 times stronger than the Earth’s. This method reduces measurement time and improves spatial resolution and image contrast. JARA-BRAIN scientists in Aachen and Jülich are currently working with 3 Tesla equipment, but the unique research unit can do more: In addition to the 9.4 Tesla MRI scanner, the hybrid also has a positron emission tomography (PET) scanner. This maps metabolism in brain cells with the help of weakly radioactive substances, allowing scientists to use a single device to pinpoint to the exact millimeter diseased tissue and disturbances in the metabolism of the brain structure.

Exploring the Brain

Neuroscientist Prof. Dr. Katrin Amunts and her team go on a unique research expedition to create a three-dimensional atlas of the brain.

At first glance, the “route” is limited. The human brain contains about 1,500 cm³ of brain tissue, and the terrain is quite something. Neuroscientist Prof. Dr. Katrin Amunts explains that her goal “is to develop a realistic, three-dimensional computer brain model based on structural, cytoarchitectonic, genetic, and molecular characteristics.”

As part of this project, scientists at Forschungszentrum Jülich are examining many thousands of histological brain sections. The sections are analyzed using modern scanning microscopes and image analysis methods. Then the cellular architecture are statistically analyzed and digitally reconstructed in 3-D. With her colleague, Prof. Dr. Karl Zilles, and a large team of medical doctors, physicists, biologists, mathematicians and graduate students, Katrin Amunts is developing a unique brain atlas that will gradually replace Brodmann’s map from 1909. “The psychiatrist and anatomist Korbinian Brodmann mapped the cerebral cortex and divided it into about 50 areas. He not only created a cytoarchi-

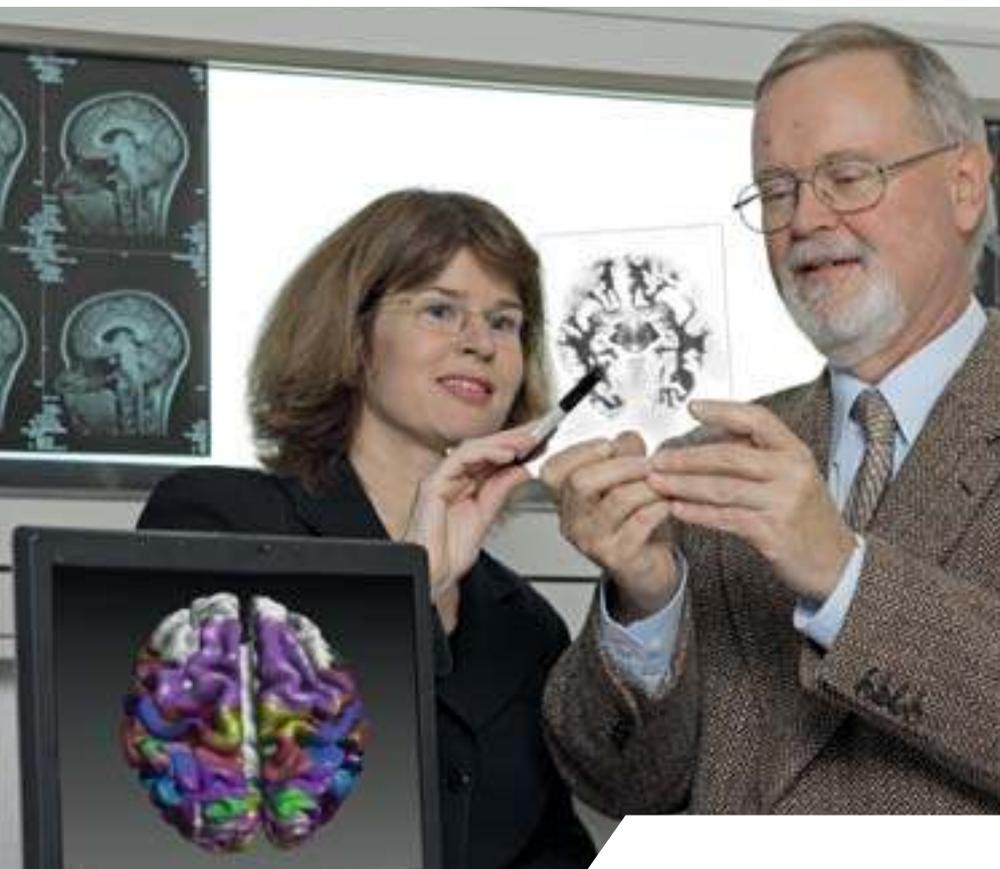
tectonic map, but also provided the basis for later comparative neuro-anatomical investigations. Brodmann was convinced that each brain area is responsible for a specific function, an assumption that could only be proven for a small fraction of the areas with the resources available at that time,” says Katrin Amunts, director of the Institute of Neuroscience and Medicine (INM-1) at Forschungszentrum Jülich, and professor of structural-functional brain mapping at the Department of Psychiatry and Psychotherapy at RWTH Aachen University.

Although Brodmann’s discovery was groundbreaking, the hundred-year-old map is merely a schematic drawing, not the three-dimensional record that is needed today as a basis for comparison in modern imaging studies to assign patient data to the microscopic structures of the brain. “We need to understand the ‘healthy’ brain before we can take the next step and distinguish differences in people suffering from neurological or psychiatric disorders,” explains Katrin Amunts.

Although only about 60 percent of the brain is mapped, the 3-D model from Jülich is already more complex than the Brodmann map. There are several reasons for this: Katrin Amunts and her interdisciplinary team analyze inter-individual differences in brain structure, then register their inter-individual variability; they not only map the cerebral cortex, but also nuclei deep in the brain. “The areas of the cortex do not operate in isolation like islands. Rather, they form networks and cooperate with the subcortical nuclei,” she explains. The 3-D brain model continues to develop with each newly defined area. The procedure is very time-consuming, as a scientist needs about a year to analyze and map a new area.

Different areas displayed as probability maps

The computer images of brain maps from Jülich are surprisingly colorful. The scientists display the different areas of the brain as probability maps, in which different probabilities are displayed in different colors. Orange and



For over ten years, Prof. Dr. Katrin Amunts (shown with JARA-BRAIN director, Prof. Dr. Karl Zilles), has been working on brain mapping. It will take several more years until the entire brain atlas is completed. The process is extremely time-consuming as it takes one scientist about a year to analyze and map a new area.

red indicate that the probability of a particular brain area being located at that point is 80 percent or higher. Decreasing probabilities are highlighted in green or blue. These two colors indicate that the variability of the position of a certain area in different brains is particularly high, while red indicates low variability.

With the 3-D brain modell scientists can observe the dynamics of volume reduction in the brain

Several clinical projects involving neurodegenerative diseases are currently using this mapping. For example, scientists from Jülich and Aachen are examining patients with Alzheimer's disease and primary progressive aphasia (PPA) to establish the brain regions in which volume reduction is

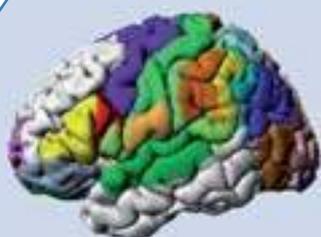
particularly intense. With the 3-D brain model and sophisticated mathematical procedures they can observe the dynamics of these processes in the brain and measure them over time. "The initial results show that the pattern of morphological changes and their dynamics is different in different groups of patients," says Katrin Amunts, who works with Prof. Walter Huber on the PPA research study. Prof. Huber leads the Neurolinguistics teaching and research area at University Hospital Aachen. "One of our main objectives is to diagnose the disease as early as possible. The earlier we can start medication, the more effective it will be."

