Hertie-Institut
für klinische Hirnforschung

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center of neurology tübingen

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Das Zentrum für Neurologie im Jahr 2006

Wie an allen Universitäten Deutschlands wurden die Wissenschaftler im Jahre 2006 über viele Monate durch den „Exzellenzwettbewerb" in Atem gehalten. Koordiniert durch Professor Peter Thier konnten die Tübinger Neurowissenschaften unter vielfältiger Beteiligung von Mitarbeitern aller Abteilungen des Hertie-Instituts für klinische Hirnforschung einen von internationalen Gutachtern als ausgezeichnet beurteilten Antrag auf ein Exzellenzcluster Zentrum für Integrative Neurowissenschaften (ZIN) vorlegen. Obwohl der Antrag in der ersten Runde knapp die Förderung verfehlte, sind alle Beteiligten sehr zuversichtlich, dass diese wichtige Hürde in der zweiten Antragsphase im Jahr 2007 unter weiter verbesserten Rahmenbedingungen erfolgreich genommen werden kann.

Derweil ging der personelle Aufbau des HIH weiter voran. Die erste selbständige tenure track Nachwuchsgruppe unter der Leitung von Dr. Simone Di Giovanni nahm ihre Arbeit auf. In der Abteilung für Neurologie mit Schwerpunkt Neurodegenerative Erkrankungen konnte für die Besetzung der zweiten W3(C3)-Professur mit Philipp Kahle aus München ein ausgewiesener Grundlagenforscher auf dem Gebiet der Biochemie und Molekularbiologie neurodegenerativer Erkrankungen gewonnen werden.

Auch im Jahr 2006 gelangen den Wissenschaftlern des HIH wieder wichtige wissenschaftliche Beiträge, die zum Teil in hochrangigen Journalen wie *Nature* und *Science* publiziert wurden und im nachfolgenden Teil des Berichts dargestellt sind. Pars pro toto sei an dieser Stelle eine Arbeit von Herrn Axel Lindner hervorgehoben, der sich mit den Mechanismen der Wahrnehmungsstörung von Patienten mit Schizophrenie beschäftigte und dafür sowohl mit dem Hertie-Forschungspreis 2006 als auch dem Attempto-Preis der Universität Tübingen ausgezeichnet wurde. Die Vielfalt der wissenschaftlichen Aktivitäten hat nach einer Evaluation der gemeinnützigen Hertie-Stiftung dazu geführt, dass das HIH inzwischen in die Spitzengruppe der europäischen Zentren der klinischen Hirnforschung vorstoßen konnte.

Nach außen sichtbar wurde die Arbeit des Zentrums durch mehrere erfolgreiche wissenschaftliche Tagungen. Besonders hervorgehoben sei das von PD Dr. Haarmeier organisierte Symposium *The Neurobiology of Eye Movements*, das anlässlich der Emeritierung des Gründers des HIH, Professor Johannes Dichgans, abgehalten wurde und Weggefährten aus vielen Jahren in Tübingen zusammen führte. Von Professor Michael Weller und Professor Wolfgang Wick wurde ein Kongress zur *Therapie maligner Gliome – Standards und Perspektiven* organisiert. Das Symposium *Alzheimer: 100 Years and Beyond* vom 2. bis 5. November 2006 fand anlässlich des einhundersten Jahrestags der „37. Versammlung Südwestdeutscher Irrenärzte" statt und wurde von Professor Mathias Jucker organisiert. In dem Hörsaal der Klinik für Psychiatrie und Psychotherapie, in dem Alois Alzheimer vor 100 Jahren erstmals die klinischen und neuropathologischen Charakteristika der später nach ihm benannten Erkrankung vorstellte, versammelten sich die führenden Alzheimer-Forscher der Welt um historische und aktuelle Aspekte zu diskutieren. Sowohl das wissenschaftliche Symposium als auch die Auftaktveranstaltung für die Öffentlichkeit fanden ein vielfältiges Echo in den Medien und wurde als einer der 365 Orte im *Land der Ideen* ausgezeichnet.

Ein wichtiger Einschnitt im Leben der Klinik war der wochenlang andauernde Ärztestreik, der von allen Beteiligten ein hohes Maß an Flexibilität und Geduld einforderte. Wenn als Ergebnis eine auch langfristig verstärkte Würdigung engagierter ärztlicher Tätigkeit resultiert, hat sich diese schwierige Zeit gelohnt.

Prof. Dr. Thomas Gasser, Prof. Dr. Mathias Jucker, Prof. Dr. Peter Thier, Prof. Dr. Michael Weller

The Center for Neurology

University Hospital for Neurology and Hertie Institute for Clinical Brain Research

In 2001, the Charitable Hertie Foundation, the State of Baden Württemberg, the University of Tübingen and its Medical Faculty and the Tübingen University Hospital signed the contract that founded the "Center of Neurology", one of the largest centers for clinical and disease-oriented brain research in Germany.
The center consists of two closely interconnected institutions, the University Hospital for Neurology and the Hertie Institute for Clinical Brain Research.
The major objectives of the Center are the care for neurologic patients by the University Hospital and the pursuit of neuroscientific research within the Hertie Institute. The center is particularly committed to the promotion of young researchers and to the dissemination of scientific progress.

Presently, the center consists of four Departments:
The Department of General Neurology (Director: Prof. Dr. M. Weller)
The Department of Neurodegenerative Diseases (Director: Prof. Dr. T. Gasser)
The Department of Cognitive Neurology (Director: Prof. Dr. P. Thier)
The Department of Cellular Neurology (Director: Prof. Dr. M. Jucker)

The first three departments provide patient care within the university hospital for neurology. The largest clinical department is the Department of General Neurology, with its main focus on neurooncology, neuroimmunology, and neurovascular diseases. This department runs the stroke-unit / ICU, providing care for patients with acute stroke. Since the end of 2006, this unit has been expanded to include a "post-stroke ward", which offers early-stage rehabilitation as early as one or two days after an acute stroke. The integration of acute emergency care and early rehabilitation in a single organisational unit implements recent scientific concepts aiming at exploiting the rehabilitative potential of the early post-stroke period.
The clinical focus of the Department of Neurodegenerative Diseases is the early differential diagnosis as well as the treatment of neurodegenerative diseases, such as Parkinson's disease, the ataxias, the spastic paraplegias, and some forms of dementia but also of other movement disorders, such as the dystonias or essential tremor. This service is provided on a 22-bed ward for inpatients and through several outpatient specialty clinics.
The Department of Cognitive Neurology provides neuropsychological testing for inpatients and outpatients of all clinical departments.
The fact that three of the four departments of the center actively (although to a variable extent) participate in the clinical care of patients with neurologic diseases is crucial to the concept of successful clinical brain research at the Hertie Institute. This is of course most obvious in clinical drug trials, which are conducted for example on the treatment of brain tumors, multiple sclerosis, and Parkinson's disease. However, the very tight interconnection of science and patient care is of eminent importance to all areas of disease-related neuroscience and forms the very center of the Hertie concept. It also distinguishes the Hertie Institute from other institutions of neuroscientific research. This concept aims to foster both, scientific excellence and clinical progress.

Das Zentrum für Neurologie

Neurologische Klinik und Hertie-Institut für klinische Hirnforschung

Mit dem im Jahre 2001 unterzeichneten Vertrag zwischen der gemeinnützigen Hertie-Stiftung (GHS) und dem Land Baden-Württemberg, der Universität Tübingen und ihrer medizinschen Fakultät sowie dem Universitätsklinikum Tübingen wurde das „Zentrum für Neurologie" geschaffen, eines der größten Zentren für klinische und krankheitsorientierte Hirnforschung in Deutschland.
Das Zentrum besteht aus zwei eng verbundenen Bereichen, der Neurologischen Klinik und dem Hertie-Institut für klinische Hirnforschung (HIH).
Die Aufgaben des Zentrums liegen in der Krankenversorgung durch die Neurologische Klinik sowie in der wissenschaftlichen Arbeit der im HIH zusammengeschlossenen Forscher auf ihren Forschungsgebieten. Besondere Aufgaben bilden die Heranbildung und Förderung des wissenschaftlichen Nachwuchses sowie der Wissenstransfer.

Das Zentrum besteht aus vier Abteilungen:
Abteilung für Allgemeine Neurologie (Direktor: Prof. Dr. M. Weller)
Abt. f. Neurologie m. Schwerpunkt neurodegenerative Erkrankungen (Direktor: Prof. Dr. T. Gasser)
Abteilung für Kognitive Neurologie (Direktor: Prof. Dr. P. Thier)
Abteilung für Zellbiologie Neurologischer Erkrankungen (Direktor: Prof. Dr. M. Jucker)

Die drei erstgenannten Abteilungen sind an der klinischen Versorgung beteiligt. Mit 52 Betten ist die Abteilung für Allgemeine Neurologie die größte klinische Abteilung. Ihre Schwerpunkte sind die Neuroonkologie, die Neuroimmunologie und die Gefäßerkrankungen des Gehirns. Sie betreibt die Schlaganfall- / Wachstation der Klinik („Stroke-Unit"), in der Patienten mit akutem Schlaganfall behandelt werden. Daran angeschlossen ist seit Ende 2006 die „Post-Stroke-Station", eine Einrichtung der Frührehabilitation, in der Patienten mit abgelaufenem Schlaganfall nachbetreut und bereits intensiv rehabilitativ behandelt werden. Die Zusammenfassung von Akuttherapie und Frührehabilitation in einer organisatorischen Einheit entspricht neuesten klinischen und wissenschaftlichen Standards und dient dazu, das Rehabilitationspotential von Patienten nach Schlaganfall optimal auszuschöpfen.
Die Abteilung Neurologie mit Schwerpunkt Neurodegenerative Erkrankungen konzentriert sich in ihrem klinischen Bereich auf die Diagnostik und Therapie von neurodegenerativen Erkrankungen wie Morbus Parkinson, Ataxien, spastische Spinalparalysen und Demenzen, sowie von anderen Bewegungsstörungen wie Dystonie und Tremor. Für die Bewältigung dieser klinischen Aufgaben stehen der Abteilung eine Schwerpunktstation mit 22 Betten und mehrere Spezialambulanzen zur Verfügung.
Die Abteilung für kognitive Neurologie verfügt nicht über Betten, stellt jedoch die konsiliarische und ambulante neuropsychologische Versorgung sicher.
Die Beteiligung dieser Abteilungen an allen Aspekten der klinischen Versorgung ist eine der wesentlichen Voraussetzungen für die erfolgreiche klinische Hirnforschung am Hertie-Institut. Dies gilt ganz offensichtlich für Medikamentenstudien, die am Zentrum zum Beispiel in der Hirntumorbehandlung sowie der Therapie der Parkinson-Krankheit und der Multiplen Sklerose in erheblichem Umfang durchgeführt werden. Aber auch in allen anderen Bereichen der krankheitsbezogenen Forschung ist die besonders enge Verknüpfung von Klinik und Grundlagenforschung ein fundamentaler Aspekt des Hertie-Konzepts und ein Alleinstellungsmerkmal gegenüber anderen Institutionen der Hirnforschung. So sollen einerseits die Exzellenz der Forschung, andererseits aber auch ihre praktische Anwendbarkeit gesichert werden.

Structure of the Clinical Department

The Center of Neurology comprises three general neurological wards, one mixed neurological-neuro-surgical ward and an intensive care/stroke unit with a total of 74 beds.
The wards, B5-Süd (44), B5-West (43), B6-West (47), as well as the intensive care/stroke unit, belong to the Department of General Neurology. The ward B5-Ost (45) belongs to the Department of Neurodegenerative Diseases. One of the general neurology wards, B5-Süd, is specialized in the care of brain tumor patients. Due to the primary care duties of the University Hospital Tübingen for the broader region, the whole spectrum of neurological diseases including traumatic lesions of the peripheral and central nervous system is covered by the Center of Neurology. It is located in the CRONA building. The central laboratory facilities, the Departments of Surgery (including Neurosurgery), Orthopedics, Radiology (including Neuroradiology), Radiooncology and Anesthesiology, as well as the Departments for Pediatrics and for Internal Medicine are in close proximity.
For 2007, a major restructuring effort is scheduled. This will involve an expansion of the intensive care/stroke unit and a relocation of the other wards. Ultimately, all neurological wards will be located on the fifth floor of tower B of the CRONA building. The intensive care/stroke unit will be connected to the neuroradiology facilities on floor B3 by an additional elevator in order to speed up, in particular, the imaging for acute ischemic stroke. The restructuring, which will be completed early in 2008, can thus be expected to increase efficiency of work within the Center of Neurology.

The general neurological outpatient clinic primarily treats referrals from neurologists and in-patients treated in other departments of the University Hospital Tübingen. In addition, there is a large number of specialized outpatient clinics. For in-patients on intensive care wards and for patients who are too ill to visit the general neurological clinic, a neurological consult service is provided. This service extends also to patients treated at the Berufsgenossenschaftliche Unfallklinik as well as geriatric patients in the Paul-Lechler-Krankenhaus in Tübingen and the hospital in Rottenburg as part of the interdisciplinary geriatric center.

Outpatient Clinics

Neurooncology

This outpatient clinic sees about 180 new patients each year and all visits add up to more than 850 patient contacts. The main focuses are (i) monitoring of outpatients' chemotherapies, (ii) follow-up examinations of patients without current specific anti-tumor therapy at longer intervals, and (iii) evaluation of patients who have been diagnosed and treated at a community facility and are informed about futher diagnostic and therapeutic options, including experimental therapies within neurooncological trials. A fraction of these patients are included into the regular follow-ups of the clinic. Patients are regularly seen on Mondays, Tuesdays and Wednesdays, but there are flexible appointments for urgent situations at any time. This outpatient clinic is run by Dr. O. Bähr and all members of the neurooncology team of the department, as well as supervised by the consultant that specializes in brain tumor patients, in 2006 PD Dr. J. Steinbach. The neurooncological outpatient clinic serves as an interdisciplinary clinic of the Center of Neurooncology at the Südwestdeutsche Tumorzentrum / Comprehensive Cancer Center Tübingen. This implies a regular dialogue with colleagues of the Departments of Neurosurgery, Radiooncology, Neuroradiology, Pediatrics and Oncology. Complex diagnostic or therapeutic tasks are discussed by the Brain Tumor Board (Coordination by Dr. O. Bähr and PD Dr. J. Steinbach) on Tuesdays at 4 p.m. Since October 2004, the German Cancer Council sponsors clinical neurooncology in Tübingen within the German Glioma Network (www.gliomnetzwerk.de).
M. Jeric, S. Schwarze, and U.Küstner are appointed study nurses and involved in the organization of all outpatient clinics and unicenter as well as large multicenter trials and specific training for the patients.

Neuroimmunological Disorders

Patients with multiple sclerosis, myasthenia gravis, immune-mediated neuropathies, and other neuroimmunological disorders are regularly seen in the clinic for neuroimmunological diseases. Complex cases may be discussed in interdisciplinary conferences with collegues from rheumatology, neuroophthalmology, neuroradiology, and neuropathology.
Patients with multiple sclerosis are referred for diagnosis, follow up, or second opinion. Counselling about immunomodulatory and immunosuppressive therapy follows the guidelines by the German 'Multiple Sclerosis Therapy Consensus Group'. Standardized examination of patients is performed according to the Expanded Disability Status Score (EDSS) and the Multiple Sclerosis Functional Composite Score (MFSC). Patients interested to take part in clinical trials are interviewed, screened, and recruited after presentation in this clinic. M. Jeric (study nurse) is organizing appointments and offers training for injection of interferons and copaxone.
In 2005 and 2006 the clinic was run by Dr. M. Albert, Dr. S. Gaertner, Dr. M. Pick, and Dr. B. Greve under the supervision of Prof. A. Melms and Prof. R. Weissert.

Outpatient Clinics

Headache and Neuropathic Pain

Our Headache Outpatient Unit focuses on the diagnosis and treatment of primary headache disorders and facial pain. Patients can be referred by either their general practioner or neurologist. Apart from treatment of patients with episodic migraine, we are specialized in the therapy of chronic headache disorders like chronic migraine, chronic tension type headache, and medication overuse headache. Moreover, we take care of patients with rare primary headache disorders like cluster headache, hemicrania continua, or SUNCT-syndrome. PD Dr. J. Steinbach is the head of the Headache Outpatient Unit. Since 2006, the patients are seen by Dr. S. Schuh-Hofer, who has specialized on headache and neuropathic pain during her training at the Department of Neurology at the Charité University Hospital Berlin. In November 2006, Dr. S. Schuh-Hofer organized a symposium on the pathophysiology and therapy of primary headache disorders in order to intensify the contact of our Department with general practioners, anaesthesiologists and neurologists who are interested in the field of headache.
Within the UKT, there is a close collaboration with the Department of Anesthesiology which organizes interdisciplinary pain conferences. Moreover, the Department of Neurology closely collaborates with the "Palliative Care Unit" in Tübingen ("Tübinger Projekt zur häuslichen Versorgung Schwerkranker", Dr. T. Schlunk).

Neurovascular Diseases & Neurorehabilitation

The neurovascular outpatient clinic provides services for patients with neurovascular diseases including ischemic and hemorrhagic stroke, cerebral and cervical artery stenosis, microvascular disease, cerebral vein thrombosis, vascular malformations, and cerebral vasculitis. Its focus is on diagnosis, discussion and decision about treatments, secondary prevention, and neurorehabilitation strategies and schedules. Diagnostic tests performed as part of an outpatient visit include: Blood tests, Duplex Ultrasound of cervical and intracranial vessels, Electrocardiogram, Echocardiogram, and Evaluation by a physiotherapist focusing on rehabilitation potentials. Computed tomography and magnetic resonance imaging are carried out in cooperation with the Department of Neuroradiology at the University of Tübingen.
The clinic is staffed with a resident and an attending physician (PD Dr. A. Luft, Prof. A. Melms).

Epilepsy

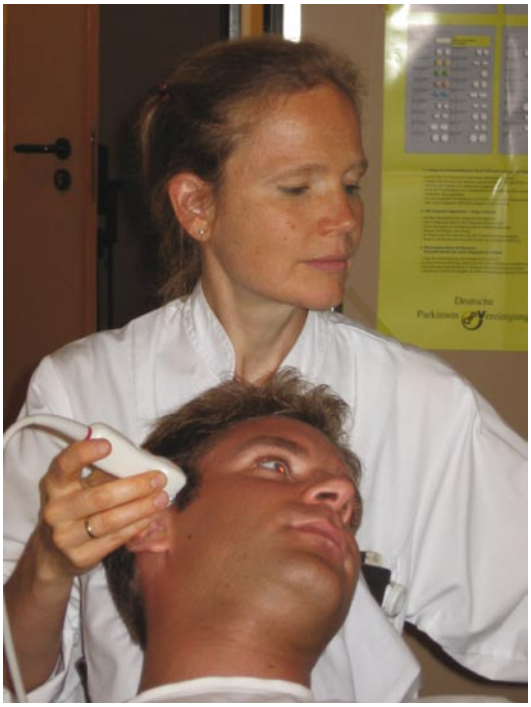
The clinic for patients with epilepsy is held Fridays, 9:00 a.m until noon. Currently, there are approximately 150 patients who visit the clinic regularly.
All aspects of this disorder are covered, including diagnosis, initial treatment, and care for patients with refractory disease. Many patients are referred by neurologists to answer questions regarding the management of difficult clinical situations, e. g. pregnancy or permission to drive motor vehicles. Inpatients from other departments are also seen when epilepsy is caused by a systemic disease or is complicating treatment.
Within the University Hospital, there is a close collaboration with the Department of Neurosurgery and the Epilepsy Clinic of the Neuropediatric Department. There is also interaction with the centers for epilepsy at the University hospitals in Freiburg and Bonn.
This clinic is run by Dr. S. Schuh-Hofer and supervised by PD Dr. T. Haarmeier.

Outpatient Clinics

Geriatrics

The Center of Geriatric Medicine was established at the University Medical Center of Tübingen in 1994 to improve the care for geriatric patients in this region. The activities of the University Clinics for Medicine IV, Neurology, and Psychiatry are currently coordinated by the University Clinic for Psychiatry and Psychotherapy. External partners are the Paul-Lechler-Krankenhaus in Tübingen, the community hospital in Rottenburg and the rehabilitation clinic in Bad Sebastiansweiler near Tübingen. The supervisors of the neuro-geriatric team provide a regular consult service for these institutions. The neuro-geriatric team takes an active part in seminars, teaching, and training activities of the Center of Geriatric Medicine.
Geriatric patients are a special group of elderly people, usually more than 70 years old, who present with multiple and complex medical problems. In our patients, disabilities from cerebrovascular and neurodegenerative diseases are most prevalent in combination with cardiovascular, respiratory, and metabolic disorders. Approximately 30% of the patients admitted to the department including the stroke unit are over 65 years old and most of them conform to the definition of geriatric patients. Geriatric patients are often handicapped by incontinence, cognitive decline or dementia, and susceptibility to falls, all of which complicate the reconvalescence from the primary disease. Specific deficits are identified by geriatric assessments. Neuro-geriatric patients receive physiotherapy for mobility training, neuropsychological training for spatial neglect, speech therapy for aphasia and dysphagia, and occupational therapy for handicaps concerning activities of daily living. Allocation of therapy and resources are discussed in an interdisciplinary geriatric team. Counselling of patients, spouses, and family members about community services and organization of geriatric rehabilitation is managed by Dipl. Soz.Päd.-FH A. Steinhauser and Dipl.Soz.Päd. van der Lipp from the social-medicine service. This clinic is managed by Prof. A. Melms, PD Dr. R. Haarmeier, and PD Dr. R. Krüger.

Parkinson's Disease



The Center of Neurology at the University of Tübingen runs the largest outpatient clinic for patients with Parkinsonian syndromes in southern Germany. More than 100 patients are seen every month. A major focus of the clinic is the early differential diagnosis of different Parkinsonian syndromes. The development of transcranial sonography by members of the department draws patients from all over Germany to confirm their diagnosis which, if necessary, is substantiated by other tests, like the smelling test or neuroimaging investigations with SPECT and/or PET. Genetic testing is offered to patients and relatives with familial Parkinsonian syndromes who may obtain genetic counseling in cooperation with the Department of Medical Genetics.
The second focus is the treatment of patients in later stages of the disease with severe non-motor symptoms or drug-related side effects. In some of

Outpatient Clinics

these patients, treatment may be optimized by intermittent or continuous apomorphine application, which is supervised by a specially trained nurse. Other patients may be referred for deep brain stimulation (DBS) of the subthalamic nucleus or the thalamus.
Various multicenter drug trials, for patients in different stages of the disease, offer the possibility to participate in new medical developments. Currently, we offer participation in studies involving a highly selective glutamate receptor antagonist of the AMPA type, a combination of Levodopa, Carbidopa, and the COMT-inhibitor entacapone (Stalevo ®), the novel MAO-B-inhibitor, rasagiline, the dopamine agonist pramipexol, and a new application form of apomorphin as nasal powder. These activities are supported by the study nurses Marion Jeric and Susanne Schwarze. Additionally, the impact of various standardized physical activities on motor function as well as neuronal plasticity, determined by MRI-measurement, is being investigated in studies in cooperation with the Sports Departments at the Universities of Tübingen and Stuttgart.
With the improvement of motor control by new treatment strategies, non-motor symptoms in patients with advanced Parkinsonian syndromes are an area of increasing importance. In particular, dementia and depression have been recognized to be frequent in these patients. Standards in diagnosis of these symptoms are being established (for depression in a multicenter benchmarking project, supported by the BMBF) and optimized treatment is offered.
Seminars and courses on specific topics related to diagnosis and treatment for neurologists, in cooperation with the lay-group for Parkinson's patients (the Deutsche Parkinson-Vereinigung, dPV) are organized. Moreover, visitors from all over the world are trained in the technique of transcranial sonography in monthly hospitations.
Appointments are scheduled daily in the outpatient clinic of the Center of Neurology. Patients are seen by Prof. Gasser, PD Dr. Berg, Dr. K. Schweitzer, Dr. A. Gänslen, A. Di Santo, J. Godau, and Dr. rer nat. I. Liepelt .

Deep Brain Stimulation

Also named "brain pacemaker", deep brain stimulation (DBS) is considered the most significant progress in the treatment of neurodegenerative movement disorders over the last decades. As a novel treatment option DBS has been implemented in Tübingen in cooperation with the Department of Neurosurgery in 1999. The concept of treatment and medical attendance developed by the task group 'deep brain stimulation' of the University Clinic of Tübingen involves close interaction between neurologists, neurosurgeons, neuropsychologists, and physiotherapists. Patients are referred from resident specialists as well as our outpatient

clinics for Parkinson's disease and dystonia. In 2006 the indication for DBS was given and successful intervention was performed for 20 patients with Parkinson's disease (12 patients), essential tremor (6 patients), and dystonia (2 patients).
Patients that are considered to benefit from DBS undergo a detailed program of standardized neurological, neuropsychological, neuroradiological, and cardiological examinations on our ward for neurodegerative disorders. Patients treated with DBS are closely followed by our outpatients clinic to ensure optimal adjustment of stimulation parameters.
The outpatients clinic for DBS is focused on patient selection and counselling of patients eligible for DBS based on neurological examination and medical history. Moreover the task group 'deep brain stimulation' organizes regular informative meetings for patients and relatives in cooperation with the German Parkinson's disease Association (dPV, *see figure left side*).
Appointments are scheduled weekly in the outpatient clinic for DBS.
Patients are seen by PD Dr. R. Krüger, Dr. T. Wächter, Dr. S. Breit.

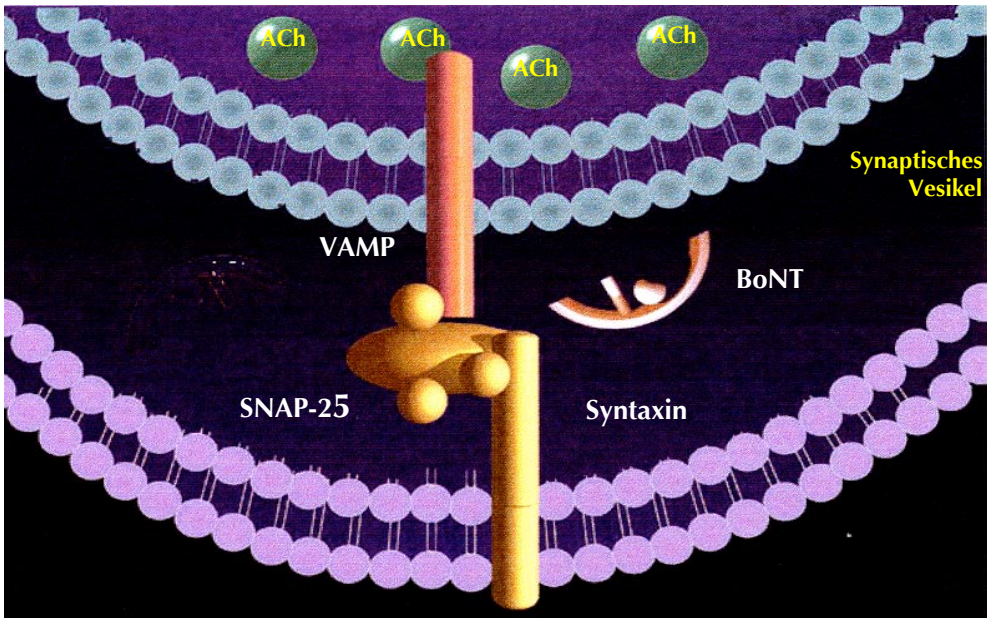
Restless Legs Syndrome

Restless Legs Syndrome (RLS) affects more than 4 million people in Germany. Although one of the most common neurological disorders, RLS is largely underdiagnosed and often not sufficiently treated. One major problem is the lack of morphological markers for RLS. To date, diagnosis is based only on the patient's history.
In the RLS outpatient clinic about 50 patients with different disease stages are seen every month. The main focus lies on the evaluation of a detailed medical history, neurological examination, and transcranial sonography. Typical comorbidities such as depression and anxiety disorders, sleep disorders, chronic pain syndromes, and movement disorders such as periodic limb movements and essential tremor are routinely assessed in all patients. In close cooperation with the Neurosonology and Electromyography laboratories differential diagnoses are followed. This thorough workup enables differentiation of RLS subtypes in order to optimize the treatment strategies according to the patient's specific needs. Since effective medical treatment can only be achieved by concomitant adaptation of daily habits, including nutrition, exercise, and sleep habits, individual counseling concerning life style management is offered in close cooperation with local lay groups (RLS association).
We have a major interest in a more profound understanding of the RLS pathophysiology in order to improve diagnosis and treatment of this common disorder. By establishing a sonographic marker for RLS, we were able to improve the diagnostic approach to RLS. Within the scope of our RLS outpatient clinic we perform clinical and epidemiologic studies to evaluate the diagnostic value of transcranial sonography for RLS and to assess the connection between RLS and its common comorbidities. Moreover, our patients are offered to take part in studies investigating possible alterations of the brain iron metabolism using MRI and CSF examinations. Additionally, we collect DNA samples from patients with sporadic and familial RLS for genetic analysis.
Patients are seen by J. Godau and PD Dr. D. Berg.

Outpatient Clinics

Dystonia

Our outpatient clinic offers a comprehensive evaluation and a full range of therapies for patients with different forms of dystonia, spasticity, and hyperkinetic movement disorders.
About 450 outpatients are regularly treated with botulinum toxin (BoNT) injections in intervals of 3-4 months. Most of our patients suffer from cranial, cervical, or segmental dystonia. New treatment approaches for rare dystonic syndromes like Pisa syndrome or camptocormia are evaluated.
For complex patients, who are admitted with insufficient treatment response to BoNT, EMG and ultrasound-guided injection techniques are used. Eligible patients with severe forms of idiopathic segmental or generalized dystonia are referred for pallidal deep brain stimulation (DBS) to our Department of Neurodegenerative Diseases.
Treatment evaluations also include physical and ergotherapeutic therapies with a special focus on task-specific dystonias. With the help of Frau Wiesemeier, Therapiezentrum UKT, an ergotherapeutic approach for the treatment of writer's cramp is offered.
Bi-annual basic courses in botulinum toxin injection therapy for cranial and cervical indications have been successfully conducted for colleagues, who wanted to acquire skills in treatment approaches for dystonias and the injection techniques of botulinum toxins.



In January 2006 an expert meeting on the new developments in botulinum toxin therapy was held, covering topics like the genetics of dystonias, the evaluation of transcranial ultrasound in the diagnosis of dystonias, the use of EMG and imaging techniques as well as immunological aspects of the new complex-free botulinum toxin A (NT 201).
In August 2006 another expert meeting took place with the focus on the management of tardive syndromes. Talks were given about recent developments in neuroleptic therapy, the management of tardive dyskinesias by botulinum toxin injections and about DBS as a valuable treatment alternative.
Together with the dystonia clinic at the University of Innsbruck, Prof. Dr. J. Müller, a specific screening questionnaire for relatives of index patients in dystonia families was applied to acquire a larger collective of patients with hereditary dystonias. *(see figure: Molecular action of Botox)*.

Outpatient Clinics

Appointments are scheduled every week on Wednesdays and Thursdays in the Outpatient Clinic of the Center of Neurology. (Dr. F. Asmus, Prof. Dr. T. Gasser)
Medical Staff: Dr. F. Asmus, Dr. C. Kamm, Dr. R. von Coelln, Dr. S. Hansmann, Dr. T. Lindig

Memory Clinic

Dementia is one of the most common syndromes of the elderly population and a major cause of disability and mortality. Causes of dementia are very variable. The most common neurodegenerative form of dementia is Alzheimer Disease. However, dementia associated with Parkinsonian syndromes, including idiopathic Parkinson's disease, diffuse Lewy body disease, Progressive supranuclear palsy, and Corticobasal ganglionic degeneration, are also frequent.
Behavioral symptoms in dementia (e. g. depression, apathy) are an important predictor for nursing home placement, mortality, and a major source of distress both to patients and their families which can, in the case of dementia with Parkinsonian symptoms, even be more debilitating than the motor impairment. Up to now, the etiology and the disease course of dementia with Parkinsonian symptoms as well as the similarities and differences to other dementias are only partly understood.
In a weekly memory outpatient clinic (Dr. W. Maetzler, PD. Dr. D. Berg) patients are investigated by a thorough clinical examination, neuropsychological testing (Dr. rer. nat. Dipl.-Psych. I. Liepelt), serum and CSF-analyses as well as MRI and PET. Moreover, multimodal therapeutic strategies including medication, memory training, and social counseling are provided, in co-operation with the memory clinic of the Department of Psychiatry.
Aims of our clinical (e. g. treatment studies) and imaging studies (PET) are a better understanding of general mechanisms leading to dementia. Furthermore, we focus on the time course of disease progression and the efficacy of existing and new treatment options.
Medical Staff: Dr. W. Mätzler, Dr. rer. nat. Dipl.-Psych. I. Liepelt, PD Dr. D. Berg

Ataxia

The ataxia clinic of the Center of Neurology provides tools to discover the cause of ataxia in close cooperation with the Department of Neuroradiology (MRT, MR-Spectroskopy) and Radiopharmacy (PET). For patients and families with hereditary forms of ataxias, research projects in cooperation with the Institute of Medical Genetics offer molecular genetic analyses beyond the scope of routinely available genetic diagnostics.
Therapeutic options depend largely on the underlying cause of ataxia, the genetic defect, and concomitant symptoms. In cooperation with the Center of Physiotherapy, we developed special exercise programs for ataxia and evaluate therapeutic effects by ataxia scores, gait analysis, and quantitative tests for fine motor skills.
Within the European research initiative EURO-SCA (http://www.eurosca.org/) and the German Network for hereditary Movement disorders (GeNeMove) (http://www.genemove.de), we offer a placebo-controlled trial with idebenone in Friedreich's ataxia and analyze progression markers and factors modifying the course of spinocerebellar ataxias in a prospective natural history study.
This clinic is run by Dr. C. Globas and Dr. C. Linnemann and is supervised by Prof. Dr. L. Schöls.

Outpatient Clinics

Spastic Paraplegia

The outpatient clinic for spastic paraplegia offers a specialist setting for the differential diagnostic workup and genetic characterization of patients with spastic paraplegia using the facilities of the Hertie Institute for Clinical Brain Research and cooperations with the Institute of Medical Genetics and the Department of Neuroradiology.
Therapeutic options depend essentially on the underlying cause of the disease. If no causal treatment is available, therapeutic options include antispastic drugs, intrathecal application of Baclofen, and local injections of Botulinum toxin.
A national network for hereditary spastic paraplegia research, funded by the German Ministry of Education and Research (BMBF), is coordinated in Tübingen as part of the German Network of Hereditary Movement disorders (GeNeMove) (http://www.genemove.de). This project runs a natural history study and develops progression markers for spastic paraplegia as an essential prerequisite for forthcoming therapeutic trials aiming to slow the progression of the disease. To this end, a novel spastic paraplegia rating scale was developed and evaluated as a reliable and valid score of disease severity.
The clinic is run by R. Schüle and K. Karle and is supervised by Prof. Dr. L. Schöls.

Leukodystrophies in Adulthood

Leukodystrophies are usually regarded as diseases that occur in infancy and childhood. However, for most leukodystrophies adult-onset forms have been identified but still frequently escape attention. The German Ministry of Education and Research (BMBF) supports a national research network for leukodystrophies (LeukoNet) (http://www.leukonet.de/) that analyzes the natural course of the diseases and especially adult variants as an essential prerequisite for therapeutic studies. Nerve conduction studies and evoked potentials are currently investigated as potential progression markers. Genotype-phenotype studies help to recognize unusual disease manifestations and to identify factors modifying the course of leukodystrophies.
Patients are seen by Prof. Dr. L. Schöls.

Motoneuron Disease

Motoneuron diseases are caused by the degeneration of primary motor neurons in the cerebral cortex (upper motor neuron) and the ventral horns of the spinal cord (lower motor neurons). In the most common form of motoneuron disease – amyotrophic lateral sclerosis (ALS) – both upper and lower motor neurons are affected. In less frequent types of motoneuron disease the upper or the lower motor neuron is affected selectively.
Detailed neurological examination provides essential diagnostic information. Instrumental tests include nerve conduction studies, electromyography, and evoked potentials. Additional diagnostic procedures (e. g. blood tests, lumbar puncture for cerebrospinal fluid, and imaging of the brain and spinal cord) are necessary to exclude rare diseases mimicking ALS. Therefore, in most cases an inpatient treatment is required to confirm the diagnosis of ALS. Follow-up of those patients as well as management of symptoms and complications are provided by the clinic.
The clinic is run by Dr. W. Mätzler, supervised by Prof. L. Schöls.

Outpatient Clinics

Dizziness Service

The dizziness outpatient service offers state-of-the-art diagnostic evaluation, treatment and follow-up for patients suffering from acute or chronic dizziness. As the limited resources of the unit should be primarily devoted to the assessment of patients suffering from specific forms of dizziness, admitting institutions are requested to filter out patients whose complaints are an unspecific reflection of a more general problem. The dizziness service is available for outpatients on Wednesday mornings. The diagnostic work-up starts with a precise assessment of the history and character of the complaints, followed by a thorough clinical examination with special emphasis on visual, vestibular, and oculomotor functions complemented by electronystagmography, measurement of subjective vertical, electroencephalography, and ultrasound examination of the major blood vessel supplying the brain. If needed, high resolution 3D eye movement measurements based on cutting-edge video or search coil techniques are added. As a result of this work-up, functional alterations compromising spatial vision and orientation may be disclosed, which in many cases do not have a morphological basis ascertainable by brain imaging techniques.

Revealing specific forms of dizziness leads to the application of specific therapeutic measures such as exercises customized to treat benign paroxysmal positional vertigo. Most of the patients seen in the unit suffer from dysfunction of the organ of equilibrium, the vestibular labyrinth, or a disturbance of the brain mechanisms processing vestibular information. In others, the dizziness can be understood as a specific form of phobia or related psychological maladjustment. Currently, attempts are being made to establish improved therapeutic offers also for this latter group of patients not suffering from a primary neurological or otological condition.
The dizziness service is run by PD Dr. T. Haarmeier and Dr. J. Pomper.

Neuropsychology

Strokes not only lead to motor and sensory impairments but often also cause disorders of higher brain functions such as speech, attention, perception, memory, intelligence, problem solving, or spatial orientation. The prerequisite for designing a treatment strategy which is effective and tailored to the patient's particular needs is a careful neuropsychological evaluation of the specific pattern of disorders. The Neuropsychology Outpatient Clinic determines, for example, whether a patient exhibits an abnormal degree of forgetfulness, whether a patient exhibits signs of dementia, whether he is capable of planning appropriate actions to perform given tasks, whether speech is impaired, or which kinds of attention-related functions may have been damaged and need to be treated. These and other examinations are carried out in the Neuropsychology Outpatient Clinic of the Neuropsychology Section (Elisabeth Becker and Prof. Dr. Dr. H.-O. Karnath).
Contact: Dipl.-Psych. Elisabeth Becker, phone 07071 29-85166, elisabeth_becker@gmx.de

Laboratories

Neurosonology and Echocardiography Laboratory

The ultrasound laboratory is equipped with a Toshiba and Siemens Sequoia Color-coded Duplex sonography systems as well as portable CW/PW Doppler probes. Routine diagnostic tests include Duplex imaging of carotid, vertebral, and subclavian arteries, as well as the Circle of Willis (with and witout contrast). Functional testing for vertebral steal, persistent foramen ovale, cerebral microembolism (HITS), and CO_2 vasoreactivity tests are routinely performed.
The laboratory consists of a unit in the neurology outpatient department focusing mainly on neurosonology of extracranial and intracranial arteries. The ultrasound unit in close proximity to the Stroke Unit is run by Dr. Erharhaghen, a cardiologist and intensive care specialist who performes transthoracic and transesophageal echocardiography. The mobile ultrasound scanner can be moved to the Stroke Unit for various ultrasound applications (abdomen, thyroid, peripheral vessels). The scanner is equipped with a high-resolution linear probe to allow for an assessment of stenosis and plaque morphology. Each year we conduct approximately 4,000 examinations of extracranial arteries and approximately 3,000 transcranial Doppler or color-coded Duplex exams. Dr. Erharhaghen performed approximately 1000 transthoracic and 200 transesophageal echocardiographies each year. Our residents are trained according to DEGUM guidelines for 4 months in the neurosonology laboratory. Laboratory staff: neurology resident, R. Mahle (staff technician); PD Dr. A. Luft (head of laboratory).

EEG Laboratory

The electroencephalography (EEG) laboratory is equipped with 1 mobile digital and 3 stationary recording places (IT-Med). For analysis, 5 additional PC-based EEG terminals are available. The recording and analysis workstations are connected via an internal network, and digital EEG data are stored on local servers making all previous and current EEGs available 24 hours a day, 7 days a week. An additional mobile paper EEG recording unit is used for brain-death diagnostics. On the neurological stroke unit, a digital 4-channel EEG unit is available and is used to continuously monitor patients with severe brain dysfunction such as after status epilepticus, or in various forms of coma. Each year, approximately 3,000 EEGs are recorded in outpatients and inpatients. The typical indications for EEG testing are epilepsy, brain tumors, stroke, brain injury, neurodegenerative disorders, and coma or milder forms of altered consciousness. EEG training is conducted according to the DGKN guidelines. The EEG training course lasts for 1 year and is provided for 6 neurological residents at a time. Laboratory staff: M. Dengler, B. Wörner (staff technicians); PD Dr. T. Haarmeier (head of laboratory).

Laboratories

Polysomnography Laboratory

The polysomnography laboratory (sleep laboratory) is available for the evaluation of patients with nocturnal movement disorders (periodic leg movements in sleep [PLMS]), restless-legs syndrome [RLS], myoclonus, sleep-disordered breathing (sleep apnea syndrome; including nCPAP and nBiPAP therapy), and narcolepsy (e. g., multiple sleep latency test). The laboratory is equipped with a digital EEG recording unit (Nihon Kohden) and an infrared video camera system. For analysis, EEG and video data are synchronized and can be viewed simultaneously. Patients rest in a single-bed room located on a neurological inpatient ward (B5-Süd) and are monitored from a separate computer room. Currently, approximately 80 polysomnographies per year are recorded according to the guidelines of the DGSM (German Society of Sleep Medicine). Laboratory staff: Dr. T. Wächter, Dr. G. Eisele (residents); B. Wörner, M. Dengler (staff technicians); Dr. C. Globas, PD Dr. A. Luft (heads of laboratory).

EP Laboratory

The EP (evoked potentials) laboratory provides a full range of evoked potential procedures for both inpatient and outpatient testing. All recordings are performed using a 4-channel system and can be conducted in the laboratory as well as in patient rooms, intensive care units and operating rooms. Procedures include visual evoked potentials, brain stem auditory evoked potentials, short latency somatosensory evoked potentials of the upper and lower extremities, and spinal evoked potentials. Around 2,500 examinations are performed each year on more than 1,600 patients. The recordings are conducted by M. Berger (until 3/2006), A. Deutsch, and J. Grimm who are supervised by PD Dr. T. Haarmeier. According to the guidelines of the German Society for Clinical Neurophysiology, the recordings are analyzed and interpreted during daily conferences visited by up to six interns. Apart from the interns of our own clinic who attend for at least one year, colleagues from the Departments of Neurosurgery and Neuropediatrics make use of this continuing training.

Electromyography Laboratory

The EMG Laboratory offers all the standard electromyography and neurography procedures for the electrodiagnosis of neuromuscular diseases including polyneuropathies, entrapment neuropathies, traumatic nerve lesions, myopathies, myasthenic syndromes, and motor neuron diseases. In selected cases, polygraphic recordings for tremor registration, registration of brainstem reflexes, exteroceptive reflexes and reflexes of the autonomous nervous system are performed. The laboratory is equipped with two digital systems (Nicolet Viking IV and Toennies Multiliner). A portable system (Nicolet Viking Quest) is available for bedside examinations. A backup system (Nicolet Viking IV) is currently used in the dystonia outpatient clinic. In 2006, more than 3,000 patients were seen and more than 20,000 recordings were done. In most cases (approximate 80%), a combination of neurography and electromyography is requested. In addition, a Magstim 200 stimulator is available for transcortical magnetic stimulation and recording of motor cortex-evoked potentials in approximately 500 patients per year. The EMG Laboratory is organized by Mrs. J. Grimm who also performs neurography with surface electrodes. In 2006, colleagues Dr. H. Golla, Dr. M. Hermisson, Dr. F. Bischof, Dr. F. Asmus, Dr. S. Breit were trained in EMG techniques and supervised by Prof. W. Wick, PD Dr. T. Haarmeier and Prof. A. Melms.

Laboratories

ENG Laboratory

Approximately 300 patients suffering from otoneurological or neuro-ophthalmological problems are examined each year using electronystagmography (ENG). Most patients examined present specific vestibular syndromes (also see Dizziness Service). For diagnosis, eye movements are recorded binocularly using DC oculography, are digitally stored and analyzed off-line. Eye movements are induced by single diodes to test saccades or gaze holding, by a laser system eliciting smooth pursuit eye movements, and by whole field visual stimuli to evoke optokinetic nystagmus in all directions. Besides testing of visually guided eye movements which provide information on cerebellar and brainstem functions, emphasis is placed on the examination of the vestibular system including the search for spontaneous nystagmus, head shaking nystagmus, positioning/positional nystagmus, and the assessment of the vestibulo-ocular (VOR) reflex (caloric and rotation tests). The recordings are performed by G. Schönwälder and analyzed by Dr. J. Pomper. For more complex questions, e. g., isolated testing of single canals, and for research, a unique vestibular stimulator (Dornier) is available which allows the rotation of a human subject around any axis relative to the body and relative to gravity. The subject sits in a capsule, on which spherical inner surface visual stimuli can be projected. Movements of the eyes and head, as a function of head rotation and visual stimulation, are measured in three dimensions using magnetic search coils. The laboratory also offers otolith testing such as the measurement of the subjective visual vertical assessed by asking a patient to adjust a line (laser) to their subjective vertical.
The laboratory is supervised by PD Dr. T. Haarmeier.

Clinical Chemistry Laboratory

The Clinical Chemistry Laboratory collects more than 2,500 samples of cerebrospinal fluid (CSF) per year throughout the university medical center. Routine parameters include cell count, glucose, lactate and protein analysis, i. e., albumin and IgG in serum and CSF. Oligoclonal bands in CSF and serum are detected by isoelectric focusing and silver staining. Cytotology of CSF is analyzed on cytospins after Giemsa or Pappenheim staining. Junior staff are routinely trained to perform basic CSF examination techniques and the interpretation of results as part of their speciality training. The laboratory takes part in quality management activities of CSF parameters and drug levels. Immunopathology includes the determination of a set of autoantibodies for the diagnosis of certain neuroimmunological syndromes: autoantibodies to acetylcholine receptors, autoantibodies to muscle specific tyrosine kinase (MuSK), autoantibodies to titin for myasthenia gravis, and autoantibodies to gangliosides for immunoneuropathies. More recently, CSF-levels of amyloid peptide beta42, tau, and phospho-tau are measured to differentiate various forms of dementia. The laboratory measures drug levels of anticonvulsive drugs including carbamazepine, diphenylhydantoin, valproic acid, phenobarbital, and primidone.
The laboratory is supervised by Prof. Dr. A. Melms.

Laboratories

Cardiological Diagnostics

Cardiac diseases represent the leading cause of death. This is mainly due to ischemic heart disease. The Dutch TIA Study demonstrated that patients with a TIA or minor stroke have an increased cardiovascular mortality. Stroke, therefore, seems to represent an index event for cardiac diseases. Cardiovascular investigations after stroke not only identify cardio-embolic sources of cerebral events but also allow for the identification of vascular risk factors.
Diseases of the heart are responsible for 20% of all strokes and usually cause territorial apoplexies. Hypertension is the main risk factor for strokes. After an acute stroke, cardiac investigations are urgently required to find potential cardiac causes for stroke in order to reduce the risk of recurrence of an early stroke within days or weeks. Our department has its own laboratory for neurocardiology, manned by J. Erharhaghen, specialist physician. The laboratory is fully equipped with a modern ultrasound and echocardiography machine (Acuson Sequioa 512, Siemens) including probes for transthoracic and transesophageal investigations as well as abdominal and other soft tissue ultrasound (pleural, thyroid etc). The same equipment can be used for Doppler investigation of the extracranial as well as intracranial vessels. This enables us to perform bedside Doppler investigations and echocardiography of stroke patients on the ward immediately after diagnosis.
In 2006, we performed 1050 echocardiographic investigations, including M-Mode, 2-D mode, pulse-waved and continuous Doppler and color Doppler investigations as well as contrast-enhanced echocardiography. The younger the patients are, the higher is the probability of identifying a cardiac cause of stroke. In younger patients, we regularly search for a patent foramen ovale and atrial septum aneurysm using a transesophageal device with contrast-enhancement. All investigations are done according to the guidelines of the German and European Society of Cardiology.
Atrial fibrillation represents the most common rhythm disorder in the elderly. Atrial fibrillation, in combination with additional risk factors, represents a very common cause of stroke. In our stroke unit, we have a completely equipped long term registration unit consisting of 24-hour ECG (Holter ECG), 24-hour ambulatory blood pressure measurement, and 7-day event recorders. In 2006, we recorded ~800 24-hour ECGs and ~750 24-hour ambulatory blood pressure measurements. In order to find the underlying causes of syncope, we perform tilt table investigations. To identify a hypersensitive carotid bulb, carotid pressure testing is performed. Specialist physician J. Erharhaghen is responsible for these cardiac investigations.

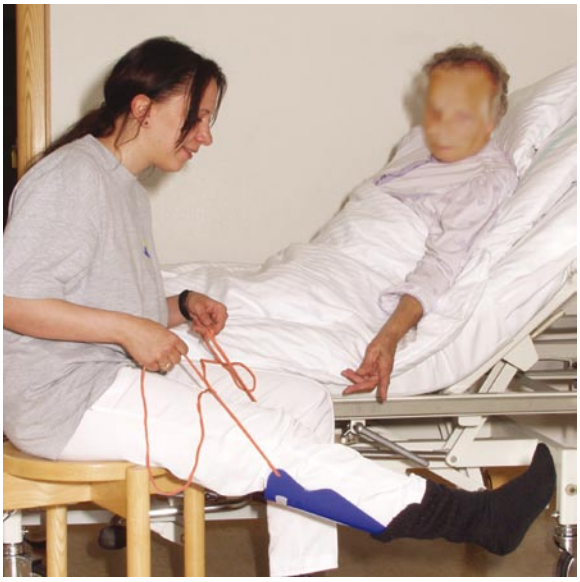
Neuropsychological Testing

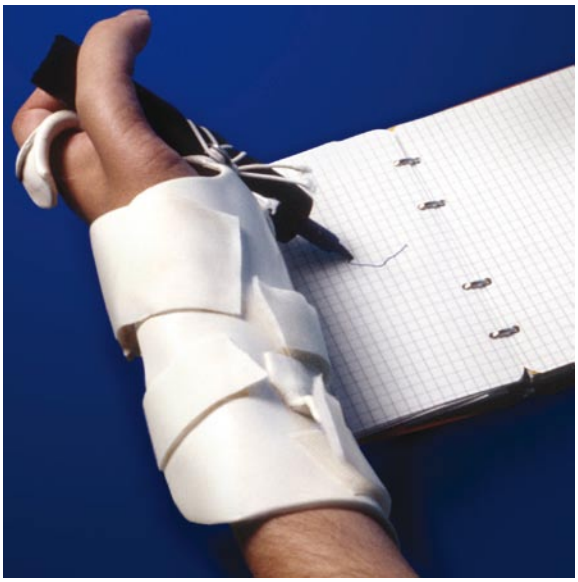
In addition to motor and sensory impairment, stroke often leads to cognitive or affective disorders. These disorders affect attention, perception, memory, language, intelligence, planning and action, problem solving, spatial orientation, or sensori-motor coordination. Effective treatment of these impairments requires a careful neuropsychological examination of the impairment. Neuropsychological examinations for the Center of Neurology are conducted at the Neuropsychology Section (head Prof. Dr. Dr. H.-O. Karnath) and involve standardized protocols and psychological testing.

Physical, Occupational & Speech Therapy

Physiotherapy

All neurological inpatients with sensory or motor deficits, movement disorders, pain syndromes, and degenerative spinal column disease are allocated to individualized physiotherapy according to the decision of the responsible physician. Furthermore, group treatments are offered to several patient groups. Doris Brötz leads the team of physiotherapists within the "Therapiezentrum" responsible for the neurological wards. Specialized concepts for certain disease groups have been worked out scientifically. These include diagnostics and therapy of lumbar disk prolapse, pusher syndrome, and back pain in patients with Parkinson's disease.





Occupational Therapy

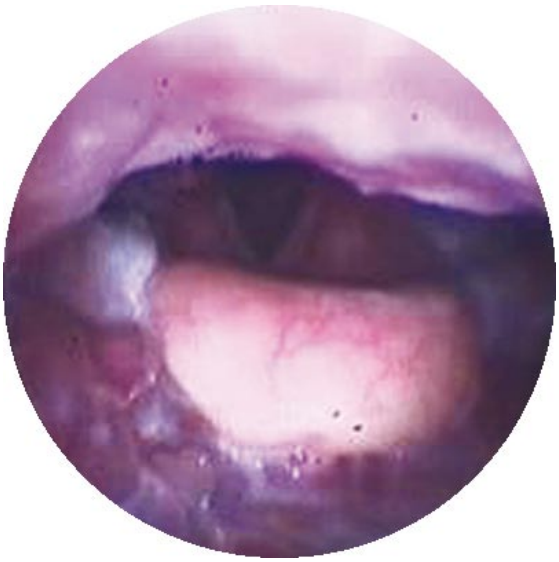
Currently, four occupational therapists are working part-time in the department (I. Hartmann, A. Nölk, M. Wallis, S. Wiesemeier). The treatment program is focused on patients with handicaps from acute strokes, brain tumors, inflammatory diseases, movement disorders, neurodegenerative diseases, and disabilities from disorders of the peripheral nervous system. In 2005, approximately 700 patients were seen. Among these, about 300 were geriatric patients.