Although the Jülich brain atlas is already being used and is already incorporated into several international da-

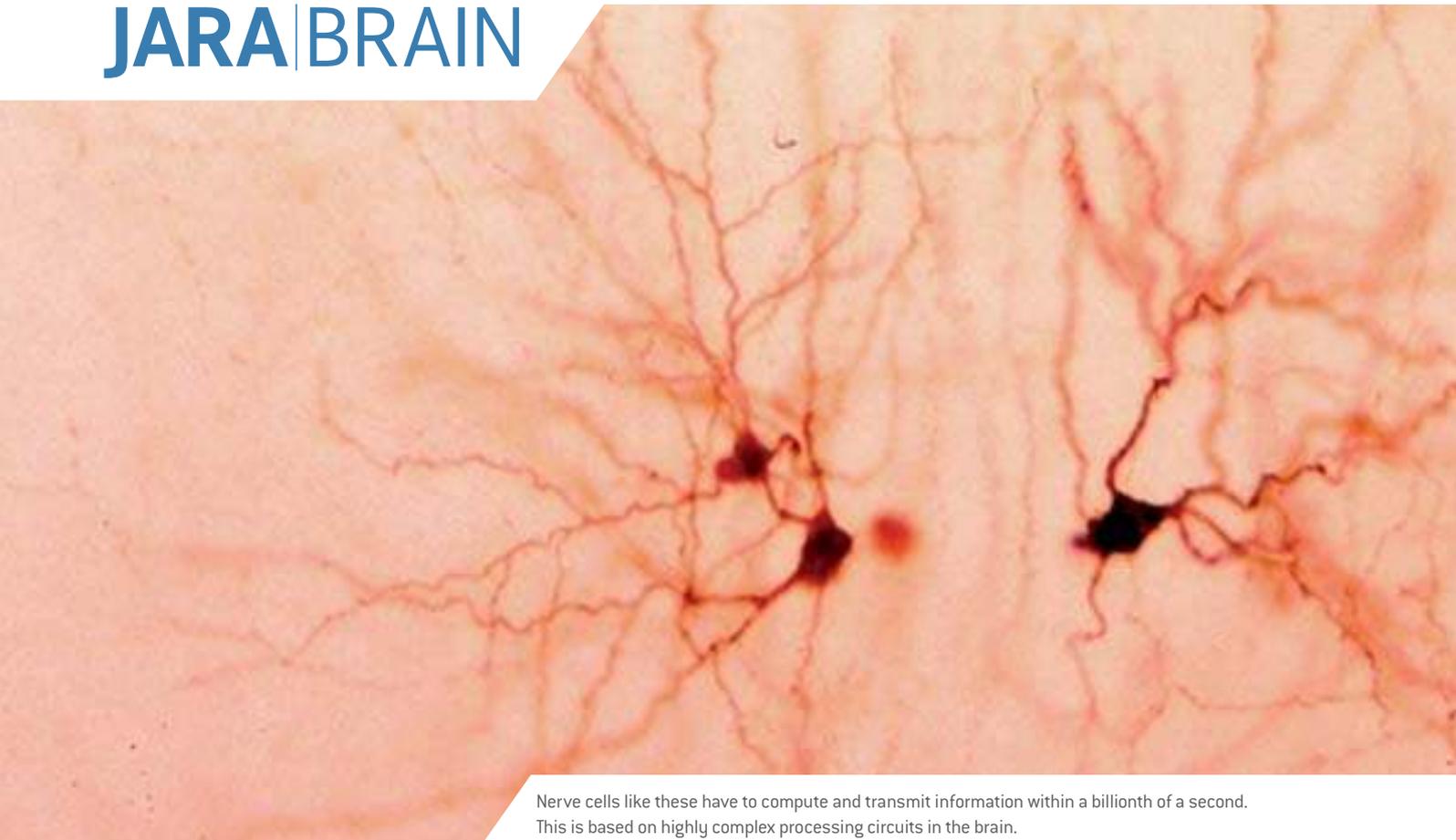
tabases, it will be several years before it is finished. Once it has been completed, however, it will provide a useful modern reference for clinical practice.

Brain atlas is freely available to the scientific community

Anyone who has an interest in the Jülich brain map need only turn on the computer. The Jülich scientists have made the atlas and the appropriate software freely available to the scientific community online. Katrin Amunts says that there is lot of interest in the project: "In the past four years, we counted more than 10,000 downloads."



About 60 percent of the brain has now been mapped. Thousands of histological brain sections have been, and are being, investigated at Forschungszentrum Jülich. The tissue samples are scanned using microscopes and advanced image analysis techniques. They are then statistically analyzed and reconstructed on a computer in 3-D.



Nerve cells like these have to compute and transmit information within a billionth of a second. This is based on highly complex processing circuits in the brain.

Ideal Mediators in the Brain

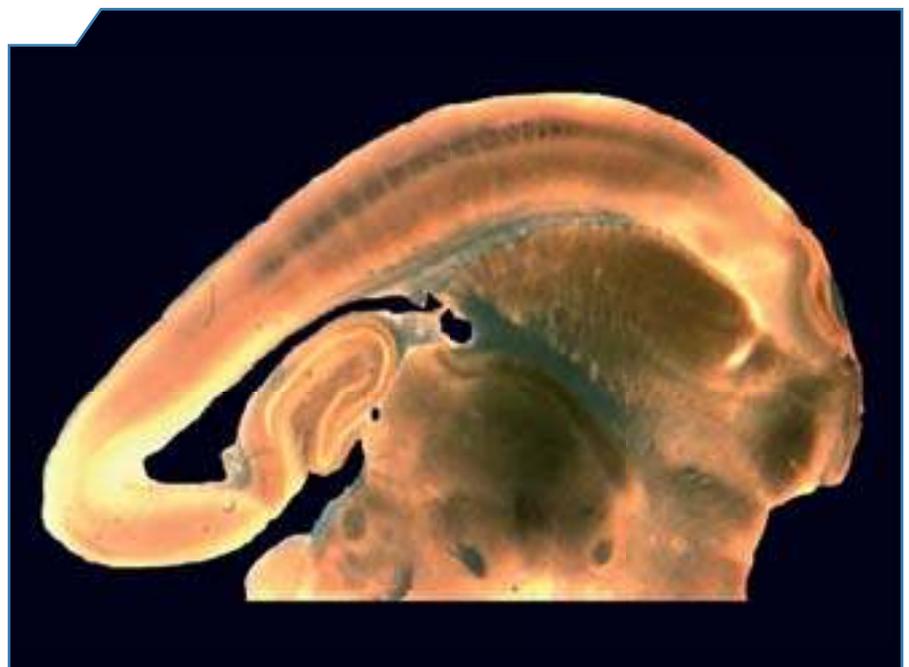
Approximately 20 billion nerve cells work in the human cerebral cortex, where incoming sensory stimuli are analyzed and evaluated. JARA-BRAIN researchers investigate how nerve cells process these signals.

If you are holding a match and the flame comes into contact with your finger, you blow it out immediately. Why? The tactile stimulus on the fingertip is transferred within billionths of a second over nerve pathways to the brain. The signal is interpreted and then triggers us to put out the flame. This sounds simple at first, but actually requires highly complex information strategies and pathways in the human cerebral cortex, many of which we know nothing about.

JARA-BRAIN researcher Prof. Dr. Dirk Feldmeyer is working on filling in this knowledge gap: “I’m interested in the structure of the brain at the cellular level. How do nerve cells analyze and evaluate signals? And how do they pass them on?” To better understand the circuits of nerve cells in the human

brain, the scientist, head of the “Function of Cortical Circuits” research group at the Institute of Neuroscience and Medicine at Forschungszentrum Jülich, and professor on the same topic at the Department of Psychiatry and Psychotherapy at RWTH Aachen University, concentrates on a particular section of the cerebral cortex. “The somatosensory cortex specializes in sensory information such as touch, temperature, and pain. It is a prime example of the structure-function relationship in the processing of sensory impressions,” he says. Dirk Feldmeyer analyzes the somatosensory cortex of rodents to better understand the molecular and neurochemical processes in nerve cells. “The structure of the mammalian cerebral cortex is relatively stereotypical. We investigate the neurotransmitter receptors from nerve cells, how

nerve cells communicate with each other, and the structure of nerve cell clusters in rats and mice. From that, we can draw conclusions about the human brain, which is obviously more complex, but similar in structure.” Dirk Feldmeyer works with brain slices in an in vitro system, which allows him and his team to more accurately analyze the somatosensory cortex, its six layers, and variety of nerve cells. Layer four functions as a central “gateway,” as this is where the body’s nerve signals arrive in the cortex from the nerves of the body. The subsequent signal communication is based on a division of labor: “Layer four sends the information further into the cortical pillar or column, i.e. vertically into the other layers. Layers one, two, three, five, and six then distribute information vertically and laterally in the cortex.”



To improve the understanding of the circuits of nerve cells Prof. Dr. Dirk Feldmeyer and his team analyze the somatosensory cortex in the animal brain. This cortex area, responsible for sensory information such as touch, temperature, and pain, consists of six different layers with different types of nerve cells. Layer four (indicated by the dark spots in the image) functions as an entry portal. This is where nerve signals from the body arrive before being forwarded to other layers.

Messengers refine the signal

At laboratories in Jülich and Aachen, Dirk Feldmeyer uses an electro-physiological apparatus known as a patch clamp device to measure the electrical signals of individual, synaptically coupled neurons with glass microelectrodes. In other words, he measures how nerve cells communicate with each other. “With our method it is possible to measure the signal in one cell in the form of an action potential, and the signal transmission to another neuron, i.e. the synaptic response,” he says. Neurotransmitters are released to transmit the sensory stimuli from one nerve cell to another. These biochemical postmen also transmit information about the contact points, or synapses, of the nerve cells. “There are a variety of excitatory and inhibi-

tory transmitters that modify the signals,” Dirk Feldmeyer explains.

Dirk Feldmeyer’s working group recently investigated the effects of the neurotransmitter acetylcholine on nerve cells in the cerebral cortex. This neurotransmitter is released mainly from neurons of the basal forebrain. Explaining his choice of focus, Prof. Feldmeyer says, “Current literature tends to just say that acetylcholine excites the nerve cells. This struck us as too simple.” He therefore examined more closely the effects of acetylcholine in the somatosensory cortex. The results confirmed the researchers’ hypotheses. The nerve cells of the different layers responded very differently to the neurotransmitter. “We were able to demonstrate that the nerve cells in other layers of the cerebral cortex

were excited. The responses of the nerve cells in input layer four, however, were inhibited.” The routed signal is more finely tuned by these biochemical processes and thereby intensified, which has the effect of producing a better sense of touch, hearing or sight. “For me as a basic researcher, it is important, per se, to know how neural circuits function. However, it is possible that clinical science can draw conclusions from our results and apply these to developing more targeted medicines,” explains Dirk Feldmeyer. For example, evidence shows that the cholinergic system (acting via acetylcholine) is affected in patients suffering from schizophrenia or neurodegenerative diseases like Alzheimer’s.

Dual Leadership for JARA-BRAIN

Two directors with a common goal: Prof. Dr. Dr. Frank Schneider of RWTH Aachen University and Prof. Dr. Karl Zilles of Forschungszentrum Jülich share scientific interests in the human brain. The editors spoke with the two JARA-BRAIN directors about research topics and visions.

What do you see as the greatest challenges to brain research today?

Professor Schneider: The human society is getting older and this brings advantages and disadvantages. Given the demographic trends, I think it is particularly important that we find ways of ensuring earlier recognition of neurodegenerative diseases like Alzheimer's and Parkinson's, and develop better treatment through improved diagnosis and therapies tailored to individual patients. This also applies to other psychiatric disorders, such as schizophrenic psychosis, depression, and autism.

Professor Zilles: Quite a bit of basic research is still needed to successfully overcome these clinical challenges. Much of the human control center is largely unexplored, even though science has made huge leaps of knowledge in recent years. How

is the structure of the brain linked in all its complexity and its functions? What is going on at the level of cells and synapses, where certain benefits or deficits are observed in humans? There is a lot of unexplored terrain for scientists in this field.

What are the major issues of research for JARA-BRAIN?

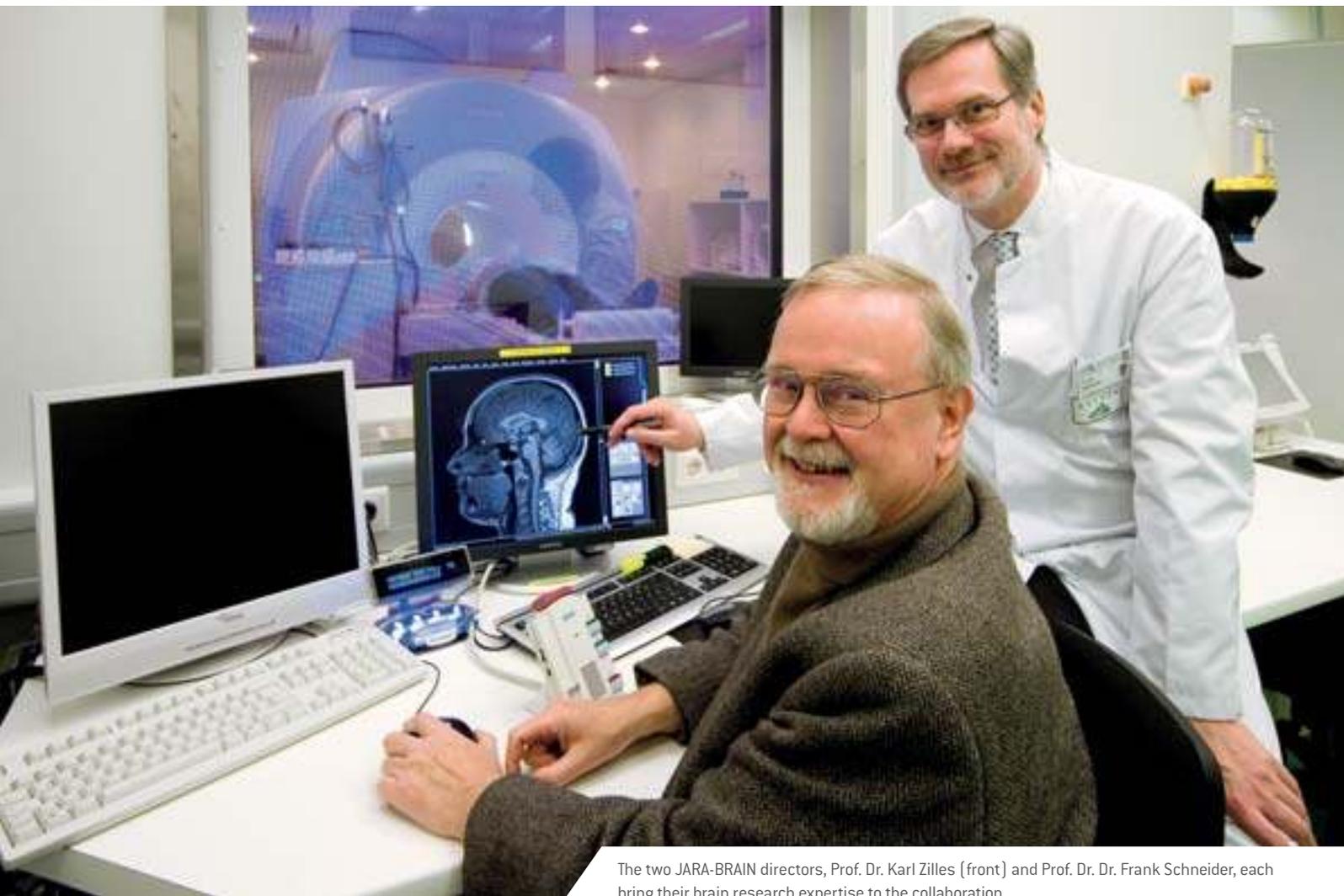
Professor Zilles: We are particularly interested in the structure and function of the human cerebral cortex. This part of the human brain has evolved the most and it is also important for many cognitive and emotional activities. Another research focus of JARA-BRAIN is the type of communication between nerve cells, or synapses, in the different areas of the brain. We need modern imaging techniques and, of course, patients to be able to portray and analyze these processes in the human brain.