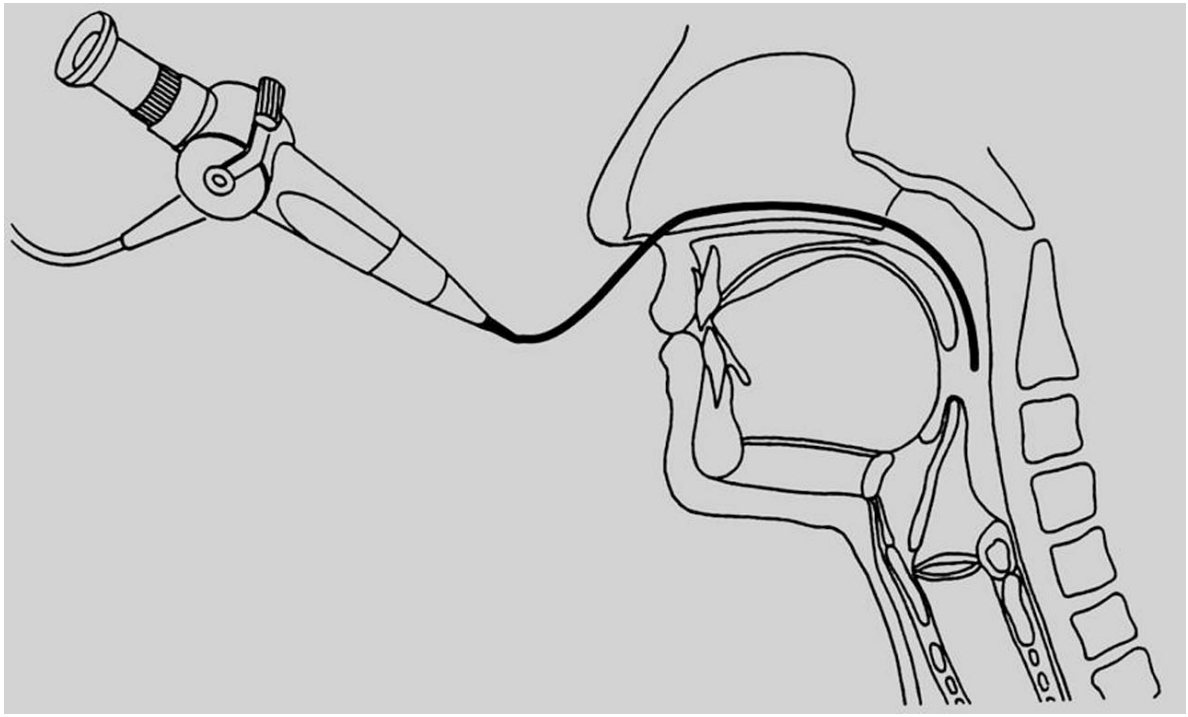
Occupational therapy provides the following training programs: training in motor function to improve patient´s ability to perform daily activities, training in sensorimotor perception, adaptive equipment recommendations and usage training, cognitive training, occupational training for writer´s cramp in dystonia patients, and counselling of spouses and relatives.

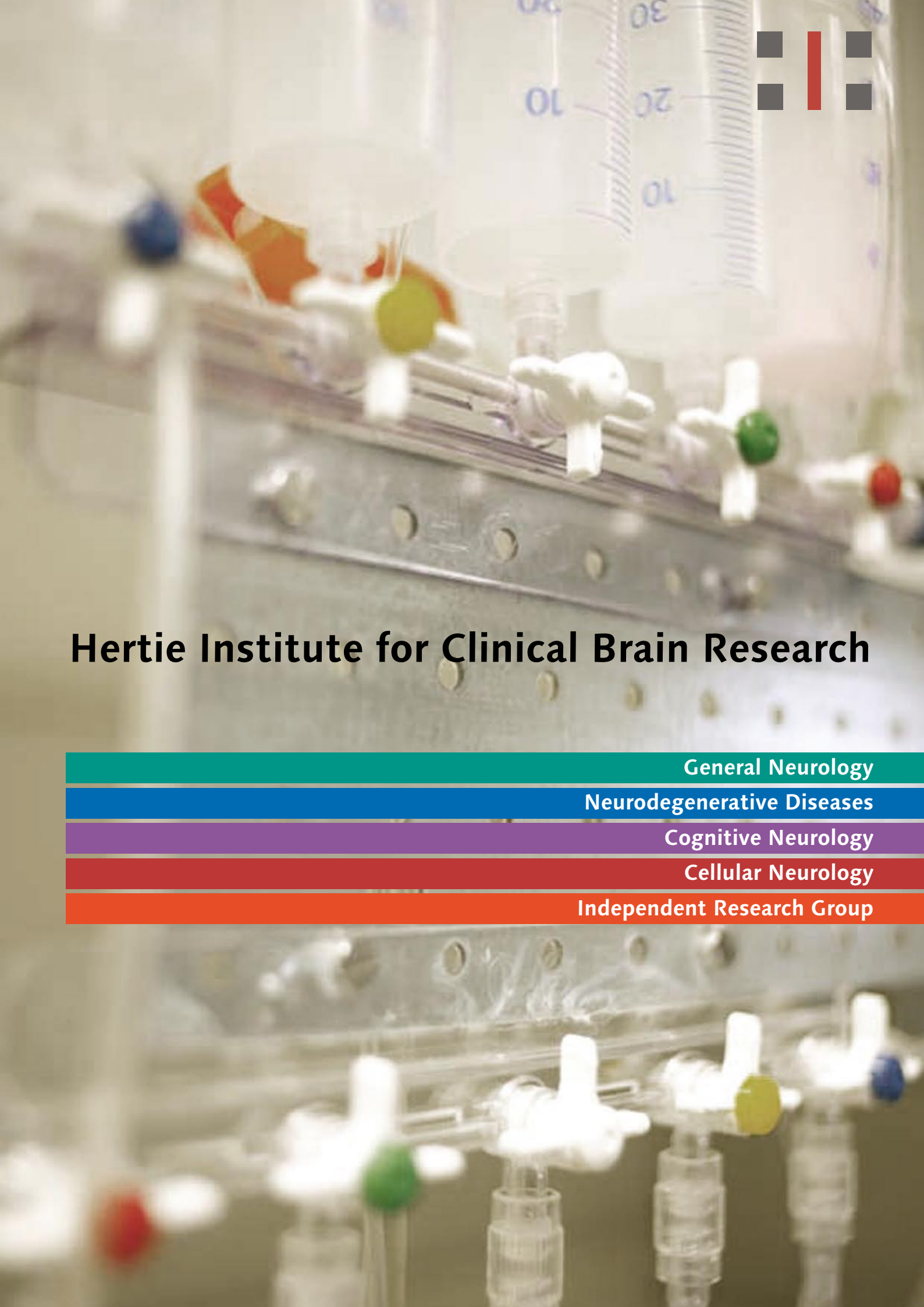
Physical, Occupational & Speech Therapy

Speech Therapy

Neurological patients with swallowing and language disorders receive speech therapy while staying in hospital.
The emphasis within the team of three speech therapists is the treatment of patients with dysphagia (800 patients in 2006).
Every acute stroke patient receives a bedside and, if necessary, a videoendoscopic or videofluoroscopic swallowing examination. Therefore dysphagia can be recognized at an early stage, an aspiration pneumonia can be prevented and a specific therapy can be planned for every individual patient.
Additionally, in 2006 400 patients with aphasia and dysarthria received an intensive language treatment. The aim of the speech therapy is to improve their communication ability.







Hertie Institute for Clinical Brain Research

General Neurology

Neurodegenerative Diseases

Cognitive Neurology

Cellular Neurology

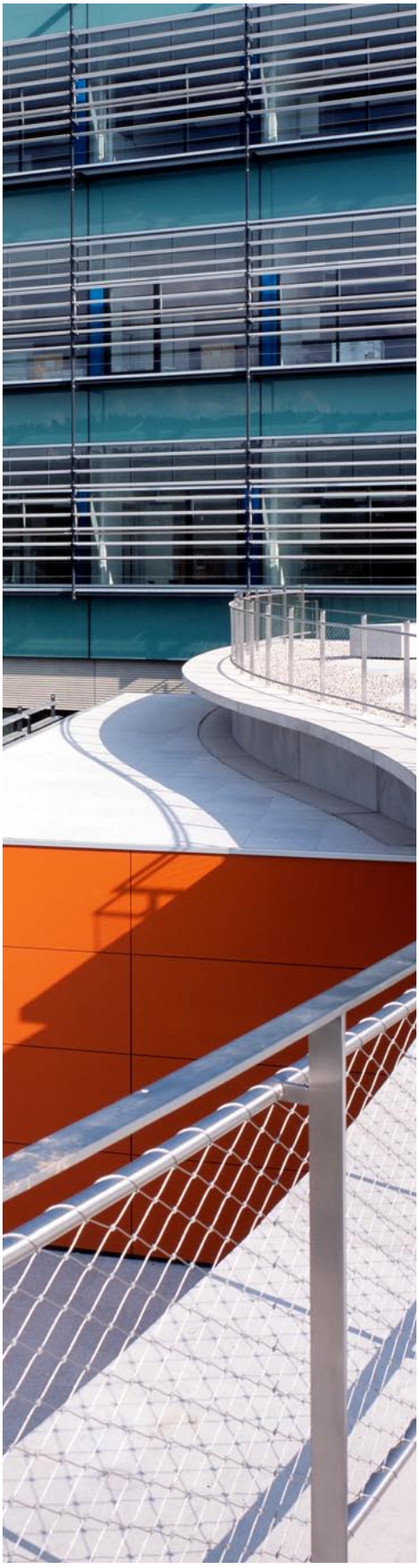
Independent Research Group

The Hertie Institute for Clinical Brain Research (HIH) is in many ways an innovative institution, even an experiment. In Germany, the HIH is without precedent in its close relationship to the Clinical University Department of Neurology. Three of the four HIH-departments are directly involved, although to different degrees, in patient care. In every-day practice this means that many of the scientists at the HIH are physicians, and they regularly switch the main focus of their work: from the lab-bench to the ward, and back. This structure is both promising and demanding: it is intended to promote patient- and disease-oriented research at the highest possible level, true "translational medicine", as it is often called today. But it is also demanding, as it calls for a higher degree of flexibility and cooperation on the part of all members of the institute than what is often found in traditional university settings. The internal organization of the HIH is no less innovative, and diverges from the traditional structure of university institutes. The HIH is governed by its board of directors, who elect a chairman for a two-year term on a rotating basis. Following a regular monthly schedule, the chairman reports to the assembly of research group leaders of the HIH. Through this meeting, the (at latest count) twenty-two research group leaders of the HIH participate in the development of the institute. They are represented in the election committee when the institute hires new group leaders, and their voice is heard in matters of investment into new equipment and infrastructure.

Another innovative feature of the HIH is that it hosts independent junior research groups on tenure track. The first one, focussing on neuroregeneration in the spinal cord, has been established in 2006, a second group with a focus on in vivo imaging of the brain, has been advertised. These groups are funded by a "research pool" for three to five years. Following an independent evaluation of their work, the group leaders will be eligible for tenure at the institute.

Twice a year, the board of directors presents the new developments of the institute to the "Kuratorium", the oversight committee consisting of distinguished neuroscientists, who are following the institute with constructive criticism and advice.

In the four years of its existence, the HIH has been growing rapidly. Its development is far from complete. The establishment of new research groups, possibly even an additional department, are planned, and with the support of the Medical Faculty, the University Hospital, and the Land of Baden-Württemberg, a second research building may become reality.



Das Hertie-Institut für klinische Hirnforschung (HIH) ist in vielerlei Hinsicht eine innovative Institution, ja sogar ein Experiment.

In Deutschland ist die enge und vielseitige Verbindung, die das HIH mit der Neurologischen Klinik verknüpft, ohne Beispiel. Drei der vier Abteilungen des HIH sind direkt, wenn auch in unterschiedlichem Ausmaß, an der Patientenversorgung beteiligt. In der täglichen Praxis bedeutet das, dass viele der Wissenschaftler am HIH auch Ärzte sind - und dass sie regelmäßig ihren Arbeitsplatz wechseln: von der Laborbank zum Krankenbett und zurück. Diese Struktur ist ein Vorteil, gleichzeitig aber auch eine Herausforderung: sie soll in einer Weise, wie sie an traditionell aufgebauten Universitätskliniken kaum möglich ist, die patienten- und krankheitsorientierte Forschung auf höchstmöglichem Niveau fördern, und – um es mit einem heute gängigen Begriff auszudrücken – translationale Medizin ermöglichen. Diese Struktur ist aber auch dehalb eine Herausforderung, da sie mehr Flexibilität und Kooperationsbereitschaft erfordert, als dies in oft traditionellen Universitätsstrukturen üblich ist.

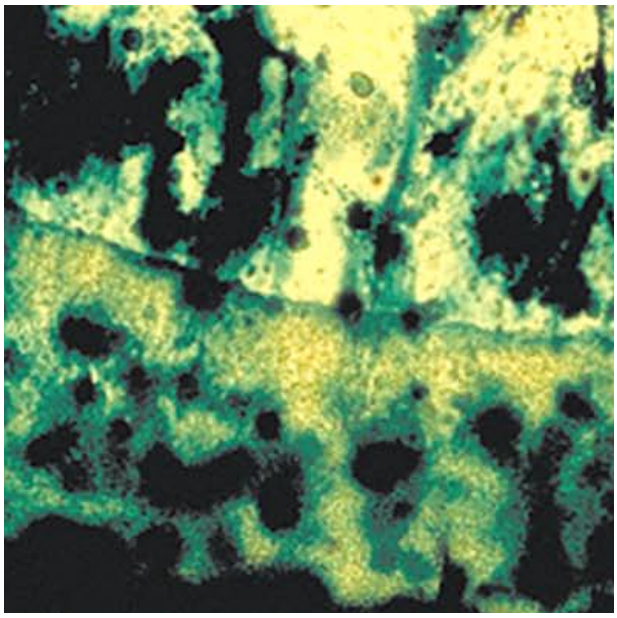
Auch die Binnenorganisation des HIH ist nicht weniger innovativ und weicht von der traditionellen Struktur eines Universitätsinstituts ab. Das HIH wird von seinem Vorstand geleitet, der sich aus den vier Abteilungsleitern zusammensetzt und der sich für einen zweijährigen Turnus einen Vorsitzenden wählt. Der Vorsitzende unterrichtet monatlich die Arbeitsgruppenleiter über neue Entwicklungen im HIH. Durch die Empfehlungen dieser Versammlung nehmen die derzeit zweiundzwanzig Arbeitsgruppenleiter aktiv an der Gestaltung und Weiterentwicklung des HIH teil. Die AG-Leiter sind bei der Auswahl neuer Gruppenleiter vertreten und beraten den Vorstand bei der Tätigung von Investitionen.

Ein weiterer innovativer Aspekt des HIH ist die Einrichtung von abteilungsunabhängigen Junior-Arbeitsgruppen im „Tenure Track-Verfahren". Die erste dieser Arbeitsgruppen, die sich schwerpunktmäßig mit neuroregenerativen Prozessen des Rückenmarks beschäftigt, wurde im Frühjahr 2006 eingerichtet, eine zweite Gruppe, mit dem Fokus auf „in vivo Bildgebung des ZNS" ist derzeit ausgeschrieben. Diese Gruppen werden für drei bis fünf Jahre aus dem zentralen Forschungspool des HIH finanziert.

Zweimal im Jahr wird das HIH von seinem Kuratorium, das sich aus namhaften deutschen Neurowissenschaftlern zusammensetzt, besucht. Die Evaluationen dieses Gremiums sind dem Institut eine wertvolle Hilfe bei der weiteren Entwicklung.

Das Hertie-Institut ist in den vier Jahren seiner Existenz rasch gewachsen. Seine Entwicklung ist noch lange nicht abgeschlossen. Die Einrichtung weiterer Forschungsgruppen und möglicherweise sogar eines weiteren Lehrstuhls ist in Planung, und mit der Unterstützung der medizinischen Fakultät, des Universitätsklinikums und des Landes Baden-Württembergs scheint sich auch die Realisierung eines zweiten Forschungsgebäudes abzuzeichnen.

Director: Prof. Dr. Michael Weller



Department of General Neurology

Departmental Structure

The Department of General Neurology covers on a wide spectrum of neurological diseases. As a primary care institution the University Hospital in Tübingen provides care for all patients with neurological symptoms or signs. These patients are admitted to the either the Dept. of General Neurology or the Dept. of Neurodegeneration, depending on capacity and patient load. Patients are referred to the Department from other areas of Germany as well as internationally according to the clinical and scientific focus areas of the Department, i.e., neurooncology, cerebrovascular diseases (ischemia, intracranial hemorrhage, vasculitis and others) and neuroimmunology (multiple sclerosis, myasthenia gravis and others). Specialized neurooncology and stroke (stroke unit and early rehabilitation) wards provide multidisciplinary expert care for these diseases. Specialized outpatient clinics including a neuroimmunology clinic, provide long term care for the respective patients. Other specialized outpatients clinics include epilepsy, headache and pain syndromes and sleep disorders. The aim of these outpatient clinics are not only to offer best and updated care for a selected patient populations but to provide an infrastructure for clinical studies that help in the development of novel therapies and disease mechanisms. Specialized wards and outpatient clinics of the Department of General Neurology therefore provide the clinical basis for its research groups. Research groups work in neurooncology (Prof. Weller, Prof. Wick, PD Dr. Steinbach), cerebrovascular diseases, rehabilitation and neuroplasticity (PD Dr. Luft), neuroimmunology (Prof. Melms, Prof. Weissert) and brainstem/cerebellar systems neurophysiology (PD Dr. Haarmeier). These research groups are based in the immediate proximity to the clinical space either in the CRONA building of the Hertie Institute for Clinical Brain Research. Close collaboration exists with the other departments and research groups at the Hertie Institute. The department cooperates closely with the physical therapy department at the University Hospital (Therapiezentrum). The Neurology section of this department is focused on physical therapy for back pain and stroke rehabilitation.

This Department of General Neurology offer different lecture series for medical students, physicians in training, nursing staff, and physical and speech therapists. The grand round series features internationally renown clinical and basic scientists speaking on clinically relevant topics. A neurovascular lunch conference and a general neurology therapy seminar covers recent topics in neurology, internal medicine, neurosurgery, ophthalmology, neuroradiology and other fields relevant to the treatment of patients with neurological diseases. The main neurology lecture, the neurology seminar, neuroexamination course and the intracranial pressure seminar are offered as part of the Medical School curriculum.

Arbeitsgruppe Neuro-Onkologie

Arbeitsgruppenleiter:
Ulrike Naumann, Joachim Steinbach, Michael Weller, Wolfgang Wick

Die Arbeitsgruppe Neuro-Onkologie befasst sich mit verschiedenen Fragen der Biologie und der Therapie bösartiger Hirntumoren und betreut die Tumorambulanz und Neuro-Onkologische Schwerpunktstation (B5-Süd) der Neurologischen Klinik. Die wissenschaftlichen Arbeiten werden durch das Bundesministerium für Bildung und Forschung, die Deutsche Forschungsgemeinschaft, die Deutsche Krebshilfe, die Landesstiftung Baden-Württemberg, die Wilhelm Sander-Stiftung, das Interdisziplinäre Zentrum für Klinische Forschung und das Fortüne-Programm der Universität Tübingen unterstützt.

Hauptforschungschwerpunkte der Arbeitsgruppe umfassen die Aufdeckung von Mechanismen, die zur Entstehung des Glioblastoms, des bösartigsten Hirntumors, führen. Des Weiteren werden Mechanismen untersucht, die dazu führen, dass sich diese Tumoren weitestgehend resistent gegenüber konventionellen Behandlungsmethoden wie Chemotherapie und Bestrahlung verhalten. Parallel werden neue Strategien zur Therapie des Glioms entwickelt: So wird versucht, Gliomzellen mittels Behandlung mit Todesliganden oder durch Einschleusung von „Apoptose-Proteinen“ zu eliminieren. Apoptose (= programmierter Zelltod) ist ein für die Entwicklung und Aufrechterhaltung des Organismus lebenswichtiger Mechanismus. Nur wenn die Neubildung und das Sterben von Zellen im Gleichgewicht stehen, bleibt der Organismus gesund. Gerät dieses Gleichgewicht außer Kontrolle, sind krankhafte Erscheinungen wie Krebs die Folge. Mittels Viren können Gene, die aktiv oder indirekt an der Apoptose beteiligt sind, in Krebszellen eingeschleust und als mögliche Therapie-Gene getestet werden. Weitere Ansätze zielen darauf, das körpereigene Immunsystem, das durch TGF-β, ein vom Gliom gebildetes Protein, gehemmt wird, wieder zu aktivieren. Derart „bewaffnete“ Immunzellen könnten dann die Gliomzellen erkennen, diese vernichten und so den Tumor entfernen.

Die Entwicklung von Viren, die für die Gliom-Therapie eingesetzt werden können, ist ein weiterer Forschungsschwerpunkt: Viren sind als Krankheitserreger bekannt. Nicht jedes Virus ist jedoch gefährlich für den Menschen. So können Viren auch zu krebsbekämpfenden, onkolytischen (= krebsauflösenden) Viren umfunktioniert werden. Um Viren gezielt auf den Kampf gegen Krebszellen umzufunktionieren, müssen ihnen gentechnisch Informationen eingebaut werden, mit deren Hilfe sie Tumorzellen erkennen. Das Virus infiziert die Tumorzelle und beginnt, sich dort zu vermehren. Unter der Last der neu entstehenden Viren "zerfällt" die Tumorzelle, und die frei werdenden Viren befallen weitere, umliegende Krebszellen. Das Virus ist jedoch nicht fähig, sich in „normalen“ Körperzellen zu vermehren, diese bleiben daher intakt. Bei der Therapie des Glioms werden momentan Viren, die sich exklusiv in chemotherapieresistenten Tumorzellen vermehren, in der Maus getestet. Viren werden auch eingesetzt, um körpereigene Zellen (z.B. Stammzellen aus dem Blut) zu Transportsystemen umzufunktionieren. Diese Stammzellen wandern spezifisch zum Tumor und können so für die Therapie benötigte Proteine gezielt zum Ort des Tumors tragen.

Des Weiteren befassen sich die Forscher der Arbeitsgruppe mit der Einwanderung von Tumorzellen in das gesunde Hirngewebe, erforschen, warum Gliomzellen mit nur geringen Konzentrationen an Sauerstoff und Nährstoffen überleben, analysieren Mechanismen der Friedreich-Ataxie und befassen sich mit neuen Behandlungsmethoden der Autoimmunerkrankung Multiple Sklerose.

Neuro-Oncology

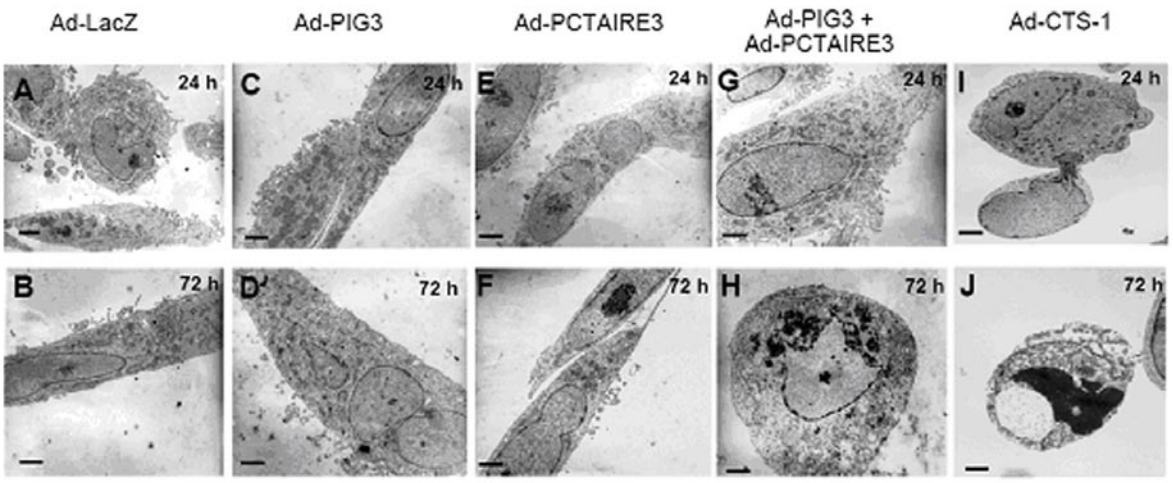
Group leaders:
Ulrike Naumann, Joachim Steinbach, Michael Weller, Wolfgang Wick

The Laboratory of Molecular Neuro-Oncology focuses mainly on molecular, cell biological and immunological aspects of malignant brain tumors. Further, the development of new strategies for glioma treatment including viral and molecular gene therapy is an emphasis of the laboratory. The main subjects are: the biology of primary CNS lymphoma (PCNSL) and optimization of PCNSL therapy, cell death induction via death receptors in glioma cells, the development of new stategies for glioma gene therapy, antagonizing the immunosuppressive effects of malignant brain tumors, e.g. by antagonizing the effects of tumor-derived transforming growth factor (TGF)-β or of regulatory T-cells (Tregs), the molecular and biochemical characterization of hypoxia-induced cell death in glioma, the isolation and characterization of glioma stem cells, the mechanisms of glioma tropism of hematopoietic stem cells and in how far these cells can be feasible as transport-vehicles of therapeutic genes. In addition, projects to develop an *in vitro* paradigm of Friedreich ataxia and for the treatment of experimental allergic encephalomyelitis (EAE) with tryptophan metabolites are in process.

PCNSL are highly malignant B cell lymphomas with arise in the brain and are restricted to the brain in most cases. A part of the multi-institutional cooperation in the German primary CNS lymphoma study group G-PCNSL-SG-1 is the examination of molecular and immunological aspects of PCNSL biology. Most patients with PCNSL are treated in clinical studies such as the G-PCNSL-SG-1 trial which investigates molecular and immunological aspects of PCNLS development.

Death ligands such als Apo2L/TRAIL or CD95 mainly kill tumor cells but leave nontransformed cells largely unaffected. Stereotactic injection of Apo2L/TRAIL into experimentally grown glioma in mice prolongs the survival of mice. In Apo2L/TRAIL-insensitive glioma cells, Apo2L/TRAIL works synergistically with a variety of alkylating chemotherapeutic agents including temozolomide, with overexpression of the tumor suppressor p53 and with XIAP depletion.

Apoptosis is a well organized process of cellular suicide. Insufficient apoptosis results in uncontrolled cell survival, an important process in the development of cancer. We have tested whether viruses expressing apoptosis-inducing genes are useful tools for future glioma gene therapy: The proapototic proteins Bcl-2-associated protein X (BAX)

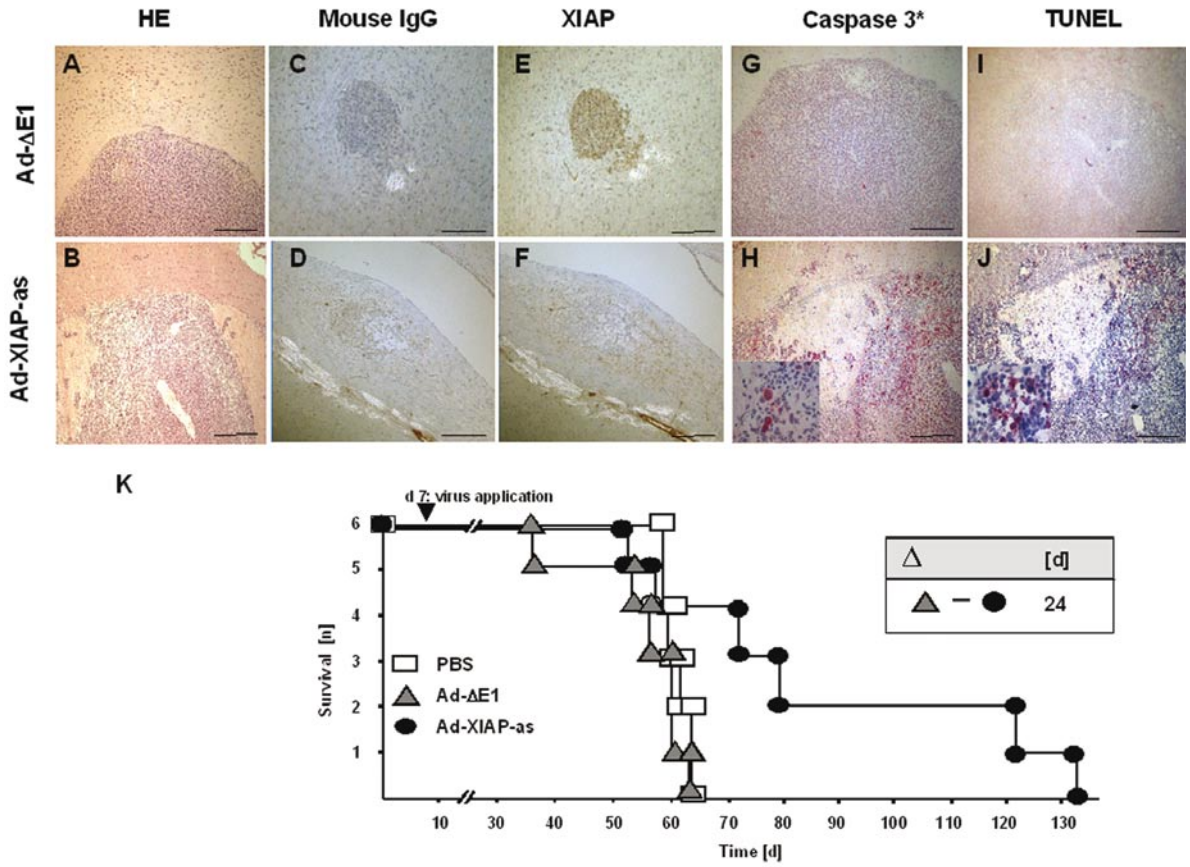


▲ Figure 1: Morphological features of cell death induced by PCTAIRE3, PIG3 and CTS-1.In LNT-229 glioma cells infected with an adenovirus expressing either CTS-1 or PCTAIRE3 + PIG3, cell death is induced whereas control-infected (Ad-LacZ) cells survive.

and natural born killer (NBK) are often downregulated in cancer cells. Adenoviral-mediated expression of NBK induces cell death in glioma cells and prolongs the median survival of glioma-bearing mice. Chimeric tumor suppressor-1 (CTS-1) is a synthetic relative of the transcription factor p53 which is mutated in more than 50% of tumors. Viral transduction of CTS-1 induces cell death and acts synergistically with chemotherapy, radiation and death ligands. By cDNA microarray analysis, we identified two genes induced by CTS-1, PCTAIRE3 and PIG3. Overexpression of PCTAIRE3 induced growth arrest and cell death. Coexpression of PCTAIRE3 and PIG3 resulted in enhanced growth inhibition *(see fig. 1)*. In a recently initiated project we developed CTS-1-resistant glioma cell lines. Using these cells, new apoptosis-regulated genes will be isolated and characterized regarding their ability to serve as therapeutic genes for glioma gene therapy in the future. XIAP expression contributes to the resistance of cancer cells to apoptosis. We have shown that the infection of glioma and several other tumor cell lines with adenoviruses encoding antisense RNA to XIAP (Ad-XIAP-as) promotes apoptosis whereas non-neoplastic cells resist these effects. Ad-XIAP-as gene therapy induces cell death in orthotopic glioma xenografts, prolongs survival of tumor-bearing mice and acts in synergy with Apo2L/TRAIL *in vivo (see fig. 2)*. Altogether these data reinforce the possible role of XIAP as a therapeutic target in human glioma.

TGF-β has been associated with the malignant progression of glioma and interferes with several mechanisms of antitumor immune responses like the NKG2D system. NKG2D is an activating immuno-receptor present on natural killer (NK) cells and CD8+ T cells. Its ligands are the MHC class I-chain related molecules MICA, MICB and UL16-binding proteins (ULBP)1-3, ULBP4/RAET1E and RAET1G. Physiologically,

▼ Figure 2:
Ad-XIAP-as reduces XIAP levels and induces cell death in intracranial LNT-229 xenografts and prolongs survival in tumor bearing mice.

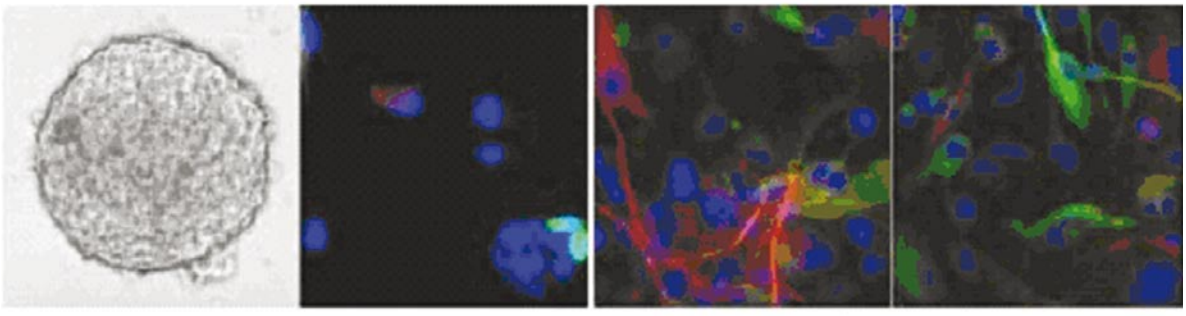


NKG2DL expression is restricted to intestinal epithelium. Pathologically, NKG2DL expression is often upregulated. NKG2DL represent danger signals which mark cells as harmful and as targets for an immune response. Tumor cells may evade NKG2D-mediated immune surveillance by downregulation of the NKG2DL or by proteolytical shedding of MIC und ULBP molecules. NKG2DL are expressed almost de novo in glioma in vivo and may thus label tumor cells for immune effector cells. However, MICA and ULBP2 expression levels are decreased close to baseline with malignant progression to grade IV tumors. Depletion of TGF-β by RNA interference upregulates MICA and ULBP2 levels and increases NK cell-mediated lysis of TGF-β-depleted cells. Our *in vitro* data implicate that the TGF-β-mediated repression of MICA and ULBP2 together with a metalloproteinase-(MP)-mediated shedding of NKG2DL as major factors contribute to the immune escape of gliomas. The two mechanisms outlined here are particularly attractive since clinically applicable concepts for the inhibition of TGF-β and MP have already been developed and could thus be applied here in a novel context.

The antifibrotic drug pirfenidone (PFD) elicits growth-inhibitory effects and reduces TGF-β2 protein levels in human glioma cell lines. PFD leads to a reduction of TGF-β2 mRNA levels and of the mature TGF-β2 protein due to decreased expression and direct inhibition of the TGF-β pro-protein convertase furin. In addition, PFD reduces the protein levels of MMP-11, a TGF-β2 target gene and furin substrate involved in carcinogenesis.

There is compelling evidence that Tregs suppress exuberant reactions of the immune system by directly inhibiting T effector cells or by preventing activating stimuli of dendritic cells. Tumors presumably misuse this system to evade immune surveillance. Thus cancer patients indeed exhibit activated tumor-specific T cells, which prove to eliminate tumor cells *in vitro*, but fail to eradicate tumors *in vivo* due to sustained regulatory T cell-mediated suppression of cytotoxic and T helper cells. Gliomas seem to increase the regulatory T cell fraction thus raising the suppressive capacity of regulatory T cells *in vivo*. To understand how Tregs are recruited by glioma we are interested in the mechanisms guiding Tregs to the tumor site to enable direct cell-cell contact, which is required for efficient immunosuppression. Based on the linage-model of T cells the TGF-β/TGF-β-receptor system is thought to determine Treg commitment.

Further, we have studied the consequences of deregulated activity of key signal transduction pathways in malignant gliomas under the specific conditions of the tumor microenvironment. For this purpose, we have characterized an *in vitro* paradigm of hypoxia-induced cell death in malignant glioma cells, that faithfully reproduces many features of cell death observed in human glioblastoma biopsies. With the aid of this model, we have shown that while inhibition of the epidermal growth factor receptor (EGFR) sensitizes glioma cells towards apoptosis under normoxic conditions, it confers protection against hypoxia-induced cell death by reducing their energy expenditure. Current projects investigate the interaction of p53 with EGFR signalling and the role of



▲ Figure 3: Glioma stem cells in vitro: Cells grow in neurosphere formation and express nestin. Differentiated cells express Tuj 1 (red) and GFAP (green).

pathways downstream of the EGFR. Examples include the FOXO family of transcription factors and the mTOR kinase, which has been identified as a critical downstream signaling molecule that mediates the hypoxia-protective effects of EGFR inhibition, but does not alter the sensitivity of glioma cells towards death ligand-induced apoptosis.

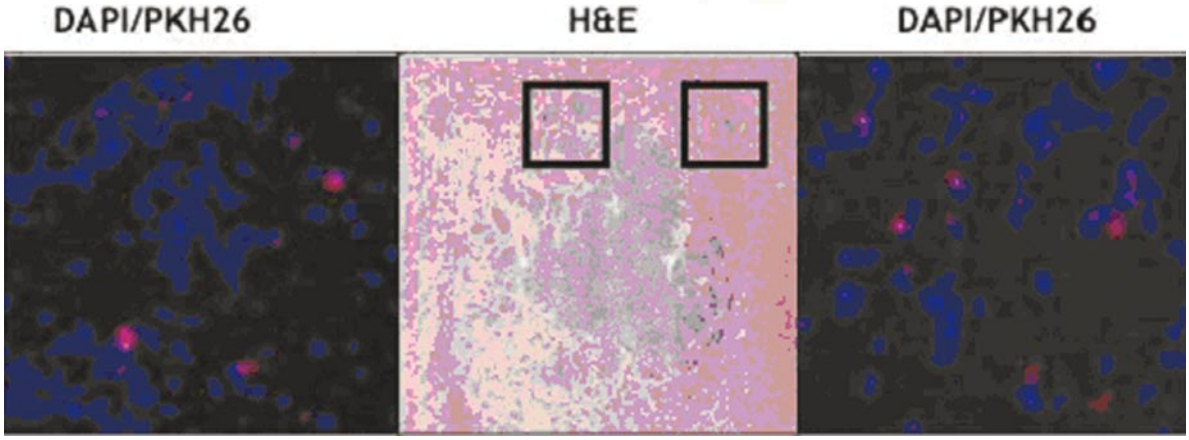
Recent evidence suggests that cancer stem cells exist in human gliomas. According to Singh et al., these brain tumor stem cells can be isolated based on the expression of CD133. We isolated cells from human gliomas which form neurospheres and display characteristic stem cell features *in vitro*: i) multipotency with evidence of astroglial or neuronal differentiation *in vitro (see fig. 3)*; ii) self-renewal capacity at single cell level; iii) migration as shown in 3D collagen spheroid invasion assays. Most importantly, these cells are tumorigenic *in vivo*: 50 single cells suffice to establish tumors after orthotopic intracerebal implantation and serial orthotopic transplantations *in vivo* ressembling the histological features of the original human gliomas.

In our recent work, we demonstrated that intracerebral experimental gliomas attract intravenously administered adult hematopoietic progenitor cells by TGF-β-dependent secretion of the chemokine CXCL12. Therefore, these easily accessible adult stem cells are promising candidates for a cell-based gene therapy of experimental gliomas. As radiotherapy is a standard treatment modality of glioma patients and hypoxia is a key histological feature of malignant gliomas, we analyzed the impact of irradiation and hypoxia on the glioma-tropism of hematopoietic progenitor cells *(see fig. 4)*. Supernatants of irradiated and hypoxic glioma cells enhanced the migration of hematopoietic progenitor cells *in vitro*. Irradiation and hypoxia of glioma cells increase the secretion of CXCL12, depending on the presence of HIF-1α. Cerebral irradiation of glioma-bearing nude mice *in vivo* induces tumor satellite formation and promotes the attraction of hematopoietic progenitor cells. Taken together, the use of hematopoietic progenitor cells as cellular vectors might be combined with irradiation or anti-angiogenic therapies. Currently, we analyze mechanisms of adhesion of hematopoietic progenitor cells to tumor endothelial cells.

An independent project established an *in vitro* paradigm of Friedreich ataxia in cerebellar granule neurons. In this model, the molecular mechanisms that lead to cell death in neurons deficient for frataxin are analysed.

A further non-oncological project focuses on pathways which are shared between tumor growth and neuroinflammation. In this project, mesenchymal stem cells expressing indoleamine 2,3-dioxygenase (IDO) are analysed as therapeutic vehicles in a mouse model of multiple sclerosis.

▼ Figure 4:
Intravenous administration of PKH26-stained hematopoietic progenitor cells after cerebral irradiation of glioma-bearing nude mice. Boxes in the H&E staining of an irradiated glioma (magnification x 40) show irradiation-induced tumor satellite formation. These areas are displayed in greater magnification in the left and right pictures. Fluorescence was used to visualize the nuclei by DAPI (blue) and the CD34+ HPC by PKH26 (red) (magnification x 100).



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homepage: http://www.hih-tuebingen.de/an/researcho/neuro-onkologie/

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Naumann U, Huang H, Wolburg H, **Wischhusen J, Weit S**, Ohgaki H, **Weller M** (2006) PCTAIRE3: a putative mediator of growth arrest and death induced by CTS-1, a dominant-positive p53-derived synthetic tumor suppressor, in human malignant glioma cells. Cancer Gene Ther 13:469-78

Tabatabai G, Frank B, Mohle R, **Weller M, Wick W** (2006) Irradiation and hypoxia promote homing of haematopoietic progenitor cells towards gliomas by TGF-beta-dependent HIF-1alpha-mediated induction of CXCL12. Brain 129:2426-35

Wick W, Naumann U, Weller M (2006) Transforming growth factor-beta: a molecular target for the future therapy of glioblastoma. Curr Pharm Des 12:341-9

Arbeitsgruppen Neurorehabilitation & Neuroplastizität

Arbeitsgruppenleiter: Andreas R. Luft

Für Schlaganfallpatienten mit motorischer Behinderung stellen physiotherapeutische Verfahren eine der erfolgreichsten Behandlungsformen auch mehrere Jahre nach dem Schlaganfall dar.

Besonders vielversprechend sind neuartige Trainingsprogramme für Arme und Beine, die die Lernfähigkeit des Gehirns nutzen, um verlorene Bewegungen wieder zu erlangen. Beidseitiges rhythmisches Armtraining des kranken und des gesunden Armes gleichzeitig ist so eine Therapieform für die obere Extremität. Gangtraining auf einem Laufband ist eine entsprechende Therapie für die untere Extremität. Unklar blieben bisher die (neuro)-wissenschaftlichen Grundlagen dieser Therapien. Wir untersuchen die Veränderungen in Netzwerken des Gehirns, die durch diese Therapien ausgelöst werden und die Wirksamkeit der Therapie möglicherweise erklären können. So konnten wir zeigen, dass beidseitiges Armtraining den Cortex der gesunden Hirnhälfte aktivieren kann, Laufbandtraining fördert neuronale Netzwerke in Hirnstamm und Kleinhirn. Der Erfolg der Therapie korreliert mit den Veränderungen an diesen Netzwerken. Zukünftige Studien untersuchen diese Veränderungen genauer und versuchen Fragen zu beantworten wie „sind diese Veränderungen anhaltend oder temporär?“, „verändert sich die Hirnstruktur?“ oder „verändert die Therapie die Blutversorgung des Gehirns?“.

Diese Therapien basieren auf den Prinzipien des motorischen Lernens. Motorisches Lernen ist eine wichtige Fähigkeit nicht nur in der Entwicklung und im täglichen Leben. Lernen erlaubt auch, dass das nach einer Hirnverletzung verbleibende Gehirn, z.B. nach einem Schlaganfall, Funktionen zur Bewegungssteuerung der zerstörten Hirnareale übernehmen kann. Diese Vorgänge erfordern plastische Veränderungen an Nervenzellen und den aus ihnen zusammengesetzten Netzwerken. Motorisches Lernen wird ebenfalls durch solche „plastischen“ Vorgänge im Motorkortex vermittelt. Wir studieren diese Vorgänge, die Neurotransmitter und Eigenschaften von Neuronen, die diese Vorgänge vermitteln. Unser Schwerpunkt liegt dabei auf dem dopaminergen und dem GABAergen (inhibitorischen) System im Motorkortex. Unser Ansatz verbindet Verhalten mit Elektrophysiologie und Molekularbiologie.

Neurorehabilitation & Neuroplasticity

(Group leader: Andreas R. Luft)

Clinical studies

With more than 120.000 new strokes happening in Germany every year and an aging population, neurorehabilitation is of high interest for patients and society alike. Despite the effectiveness of acute stroke therapies (thrombolysis and stroke unit care), 30-50% of stroke patients are left disabled, either due to motor, speech, visual or cognitive impairment. Exploring the brain's plasticity that can provide functional compensation and recovery, is necessary to develop novel treatment approaches and protocols. Several interventions consisting of training, pharmacological, and electrical stimulation have been developed and tested empirically as well as in initial randomized controlled trials. Despite testing clinical effectiveness, it is necessary to understand the physiology of recovery. Better understanding will help to optimize and individualize treatment protocols and to develop novel rehabilitative strategies.

Projects

Bilateral arm training: In cooperation with the Department of Physical Therapy and Rehabilitation Medicine, University of Maryland and the Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, MD, USA, we have studied brain plasticity mechanisms involved in two rehabilitation therapies that help chronically impaired stroke survivors. Bilateral arm training with rhythmic auditory cueing (BATRAC) improves arm and hand function and is associated with de novo recruitment of premotor cortex in both the damaged and the intact hemisphere, as determined by functional magnetic resonance imaging. Aerobic treadmill training exercise (T-EX) improves walking velocity, cardiovascular fitness, and economy of gait and leads to recruitment of subcortical networks (midbrain-cerebellum) for leg movement. These findings indicate that specific rehabilitation interventions can augment certain brain circuits to improve motor function in chronic stroke survivors. Targeting these circuits may lead to novel approaches in neurorehabilitation and may provide further benefits to the patient. *(see fig. 1)*

Reward based physiotherapy: BATRAC and T-EX are based on principles of motor learning and brain plasticity. Practice and repetition are necessary components of these therapies. However, motor learning only works if success is rewarded. Reward leads to the release of dopamine in the basal ganglia and subsequent induction of plastic changes in cortex. The rehabilitating stroke survivor feels little reward because improvements are slow or ignored because of to depressed mood (post-stroke depression). We hypothesize that adding humorous and financial rewards will improve BATRAC. This will be tested in a randomized controlled trial comparing BATRAC with humorous reward to BATRAC alone in chronically impaired stroke survivors. The primary end point is better motor function, secondary end points are quantitatice assessments of mood and motivation.

Aerobic exercise training: In collaboration with the Robert Bosch Hospital in Stuttgart,

Key Publications

Paul JS, Fwu-Shan S, **Luft AR** (2006) Early adaptations in somatosensory cortex after focal ischemic injury to motor cortex. Exp Brain Res 168(1-2): 178-85

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Manto M, Oulad ben Taib N, **Luft AR** (2006) Modulation of excitability as an early change leading to structural adaptation in the motor cortex. J Neurosci Res 83(2):177-80

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Luft AR, Hanley DF (2006) Stroke Recovery: Moving into an EXCITEing direction. JAMA 296:2141-3

we are conducting a clinical trial to test the effects of treadmill aerobic exercise therapy on cerebrovascular pathophysiology. Modern imaging techniques (arterial spin labeling, fMRI and structural MRI) will be employed to test the hypothesis that T-EX improves cerebrovascular reactivity and reduces microvascular damage.

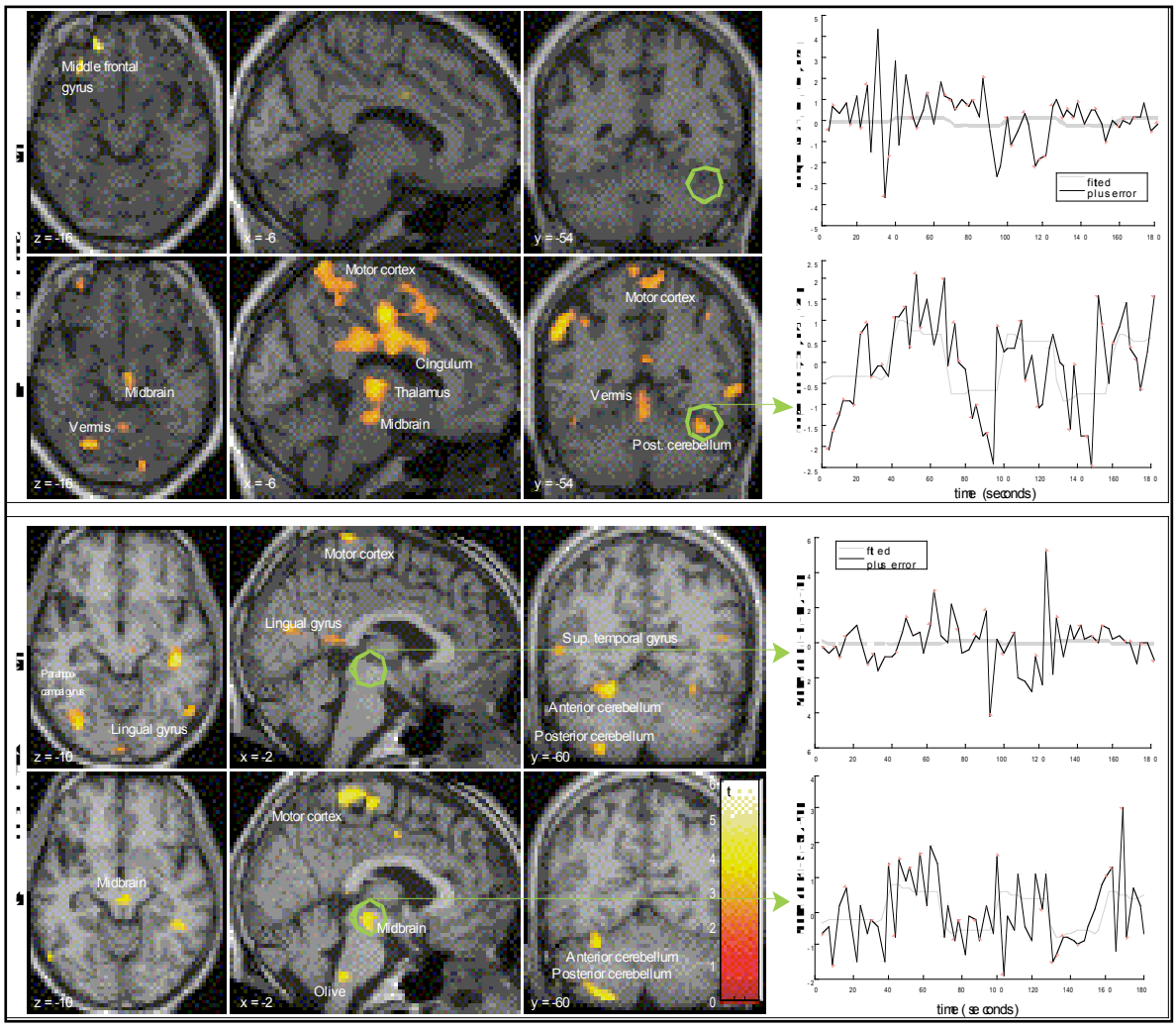
▼ Figure 1: Functional magnetic resonance imaging (fMRI) of two exemplary patients trained in the aerobic exercise treadmill program over 6 months. After training increased fMRI activation is found in midbrain and cerebellum. In group data, increases in cerebellar activation correlated with improved walking velocity on the treadmill.

Basic science

Our main interests are the mechanisms of plasticity in the motor cortex during learning and recovery. We assess learning on a behavioral level using a well-calibrated behavioral model (single pellet reaching) in rats. We combine electrophysiological, morphological and molecular approaches with the objective of understanding how motor memories are stored so safely that they are hardly forgotten and whether this potential can be used to improve motor function after brain injury. The techniques we use in order to assess our questions are: brain stimulation and recording of field potentials, immunohistochemistry, 3D-reconstruction of neurons, Western Blot, RT-PCR.

Projects

Cortical plasticity in motor learning: Because our previous studies showed that consolidation of a motor skill requires protein synthesis in motor cortex, we investigated which proteins are being synthesized using a microarray genechip experiment. Candidate genes were verified using quantitative RT-PCR. A series of genes are up- or down- regulated during the early stage of motor skill learning. Two of these encode



for Dopamine D2 receptor and Tachykini-1, the precursor of Substance P. We tested pharmacologically in vivo whether dopamine and D1/D2 antagonists as well as Substance P affect learning. The injection of Sub P or Dopamine into the motor cortex prior to training enhances the acquisition of the skill. Dopamine antagonists impair learning indicating the existence of a dopaminergic system in motor cortex that supports learning and possibly cortical plasticity.

Neuroplasticity after stroke: Motor recovery after stroke depends in part on cortical plasticity and reorganization in the motor system. These events may be similar to the ones mediating motor learning in the healthy. To prove this hypothesis we explore whether recovery requires similar processes in cortex as motor learning. Using a rat model of cortical stroke by phtothrombosis, we explore whether recovery depends on protein synthesis in motor cortex.

Cortical electrophysiology: Transient expansion of the forelimb representation in motor cortex occurs during learning, correlates in extent with the gain in performance, and is reversed after a short rest period. If prevented, e.g. by removing cholinergic input to motor cortex, learning does not occur (Conner et al. 2003). Therefore, this change in motor cortex organization seems to be required for movement learning.

We perform cortical stimulation mapping and recording of the somatosensory evoked potential using a novel epidurally implanted thin-film microelectrode array (Molina-Luna et al. 2006). This array technology does not damage the integrity of cortex while providing accurate estimates of motor cortical maps and SEP recordings with high signal-to-noise ratio. *(see fig. 2)*

Supported by: Deutsche Forschungsgemeinschaft (SFB 550), IZKF University of Tübingen, U.S. Veterans Administration.

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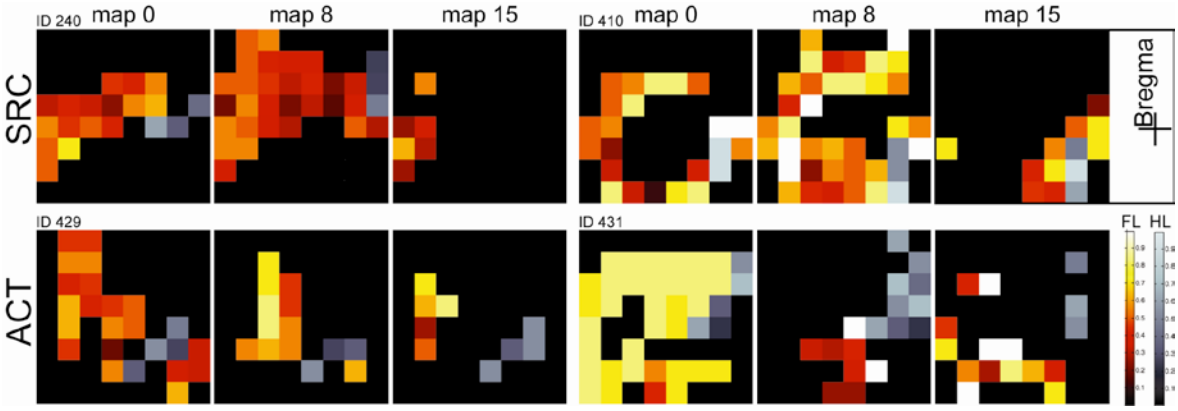


▼ Figure 2: Cortical somatotopy maps of primary motor cortex of 2 rats trained in skilled reaching (SRT) and 2 animals performing forelimb movements without learning (activity - ACT). The color reflects the inverse of the motor threshold at a given position (1/threshold in mA). Forelimb responsive sites are shown in red to yellow, hindlimb sites in gray to blue. For the upper right map, its relative position to Bregma is indicated by the cross. Expansion of the forelimb area is noted during 8-day training of SRT (map 0 – map 8) but not ACT. The expansion in SRT is not maintained but reversed during a rest phase after training (map 8 – map 15). The skill is maintained after rest indicating that skill memory does not rely on reorganized somatotopy.

Arbeitsgruppe Neuroimmunologie

Arbeitsgruppenleiter: Arthur Melms

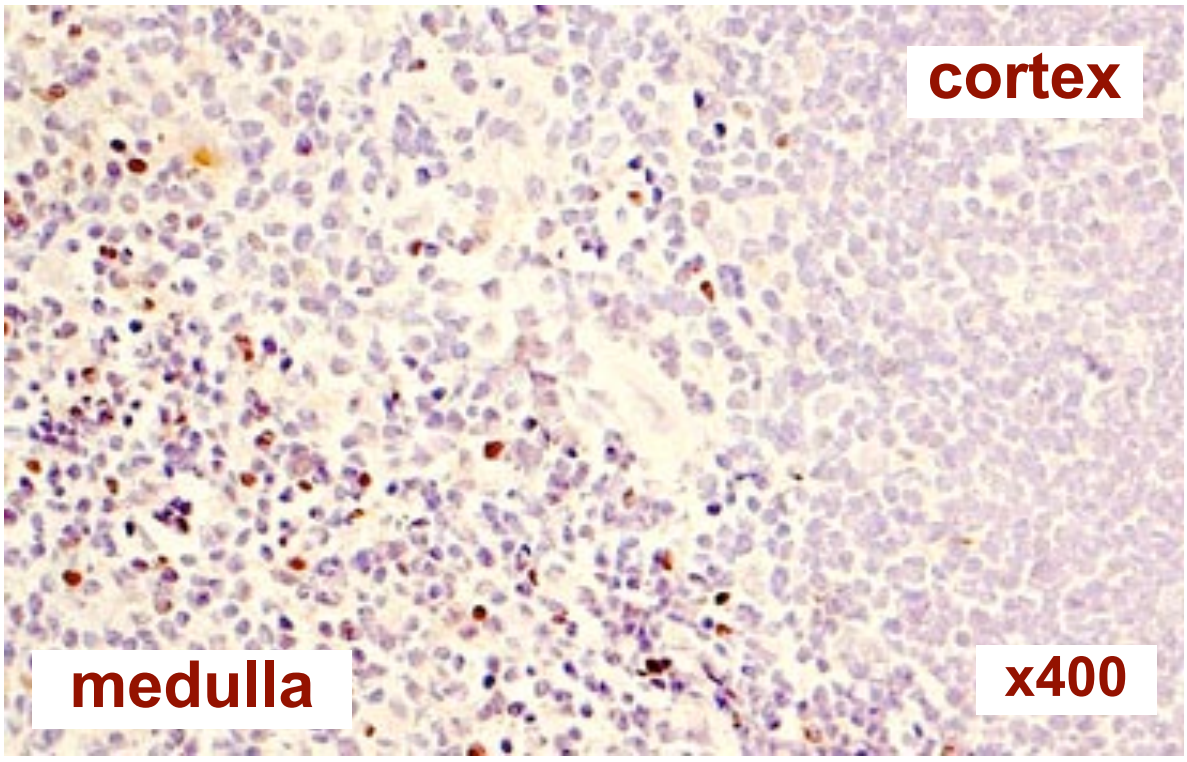
Wir beschäftigen uns mit grundlagenwissenschaftlichen Fragen zur Entstehung neuroimmunologischer Krankheiten wie der Multiplen Sklerose, der Myasthenia gravis und entzündlichen Muskelkrankheiten. Diese Erkrankungen werden durch autoreaktive T- und B-Lymphozyten hervorgerufen, die im Immunrepertoire jedes Individuums vorhanden sind und sich normalerweise in einem nicht-aktivierten Zustand befinden. Ein wichtiges Element der Immunüberwachung zur Unterdrückung unerwünschter Immunreaktionen sind regulatorische T-Lymphozyten, die im Thymus heranreifen und sich mithilfe bestimmter Merkmalen von anderen Lymphozytenpopulationen unterscheiden lassen. Wir verglichen diese Zellpopulation zwischen gesunden Probanden und Patienten mit Multipler Sklerose oder Myasthenia gravis und fanden, dass regulatorische T-Lymphozyten bei beiden Gruppen zwar in ähnlicher Häufigkeit vorhanden waren, aber bei Patienten mit diesen neuroimmunologischen Krankheiten eine Funktionsstörung aufwiesen, die bei unbehandelten Patienten am deutlichsten ausgeprägt war. Verlaufsuntersuchungen zeigten, dass dieses Defizit durch Behandlung mit Corticosteroiden und anderen in der Standardtherapie eingesetzten Medikamenten teilweise korrigiert werden kann. Die Aufklärung dieser Funktionsstörung könnte es ermöglichen, neue Ansatzpunkte zur Verbesserung der Therapie von Autoimmunerkrankungen wie der Multiplen Sklerose zu entwickeln.

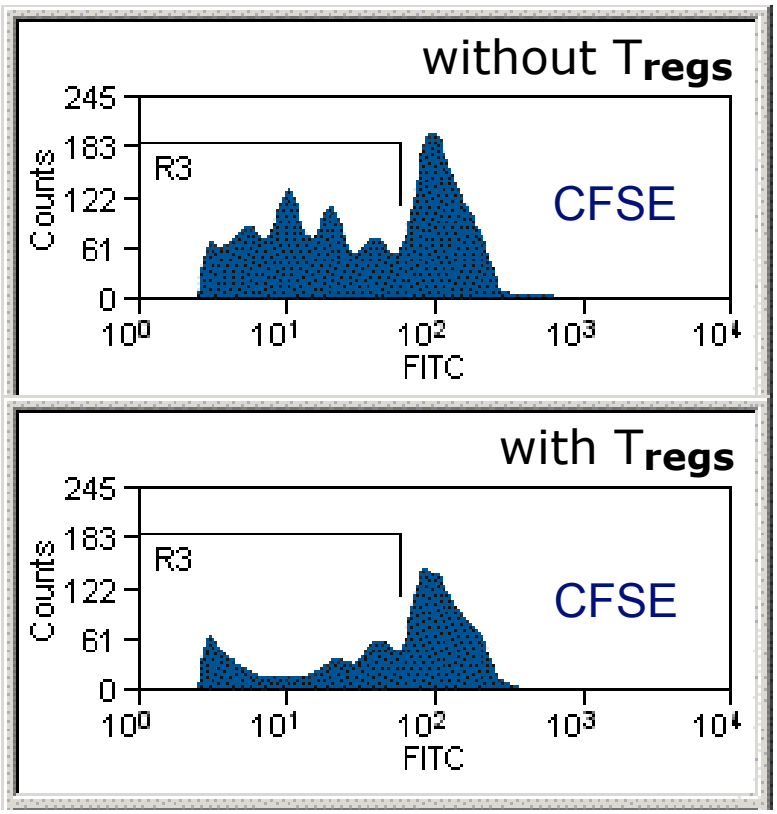
Bei der Multiplen Sklerose gelangen autoreaktive T-Lymphozyten über die Blut-Hirn-Schranke in das Hirngewebe und rufen dort die für diese Erkrankung typischen entzündlichen Entmarkungsläsionen hervor. Wir untersuchen am Tiermodell der experimentellen autoimmunen Enzephalomyelitis (EAE) nach Immunisierung mit einem Peptid des Proteolipidproteins (PLP), einem Myelinantigen, die Schlüsselvorgänge der T-Zellaktivierung und das Migrationsverhalten autoreaktiver T-Lymphozyten auf ihrem Weg vom lymphatischen Gewebe in das zentrale Nervensystem (ZNS). Zur Detektion und Quantifizierung autoreaktiver T-Lymphozyten verwenden wir Tetramere löslicher MHC-Moleküle, die mit einem PLP-Peptid beladen sind und somit komplementär an die T-Zellrezeptoren PLP-spezifischer T Zellen binden. Mithilfe einer Kombination Fluoreszenz-markierter Tetramere und monoklonaler Antikörper gegen Oberflächenmerkmale lassen sich bestimmte Zellpopulationen voneinander abgrenzen und Informationen über ihren jeweiligen Aktivierungszustand gewinnen. So konnte man zeigen, dass nur aktivierte T Zellen in der Lage sind, die Blut-Hirnschranke zu überwinden und in das ZNS einzuwandern. Antigen-spezifische T Zellen stellen davon nur eine Minderheit dar. Im Gegensatz zur Multiplen Sklerose, deren Zielantigene noch nicht eindeutig identifiziert sind, erlaubt unser Modellsystem bei der EAE auch die Detektion autoantigen-spezifischer (PLP-spezifischer) regulatorischer T Zellen, deren Anteil im Verlauf der EAE relativ zu den PLP-spezifischen T-Effektorzellen zunimmt. Sind regulatorische T Zellen nicht mehr in der Lage, autoaggressive Effektorzellen zu hemmen, liegt eine fundamentale Störung des immunologischen Netzwerkes vor, die die Entwicklung eines chronischen Entzündungsprozesses im ZNS begünstigt und möglicherweise aufrecht erhält.

Neuroimmunology

(Group leader: Arthur Melms)

The neuroimmunology group investigates the pathogenesis of multiple sclerosis, myasthenia gravis, and inflammatory muscle diseases. These autoimmune diseases are mediated by autoreactive T and B lymphocytes which are present in the normal immune repertoire but usually remain in an inactive state. There are several checkpoints in the immune system to control autoreactive T cells. These include the generation of T cell repertoire in the thymus, the activation of autoreactive T cells in the periphery, the engagement of costimulatory signals and upstream of these events the presentation of immunogenic peptides by antigen presenting cells (APC). The focus of our research, in recent years, has been the characterization of lysosomal proteases involved in antigen processing in APC. To this end, we have conducted extensive quantitative gene expression studies with real-time PCR of highly purified cell populations. These revealed different APC signatures of molecules involved in the antigen presentation pathway, especially a heterogeneous pattern of lysosomal proteases in dendritic cells (DC), monocytes, B lymphocytes, thymic epithelial cells, and myoblasts. In the context of myasthenia gravis, we found an increased expression of certain proteases in the thymus, which may contribute to the presentation of peptides to select autoreactive T cells. Modulation of antigen processing may offer a novel approach to interfere with the activation of autoimmune T lymphocytes. Another focus is on regulatory T cells, which are a particular subset of T cells with the ability to suppress immune responses. A loss of regulatory T cells is usually associated with complex autoimmune syndromes. In myasthenia gravis, the frequency of CD4+CD25+ Treg cells which originate from the thymus is not different from healthy controls, but Tregs in myasthenia are functionally impaired. This has also been observed in patients with multiple sclerosis, suggesting a more common dysfunction in autoimmune diseases. Immunosuppressive treatment partially compensates for this deficit. Tuning of regulatory T cells has a therapeutic potential for cell therapy in autoimmune diseases.





◄ Figure 2:
CD4+CD25+ Tregs are suppressor cells and inhibit T cell proliferation. CD4+ CD25- T effector cells were labelled with CFSE and cultured in the presence of anti-CD3 and alloantigenic stimulators in the absence (top) or presence (bottom) of 1:1 Treg cells. The proliferation of the effector cells is measured by the decrease in CFSE staining, which after each division is distributed equally between the daughter cells. Treg cells significantly decrease the proliferation of T effectors.

Finally, we investigated the T cell traffic from the priming in regional lymph nodes to the invasion of the CNS. Autoreactive T cells were tracked by murine MHC class II tetramers and gave novel insight into the dynamics, frequency, and recruitment of autoreactive T cells experimental autoimmune encephalomyelitis (EAE) in an animal model of multiple sclerosis.

◄ Figure 1:
Development of Tregs in the human thymus. Immunohistochemical staining for FOXP3, the transcription factor that drives the development and function of Treg cells, in the thymus. FOXP3-positive cells are readily detected in the thymic medulla, but not in the cortical area (400x)

Current projects address the following issues: Selection of autoreactive T cells in the thymus and dysfunction of regulatory T cells in myasthenia gravis (Dr. E. Tolosa). Frequency, function and distribution of regulatory T cell populations in neuroimmunological diseases (Dr. E. Tolosa)

Manipulation of antigen processing as an approach to modulate the activation of autoreactive T cells:

- Preservation or destruction of peptides forming T cell epitopes by differential expression of lysosomal proteases in antigen presenting cells (Dr. E. Tolosa)

- Modulation of antigen presentation as an experimental strategy to treat EAE (Dr. F. Bischof)

- Immunological memory and chronicity in autoimmunity (Dr. F. Bischof)

Techniques used in the laboratory include basic immunological methods, cell separation and tissue culture, proliferation-/suppression assays, cytofluorometry, molecular biology techniques to clone and express recombinant polypeptides, quantiative RT-PCR for gene expression studies, confocal laser-scanning microscopy, immunohistochemistry, and preparative and analytical HPLC. In 2006, our work was supported by grants from the DFG (SFB 685 and GK 794), the Gemeinützige Hertie Stiftung, the MWFK Baden-Württemberg and the intramural programs of the Medical Faculty of the University of Tübingen (Fortüne and IZKF).

Staff:
F. Bischof, V. Brucklacher, E. Dubois, U. Feger, W. Kornberger, S. Lauer, C. Luther, M. Mitsdörffer, C. Netzer, M. Pick, S. Pöschel, C. Stoeckle, M. Scholl, P. Schroth, K. Steinbach, K. Stürner, E. Tolosa, M. Wasmer

Key Publications

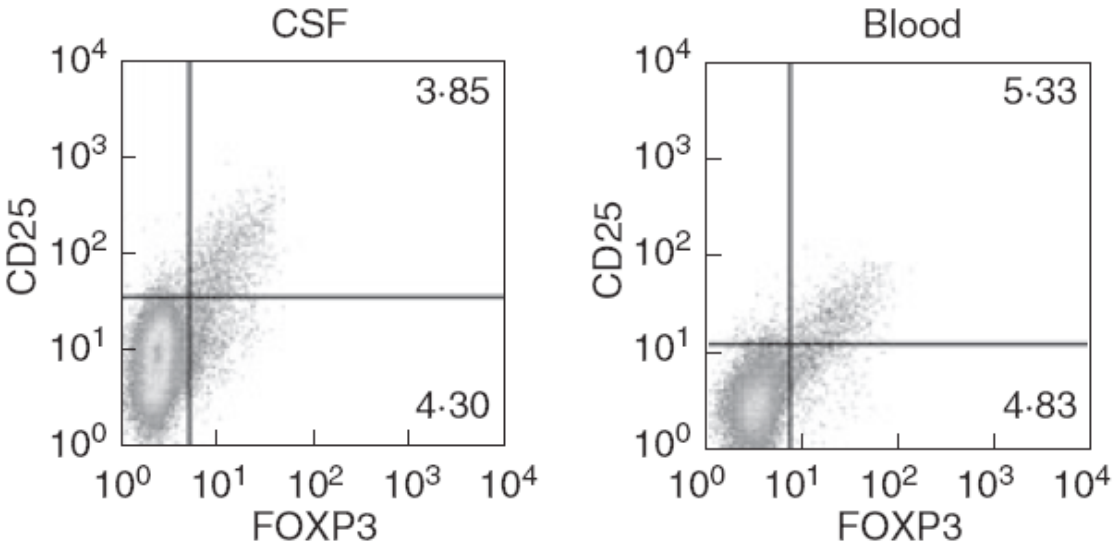
Amend B, Doster H, Lange C, Dubois E, Kalbacher H, **Melms A**, Bischof F (2006) Induction of autoimmunity by expansion of autoreactive CD4+CD62low cells in vivo. J Immunol 177:4384-90

Melms A, Luther C, Stoeckle C, Pöschel S, Schroth P, Varga M, Wienhold W, **Tolosa E** (2006) Thymus and myasthenia gravis: antigen processing in the human thymus and the consequences for the generation of autoreactive T cells. Acta Neurol Scand - Suppl 183:12-13

Schreiner B, Voss J, **Wischhusen J**, Dombrowski Y, Steinle A, Lochmüller H, Dalakas M, **Melms A**, Wiendl H (2006) Expression of toll-like receptors by human muscle cells in vitro and in vivo: TLR3 is highly expressed in inflammatory and HIV myopathies, mediates IL-8 release and upregulation of NKG2D-ligands. FASEB J 20:118-120

homepage: http://www.medizin.uni-tuebingen.de/neurologie/o/NktaanDo_F_NIm.html)

▼ Figure 3: FOXP3 coexpression of CD25+ Tregs in CSF and blood of a multiple sclerosis patient



Arbeitsgruppe Experimentelle Neuroimmunologie

Arbeitsgruppenleiter: Robert Weissert

In der Arbeitsgruppe werden Untersuchungen zum Verständnis der Neuroinflammation bei Erkrankungen des zentralen und peripheren Nervensystems durchgeführt. Die Multiple Sklerose (MS) ist eines der Hauptarbeitsgebiete. Neben Bioproben und Autopsiematerial werden Tiermodelle der MS eingesetzt. Im Besonderen soll ein verbessertes Verständnis der Pathogenese der Erkrankung erreicht und neuartige Therapieansätze untersucht werden.

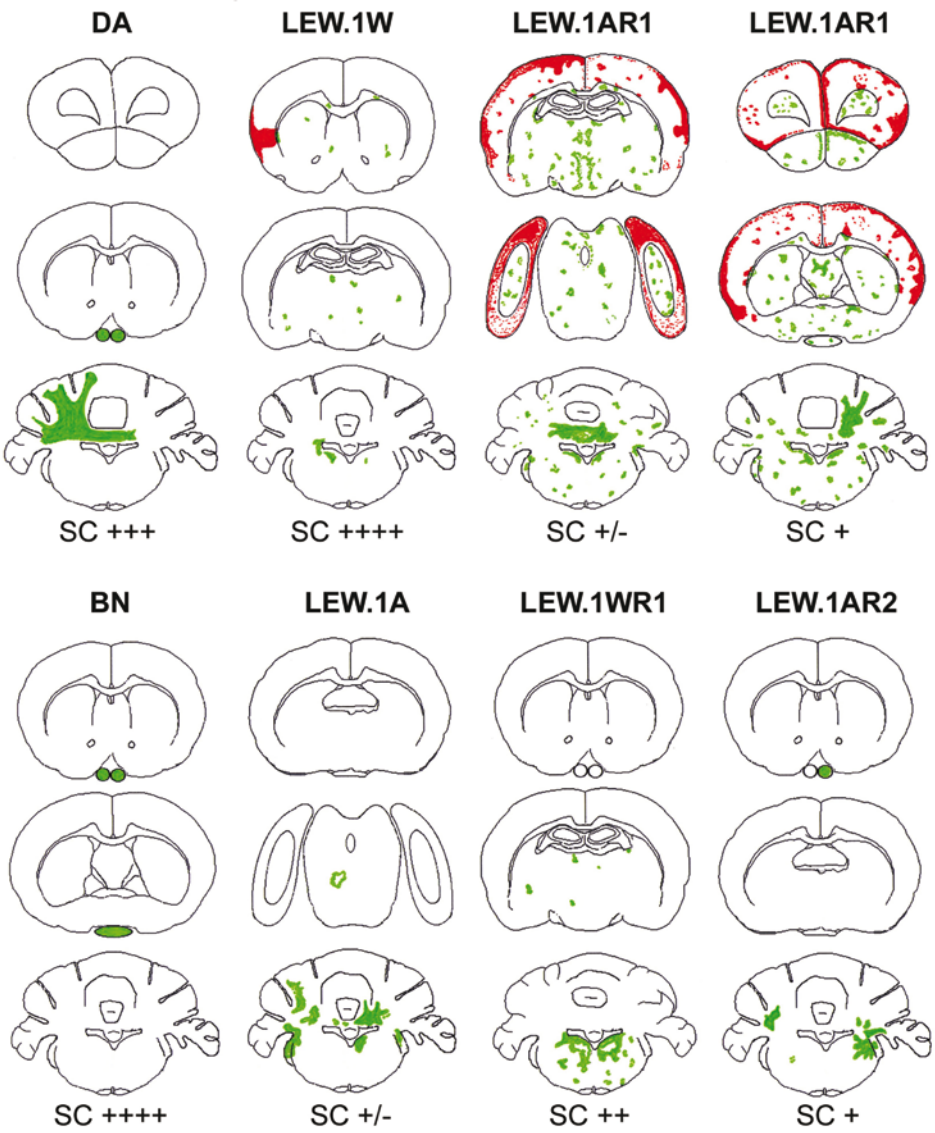
Bei der MS besteht eine genetische Prädisposition, die durch das Zusammenspiel von verschiedenen Genvarianten zu Stande kommt. Dieses bedeutet, dass man bei dem Vorhandensein einer bestimmten genetischen Ausstattung ein etwas erhöhtes Risiko hat, die MS zu entwickeln im Vergleich zu Personen, die eine andere genetische Ausstattung haben. Die Gene des HLA-Komplexes spielen dabei eine besonders wichtige Rolle, da diese die Immunantwort kontrollieren. Bestimmte Ausprägungen dieser Gene sind daher auch mit einer besonders hohen Empfänglichkeit gegenüber der MS vergesellschaftet. Neben der Beeinflussung der generellen Empfänglichkeit gegenüber Krankheit können Gene die Krankheitsausprägung steuern. So konnten wir zeigen, dass bestimmte Formen der Läsionsverteilung im zentralen Nervensystem (ZNS) im Tiermodell der MS genetisch bestimmt werden. Neben Genen spielen auch noch unbekannte Faktoren in der Umwelt bei der Auslösung und Aufrechterhaltung der MS eine Rolle. Es ist bisher nicht verstanden, welche Umweltfaktoren dieses sind. So könnten bestimmte infektiöse Erreger zur Auslösung der MS beitragen. In dem Labor für Experimentelle Neuroimmunologie versuchen wir zu entschlüsseln, welche Gene und Umweltfaktoren besonders wichtig für die MS sind und wie diese Einfluss auf die Erkrankung nehmen.

Neben diesen grundlegenden Untersuchungen zum Verständnis der MS untersuchen wir auch neue experimentelle Therapiestrategien. Dabei versuchen wir gezielt den krankheitsauslösenden Einfluss von bestimmten Genvarianten zu beeinflussen. Dazu verwenden wir neuartige kurze Eiweissmoleküle. Ebenso versuchen wir den Einfluss von ausgewählten Signalmolekülen, die die Entzündung im ZNS regulieren, durch pharmakologische Substanzen zu beeinflussen. Zu diesen gehören nukleäre Signalmoleküle wie NF-κB. Diese leiten die Signale von der Zelloberfläche in den Zellkern und führen damit zu einer Veränderung des funktionellen Programms einer Zelle. Wir hoffen, dass diese Untersuchungen eines Tages die Therapie von der MS deutlich verbessern können.

Experimental Neuroimmunology

(Group leader: Robert Weissert)

In the group of Experimental Neuroimmunology investigations for a better understanding of neuroinflammation in the peripheral and central nervous system are performed. Multiple sclerosis (MS) is one of the main research areas of the group. Beside samples and autopsy material from MS patients animal models are used to reach the goals. Especially an improved understanding of the pathogenesis of the disease will be obtained and novel therapeutic approaches are analyzed.



▼ Figure 1:
Cortical demyelination is controlled by MHC genes.
Cortical pathology selectively develops in LEW.1AR1 (RT1r2) rats after immunization with MOG 1-125 indicating that such pathology is genetically controlled (red areas indicate areas of cortical demyelination in grey matter, green areas of focal white matter lesions).

Elucidation of immunopathogenesis of MS

Autoimmune diseases are associated with certain HLA haplotypes. Analysis in animal models demonstrate that the HLA haplotype determines the specificity regarding the affected target organ of a specific autoimmune disease. In twin studies it has been shown that there is a strong genetic predisposition in MS. The strongest association in Europe and the USA exists with the MHC class II allelic variant DRB1*1501. Animal experimental findings suggest that the HLA association comes about by defined autoantigenic peptides that are presented on MS-associated MHC class II molecules in lymphoid organs that lead to an autoimmune reaction in the nervous system resulting in tissue damage. We try to define in experimental in vivo models how certain MHC isotypes and alleles predispose for MS. To assess these goals we use different MHC congenic rat strains, purified MHC class II molecules, peptides and various cellular and molecular immunological methods. In addition to the effort to better understand MHC function we elucidate the influence of other genes in MS. Following this line of research, currently we are performing studies regarding the functional influence of polymorphisms in the CTLA-4 gene. So far there is no evidence that polymorphisms in the CTLA-4 gene influence susceptibility to MS.

The best characterised autoantigen for the autoantibody mediated demyelination of the myelin sheath in the MS is myelin-oligodendrocyte-gly-

coprotein (MOG). MOG is 218 amino acids long and belongs to the immunoglobulin superfamily. It is presented on the surface of the myelin sheath. The function of the MOG is unknown. We investigate the role of the conformation of MOG for the recognition by antibodies and for encephalitogenicity in patients with MS and animal models of MS. We have demonstrated that subgroups of MS patients have elevated titers of antibodies directed against native MOG. Recently, by other groups it has been confirmed with MOG transfected cell lines that MOG antibodies can be found in MS patients. Studies in animal models indicate that such antibodies have a pathogenic potential.

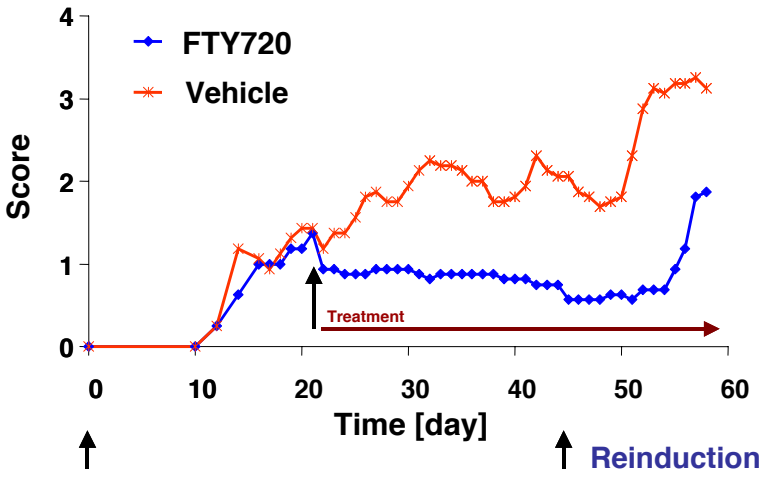
Not long ago it has been demonstrated that cortical pathology is present in MS. So far it is not well understood how cortical lesions develop and to what extent they contribute to the disease manifestation. Potentially they are the primary correlate for progressive disability and cognitive impairment in MS. We have developed an animal model of cortical pathology in an MHC congenic LEW rat strain (LEW.1AR1 [RT1r2]. These rats show after active immunization with the extracellular domain of MOG all types of cortical lesions that have been shown to be characteristic in chronic MS. In this model we are presently evaluating the mechanisms which lead to this type of pathology which is dependent on a specific MHC haplotype. These findings underscores that also in MS development of cortical pathology may be genetically controlled. We explore this model regarding pathogenetic mechanisms leading to cortical lesions by histopathology, immunology and molecular biology and evaluate the efficacy of preclinical therapeutic interventions which may be used for treatment of MS *(see fig. 1)*.

Experimental therapeutic approaches

Autologous bone marrow transplantation (BMT) and stem cell transplantation are sometimes used as a therapy for severe cases of autoimmune diseases with fast progression. We have elucidated the basic mechanisms operating in the therapeutic effects mediated by bone marrow transplantation. Interestingly the therapeutic effects seem to work by reducing autoantigen-specific B cell responses and by inducing regulatory T cells as well as altered T cell epitope recognition.

Emerging experimental therapeutic approaches in animal models employ mesenchymal and neural stem cells and focus on immune deviation, regeneration and myelin repair. We employ in different in vivo model systems mesenchymal and neural stem cells and assess the influence of the application on clinical, pathological and immunological outreads. In addition we use stem cells as a gene delivery vehicle for immunomodulating molecules.

Fingolimod (FTY720) is an orally active sphingosine 1-phosphate (S1P) receptor modulator in Phase 3 trials for the treatment of MS. To elucidate its beneficial effects in the CNS, we compared functional parameters of nerve conductance in the DA rat model of MOG-induced experimental autoimmune encephalomyelitis (EAE) after preventive and therapeutic oral treatment with FTY720. We found FTY720 to be effective in reversing clinical disease and restoring nerve conductance. Evidence thus far supports its role in the reduction of inflammation and preservation of blood-brain-barrier integrity. FTY720 may also act via S1P receptors expressed by glial cells and/or neurons to promote endogenous repair mechanisms that complement its immunomodulatory action *(see fig. 2)*.



◄ Figure 2: Treatment with the sphingosine-1-phosphate modulator in EAE. Oral treatment of DA rats with FTY720 leads to amelioration from EAE in a therapeutic setting. Re-induction of disease with MOG 1-125 leads to worsening of EAE even after continued application of FTY720.

A targeted modulation of the immune response with systemic peptides and peptidomimetics is the basis for a new generation of prophylactic and therapeutic vaccines and is an opportunity for treatment of diseases that result from an incorrectly directed or insufficient immune response. With the introduction of combinatory peptide collections that are built by one or some degenerated and defined sequence positions a fundamental acceleration of the search for new peptide ligands could be reached. Extensive experiments in the rat model of MS, EAE, showed that the peptide recognition patterns from disease-associated MHC class II molecules of the rat can be defined with combinatory peptide libraries. This pattern was the basis for the prediction of short peptides that bind with high affinity to MHC class II molecules. From a restricted number of synthetic peptides the sequence with the optimal binding to the MHC allele was chosen. High affinity peptides were optimized for binding on MHC class II molecules and showed no sequence similarities to known antigens. Interestingly some of these peptides were able to prophylactic and therapeutically inhibit or reduce symptoms of EAE in the rat.

We assess how through manipulation of proteases in vivo models of MS can be influenced in regard to disease course and pathology. We selectively inhibit cathepsin S (CatS), a key player in controlling MHC class II maturation, transport and function. We investigate the contribution of MHC I pathway on disease development by treatment studies with proteasome inhibitors. We elucidate if the effects of controlling MHC I and MHC II presentation are acting on the level of the peripheral immune organ or in the CNS. Our studies aim at identifying molecules with high therapeutic value for the prevention or treatment of EAE *(see fig. 3)*. These strategies will be the basis for future clinical trials for the treatment or prevention of MS and possibly other autoimmune diseases in humans.

Key Publications

Weissert R (2006) The curtain has drawn for both natalizumab and fingolimod (FTY720): a new era of multiple sclerosis therapy has arrived. Exp Rev Neurother 6:1587-90

Storch MK, Bauer J, Linigton C, Olsson T, **Weissert R**, Lassmann H (2006) Cortical demyelination can be modelled in specific rat models of autoimmune encephalomyelitis and is MHC haplotype related. J Neuropath Exp Neurol 65:1137-42

Kort JJ, Kawamura K, Fugger L, **Weissert R**, Forsthuber T (2006) Efficient presentation of myelin-oligodendrocyte-glycoprotein peptides but not protein by astrocytes from HLA-DR2 and HLA-DR4 transgenic mice. J Neuroimmunol 173:23-34

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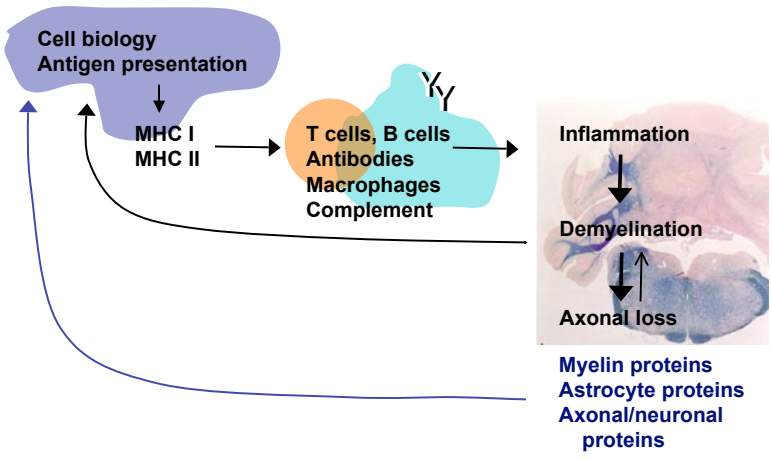
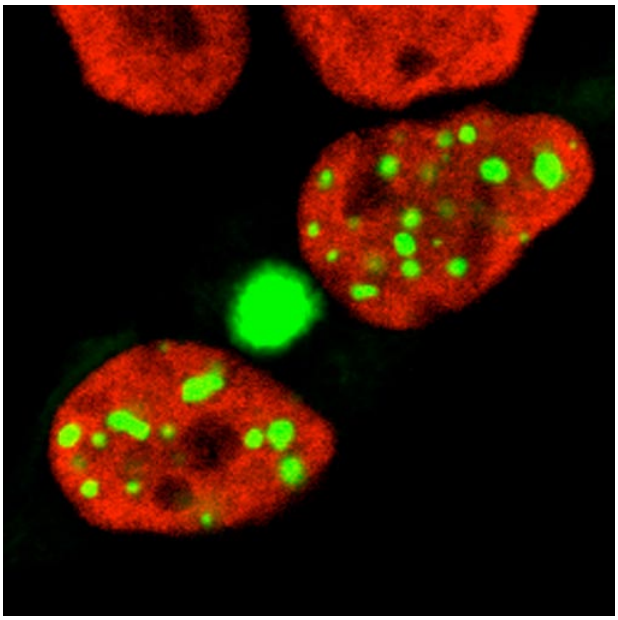
***Mhc* function in neuroinflammation**



◄ Figure 3:
Supposed pathogenesis of MS and targets for interventions.
Antigens are presented on MHC I and II molecules which lead to an immune response against CNS antigens. This results in tissue damage by inflammation leading to demyelination and axonal loss. Tissue breakdown leads to presentation of additional antigens on CNS resident antigen presenting cells as well as antigen presenting cells in the periphery. This presentation of antigens leads under stimulatory conditions to further immune activation and more tissue damage (vicious circle). Endogenous counter regulatory mechanisms are operative at different stages (i.e. regulatory T cells, endogenous tissue repair). Pre-clinical therapy should prevent presentation of antigens leading to breakage of tolerance to CNS antigens, affect tissue damage of immune cells in the CNS and induce repair.

Director: Prof. Dr. Thomas Gasser



Department of Neurodegenerative Diseases

Departmental Structure

The Department of Neurodegenerative Diseases (Chairman: Prof. Dr. Thomas Gasser) was founded with the generous support of the Charitable Hertie Foundation and started operations on September 1, 2002. The department provides a comprehensive approach towards basic and clinical research in the field of neurodegenerative diseases and movement disorders, from their molecular genetic basis and diagnosis to treatment.

Through its clinical division, the department provides care predominantly for patients with neurodegenerative diseases and movement disorders in one inpatient unit of 22 beds (Ward B5-Ost, under the supervision of Prof. Schöls and PD Dr. Krüger) and a number of specialized outpatient clinics. Diagnosis, differential diagnosis, and treatment of these disorders are provided by specially trained staff on all levels, including nursing staff, physiotherapists, ergotherapists, speech therapists, and neurologists.

The department also offers specialized and up-to-date diagnostic procedures for neurodegenerative diseases, including innovative techniques such as transcranial sonography of the brain parenchyma, smelling testing, and neuropsychological testing, and has full access to the entire spectrum of diagnostic procedures provided by the Center of Neurology. For many inherited neurodegenerative diseases and movement disorders, genetic testing is offered, in close collaboration with the Department of Medical Genetics.

Innovative treatment for patients with Parkinson's disease and other movement disorders include deep brain stimulation (DBS, supervised by PD Dr. Krüger in close collaboration with Dr. Freudenstein of the Department of Neurosurgery), but also continuous and intermittent apomorphine treatment in Parkinson's patients with severe fluctuations, or botulinum toxin treatment in patients with dystonias and spastic gait disorders.

The close collaboration of the specialized inpatient unit with the outpatient clinics for Parkinson's disease, dementias and Restless legs syndrome (supervised by PD Dr. Berg), dystonias, ataxias, spastic paraplegias, dementia, and neurogenetic disorders provides a highly flexible and optimized patient management structure. The equally close interaction with basic research groups of the Hertie Institute for Clinical Brain Research, on the other hand, allows rapid transfer of scientific progress into clinical practice.

This innovative concept includes active education and training of scientific and clinical junior staff. For example, the "Deutsche Parkinson-Vereinigung" (dPV) supports a training grant for "Clinical Parkinson's Research" which allows young physicians to gain experience in the diagnosis and treatment of this disorder while at the same time establishing a career in Clinical Parkinson's Research.

The "Section for Clinical Neurogenetics", established in 2004 and headed by Prof. Schöls, with its focus on ataxias and spastic paraplegias, attracts patients with these rare diseases from all over Germany.

In 2006, the basic research of the department was further strengthened by Prof. Kahle, who joined the department coming from Munich, and who will provide his expertise in the biochemistry and cell biology of neurodegeneration.

Arbeitsgruppe Genetik

Arbeitsgruppenleiter: Thomas Gasser

Viele neurodegenerative Erkrankungen und Bewegungsstörungen, wie die Parkinson-Krankheit, die Amyotrophe Lateralskerose oder die Torsionsdystonie sind „genetisch komplexe“ Erkrankungen. Dies bedeutet, dass die Erkrankungen nur bei einem kleinen Teil der Patienten familiär gehäuft auftreten und durch Mutationen in bestimmten Genen verursacht werden, während die Ursache bei dem weitaus grösseren Teil der Patienten weiterhin unklar ist. Es gibt jedoch viele Hinweise dafür, dass auch bei der zuletzt genannten Patientengruppe bestimmte Veränderungen in den identifizierten Krankheitsgenen zum Krankheitsrisiko beitragen.

Die Arbeitsgruppe beschäftigt sich mit der Identifizierung und Charakterisierung dieser Gene, und setzt dazu Methoden der Gensequenzierung, der Kopplungsanalyse und der Assoziationsstudien ein. Auch biochemische und zellbiologische Methoden werden eingesetzt, um die Funktion der Genprodukte und die Folgen der krankheitsverursachenden Mutationen zu analysieren.

Im Jahre 2004 konnten wir nachweisen, dass Mutationen in dem Gen für die „Leucin-rich repeat kinase 2“ (LRRK2) eine autosomal-dominant erbliche Form der Parkinson-Erkrankung verursachen. Inzwischen wurde gezeigt, dass Mutationen in diesem Gen die häufigste bekannte Ursache der Parkinson-Krankheit überhaupt sind. Die Arbeitsgruppe beschäftigt sich weiter intensiv mit diesem Gen, wobei die Suche nach neuen Mutationen, die Untersuchung der Beziehung zwischen Mutation und klinischem Erscheinungsbild (Phänotyp) und die Identifzierung krankheitsmodifzierender Faktoren im Vordergrund steht.

Aber auch andere „Parkinson-Gene" werden untersucht, wie etwa das Gen für „α-Synuklein“ und das “Parkin-Gen", das die häufigste rezessiv erbliche Form der Erkrankung verursacht.

Letztlich besteht das Ziel all dieser Studien darin, die molekularen Mechanismen der Krankheitsentstehung zu verstehen und auf dieser Basis neue Methoden der Frühdiagnose und Therapie zu entwickeln.

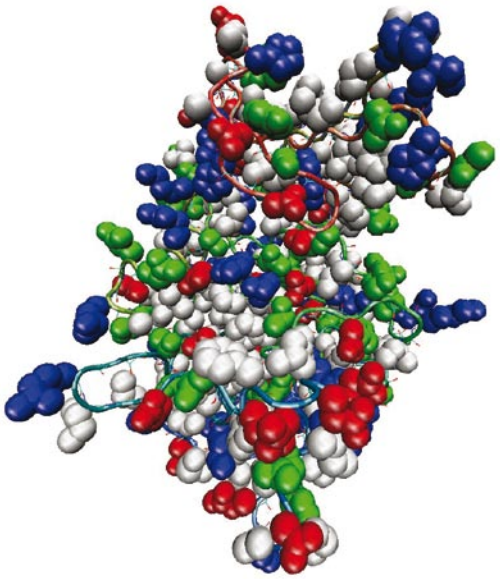
Die enge Verbindung von Klinik und Grundlagenwissenschaften am Hertie-Institut für klinische Hirnforschung bietet für diese Arbeiten ein besonders geeignetes Umfeld.

Genetics of Parkinson's Disease and Other Neurodegenerative Diseases

(Group leader: Thomas Gasser)

It is generally assumed that many genes and genetic loci contribute to familial and sporadic Parkinson's disease (PD) and other neurodegenerative disorders. Mutations in some of these genes cause very rare familial variants of the respective disease, whereas others are thought to contribute to susceptibility to the common sporadic form of the disorder. Using the methods of linkage and association studies, we are studying those genes and loci in a large number of families and patients. The indispensable prerequisite for these studies is a large collection of DNA-samples from carefully characterized patients. Blood and clinical data are collected in the University Hospital Department of Neurology but also sent in by mail from many collaborating physicians. DNA is isolated and clinical data are entered into a server-based SQL data-bank by Petra Leitner and Marita Munz.

▼ Figure 2: Putative structure of the LRRK2-protein



Leucine rich repeat kinase 2 (LRRK2, Park8)

In 2004, we have identified mutations of the LRRK2 gene (Leucine rich repeat kinase 2) as a cause for autosomal-dominant Parkinson's disease. This gene is the most common cause for familial PD known to date, accounting for about 5 to 15% (in some isolated populations even as many as 30 to 40%) of familial cases. The clinical and pathologic picture closely resembles typical idiopathic PD, underlining the potentially high relevance of this pathway in the pathogenesis of the sporadic disorder.

As a consequence of the reduced penetrance of at least some of the mutations and the late age of onset in affected individuals (~59 years, on average), mutations are found also in patients with clinically typical sporadic PD. In a large screen of our own cohort of about 1000 individuals, Claudia Schulte and others have found 12 mutations, the "common" mutation G2019S accounting for half of these cases (Schulte et al., submitted). *(see fig. 1)*

The reduced penetrance and variable clinical expressivity of LRRK2-mutations immediately leads to the question as to what other factors are involved in determining the clinical phenotype. International Graduate School student Yulia Golub and Post-doctoral fellow Julia Fuchs have studied variants in a number of genes, including α-synuclein, tau, and ApoE in a group of more than 50 LRRK2-mutation carriers. While the influence of the position of the LRRK2-mutation on age of onset and disease severity was almost negligible, a significant association with α-synuclein haplotypes could be found, indicating a close cross-talk between these pathways in PD.

Using the LRRK2 antiserum and commercial antibodies specific for tags, Christian Klein has established IP procedures that will be further developed to identify LRRK2 binding partners and potential substrates. In a different approach, Dr. Nadja Patenge has been successful in producing soluble LRRK2 domains in E. coli. The recombinant protein fragments will be used for X-ray crystallography in order to gain insight into the structure-function-relationship of LRRK2 specific domains, in collaboration with Prof. T. Stehle. *(see fig. 2)*

Functional Characterization of the Parkin Gene

Mutations in the parkin gene cause early onset autosomal recessive juvenile Parkinsonism (AR-JP). The parkin gene product is a E3 ubiquitin protein ligase. Ubiquitinylation of parkin substrates leads eventually to their degradation by the cellular proteasome. However, there are several leads that parkin may play a role in further cellular functions rather than being a mere E3-Ligase. In order to study these possible parkin properties, Oliver Rothfuss and Nadja Patenge use a variety of different techniques: cell biology (tissue culture, immunocytochemistry, functional assays, e. g. viability assays), protein biochemistry (western

▲ Figure 1:
LRRK2 domain topology. The number of repeats is given below the respective domain. Numbers above the sequence depict amino acid positions. Putative protein-protein interacting domains are shown in blue, catalytic domains are shown in brown. ARM, armadillo; ANK, ankyrin; Mid, fragment used for antibody generation; LRR, leucine-rich repeat; ROC, ras of complex proteins; COR, C-terminal of ROC.

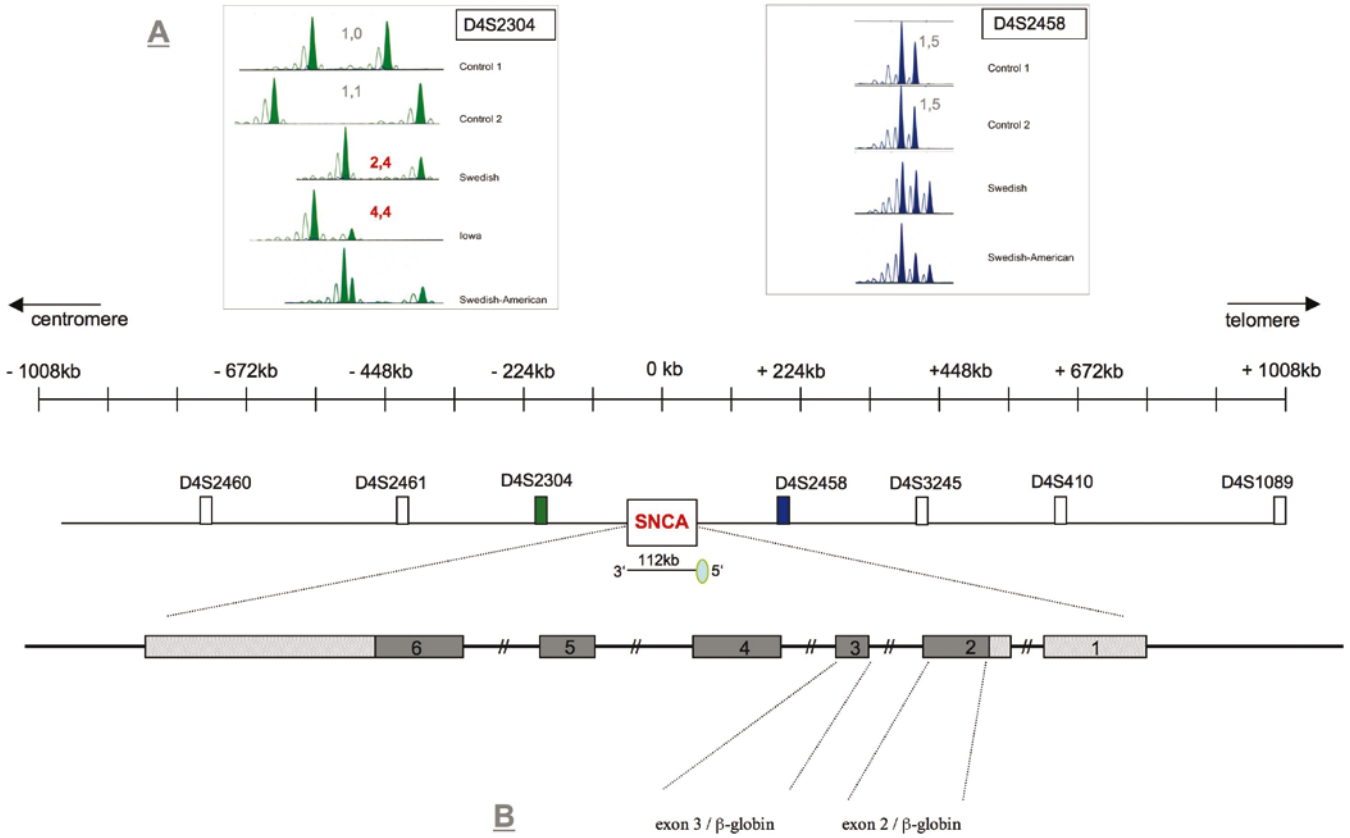
blot, IPs, protein purification), and molecular biology (PCR, RT-PCR, cloning). This work is supported by the Fortüne-Programm.

α-synuclein and Parkinson disease

The α-synuclein-gene (abbreviated as SNCA) is probably still the prototypical PD-gene, although mutations in the coding region are much less common than those in LRRK2 or parkin. Two observations put SNCA at the center of the pathogenesis of PD: the α-synuclein protein is the major component of the Lewy-body, the characteristic protein inclusions found in familial and sporadic PD, and duplications and triplications of SNCA have been identified as another cause of familial PD in a few families, indicating that an increase in wild-type protein load is sufficient to cause neuronal damage.

In collaboration with Dr. Farrer, Mayo Clinic Jacksonville and Dr. Christer Nilson, University of Lund, Sweden, we have identified a family that sheds new light on the consequences of SNCA gene dosage mutations. In one branch of the

▼ Figure 3:
Gene dose relationship of SNCA multiplications: a triplication of the genomic region containing the SNCA gene leads to an early-onset phenotype of Lewy-body dementia in a Swedish-American proband, while a duplication results in late-onset parkinsonism in a Swedish proband. Both family-branches can be traced back to a common ancestor.



family, Julia Fuchs detected a duplication of the gene, causing late-onset parkinsonism resembling multiple systems atrophy (MSA), while in another branch, the identical genomic fragment is triplicated, resulting in early-onset parkinsonism and dementia (Fuchs et al., 2007). This finding indicates a clear dose-effect relationship of SNCA mutations and neurological phenotype. Incidentally, these two branches of the family were unaware of their ancestral relationship. It was only the genetic findings that brought to our attention that they both belong to an extended family that made neurologic history: The family was the subject of a seminal paper by Henry Mjönes in 1949, in which he described, for the first time, families with a clearly dominant inheritance of Parkinson's disease. *(see fig. 3)*

In addition to a mere dose effect, abnormal phosphorylation may be a mechanism by which α-synuclein is inducing cytotoxicity. With the support of a Fortüne-grant, Dr. Rainer von Coelln is using methods of molecular biology, biochemistry, and cell biology to study the effects of phosphorylation and ubiquitination on properties of α-synuclein are characterized.

Other genes that have been studied successfully include the gene for sepiapterin reductase (SPR, Sharma et al, 2006) and inducible nitric oxide synthase (iNOS; Schulte et al., 2006).

Genes for ALS and torsion dystonia

Amyotrophic lateral sclerosis (ALS) is a disorder characterized by a loss of motor neurons, leading to progressive weakness and muscle wasting. Mutations in several genes have been found in rare familial forms of the disease, the most common of them is the gene for superoxide dismutase (SOD). Recently, polymorphisms in the gene for vascular endothelial growth factor (VEGF) have been found to be associated with ALS in some populations but not in others. In cooperation with the Neurology Departments of the Universities of Ulm and Munich, Rubén Fernández Santiago analyzed these variants and found a gender specific effect on disease risk (Fernández-Santiago et al., 2006). This finding may explain the discrepancies of previous studies as a consequence of variations in the gender-ratios of the study populations.

Another genetically complex disorder studied by our group is torsion dystonia (TD). The most common genetic form, generalized early-onset torsion dystonia, is caused by mutations in the gene for TorsinA (TOR1A). The cause for the much more prevalent form of dystonia, late-onset focal dystonia such as torticollis or blepharospams, is still unknown. Following the general hypothesis that common variants in the same genes that are responsible for rare monogenic forms could influence the risk to develop the common sporadic disorder, single-nucleotide polymorphisms (SNPs) within the TOR1A-gene have been suggested to be associated with sporadic late-onset focal dystonia in a single study. Christoph Kamm performed a thorough haplotype-based association study and was able to confirm the reported association. Interestingly, risk and protective haplotypes differed in the two studies, indicating population-specific effects.

homepage: http://www.hih-tuebingen.de/nd/forschung/parkinson/

Key Publications

Sharma M, Mueller JC, Zimprich A, Lichtner P, Hofer A, **Leitner P**, Maass S, **Berg D**, Durr A, Bonifati V, De Michele G, Oostra B, Brice A, Wood NW, Muller-Myhsok B, **Gasser T** (2006) The sepiapterin reductase gene region reveals association in the PARK3 locus: analysis of familial and sporadic Parkinson's disease in European populations. J Med Genet 43 (7):557-62.

Schulte C, **Sharma M**, Mueller JC, Lichtner P, Prestel J, **Berg D, Gasser T** (2006) Comprehensive association analysis of the NOS2A gene with Parkinson disease. Neurology 67: 2080-2

Fernández-Santiago R, Sharma M, Mueller JC, Gohlke H, Illig T, Anneser J, Munch C, Ludolph A, **Kamm C, Gasser T** (2006) Possible gender-dependent association of vascular endothelial growth factor (VEGF) gene and ALS. Neurology 66 (12):1929-31

Kamm C, Asmus F, Mueller J, Mayer P, **Sharma M**, Muller UJ, Beckert S, Ehling R, Illig T, Wichmann HE, Poewe W, Mueller JC, **Gasser T** (2006) Strong genetic evidence for association of TOR1A/TOR1B with idiopathic dystonia. Neurology 67:1857-9

Staff:
R. v. Coelln, R. Fernández Santiago, J. Fuchs, P. Leitner, C. Kamm, C. Klein, M. Munz, N. Patenge, O. Rothfuss, C. Schulte, M. Sharma

Arbeitsgruppe Bildgebende Verfahren bei Parkinson, neurodegenerativen Demenzen und Restless-Legs-Syndrom

Arbeitsgruppenleiterin: Daniela Berg

Obwohl es sich bei der Parkinsonerkrankung, den neurodegenerativen Demenzen (z.B. Alzheimer Demenz, Parkinson-Demenz, Lewy-Körperchen-Demenz) und dem Restless-Legs-Syndrom (RLS – Bewegungsunruhe der Beine) aufgrund des häufigen Vorkommens um „Volkskrankheiten" handelt, ist die sichere Diagnose insbesondere im Anfangsstadium häufig schwierig zu stellen. Spezifische Therapien werden daher oft erst mit Verzögerung eingeleitet.