Professor Schneider: The research

framework of JARA-BRAIN is very complex indeed. We conduct what we call translational research. That means we cover the entire chain of knowledge from basic research through to clinical application. In addition to basic research, many scientists are also working in applied brain research. For instance, how do tics in a Tourette's patient correspond to processes in the brain? What abnormalities are seen in certain areas of the brain in autistic people? What happens in the brain when a schizophrenic patient hears voices? These are issues that we can analyze scientifically using modern imaging techniques.

Professor Zilles, what benefits do you feel your partner, RWTH Aachen University, brings to the alliance?

Professor Zilles: The clinical and scientific expertise, and, of course, the excellent personal contacts. University



The two JARA-BRAIN directors, Prof. Dr. Karl Zilles (front) and Prof. Dr. Frank Schneider, each bring their brain research expertise to the collaboration.

Hospital Aachen focuses on patient care, including highly specialized medical care, while Jülich is a pure research center. In addition, University Hospital Aachen accommodates the medical faculty and is therefore similarly scientifically focused. A good example of the combination of clinical and research activities are our four JARA-BRAIN junior professors, our “clinician scientists” or clinical researchers. Each of the four has patient-orientated tasks at University Hospital Aachen and also carries out scientific research with a special working group in Aachen and Jülich.

Professor Schneider, what key benefits does Forschungszentrum Jülich bring to JARA-BRAIN?

Professor Schneider: Forschungszentrum Jülich offers outstanding expertise in basic research, methodological expertise in the field of imaging, and excellent technical equipment. As a

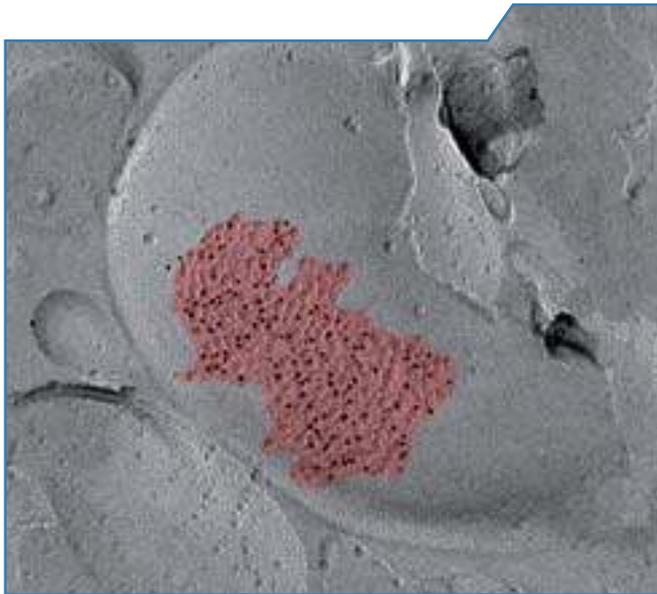
major research center of the Helmholtz Association, Jülich has magnetic resonance imaging and positron emission tomography scanners, which are not currently used in normal hospital environments. Jülich scientists have superior knowledge in the operation of these devices.

What would you personally hope for from brain research in the next few years?

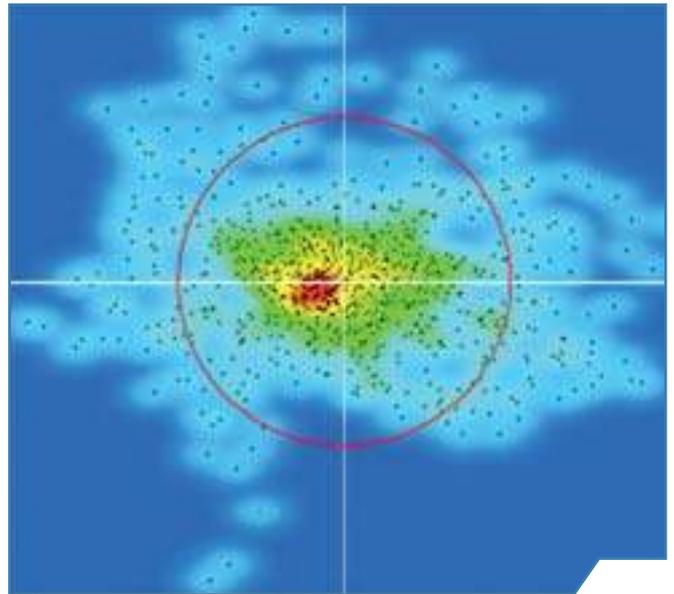
Professor Zilles: Understanding the complexity of information processing in the brain, both at a structural and functional level. For this, we need to understand brain development during fetal and postnatal development. And we need to understand brain development in the interplay of evolution from nonhuman primates to humans. The brain has more history than any other organ in our body.

Professor Schneider: I hope for bet-

ter and earlier diagnoses, and a clear prediction of disease probabilities and risk factors for mental disorders. Then it would be possible to prevent the outbreak of the disorder, or at least delay it, through preventive measures. This would benefit patients, their families, and our healthcare system.



Electron micrograph of a brain cut showing part of a nerve cell (dendrite) with a transmitter release site (marked in red) that contains AMPA receptors.



The density of receptors at each synapse is their individual “fingerprint.” The red area at the center indicates the highest density of receptors.

Well-Connected Experts

Synapses are highly specialized contact points between individual nerve cells. They rapidly carry information, such as visual and aural impressions and taste sensations, to the brain. Each synapse is specialized in particular tasks.

The human brain is a powerful information and control center. It coordinates all our senses and cognitive and emotional processes – from speaking and smelling to thinking, running, and performing any one of the many other functions of everyday life. There are between 20 and 40 billion nerve cells at work in the human cerebral cortex alone. Each of these nerve cells receives up to 15,000 synaptic inputs. JARA-BRAIN scientists investigate what structural, functional, and molecular differences in synapses of different brain regions make the specialization possible.