Bei den neurodegenerativen Erkrankungen sind meist bei Auftreten erster Symptome, welche die Diagnose einer Parkinsonerkrankung oder Demenz erlauben, bereits so viele Nervenzellen geschädigt, dass eine nervenzellschützende Therapie nur noch wenig bewirken kann. Ziel muss daher sein, durch die Entwicklung zusätzlicher Verfahren eine frühe, sichere Diagnose zu ermöglichen und Verfahren zur Identifikation von Risikogruppen zu etablieren, die langfristig eine nervenzellschützende Therapie ermöglichen.

Mit Hilfe einer Ultraschalluntersuchung des Gehirns (transkranielle Sonographie – TCS) konnten wir eine für die Parkinsonerkrankung typische Auffälligkeiten [vermehrte Echogenität =Hyperechogenität] der Substantia nigra im Hirnstamm von Parkinsonpatienten beschreiben. Gewebs- und Kernspin-Untersuchungen weisen darauf hin, dass eine vermehrte Eiseneinlagerung, für die eine genetische Veranlagung besteht, für die Ultraschallveränderung ursächlich ist. Da sich dieses Merkmal bei Patienten mit ähnlichen Beschwerden aber anderer Krankheitsursache in der Regel nicht findet, kann die Untersuchung hilfreich für die Frühdiagnostik der Parkinsonerkrankung sein. Der Beitrag der Ultraschalluntersuchung zur Früherkennung der Parkinsonerkrankung, also bevor sich erste Symptome zeigen, wird derzeit in einer großen Verlaufsuntersuchung an gesunden Menschen geprüft.

Die Signalausdehnung der Substantia nigra ist jedoch nicht nur für den Morbus Parkinson von Bedeutung. Wir konnten zeigen, dass sich bei RLS-Patienten eine verminderte Echogenität der Substantia nigra findet. Ersten Gruppenanalysen zur Folge lassen sich mit Hilfe dieses Ultraschallmerkmals Untergruppen der Erkrankung unterscheiden, was für die Therapie von Bedeutung sein kann. Bei Kernspinuntersuchungen konnten wir zeigen, dass beim RLS ein verminderter Eisengehalt nicht nur, wie bereits bekannt, die Substantia nigra, sondern auch weitere Strukturen des Gehirns betreffen kann. Diese Entdeckung kann zukünftig nicht nur zur besseren Diagnostik, sondern auch zum besseren Verständnis der Erkrankung und zur Entwicklung weiterer Therapien beitragen.

Viele Menschen leiden an neurodegenerativen Demenzen, deren Unterscheidung in der Frühphase der Krankheit oft schwierig ist und deshalb eine spezifische Behandlung häufig erschwert. Darüber hinaus sind die Kriterien, die eine Demenz z. B. bei der Parkinsonerkrankung ausmachen, derzeit noch nicht klar definiert. In einer Untersuchung an 100 Parkinsonpatienten wird derzeit das Muster kognitiver Veränderungen bei der Parkinsonerkrankung untersucht und in PET (Positronen-Emission-Tomographie)-Untersuchungen mit dem Stoffwechsel in verschiedenen Regionen verglichen. Mittels PET-Untersuchungen mit einem Marker ([11C]PIB), der an im Gehirn vorhandene Ablagerungen bindet, können verschiedene Demenzformern unterschieden und wichtige Aspekte des Krankheitsprozesses nachvollzogen werden. Auch hieraus können sich wichtige Ansätze für unterschiedliche Therapieformen ergeben.

Neuroimaging and Clinico-genetic Studies in Parkinson Disease, Neurodegenerative Dementia and Restless Legs Syndrome

(Group leader: Daniela Berg)

Parkinson's disease (Schweitzer; Gaenslen; Liepelt; Di Santo; Godau)

Previous studies showed that more than 90% of Parkinson's disease (PD) patients display the typical ultrasound marker "hyperechogenicity of the substantia nigra (SN)" on transcranial sonography (TCS), which allows the differentiation between PD and atypical Parkinsonian syndromes. The hypothesis that SN hyperechogenicity may be used as a biomarker for PD could be substantiated with support of the Michael J. Fox Biomarker Award. First analyses of a still ongoing prospective study investigating the validity of the method to differentiate PD from atypical Parkinsonian syndromes show high positive predictive values for diagnosis.

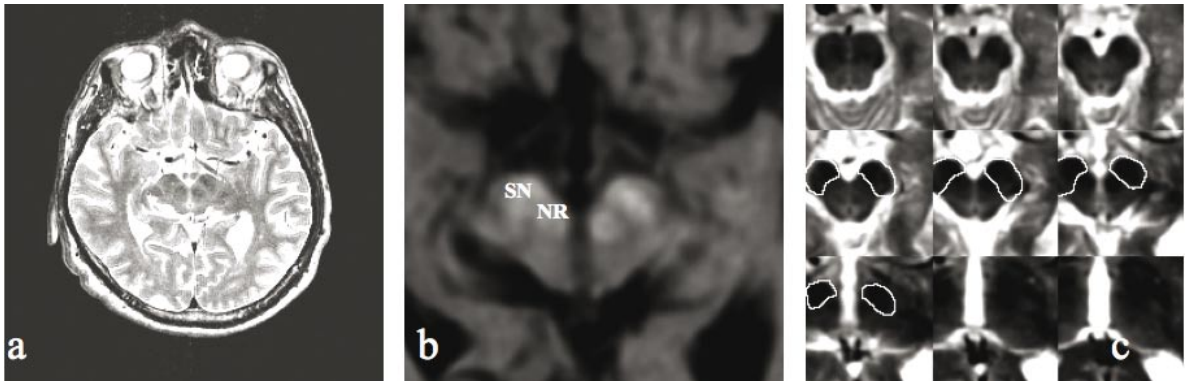
As hyperechogenicity of the SN may even be visible before disease manifestation, a large tricentric study (cooperation with the departments of Neurology at the University of Innsbruck and Homburg/Saar) has been initiated to evaluate the prospective value of hyperechogenicity of the SN as a risk marker for PD in more than 2000 healthy subjects aged 50 years and older. First analyses indicate that SN hyperechogenicity constitutes a genetically determined marker, independent from all other putative risk markers of PD. Follow-up investigations after 2 and 5 years will reveal whether subjects with increased SN echogenicity will indeed constitute a subgroup at risk for PD.

More than 40% of first degree relatives of PD patients show the same hyperechogenicity of the SN as the affected family member. This finding supports the hypothesis that there is a genetic susceptibility to idiopathic PD. Interestingly, a significant proportion of these healthy relatives had olfactory dysfunction, while none of the relatives without SN hyperechogenicity showed this symptom, which is thought to constitute a premotor sign for PD. Supported by the National Genome Research Network (NGFN) we are currently searching for genes that account for the hyperechogenicity.

In patients with monogenetic PD hyperechogenicity of the SN could also be detected, which however, was less prominent than in idiopathic PD. As SN hyperechogenicity could be related to an increased iron content of the SN, these results suggest that iron may play a less significant role in the pathogenesis of monogenetically caused compared to idiopathic PD.

Previous findings that one reason for SN hyperechogenicity is an increased iron content could be confirmed in post mortem analyses. MRI studies also confirm the hypothesis that increased iron levels account for increased SN echogenicity.

The form and distribution of the stored iron is currently being investigated in cooperation with the Mayo-Clinic in Jacksonville, Florida.



▲ Figure 1:
T2-relaxometry, with depiction of the whole brain (a) and specific focus of the substantia nigra (SN) und red nucleus (RN) for calculation fo R' from T2-relaxometry Daten: (b) Depiction of the SN at different levels for calculation of the whole area (c).

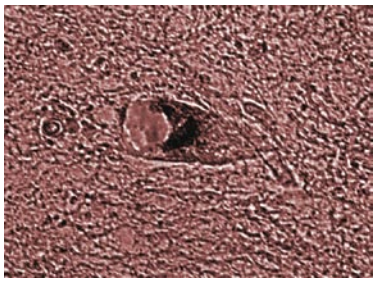
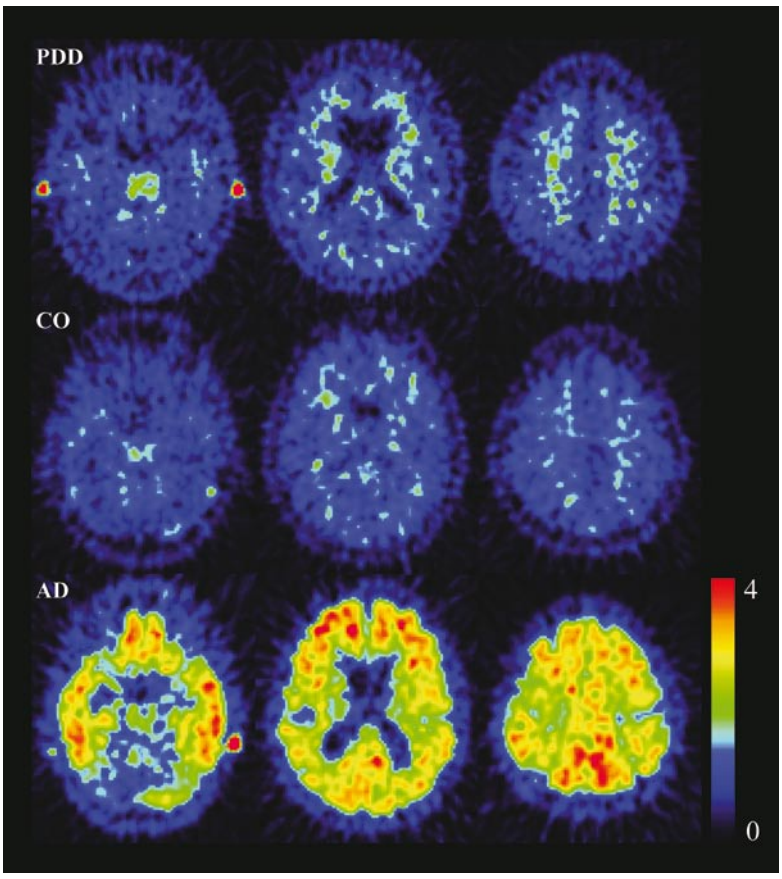


Figure 2 and 3 :
Lewy bodies in the SN of a patient with Parkinson's disease (▲) fluoresce after treatment with the mother substance of PIB, thioflavin T (▼).

Neurodegenerative dementias (Maetzler; Liepelt)

Dementia in Parkinson's disease is the second most common form of neurodegenerative dementia. However, until now, there are no definite criteria for clinical diagnosis. In a study comprising 100 subjects with clinically defined PD the pattern and extent of cognitive impairment is being defined and compared to findings in FDG-PET to set up criteria for the diagnosis of dementia. To investigate the pathophysiological process [11C]PIB (11C-6-OH benzothiazole) is used. [11C]PIB reflects the regional distribution of beta-amyloid in patients with Alzheimer's disease (AD). However, we were able to show that also Parkinson's disease subjects with dementia (PDD) show distinct PIB binding, displaying a pattern of decreasing tracer binding from the brainstem up to cortical areas. PIB binding to Lewy bodies was confirmed in postmorten brainstem sections of PD-patients. Preliminary data from 12 PIB-PETs of PD patients (without dementia) compared to the PDD PIB-PETs suggest that there are quantitative differences in tracer binding e.g. in the thalamus and the basal ganglia.

▼ Figure 4:
Typical findings of [11C]PIB-PET in a subject with Parkinson's disease with dementia (PDD), a healthy control subject (CO) and a patient with Alzheimer's disease (AD) with increased PIB binding in the brainstem of the PDD subject, and the lack of specific PIB binding in cortical areas compared to extensive cortical amyloid in AD.



Moreover, in cooperation with the department of Neuroradiology, MRI voxel-based morphometry and DTI-measurements are being performed to detect possible structural alterations in PD and subjects at risk.

Under the hypothesis that even a brain affected by neurodegeneration may exert some neuroplasticity these methods are also used to determine the effect of different forms of physical activity on white and grey matter of the brain in collaboration with the Sports departments of the University of Tübingen and Stuttgart, as well as the departments of Cognitive Neurology and Neuroradiology at the University of Tübingen.

Restless-Legs-Syndrome (Godau)

Restless-Legs-Syndrome (RLS) is with a prevalence of 5-15% a very common sensorimotor disorder. However, there are currently no morphologic abnormalities in idiopathic RLS to objectively detect this common disorder in the clinical setting. MRI and neuropathological examinations show a decreased substantia nigra (SN) iron content in idiopathic RLS patients.

As previous studies demonstrated that SN echogenicity correlates with SN iron content, RLS patients were investigated by TCS to determine the area of SN echogenicity. Indeed, we could show that SN echogenicity is significantly decreased in RLS patients compared to healthy controls ($p<0.001$).

Moreover, first MR examinations point towards a disturbance of iron metabolism affecting the whole brain in patients with idiopathic RLS. These findings are currently substantiated by further MRI and histopathological investigations.

Based on our first sonographic findings, epidemiologic and sonographic evaluations are being performed in a large cohort of patients in order to establish SN hypoechogenicity as a clinical marker for the diagnosis, differential diagnosis and subgroup description in RLS. First data demonstrate that RLS is not only associated with sonographic abnormalities of the SN but also of the raphe, the basal ganglia and the red nucleus. Those findings are being correlated with special clinical features and comorbities such as periodic limb movements and depression, which are present in the majority of patients, have a marked impact on the quality of life and are only partly understood concerning their relation to the RLS pathophysiology. In order to investigate structural abnormalities associated with clinical and sonographical findings HR-3D-MRI and DTI-imaging are currently performed.

Staff:
A. Di Santo, A. Gaenslen, J. Godau, I. Liepelt, W. Maetzler, K. Schweitzer

Key Publications

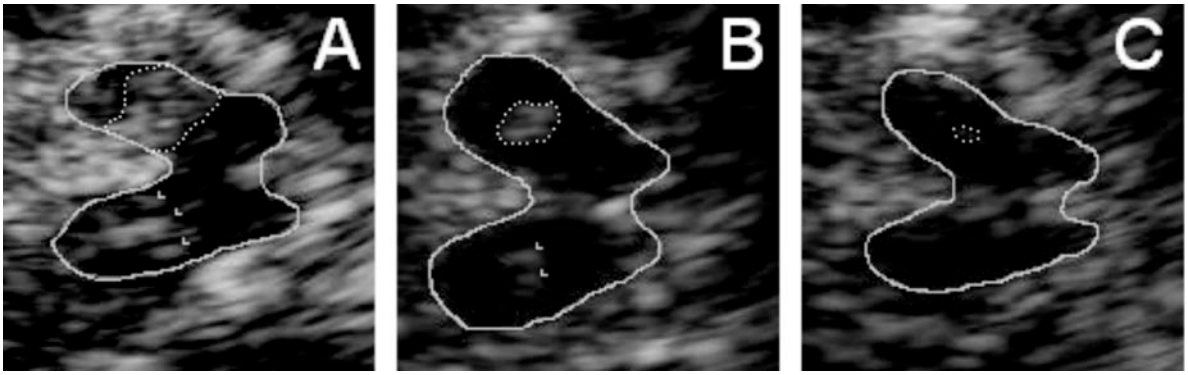
Prestel J, Schweitzer KJ, Hofer A, **Gasser T, Berg D** (2006) Predictive value of transcranial sonography in the diagnosis of Parkinson's disease. Mov Disord 21:1763-5

Schweitzer K, Hilker R, Walter, U Burghaus L, **Berg D** (2006) Substantia nigra hyperechogenicity as a marker of predisposition and slower progression in Parkinson's disease. Mov Disord 21:94-98

Berg D, Hochstrasser H, Schweitzer K, Riess O (2006) Disturbance of iron metabolism in Parkinson's disease - Ultrasonography as a biomarker. Neurotox Res 9:1-13

Maetzler W, Berg D, Schalamberidze N, **Melms A**, Schott K, Mueller JC, Liaw L, **Gasser T**, Nitsch C (2006) Osteopontin is elevated in Parkinson's disease and its absence leads to reduced neurodegeneration in the MPTP model. Neurobiol Dis [Epub 2006, Dec 26]

▼ Figure 5:
Representative ultrasound images of the human mesencephalic brainstem (encircled with full line). A: patient with Parkinson's disease and typical hyperechogenicity of the SN, B: healthy control, C: RLS patient with typical hypoechogenicity of the SN. (SN, marked ipsilaterally with dotted lines and contralaterally with arrows). The area of hyperechogenic substantia nigra (SN) signals is planimetrically measured from the ipsilateral side.



Arbeitsgruppe Funktionelle Neurogenomik

Arbeitsgruppenleiter: Rejko Krüger

Noch vor 10 Jahren war eine Beteiligung erblicher Faktoren bei der Entstehung der Parkinson-Krankheit höchst umstritten. Erst mit der Identifikation von Mutationen im alpha-Synuklein Gen als Ursache für die Parkinson-Krankheit in wenigen Familien mit vielen Betroffenen konnte eine Beteiligung vererbter Ursachen an der Krankheitsentstehung beispielhaft gezeigt werden. Heute kennen wir 7 Gene, die verschieden vererbte Formen eines familiären Parkinson-Syndroms verursachen können. Darüberhinaus ergeben sich Hinweise für eine Anzahl weiterer Gene, die nicht allein, aber möglicherweise zusammen mit anderen Erb- und/oder Umweltfaktoren die Parkinson-Krankheit auch bei sogenannten sporadischen Patienten, bei denen keine weiteren Betroffenen in der Familie bekannt sind, verursachen können.

Unsere Arbeitsgruppe beschäftigt sich mit der Identifikation von Krankheitsgenen bei der Parkinson-Krankheit und der Untersuchung neu gefundener Gen-Mutationen hinsichtlich ihrer Auswirkungen auf das Funktionieren der Nervenzellen. Hierzu werden neben molekulargenetischen Methoden zur Mutationssuche in Kandidatengenen auch Screening-Methoden zur Identifikation von neuen Genen bei der Parkinson-Krankheit eingesetzt. Darüberhinaus nutzen wir genetische Zellkultur- und Tiermodelle, um die Signalwege, über die krankheitsverursachende Mutationen die Nervenzellen schädigen, zu definieren und zu beeinflussen.

Beispielhaft haben wir im Jahre 2005 ein neues Gen als Ursache für die Parkinson-Krankheit bei der DNA Untersuchung von mehr als 500 Parkinson Patienten identifiziert. Mutationen im Omi/HtrA2 (PARK13) Gen sind eine seltene Ursache der Parkinson-Krankheit, allerdings scheinen die Signalwege, über die Mutationen die Zellfunktion stören, auch bei anderen erblichen und nicht-erblichen Formen der Parkinson-Krankheit eine Rolle zu spielen. Dies konnten wir in Zellkulturversuchen durch Schädigung der Mitochondrien als Kraftwerke der Zelle zeigen. Im letzten Jahr konnten wir in einer gemeinsamen Studie mit Arbeitsgruppen aus 12 Ländern von 4 Kontinenten zeigen, dass eine Veränderung in der regulatorischen Sequenz des alpha-Synuklein Gens das Risiko an Parkinson zu erkranken bei sporadischen Patienten erhöht.

Ziel der Arbeiten ist die Identifikation neuer genetischer Ursachen der Parkinson-Krankheit und das Verständnis der damit verbundenen Mechanismen des Zelltods dopaminproduzierender Zellen, um neue Strategien zu entwickeln, wie frühzeitig in den Krankheitsprozess eingegriffen werden kann und die Funktion der Nervenzellen bewahrt werden kann.

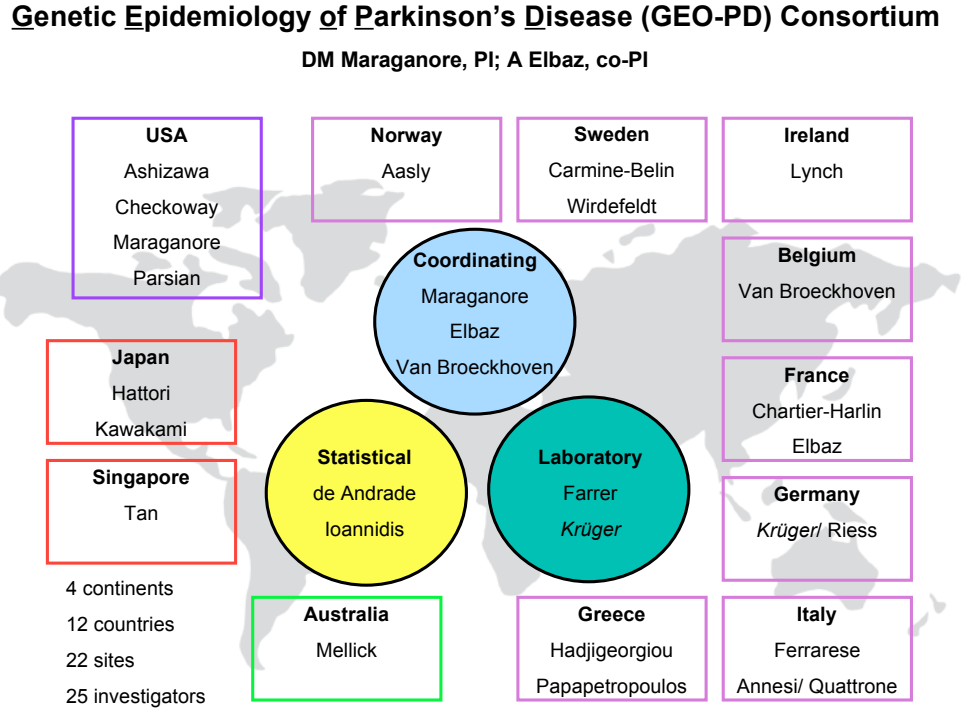
Functional Neurogenomics of Parkinson's Disease

(Group leader: Rejko Krüger)

One major focus of the group is the elucidation of molecular signaling pathways leading to neurodegeneration in Parkinson's disease. Using mutation screenings in a large sample of German PD patients, we identified novel mutations in genes that are responsible for familial PD and deciphered genetic variants in candidate genes that are associated with sporadic PD. We intensively study functional consequences of the identified mutations, investigating molecular signalling cascades in the pathogenesis of PD. In this context, we are interested in the identification of novel interacting proteins, characterization of proteasomal function, analysis of mitochondrial homeostasis, and the effects of cell viability in cellular models of the disease. These studies focus on the development of novel neuroprotective therapeutic strategies in the treatment of PD as the most common neurodegenerative movement disorder.

Definition of susceptibility alleles in the α-synuclein gene

Alpha-synuclein was the first gene identified in families with an autosomal dominantly inherited form of the disease. Moreover, dosage effects of physiological alpha-synuclein may be genetic risk factors for sporadic PD, and the elucidation of regulatory polymorphisms in the alpha-synuclein gene related to sporadic PD is of major interest. As part of the laboratory core of the GEO-PD-Consortium (funded by the Michael J. Fox Foundation; Maraganore et al., Neuroepidemiology, in press) we performed a large collaborative-pooled analysis of SNCA REP1 promoter polymorphism in PD cases and controls. Participating sites of the consortium provided detailed clinical and genetic data. For confirmation and validation of genetic data, reference genotyping was performed in the laboratory core. We confirmed that allele-length variability is associated with an increased risk for sporadic PD. Our findings support therapies targeting SNCA expression in affected brain regions (Maraganore et al., JAMA, 2006). In a second MJFF-funded collaborative project we genotyped PD-linked genetic markers from the first whole genome association approach in PD. This large validation study failed to confirm any of the 12 risk loci identified in the pilot study and gives important information for the design of future whole genome association approaches in complex diseases (Elbaz et al., Lancet Neurology, 2006). *(see fig. 1)*



▼ Figure 1: Structure of the GEOPD Consortium

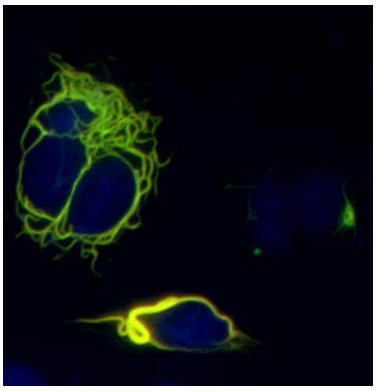
Identification of Omi/HtrA2 as a novel gene in the pathogenesis of Parkinson's disease

Current concepts of neurodegeneration in PD implicates aggregation of misfolded proteins and mitochondrial dysfunction. Recently, we identified the first mutations in the Omi/HtrA2 gene in PD, two heterozygous amino acid substitutions (A141S and G399S; Strauss et al., 2005). Based on molecular genetics and cell culture experiments our results on mutations in the Omi/HtrA2 gene in PD underscored an important link between mitochondrial dysfunction and neurodegeneration in PD.

Therefore further characterization of Omi/HtrA2 mutations regarding mitochondrial function, chaperone activity and differential substrate binding is subject of a DFG-supported project that started in 2006 (KR2119/3-1). With the support of a Fortüne-grant we currently generate Omi/HtrA2 transgenic mice to validate our findings in vivo and to further characterize the phenotype of Omi/HtrA2 mutations based on behavioral observations, biochemical and immunocytochemical experiments and functional brain imaging. *(see fig. 2)*

Significance of the cytoskeletal protein neurofilament for neurodegeneration

We identified two novel mutations in the neurofilament M gene in PD, a Pro725Gln substitution in one patient with apparently sporadic PD, and an amino acid deletion in position 829 in another patient with familial PD. Subsequent DFG-funded studies on the identified mutations, that focus on neuronal integrity and cell death mechanisms, showed specific effects of the mutant proteins on cell viability, protein aggregation and proteasomal function. This project aims to elucidate mechanisms of neurodegeneration, analyzing effects of structural changes of cytoskeletal proteins in terms of axonal transport, protein solubility, and protein degradation. *(see fig. 3)*

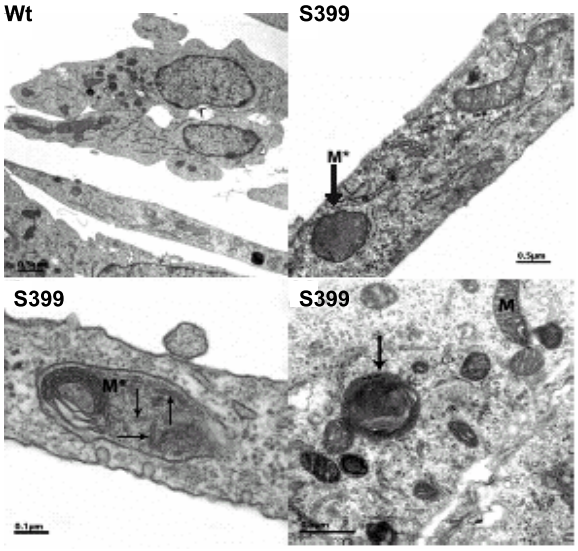


◄ Figure 3:
Reconstitution of filament formation by overexpression of neurofilament L and neurofilament M protein in cellular models with deficiency of intermediate filaments

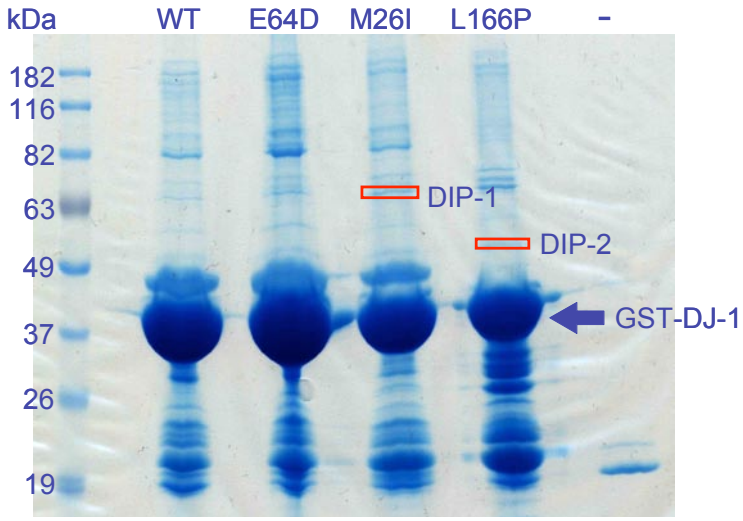
Identification of novel DJ-1 interacting proteins

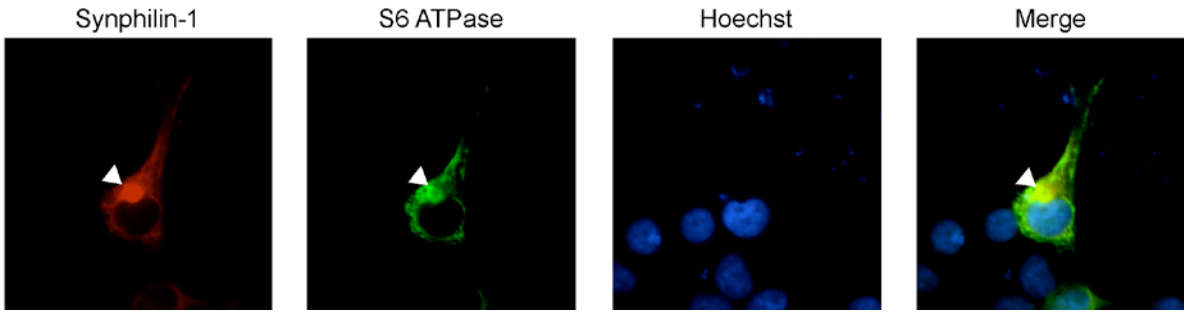
Mutations in the DJ-1 gene represent a rare cause of early onset Parkinsonism. How mutations of the DJ-1 protein contribute to PD is currently unknown. To understand the function and potential signalling pathways of the DJ-1 protein we performed GST pulldown assays with physiological and mutant DJ-1 and subsequent mass spectroscopy to define novel interacting proteins. We identified two novel interacting proteins of the DJ-1 that were validated by immunoprecipitation and subcellular colocalization using immunofluorescence. These proteins are involved in endoplasmatic reticulum stress (DIP-1) or responsible for the maintainance of mitochondrial function (DIP-2), respectively. Moreover we identified DIP-1 as a component of Lewy bodies in brains of sporadic PD patients. The characterization of the identified interaction of DJ-1 with molecular chaperones is of major interest to define mechanisms of susceptibility to cellular stress by differential effects of these novel interactors with mutant DJ-1 protein. *(see fig. 4)*

▼ Figure 2:
Swollen mitochondria and broken cristae in cells overexpressing mutant Omi/HtrA2



▼ Figure 4:
Identification of novel DJ-1 interacting proteins)





▲ Figure 5:
Colocalization of synphilin-1 and S6 in intracytoplasmic protein inclusions in human dopaminergic cell lines

The role of synphilin-1 and S6 ATPase in neurodegeneration in Parkinson's disease

Synphilin–1 is linked to abnormal protein degradation in PD, based on its role as an alpha-synuclein interacting protein and substrate of the ubiquitin E3 ligase parkin, and due to its presence in Lewy bodies (LB) in brains of PD patients. We identifed a novel specific interaction of synphilin-1 with the regulatory proteasomal protein S6 ATPase (tbp7; Marx et al., FASEB J, in press). Functional characterization of this interaction on a cellular level revealed co-localization of S6 and synphilin-1 in aggresome-like intracytoplasmic inclusions. Overexpression of synphilin-1 and S6 in cells caused reduced proteasomal activity associated with a significant increase in inclusion formation compared to cells expressing synphilin-1 alone. Steady state levels of synphilin-1 in cells were not altered after co-transfection of S6 and co-localization of synphilin-1-positive inclusions with lysosomal markers suggests the presence of an alternative lysosomal degradation pathway. Subsequent immunohistochemical studies in brains of PD patients identified S6-ATPase as a component of Lewy bodies. Our data indicate a direct interaction of synphilin-1 with the regulatory complex of the proteasome modulating proteasomal function. *(see fig. 5)*

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homepage: http://www.hih-tuebingen.de/gen.html

Patents:

German Patent No.: 10200 400 4924, *A141S und G399S mutations in the Omi/HtrA2 protein in Parkinson's disease*

US Patent and European Patent pending.

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Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, **Krüger R**, Rocca WA, Schneider NK, Lesnick TG, Lincoln SJ, Hulihan MM, Aasly JO, Ashizawa T, Chartier-Harlin MC, Checkoway H, Ferrarese C, Hadjigeorgiou G, Hattori N, Kawakami H, Lambert JC, Lynch T, Mellick GD, Papapetropoulos S, Parsian A, Quattrone A, Riess O, Tan EK, Van Broeckhoven C, on behalf of the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium (2006) Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson's disease. JAMA 296:661-70

Elbaz A, Nelson LM, Payami H, Ioannidis JPA, Fiske BK, Annesi G, Carmine A, Factor SA, Ferrarese C, Hadjigeorgiou GM, Higgins D, Kawakami H, **Krüger R**, Marder K, Mayeux R, Mellick G, Nutt J, Ritz B, Samii A, Tanner CA, Van Broeckhoven C, Van Den Eeden SK, Wirdefeldt K, Zabetian C, Dehem M, Montimurro JM, Myers RM, Southwick A, Trikalinos TA (2006) Whole-genome association and Parkinson's disease: a large-scale international replication study. Lancet Neurology 5:917-23

Franck T, **Krüger R**, Woitalla D, Müller T, Engelender S, Riess O (2006) Mutation analysis of the seven in absentia homolog 1 (SIAH1) gene in Parkinson's disease. J Neural Transm 113(12):1903-8

Arbeitsgruppe Genetik und Molekularbiologie von Dystonien und Dystonie-Plus-Syndromen

Arbeitsgruppenleiter: Friedrich Asmus

„Dystonie“ ist der Überbegriff für neurologische Erkrankungen, bei denen die willkürliche Kontrolle über Bewegungen einzelner Körperregionen bis hin zum gesamten Körper gestört ist. Auftreten können sowohl ungewollte, anhaltende (tonische) aber auch wiederholte (repetitive, phasische) Bewegungen.

Dystonien werden in der Klinik nach ihrer Ursache klassifiziert. Forschungsthema unserer Gruppe ist der Einfluss erblicher Faktoren auf die Entstehung der sog. idiopathischen Torsionsdystonien und der „Dystonie-Plus-Syndrome“.

Verschiedene neuere epidemiologische Studien zeigen, dass entgegen früherer Annahmen Verwandte von Dystonie-Patienten in bis zu 20% der Familien auch Symptome der Dystonie zeigen. Dies legt nahe, dass genetische Faktoren einen wichtigen Beitrag zur Entstehung von Dystonien leisten.

Unsere Arbeitsgruppe verwendet dabei verschiedene Untersuchungstechniken:

• „Klassische Familien-Analyse“. Gerade bei den Dystonie-Plus-Syndromen, bei denen zusätzlich zur Dystonie andere Symptome einer Bewegungsstörung, wie z.B. Myoklonien auftreten, folgt die Vererbung einem klassischen Vererbungsmuster nach Mendel, wird also dominant, mit 50%igem Risiko einer Vererbung an Kinder Betroffener oder rezessiv mit 25%igem Risiko der Weiterverebung übertragen. Unser besonderes Interesse gilt dabei der dopa-responsiven Dystonie (DYT5) sowie der Myoklonus-Dystonie (DYT11). Durch die genetische und funktionell biochemische Arbeit unserer Gruppe soll auch das Verständnis der idiopatischen, sporadischen Dystonien verbessert werden.

• „Assoziations-Studien“. Gibt es histologische oder biochemische Untersuchungen, die einen Beitrag bestimmter Gene oder von Stoffwechselkaskaden bei idiopathischen Dystonien wahrscheinlich machen („Kandidaten-Hypothesen“), kann hier eine Assoziation genetischer Varianten in den entsprechenden Genen durch Fall-Kontrollstudien mit SNP (singel nucleotide polymorphism)-Genotypisierung untersucht werden. In diesen Studien wird kein Befund für einzelne Patienten erhoben. Das Ergebnis gilt nur für die gesamte Gruppe untersuchter Dystonie-Patienten im Vergleich zu den gesunden Kontrollen. Auf diese Weise konnten wir zum Beispiel unlängst eine Assoziation bei sporadischen Dystonien mit dem MTHFR-Gen aus dem Homocystein-Stoffwechsel feststellen.

Genetics and Molecular Biology of Dystonia and Dystonia Plus Syndromes

(Group leader: Friedrich Asmus)

In a large study on psychiatric comorbidity in Myoclonus-Dystonia using the CIDI instrument, a specific pattern of comorbid conditions in symptomatic SGCE mutation carriers could be determined.

Affective and anxiety disorders including phobias were highly associated with a SGCE mutation carrier status. A large, age-matched control group from the Bundesgesundheitssurvey and interviews of pedigree members without SGCE mutations served as controls.

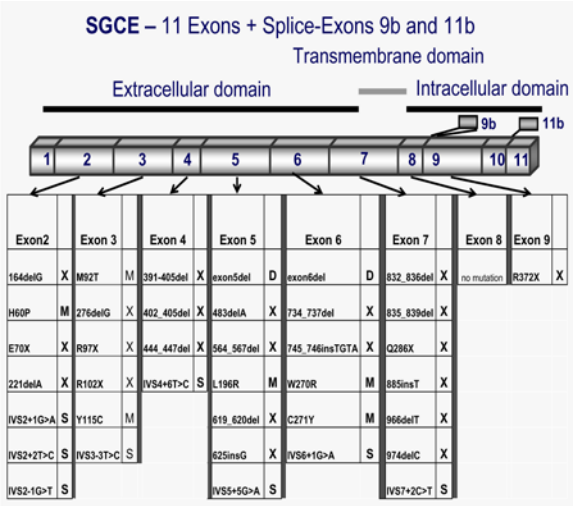
The pattern of psychiatric comorbidity apparently consists of affective and anxiety disorders, which can be treated with GABAergic substances. Ethanol, which has strong agonist effect on GABA-A receptors almost completely, abolished movement disorder symptoms in M-D patients. Hereby, a common aetiology for neurological and psychiatric features of M-D patients is suggested.

Benign Hereditary Chorea (BHC) is a rare, infancy-onset chorea with no continuos mental deterioriation and a normal life span. In its genetic form it is caused by mutations in the homeobox transcription factor Nkx2.1/TITF-1. In BHC patients hyperkinetic movements are variable and a considerable overlap to other movement disorders like Myoclonus-Dystonia (M-D) has been described. We used a systematic, video-based review of genetically proven BHC and M-D caused by epsilon-sarcoglycan (SGCE) mutations to work out discriminating clinical features. Only BHC but not M-D patients displayed continuous choreatic limb movements. Beside slower jerky movements detectable in both conditions, only the M-D patients with SGCE mutations displayed lightning-like myoclonic jerks almost uniformly aggravated by action. Both criteria combined will allow an accurate clinical diagnosis and referral for genetic testing.

The molecular pathophysiology of late-onset sporadic focal and segmental dystonias like blepharospasm or cervical dystonia is still poorly understood. In cooperation with the Dystonia Research Group, Prof. J. Müller, Innsbruck the genetic contribution to elevated homocysteine levels in sporadic dystonia patients was assessed. We have tested functional polymorphisms of the main regulatory enzymes influencing plasma homocysteine levels. We used a systematic approach with tagging single nucleoted polymorphism (SNP) for the MTHFR gene.

A highly significant association was detected for a dystonia-associated haplotype of the MTHFR gene. This association could be confirmed in an independent sample of 150 additional dystonia patients compared to age matched controls. Further work will focus on the detection of the molecular basis of this association and its role in the pathophysiology of late-onset dystonia.

▼ Figure: The epsilon-sarcoglycan gene encompasses 12 exons and the splice exons 9b. The majority of heterozygous SGCE mutations known to date are nonsense (X) and splicing (S) mutations. In addition exon deletions (D) and missense (M) mutations have been reported. All except one mutation are located in extracellular domain of the gene.



Key Publications

Deutschlander A, **Asmus F**, Marelli E, Klopstock T, **Gasser T**, Botzel K (2006) Excellent response to apomorphine in Parkinsonism with optic atrophy unresponsive to oral anti-parkinsonian medication. Mov Disord 21:1523-5

Kamm C, Asmus F, Mueller J, Mayer P, **Sharma M**, Muller UJ, Beckert S, Ehling R, Illig T, Wichmann HE, Poewe W, Mueller JC, **Gasser T** (2006) Strong genetic evidence for association of TOR1A/TOR1B with idiopathic dystonia. Neurology 67:1857-9

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Sektion Klinische Neurogenetik

Sektionsleiter: Ludger Schöls

Neurogenetische Erkrankungen stehen trotz ihrer Seltenheit im Zentrum neurologischer Forschung, da in jüngster Zeit für viele Formen die genetische Ursache aufgedeckt werden konnte. Dies ermöglicht neue Einblicke in die pathophysiologischen Mechanismen, die vom Gendefekt zur Krankheit führen. Diese Mechanismen sind nicht nur für die konkrete neurogenetische Erkrankung von Interesse, sondern liefern auch vielfältige neue Einblicke in neurodegenerative Prozesse, die z. B. auf die Parkinson oder Alzheimer Krankheit übertragen werden können.

Die Ataxien sind Erkrankungen des Kleinhirns, die zu Koordinationsstörungen mit unsicher-schwankendem Gang, Ungeschicklichkeit der Hände, undeutlichem Sprechen und Augenbewegungsstörungen führen. Ataxien sind trotz ihrer Seltenheit genetisch sehr heterogen. Für die häufigsten, autosomal dominanten Formen, die Spinocerebellären Ataxien (SCA) Typ 1, Typ 2, Typ 3 und Typ 6 wird in einem von der EU geförderten Projekt ein reproduzierbares Maß für die Schwere der Ataxie und Marker für das Fortschreiten der Erkrankung entwickelt. Eine Untersuchung des natürlichen Erkrankungsverlaufs ermittelt Daten, die für die Planung zukünftiger Therapiestudien unverzichtbar sind. Parallel werden an transgenen Mausmodellen Substanzen getestet, die das Fortschreiten einer SCA stoppen können. Für die häufigste Form der rezessiven Ataxien, die Friedreich-Ataxie, läuft derzeit eine multizentrische Studie mit Tübinger Beteiligung, in der verschiedene Dosierungen von Idebenone gegen Placebo getestet werden.

Die hereditären spastischen Spinalparalysen (HSP) führen zu einer schleichend zunehmenden Gangstörung durch Einsteifen und Schwäche der Beine aufgrund zunehmender Spastik. In Tübingen wird ein vom BMBF gefördertes deutschlandweites Netzwerk für HSP koordiniert, in dem die Grundlagen für künftige Therapiestudien erarbeitet werden. Hier haben wir die Spastic Paraplegia Rating Scale (SPRS) als erstes verlässliches Maß für die Schwere einer HSP entwickelt und untersuchen nun damit den natürlichen Erkrankungsverlauf, um ermitteln zu können, wie viele Patienten über welchen Zeitraum eine Therapiestudie einschließen muss, um nachweisen zu können, dass eine Substanz z. B. den Erkrankungsverlauf um 50% verlangsamt.

In genetischen Studien suchen wir nach neuen Genen, die HSP verursachen und haben hier für dominant vererbte HSPs einen neuen Genort (SPG36) und die ersten Mutationen für die SPG10 in deutschen Familien gefunden. Da eine Störung des Transports in den langen Zellfortsätzen (Axon) ein wesentlicher Faktor in der Entstehung der HSP zu sein scheint, untersuchen wir die Veränderungen des axonalen Transports, die durch Mutationen in den HSP-Genen hervorgerufen werden. Hierzu ermitteln wir die Laufgeschwindigkeit von sogenannten Motoren gegenüber den Zellgerüstproteinen, untersuchen den Einfluß von Mutationen auf das Axonwachstum in kultivierten motorischen Nervenzellen und analysieren den axonalen Transport in Fruchtfliegen, die die gleichen Mutationen tragen, wie sie bei der menschlichen SPG10 vorkommen.

Clinical Neurogenetics

(Group leader: Ludger Schöls)

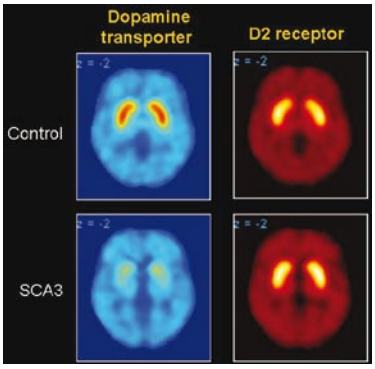
Neurogenetics receive special interest since recent genetic research disclosed the molecular cause of many neurological diseases. This facilitates precise diagnostics and enables further research into molecular pathogenesis of neurodegenerative or neurometabolic disorders. Although neurogenetic disorders are per se rare diseases they attract particular attention since they generate pathogenetic models of neurodegenerative processes that provide also clues for more prevalent diseases like Parkinson's or Alzheimer's disease.

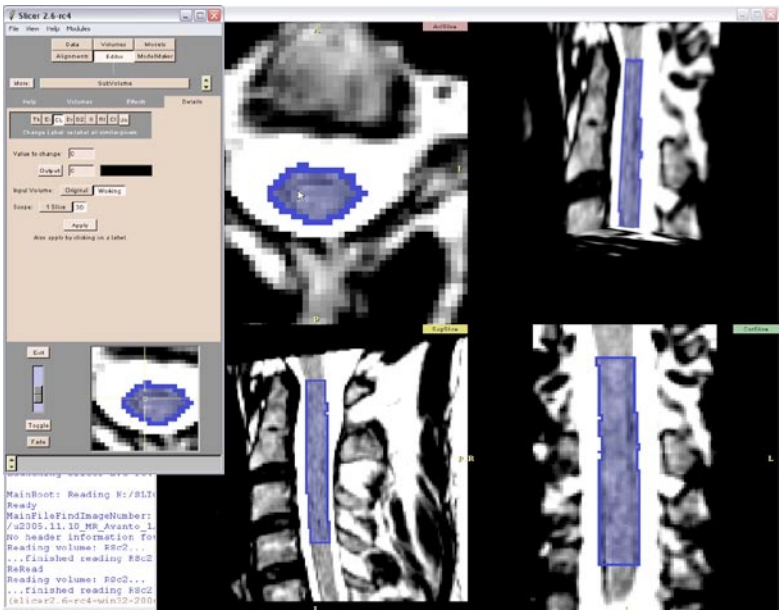
Ataxia

Cerebellar ataxia divides in a still increasing number of genetic subtypes. Autosomal dominant ataxias are genetically recognised as spinocerebellar ataxias (SCA) with 28 subtypes identified so far. In a consortium supported by the European Union (EUROSCA; http://www.eurosca.org/) we set up a registry for SCA that already includes more than 3.000 patients with these rare diseases. In preparation for upcoming intervention studies we developed and evaluated a new scale to assess severity of ataxia and perform a natural history study to reveal the progression of the disease. Additionally, biomarkers are developed using electrophysiological, imaging and transcriptional analyses. In the more frequent subtypes (SCA1, SCA2, SCA3 and SCA6) Christoph Globas looks for modifiers that influence the age at onset of symptoms.

In cooperation with the PET center at the University of Tübingen and Udo Rüb (Neuroanatomy, University of Frankfurt) we investigate morphological and functional changes of basal ganglia with special respect to the dopaminergic system in SCA2 and SCA3. In this DFG-funded project we use the combined approach of post mortem analyses and in vivo imaging techniques like 3D magnetic resonance imaging (MRI), transcranial brain parenchyma sonography and positron emission tomography (PET). Preliminary results especially in SCA3 show that major dopaminergic deficits in PET can be compensated by still unknown mechanisms without the development of clinical signs of parkinsonism *(see fig. 1)*.

▼ Figure 1:
Positron emission tomography (PET) in a SCA3 patient demonstrates severe dopaminergic deficits in dopamine transporter (11C-Methylphenydate) and D2 receptor (11C-Raclopride) imaging. Despite these dopaminergic deficits the patient failed to present typical Parkinson features.





◄ Figure 2:
In vivo volumetry of the spinal cord by magnetic resonance imaging (MRI). The cervical spinal cord is separated from a 3D dataset of T2-weighted images using a fast, semiautomatic approach. To ensure broad accessibility free software tools (3D Slicer) are used for this novel technique.

The most frequent form of autosomal recessive ataxia is Friedreich's ataxia. It normally starts around puberty and leads to progressive ataxia and weakness due to degeneration of the dorsal root ganglia and pyramidal tracts. Mutations in the FA gene cause a lack of frataxin, a mitochondrial protein involved in the assembly of iron-sulfur clusters that are essential e.g. for generation of respiratory chain complexes I - III. Idebenone is a short-chain analog of coenzyme Q10 that readily passes the blood-brain barrier and is supposed to compensate for at least some problems caused by frataxin deficiency. In a placebo controlled multicenter trial Chris-

toph Linnemann investigates different dosages of idebenone on ataxia and cardiomyopathy that frequently accompanies neurological disease in Friedreich's ataxia.

Hereditary spastic paraplegia (HSP)

HSP is characterized by distal-onset degeneration of the corticospinal tract. Corticospinal fibres to the lower extremities contain the longest axons of the nervous system. Other long fibre tracts like dorsal columns and peripheral sensory and motor fibres are also affected frequently. Clinically HSP presents as slowly progressive spastic gait disorder with variable additional symptoms depending on the affection of other parts of the nervous system.

In a German network of hereditary movement disorders (GeNeMove; http://www.genemove.de) sponsored by the BMBF Rebecca Schüle coordinated the development and evaluation of the spastic paraplegia rating scale (SPRS) as the first valid tool to measure disease severity in HSP. At present this scale is used to assess disease progression in a natural history study.

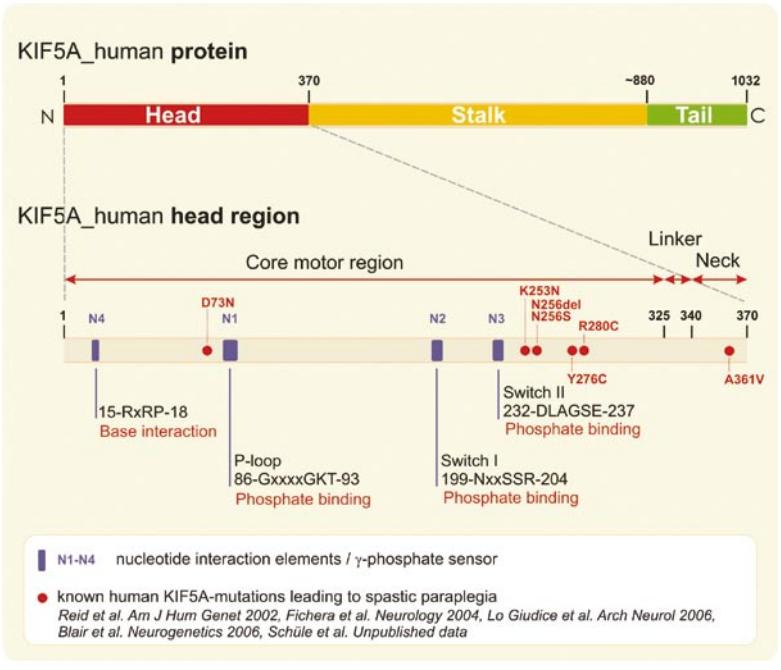
Tobias Lindig evaluates MRI tools for volumetric assessment of the spinal cord. Using a semi-automated approach he quantifies spinal cord atrophy in different HSP genotypes *(see fig. 2)*. In a longitudinal study the new MR volumetry tools are used to investigate the development of spinal atrophy as a surrogate marker indicating disease progression in HSP.

Although HSP is an overall rare disease it is genetically highly heterogeneous with more than 30 genetic loci identified so far. This makes genetic diagnostics extremely laborious and expensive in HSP. To improve availability and cost-effectiveness of molecular genetic testing in HSP Andrea Seibel developed in cooperation with Dr. Bonin of the Microarray Facility in Tübingen a resequencing chip that covers all HSP genes cloned until the beginning of 2006. After evaluation of this microarray, 11 genes can be sequenced in a single hybridisation.

Within the GeNeMove consortium we determined the frequency of SPG10, a dominant form of HSP that is caused by mutations in KIF5A. We found 3 novel mutations and estimated the frequency of SPG10 to be about 3.5% of autosomal dominant HSP in Germany. KIF5A *(see fig. 3)* encodes the neuronal kinesin heavy chain, a main motor of axonal transport. SPG10 can therefore be used as a model system for other forms of HSP in which defects of axonal transport have been described. At present Rebecca Schüle in cooperation with Günther Wöhlke at the Technical University of Munich investigates the motor properties of the newly identified KIF5A mutants in various in vitro assays.

For further analysis of axonal transport, primary cultures of motor neurons and dorsal root ganglia are established by Kathrin Karle to assess axonal outgrowth and transport of mitochondria using live cell imaging. Transgenic mouse models of HSP but also of SCA and Huntington's disease will be investigated for axonal transport properties since axonal defects have recently been recognized as early changes in a broad variety of neurodegenerative diseases.

With support of the DFG we identified a new locus for autosomal dominant HSP, SPG36, on chromosome 12 in a large German family in which spastic gait is accompanied by peripheral neuropathy. At present we investigate the SPG36 region for the disease gene by sequencing candidates with potential function in axonal transport or homologies to established HSP genes.



▼ Figure 3: Structure and mutations of the KIF5A gene coding for kinesin, the motor of antegrade axonal transport. KIF5A mutations cause autosomal dominantly inherited spastic paraplegia and are restricted to the motor domain that provides contact to microtubules and is responsible for ATP handling.