Synapses are, evolutionarily speaking, very old, but they behave in a distinctly modern fashion. “Each individual synapse works as an expert by structurally and functionally com-

pletely adapting to their assigned task and brain region,” says Professor Joachim Lübke. He has been a professor of structural cortical circuits at the Department of Psychiatry and Psychotherapy of the Medical Faculty at RWTH Aachen University since July 2008. He also chairs the “Structure of Synapses” working group at the Institute of Neurosciences and Medicine INM-2 at Forschungszentrum Jülich.

To better understand the functioning of synapses, Joachim Lübke has spent many years examining individual synapses down to the smallest detail and has created three-dimensional, quantitative models of them on the computer. Although the term “synapse” has long existed, only a few laboratories worldwide are working on virtual, three-dimensional models of synapses. “Until

a few years ago, the quantitative geometry and the molecular structure of a synapse were a kind of black box,” says Joachim Lübke. The research of his team and teams at other laboratories, whose work is highly interconnected, has meant that brain research has drastically advanced. Thus, research into the “Calyx of Held,” the “Mossy Fiber Bouton,” and other synapses show how the contact points develop differently, despite having the same components.

“All synapses consist of a presynaptic membrane of the signal-sending neuron and a postsynaptic membrane of the signal-receiving neuron,” explains Joachim Lübke. Between them is the synaptic cleft, a sort of trench that the chemical messengers (neurotransmitters) must cross as information carriers. This jump works because the

sending cell carries the messengers, which are packed into small bubbles (vesicles), to the presynaptic membrane where they then fuse with it. Within milliseconds, a certain amount of the neurotransmitters is released from the vesicles to the “launch pads,” or transmitter release points. This then diffuses through the synaptic cleft towards the post-synaptic membrane of the target nerve cell where it binds to specific receptors. This process is regulated differently at the various synapses in the brain. Some of these signaling cascades are well-known, but many have not yet been identified.

Synapses consist of the same components, but these differ in number and distribution.

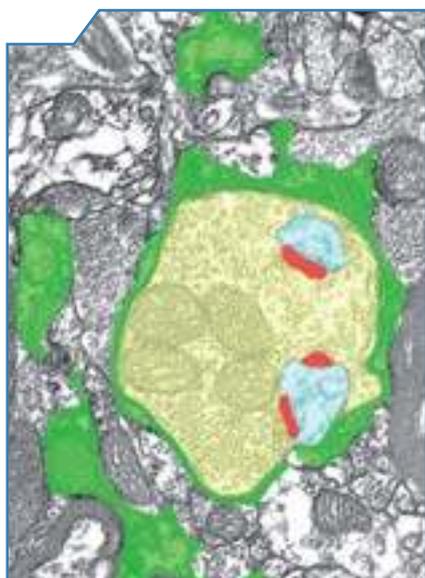
Although all synapses are composed of the above mentioned components, they differ significantly in the number and distribution of the individual structural elements. This is the key to their existence. “Some synapses like the Calyx of Held have, for example, about 600 transmitter release sites, while others like the Mossy Fiber Bouton have only 25, and cortical synapses usually have only one,” says Joachim Lübke. The

number and organization of synaptic vesicles varies greatly between individual synapses and synapses of different brain regions. These structural differences are associated with different tasks. While the Calyx is partly responsible for aural impressions, the Mossy Fiber Boutons are involved in learning and memory processes. “Synapses are perfectly suited to their specific tasks,” explains Joachim Lübke.

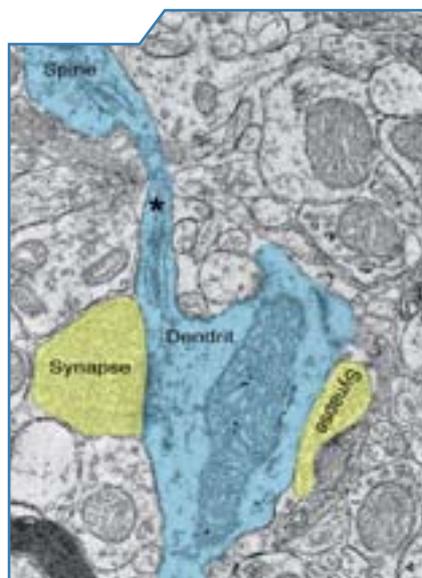
To understand the specialized synapses even better, JARA-BRAIN scientists use the latest technology to allow for a detailed analysis of the density and distribution of certain neurotransmitter receptors at synapses. With the aid of ultra-thin sections, freeze fracture replica of brain tissue combined with highly sensitive postimmunogold immunohistochemistry, electron microscopes show synaptic structures and receptors down to the smallest detail. “This new imagery helps us to analyze where individual receptors, their subunits and cocktails of receptors are located within the synapse,” explains Joachim Lübke. Two main players in the neocortex are AMPA and NMDA receptors. Beside, there are also many other receptors involved that create a bal-

ance between excitatory and inhibitory influences in the brain. This balance is significantly disrupted in, for example, neurodegenerative and neurological diseases.

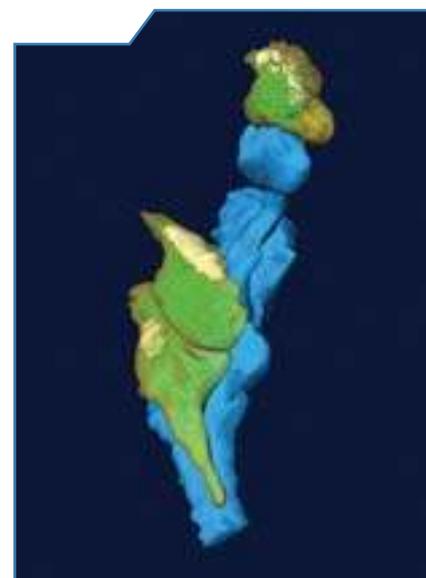
At a molecular level, the receptor profiles are just a small part of a complete synaptic map. As yet, such a map remains a vision for the future, in which advanced knowledge of the structure and function of the communication interface in the normal brain will help to better understand and ultimately develop therapeutic approaches to neurodegenerative diseases like Alzheimer’s or Parkinson’s. “In all neurodegenerative diseases, there are massive structural changes in nerve cells and synapses, which ultimately lead to the overall dysfunction,” explains Prof. Lübke. Given the steady increase in neurodegenerative diseases brought about by demographic changes, modern brain research has a major social role to play in this regard.



Electron microscopic picture of a synaptic complex comprising the synapse (yellow), two dendritic spines (blue), and transmitter release sites (red).



Detailed picture of a spine attached to the root dendrite. Synapses (yellow) terminate near the spine (left) and at the dendritic pole.



3-D reconstruction of a dendrite with three synapses. Shown here are mitochondria (white) and synaptic vesicles (green).

In Search of the Best Therapy

Approximately 800,000 people in Germany suffer from schizophrenia. The mental disorder has genetic, biological, and psychosocial causes. JARA-BRAIN scientists analyze the neurochemical processes in the brain and explore how these can be positively influenced by medication.