Leukodystrophies and neurometabolic disorders in adulthood

Leukodystrophies are commonly regarded as diseases of infancy although for most leukodystrophies adult-onset forms have been defined. The BMBF supports a national research network for leukodystrophies (http://www.leukonet.de/) that analyzes the natural course of the diseases as an essential prerequisite for therapeutical studies. Nerve conduction studies and evoked potentials are currently investigated as potential progression markers in leukodystrophies.

Since patients with leukodystrophies in adulthood frequently present with atypical phenotypes and do not always show white matter abnormalities on MRI we screen patients with apparently idiopathic forms of ataxia, spastic paraplegia, dystonia, demyelinating peripheral neuropathy, dementia and epilepsy for underlying leukodystrophies.

In some leukodystrophies metabolic abnormalities can be improved by restrictive diets or supplementary therapy. For example cerebrotendinous xanthomatosis can be cured by chenodeoxycholic acid substitution if introduced early in the disease *(see fig. 4)*. In other forms like metachromatic leukodystrophy enzyme substitution is an upcoming new therapeutic option.

Genetics of executive dysfunction

In a collaborative project with Dr. T. Münte (Neuropsychology Magdeburg) and Dr. A. Rodriguez-Fornells (Neuropsychology Barcelona) we investigate the effect of genetic variations of the dopaminergic system on cognitive function. A cohort of 650 probands from the University of Barcelona is analyzed for polymorphisms in four genes (DRD4, COMT, MAO, DAT) that are modulating dopaminergic function. Influence of genotypes on executive function is studied by an extensive neuropsychological test battery, event-related brain potentials and functional MRI. Preliminary results of this association study approach identified certain genotypes that are related to brain activity in a conflict monitoring task whereas other polymorphisms influence individual performance of working memory. To confirm the relevance of these findings we now aim to replicate our results in a second independent cohort of volunteers from Magdeburg. This study is supported by the Volkswagen foundation.

Staff:

Ch. Globas, K. Karle, S. Kullmann, T. Lindig, Ch. Linnemann, R. Schüle, A. Seibel

Key Publications

Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, Giunti P, **Globas C**, Infante J, Kang JS, Kremer B, Mariotti C, Melegh B, Pandolfo M, Rakowicz M, Ribai P, Rola R, **Schöls L** et al (2006) Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 66: 1717-20

Rüb U, de Vos RA, Brunt ER, Sebesteny T, **Schöls L** et al (2006) Spinocerebellar ataxia type 3 (SCA3): thalamic neurodegeneration occurs independently from thalamic ataxin-3 immunopositive neuronal intranuclear inclusions. Brain Pathol 16:218-27

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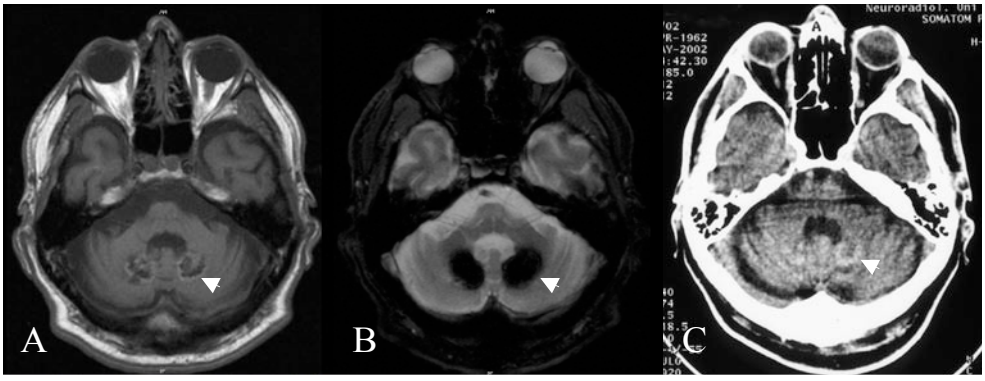
Schöls L, Nägele T, **Schüle R, Berg D** (2006) Cerebrotendinous xanthomatosis. Neurology 67:E20



▼ Figure 4:
Cranial computertomography (CT) and magnetic resonance imaging (MRI) demonstrates characteristic calcification and hemosiderin deposits at the dentate nucleus in cerebrotendinous xanthomatosis (CTX), a neurometabolic disease presenting as variable movement disorder and potential cure by supplementation of cholic acids.

Arbeitsgruppe Funktionelle Neurogenetik

Arbeitsgruppenleiter: Philipp Kahle

In heutigen Zeiten erhöhter Lebenserwartung stellen altersabhängige neurodegenerative Erkrankungen mehr denn je eine zunehmende Belastung nicht nur für den einzelnen Patienten, sondern auch für die gesamte Gesellschaft dar. Sämtliche dieser chronisch fortschreitenden Erkrankungen wie z.B. Morbus Parkinson (PD), Lewy Körper Demenz (LBD), Morbus Alzheimer (AD), Frontotemporale Demenz (FTD) sowie Amyotrophe Lateralsklerose (ALS) sind durch intrazelluläre Eiweiß-Ablagerungen und neuronalen Zelltod charakterisiert. Auf zellulärer Ebene, und vom klinischen Bild einmal abgesehen, unterscheiden sich diese Krankheiten somit lediglich durch die Natur des jeweiligen zur Ablagerung neigenden Proteins, der subzellulären Lokalisation der entstehenden Aggregate, sowie letztendlich durch den Zelltod verschiedener neuronaler Subpopulationen.

Somit scheint all diesen neurodegenerativen Erkrankungen eine zelluläre Fehlfunktion hinsichtlich Faltung, Modifikation und Abbau von Proteinen zu Grunde zu liegen. Nachfolgend führt dies zu Veränderungen verschiedener Signaltransduktionswege bis hin zum Zelltod. Tatsächlich sind alle bislang identifizierten Krankheitsgene, direkt oder indirekt, an der Bildung oder dem Abbau von eben diesen Einschlüssen beteiligt. Dabei spielt physiologisch wie pathologisch vor allem die Modifikation von Proteinen wie Prozessierung, Oxidation, Phosphorylierung und Ubiquitylierung eine ganz entscheidende Rolle.

Die Arbeitsgruppe befasst sich mit den molekularen und zellulären Mechanismen dieser einerseits so unterschiedlichen, andererseits so ähnlichen neurodegenerativen Erkrankungen. Dabei bedient sich die Arbeitsgruppe diverser "Modellsysteme" von einfachen Zellkulturen bis hin zu komplexen, lebendigen Tiere wie dem Fadenwurm C. elegans oder der Maus. Darüber hinaus werden hauptsächlich biochemische und zellbiologische sowie genetische und pharmakologische als auch neueste mikroskopische Methoden eingesetzt. Ziel unserer Forschung ist es, die physiologischen Funktionen der Krankheitsgenprodukte sowie die pathogenen Wirkmechanismen der entsprechenden Mutationen (Funktionsverlust oder Fehlfunktion) genauestens aufzuklären. Darüber hinaus wollen wir sowohl die Ursachen als auch die Auswirkungen von Proteinaggregation im Kontext neurodegenerativer Erkrankungen auf zellulärer wie auch auf Ebene des Gesamtorganismus besser verstehen. Dazu betrachten wir nicht nur die biologische Rolle jedes einzelnen Gens, sondern vielmehr das komplexe Zusammenspiel aller. Dazu zählen neben Aufklärung der funktionellen Rolle(n) jedes einzelnen Krankheitsgens auch die Identifikation, Analyse und Integration anderer bislang unbekannter genetischer und epigenetischer Faktoren (wie Alterung und Umweltfaktoren etc.), so genannter „Modifier".

Functional Neurogenetics

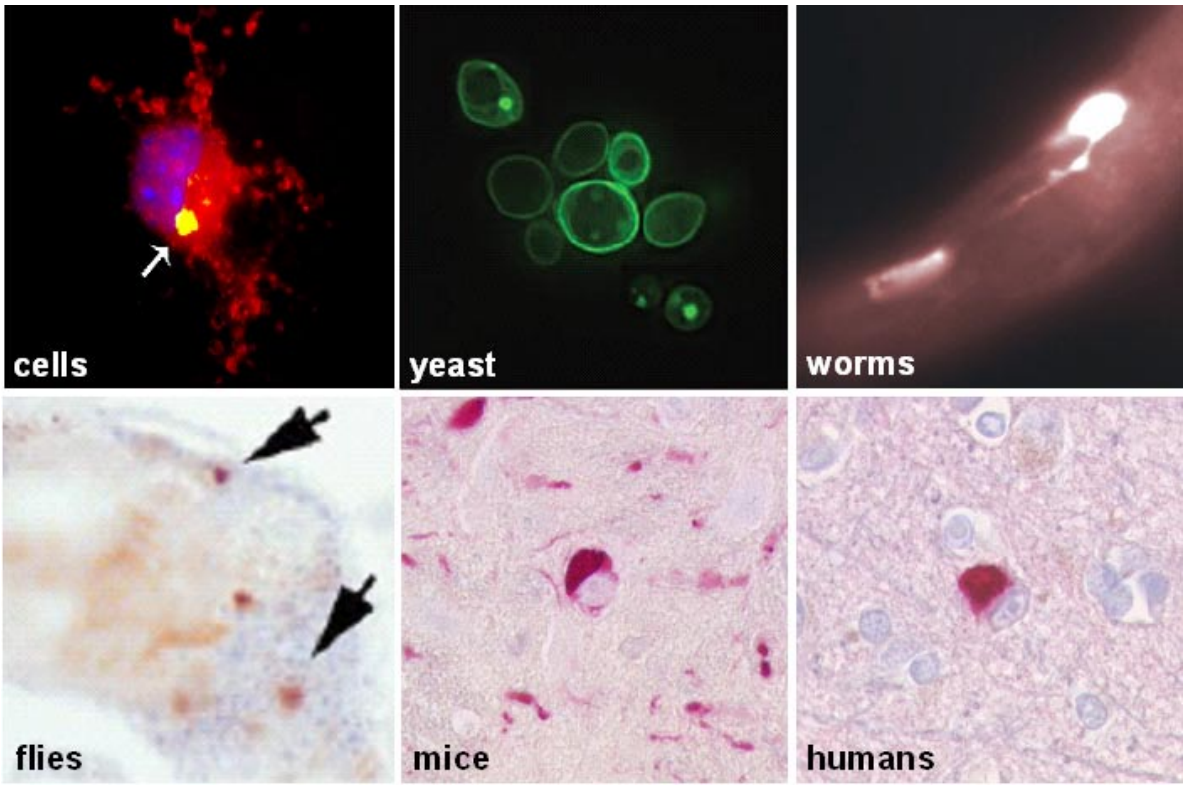
(Group leader: Philipp Kahle)

Age-related neurodegenerative diseases are a severe and increasingly worrisome burden for our aging population. Most of the chronic neurodegenerative diseases (Parkinson's disease [PD], Lewy body dementia [LBD], Alzheimer's disease, frontotemporal dementia [FTD], amyotrophic lateral sclerosis [ALS], etc.) are characterized by intracellular protein inclusions that are specific for each of these diseases. We investigate the molecular, cellular, and histopathological mechanisms underlying aggregation of the PD/DLB-associated synaptic protein α-synuclein and the FTD/ALS-associated TAR DNA-binding protein. Pathological proteolytic processing, phosphorylation pathways, and oxidative modifications are modelled in cell culture and transgenic animal models such as mice and worms. Cytotoxic mechanisms including impairments of the ubiquitin-proteasome system and mitochondrial malfunction modulated by PD-associated genes (parkin, DJ-1, LRRK2, PINK1, HtrA2/Omi, and others) are studied. We wish to understand the molecular basis of the remarkable specificity of intracellular protein aggregation killing particular neuronal subpopulations, which cause the characteristic syndromes of neurodegenerative movement disorders and dementias in human patients and are recapitulated in our transgenic mouse models *(see figure).*

▼ Figure: Aggregation/Lewy body formation of α-synuclein in various model systems

Characterization and Behavioural Consequences of α-Synucleinopathy in Transgenic Mice

We have established transgenic mice ectopically expressing human α-synuclein A30P mutation under the control of the Thy1 promoter, which recapitulate human α-synucleinopathy down to the ultrastructural level (Neumann et al., 2002). The dopaminergic system of αSYN transgenic mice is remarkably spared, but cognition of aged (Thy1)-h[A30P]aSYN mice is severely impaired, most likely due to their amygdala neuropathology (Freichel et al., 2006). Moreover, old transgenic mice ultimately die of locomotor deterioration, caused by brain stem and spinal motoneuron pathology. Based on our experimental evidence these transgenic mice serve as a valuable model for LB dementia. Heinrich Schell analyzes and characterizes the



effects of α-synuclein aggregation, fibrillization, and the resulting cytotoxicity and behavioral impairments. This work is supported by the Sonderforschungsbereich SFB596.

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Freichel C, Neumann M, Ballard T, Muller V, Woolley M, Ozmen L, Borroni E, Kretzschmar HA, Haass C, Spooren W, **Kahle PJ** (2006) Age-dependent cognitive decline and amygdala pathology in alpha-synuclein transgenic mice. Neurobiol Aging

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Signal Transduction of Leucine-Rich Repeat Kinase 2 (LRRK2)

The two monogenic autosomal-dominant hereditary PD genes encode leucine-rich repeat kinase-2 (LRRK2) and α-synuclein. In collaboration with Novartis Pharma Ltd., Basel, Switzerland, Iria Carballo Carbajal was able to show that these two genes are linked in a pathway whereby LRRK2 induces α-synuclein mRNA and protein expression in cell culture, and, moreover, that this induction is dependent on LRRK2 kinase activity. Since LRRK2 shows homology to mitogen-activated protein kinase (MAPK) kinase kinases, we have systematically investigated the three MAPK modules. Expression of LRRK2 stimulated the activating tyrosine phosphorylation of extracellular signal-regulated kinases (ERK1 and ERK2), but not c-Jun N-terminal kinases and p38 MAPKs. We propose that the physiological role of LRRK2 involves initiation of the ERK pathway and eventually induction of α-synuclein expression as part of a pro-survival pathway. This work is supported by the fortüne-Programm.

Cytoprotective Role of Parkin on Dopaminergic Neurodegeneration

The importance of parkin expression to nigral cell survival is probably related to its multifaceted cytoprotective functions. Among numbers of culprits involved in dopamine (DA)-induced cytotoxicity, to further clarify the molecular mechanism of how parkin functions in protecting cells from DA-induced neurodegeneration, Dr. Takafumi Hasegawa has developed novel neuronal cell lines co-expressing human parkin and transcriptionally regulated tyrosinase (Hasegawa et al., 2003). Tyrosinase, a key enzyme in the biosynthesis of melanin, catalyzes both the hydroxylation of tyrosine to L-DOPA and the subsequent conversion of L-DOPA and DA to their specific o-quinones. Thus, our tyrosinase-inducible cellular model could be a useful tool to investigate the neurotoxicity elicited by catechol-metabolites. Dr. Hasegawa is recipient of a Humboldt fellowship.

Regulation and Modulation of the E3 Ubiquitin Ligase Parkin

Most of the familial PD cases are caused by mutations in the parkin gene, causing autosomal recessive juvenile Parkinsonism (AR-JP). The parkin gene product has been suggested to function as an E3 ubiquitin protein ligase for a variety of unrelated substrate proteins. Modification of proteins with ubiquitin often leads to their proteasomal targeting and subsequent degradation. However, dependent on the quantity of ubiquitin moieties ligated, their specific linkage, as well as the usage of various ubiquitin-like modifiers (UBLs), further complex regulatory functions, other than simple degradation, have already been anticipated. Moreover, a relationship between the specific ubiquitin linkage and the formation of aggresome/Lewy bodies has already been proposed. To shed light into the diverse effects of protein modification by UBLs, Dr. Wolfdieter Springer inves-

tigates parkin as well as the seven-in-absentia homolog-1 and dorfin, two enzymes of the same functional class involved in PD. He studies the regulatory and modulatory effects of post-translational modifications on function and activity of these different E3 ligases (Yamamoto et al., 2005), as well as the cooperative actions of these enzymes with respect to linkage and ligation of ubiquitin and related modifiers in cell-free assays, transfected cell lines, and C. elegans (Springer and Kahle, 2006). This work is supported by the BMBF NeuroNet-2 (NGFN-2).

Molecular Mechanisms of DJ-1 Mediated Anti-Oxidative Stress Response

The recessive PD gene PARK7 encodes DJ-1, a protein with redox signalling and transcriptional modulator activity. DJ-1 was shown to be a component of the androgen receptor complex and the apoptosis signal regulated kinase-1 complex. However, these activities do not fully explain the selective dopaminergic neuron loss in PD. Jens Waak found that the loss of survival-promoting activity of the DJ-1 mutants with destabilizing C-terminal mutations correlated with impaired anti-apoptotic signalling. Furthermore, wild-type, but not mutant DJ-1 facilitated the Akt pathway and simultaneously blocked the apoptosis signal-regulating kinase 1, with which DJ-1 interacted in a redox-dependent manner (Gorner et al., 2007). This work is supported by the Sonderforschungsbereich SFB 596, NGFN-2, and Novartis Pharma Ltd., Basel, Switzerland.

Regulation of Mitochondrial Integrity by Parkinson's Disease Associated Genes

Besides dysfunctions of the cellular protein folding/degradation systems, mitochondrial respiration defects and the resulting oxidative stress as well as cell death signals derived from these organelles, seem to contribute to the pathogenesis of PD. Two recently identified genes, both of which are localized to mitochondria, the kinase PINK1 and the protease HtrA2/Omi thus provide a direct link. Kira Holmström analyzes the physiological roles of both, PINK1 and HtrA2/Omi, their protein-protein interactions as well as the pathogenic mechanisms originating from distinct familial mutations. Ms. Holmström is a member of the NEUROTRAIN Early Stage Research Training Programme funded through the EU FP6.

Cell Biology of the Frontotemporal Dementia Associated Nuclear Splice Factor TDP

Like α-synuclein, as the major constituent of Lewy Bodies, proteolytic fragments of the nucleic acid binding protein TDP-43 in cytosolic and nuclear inclusions were recently identified as neuropathological hallmarks of frontotemporal dementias and amyotrophic lateral sclerosis. It is to show now if the cytosolic aggregates are actively neurotoxic or if the cytosolic sequestration of the nuclear protein TDP deprives neurons of a vital splicing / transcription factor. Therefore, Fabienne Fiesel in cooperation with Manuela Neumann from the Center for Neuropathology And Prion Research, Ludwig-Maximilians University, Munich, Germany, is generating suitable vectors for overexpression and silencing of potentially neurotoxic TDP fragments for usage in cell culture and in vivo. First experimental data provide evidence that TDP is indeed able to aggregate in our cell culture system. Thus, our established model system recapitulates the aggregation properties and can now be used to analyze the pathogenic mechanisms as well as the biological functions of TDP.

homepage: http://www.hih-tuebingen.de/nd/research/funct-neurogenet/

Staff:

I. Carballo Carbajal, F. Fiesel, T. Hasegawa, K. Holmström, S. Horn, N. Klatt, H. Schell, W. Springer, J. Waak

Nachwuchsgruppe C. elegans

Projektgruppenleiter: Wolfdieter Springer

Der Fadenwurm Caenorhabditis elegans ist ein harmloser kleiner Bodenbewohner (Länge 1 mm, Durchmesser 70 µm) der sich von Mikroorganismen ernährt und in allen Erdteilen beheimatet ist. Obwohl eher unscheinbar, so treten doch seine Vorteile als Modellorganismus umso deutlicher ins Licht. Dazu zählen neben der kurzen Generationszeit (2,5 Tage bei 25°C vom Ei über vier Larvenstadien bis zum reproduktiven Tier) und der hohen Nachkommenzahl (>300), sicherlich auch die konstante Anzahl von nur 959 Zellen. Aufgrund seiner einzigartigen Transparenz kennt man den Ursprung und die Entwicklung jeder einzelnen Zelle ganz genau. Die anspruchslose und kostengünstige Haltung der Würmer erfolgt auf Agarplatten, in Flüssigmedium oder auch in Mikrotiterplatten, darüber hinaus lässt er sich sogar problemlos bei -80° C einfrieren. Überaus bemerkenswert ist, dass die Aktivität jedes einzelnen seiner rund 19.000 Gene ganz einfach durch „Füttern" entsprechender dsRNA-produzierender Bakterien manipuliert werden kann („RNAi/gene silencing"). Somit ist C. elegans wie geschaffen für automatisierte „High Throughput Screens" chemischer und genetischer Bibliotheken („genome-wide").

Obwohl das Nervensystem des Wurms im Vergleich zum Menschen selbstredend äußerst einfach gebaut ist, befähigt es ihn zu komplexen Verhaltensmustern. Basierend auf der Morphologie, der Verschaltung und des chemischen Inhalts können die insgesamt 302 Nervenzellen (über 30% aller Zellen) 118 verschiedenen neuronalen Klassen zugeordnet werden. Darüber hinaus findet sich zu rund 65% aller bislang identifizierten humanen Krankheitsgene ein homologes Gen im Genom des Wurms. Das Forschungsziel der Nachwuchsgruppe C. elegans ist eine möglichst umfassende und systematische Analyse physikalischer wie genetischer Interaktionen aller Parkinson-relevanten Genprodukte. Die meisten dieser sowie sämtliche Gene des Dopamin-Stoffwechsels und der -Neurotransmission sind im Wurm hoch konserviert. Darüber hinaus enthält C. elegans lediglich acht dopaminerge Neurone, diese sind jedoch frei zugänglich und können somit im lebenden Tier studiert werden. Es wurde bereits erfolgreich ein C. elegans Modellsystem für Parkin und α-synuclein entwickelt, welches die Suche nach weiteren genetischen und chemischen Modulatoren („suppressor/enhancer") erlaubt. Weiterhin erlauben transgene Würmer die einfache und schnelle Untersuchung sämtlicher humaner Mutationen und somit die funktionelle Charakterisierung der entsprechenden Genprodukte.

Die genetische Manipulierbarkeit von C. elegans und die enorme Konservierung biochemischer und zellulärer Komplexität machen dieses schlichte Lebewesens zu einem mehr als berechtigten Modellorganismus der biologischen wie auch der biomedizinischen Forschung.

C. elegans - An Experimental Model to Study Neurodegenerative Diseases

(Project leader: Wolfdieter Springer)

We use the nematode Caenorhabditis elegans to identify the biological functions of genes involved in various neurodegenerative diseases, and, moreover, to completely dissect the implicated key regulatory pathways. Given its simplicity and genetic tractability, the model organism C. elegans is well suited for this purpose, since its genome encodes homologs for about 65% of all known human disease genes. Moreover, it easily and rapidly allows the establishment of transgenic lines, and therefore, facilitates screening and characterization of human disease-causing mutations in vivo. We are particularly interested in the elucidation of molecular and cellular pathogenic mechanisms resulting in Parkinson's disease (PD).

In contrast to mammals, C. elegans contains only eight dopaminergic neurons, however these are well accessible and therefore morphology as well as synaptic connectivity can be studied in vivo. Moreover, all genes involved in dopamine signalling (genes for synthesis, metabolism, transport, re-uptake, as well as neurotransmission) are highly conserved in C. elegans. Indeed, it has already been shown that dopamine regulates a variety of different behaviors (e. g. locomotion and egg-laying), and, in addition, that PD-relevant medications and toxins are specifically effective in C. elegans.

◄ Figure:
Severe developmental defects caused by specific proteotoxicity of αSYN[A53T] in pdr-1(lg103) C. elegans parkin mutants; DA-neurons are labelled by GFP.

Comprehensive and Systematic Analyses of Genes and Pathways Involved in PD

We are studying the physical and genetic interactions among various PD-related genes and moreover with genes involved in key pathways such as the cellular protein folding and degradation machineries, stress response and detoxification systems, as well as mitochondrial integrity and function, signal transduction and cell death in general. For ongoing studies we have collected a great variety of different C. elegans deletion mutants for homologs of all these PD-linked genes. Dr. Wolfdieter Springer has already successfully established "screenable" models for parkin/α-synuclein-mediated toxicity (Springer et al., 2005) as well as for the Parkin-associated E4 enzyme CHIP (Hoppe et al., 2004).

Lysosomal Contribution to the Pathogenesis of PD

Impairments of cellular protein degradation systems clearly contribute to the pathology of neurodegenerative diseases. However, until now mainly the involvement of the 26S proteasome has been studied, whereas the contribution of the lysosomal pathway remains enigmatic. Moreover, permeabilization of the lysosomal membrane has been suggested to result in various types of cell death. In order to completely understand the molecular mechanisms of aggregation-prone protein metabolism, we are investigating the lysosomal/autophagosomal involvement as well as cell death routes deriving from these organelles. This work is supported by the fortüne-Programm.

homepage: http://www.hih-tuebingen.de/nd/research/funct-neurogenet/

Staff:
N. Klatt

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Hoppe T, Cassata G, Barral JM, **Springer W**, Hutagalung AH, Epstein HF, Baumeister R (2004) Regulation of the myosin-directed chaperone UNC-45 by a novel E3/E4-multiubiquitylation complex in C. elegans. Cell 118:337-49

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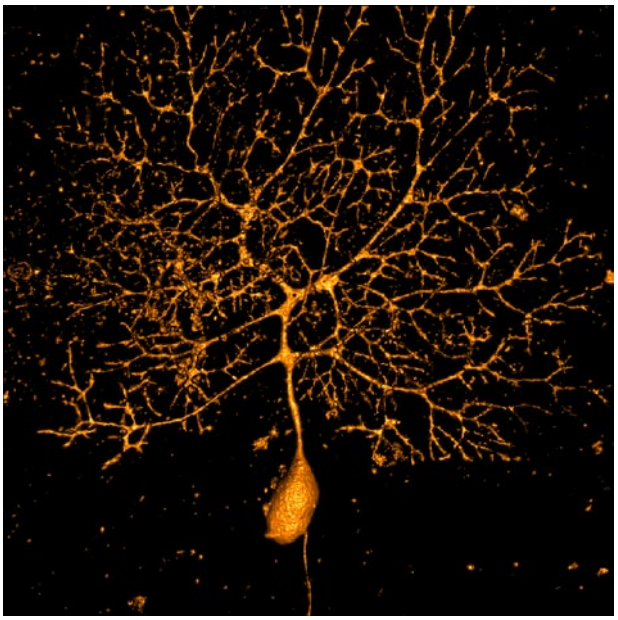
Director: Prof. Dr. Peter Thier



Department of Cognitive Neurology

Departmental Structure

The Department of Cognitive Neurology (DCN), headed by Prof. Dr. P. Thier, was founded in the year 2000 with support from the program "C4-Department of Neuroscience at Neurology Clinics" of the Hermann and Lilly-Schilling Foundation. In the year 2002, in which the Neurology Clinic was reorganized, the DCN became a constitutional part of the newly founded twin institutions, namely the Center of Neurology and the Hertie Institute for Clinical Brain Research. In the beginning of 2004, it was reinforced by the formation of a Section on Neuropsychology associated with a professorship for neuropsychology both taken over by Prof. Dr. Dr. H.-O. Karnath.

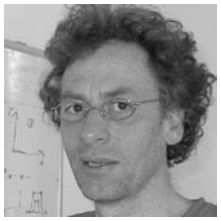
The DCN is devoted to research on the basis of higher brain functions and their disturbances due to disease of the nervous system. To this end, the DCN adopts multifarious approaches: the consequences of circumscribed brain lesions are analysed using classical neuropsychological techniques in conjunction with state-of-the-art psychophysical, behavioral and radiological methods. In order to explore the neuronal underpinnings of higher human brain functions in more detail, primate as well as rodent models are used, allowing recording of single- and multi-neuron signals and the correlation of these signals with well-defined behaviors or perceptual states as well as the targeted manipulation of neurons and neuronal circuits and their consequences for function. In-vitro techniques such as whole cell patch clamp recordings from isolated brain slices are being applied in an attempt to characterize the membrane and synaptic properties of identified neurons participating in neuronal circuits underlying higher brain functions, such as learning and memory. In close collaboration with the interdisciplinary centers for magnetoencephalography and magnetic resonance imaging (MRI) at the Medical Faculty functioning imaging experiments are carried out that tie up the behavioral experiments on patients with brain lesions, on the one hand, and experiments on animal models, on the other hand.

Several members of the DCN are engaged in the neuroscientific Collaborative Research Center (Sonderforschungsbereich) 550: "Recognizing, localizing, acting: Neurocognitive mechanisms and their flexibility", supported by the German Research Council (Deutsche Forschungsgemeinschaft, DFG) and coordinated by P. Thier. Both the DCN and the SFB 550 have contributed significantly to the successful bid for the acquisition of a DFG-funded 3Ts NMR-scanner, which has become the core of the aforementioned interdisciplinary MRI center.

Two young investigator groups supported by external funding contribute to research at the DCN: the first one is a young investigator group on "Neuronal mechanisms of numerical categories and concept formation", headed by Dr. A. Nieder and set up within the framework of the SFB 550. The second one on the "Representation of action and learning" is headed by Dr. M. Giese and funded by the Volkswagen Foundation. Two former young investigator groups, supported by the BMBF program "Biofuture 2000" (PD Dr. C. Schwarz) and the Heisenberg program of the DFG respectively (Prof. Dr. U. Ilg), are being continued as independent research groups within the DCN. All members of the DCN contribute significantly to research-oriented teaching at the Tübingen International Graduate School for Neural and Behavioural Sciences. Further teaching is deployed at the Faculties of Biology (Prof. Dr. U. Ilg) and Informatics (Drs. M. Giese and W. Ilg) and, of course, at Tübingen Medical School.

MRI-Labor

Arbeitsgruppenleiter: Fahad Sultan, Peter Dicke



Diese Arbeitsgruppe nutzt kernspintomographische Techniken, um Einblicke in die Architektur und die Arbeitsweise des Gehirns zu nehmen und den Einsatz elektrophysiologischer Untersuchungsmethoden in der Analyse von Nervenzellen und Nervenzellverbänden zu optimieren. Neben der Anwendung etablierter kernspintomographischer Techniken in der Untersuchung des menschlichen und tierischer Gehirne gilt ein wesentliches Augenmerk der Arbeitsgruppe der Entwicklung nicht-invasiver und invasiver kernspintomographischer Untersuchungstechniken, die Einblicke in die funktionelle Organisation von Gehirnen versprechen, die mit traditionellen Methoden nicht erreichbar erscheinen. Ein Beispiel hierfür stellen korrelierende Human- und Affen-fMRI-Experimente dar, die den Brückenschlag zwischen einzelzellelektrophysiologischen Untersuchungen an Affen und fMRI-Experimenten an Menschen ermöglichen. Mit diesem Ansatz untersucht die Arbeitsgruppe derzeit u.a. die Grundlagen der Wahrnehmung der Blickrichtung Anderer, ein wesentliches Element in der nichtverbalen sozialen Kommunikation. Ein zweites Beispiel stellen Versuche dar, kernspintomographische Verfahren zur Darstellung mono- und polysynaptischer Verbindungen zu nutzen. In Zusammenarbeit mit Prof. Nikos Logothetis vom Max-Planck-Institut für Biologische Kybernetik und unter Nutzung der tierexperimentellen Scanner dieser Arbeitsgruppe versuchen wir, elektrische Stimulation mit fMRI zu kombinieren, um den Nachweis von stimulations-evozierten BOLD-Signalen zur Charakterisierung von funktionell relevanten Verbindungen zu nutzen.

In Ergänzung dieser Ansätze, in deren Zentrum die funktionelle Kernspintomographie steht, stellt einen weiteren Schwerpunkt des Labors die Entwicklung maßgeschneiderter Implantate auf der Grundlage struktureller MR-Aufnahmen dar, die von den primär elektrophysiologisch arbeitenden Arbeitsgruppen der Abteilung benötigt werden. Um mechanisch stabile Bedingungen für die Einzelzellableitung einzelner Hirnzellen zu gewährleisten, ist es notwendig, einen stereotaktisch definierten Zugang zu den Zielregionen des Hirns mit möglichst großer Reproduzierbarkeit (<100µm) zu gewährleisten. Grundlage für die Produktion angepasster Implantate sind kernspintomographische Aufnahmen des Kopfes und CAD-Rekonstruktionen der Schädeloberfläche, die die Anpassung passgenauer Implantate ermöglichen. Diese Implantate werden aufgrund der guten Anpassung und der Nutzung biokompatibler Materialien gut akzeptiert und ermöglichen so lange Standzeiten und eine geringe Infektanfälligkeit. Die Arbeiten des Labors werden durch Spezies-vergleichende anatomische Untersuchungen komplettiert, in denen strukturelle Kernspintomographie in Ergänzung konventioneller neuroanatomischer Techniken eingesetzt wird, um ein besseres Verständnis der Phylogenese des Kleinhirns und seiner möglichen Beiträge zu nichtmotorischen Leistungen zu erzielen.

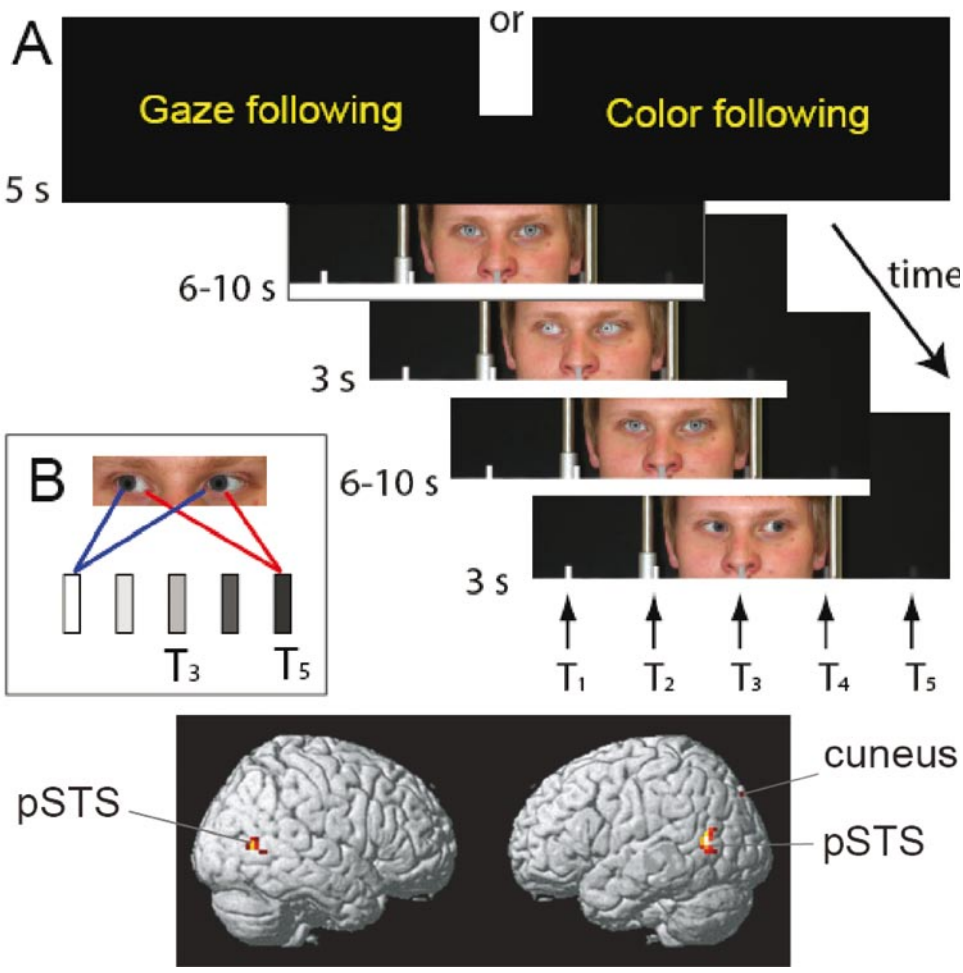
MRI-Laboratory

(Group leaders: Fahad Sultan, Peter Dicke)

We humans impress by the unparalleled expansion of our brains after an evolutionary process that distanced us from our fellow primates. Functional magnetic resonance imaging (fMRI) exploiting magnetic alterations induced by the level of blood-oxygenation saturation (BOLD) and structural MRI has allowed us to observe many aspects of the human brain in an unparalleled way. Nevertheless, aside from the temporal and spatial limits of fMRI and MRI, the method only allows us to observe some aspects of the complex actions and structures of the neuronal machinery, requiring invasive methods to further elucidate the underlying mechanisms. The work in this laboratory on the one hand uses MRI to optimize other invasive techniques with better temporal and spatial resolution (such as single unit recordings) and on the other hand together with Prof. Dr. Nikos Logothetis from the Max Planck Institute for Biological Cybernetics we are using invasive techniques such as electrical stimulation in animals to utilize the unique 3D capabilities of MRI to image the brains functional connectivity.

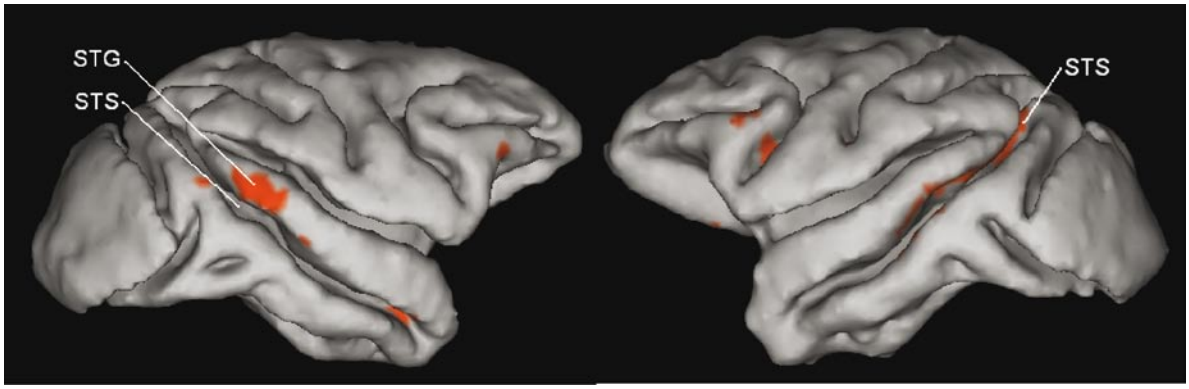
Correlative human and monkey fMRI

fMRI of gaze following in humans: The direction of a person's gaze indicates what object he or she is paying attention to and a shift in gaze direction indicates a change of the object of attention. Hence, gaze direction may serve as a key to developing an understanding of the other one's interests and possible intentions. Indeed, humans make use of eye-gaze, i.e. the orientation of someone else's eyes relative to objects in the world, very early during development and impaired processing of gaze information may be the basis of disturbances of social communication such as autism. The substrates and the principles underlying gaze direction are only insufficiently understood. We have used fMRI to delineate the relevant areas in the human brain and (see B) to characterize analogue areas in the monkey brain, which – in the long run – will be explored using electrophysiological techniques. In an event-related functional magnetic



▶ Figure 1: A: Example of the pictures presented in both conditions: gaze following and color following. The numbers indicate how long each picture is presented. T1-5, target 1-5. B: Schematic illustration of the stimulus. The eyes are directed at target 1 (blue lines) and the iris color corresponds to target 5 (red lines). Lower part: Group data (n=15) showing the activation pattern for the gaze following – color following contrast superimposed on a SPM brain template. pSTS: posterior superior temporal sulcus.

resonance imaging experiment, human subjects actively followed the directional cue provided by the eyes of another person towards an object in space or, in the control condition, used a non-directional symbolic cue (iris color) to make an eye movement towards an object in space. Our results (Materna et al. 2007) show that the posterior part of the STS region und the cuneus are specifically involved in extracting and using detailed directional information from the eyes of another person to redirect ones own gaze and establish joint attention. The IPS, on the other hand, seems to be involved in encoding spatial direction and mediating shifts of spatial attention independent of the type of cue that triggers this process. *(see fig. 1)*



fMRI of gaze following in monkeys: We have established a monkey fMRI setup, using a standard clinical 3T scanner (TimTrio Siemens). The monkey is studied in a "sphinx" posture heading in the direction of the bore of the scanner. Visual stimuli are projected onto a fronto-parallel screen placed 30cm away. The eyes are tracked using a home-made, MRI-compatible eye tracker, consisting of a low cost CMOS-camera in conjunction with infrared illumination and software that extracts the center of the pupil. Due to the motion sensitivity of the EPI sequences, one major prerequisite of the experiment is that the monkey does not move, which is assured by using primate chairs with particularly robust design and training protocols that emphasize the avoidance of movements. Training is carried out in a dummy scanner having the same geometrical scale as the 3T scanner. The principal aim of this project is the identification of areas in the monkey brain that are functionally equivalent to those of humans, allowing one to use results obtained by electrophysiologically exploring the activated areas in the monkey brain in order to draw inferences on the properties of the activated areas in the human brain. We are currently using this approach to analyze the neuronal underpinnings of gaze direction processing (see A). Rhesus monkeys have been successfully trained to use gaze direction as offered by portraits of other monkeys in order to reallocate their attention to particular objects. One of the animals trained has been studied successfully in an fMRI experiment which showed that gaze following activates a region in and around the superior temporal sulcus, whose location seems to correspond to the area seen in the corresponding experiments on humans. *(see fig. 2 ▾)*

The relative contributions of eye vs. head direction in gaze following: The direction of gaze in space depends on two linked coordinate systems: the eye-in-head and the head-in-space frame of reference. In this study we address the question whether the processing of gaze in space is carried out in a single brain region, or whether different regions code eye-in-head and head-in-space separately. The latter seems to be favored by psychophysical experiments that show that the angle of the eyes with respect to the head influences the perception of gaze although gaze angle in space is unchanged. Our first results with 18 subjects suggest separate regions in the STS for the processing of eye gaze and head gaze respectively.

fMRI in anaesthetized animals: in-vivo imaging of brain connectivity

The primate brain is composed of highly organized polysynaptic pathways that have evolved to subserve specific functions. We are developing polysynaptic tracing techniques with Prof. Dr. Nikos Logothetis (Max Planck Institute for Biological Cybernetics) by combining different methods with MRI. Together with Dr. A. Tolias we have recently (Tolias et al., 2005) established the microstimulation-evoked BOLD technique to study cortical projections in the monkey brain in vivo.

Microstimulation-evoked BOLD responses in striate cortex: Microstimulation-evoked BOLD responses were studied in a 4.7T scanner following electrical activation of primary visual cortex (V1) through specially devised microelectrodes. Current parameters (biphasic charge-balanced pulses and up to 1 mA and 200 µs pulse width per phase) enable us to evoke BOLD responses in V1 and in sufficiently remote areas known to receive direct V1 projections (MT), hence excluding a direct stimulation of these projection sites. We found that the excitability (as measured with chronaxie) of the stimulated V1 elements yielding the fMRI response ranged from 199 to 421 µs. These excitability values are similar to those that have been reported for cortical pyramidal neurons. Microstimulation of V1 activated V2, V3, V3A, V4, and middle temporal cortex (MT/V5), which is consistent with the known anatomy of striate and extrastriate cortex. *(see fig. 3)*

Functional connectivity of the extrastriate cortex in primates: We have now extended the technique of combined electrical microstimulation to the extrastriate area V5/MT. We electrically stimulated V5/MT in the anaesthetized macaque and evoked BOLD responses consistently in a number of brain areas known to be directly connected to V5/MT. BOLD responses were observed in ipsilateral V2, V3, V4, V4t, PO, MST, in the anterior and posterior banks of the IPS (corresponding to LIP) and in the superior colliculus. Two types of projection patterns could be discerned by stimulation of either the peripheral or the foveal retinal representation of area V5/MT. The latter showed activation of regions located on the lateral surface of the occipital cortex while the former showed activity in mesial occipito-parietal cortex. Currently, we are extending the method to study the projections of subcortical structures.

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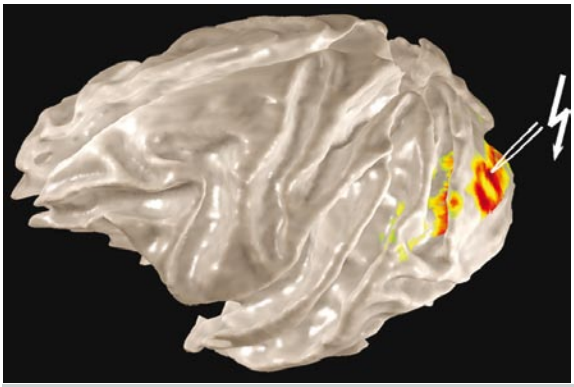

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Tehovnik EJ, Tolias AS, **Sultan F,** Slocum WM, Logothetis NK (2006) Direct and indirect activation of cortical neurons by electrical microstimulation. J Neurophysiol 96(2):512-21

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Okulomotorik Labor

Arbeitsgruppenleiter: Uwe J. Ilg

Die Aufklärung der neuronalen Grundlagen von zielgerichtetem Verhalten stellt das Anliegen dieser Arbeitsgruppe dar.

Die Nutzung eines zentralnervösen Modells der Umwelt, welches die Integration von sensorischen und motorischen Signalen erfordert, ist die zentrale Hypothese, die durch die Resultate ganz unterschiedlicher experimenteller Ansätze geprüft wird. So werden psychophysische Studien und Aufzeichnungen der Augenbewegungen von gesunden Probanden durchgeführt. Parallel dazu werden sehr ähnliche Experimente mit trainierten Rhesusaffen durchgeführt, die die Möglichkeit eröffnen, die Aktivität individueller Nervenzellen während der Ausführung der diversen Aufgaben aufzuzeichnen. Wenn Versuchspersonen einen Balken verfolgen, der bezüglich seiner Bewegungsrichtung verkippt ist, ist die Initiierung der Folgebewegung durch einen Richtungsfehler charakterisiert, der in etwa senkrecht zum bewegten Balken verläuft. Dieser Fehler ist durch die Eigenschaften der elementaren Bewegungsdetektoren vorhersehbar: diese Detektoren sind nur in der Lage, Bewegung senkrecht zu einer bewegten Kante zu extrahieren. Die Resultate der Arbeitsgruppe zeigen deutlich, dass dieser anfängliche Richtungsfehler nicht auftritt, wenn die Versuchspersonen illusionäre Kanten verfolgen. Dies belegt, dass die Signale, die zur Wahrnehmung einer illusionären Kante führen, unterschiedlich zu den Signalen sind, die die Augenbewegungen ansteuern.

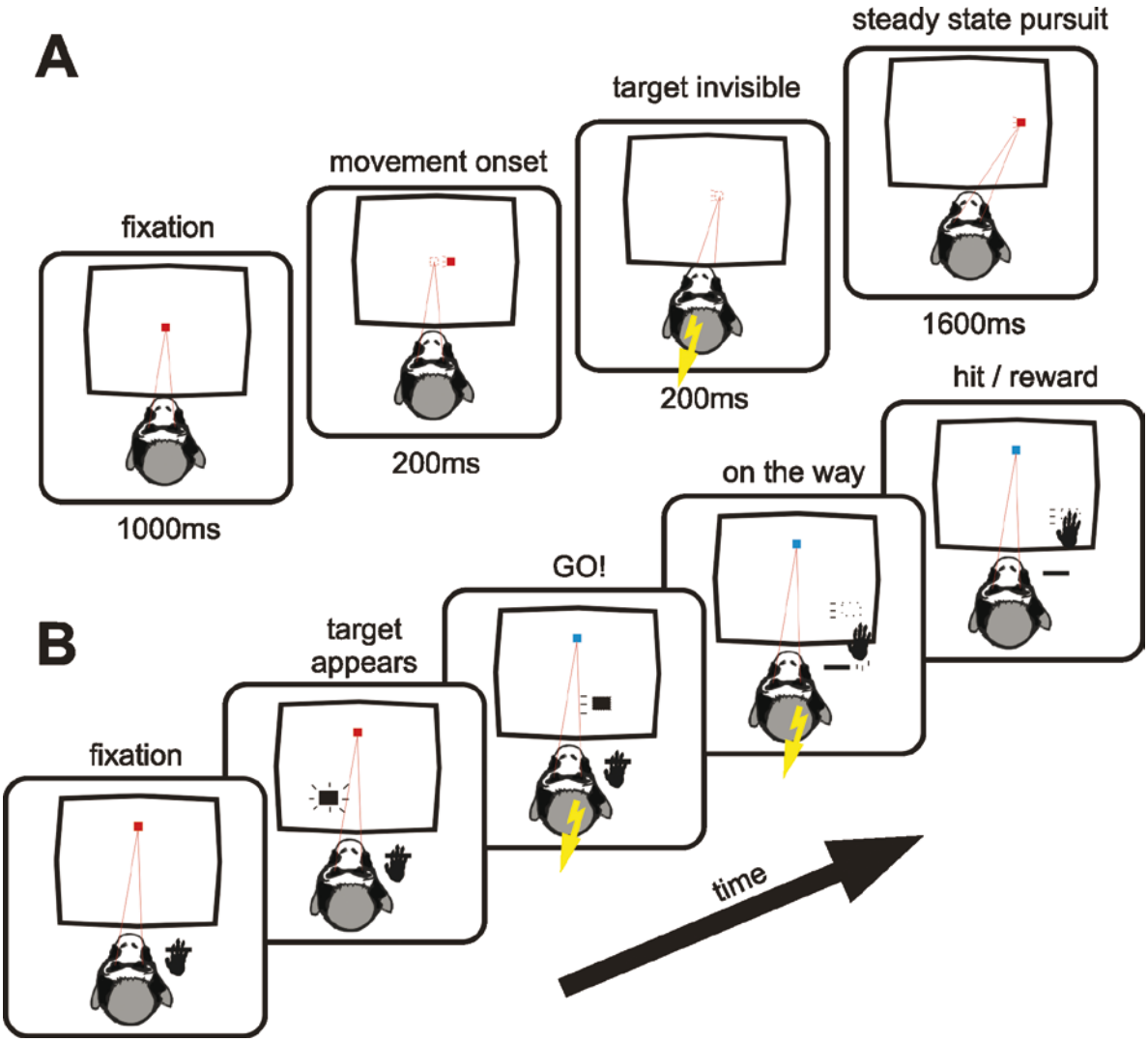
Eine andere Studie der Arbeitsgruppe dokumentiert den Nachweis von Geschwindigkeitsillusionen beim Menschen und Affen. Ein kleiner bewegter Stimulus erscheint zum Beispiel schneller als ein großer. In Übereinstimmung mit dieser Illusion zeigt die Modulations-Übertragungsfunktion für die Stimulusgeschwindigkeit individueller Neurone aus dem mittleren temporalen Areal (MT) eine Abhängigkeit von der Größe des Reizes. Eine wichtige Quelle für interne Signale, die zur Erzeugung eines Modells der Umwelt beitragen, ist die Fähigkeit, zukünftige Ereignisse auf der Basis von vergangenen Ereignissen vorherzusehen. Die Existenz der antizipatorischen Initiierung von Augenfolgebewegungen belegt, dass solche internen Signale das okulomotorische Kontrollsystem beeinflussen können. Diese Signale finden sich in der Aktivität einiger Neurone aus dem frontalen Augenbewegungsfeld: kann der Affe den Beginn und die Bewegungsrichtung eines Blickziels vorhersehen, so steigt die Aktivität an lange bevor das Ziel sichtbar wird.