You hear voices, feel restless and harassed. Schizophrenia is a mental disorder that produces changes in thought, perception, and behavior. Around one percent of the population suffers from it at least once in their life. Between 10 and 15 percent are so badly affected that they commit suicide. While various symptoms can be treated with medication, schizophrenic disorders are not yet fully curable, although some patients suffer only one acute episode. The severity of the disease is also reflected in the occupancy levels of psychiatric hospitals. “Around 30 to 40 percent of all hospitalized patients have schizophrenia,” explains Prof. Dr. Gerhard Gründer, deputy director of the Department of Psychiatry at University Hospital Aachen. This also makes the disease an economic issue. Schizophrenia is the most expensive mental illness in Germany, responsible for around €3.5 billion per year in health-care costs. The suffering of those affected, along with the economic dimension, makes the scientific study of this disease a central health policy problem. Under Prof. Gründer, JARA-

BRAIN scientists in Aachen and Jülich have therefore been tracking the neurochemical causes of the disease for years. “We expect the dopaminergic neurotransmitter system in specific brain regions belonging to the limbic system to be hyperactive in patients with schizophrenia,” says the psychiatrist, who leads the teaching and “Experimental Neuropsychiatry” research area in the Department of Psychiatry and Psychotherapy at RWTH Aachen University. Neurotransmitters are biochemical messengers that pass information from one nerve cell to another.

PET scans are supposed to identify imbalances between neurotransmitter systems

In a study funded by the German Research Council, JARA-BRAIN scientists investigate how the interaction between the dopaminergic and the cholinergic system is disrupted in patients with schizophrenic disorder. “There is good evidence that the patient’s brain tries to compensate for increased dopamine secretion

by increased production of acetylcholine, another neurotransmitter. We now suspect that there is a kind of imbalance between the two neurotransmitter systems in patients with schizophrenia,” says Gerhard Gründer. To further characterize this imbalance, patients are examined twice with positron emission tomography (PET). “First, we measure dopamine release without medication in healthy subjects and patients with a schizophrenic disorder. The second investigation takes place after the subjects have taken a drug that inhibits the cholinergic neurotransmission,” he explains. The scientists suspect that the dopamine release is more strongly disinhibited in patients with schizophrenia than in healthy subjects. The results are relevant to new pharmacological therapies because “patients with schizophrenia can demonstrate so-called positive and negative symptoms,” Gerhard Gründer continues. “There is good evidence that increased dopaminergic neurotransmission underlies positive symptoms, such as hallucinations or auditory hallucinations. In contrast,



at least some of the negative symptoms, like social withdrawal and affective flattening, are probably due to a compensatory increase in cholinergic transmission. Our research will help to understand how we can influence these imbalances with drugs.”

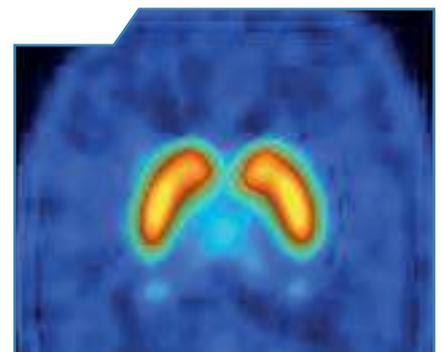
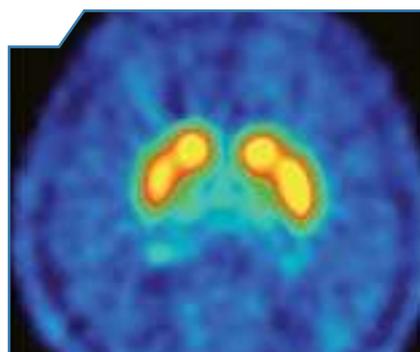
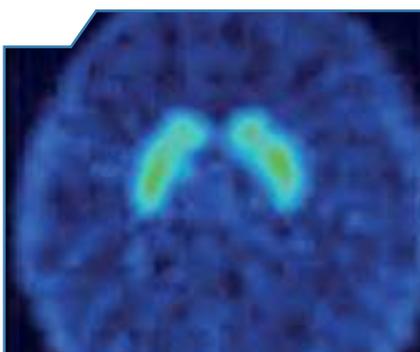
“We need to develop antipsychotics with minimal side effects”

Currently, the positive symptoms can be relatively well controlled by antipsychotics. In contrast, cognitive disturbances and negative symptoms

can, as yet, be only moderately treated.

Gerhard Gründer believes this represents a large field of scientific activity. “In order to provide patients with long-term quality of life, we need to develop acceptable antipsychotics with minimal side effects that also reduce the negative symptoms or cognitive impairment.” He is therefore taking part in a major multicenter pharmacological study funded by the Federal Ministry for Education and Research (BMBF). Approximately 650 patients with schizophrenic disorders in ten

German hospitals are involved in the study, which is comparing treatment with established antipsychotics and new substances with regard to treatment outcomes, side effects, and costs. Many of the new compounds are criticized for being too expensive, and failing to deliver major improvements in treatment. Gerhard Gründer points out, “Independent, public research is a useful and necessary addition to research conducted by the pharmaceutical industry in order to arrive at insights that are not influenced by industry interests.”



Schizophrenia patients need medication that blocks dopamine receptors in the brain. The images from positron emission tomography (PET) show how intensively three different antipsychotics bind to dopamine receptors. For Aripiprazole (left), the blue and green colors indicate that many receptors are occupied. The red and yellow areas, with Clozapine (center) and Quetiapine (right), show that the drug has failed to bind to many of the receptors.



Approximately 800,000 people in Germany suffer from Tourette's syndrome. Typical symptoms of the disorder are motor and vocal tics that may occur spontaneously and are difficult to control by those affected. Researchers have found that Tourette's syndrome can be explained by, among other things, structural changes in the basal ganglia.

A Tic Different

It begins with a wink or a head twitch, sometimes with coughs or grimaces. Tourette's syndrome is a neurobiological disorder that induces spontaneous motor or vocal tics.

Patients of Dr. Irene Neuner, senior physician at the Department of Psychiatry and Psychotherapy at University Hospital Aachen, come from far and wide. Only a few German hospitals currently offer Tourette's syndrome consultations, even though the neurobiological disorder is found in about one percent of the population. This means that approximately 800,000 people in Germany suffer from spontaneous motor and vocal tics, which sufferers find it very difficult to control. "Tourette's syndrome is a psychiatric illness that is usually first diagnosed in children of elementary-school age. Symptoms often become most intense during puberty, and fully regress dur-

ing early adulthood in up to 60 percent of cases," says Irene Neuner. Although atypical antipsychotics can alleviate the symptoms, a successful treatment with hope of complete recovery does not yet exist.

Thanks to modern imaging techniques, scientific knowledge is considerably further along than at the beginning of the 19th century, when the French neurologist Georges Gilles de la Tourette first described the syndrome. Nowadays, doctors and psychologists can observe what happens in the brain of a Tourette's patient during a tic using functional magnetic resonance imaging (fMRI). Today we

also know that the disorder can be explained through structural changes in a particular brain area, the basal ganglia. "The basal ganglia are hyperactive in Tourette's patients, and this is in part caused by the neurotransmitter dopamine," says Irene Neuner. When sufferers experience stressful situations, the amygdala, which is responsible for the emotional processing of events in the brain, fires up the basal ganglia. Thus, the patient experiences an increasing number of tics, which in turn trigger new stress factors, creating a downward spiral. On the other hand, activities that require high concentration and attention, during which prefrontal brain areas are active, may

slow down the basal ganglia, and the patient hardly tics at all. In particularly serious cases, an innovative treatment option is deep brain stimulation, which involves a neurosurgeon placing a brain pacemaker under the collarbone of a Tourette's patient. This sends signals to electrodes through two elongated, needle-thin cords inserted into the basal ganglia. This promising intervention, however, has only been performed about 60 times around the world.

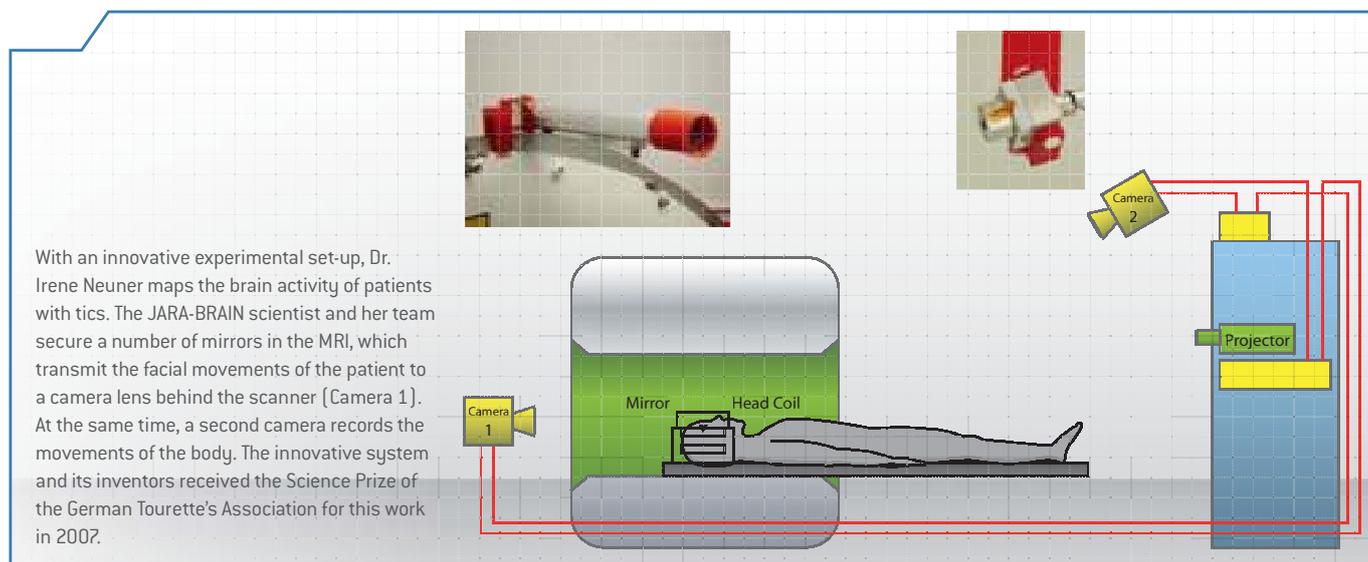
Innovative “mirror cabinet” shows what happens in the brain during a tic

Tourette's syndrome is a major scientific challenge for scientist Irene Neuner: “The neurobiological basis of Tourette's has long been denied.” However, advances in structural and functional brain research have played a major role in proving that tics are not a result of “bad” habits due to environmental factors, but of tangible neurobiological disorders. JARA-BRAIN researchers at Jülich and Aachen track their causes. Mobile camera equipment, developed by Irene Neuner and physicists Prof. Dr. N. Jon Shah, Dr. Tony Stöcker, and Hans-Peter Wegener from Jülich, is a great help to them. It makes a small “mirror cabinet” of an examination room with a magnetic resonance imaging scanner.

“Our problem is that we simply could not install a camera in the MRI. This would have disturbed the magnetic field, the basis of our brain images,” says Irene Neuner. Not even an earring or a belt buckle is allowed in the tube, as this would interfere with the results. The JARA-BRAIN researchers solved this problem by using a camera system built from MR-compatible materials and several mirrors mounted over the face of the subject. These direct the images of the facial movements into a camera lens behind the scanner. At the same time, a mirror on the ceiling of the testing area catches the movements of the entire body. The data is then evaluated outside the area with a computer. The innovative system and its inventors received the 2007 Science Prize of the German Tourette's Association for their work.

Irene Neuner also values the interdisciplinary collaboration in her other research areas: “The JARA-BRAIN cooperation is really fascinating. I have interesting clinical issues and they can be discussed and analyzed across disciplines in Aachen and Jülich – a prime example of translational research.” In addition to exploring functional abnormalities in the brain in Tourette's patients, she also examines the structural changes. For example, she and her team were able to demonstrate by

diffusion tensor imaging (DTI) that the nerve fiber connections of Tourette's patients in the “pyramidal tract,” the major neural pathway for movement, differ from those of healthy subjects. DTI can represent the fiber tracts in the brain by exploiting the following phenomenon: “While the diffusion of water in the brain in healthy subjects is orderly and takes place parallel to the nerve pathway, it became apparent that the fiber tracts are impaired in Tourette's patients – the diffusion is disorderly and runs in many directions,” says Irene Neuner. The methodological expertise of the Jülich/Aachen cooperation is particularly groundbreaking. The Tourette's researchers have, for instance, been combining functional magnetic resonance imaging with electrophysiological methods for some time. In contrast to MRI, which has a high spatial but poor temporal resolution, electrophysiological signals have a resolution in the range of milliseconds. It is possible to combine the MRI signals with electrophysiological methods, such as EEG or evoked potentials, to characterize neural networks more precisely. Thus, the work on Tourette's highlights the unique benefits of JARA-BRAIN: its combination of comprehensive basic research expertise, the clinical care of patients, and the development of new therapies.



New Measurement Techniques for Young Patients

More refined methods of measurement are required to explore mental illnesses, such as Attention-Deficit and Hyperactivity Disorder (ADHD) or autism, in children and young people. For this purpose, psychiatrists, physicists and computer scientists are further developing imaging methods.

Sitting or lying quietly for long periods is not easy, even for healthy children. This makes it especially difficult for young ADHD patients, often suffering from impulsive actions and hyperactivity, to lie still for 30 to 60 minutes in a narrow MRI tube. However, this is the time currently required to obtain usable images in diffusion tensor imaging, which provides information on the course of the fiber connections between different brain areas. "Many mental disorders, such as ADHD and autism, can be attributed to factors such as disruption in the interaction of different areas of the brain," explains Prof. Dr. Kerstin Konrad, who leads the "Clinical Neuropsychology of Childhood and Adolescence" teaching and research area at the Clinic for Child and Adolescent Psychiatry at University Hospital Aachen. She, like her colleagues, is dependent on precise, high-contrast images in order to observe brain development and other possible changes in children and adolescents suffering from these

disorders. "The child's brain is not only somewhat smaller than an adult brain," she explains, "but it also shows developmental changes in specific brain regions."

Adolescents often search for an emotional kick

Subcortical areas of the brain, like the amygdala and nucleus accumbens in the basal ganglia areas, which process reward stimuli, mature earlier than the prefrontal cortex, which is responsible for cognitive decisions and control functions. Therefore, the adolescent brain often assesses risk situations differently than the adult brain. "Adolescents often search for an emotional kick," says Kerstin Konrad. These may be relatively harmless things, like small tests of courage, but may also include illegal activities, such as shoplifting, train surfing, or drug abuse. As yet, there has been little scientific research into exactly how the interaction between different

brain areas, at both the structural and functional level, is manifested in the course of development, and when developmental problems can occur.