Oculomotor Laboratory

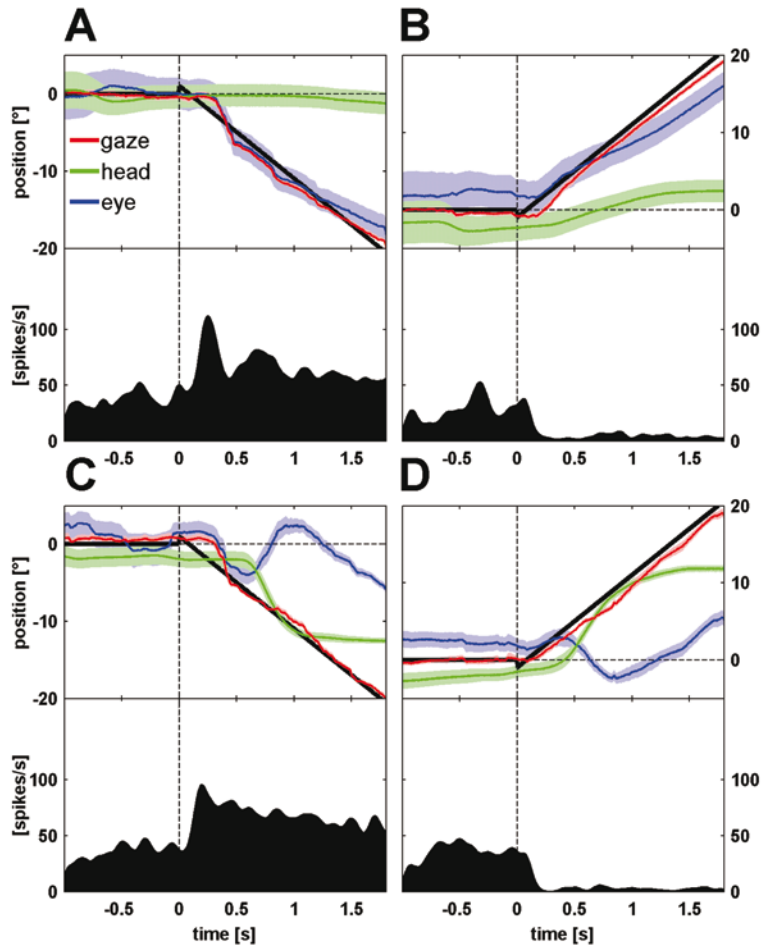
(Group leader: Uwe J. Ilg)

The oculomotor lab tries to reveal the basic mechanisms of sensorimotor integration underlying the execution of goal-directed behavior. Therefore, single-unit responses recorded from awake and trained rhesus monkeys are directly compared to the results of perceptual and behavioral studies in healthy subjects. In doing so, we focus on the role of the middle temporal (MT) and medial superior temporal (MST) area for the processing of moving visual stimuli in order to generate goal-directed behavior. Examples of these behaviors are smooth pursuit eye movements and goal-directed hand movements. In detail, we applied either microstimulation or inactivation by means of Muscimol-injections in MST during the execution of eye and hand movements. Manipulations, artificial increase or decrease of activity within MST, resulted in clear modulations of goal-directed eye and hand movements. This result indicates that MST is not only involved in the generation of smooth pursuit eye movements, but also in the generation of pointing movements aiming towards moving targets. In addition to this experiment, the lab tries to gain deeper insights related to the following three different topics:

Firstly, an essential shortcoming of elementary motion detectors (EMD) is the fact that these detectors are only able to signal motion perpendicular to the orientation of a moving line. This shortcoming provides the basis for the Barber pole illusion, for instance. It was earlier shown by other groups that the initiation of smooth pursuit eye movements (SPEM)



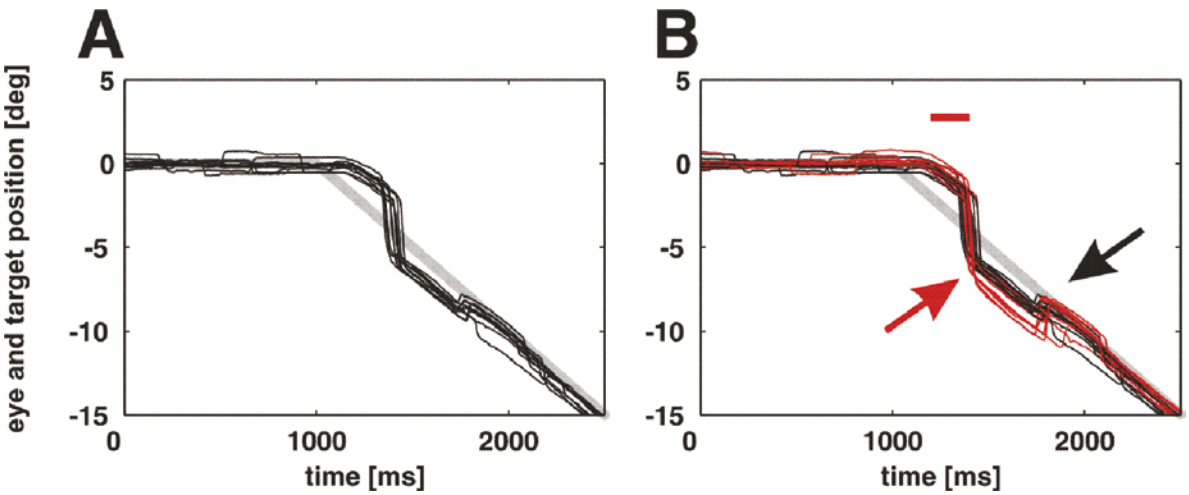
▶ Figure 1: Paradigm used in a recent microstimulation study. Either during execution of smooth pursuit (**A**) or during visually-guided pointing movements (**B**), a small current (visualized as yellow arrow) was applied through a microelectrode towards the middle superior temporal area (MST). This manipulation was able to modify ongoing eye and arm movements as shown by a recent paper of the lab (Ilg and Schumann, 2007)



▲ Figure 2:
Single-unit activity recorded from the medial superior temporal area while the monkey performed eye (A and B) or combined eye and head (C and D) movements. In A and C the target moved in the preferred direction of the recorded neuron, in B and D in the opposite direction. The fact that the neuronal response was quite similar in both tracking conditions suggested that this neuron represented target trajectory in an external frame of reference (for more details see Ilg et al., 2004).

displays a directional error if a moving bar is titled with respect to its motion direction. The directional error was always approximately perpendicular to the bar orientation as predicted by the behavior of EMDs. We asked whether this error is also present if subjects pursue illusory contours. In our study, we initially replicated successfully the results from the literature. If a rightward moving bar was tilted 45 deg clockwise, the initial phase of SPEM was directed 30 deg below the horizontal meridian. Subsequently, we provided new data showing that illusory contours do not introduce a directional error during SPEM initiation.

▼ Figure 3:
Effect of microstimulation in the medial superior temporal area on smooth pursuit eye movements. A shows target and eye position in the control condition directed in the preferred direction of this site (rightward and downward, -25°). B shows superimposed eye position during stimulation (in red) and control trials (in black). The red horizontal bar shows the stimulation period. Note that microstimulation did not produce a change in the latency of the eye movement. The red arrow marks the stimulation-induced overshoot in eye position; the black arrow marks the backward compensation.



Secondly, our perception of speed is not always correct. In case of random dot kinematograms (RDK), the dots within a small stimulus appear to move faster compared to dots moving in a large stimulus. We performed psychophysical studies with human and monkey subjects and demonstrated that monkeys perceive this speed illusion in a similar way as human subjects. Based on this finding, we examined the speed transfer function of single neurons recorded from the middle temporal (MT) and middle superior temporal (MST) area. For the population of MT and MST neurons, we found that the optimal velocity of a moving stimulus increases with increasing stimulus size. The fact that the speed illusion is already present in the activity of individual MT and MST neurons suggests that the illusion is due to a mechanism in early vision.

Thirdly, we performed experiments in which human and monkey subjects were asked to initialize SPEM in the anticipation of an appearing target. The disappearance of a stationary fixation target signaled the motion onset of an initially invisible target. After a delay of 500 ms, the moving target became visible. We were able to demonstrate that humans and monkeys are able to scale the anticipatory SPEM initiation to the expected target velocity. The amount of eye movement can be used to quantify the amount of anticipation in a given trial. Single-unit responses recorded from the pursuit sub-area in the frontal eye field (FEF) showed that these neurons increase their activity in parallel to the expectation of the monkey.

In summary, the work of the oculomotor lab provided several new experimental results concerning the mechanisms of sensorimotor integration. Special emphasis was directed to the fact that these mechanisms were independent of the actual performed motor output as well as the influence of higher cognitive functions such as anticipation on the generation of eye movements.

Key Publications

Lindner A, Ilg UJ (2006) Suppression of optokinesis during smooth pursuit eye movements: The role of extra-retinal information. Vision Res 46:761-7

Ilg UJ, Jin Y, Schumann S, Schwarz U (2006) Preparation and execution of saccades: facing the problem of limited capacity of computational resources. Exp Brain Res 171: 7-15

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homepage: http://www.hih-tuebingen.de/kn/forschung0/okulomotorik-labor/

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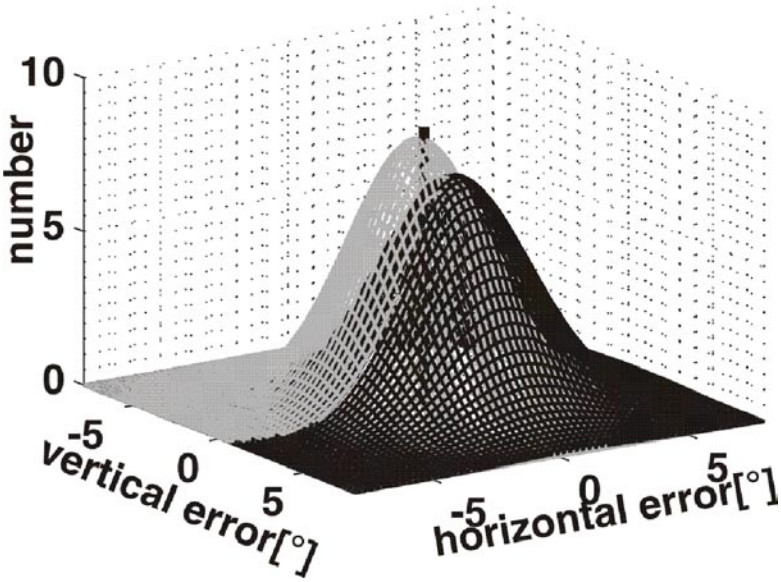


▶ Figure 4:
Effect of microstimulation in the medial superior temporal area on goal-directed hand movements. The pointing error of every single trial with and without microstimulation was fitted by two Gaussian functions (control grey: x0= -0.4°, y0= 0°, STD= 2.6°; microstimulation black: x0= 0.8°, y0= 0.6°, STD= 2.8°). The direction of the stimulation-induced shift in pointing was 25°; which was very similar as the preferred direction at this site. The two distributions are significantly different (p=0.00049, t-test).

Labor Sensomotorik I

Arbeitsgruppenleiter: Peter Thier

Die Arbeit dieses Labors wird von der Überzeugung bestimmt, dass jeder Versuch, die Funktion der menschlichen Großhirnrinde, des "menschlichsten" Teiles unseres Gehirns, zu verstehen, nur gelingen kann, wenn wir die mögliche Rolle der "Gespräche" berücksichtigen, die es mit einer Vielzahl anderer Teile des Gehirns führt. Diese Interaktionen basieren auf reichen anatomischen Verbindungen und beziehen eine Reihe subkortikaler Kernsysteme wie die Basalganglien, das Kleinhirn oder den Thalamus ein, um nur einige wesentliche subkortikale "Koprozessoren" zu nennen.

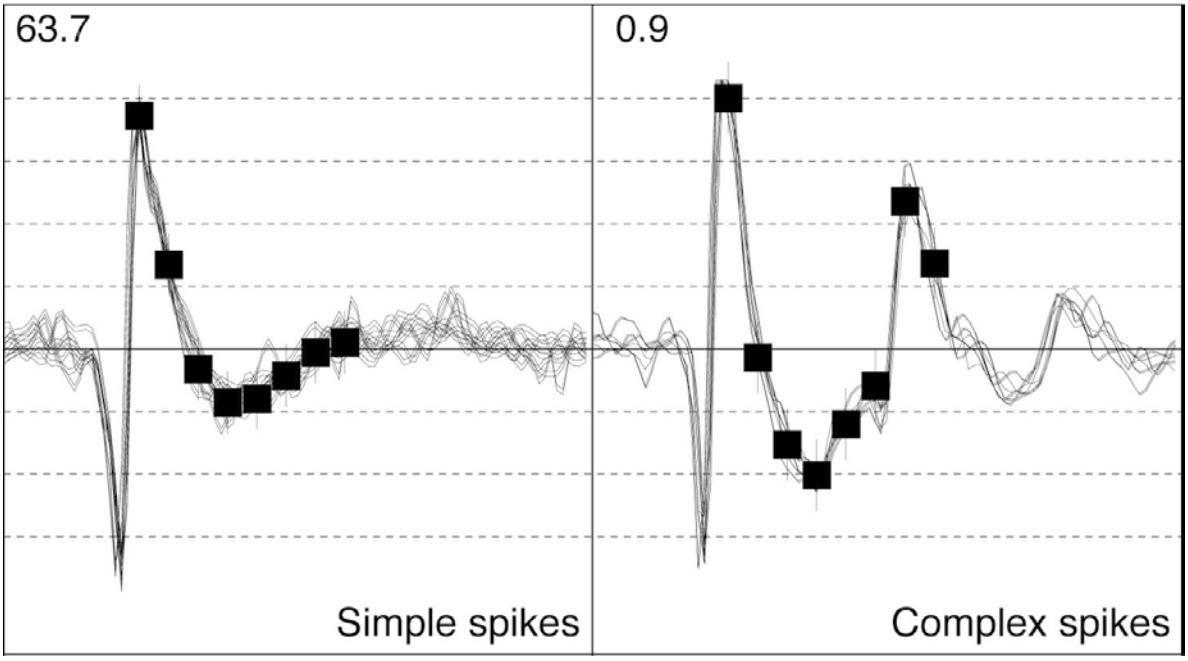
In den zurückliegenden Jahren hat sich die Arbeitsgruppe schwerpunktmäßig mit der Rolle des Kleinhirns befasst, eines Teiles des Gehirns, der den wesentlichen Teil der von ihm verarbeiteten Informationen unter Vermittlung der Brückenkerne aus der Großhirnrinde bezieht und seinerseits über die Kleinhirnkerne in die Großhirnrinde zurückprojiziert. Es besteht wenig Zweifel daran, dass eine zentrale Leistung des Kleinhirns die Ermöglichung motorischen Lernens ist, ein Gedanke, der erstmals überzeugend von David Marr Ende der 60er Jahre des vergangenen Jahrhunderts formuliert wurde. Mit dem Begriff des motorischen Lernens wird im Allgemeinen ganz global die Verbesserung motorischer Leistungen durch Lernen und Üben bezeichnet. Lernen kann auf unterschiedlichen Zeitskalen stattfinden. Es kann Bewusstsein erfordern oder aber nicht. Motorisches Lernen ist vielschichtig. Was genau ist der spezifische Beitrag des Kleinhirns, wodurch unterschiedet er sich von denen des Großhirns und welchen Bezug hat er zu Beiträgen des Kleinhirns zu anderen, nichtmotorischen Leistungen?

Die Arbeitsgruppe hat in Zusammenarbeit mit Dr. S. Barash vom Weizmann Institut in Rehovot und Dr. M. Glickstein vom University College London sakkadische Adaptation als Beispiel kleinhirnabhängigen motorischen Lernens etabliert und die Mechanismen sakkadischen Lernens in tierexperimentellen Untersuchungen sowie in ergänzenden Untersuchungen an Patienten mit Kleinhirnerkrankungen untersucht. Die Quintessenz dieser Untersuchungen ist die, dass sakkadisches Lernen dazu dienen dürfte, natürliche Veränderungen der Eigenschaften der Sakkadeneffektoren, wie sie beispielsweise aus gebrauchsabhängiger Ermüdung der Muskeln resultieren, zu kompensieren. Grundlage dieser Kompensation ist ein Populationssignal, basierend auf der kollektiven Aktivität einer größeren Gruppe von cerebellären Purkinjezellen, das durch Rückmeldungen über die Angemessenheit der Bewegung in eine Form gebracht wird, die ihm die Optimierung von Sakkaden ermöglicht. Das Purkinjezellpopulationssignal kann somit als biologische Realisierung eines inversen dynamischen Modelles der Sakkadeneffektoren bzw. ganz generell der motorischen Peripherie betrachtet werden, wie es von manchen theoretischen Konzepten zur motorischen Kontrolle gefordert wird.

Sensorimotor Laboratory I

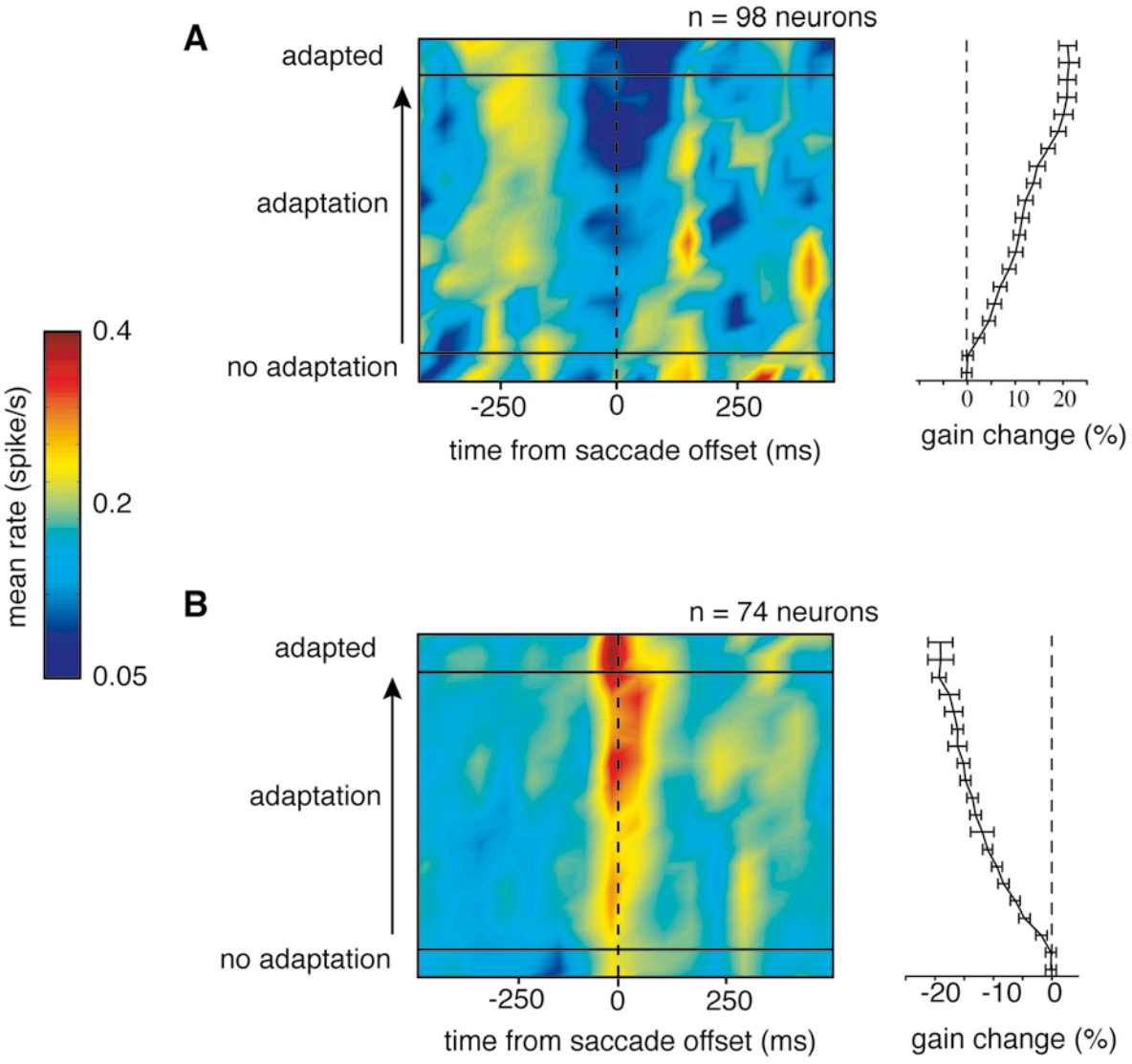
(Group leader: Peter Thier)

Work in this group is guided by the conviction that any attempt to understand the function of cerebral cortex, the most „humane" part of our brains, will only be successful if we take into account its interactions with a number of subcortical structures supported by extensive fiber systems connecting cortex with the basal ganglia, the cerebellum or thalamus, to mention only the most important of these subcortical „coprocessors". In recent years, the laboratory has focused on the role of the cerebellum, a part of the brain that receives most of its input from cerebral cortex by way of the pontine nuclei and in turn projects back to extensive parts of cerebral cortex. There can be little doubt that one major function of the cerebellum is motor learning, the optimization of motor behavior, a concept that was first formulated cogently by the late David Marr. However, what is the specific cerebellar contribution to motor learning and how is this contribution realized by neuronal circuits in the cerebellum? Furthermore, what is the relationship of a cerebellar role in motor learning to its putative role in a number of cognitive operations? Can we identify a computational principle common to all of them? In order to come up with answers to these questions the group has, in close collaboration with Dr. S. Barash from the Weizmann Institute, Rehovot, and Dr. M. Glickstein, from the University College London, established saccadic adaptation as a model of cerebellar-dependent motor learning and explored this specific form of learning in experimental animals as well as in patients suffering from cerebellar disease. The bottom line of this work on saccadic adaptation, supported by recent studies of other forms of motor learning (smooth pursuit eye movements, visually guided hand movements) in the laboratory is that the cerebellum uses a population code in order to continuously adjust an idealized sketch of a movement to the ever changing physical properties of the body and its interaction with the physics of the world. The population signal may be understood as the neuronal realization of an internal model as envisaged by theoreticians. The elements on which the population signal is based are Purkinje cells — specifically their simple spike responses. Purkinje cells are the only neurons in cerebellar cortex, whose axons leave cerebellar cortex, contacting neurons in the deep cerebellar nuclei, the major gateway to the rest of the brain. Cerebellar Purkinje cells (PCs) generate two responses: the simple spike (SS), with high firing rates (>100 Hz) and the complex spike (CS), characterized by conspicuously low discharge rates (1-2 Hz). *(see fig. 1)*



▶ Figure 1: Example of simple and complex spikes recorded from a single Purkinje cell. The squares define the 8-point template against which the records are compared. Note the consistency of the individual waveforms, detected as simple and complex spike waveforms respectively. The temporal extent of each window is 6.6 msec.

Our previous work on the posterior vermis, the major representation of saccades in the cerebellum, studied the role of PC simple spike responses. When tested in the memory-saccade paradigm, in which center-out saccades are made in darkness towards the remembered location of a cue, turned off a couple of 100 ms before the saccade is carried out, most saccade-related Purkinje cells exhibit pure saccade-related bursts. When saccades of different amplitudes are carried out in the preferred direction of a given cell, the amplitude-dependency of the saccade-related bursts is highly idiosyncratic. Whereas some cells may show a monotonous increase in the number of spikes fired



▲ Figure 2:
Change in complex spike population responses in the course of adaptation. (A) The left panel depicts the population response based on 98 posterior vermal PC studied during outward adaptation and the right panel the mean saccadic gain change (+/- s.e.m.) as a function of adaptation level for the 54 outward adaptation sessions which were necessary to collect the PC contributing to the population data. (B) The left panel shows the population response for 74 posterior vermal PC (not overlapping with the "outward" population) studied during inward adaptation. The right panel depicts saccade gain change (+/- standard error) as a function of adaptation level based on 42 inward adaptation sessions which were required to collect the sample of PC. Complex Spike population responses are plotted as function of time relative to saccade offset (x-axis; 0) and normalized adaptation level (y-axis) from no-adaptation (horizontal line) to full adaptation (top). The part underneath the horizontal line represents trials prior to the onset of target displacements. The colour code represents the mean rate of CS activity in the population for time bins of 25 ms (x-axis) and adaptation bins, corresponding to 1/20 of the range from no to full adaptation. We used a Gaussian filter (s.d. 50 ms) to smooth the plot along the x-axis.

with increasing saccade amplitude, others show preferred amplitudes or no dependency on amplitude at all within a range of amplitudes up to 40°. In other words, one would most probably fail if one tried to determine the duration or amplitude of a saccade made by the monkey by monitoring the discharge pattern of individual cells. Unlike individual cells, though, larger groups of these saccade-related Purkinje cells provide a precise signature of saccade duration and amplitude. This is suggested by the intriguingly precisely relationship between saccade duration and the duration of the population burst, the instantaneous discharge rate of a larger (>n=50) group of saccade-related Purkinje cells, obtained by considering the timing of each spike fired by each cell in the sample. The population burst typically starts, independent of saccade duration a couple of 10 ms before saccade onset and peaks exactly at the time the saccade starts, again independent of saccade duration. It is the decline of the population burst, which depends on saccade duration: it takes the longer the longer the saccade lasts. Independent of saccade duration, the burst ends at the end of the saccade, suggesting that it may be the end of the population signal that determines saccade duration and — considering the linear relationship between duration and saccade amplitude — also saccade amplitude. Hence, changing saccade amplitude, i.e. saccadic learning, could be based on changing the duration of the PC simple spike population burst. That this is indeed the case has been recently demonstrated by us in as yet unpublished experiments.

Changes in saccade amplitude, studied in experiments on saccadic learning, take place if the end points of saccades deviate from the desired spatial location — in other words, saccadic learning is driven by a performance error. If — as suggested before — it is the simple spike population response that sets the saccade amplitude, the performance error should have an effect on the population response, changing its duration in a way that leads to a reduction of the error. Contemporary theories of cerebellar learning suggest that it is the CS discharge pattern that encodes the error signal that drives changes in SS activity ultimately related to motor behavior. This then predicts that CS will discharge in relation to the size error and at random once the error has been eliminated by the new behavior. We tested this hypothesis by recording CS from PCs of the posterior vermis before, during and following saccadic adaptation. Surprisingly, in clear contradiction to the "error signal" concept, we found that CS occurred at random before adaptation onset, i.e. when the error was maximal and built up to a specific saccade-related discharge profile during the course of adaptation. This profile became most pronounced at the end of adaptation, i.e. when the error had been eliminated (see figure 2). We therefore suggest that CS firing may underlie the stabilization of a learned motor behavior, rather than serving as an electrophysiological correlate of an error. Currently, a major effort is being made to understand the role of a specific type of cerebellar interneuron, the Golgi cell, in shaping the population signal.

Key Publications

Lindner A, Haarmeier T, Erb M, Grodd W, **Thier P** (2006) A cerebro-cerebellar circuit for the perceptual cancellation of eye-movement-induced retinal image motion. J Cogn Neurosci 18:1899-1912

Synofzik M, Thier P, Lindner A (2006) Internalizing agency of self-action: perception of one's own hand movements depends on an adaptable prediction about the sensory action outcome. J Neurophysiol 96:1592-1601

Catz N, Dicke PW, Thier P (2005) Cerebellar complex spike firing is suitable to induce as well as stabilize motor learning. Current Biology 15:2179-89

In close interaction with the Visual Perception Laboratory (see below), the idea that the cerebellum optimizes inverse dynamics as well as forward models of actions and effectors has been successfully used in order to get a handle on the role of the cerebellum in perception. In related work, the subcortical basis of spatial attention has been addressed with focus on the superior colliculus and its interaction with the frontal eye fields. *(see fig. 2)*

homepage: http://www.hih-tuebingen.de/kn/forschung0/sensomotorik-labor-i/

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Labor Sensomotorik II

Arbeitsgruppenleiter: Cornelius Schwarz

Die Arbeitsgruppe studiert aktive Wahrnehmung und ihre neuronalen Grundlagen anhand des Vibrissensystems von Ratten und Mäusen. Analog zur aktiven taktilen Exploration, die Menschen und andere Primaten mittels Bewegungen der Hand und Fingerspitzen ausführen, ist die aktive Vibrissenbewegung dieser Tiere grundlegender Bestandteil der sensorischen Informationsaufnahme und der Wahrnehmung. Der Vorteil des Vibrissensystems ist, dass die Bewegung (und entsprechende neuronale Steuersignale) relativ einfach ist, und dass neokortikale Gebiete im lisenzephalen Nagerkortex leicht zugänglich für optische als auch elektrophysiologische Verfahren sind.

Die Arbeitsgruppe hat in den letzten Jahren ein weltweit einzigartiges experimentelles System aufgebaut, in dem sowohl die taktile Wahrnehmung, die Vibrissenbewegung, als auch neuronale Multielektrodensignale aus Motorkortex und primärem somatosensorischem Kortex gemessen werden können. Die Attraktivität dieses Ansatzes ergibt sich aus der leichten Kombinierbarkeit mit modernen Methoden der Bildgebung subzellulärer Elemente (Zwei-Photonen Mikroskopie) und gezielter genetischer Veränderung von neuronalen Funktionen in Nagern (transgene Mausmutanten, lokale Genmodulation mittels viraler Vektoren etc.).

Die Beschreibung, wie Vibrissenbewegung die Signalprozessierung im primären somatosensorischen Kortex verändert, war ein wichtiges Ergebnis, das 2006 publiziert wurde. Es konnte gezeigt werden, dass die neuronale Input-Output Funktion durch bewegungsabhängige Anhebung der mittleren Feuerrate erheblich verändert wird. Die Quelle dieser Modulation ist höchstwahrscheinlich das zentrale motorische System, ein von der Arbeitsgruppe neu beschriebenes Areal im Motorkortex (Hentschke et al., 2006). Die Wahrnehmung (Detektion) von Vibrissenauslenkungen wurde im Detail vermessen und ihre neuronale Grundlage in primär afferenten Ganglien studiert (Stüttgen et al., 2006).

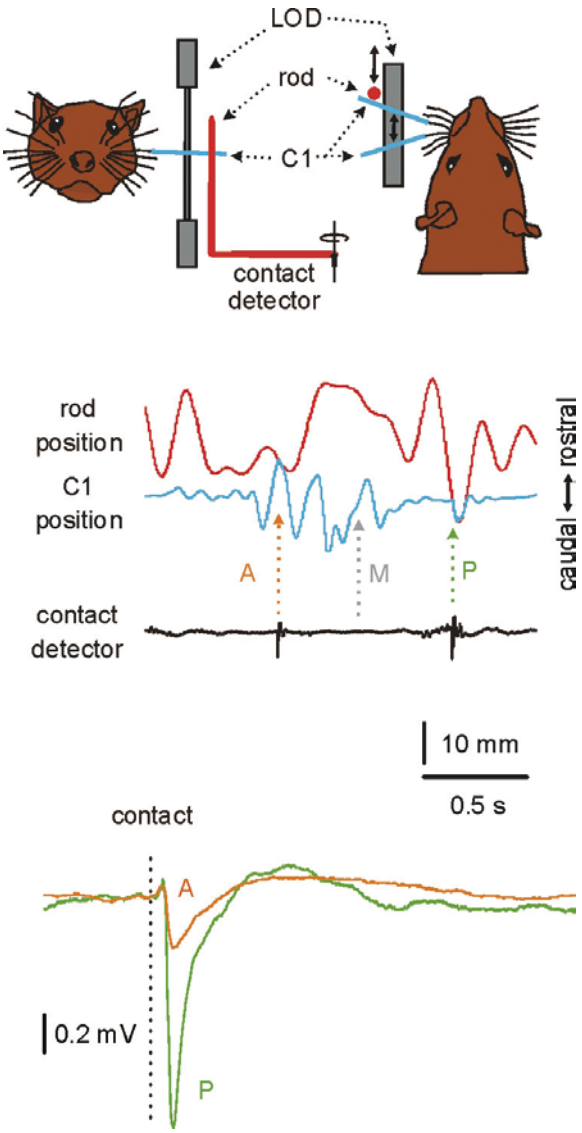
Das Modellsystem der aktiven Wahrnehmung wird in einem weiteren, mehr anwendungsorientierten Ansatz, ausgenutzt. Es wird untersucht, inwieweit die direkte kortikale Signaleinspeisung mittels Maschine-Hirn Schnittstellen vom Kontext der neuronalen Verarbeitung abhängt. Die detaillierten neuronalen Antworten auf Mehrkanal-Mikrostimulation wurden untersucht (Butovas et al., 2006) und werden derzeit mit der Wahrnehmung von Mikrostimulation im primären somatosensorischen Kortex in Beziehung gesetzt.

Sensorimotor Laboratory II - Action and Perception

(Group leader: Cornelius Schwarz)

Background: Perception is an active process as sensory signals are modulated by 'top-down' processes on all levels of neural processing. The research group exemplarily investigates how perception is influenced by movement-dependent modulation of tactile signal processing. The model system employed for this purpose is active whisking behavior in rats and the underlying sensorimotor signals in primary somatosensory ('barrel') and primary motor cortices. Similar to humans and other primates, which use rhythmic movements of fingertips, rats discriminate texture and form of objects by rhythmically sweeping their vibrissae over it. The beauty of the rat whisker system is that the motor action is relatively simple (in essence a whisker rotation around one pivot point in the skin) compared to arm and hand movements in primates.

Methods: Recording and stimulation via highly parallel multielectrode arrays are combined with precise tracking of the fine vibrissae and the measurements of the animal's perception. Active vibrissae movements in head-fixed rats are operantly conditioned. The trajectories of the vibrissae, as well as minute contacts with an object are tracked and detected at a high spatial and temporal resolution and can be used in real-time for dynamic experimental control. Furthermore, the assessment of psychometric data is possible. Compared to other laboratories in the field, this setup offers a unique level of experimental control for the investigation of the rat's vibrissal system. It combines advantages known since many years from research on primates (head-fixation, precise tracking, operant conditioning) with advantages that arise from the use of rodents (highly explorative approaches and the usage of higher numbers of animals possible, well accessible lissencephalic brain, possible combination with in vitro approaches, behavioral pharmacology, and experiments on genetic rat and mouse models).



◄ Figure 1: Schematic how active and passive touch is investigated in head fixed rats. The rat is operantly conditioned to actively touch a rod that moves on a random trajectory Vibrissal movement (red, C1 traj.) and rod movement (blue, rod traj.) determine the classification of a contact as active (A) or passive touch (P) or as movement alone (without contact, M). Bottom: Contact evoked field potentials in barrel cortex differ between active and passive touch

In summary the characteristics of the setup are the following

- Rat as experimental animal
- Head-fixation
- Behavioral training, operant conditioning
- Chronic implantation of moveable and static microelectrode arrays

• Detection of licking movements (e.g. as an indicator response)

• Tracking of vibrissae movements using an optoelectronic device

• Detection of whisker contact with an object

• Measurement of psychophysical parameters (detection, discrimination)

• 128 channel multielectrode electrophysiology (action potentials, local field potentials, EEG, EMG, ENG)

• 16 channel multielectrode stimulation

Results: To characterize movement-dependent modulation, a sensorimotor behavior ('active touch') was dissected into its sensory ('passive touch') and motor parts ('movement alone') while multielectrode signals were recorded in barrel cortex in head fixed and behaviorally conditioned rats (Hentschke et al., 2006). This study showed that a movement-dependent signal switches the characteristics of tactile processing in barrel cortex. The modulatory signal is non-rhythmic, thus it must originate upstream from motor neurons and the presumed brainstem oscillator that generates the whisking rhythm. Furthermore, the modulatory signal is of central origin as it is present after severing the peripheral sensory nerve (infraorbicular nerve) that carries tactile signals from the vibrissae. The current working hypothesis is that it originates from a newly found sub-area of the whisker representation in motor cortex (Haiss and Schwarz, 2005).

Toward elucidation of perceptual consequences of active touch, we have measured the psychophysical performance and neuronal activity in primary afferents of rats using highly precise whisker deflections. This work established the presence of two psychophysical channels in the rat whisker system which likens it to tactile sensing using fingertips in primates (Stüttgen et al., 2006).

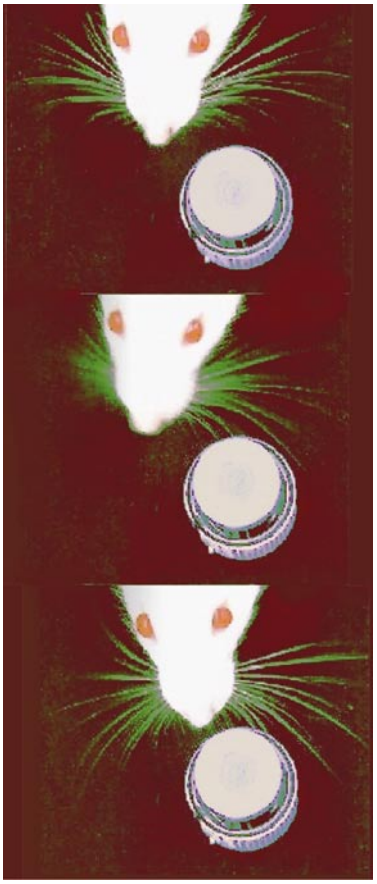
Perspectives. Psychophysical measurements will be studied under conditions of active and passive touch. The origin of the modulatory signal is being investigated by multielectrode recordings and stimulation in motor and barrel cortex.

Barrel cortex and vibrissae motor cortex are structures that are accessible at the surface of the brain. The group has started to work on the future goal to use in vivo structural and functional imaging (two-photon microscopy). Presently we investigate structural changes in dendritic spines during learning.

Dynamic microstimulation/ Central machine-brain interface

Background. We hypothesize that the input-output function of a central machine-brain interface (describing the relationship between electrical stimulation command and evoked neuronal activity) is dynamically changing due to stimulation context (the effect of a single stimulation pulse is subject to modulation depending on its position in space and time within a spatiotemporal stimulation pattern). We investigate these two interrelated kinds of problems using the model system of active perception.

Results. We found complex non-linear interactions between single stimulation pulses presented via electrodes closer than 2.7 mm and with repetitive stimulation frequency higher than 5 Hz due to responses mediated by cortical, electrically interconnected, GABAergic inhibitory networks (Butovas et al., 2006). The movement dependent modulatory signal influences the local inhibitory response to cortical microstimulation but leaves the excitatory response unaffected.



Perspectives. We have begun to assess the perceptual reflections of the above described context dependencies using

psychophysical measurement of detection and discrimination of microstimulation in head-fixed rats (Butovas and Schwarz, 2007).

Cellular mechanisms of timing of cerebellar signals

(Group leader:
Christine M. Pedroarena)

Background. Although all forms of cerebellar dysfunction are characterized by severe impairment in the timing of muscular activation and consequent uncoordinated movements the cellular underpinnings of the control exerted by cerebellum remain unknown. Understanding these mechanisms may provide the basis for rational therapeutic interventions for cerebellar diseases. All output cerebellar signals are carried by the neurons of the deep cerebellar nuclei. Cerebellar nuclei neurons are the only targets of the cerebellar cortex signals and in addition receive a copy of all afferent information reaching the cerebellar cortex. In most types of cerebellar diseases, deep cerebellar nuclei neurons are spared and their function is altered only secondarily to the alterations occurring at the cerebellar cortex. Hence, cerebellar nuclei are a natural place for compensatory mechanisms to diseases affecting the cerebellar cortex. Indeed, studies from cerebellar diseases models provide evidence that some compensatory mechanisms actually take place in the cerebellar nuclei after degeneration affecting the cerebellar cortex Purkinje cells. However at present very little therapeutic help can be provided to improve functional recovery to patients suffering the devastating effects of cerebellar cortex diseases. Understanding the mechanisms that control the tonic and phasic activity and timing of cerebellar nuclei output signals is essential for envisaging compensatory therapeutics. 1. Cerebellar nuclei neurons as well as the inhibitory Purkinje cells — the output cells of the cerebellar cortex — are continuously active. One of the effects of cerebellar cortex diseases is most probably a change in the tonic activity of cerebellar nuclei signals as a result to the lack of continuous inhibition from the cerebellar cortex. 2. Activity of the cortical Purkinje cells is modulated during movements most probably providing essential signals to set the timing of cerebellar nuclei neurons phasic activity, aimed to control the moment of muscular contraction.

Goals and Approach. Synaptic and intrinsic mechanisms that determine the timing of the cerebellar nuclear output during tonic and phasic activity and how plasticity of these mechanisms may contribute to adaptation under physiological as well as pathological conditions. For these purposes we employ an in vitro approach in rodents, including the use of transgenic animals, using the electrophysiological, whole cell patch recordings, and anatomical techniques.

homepage: http://www.hih-tuebingen.de/kn/forschung0/sensomotorik-labor-ii/

Staff:

S. Butovas, T. Gerdjikov, N. Kuohn, U. Pascht, C. Pedroarena, M. Stüttgen

Key Publications and References

Hentschke H, **Haiss F, Schwarz C** (2006) Central signals rapidly switch tactile processing in rat barrel cortex during whisker movements. Cerebral Cortex 16:1142-56

Möck M, **Butovas S**, **Schwarz C** (2006) Functional unity of pontine and cereballar signal processing: evidence that intrapontine communication is mediated by a reciprocal loop with the cerebellar nuclei. J Neurophysiol 95:3414-25

Butovas S, Hormuzdi SG, Monyer H, **Schwarz C** (2006) Effects of electrically coupled inhibitory networks on local neuronal responses to intracortical microstimulation. J Neurophysiol 96:1227-36

Linnemann C, **Schmeh I, Thier P, Schwarz C** (2006) Transient change in GABAA receptor subunit mRNA expression in Lurcher cerebellar nuclei during Purkinje cell degeneration. BMC Neuroscience 7:59

Stüttgen MC, Rüter J, **Schwarz C** (2006) Evidence for two separate psychophysical channels as revealed by precise whisker deflections in operantly conditioned rats. J Neurosci 26: 7933-41

Butovas S, Schwarz C (2007) Intracortical microstimulation in barrel cortex of awake, head-restraint rats: assessment of detection thresholds. Eur J Neurosci 25:2161-9

Haiss F, Schwarz C (2005) Spatial segregation of different modes of movement control in the whisker representation of rat primary motor cortex. J Neurosci 25:1579-87

Labor für Handlungsrepräsentation und Lernen

Arbeitsgruppenleiter: Martin Giese

Die Arbeitsgruppe für Handlungsrepräsentation und Lernen (ARL) untersucht Repräsentationen komplexer Körperbewegungen durch Lernen in biologischen und technischen Systemen. Einen besonderen Schwerpunkt bildet die Entwicklung von Verfahren für die quantitative Erfassung von Bewegungsdefiziten bei neurologischen Patienten, z.B. bei Kleinhirnstörungen oder der Parkinson-Krankheit.

Ein zentrales Forschungsthema der Gruppe sind biomedizinische Anwendungen. Durch Anwendung von Verfahren aus der Systemtheorie und dem Maschinenlernen werden Bewegungsveränderungen bei neurologischen Patienten quantitativ erfasst und modelliert. Ziel dieser Arbeiten ist die Unterstützung der Diagnose und die Bewertung von Therapie- und Rehabilitationsmaßnahmen bei neurologischen Erkrankungen. Außerdem werden preiswerte Systeme zur Analyse alltagsrelevanter Bewegungen entwickelt, die für niedergelassene Neurologen erschwinglich sind, und daher die Untersuchung großer Patientengruppen ermöglichen (z.B. für die Früherkennung von Parkinson-Symptomen). Algorithmen zur Repräsentation von Bewegungen durch Lernen können auch für andere technische Anwendungen eingesetzt werden, z.B. in der Computergrafik, der Robotik oder die Analyse von Bewegungen im Sport. Gegenwärtige Arbeiten in diesem Bereich zielen auf die Modellierung von emotionalen Körperbewegungen für Echtzeitanwendungen, z.B. für Computerspiele.

Der zweite Schwerpunkt der Arbeitsgruppe ist die Erforschung der neuronalen Mechanismen der visuellen Erkennung von Bewegungen. Im Rahmen dieser Arbeiten werden physiologisch plausible Modelle entwickelt. Vorhersagen aus diesen Modellen werden mit verschiedenen experimentellen Methoden getestet. Momentane Forschungsschwerpunkte in diesem Bereich sind neuronale Mechanismen im so genannten "Spiegelneuronen-System" und für die Enkodierung von Gesichts- und Bewegungsräumen. In Zusammenarbeit mit dem Max-Planck-Institut für Biologische Kybernetik werden außerdem Nacheffekte bei der Wahrnehmung von Gesichtsbewegungen experimentell untersucht.

ARL arbeitet eng mit dem Zentrum für Neurologie und anderen Gruppen des Hertie-Institutes zusammen. Zudem bestehen enge Kontakte zum Max-Planck-Institut für Biologische Kybernetik (Tübingen) und internationalen Forschungszentren, z.B. dem M.I.T. (Cambridge, USA), dem Weizmann-Institut (Rehovot, Israel) und dem Collège de France (Paris).

Laboratory for Action Representation and Learning

(Group leader: Martin Giese)

The group for Action Representation and Learning (ARL) investigates the representation of complex body movements and actions by learning in the brain and in technical systems. The group is highly interdisciplinary and combines research in theoretical and experimental neuroscience, computer science and machine learning. ARL has been founded as Independent Young Researcher Group of the Volkswagen Foundation in 2001. The group has built up a well-equipped motion laboratory with high-end motion capture system (VICON), EMG recording system, etc. The unit receives additional funding from the German Research Council within the framework of the Collaborative Research Center 550 'Recognizing, localizing, acting' and the Research Unit 'Perceptual Graphics', from the Human Frontier Science Program, and the European Community.

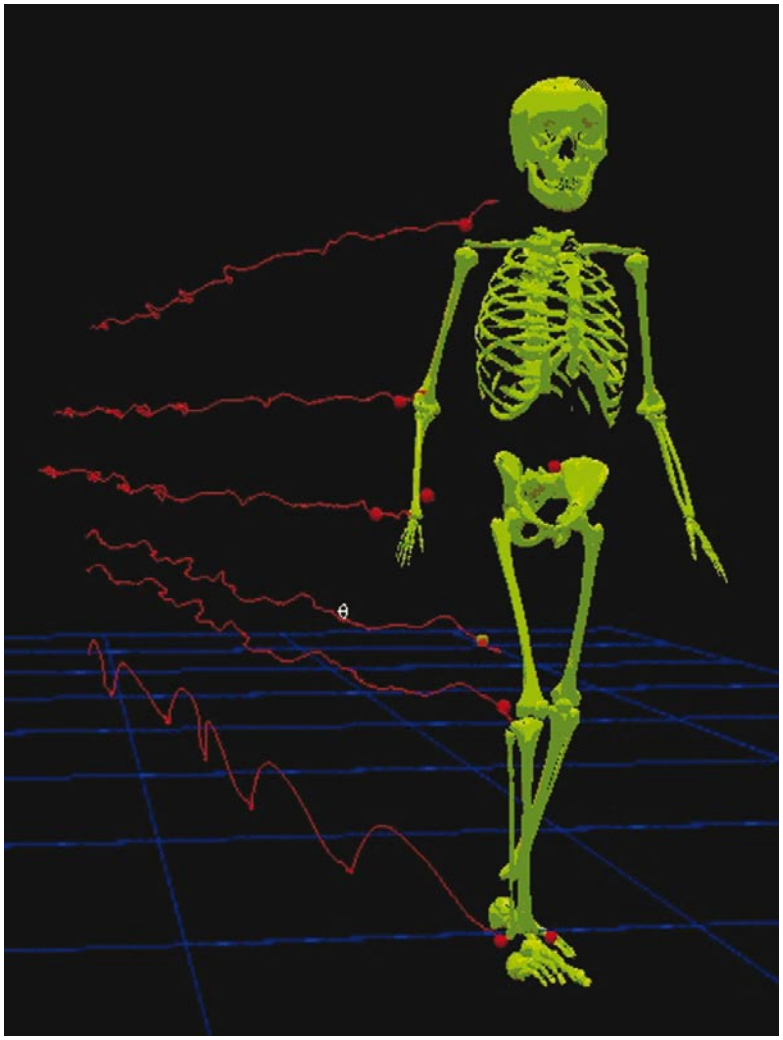
In neuroscience, the group studies neural mechanisms of visual movement and action recognition. This research combines the development of physiologically inspired neural models, and the experimental testing of predictions from such models with psychophysical and imaging experiments. In collaboration with the Laboratory for Neurophysiology (P. Thier) at the Hertie Institute ARL is also strongly involved in the detailed study of the neural mechanisms of action recognition. One particular project (realized in the SFB 550) is the study of the visual properties of 'mirror neurons' in area F5 of the monkey by combination of electrophysiological experiments and quantitative neural modeling. Another project is the investigation of possible neural mechanisms for the encoding of face spaces, collaborating with D. Leopold (NIMH, Bethesda, MD, USA) who records face-selective neurons in the inferotemporal cortex. Goal of this work is to test possible neural mechanisms in close comparison

▶ Figure 1: Influence of non-visual motor learning on action recognition

with electrophysiological and other empirical data, in order to identify essential computational steps of object and action processing. In addition, the group is involved in a variety of behavioral and fMRI experiments on visual action recognition studying the visual and motor learning of biological and non-biological motion patterns (Fig. 1), predictive processes in action recognition, and the perception of emotional body movements. Such experiments are realized in collaboration with the MPI of Cognitive Brain Science (Leipzig, D), the Dept. of Psychology (Birmingham, UK) and the Weizmann Institute (Rehovot, IL) and the McGovern Institute for Brain Science (M.I.T.) In addition, the group collaborates with the MPI for Biological Cybernetics, Tübingen) on the recognition of facial movements. (*see fig. 1)*

In the domain of technical applications the group works on the analysis and synthesis of complex body movements. A particular focus is the analysis of movement deficits, in particular in neurological patients. Applying appropriate theoretical methods from systems theory and machine efficient algorithms for the learning of accurate models of complex body movements are developed. Such methods are suitable for a very accurate quantification and discrimination, e.g. of deficits in movement disorders (Fig. 2). Since these methods are applicable for the analysis of complex movements in everyday life situations and to high-dimensional coordination patterns, they go far beyond what can be achieved with classical clinical movement analysis. This makes them particular interesting for the evaluation of the effects of physiotherapy in normal everyday life situations. Such methods are also applied to detect subtle changes that are potentially useful to detect neurological movement disorders at preclinical stages, e.g. for Parkinson's disease. In collaboration with D. Berg (Dept. Neurodegenerative Diseases) the relationship between changes in the substantia nigra, detected by transcranial sonography, and subtle changes in movement patterns is studied in detail. In addition, the group tries to develop low-priced technical devices for the measurement of subtle changes in the movement behavior of patients that are suitable for a broader market than traditional clinical movement analysis systems. Further studies address predictive phenomena in the control of gait, specifically for cerebellar ataxia patients. In the context of these clinical applications the group collaborates tightly with the Department of Neurodegenerative Diseases (D. Berg, L. Schöls, T. Gasser), the Department of Sports Medicine (Tübingen) and the University Clinic Essen (D. Timmann-Braun). *(see fig. 2)*

▼ Figure 2:
Movement trajectories of a patient



Learning-based methods for the modeling of complex body movements have also many other applications. One example is the quantification of movements in sports in order to detect different skill levels. Another central project is the learning of critical features for the generation of movement styles, and specifically emotions. As part of the DFG research group 'Perceptual Graphics' learning-based methods for trajectory modeling are also applied for action synthesis in real-time computer animation systems. Models based on learned temporal and spatial movement primitives allow the on-line generation of interactive behavior and movement styles for computer-generated agents (avatars). In addition, by application of novel concepts from dynamic stability theory methods for the engineering of large systems integrating many primitives are being developed. Similar approaches are interesting for the generation of movements in humanoid robots. In this area ARL collaborates closely with the Weizmann Institute, the Dept. of Mechanical Engineering (M.I.T.), the Collège de France (Paris) and the Dept. for Computer Graphics (Tübingen). (*see fig. 3)*

◄ Figure 3: Simulation of Karate movements

Key Publication

Leopold DA, Bondar IV, **Giese MA** (2006) Norm-based face encoding by single neurons in the monkey inferotemporal cortex. Nature 442:572-5

homepage: http://www.hih-tuebingen.de/kn/forschungo/labor-fuer-handlungsrepraesentation-und-lernen/

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Labor PrimatenNeurokognition

Arbeitsgruppenleiter: Andreas Nieder

Zahlensymbole sind mentale Werkzeuge, die wir als Kinder erwerben müssen. Tiere und menschliche Säuglinge, denen die Fähigkeit zu sprechen nicht oder noch nicht gegeben ist, können ohne Zahlensymbole nicht sprachlich-präzise zählen oder rechnen. Aber sprachliches Zählvermögen beim Menschen tritt nicht de novo in der Evolution auf, sondern entsteht aus biologischen Vorläufern. Unsere Arbeitsgruppe untersucht die neuronalen Grundlagen numerischer Kategorien und Konzepte an verhaltenstrainierten Rhesusaffen mittels kombinierter psychophysischer und neurophysiologischer Studien. Nicht-sprachliche Anzahls-Repräsentationen bei Affen sind aufgrund der relativen Ähnlichkeit von Menschen- und Affengehirn von besonderem Interesse. Schwerpunktmäßig werden der Präfrontalkortex und der posteriore Parietalkortex untersucht, Hirnareale, die bei Primaten eine dominante Rolle bei der Kodierung numerischer Information spielen.

Mensch und Tier können visuelle Elemente sequentiell aufzählen, oder sie schätzen die Anzahl von gleichzeitig gezeigten Elementen „auf einen Blick". Wir haben herausgefunden, dass derartige Anzahlschätzungen von getrennten Zellpopulationen in der Tiefe des intraparietalen Sulcus von Affen bewerkstelligt werden. Sobald aber die eigentliche Aufzählung abgeschlossen ist, repräsentiert eine andere Population von Zellen die abstrakte Anzahl einer Menge, unabhängig davon, ob diese sequentiell oder simultan präsentiert wurde. Diese Daten deuten auf getrennte neurale Verarbeitungsschritte für unterschiedliche numerische Formate hin. Anschließend konvergieren jedoch diese vormals aufgetrennten Informationen um höchst abstrakte Repräsentationen von Quantitäten zu formen. Die Ergebnisse dieser Studie wurden in der Zeitschrift Science veröffentlicht.

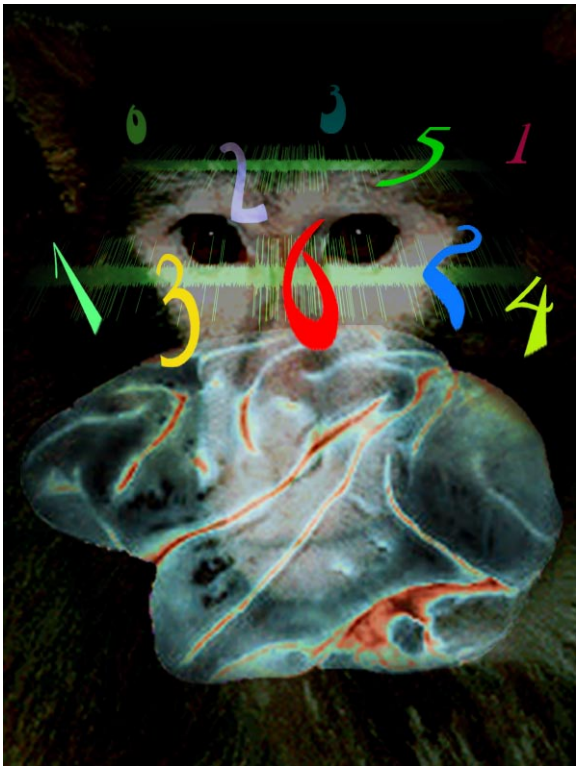
In einem weiteren Projekt untersuchen wir die Mechanismen der Kartierung von Anzahlinformation auf visuelle Zeichen („Symbole"). Kinder lernen den Gebrauch der Zahlsymbole, während sie ihre Sprachfähigkeiten ausbauen. Um die neuronalen Korrelate dieses abstrakten Assoziationsprozesses auf einer vorsprachlichen Stufe zu untersuchen, haben wir zwei Affen trainiert, Anzahlen von eins bis vier (präsentiert als Punkte) zu diskriminieren und mit numerischen „Symbolen" (Ziffern von 1 bis 4) zu assoziieren. Einzelzellableitungen zeigten, dass Neuronen im Präfrontalkortex – aber nicht im posterioren Parietalkortex – für derartige Assoziationen verantwortlich zeichnen.

Schließlich untersuchen wir den Zusammenhang von diskret-numerischer (Anzahlen) und kontinuierlich-räumlicher Größeninformation. Hierzu haben wir Affen trainiert, in einer Sitzung sowohl Anzahlen (Punktmuster) als auch Linienlängen zu unterscheiden. Die anschließenden Ableitungen aus dem Intraparietalsulcus (IPS) ergaben, dass etwa 20 % der abgeleiteten Zellen im IPS als Funktion entweder der Anzahl oder der Linienlänge antworteten. Durch Populationsanalysen mittels statistischer Klassifizierungsalgorithmen konnten wir zeigen, dass Zellen in diesem Areal beide Arten von quantitativer Information robust und eindeutig kodieren.