In order to better map the abnormalities in children and adolescents, Kerstin Konrad cooperates, in the context of JARA-BRAIN, with Prof. Dr. N. Jon Shah, head of the "Magnetic Resonance Physics" working group and director of the Institute of Neurosciences and Medicine 4 at Forschungszentrum Jülich. The physicist and his team are developing methods of magnetic resonance imaging (MRI) that adapt to the characteristics of the child's brain and reduce measurement time by improving imaging sequences. "Our common goal is to reduce MRI measurement time to fifteen minutes for children," says Kerstin Konrad. The JARA-BRAIN scientists also want to establish diffusion tensor imaging (DTI) for children and adolescents. With this imaging method, it is possible to measure the diffusion of water molecules in brain



Approximately five percent of all school children suffer from Attention-Deficit and Hyperactivity Disorder (ADHD). They find it difficult to concentrate and are hyperactive. Modern imaging techniques and methods adapted to young patients show that the interaction of different areas of the brain is disrupted in ADHD patients.

tissue, and thus to investigate the white matter in the brain and to draw conclusions about the course of the fiber bundles. “Here, we benefit from the excellent technical expertise of our Jülich colleagues,” says the psychologist. There are a number of other changes in the development of, or in the interaction between, brain areas of children and young people suffering from mental disorders. For example, scientists suspect that the long fiber connections in the brain (e.g. between the anterior and posterior cingulum) are reduced in ADHD children and young people. As Prof. Konrad points out, “This would, for instance, explain

why the top-down control, and thus the greater cognitive control of emotional impulses and emotions, is often limited in ADHD patients.”

New measuring sequences show changes in the brain in patients with eating disorders

Thanks to anatomical imaging and a new measurement sequence for fast and high-resolution determination of the absolute local water concentration in brain tissue, it is now possible to more accurately represent brain changes in children with eating disorders. Thus, the scientists from the

Clinic for Child and Adolescent Psychiatry at Aachen University Hospital, along with Prof. Shah, recently conducted a study in which they measured the brain volume of new clinical patients with anorexia nervosa. The results were striking. “The anorexic girls showed an extreme loss of brain volume, i.e. the brain shrinks greatly as a result of the strain placed on it by the disorder,” says Kerstin Konrad. The new studies now allow more accurate initial assessments of whether fats are eliminated in the first place, or if the decrease in volume is due to changes of water content in brain tissue. However, as Prof. Konrad points out, the good news is that “these processes in the brain are highly reversible. As the patients gain weight, the volume of the brain also tends to increase.”

Brain volume decreases dramatically in patients with anorexia. On the left is the brain of a 16-year-old girl with anorexia nervosa and a body mass index of 14. On the right is the brain of a healthy 16-year-old girl with a body mass index of 20.



Facts and Figures

JARA-BRAIN:	Section
Foundation:	August 2007
Founding directors:	Prof. Dr. Dr. Frank Schneider, RWTH Aachen University, Prof. Dr. Karl Zilles, Forschungszentrum Jülich GmbH
Funding:	JARA-BRAIN receives funding within the framework of the Excellence Initiative of the federal and state governments of Germany. The funding period lasts from November 2007 until October 2012 and totals over €5 million.
Allocation of funds:	Appointment of four junior professors and their scientific and non-scientific positions Seed Funds for innovative high-risk projects Full-time management board
History:	The Jülich Aachen Research Alliance (JARA), established in August 2007, created a new partnership model for university and non-university research with great international visibility. The new organizational and contractual framework takes the cooperation between RWTH Aachen University and Forschungszentrum Jülich to a new level. JARA specifically combines international research fields that will complement each other in terms of their areas of expertise, and therefore increase their achievement potential.
Unique conditions:	<p>With about 3,600 staff members and an annual budget of some €360 million, JARA creates unique conditions for research and teaching. The alliance is already active in four promising research areas:</p> <ul style="list-style-type: none">· JARA-BRAIN Translational Brain Medicine· JARA-FIT Fundamentals of Future Information Technology· JARA-SIM Simulation Sciences· JARA-ENERGY <p>JARA-BRAIN strengthens the existing cooperation in multiple projects between researchers from faculties in Aachen, such as engineering, physics, computer science, and medicine, and from the corresponding institutes at Forschungszentrum Jülich.</p>

Links:

JARA and JARA-BRAIN:	www.jara.org
RWTH Aachen University:	www.rwth-aachen.de
Forschungszentrum Jülich:	www.fz-juelich.de
University Hospital Aachen:	www.ukaachen.de
International Research Training Group (IRTG) 1328:	www.irtg-schizophrenia-autism.de

Seed Fund Projects:

The JARA-BRAIN research projects cover the entire spectrum of translational research in neurosciences, from basic research and imaging technologies to research projects with immediate clinical relevance. This is especially visible in the JARA-BRAIN Seed Funds, which have made a total of €850,000. One highly interdisciplinary research group to benefit from this funding comprises clinicians, psychologists, and computer scientists who are developing complex computer simulations to simulate functional imaging research by means of magnetic resonance tomography, and to perform statistical analyses of this data. Another project is dedicated to adapting imaging methods such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to the special requirements for research in children and young people. There is also a JARA-BRAIN project focusing on patients with primary progressive aphasia. Other topics cover real-time imaging, optimizing a brain stimulator, prediction of schizophrenic episodes, and the synaptic signal transduction in the human brain.

JARA-BRAIN Members:

As of January 2010, 37 professors from RWTH Aachen University and Forschungszentrum Jülich

Univ.-Prof. Dr. Til Aach, Univ.-Prof. Dr. Katrin Amunts, Univ.-Prof. Dr. Cordian Beyer, Univ.-Prof. Dr. Heinz H. Coenen, Univ.-Prof. Dr. Michael J. Eble, Univ.-Prof. Dr. Simon Eickhoff, Univ.-Prof. Dr. Dirk Feldmeyer, Univ.-Prof. Dr. Jürgen Floege, Univ.-Prof. Dr. Siegfried Guggel, Univ.-Prof. Dr. Joachim Michael Gilsbach, Univ.-Prof. Dr. Gerhard Gründer, Univ.-Prof. Dr. Ute Habel, Univ.-Prof. Dr. Beate Herpertz-Dahlmann, Univ.-Prof. Dr. Ralf-Dieter Hilgers, Univ.-Prof. Dr. Ludwig Jäger, Univ.-Prof. Dr. Leif Kobbelt, Univ.-Prof. Dr. Iring Koch, Univ.-Prof. Dr. Kerstin Konrad, Univ.-Prof. Dr. Joachim Lübke, Univ.-Prof. Dr. Dr. Klaus Mathiak, Univ.-Prof. Dr. Johannes Noth, Univ.-Prof. Dr. Kathrin Reetz, Univ.-Prof. Dr. Rolf Rossaint, Univ.-Prof. Dr. Stefan Schael, Univ.-Prof. Dr. Dr. Frank Schneider, Univ.-Prof. Dr. Jörg B. Schulz, Univ.-Prof. Dr. N. Jon Shah, Univ.-Prof. Dr. Peter Tass, Univ.-Prof. Dr. Armin Thron, Univ.-Prof. Dr. Christian Trautwein, Univ.-Prof. Dr. Ingo B. Vernaleken, Univ.-Prof. Dr. Hermann Wagner, Univ.-Prof. Dr. Joachim Weis, Univ.-Prof. Dr. Klaus Willmes-von Hinckeldey, Univ.-Prof. Dr. Florian D. Zepf, Univ.-Prof. Dr. Klaus Zerres, Univ.-Prof. Dr. Karl Zilles

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Publishing Information

Publisher: JARA-BRAIN

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Translation: Julia Sydnor

Design: POWER+RADACH Werbeagentur GmbH
Drehturm Belvedereallee 5
52070 Aachen / Germany
Telefon: +49 241 91880-0

Printing: Druck Center Meckenheim GmbH
Werner-von-Siemens-Str. 13
53340 Meckenheim / Germany
Telefon: +49 2225 8893-550

Circulation: 1,000

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