Primate NeuroCognition Laboratory

(Group leader: Andreas Nieder)

Linguistic numerical competence does not emerge de novo in evolution but arises from biological predispositions. This hypothesis is supported by studies in infants and animals. We aim to investigate the neural formation of numerical concepts in macaque monkeys in combined psychophysical and neurophysiological studies. Quantity representations in monkeys are of special interest because of the relative similarity between the human and monkey brain. The target brain areas are the prefrontal (PFC) and the posterior parietal cortices (PPC), which play dominant roles in coding of numerical information in primates. The results of this study should be suited to develop a more detailed understanding of the neural mechanisms of counting, and help to understand neurological disorders involving number processing in human patients.



In a study published this year, we investigated how numerical quantity cued via multiple-item displays or sequences of items is represented in the brain. These are two fundamentally different ways of presenting numerical quantity and engage either parallel or serial enumeration processes. Neurons in the posterior parietal cortex were differentially involved in processing simultaneously or sequentially presented numerical information while monkeys performed a visual quantity discrimination task. Our data provide insight into the mechanisms of how neuronal circuits in the parietal lobe form cooperating networks to extract and store abstract numerical information across time and space.

In another project, we explore how the relationship between an initially arbitrary sign and its associated numerical meaning is established at the level of single neurons. We trained monkeys to associate visual shapes with numerical categories. Single cells in the prefrontal cortex have the capacity to map signs onto abstract numerical categories, and we show that the activity of associative cells predicts the monkeys' success or failure in the association task. In contrast, associative neurons were almost absent in the parietal lobe.

Quantity can be continuous (e.g., the amount of water) or discrete (e.g., the number of individuals). We show in yet another project that the continuous quantity "length" and the discrete quantity "numerosity" are encoded by distinct, but functionally overlapping groups of neurons in the parietal cortex of behaving monkeys. Using a statistical classifier (i.e. a neuronal network algorithm) to quantify information in neuronal populations, we found that a small group of quantity-selective neurons conveyed robust categorical information. Our data suggest that the neuronal network in the posterior parietal cortex may indeed function as a generalized magnitude system.

Key Publication

Nieder A, **Diester I, Tudusciuc O** (2006) Temporal and spatial enumeration processes in the primate parietal cortex. Science 313:1431-5

homepages:

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Sektion Neuropsychologie

Leiter: Hans-Otto Karnath

Nach einem Schlaganfall kommt es häufig nicht nur zu Lähmungen eines Armes oder Beines, sondern auch zu Störungen der „höheren Hirnleistungen“ wie der Sprache, der Aufmerksamkeit, der Wahrnehmung, des Gedächtnisses, der Intelligenz, des Problemlösens oder der Orientierung im Raum. Um für den Betroffenen eine möglichst effiziente und auf sein jeweiliges Problem genau abgestimmte Behandlung planen zu können, ist eine differenzierte neuropsychologische Untersuchung erforderlich, die das Ausmaß und die Art der jeweiligen Beeinträchtigung feststellt. Die neuropsychologische Ambulanz untersucht z.B., ob das Vergessen von Ereignissen krankhaft oder noch im Bereich des Normalen liegt, ob bei dem Patienten eine Demenz vorliegt, ob Handlungen der jeweiligen Aufgabe entsprechend richtig geplant werden können, ob Sprachstörungen bestehen oder welche Bereiche der Aufmerksamkeitsfunktionen möglicherweise geschädigt wurden und nun trainiert werden müssen. Solche und andere Untersuchungen werden in der Neuropsychologischen Spezialambulanz der Sektion durchgeführt.

Section Neuropsychology

(Section Head: Hans-Otto Karnath)

The Section is responsible for clinical and neuropsychological patient care within the Center of Neurology, and also carries out research in cognitive neuroscience and neuropsychology. Research in the section is focused on human spatial orientation and object recognition. Studies of both healthy and brain-damaged subjects are carried out using functional imaging (fMRI), transcranial magnetic stimulation (TMS), and recordings of eye and hand movements. These studies explore the mechanisms underlying the perception of body orientation, processes of attention and spatial exploration, and visuomotor coordination processes involved in pointing and reaching. The overarching question of the section's research is how organisms accomplish successful sensorimotor coordination. In order to generate meaningful motor actions, such as reaching and grasping or movements required to explore or orient oneself in space, a wide range of sensorimotor information must be used and integrated; in addition, the information which needs to be integrated may be changing constantly and is provided in different coordinate systems. The brain's ability to perform this integration task constitutes a central research question in the field of cognitive neuroscience. The results of this research not only allow us to understand the underlying mechanisms, but also provide a basis for developing new strategies to treat stroke patients who suffer from cognitive disorders.

homepage: http://www.medizin.uni-tuebingen.de/institute/hih/sek_neuropsychology.html

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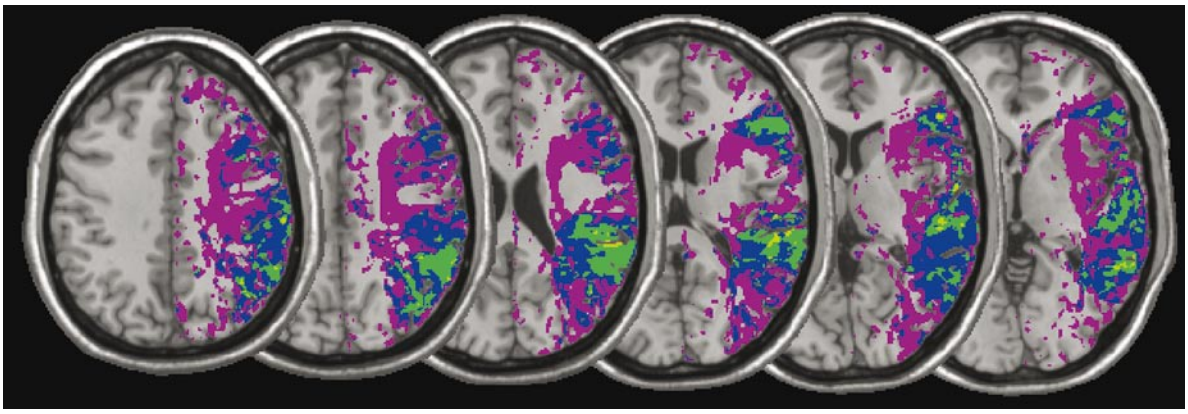
Key Publications

Karnath H-O, Dieterich M (2006) Spatial neglect – a vestibular disorder? Brain 129:293-305

Goldenberg G, **Karnath H-O** (2006) The neural basis of imitation is body part specific. J Neurosci 26:6282-7

Gharabaghi A, **Fruhmann Berger M**, Tatagiba M, **Karnath H-O** (2006) The role of the right superior temporal gyrus in visual search – insights from intraoperative electrical stimulation. Neuropsychologia 44: 2578-81, Corrigendum 45:465



▲ Figure: Normalized Perfusion-Weighted Imaging (PWI). In patients with stroke lesions, we use PWI to identify the abnormally perfused brain area(s) that receive enough blood supply to remain structurally intact, but not enough to function normally. In order to recognize these common areas in groups of patients, we analyse the increase of time-to-peak (or TTP) lesion-inducted delays by using spatial normalization of PWI maps as well as symmetric voxel-wise inter-hemispheric comparisons. These new techniques allow comparison of the structurally intact but abnormally perfused areas of different individuals in the same stereotaxic space, and at the same time avoid problems due to regional perfusion differences and to possible observer-dependent biases.

Labor für visuelle Wahrnehmung

Arbeitsgruppenleiter: Thomas Haarmeier

Neurologische Erkrankungen können Störungen des Sehens nach sich ziehen, die durch die in der Vergangenheit verfügbaren Sehtests wie die konventionelle Bestimmung der Sehschärfe oder des Gesichtsfeldes nicht erfasst wurden. Einige dieser Sehdefizite sind die Folge erkrankungsbedingter Störungen der Augenbewegungen (der Okulomotorik), andere bedingt durch Läsionen des zentralen Nervensystems außerhalb der primären Sehrinde. Eines der wesentlichen Ziele der Arbeitsgruppe ist es, diese Störungen, die häufig nur Teilleistungen des Sehens betreffen, unter Einsatz geeigneter psychophysischer Testverfahren zu erfassen. Ein Hauptaugenmerk gilt hierbei der Frage, in welcher Weise sich gestörte Augenbewegungen auf das Sehen auswirken, ein zweites gilt den neuronalen Grundlagen unserer bewussten visuellen Wahrnehmung, ihren Störungen und deren Auswirkungen auf visuomotorisches Verhalten. Die zur Klärung dieser Fragen eingesetzten Methoden umfassen Patientenstudien, in denen die Auswirkungen von umschriebenen Hirnläsionen auf okulomotorische Leistungen oder auf zuvor psychophysisch charakterisierte Sehleistungen geprüft werden, sowie die Untersuchung von Gesunden und Patienten mittels funktioneller Bildgebung (Magnetenzephalographie, funktionelle Kernspintomographie) oder transkranieller Magnetstimulation.

Aktuelle Projekte bearbeiten folgende Fragen:

(a) Ziel einer ersten Reihe von Untersuchungen ist es, zu klären, ob die funktionellen Beiträge des Kleinhirns auf die Formung motorischer Leistungen beschränkt sind oder aber auch solche Leistungen einschließen, die im Bereich perzeptuell-kognitiver Funktionen angesiedelt sind. Wir studieren cerebelläre Beiträge zu nicht-motorischen Leistungen modellhaft am Beispiel der visuellen Wahrnehmung und versuchen, die möglicherweise aus Kleinhirnläsionen resultierenden Funktionsstörungen des cerebralen Kortex zu charakterisieren.

(b) In psychophysischen und funktionell bildgebenden Untersuchungen werden die Mechanismen und neuronalen Substrate, die der räumlichen Ausrichtung visueller Aufmerksamkeit zugrundeliegen, beleuchtet.

(c) Augenbewegungen ziehen notwendiger Weise Bildverschiebungen auf der Netzhaut nach sich, welche nicht als Umweltbewegung interpretiert werden dürfen, um nicht die Wahrnehmung eines konstanten, stationären Raumes zu gefährden. Wir untersuchen die zugrundeliegenden Mechanismen dieser Wahrnehmungskonstanz und die Relevanz ihrer Störungen für die Entstehung von Schwindel.

(d) In enger Zusammenarbeit mit dem hiesigen MEG-Zentrum wird die Bedeutung kortikaler Oszillationen für visuelle Wahrnehmungsleistungen studiert. Besonderer Schwerpunkt liegt auf der Untersuchung langsamer Oszillationen und deren Kopplung mit hochfrequenten Aktivierungen als möglicher Grundlage perzeptueller Entscheidungsprozesse.

(e) Ziel eines Kooperationsprojektes mit der Klinik für Neurochirurgie schließlich ist es, funktionelle Kernspintomographie mit intraoperativen Stimulationstechniken zu kombinieren, um die funktionelle Topographie des visuellen Kortex zu verfeinern und das Risiko für operationsbedingte Sehstörungen reduzieren zu helfen.

Visual Perception Laboratory

(Group leader: Thomas Haarmeier)

Neurological disorders may cause visual deficits that have not been covered in the past by standard visual tests such as the assessment of visual acuity or perimetry. Some of these deficits are due to oculomotor disturbances while others are a consequence of cerebral lesions outside primary visual cortex. One of the major goals of this group is to quantitatively measure such deficits which frequently involve only particular aspects of vision using appropriate psychophysical tools. A main focus in this respect is the dependency of visual perception on the quality of eye movement behavior. Other studies are directed at the neural mechanisms underlying visual perception, its disturbances, and its impact on visuomotor behavior. To address these questions different experimental approaches are employed including psychophysical experiments performed with normal human subjects, the assessment of visual performances as function of oculomotor deficits or focal brain lesions, functional imaging studies (magnetoencephalography, functional magnetic resonance imaging), and transcranial magnetic stimulation of human subjects.

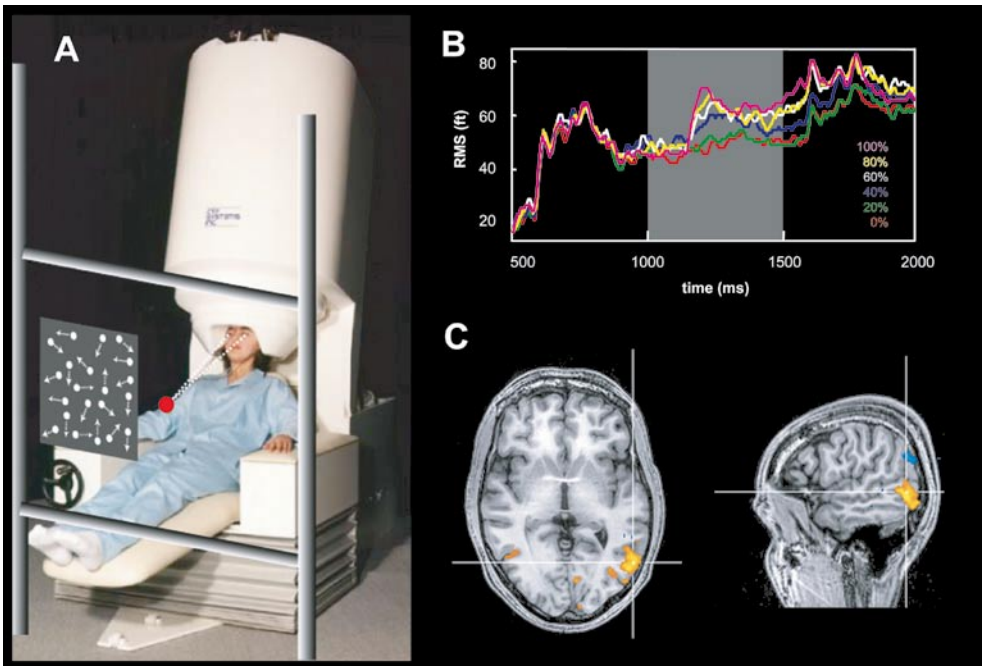
Current studies focus on the following topics. In one series of experiments we have addressed the question whether the cerebellum may be involved in functions other than motor control. For this, visual perception has served us as a model to exemplarily study the role of the cerebellum in cognition. Other experiments, performed most of all with normal human subjects, are devoted to the mechanisms underlying spatial shifts of visual attention, the perception of visual motion in the absence or presence of eye movements, and their cortical underpinnings with special emphasis placed on the potential role of synchronous oscillatory activity of the human brain. Finally, in cooperation with the local Clinic for Neurosurgery functional magnetic resonance imaging is currently combined with focal stimulation techniques in order to further characterize the functional topography of extrastriate visual cortex.

Key Publications

Haarmeier T, Thier P (2006) Detection of speed changes during pursuit eye movements. Exp Brain Research 170:345-57

Händel B, Lutzenberger W, **Thier P, Haarmeier T** (2006) Inverse dependencies on visual motion of area MT+ and early visual cortex. Cerebral Cortex. Aug 28; [Epub ahead of print].

Lindner A, Haarmeier T, Erb M, Grodd W, **Thier P** (2006) A cerebro-cerebellar circuit underlying the perceptual cancellation or retinal image motion induced by smooth pursuit eye movements. J Cogn Neurosci 18:1899-1912



▶ Figure: A – Sketch of a magnetoencephalography (MEG) experiment testing cortical responses evoked by visual motion. B – Dependency of MEG responses (average across different sensors and subjects) on the strength of visual motion (presented from 1,000-1,500ms). C –Responses to visual motion obtained from functional magnetic resonance imaging (single subject).

homepage: http://www.hih-tuebingen.de/kn/forschung0/labor-fuer-visuelle-wahrnehmung/

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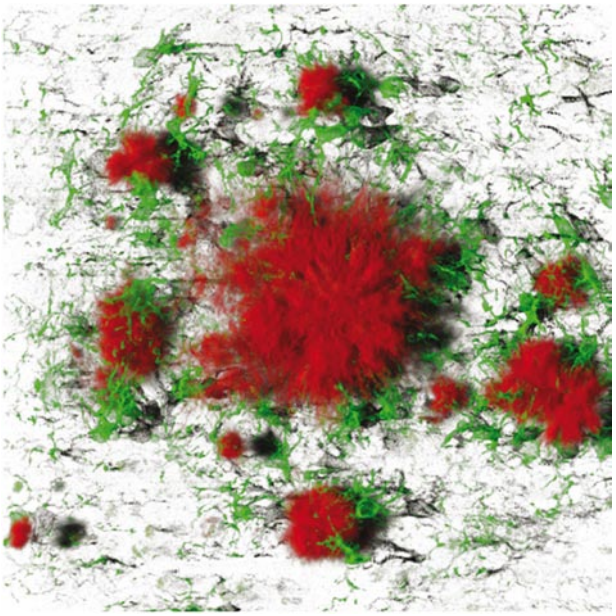


Department of Cellular Neurology

Departmental Structure

The Department of Cellular Neurology, headed by Professor Mathias Jucker, was founded in May 2003. The research of this department focuses on the cellular and molecular mechanisms of brain aging and age-related neurodegenerative diseases. Research is particularly concentrated on the pathogenesis of Alzheimer's disease, the most frequently occuring age-related dementia with more than 1 million people affected in Germany alone. It was in Tübingen that Alois Alzheimer described the disease for the first time to his colleagues 100 years ago. On this occasion, the Department of Cellular Neurology organized a milestone scientific meeting presenting 48 of the worldwide leading scientists in the field as speakers on November 3 and 4, 2006.

Despite our interest in the pathogenesis and therapy of Alzheimer´s disease, we believe that we should sustain diversity in our department since significant progress often comes from related research topics. Currently our department is composed of five research groups: The Neuropathology group uses transgenic mouse models to study the mechanisms of brain aging and in particular cerebral amyloidosis. The Neuroimmunology group works on neuroinflammatory aspects in aging and age-related neurodegenerative diseases and potential therapies. The group of Molecular Biology studies the processing and metabolism of proteins that are involved in Alzheimer's disease and other proteopathies. The group of Molecular Imaging focuses on neuronal plasticity in aging and dementia using 4D morphometric techniques including in vivo 2-photon imaging. More recently, a group using Drosophila as a model system to study aging and synaptic function has been added.

In 2006 our department hosted scientists from more than 10 nations ranging from short-term fellows, diploma students, PhD students, postdocs to group leaders from Iceland, India, Rumania, Switzerland, Canada, and USA to name but a few. The department includes two C3/W3 positions that will be filled in the coming years through recruitment of group leaders into tenure-track positions and/or recruitment of more clinically-oriented scientists to strengthen the bridge from our basic and preclinical research towards clinical applications. The goal is to build a department with expertise in brain aging and age-related neurodegenerative disease that is extramural highly competitive and intramural socially attractive for coworkers.

Arbeitgruppe Neuropathologie

Arbeitsgruppenleiter: Mathias Jucker

Es ist seit langem bekannt, dass die Missfaltung von Proteinen die Ursache von vielen neurodegenerativen Krankheiten ist. Unklar bleibt jedoch, weshalb es zu dieser Missfaltung und den darauffolgenden Ablagerungen von verdrehten Proteinen kommt und weshalb dies vorwiegend in den Gehirnen alter Menschen geschieht.

Bei der Alzheimer-Krankheit wird das missgefaltete β-Amyloid (Aβ)-Protein zwischen den Nervenzellen abgelagert (sog. Amyloid-Plaques). Dabei wird in einer ersten Phase die Kommunikation der Nervenzellen gestört und in einer späteren Phase kommt es zum Tod der Zellen. Das gleiche Aβ-Protein kann sich aber auch in der Gefäßwand ablagern, was zu einer sogenannten Amyloidangiopathie führt und dann in einer Ruptur der Gefäßwand und in gefährlichen Gehirnblutungen mündet.

Das Ziel unserer Arbeitsgruppe ist es, die Mechanismen aufzuklären, wie es zu solchen Missfaltungen und Ablagerungen kommt, und darauf basierend therapeutische Strategien zu entwickeln.

Über die letzten Jahre ist es uns gelungen, transgene Mausmodelle zu generieren, die entweder Amyloid-Plaques entwickeln und somit die Alzheimer-Pathologie widerspiegeln oder aber das Aβ-Protein in den Gefäßen ablagern und damit ein Modell für die zerebrale Amyloidangiopathie darstellen. Anhand dieser Modelle konnten wir zeigen, dass diese Amyloidablagerungen durch eine Verabreichung von hoch verdünnten Extrakten aus den Gehirnen von Alzheimer-Patienten induziert werden können. Im weiteren konnten wir zeigen, dass der Amyloid-induzierende Stoff in diesen Extrakten das Aβ-Protein in missgefalteter Form selbst ist, welches bis heute nicht synthetisch hergestellt werden kann.

Diese und andere Forschungsergebnissse erlauben uns nun, mit Hilfe unserer Mausmodelle eine Therapie gegen die Alzheimer-Krankheit zu entwickeln. Erste Versuche sind vielversprechend und die Amyloidbildung in der Maus kann verhindert werden. Unserer Annahme nach spielen hierbei sogenannte Mikroglia-Zellen, im Gehirn vorkommende Fresszellen, eine ganz entscheidende Rolle.

Ein immer wichtiger werdender Forschungsszweig in unserem Bestreben, die therapeutischen Erfolge in der Maus in die Klinik zu übertragen, ist nun, die diagnostische Füherkennung in Maus und Mensch zu verbessern, um so früh wie möglich eingreifen zu können, bevor die Amyloidablagerungen zum Sterben der Nervenzellen und somit zur Alzheimererkrankung führen, von der weltweit zunehmend viele Menschen betroffen sind.

Neuropathology

(Group leader: Mathias Jucker)

Introduction

In normal aging and Alzheimer's disease (AD), amyloid-β (Aβ) deposition occurs in both parenchymal plaques and in vessels (cerebral amyloid angiopathy, CAA). However, CAA can also occur in the absence of parenchymal amyloid plaques and vice versa. For example, patients with hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) develop a severe form of Aβ-CAA but very few amyloid plaques.

Although the most common form of cerebral amyloidosis is of the Aβ-type, there are other proteins which have been linked to severe familial forms of cerebral amyloidosis. Hereditary cerebral hemorrhage with amyloidosis Icelandic-type (HCHWA-I) is caused by a point mutation in cystatin C and patients suffer fatal hemorrhagic stroke as early as in their twenties. The amyloid in these patients consists of mutated cystatin C (ACys). Familial British Dementia (FBD) and Familial Danish Dementia (FDD) are autosomal dominant disorders with death occurring at 40-60 years of age. Both diseases are caused by mutations in the BRI2 gene, which results in the generation of the amyloidogenic ABri and ADan peptides, in British and Danish Dementia respectively, which are then deposited as amyloid in the brain.

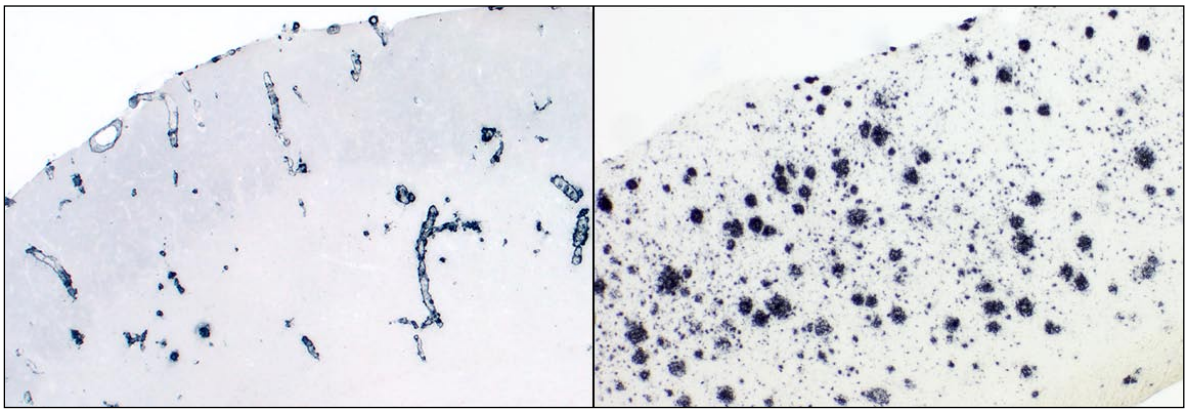
Objectives

We are interested in studying the mechanism and therapy of cerebral amyloidosis. In particular, the following objectives are pursued:

(I) AD, HCHWA-D, HCHWA-I, FBD, and FDD share cerebral amyloidosis as a common pathological hallmark, nevertheless there is a puzzling variety of additional neuropathological lesions and clinical phenotypes. For example, CAA in HCHWA-I leads to severe hemorrhagic stroke, while CAA in FBD and FDD does not lead to significant bleeding but rather contributes to dementia. Cerebral amyloidosis in AD, FBD, and FDD is thought to be the cause of neurofibrillary tangle formation, however no tangles are observed in HCHWA-D and HCHWA-I patients. Thus, a key question is whether amyloid-associated pathologies are specific to an amyloid subtype (Aβ, ACys, ABri etc.) or whether the formation of any amyloid is capable of triggering similar toxic events.

(II) Cerebral amyloidosis occurs in the aging brain. Hence it is not clear what the age-related changes are that make the aging brain susceptible to cerebral amyloid formation and deposition.

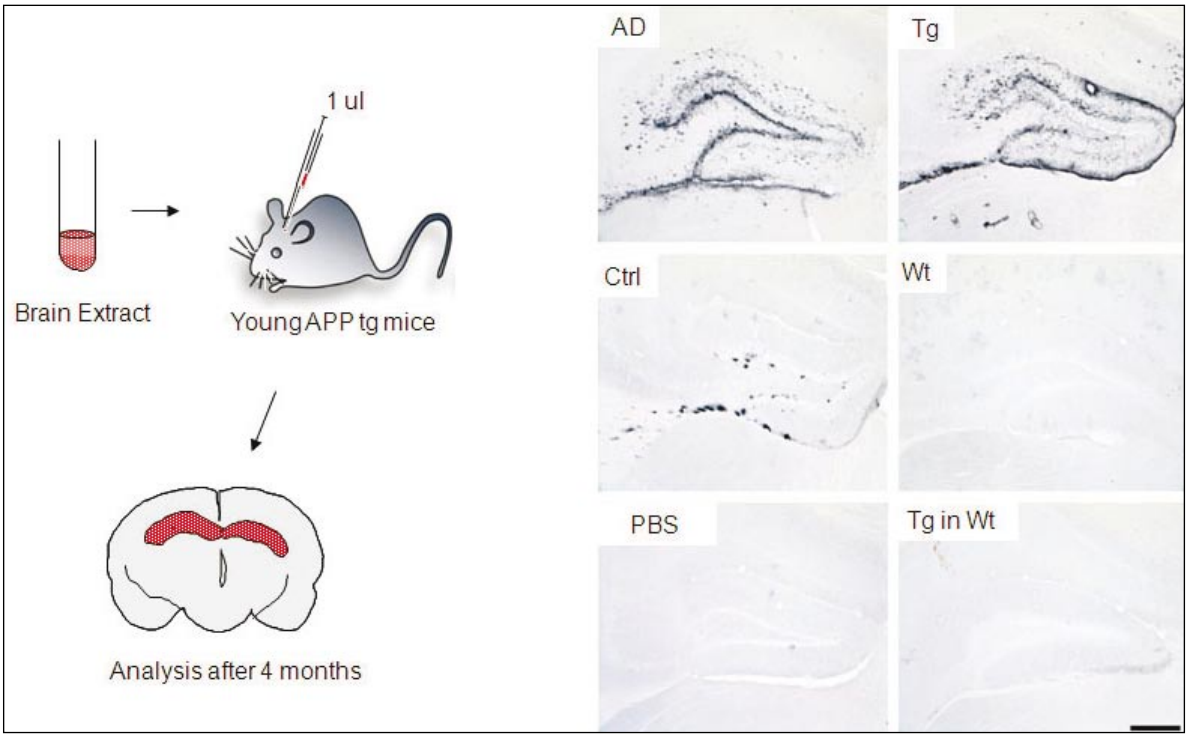
(III) Aβ-amyloidosis targeted immunotherapies have been developed but remain confined to patients that lack significant CAA due to the possibility of CAA-induced hemorrhage as a side effect. Can similar immunotherapies be developed for CAA and non-Aβ amyloidoses and what is the mechanism of amyloid induction and clearance in vivo?



▲ Figure 1:
APPDutch transgenic mice (left) develop cerebral amyloid angiopathy (CAA) in the absence of parenchymal amyloid, while APPPS1 mice (right) develop predominately parenchymal amyloid (amyloid plaques). Shown is the Aβ-immunostained neocortex.

Results

To study the significance of CAA vs parenchymal amyloidosis, we have developed various amyloid precursor protein (APP) transgenic mouse lines using a neuron-specific Thy-1 promoter. The APPDutch mice represent the first transgenic mouse model that develops extensive CAA with only very few parenchymal Aβ deposits. In contrast, APPPS1 mice develop predominantly parenchymal amyloid in the absence of CAA *(see fig. 1)*. From these studies (Herzig et al., 2004; Radde et al., 2006) we have found that the ratio of Aβ1-40/Aβ1-42 determines in which compartment the amyloid forms. A high ratio favors CAA, while a low ratio favors parenchymal deposition. The understanding that Aβ species of different length can drive amyloid pathology in different cerebral compartments has important implications for current anti-amyloid therapeutic strategies which predominantly target Aβ1-42. To study how Aβ aggregation and deposition is initiated in vivo we have shown that brain extracts from old APP transgenic mice with amyloid plaques, like extracts from Alzheimer patients, can induce plaque formation in young APP transgenic mice *(see fig. 2)*. When the Aβ protein was biochemically inactivated or removed from the brain samples, the extracts lost their ability to induce amyloid deposition, showing that the Aβ itself is necessary for the induction of the amyloid plaques and the amyloid in the vasculature. Surprisingly, synthetically produced Aβ was unable to induce amyloidosis, suggesting that the ability of Aβ to seed amyloid requires structural characteristics of Aβ that are generated in the living brain. The importance of the brain environment was underscored by experiments with brain extracts from two different APP transgenic mice. When brain extracts from one genetically engineered mouse model were injected into a different mouse model, the appearance of the induced amyloid deposits was found to depend on both the host mouse and the source of the extract. These findings indicate that cerebral amyloidosis can be induced in the brain by Aβ, and that the nature of the seeded aggregates depends on the source of the seeding material as well as the recipient. While this mechanism bears important similarities to that of prion disease, which can be triggered by exposure to abnormally folded prion proteins, there is currently no evidence that Alzheimer's disease is transmissible in the same sense as are prion diseases. However, the findings indicate that cellular or environmental seeds, in addition to genetic factors, could play a critical role in the initiation of Alzheimer's disease (Meyer-Lühmann et al., 2006) .



◀ Figure 2: Brain extracts were intracerebrally injected into the hippocampus of young APP transgenic mice. Amyloid could be induced in the mouse hippocampus after injection of an extract from an Alzheimer patient (AD) and from aged APP transgenic (Tg) mice. In contrast, few or no amyloid was detected after injections of brain extract from an aged control patient (Ctrl) and wild-type (Wt) mouse. No amyloid was observed after PBS injections or with TG extract injected into a wildtype mouse.

Outlook

To further understand how abnormal protein processing and aggregation leads to cerebral amyloidosis, cellular dysfunction, hemorrhage, and dementia we have generated cystatin C transgenic mice with the HCHWA-I mutation and BRI2 transgenic mice with the FBD/FDD mutations. These studies will now be instrumental for the investigation whether the various amyloid-associated pathogenic events are specific to certain amyloid subtypes or whether the formation of any amyloid is capable of triggering similar toxic events. Moreover by crossing Cystatin C tg mice with APP transgenic mice we have noted that Cystatin C inhibits Aβ-amyloidosis, an observation that is now rigorously followed up and may allow for development of novel therapeutic strategies. To study the mechanism of therapeutic amyloid clearance we have initiated a research program to investigate the role of microglia in the pathogenesis of cerebral amyloidosis and Alzheimer's disease.

Key Publications

Herzig MC, Winkler TD, Burgermeister P, Pfeifer M, **Kohler E**, Schmidt SD, Danner S, Abramowski D, Stürchler-Pierrat C, Bürki K, van Diunen SG, Maat-Schieman MLC, Staufenbiel M, Mathews PM, **Jucker M** (2004) Aß is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. Nature Neuroscience 7:954-60

Radde R, Bolmont T, Käser SA, Coomaraswamy J, Lindau D, Stoltze L, Calhoun ME, Jäggi F, Wolburg H, Gengler S, Haass C, Ghetti B, Czech C, Hölscher C, Mathews PM, **Jucker M** (2006) Aß42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. EMBO reports 7:940-6

Meyer-Luehmann M, Coomaraswamy J, Bolmont T, Kaeser S, Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret J, Paganetti P, Walsh DM, Mathews P, Ghiso J, Staufenbiel M, Walker L, **Jucker M** (2006) Exogenous induction of Aß-amyloidogenesis is governed by agent and host. Science 313:1781-4

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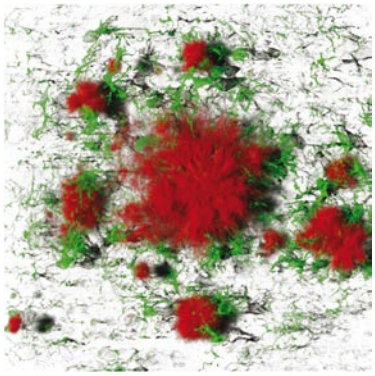


▲ Figure 3:
Microglia (green) surrounding an amyloid plaque (red)

Arbeitsgruppe Neuroimmunologie

Projektgruppenleiter: Lars Stoltze

Der Schwerpunkt der Arbeitsgruppe Neuroimmunologie liegt in der Untersuchung der Rolle des peripheren Immunsystems bei der Alzheimer (AD) und Parkinson Erkrankung (PD) mit besonderem Schwerpunkt auf der Rolle von T-Zellen. Entscheidend für die Regulation des Immunsystems sind regulatorische T-Zellen (Treg), welche bei vielen Autoimmunerkrankungen eine Rolle spielen. Daher wurden Treg von AD und PD Patienten sowie von gesunden jungen und alten Kontrollen untersucht. Es konnte festgestellt werden, dass Treg im Alter vermehrt auftreten und ihre Aktivität bei den AD und PD Patienten erhöht ist. Somit könnte die erhöhte Anzahl von Treg einen Beitrag zur verminderten Immunaktivität in Älteren leisten und Treg sowie eine neurodegenerative Erkrankung scheinen sich gegenseitig zu beeinflussen.

Zusätzlich zu Treg werden in der Neuroimmunologie-Gruppe, Amyloid-beta (Aβ)-spezifische cytotoxische T-Zellen (CTL) untersucht. CTL, welche auf ein bestimmtes Human Leukocyte Antigen (HLA) geprägt sind (HLA-A2), sind von besonderem Interesse, da bei einem kürzlichen klinischen Versuch zur Immunisierung mit Aβ starke Nebenwirkungen auftraten, die vermutlich durch T-Zellen ausgelöst wurden. Einer der zwei Patienten, die an diesen Nebenwirkungen starben, zeigte eine starke Einwanderung von CTL in das Gehirn und war HLA-A2 positiv. Ferner bewirkt der Besitz von zwei HLA-A2 Genen (homozygot) ein früheres Auftreten der spontanen AD.

Bisher konnten CTL spezifisch für drei unterschiedliche CTL-Epitope aus Aβ in gesunden Spendern nachgewiesen werden. Diese CTL können unter bestimmten Bedingungen cytolytisch aktiv sein. Weitere Studien zum Vergleich von Patienten und nicht betroffenen Personen, sowie zur Untersuchung, ob T-Zellen in behandelten Patienten Aβ-spezifisch sind, werden ergeben, ob sie eine Funktion im Krankheitsverlauf haben oder als diagnostische Marker verwendet werden können.

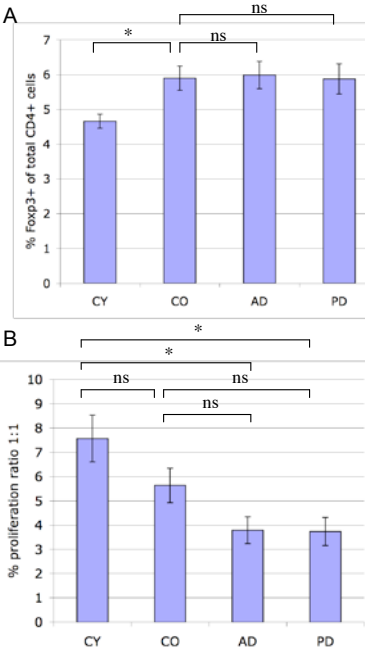
Neuroimmunology

(Project leader: Lars Stoltze)

The major focus is to investigate the involvement of the peripheral immune system in Alzheimer's (AD) and Parkinson disease (PD). To reach this goal regulatory T cells (Treg), which are involved in many autoimmune-diseases as a major regulator of cellular immunity, were analyzed in AD and PD patients as well as healthy young and old non-affected individuals. Interestingly the frequency of Treg (CD4+Foxp3+) increases with age *(fig. 1A)*. This increase is accompanied by an increased frequency of antigen experienced CD4+Foxp3+CD45RO+ Treg and intensified suppressive activity for Treg in AD and PD patients *(fig. 1B)*.

This observation may contribute to the suppressed immune function in the elderly and suggests that Treg and neurodegeneration may influence each other (Rosenkranz, et al., submitted).

▼ Figure 1: Increased frequency of Treg in the elderly measured by flow cytometry. B Higher suppressive activity in Treg from AD and PD patients is revealed by lower T cell proliferation mixing normal T cells and Treg. CY = control young, CO = control old, AD = Alzheimer and PD = Parkinson patients. Shown are the mean of each group including standard error.



▶ Figure 2: Aβ-specific CTL in healthy donors. A flowcytometry staining of expanded CTL by MHC-tetramers with three different Aβ-derived peptides and anti-CD8. B Generated CTL-lines are functional active by killing peptide-loaded (squares) and APP transfected (circles) APP-/- cells but not normal APP-/- cells (triangles) in a Chromium-release assay.

Since complications in the recent Aβ-immunization trial have been induced most likely by Aβ-specific T cells and the existence of human CD4+ Aβ-specific auto-reactive T cells has been demonstrated, we are currently analyzing Aβ-specific cytotoxic T cells (CTL). The major focus lays on the HLA-A2 allele; because homozygosity for this most common human HLA-allele results in an earlier disease onset in sporadic AD and one of the two patients who died from side effects in the Aβ-immunization trial was HLA-A2 positive.

To this end, we identified three different HLA-A2-restricted Aβ-derived CTL epitopes recognized by CD8+ CTL from healthy individuals *(fig. 2A)*. These CTL are functional in terms of cytolytic activity *(fig. 2B)* and have normal peptide avidity. Currently HLA-A2-tetrameres with these three major Aβ-peptide epitopes are used to screen healthy and patient donors for Aβ-specific CD8+ T cells, which will be validated for use as diagnostic markers (Lindau et al., manuscript in preparation)

Key Publication

Rosenkranz D, Weyer S, Tolosa E, Gänslen A, **Berg D**, Leyhe T, **Gasser T, Stoltze L** (2006) Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration. submitted

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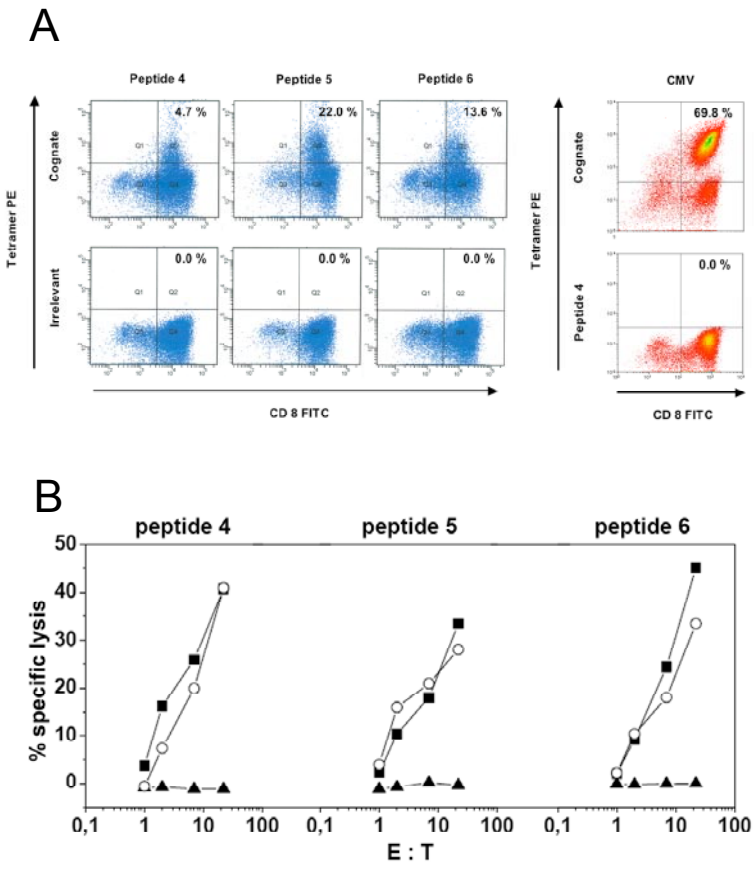


Arbeitsgruppe Molekularbiologie

Arbeitsgruppenleiterin: Ellen Kilger

Die Gruppe Molekularbiologie beschäftigt sich mit der Funktion des Amyloid Precursor Proteins (APP), welches eine wichtige Rolle bei der Entstehung der Alzheimer Demenz (AD) spielt. Das Protein wird durch mehrere Proteasen gespalten, wobei neben weiteren Produkten auch Aβ Peptide entstehen, die im Gehirn von AD Patienten in amyloiden Plaques abgelagert werden. Die physiologische Rolle des APP ist jedoch noch weitgehend unbekannt. Verschiedene Strategien, die zur Therapie der AD entwickelt werden, beinhalten Hemmstoffe der APP Prozessierung, um die Entstehung der Aβ Peptide zu senken und so deren Ablagerung im Gehirn zu verhindern. Hierbei ist es notwendig, dass keine essentiellen Funktionen des APP oder anderer Proteine beeinträchtigt werden, die zu eventuellen Nebenwirkungen führen könnten. Eine der zwei Proteasen, die zur Aβ Entstehung führen, ist der Multiprotein-Komplex γ-Sekretase, der neben APP auch weitere Transmembranproteine, unter anderem den Notch Rezeptor, schneidet. Die regulierte Proteolyse von Rezeptoren durch die γ-Sekretase stellt einen Mechanismus der Signalübertragung in Zellen dar. Im Falle des Notch Rezeptors wird ein intrazelluläres Fragment abgespalten, das in den Zellkern einwandert und dort die Expression bestimmter Zielgene steuert. Für APP wird ein ähnlicher Mechanismus diskutiert. Nach Abspaltung der APP intrazellulären Domäne (AICD) kann diese ebenfalls in den Zellkern einwandern und ist wahrscheinlich gemeinsam mit Co-Faktoren an der Regulation von Genexpression beteiligt. Über den genauen Mechanismus und mögliche Zielgene ist jedoch noch wenig bekannt.

Ein Fokus der Arbeit lag auf der Untersuchung des bekannten Tyrosinkinase Inhibitors Gleevec, der als Substanz beschrieben wurde, die Aβ senkt, jedoch nicht die Signaltransduktion des Notch Rezeptors stört. Wir konnten zeigen, dass Gleevec über einen Mechanismus wirkt, der nicht die γ-Sekretase hemmt. Die Ergebnisse weisen darauf hin, dass die Behandlung von Zellen mit Gleevec stattdessen zu einer Stabilisierung von AICD und möglicherweise zur Verstärkung von dessen Signalfunktion führt. Parallel dazu wird die Expression des Aβ abbauenden Enzyms Neprilysin verstärkt, was vermutlich zu einem verstärkten Abbau von Aβ führt. Diese Resultate legen die Grundlage zu weiteren Untersuchungen der beteiligten Signalmechanismen, die in der Zukunft zu neuen Wegen zur therapeutischen Beeinflussung der Neprilysin Expression und der Aβ Reduktion im Gehirn führen könnten.

Weiterhin wurde eine Zelllinie hergestellt, um die Regulation der Genexpression durch AICD und seinen Bindungspartner Fe65 genauer zu untersuchen. Es wurden Genexpressions-Studien mit DNA Microarrays durchgeführt, um neue Zielgene der Genregulation zu indentifizieren, die bei der Entstehung der AD beteiligt sein könnten. Die potentiellen Kandidaten werden in nachfolgenden Untersuchungen weiter analysiert.

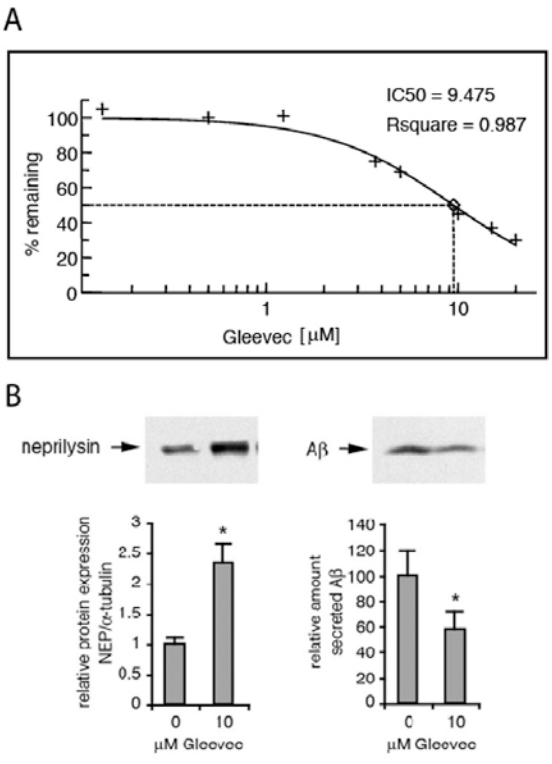
Molecular Biology

(Group leader: Ellen Kilger)

The major focus of the molecular biology group is the processing and cellular function of the amyloid precursor protein (APP). APP is one of the major proteins involved in Alzheimer's disease (AD), but its physiological function remains elusive. The group concentrates on the regulation of APP processing by secretases, with the aim to find new pathways to lower Aβ peptides as a therapeutical strategy for AD. In addition the potential role of the APP intracellular domain AICD in signal transduction is investigated, which may be an important physiological function of APP with implications in AD.

Gleevec, a known tyrosine kinase inhibitor, which is approved for treatment of chronic myeloic leukemia, has been shown to lower Aβ secretion and is considered a potential basis for novel therapies for AD. To elucidate the mechanism by which Gleevec lowers Aβ, its effect on APP cleavage products was analyzed in different cell culture models. It could be shown that Gleevec decreases Aβ *(see fig. 1A and 1B)* by a mechanism distinct from γ-secretase inhibition and without affecting Notch cleavage, which is an important safety requirement for potential therapeutics. Gleevec treatment of cells highly increases the levels of APP-C-terminal fragments and AICD, probably due to less degradation of these fragments. In addition, it was observed that Gleevec treatment leads to higher levels of the Aβ-degrading enzyme neprilysin *(see fig. 1B)*. The obtained results suggest that enhanced Aβ-degradation by upregulated neprilysin expression may cause the Aβ lowering effect of Gleevec. Increased neprilysin expression may involve transcriptional activation via AICD. This provides the basis for future analyses of the underlying signaling mechanisms leading to AICD stabilization and neprilysin upregulation, and may lead to new ways to therapeutically target neprilysin expression in the brain (Eisele et al. submitted).

▼ Figure 1: Gleevec treatment of cells leads to upregulation of the Aβ-degrading enzyme neprilysin and to a decrease in cell-secreted Aβ. A: Aβ secreted from H4-APPwt cells measured by ELISA. B: Neprilysin and Aβ levels measured by western blot analysis.

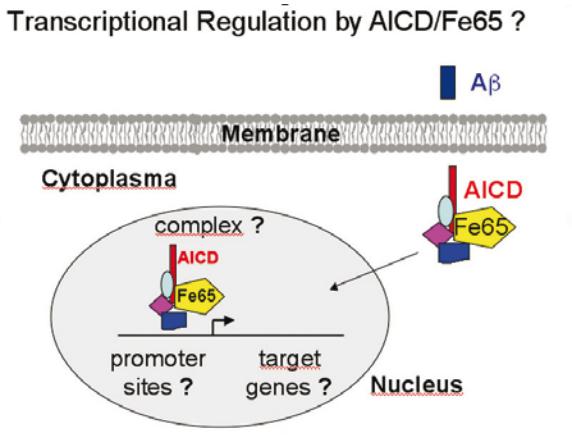


Key Publication

Eisele YS, Baumann M, Klebl B, **Nordhammer C, Jucker M, Kilger E** (2006) Gleevec increases levels of the APP intracellular domain and of the Aβ-degrading enzyme neprilysin. submitted

To study gene regulation by AICD and its interaction partner Fe65 *(see fig. 2)*, we have established H4 neuroglioma cell lines overexpressing APP together with a conditional allele of Fe65 under the control of the "tet-off" system. We showed that these cells represent a useful tool to analyze gene regulation by AICD/Fe65. The cell lines were used to identify potential new target genes of AICD/Fe65 signaling by microarray analyses. Several candidate genes were found, that have distinct functions in the brain and are currently validated by further experiments.

▼ Figure 2: Model of transcriptional activation by the APP intracellular domain (AICD) and its interaction partner Fe65. AICD is released into the cytosol after γ-secretase cleavage of APP. It binds to the adaptor molecule Fe65 and probably further interaction partners and can translocate to the nucleus. The transcriptionally active complex, promoter sites and potential target genes are investigated.



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Arbeitsgruppe Molekulare Bildgebung

Arbeitsgruppenleiter: Michael Calhoun

Die Arbeitsgruppe Molekulares Imaging verwendet modernste Bildgebungsverfahren zur Untersuchung der neuronalen Grundlage von Lernen und Gedächtnis sowie des Einflusses von Alterungsprozessen und der Alzheimer-Demenz.

Die Alzheimer-Demenz (AD) ist eine fortschreitende Erkrankung des Gehirns mit irreversiblen morphologischen und biochemischen Veränderungen. Dazu gehören die krankhafte Ablagerung verschiedener Eiweiße (Proteine) in Nervenzellen, so genannte Neurofibrillen, sowie extrazelluläre Ablagerungen im Gehirngewebe (Amyloid-Plaques) und in den Blutgefäßen. Darüber hinaus kommt es zum Verlust von Nervenzellen (Neuronen) und Synapsen in spezifischen Gehirnregionen. Um eine sinnvolle Therapie für Patienten mit bereits bestehender AD-Erkrankung zu entwickeln, ist es wichtig, nicht nur die beteiligten Faktoren der Erkrankung zu kennen, sondern auch deren Einfluss auf die neuronale Funktion zu verstehen. Ein geeignetes Modell hierfür sind in unserem Labor entwickelte transgene Mäuse, die solche spezifischen AD-Merkmale altersbedingt entwickeln. Ein Ziel unserer Studien ist es, die lokale und systemrelevante Bedeutung von Amyloidablagerungen im Gehirngewebe (Amyloid Plaques) im Unterschied zu Amyloidablagerungen in den Blutgefässen (Amyloidangiopathie, CAA) auf die Funktion der Nervenzellen zu untersuchen. Dazu verwenden wir die Methode der Fluoreszenz in situ Hybridisierung (FISH), die es uns erlaubt, die Aktivität lern-assoziierter Gene nach Verhaltenstests sichtbar zu machen und zu vergleichen. Mit dieser Technik konnten wir zeigen, dass Amyloidablagerungen sowohl im Gewebe als auch in den Blutgefäßen unabhängig voneinander die Aktivität dieser lern-assoziierten Gene reduzieren und somit beide möglicherweise zur Demenz bei Alzheimer-Patienten beitragen.

Um Lern- und Gedächtnisprozesse detaillierter untersuchen zu können, wurde in unserer Gruppe ein Verhaltenstest mit Mäusen entwickelt, der über den Verlauf von sechs Testtagen neben lernbegleitenden Aufmerksamkeitsprozessen vor allem verschiedene Lernaspekte des assoziativen Belohnungslernens sowie des Regel- und Umkehrlernens untersucht. Anhand dieses Verhaltenstests konnten wir zeigen, dass spezifische Unterregionen im präfrontalen Kortex für verschiedene Lernvorgänge verantwortlich sind. In Zukunft werden diese Ergebnisse in den unterschiedlichen Alzheimer-Mausmodellen von uns genauer erforscht werden.

Eine weitere Methode ermöglicht es uns, verschiedene mikroskopische Strukturen im Gehirn lebender Mäusen über einen gewissen Zeitraum zu beobachten. Durch die Kombination der 2-Photonen-Mikroskopie mit verschiedenen Fluoreszenz-Markern konnten wir beispielsweise die Interaktion von Mikroglia-Zellen und sich formenden Amyloid-Plaques studieren. Mikroglia-Zellen reagieren schnell und dauerhaft auf Amyloid-Plaques und können mit einem entsprechenden Stimulus auch dazu veranlasst werden, diese zu beseitigen.

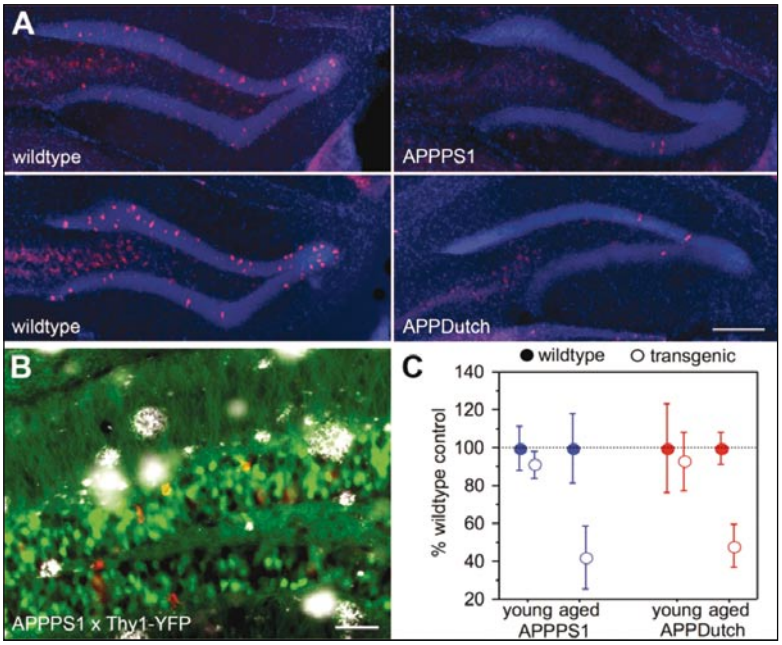
Für all diese Techniken sind hochspezialisierte analytische und computergesteuerte Auswertungsmodule erforderlich. Daher liegt ein weiterer wichtiger Schwerpunkt unserer Arbeitsgruppe auf der Softwareentwicklung zur vier-dimensionalen Visualisierung und Quantifizierung neuronaler Strukturen. Ein Projekt, das diese Technologie zur intrazellulären Lokalisierung lern-assoziierter Genprodukte in Nervenfortsätzen (Dendriten) verwendet, ist momentan in der Entwicklung.

Molecular Imaging

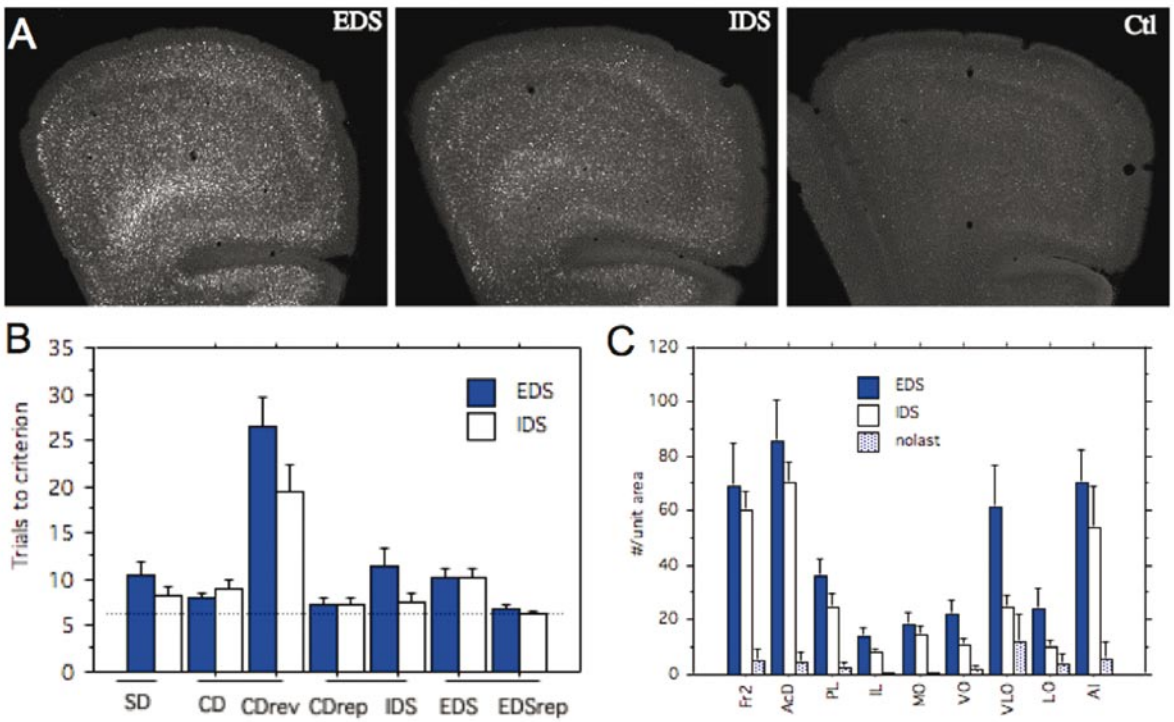
(Group leader: Michael Calhoun)

The imaging group is studying the neural substrates and systems-level organization of learning and memory, and how these are affected by aging and neurodegenerative disease. Projects use higher-order cognitive tasks, mouse models developed specifically to model diseases and/or for visualization, and advanced histological and in-vivo microscopy techniques. The following paragraphs will detail four individual projects with overlapping scientific and technical aspects.

Alzheimer's disease (AD) is characterized by numerous pathological abnormalities including neurofibrillary tangles, beta-amyloid deposition in the brain parenchyma and the vasculature, and localized neuron and synapse loss. Here we evaluate the independent contributions of cerebral vascular and parenchymal amyloid on cognitive decline by using transgenic mouse models which exhibit either vascular (APPDutch mice) or parenchymal amyloid (APPPS1 mice). The behavioral induction of Arc/Arg3.1 (activity-regulated cytoskeleton-associated protein), known to be necessary



▶ Figure 1: Massive reduction in Arc-positive dentate gyrus granule cells sollowing exploratory behavior in both mice exhibiting parenchymal and vascular amyloid

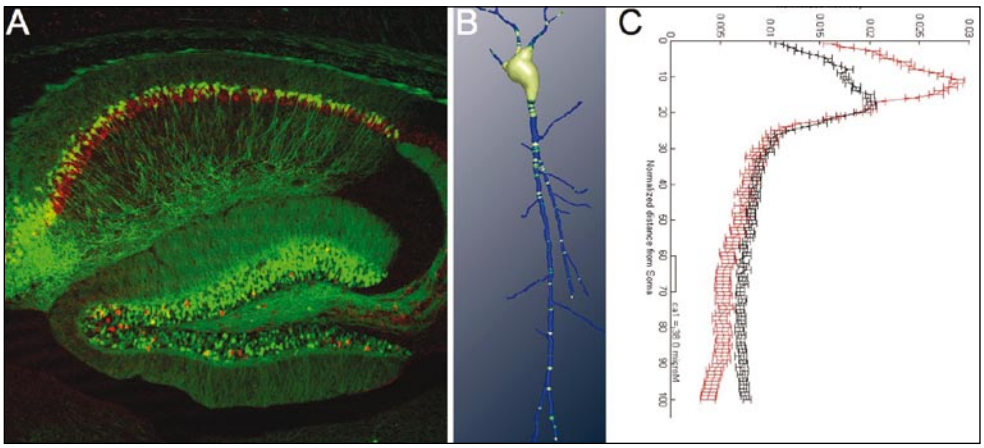


▼ Figure 2: Increased expression of Arc in specific PFC subregions following EDS

for memory consolidation and learning, was analyzed to provide a functional readout of the status of memory systems. Mice with parenchymal and vascular amyloid showed a reduced induction of Arc mRNA in the neocortex following exploration of two novel environments. Stereological quantification of the percentage of neocortical Arc mRNA-positive neurons revealed a decrease in both models (vascular: -17.5%; parenchymal: -26%), and a similar reduction in total neocortical Arc mRNA levels (-19% in both models). The dentate gyrus exhibited a more pronounced decrease in the number of Arc-expressing neurons (vascular: -51%; parenchymal: -58%). Young amyloid pre-depositing mice from both models did not reveal any changes in Arc mRNA expression, and control mRNA levels were not different between any groups. Taken together, our data indicate that both parenchymal and vascular amyloid impair the induction of an important learning-related gene, suggesting that both pathologies contribute to memory impairment in Alzheimer's disease. (Wegenast-Braun et al., submitted). (*see fig. 1)*

The prefrontal cortex (PFC) is thought to be involved in higher-level cognitive functions such as decision-making, executive function, and working memory. Regional activation via fMRI studies in primates, and lesion studies also in rodents have demonstrated specificity within cognitive domains for different PFC subregions, and electrophysiological studies have been able to demonstrate specific firing patterns for certain behaviors, but all of these techniques have limits in either the temporal or spatial domains. We have recently validated a set of behavioral techniques in mice which continue over several days with subsequent testing on simple and compound discriminations (stimuli differing both with respect to odor and digging medium), reversal learning (CDrev), followed by a new set of stimuli (intra-dimensional shift; IDS), and a shift to the previously irrelevant sensory modality (e.g., from odor to digging medium), termed EDS, which is dependent on the prefrontal cortex, and is akin to the Wisconsin card-sorting task used to test frontal function in patients. Using this task, followed by detailed anatomical mapping of the immediate-early gene Arc, we have demonstrated that a larger number of individual neurons in specific PFC subregions are activated during novel reward/stimulus associations and/or by changing attentional sets necessary to solve the tasks (manuscript in preparation). (*see fig. 2).*

Arc plays an important role in activity-dependent synaptic plasticity, including recent studies demonstrating its role in AMPA receptor recycling. Both Arc RNA and protein have been shown to be specifically localized to activated dendritic regions following electrophysiological stimulation. We have now demonstrated methodology to simultaneously visualize Arc RNA and protein within dendrites of individual neurons following behavioral tasks in mice. In both dentate gyrus granule cells and CA1 pyramidal cells, behavior induces Arc transcription in a subset of neurons, and Arc RNA is subsequently transported into dendrites. In CA1 pyramidal cells, Arc RNA is distributed in a gradient from the cell soma, extending up to 200 microns in dendrites within an hour. Although granule cells exhibit a similar gradient, Arc



◄ Figure 3: Localization of Arc RNA following behavior within dendrites of hippocampal neurons. The graph in C illustrates the shift in localization from 30 to 60 minutes following activation.

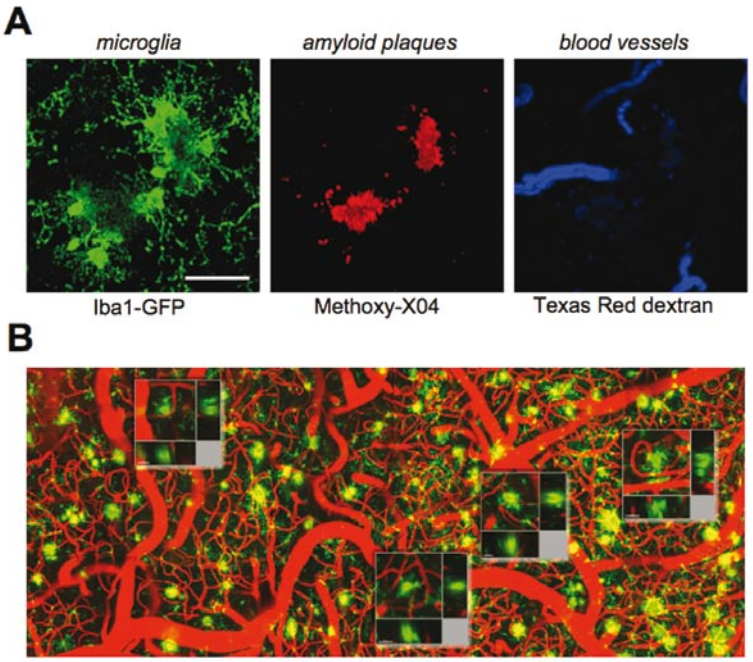
transcription within these cells is sustained, producing a relatively homogenous distribution throughout the dendritic tree by one hour following induction. A subset of Arc RNA-positive granules colocalize with Arc protein labelling, potentially indicating sites of translation. These results provide baseline data on molecular events underlying learning in-vivo, and are being applied to understand factors influencing Arc transcription, transport and dendritic translation. (*see fig. 3)*

Microglial cells aggregate around amyloid plaques in Alzheimer disease but, despite their therapeutic potential, various aspects of their reactive kinetics and role in plaque pathogenesis remain hypothetical. Through use of in-vivo, two-photon imaging in transgenic mice, we demonstrate that local resident microglia rapidly send processes halting plaque growth, and subsequently migrate to the site of plaque formation where individual microglia somata remain spatially stable for weeks. Additional microglia are added at a rate of two/plaque/month, independent of plaque volume. Larger plaques become surrounded by larger microglia, effectively covering the amyloid surface. At the plaque/glia interface, rapid membrane movement was observed, and systemically-injected amyloid-binding dye was internalized. Brain infusion of Aß-antibody resulted in a massive, transitory microglia influx, an increase in internalized Aß, and removal of existing amyloid deposits. These results demonstrate how microglia govern plaque growth and clearance, providing a model with multiple targets for therapeutic intervention. (Bolmont et al., submitted). (*see fig. 4)*

Key Publications

Fletcher BR, **Calhoun ME**, Rapp PR, Shapiro ML (2006) Fornix lesions decouple the induction of hippocampal arc transcription from behavior but not plasticity. J Neurosci 26:1507-15

Radde R, Bolmont T, Käser SA, Coomaraswamy J, Lindau D, Stoltze L, Calhoun ME, Jäggi F, Wolburg H, Gengler S, Haass C, Ghetti B, Czech C, Hölscher C, Mathews PM, **Jucker M** (2006) Ab42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. EMBO Rep 7:940-6



◄ Figure 4:
Visualization of microglia and amyloid plaques in a living Iba1-GFP x APPPS1 mouse.

homepage:http://www.hih-tuebingen.de/zellbiologie/forschungsgruppen/imaging/

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D. Eicke, C. Feichtinger, A. Fulgencio, A. Kuthiala, B. Wegenast-Braun

Arbeitsgruppe Drosophila

Projektleiter: Tobias Rasse

Im Verlauf vieler neurodegenerativen Krankheiten wie der Alzheimer-Demenz sterben Nervenzellen und Nerven-Zellkontakten werden ausgelöst. Im Unterschied dazu ist es völlig normal und für den Lernprozess geradezu wichtig, dass Synapsen sich auch wieder lösen können. Denn die Entfernung von Synapsen spielt eine wichtige Rolle bei der natürlichen Reorganisation des Vernetzungsmusters der Zellen in unserem Hirn. Solch eine Veränderung des synaptischen Netzwerkes ist die Grundlage für alle höheren Hirnfunktionen, zum Beispiel dem Erlernen neuer Fähigkeiten. Die Medikation dementer Patienten müsste sicher stellen, dass die Medikamente nur auf den Teil der Synapsen wirken, die den Gedächtnisverlust auslösen – auf nichts anderes.

Daher wollen wir untersuchen, zu welchem Grad Neurodegeneration lediglich die Folge der Fehlleitung von üblichen Signalwegen ist. Außerdem soll der Frage nachgegangen werden, welche Signalwege spezifisch während der Entstehung einer neurodegenerativen Krankheit fehlgeleitet werden. Wir hingegen wollen verstehen, wie genau das Zusammenspiel der Bausteine, die eine Synapse bilden, bei fortschreitender Neurodegeneration gestört wird.

Dabei bedienen wir uns einer selbst entwickelten Methode, die es uns erlaubt, in der lebendigen Fruchtfliegenlarve die Bedingungen zur Bildung von synaptischen Verbindungen zu untersuchen. Hierzu werden einzelne Fruchtfliegenlarven direkt am Mikroskop betäubt. Dies erlaubt es uns, die Struktur und molekulare Zusammensetzung identifizierter Synapsen zu dokumentieren. Ein paar Stunden später wird die Larve ein zweites Mal vom Futter entfernt und mikroskopisch untersucht. Hierbei können wir genau feststellen, wie sich einzelne Synapsen in der Zwischenzeit verändert haben. Diese Erkenntnisse sollten es uns langfristig ermöglichen, Strategien zu entwickeln, um neurodegenerative Krankheiten ursächlich anzugehen, und zwar von dem Ort des Informationsverlustes her: der Synapse.

Drosophila Group

(Project leader: Tobias Rasse)

Summary

Our research focuses on the molecular mechanisms that underlie memory storage and aims at elucidating how these are disturbed in the progression of neurodegenerative diseases. We want to use the Drosophila neuromuscular junction as model system, since it allows us tracing individual synapses over the time course of days in living intact animals. Motor neurons that lose at 3rd instar larval stage a significant number of their synapses without retracting completely, will be used as a model for slowly deteriorating neurons as seen in neurodegenerative diseases, e. g. Alzheimer's disease.

Methods of investigation

We want to use the in-vivo imaging assay described in Rasse et al., 2005 to study neurodegeneration. At the Drosophila neuromuscular junction 99% of all synapses are positive for both glutamate receptors and the presynaptic protein Bruchpilot. To study the stabilization of synapses we screened for mutants in which more than 5% of all neuromuscular synapses are not properly assembled synapses (lack of either glutamate receptors or Bruchpilot). The protein Bruchpilot was selected as presynaptic marker for functional, mature synapses, since its presence ensures a high vesicle release probability. Bruchpilot clusters calcium and stabilizes the overall active zone structure (Kittel et al., 2006; Wagh et al., 2006). Therefore it seems to be an important step during the "maturation" of synapses to acquire Bruchpilot. So far we identified 7 interesting mutants in which synapses are defective. These mutants will be mapped and characterized in detail.

Outlook

In these model mutants it will be checked whether the abnormalities observed at the synapses (lack of either Bruchpilot or glutamate receptors) are attributable to impaired assembly or ongoing disassembly of synapses. In vivo imaging of a suitable set of model mutants will allow us to investigate (1.) the cellular cascade leading to synapse disassembly. Furthermore, we want to find out whether (2.) disassembly of synapses follows a "uniform" temporal cascade irrespective of the underlying cause of neurodegeneration.

Next we want to study other candidate genes identified in our screens in light of our broader understanding of the cellular cascade leading to neurodegeneration. We want to understand (3.) the molecular cascades causing synapse disassembly, which should be a great aid in developing strategies to stop or delay cognitive decline in the progression of neurodegenerative diseases.

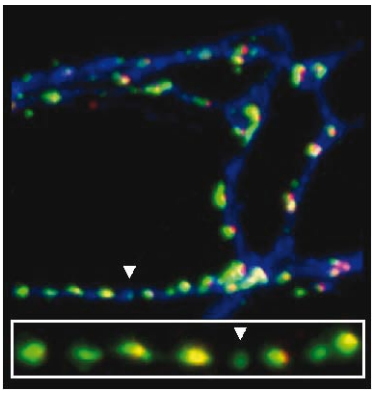
Key Publications

Kittel RJ, Wichmann C, **Rasse TM** et al (2006) The *Drosophila* Bruchpilot protein is required for presynaptic active zone assembly and calcium-channel clustering to ensure high vesicle release probability. Science 19;312(5776):1051-4

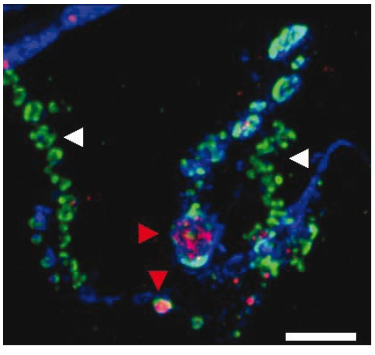
Wagh DA, **Rasse TM** et al (2006) Bruchpilot, a protein with homology to ELKS/CAST/ERC, is required for structural integrity and function of synaptic active zones in Drosophila. Neuron 16;49(6):833-44

Staff:

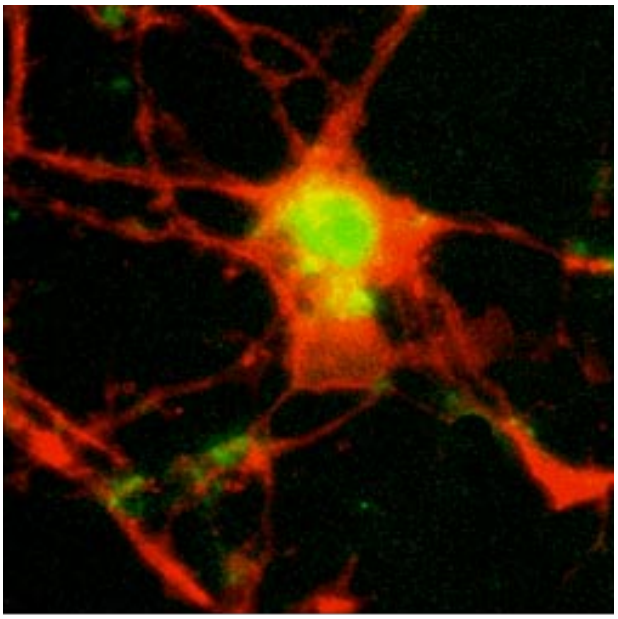
R. Beck, P. Füger, C. Hünefeld, J. Kern, S. Musch, J. Rößle, L. Yu



Characterization of mutants identified in our screen: The mutation in warteschleife (Fig1▲) and fluglotse (Fig 2 ▼) lead to severe alteration in the structure of synapses (blue: HRP marker for synaptic membranes; green: Glutamate receptor DGluRIIC - marker for PSDs, red Bruchpilot). Scale bar = 5 µm. In both mutations synapses are present, in which all synapses are negative for Bruchpilot (white arrowhead). While in fluglotse mutation all observed Bruchpilot staining is localized to synapses, both abnormal accumulation of Bruchpilot in the nerve (A, yellow arrowhead) as well as abnormal clustering of Bruchpilot in certain synaptic boutons (red arrowhead) were observed.



Group leader: Dr. Simone Di Giovanni



Independent Research Group

Arbeitsgruppe Neuroregeneration

Arbeitsgruppenleiter: Simone Di Giovanni

Die meisten akuten und chronischen neurodegenerativen Erkrankungen, zu denen unter anderen Rückenmarksverletzungen, Schlaganfälle und die Alzheimer'sche Erkrankung gehören, können bis heute nicht effektiv behandelt werden.

Diese Erkrankungen sind sowohl mit dem Absterben und Verlust von Nervenzellen verbunden als auch mit mangelhafter Bildung und Regeneration von Nervenzellen und Axonen. Diese beiden Komponenten sind für die Spätfolgen motorischer und kognitiver Beeinträchtigungen im Rahmen dieser Erkrankungen verantwortlich.

Das grundlegende Ziel unseres Labors ist, die Regeneration von Axonen bei Erkrankungen wie Rückenmarksverletzungen, Schlaganfällen und neurodegenerativen Erkrankungen im Ganzen voranzutreiben. Diesem Ziel nähern wir uns durch die genaue Untersuchung der grundlegenden molekularen Mechanismen der Neuronen. Indem wir aufdecken und verstehen lernen, woran die Regeneration der Axone im Allgemeinen scheitert, können wir neuartige Strategien zur Förderung der Regeneration entwickeln.

Wir nutzen für unsere Untersuchungen sowohl in vitro als auch in vivo Experimente, d. h. wir arbeiten sowohl mit Experimenten an Zellen als auch an Tieren wie Ratten und Mäusen, wobei wir die Gene untersuchen und verändern, die Wachstumsprogramme in Neuronen steuern.

Unsere in vivo Modelle schließen auch akute Verletzungen des zentralen Nervensystems wie Rückenmarksverletzungen ein und wir haben vor, in Kürze auch mit einem Tiermodell für Schlaganfallspatienten zu arbeiten.

Während wir Gene und Proteine untersuchen, die für die Regeneration wichtig sein können, verwenden wir auch Medikamente, die auf diesen molekularen Ebenen wirken und testen sie an unseren Modellen. Zwei der Medikamente, mit denen wir bereits jetzt in vitro Versuche durchführen und die wir auch in vivo testen wollen, sind Nutlins und TSA. Nutlins erhöht die Aktivität des Gens p53, von dem wir zeigen konnten, dass es das Wachstum und die Regeneration von Axonen fördert. Wir gehen davon aus, dass die Anwendung dieses Präparats der Einleitung von Regenerationsprozessen bei Verletzungen des Nervensystems ist. TSA ist ein Arzneimittel, das in der Krebsbehandlung angewandt wird und die zelluläre Azetylierung fördert, was unserer Annahme nach zu besserer Regeneration bei Patienten mit neurodegenerativen Erkrankungen führen kann.

Insgesamt können Arzneimittel wie diese, die sich unter unseren Untersuchungsbedingungen als effizient erweisen, unter Umständen für klinische Studien mit Patienten übernommen werden.

Laboratory for Neuroregeneration and Repair

(Group leader:
Simone Di Giovanni)

Our Research

Our research focuses on the molecular and cellular mechanisms of axon regeneration and neuronal differentiation for the repair of central nervous system (CNS) damage, with particular emphasis on Spinal Cord Injury (SCI).

Background

Spontaneous regeneration following injury in the CNS and spinal cord is extremely limited, mechanisms of axon sprouting do occur, but failure in effective axon regeneration and functional reinnervation do not allow significant behavioral recovery. The main reason for the failed axon regeneration in the CNS as opposed to the successful regeneration in the peripheral nerves is to be found in a complex network of molecules and signaling pathways that are specific of the CNS and limit axon regeneration post-injury.

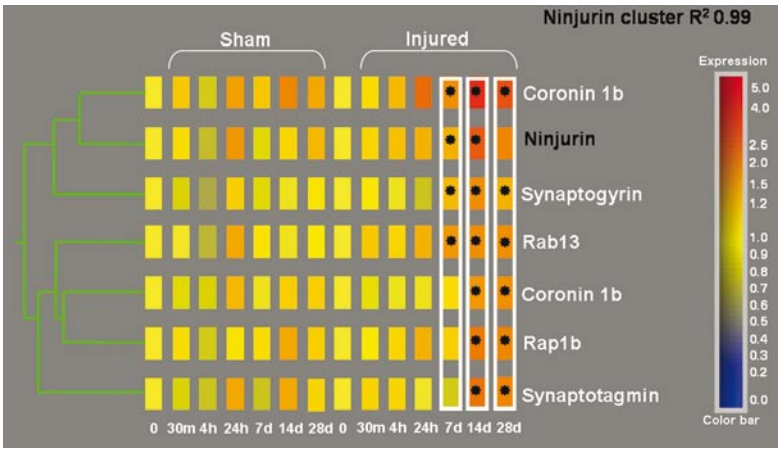
In large part, functional recovery reflects the number of surviving cells and fiber tracts, the extent of neural plasticity, and the presence of a permissive environment for regeneration. Such processes are substantially regulated by gene expression changes; temporally, these alterations include an earlier phase associated with inflammation, extension of axonal damage, cell death and loss, and a later one characterized by tentative axonal regeneration and the formation of an inhibitory environment and of the tissue scar.

Therefore, the success of the reparative processes depends upon factors able to:

1. overcome the inhibitors of axonal regeneration and limiting the scar formation;

2. facilitate the spontaneous mechanisms of neurite outgrowth and axonal regeneration;

3. protect and replacing the original cellular environment;



Aims and Approach

The major aims of our lab are to:

1. investigate the molecular pathways which mediate neurite and axon outgrowth and may mediate axon regeneration overcoming the inhibitory signaling of the CNS environment. This will allow the discovery of possible therapeutic targets for regeneration.

2. study the molecular pathways that promote neuronal differentiation form undifferentiated and progenitor cells that might reveal useful to favor regeneration by cellular therapy.

We employ an in vitro approach in both cell lines and primary neurons to study mechanisms of neurite outgrowth/axon regeneration and neuronal differentiation.

In vivo, we employ models of Spinal Cord Injury in rodents, including the use of transgenic animals to evaluate the in vivo effects of the modulation of specific molecular pathways upon regeneration and recovery of function.

▲ Figure 1:
Gene cluster (dendogram) obtained from an in vivo microarrays study (spinal cord injury site) showing a group of coordinately regulated transcripts involved in neurite outgrowth and synaptogenesis following experimental spinal cord contusion injury in rats. (Di Giovanni et al, JBC 2005)

The role of transcription factors and cytoskeleton remodeling in neurite/axon outgrowth and axon regeneration:

The overall goal is to identify key transcriptional dependent pathways that promote axon regeneration on inhibitory substrates such as myelin and proteoglycans in vitro and in

vivo. Identifications of such pathways will open opportunities for therapy by using specific molecular approaches and drugs which will hopefully be translated into a clinical use.

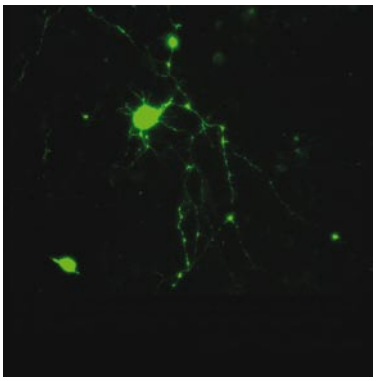
Taking advantage from data obtained from our microarrays time series study in Spinal Cord and Brain injury (see publications), and using a series of bioinformatics approaches (including Genomatix software for promoter analysis), we have recently defined a putative transcriptional cascade between upstream transcription factors and downstream cytoskeleton related gene targets functionally related to axonal plasticity and regeneration. In vitro and in vivo experiments in primary neurons and PC-12 cells have shown that these transcription factors, including p53, drive neurite-axon outgrowth and neuronal differentiation up-regulating target pro-plasticity genes, and that p53 is required for physiological nerve regeneration following axotomy.

► Figure 2:
P53 K320-GFP over-expression in primary cortical neurons enhances neurite outgrowth and is localized in axons and at the growth cones. (Di Giovanni et al, EMBO J, 2006)

Our research now focuses on the role of p53 and other transcription factors-dependent pathways on axon growth and regeneration. We use in vitro systems of neurite/axon outgrowth and in vivo models of sciatic, facial nerve transection, and spinal cord injury. This approach will be complemented by the use of drugs to promote regeneration (such as MDM2-p53 antagonists, Nutlins, in the case of the p53 dependent cascades).

Current Projects

The role of the tumor suppressor p53 in axon growth and regeneration: We have recently shown that the transcription factor p53 is required for neurite/axon growth following growth factor administration in vitro and is required for physiological nerve regeneration following axotomy in vivo (Di Giovanni et al., EMBO J, 2006). Moreover, specifically acetylated p53 preferentially exerts these effects by triggering the expression of genes involved in cytoskeleton remodeling, which promote neurite and axon outgrowth. They include the actin binding protein Coronin 1b and the GTPase Rab13, which we have recently characterized. Nevertheless, the overall pro-axon growth effects of p53 cannot be accounted for by these two proteins. Recent data in the lab have shown that p53 signaling is relevant for the activation of important pro-axon regeneration proteins such as GAP-43. Overall, this project aims at defining novel patterns of p53 signaling and new downstream p53 targets that are important for axon growth and regeneration. (Andrea Tedeschi: andrea.tedeschi@medizin.uni-tuebingen.de)



NFAT family members in axon regeneration: The nuclear factor for activated T cells (NFAT) is a transcription factor that plays an important role in axon growth and guidance during development. Developmental processes are often recapitulated after injury. Recent data in our lab have shown that NFAT is able to bind and promote transcription of crucial factors that promote axon growth. We therefore hypothesize that NFAT might promote axon growth also following SCI. To this end, we intend to generate NFAT transgenic mice and cross them with yellow fluorescent protein (YFP) transgenics, which preferentially express YFP in motor neurons and CST, with the goal to image the extent of CST sprouting and regeneration after CST transection in vivo by using two-photon fluorescent microscopy. The expression of NFAT transcriptional targets will also be evaluated in cortical motor neuron by ChIP (Chromatin immunoprecipitation) on Chip (Affymetrix promoter specific microarrays) assays in the same CST transection model. This approach will first establish methodology applicable to a broad range of questions in SCI, and will provide first data on the dynamics of CST axon retraction and regeneration, assess the contribution of the NFAT dependent transcriptional cascade, and therefore open opportunities for a specifically-targeted therapeutic approach for axon regeneration. (Tuan Nguyen: tuan.nguyen@medizin.uni-tuebingen.de)

Retinoic acid and acetyl transferases-dependent pathways in neuronal differentiation and axon regeneration: Acetylation increases gene expression and protect neurons from cell death. Recent data has suggested that acetylation of specific transcription factors can promote also axon growth. The goal of this project is to define the importance of acetylation and acetyltransferases mediated signalling in axon growth and regeneration on both permissive and inhibitory substrates (myelin) in vitro and in vivo. Our experimental data have shown so far a positive role of acetylation on axon growth and on pro-growth promoter elements. Future directions aim to unveil the molecular mechanisms that mediate such effects both in vitro and in vivo. (Perrine Gaub: perrine.gaub@medizin.uni-tuebingen.de)

Key Publications

Di Giovanni S, Knights C, Beers J, Mahadev Rao, Yakovlev A, Catania J, Avantaggiati ML, Faden AI (2006) The tumor suppressor protein p53 is required for neurite outgrowth and axon regeneration. EMBO J 25(17):4084-96

Di Giovanni S (2006) Regeneration following Spinal Cord Injury, from experimental models to humans: where are we? (Review). Expert Opinion on Therapeutic Targets. 10(3):363-76.

Di Giovanni S, Movsesyan V, Ahmed F, Cernak I, Schinelli S, Stoica B, Faden AI (2005) Cell cycle inhibition provides neuroprotection, reduces glial proliferation and scar formation after traumatic brain injury. Proc Natl Acad Sci U S A 102(23):8333-8

Di Giovanni S, De Biase A, Yakovlev A, Finn T, Beers J, Hoffman EP, Faden AI (2005) In vivo and in vitro characterization of novel neuronal plasticity factors identified following spinal cord injury. J Biol Chem 280(3):2084-91

homepage: http://www.hih-tuebingen.de/nachwuchsgruppen/neuroregeneration-and-repair/

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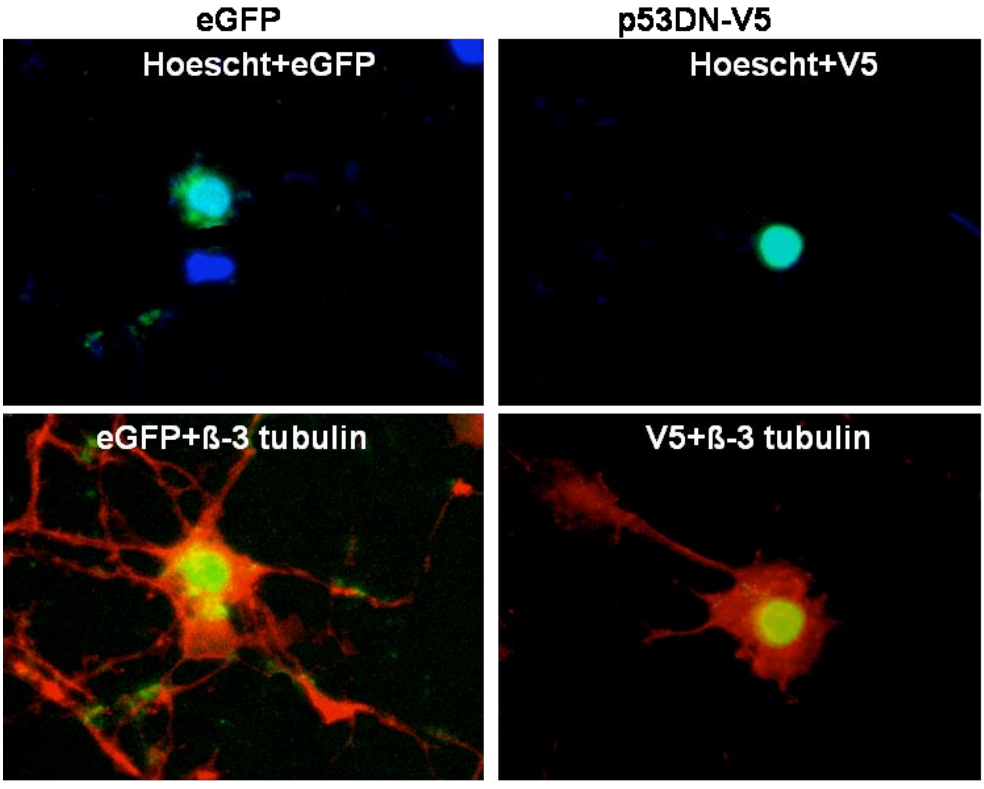
P. Gaub, T. Nguyen, E. Ninci, S. Steele, A. Tedeschi



◄ Figure 3: P53 DN-V5 overexpression in primary cortical neurons strongly reduced neurite outgrowth

General Neurology

Head of the Department of General Neurology

Prof. Dr. M. Weller (Chairman)

Attending physicians

Prof. Dr. C. Gerloff (Vice-Chairman, until 4/2006)
Dr. F. Bischof (from 12/2006)
PD Dr. B. R. Brehm (Cardiologist, until 9/2006)
PD Dr. T. Haarmeier
PD Dr. U. Herrlinger (until 3/2006)
PD Dr. A. Luft (from 7/2006)
Prof. Dr. A. Melms
PD Dr. Platten (from 10/2006)
Dr. F. Schmidt (from 12/2006)
PD Dr. J.P. Steinbach
Prof. Dr. Dr. R. Weissert
Prof. Dr. W. Wick (Vice-Chairman, until 12/2006)

Residents

Dr. M. Albers
Dr. C. Braun
Dr. C. Globas
Dr. B. Greve
Dr. S. Jacob
Dr. G. Maurer
Dr. J. Rieger
Dr. B. Schreiner
Dr. G. Tabatabai
Dr. A. Wick
Dr. O. Bähr
Dr. G. Eisele
Dr. H. Golla
Dr. C. Happold
Dr. B. Kreifelts
Dr. M. Mitsdoerffer
Dr. P. Roth
Dr. S. Schuh-Hofer
M. Theil
Dr. S. Bock
Dr. S. Gärtner
Dr. D. Gramatzki
Dr. M. Hermisson
Dr. D. Lemke
Dr. M. Pick
Dr. S. Schlipf
Dr. K. Stürner
Dr. T. Wächter

Technical staff

Dipl.-Ing. R. Berndt (Electronics, together with the Department of Cognitive Neurology)
Dipl. Inf. H. Rapp

Professorship for Neurorehabilitation

Prof. Dr. H. Ackermann
Dr. I. Hertrich

Neurodegenerative Diseases / Cognitive Neurology

Heads of the Dept. of Neurology with Focus on Neurodegenerative Diseases

Prof. Dr. T. Gasser (Chairman)
Prof. Dr. L. Schöls (Vice-Chairman, Section head)

Attending physicians

PD Dr. R. Krüger
PD Dr. D. Berg

Residents

Dr. F. Asmus
Dr. R. Schüle-Freyer
Dr. J. Fuchs
Dr. K. Schweitzer
Dr. W. Mätzler

Heads of the Department of Cognitive Neurology

Prof. Dr. P. Thier (Chairman)
Prof. Dr. Dr. H.-O. Karnath (Section Head)

Scientists

Dr. J. Pomper
Dr. S. Bock
Dipl.-Psych. E. Becker

Nursing / Technical / Administrative Staff

Senior staff

L. Wollny, M. Renner (PDL)

B5-Ost/Süd

M. Besser, F. Chmell, C. Cuk, K. Eggart, A. Eisele, S. Erath-Digeser, M. Flore, M. Glöckle, G. Häfele, A. Hoffmann, E. Kern, A. Kleefeld, H. Krauter, J. Kronmüller, S. Kurz, M. Lehnert, M. Lohmüller, R. Maier-Korneck, S. Matzka, M. Nowotny, C. Peters, K. Pfefferkorn, I. Sadowski, C. Schaumburg, G. Siegl, R. Striebel, A. Wetterau

B5-West

S. Clement, O. Fuchsmann, M. Gollmer, M. Häfele, K. Hämke, W. Hansen, C. Kirchner-Schmid, J. Körner, Z. Letzgus, C. Löw, C. Mattmüller-Wirth, D. Pacholleck, D. Rieker, E. Sommer

Intensive Care/Stroke Unit

W. Eissler, S. Fallert, U. Fischer, J. Fischer, S. Grumann, F. Hauber, M. Henzler, M. Herr, C. Hildebrand, F. Horb, J. Jünger, M. Kille, A. Kreidler, I. Lange, M. Manteufel-Samavat, P. Nipprasch, M. Rauch, C. Reuter, M. Schäfer, A. Schönberger, T. Striebich, C. Tomschitz, L. Villinger, B. Weimar, G. Weise, B. Weisser, E. Wener, U. Zimmermann

B6-West

C. Assenheimer, S. Baltes, C. Beck, J. Eisele, A. Heß, M. Heymann, R. Johner, B. Kloster, T. Kutscher, A. Mansour-Tokovic, M. Maurer, M. Peterson, A. Sautter, H.-J. Scholpp, H. Schüler, A. Siegle, K. Siegle, I. Utsch-Sellnow, A. Weber

Technicians

M. Berger (Neurosono, EP)
S. Ebner (CSF Chemistry)
B. Heberle (CSF Chemistry)
G. Schönwälder (ENG)
M. Dengler (EEG)
A. Eckert (CSF Chemistry)
R. Mahle (EEG, Neurosono)
P. Schroth (CSF Chemistry)
E. Dubois (CFS Chemistry)
J. Grimm (EMG)
S. Nippert (EG, EP)
B. Wörner (EEG)

Secretaries

S. Bentz, E. Biesinger, E. Gonglach-Pfannenschmidt, I. Marterer, J. Miller, K. Otterbach, C. Riegraf, D. Wieder, U. Wilhelm

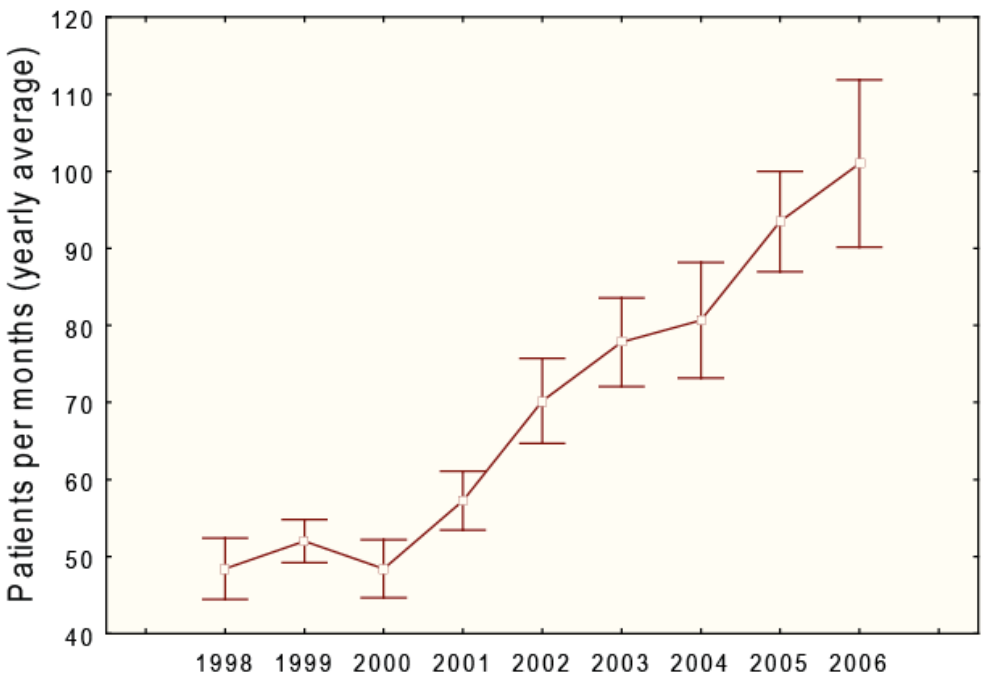
Medical Documentation

C. Brick, H. Feuerbacher

Clinic for Neurology

Statistical Efficacy Data

The year 2006 has seen an increase in the total number of admissions and shortening of the length of stay (2006: 3900 patients, mean length of stay: 6,3 days). Drastic increases were again seen in the Stroke and Intensive Care Sector where patient numbers have now doubled since the year 2000.



Increase in admissions to the Stroke/Intensive Care Unit between 1998 and 2006

The outpatient clinics have treated a total number of 21058 patients (2005: 13440).

The neurological consult service sees an average of 7 patients per day including weekends. Geriatric patients in the Paul-Lechler-Krankenhaus in Tübingen, and the hospital in Rottenburg were treated as part of the interdisciplinary geriatric center.

General Neurology

Director of the Department of General Neurology

Prof. Dr. M. Weller

Group leaders

Prof. Dr. H. Ackermann
PD Dr. R. Krüger
Prof. Dr. Dr. R. Weissert
Prof. Dr. C. Gerloff
PD Dr. A. Luft
Prof. Dr. W. Wick
PD Dr. T. Haarmeier
Prof. Dr. A. Melms

Scientific staff

B. Adams
Dr. O. Bähr
I. Burghardt
Dr. S. Gaertner
Dr. M. Hermisson
Dr. F. Hummel
K. Molina-Luna
Dr. A. Pekanovic
C. Rauner
Dr. P. Roth
Dr. G. Tabatabai
Dr. M. von Hornung
Dr. S. Anders
Dr. F. Bischof
Dr. C. Droll
Dr. K. de Graaf
M. Herrmann
Dr. D. Lemke
J. My Lin Lam
Dr. M. Pick
Dr. J. Rieger
Dr. F. Schmidt
Dr. E. Tolosa
Dr. M. Weiler
Dr. S. Aulwurm
Dr. S. Bock
Dr. G. Eisele
Dr. B. Greve
Dr. J. Hoppe
Dr. M. Mitsdörffer
C. Offenhäuser
PD Dr. M. Platten
M. Ronellenfitsch
K. M. Strauss
F. Tritschler
Dr. A. Wick

Technical staff

S. Altenberendt
U. Hamacher
S. Kautzmann
S. Pöschel
S. Barth
C. Herrmann
A. Klumpp
M. Schiffmann
B. Frank
M. Jahnke
U. Obermüller
G. von Kürthy

Medical Doctoral Students

M. Dürr
K. Horber
S. Röhrich
M. Wasmer
A. Hauser
C. Lange
A. Ryzhkova
B. Hertler
T. Lanz
M. Schubring-Giese

Neurogenerative Diseases

Director of the Department of Neurodegenerative Diseases

Prof. Dr. T. Gasser

Group leaders

Dr. F. Asmus
PD Dr. R. Krüger
PD Dr. D. Berg
Prof. Dr. L. Schöls
Prof. Dr. P. Kahle

Scientific staff

Dr. S. Breit
A. Di Santo
Dr. C. Globas
Dr. T. Hasegawa
K. Karle
Dr. I. Liepelt
Dr. W. Maetzler
R. Santiago
R. Schüle
M. Sharma
Dr. R. v. Coelln
I. Carbalo Carbajal
C. Fiesel
Dr. J. Godau
S. Horn
C. Klein
T. Lindig
Dr. N. Patenge
N. Schalamberidze
C. Schulte
Dr. W. Springer
J. Waak
D. Cebo
Dr. A. Gaenslen
Dr. S. Hansmann
Dr. C. Kamm
M. Lang
Dr. C. Linnemann
O. Rothfuss
C. Schiesling
Dr. K. Schweitzer
Dr. K. M. Strauss

Technical staff / Administration

C. Erhardt
S. Kautzmann
P. Leitner
A. Seibel
S. Eberle
U. Krauß
M. Munz
U. Wilhelm
M. Jeric
S. Kullmann
S. Schwarze

Medical Doctoral Students

N. Akbas
T. Brüssel
C. Fenske
T. Kukiolka
D. Madzar
J. Michelis
D. Schmid-Bielenberg
V. Siegert
C. Urban
A. Wendt
A. Wolpert
D. Baumann
D. Cerkez
P. Heide
J. Lehmann
C. Meiser
N. Röhrich;
R. Schäuffele
I. Swid
A. Vogel
A.-K. Wevers
G. Baysal
K. Czarkowski
S. Keller
A. Lüdke
A. Meyer
C. Schelling
C. Siefker
B. Unmuth
C.U. Wahl
B. Wolf

Cognitive Neurology / Hertie Institute Administration

Director of the Department of Cognitive Neurology

Prof. Dr. P. Thier

Group leaders

Dr. P. Dicke
PD Dr. T. Haarmeier
Dr. A. Nieder
Dr. F. Sultan
Dr. V. Gauck
Prof. Dr. U. Ilg
Dr. C. Pedroarena
PD Dr. M. Giese
Prof. Dr. Dr. H.-O. Karnath
PD Dr. C. Schwarz

Scientific staff

Dr. A. Casile
Dr. W. Ilg
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S. Bongard
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N. Daddaoua
F. Fleischer
S. Hamodeh
A. Ignashchenkova
M.-L. Lee
S. Materna
L. Omlor
B. Ritzinger
M. Stüttgen
O. Tudusciuc
Dr. N. Catz
Dr. J. Pomper
H. Becker
S. Borchers
V. Caggiano
B. de Haan
S. Freyberg
B. Händel
J. Jastorff
J. Mander
K. Merten
A.-N. Park
C. Roether
L. Ticini
K. Tziridis
Dr. M. Himmelbach
Dr. S. Richter
U. Biber
S. Bürgi
S. Dash
I. Diester
M. Fruhmann-Berger
E. Huberle
S. Kamphausen
A. Mandler
L. Misejova
M. Prsa
F. Sohn
I. Trigo-Damas
D. Vallentin

Technical staff / Administration

S. Bentz
D. Heller-Schmerold
R. Berndt
U. Pascht
U. Großhennig

Medical Doctoral Students

A. Meine
P. Szponik
I. Schmeh
C. Zrenner
M. Synofzik

Hertie Institute Administration

W. Pfaff (Business Manager)
F. Bunjes
B. Hoffmann
J. Oesterle

Cellular Neurology / Junior Research Group

Director of the Department of Cellular Neurology

Prof. Dr. M. Jucker

Group leaders / Project leaders

Dr. M. Calhoun
Dr. E. Kilger
Dr. T. Rasse
Dr. L. Stoltze

Scientific staff

T. Bolmont
J. Coomaraswamy
D. Eicke
Y. Eisele
P. Füger
S. Grathwohl
Dr. M. Herzig
T. Hug
J. Kern
S. Käser
A. Kuthiala
D. Lindau
C. Nordhammer
R. Radde
D. Rosenkranz
C. Thetard
B. Wegenast-Braun
Y. Tsai

Technical staff / Administration

S. Eberle
A. Fulgencio
B. Graus
I. Guhl
G. Kagels
E. Kohler
Dr. J. Odenthal
C. Schäfer

Medical Doctoral Students / Master Students

R. Beck
L. Behrends
C. Hünefeld
R. Kemner
U. Pfeiffer
L. Yu

Independent Research Group Leader

Dr. Dr. S. Di Giovanni

Scientific Staff

P. Gaub
Dr. T. Nguyen
E. Ninci
S. Steele
A. Tedeschi

General Neurology

Clinical Studies - Department of General Neurology

Multicenter studies (Tübingen as coordinating center):

NOA-08: Temozolomide (one week on/one week off) versus radiotherapy for first-line therapy of anaplastic astrocytoma and glioblastoma in the elderly: a randomized phase III study (Methvsalem) (phase III, recruitment ongoing)
Enrolled patients: 10 Investigators: M. Weller, W. Wick

Radiotherapy and concomitant low-dose Indometacin and temozolomide therapy and adjuvant temozolomide therapy (one week on/one week off) in newly diagnosed glioblastoma: a phase II study – UKT-05
Enrolled patients: 21 Investigators: M. Weller, W. Wick

Multicenter studies (Tübingen as participating center):

G-PCNSL-SG-1: Phase IV trial on the role of whole brain radiotherapy in the first-line treatment of primary CNS lymphoma using methotrexate (phase IV, recruitment ongoing)
Enrolled patients: 21 Investigators: U. Herrlinger, M. Weller

Glivec (imatinib mesylate) in combination with Litalir (hydroxourea) or Litalir alone as an oral therapy in temozolomide resistant progressive glioblastoma patients (phase III)
Enrolled patients: 18 Investigators: J. Steinbach, M. Weller

TransMID A phase III multicenter study of intratumoral/interstitial therapy with TransMID compared to best standard of care in patients with progressive and/or recurrent, non-resectable glioblastoma multiforme (phase II)
Enrolled patients: 3 Investigators: G. Eisele, G. Tabatabai, J. Steinbach, M. Weller

Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase III study (EORTC 22033/26033) (phase III, recruitment ongoing)
Enrolled patients: 5 Investigators: F. Schmidt, M. Weller, W. Wick

Cilengitide (EMD121 974) and temozolomide with concomitant radiation therapy, followed by cilengitide and temozolomide maintenance therapy in subjects with newly diagnosed glioblastoma. A multicenter, open-label, uncontrolled phase I/IIa study (phase I/IIa)
Enrolled patients: 4 Investigators: M. Hermisson, J. Steinbach, M. Weller

WX17798: CellCept® (mycophenolate mofetil) in Myasthenia Gravis: A prospective, randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of adjunct mycophenolate mofetil in Myasthenia Gravis. Sponsor: Aspreva Pharmaceuticals Corp. Rare Diseases Program (phase III, recruitment completed)
Enrolled patients: 3 Investigators: A. Melms

FREEDOMS; CFTY720D2301: A 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. Sponsor Novartis (phase III, recruitment ongoing)
Enrolled patients: 1 Investigators: R. Weissert

Clinical Studies - Department of Neurodegenerative Diseases

Ataxia

A phase III double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of Idebenone in the treatment of Friedreich's ataxia patients (phase III, recruitment ongoing)
Enrolled patients: 5 Investigators: L. Schöls, Ch. Linnemann

Parkinson's disease

A long term, double-blind, randomised parallel-group, carbidopa/levodopa controlled multicenter study to evaluate the effect of StaveloTM in patients with Parkinson's disease requiring initation of levodopa therapy (phase III, recruitment completed)
Enrolled patients: 10 Investigators: D. Berg, K. Schweitzer, A. Gaenslen, and co-workers

A randomised, double-blind, placebo-controlled dose-ranging study of the safety, tolerability and afficacy of E2007 in Parkinson's disease patients with "wearing-off" motor fluctuations and on-period dyskinesis (phase III, recruitment completed)
Enrolled patients: 5 Investigators: D. Berg, K. Schweitzer, and co-workers

A multicentre, randomized, double-blind, placebo controlled, parallel group study of the efficacy, safety and tolerability of E2007 in Levodpa treated Parkinson`s disease patients with motor fluctuations (phase III, recruitment completed)
Enrolled patients: 5 Investigators: D. Berg, K. Schweitzer, and co-workers

A multicenter, double-blind placebo-controlled, parallel-group study to assess Rasagiline as a disease modifying therapy in early Parkinson's disease subjects (phase IV, recruitment completed)
Enrolled patients: 15 Investigators: D. Berg, A. Gaenslen, A. Di Santo, and co-workers

A randomised, double-blind, placebo-controlled, parallel-group clinical trial to examine the efficacy and safety of early Pramipexole treatment versus delayed pramipexole treatment in patients with new onset Parkinson's disease (phase IV, recruitment ongoing)
Enrolled patients: 5 Investigators: D. Berg, A. Di Santo, A. Gaenslen, and co-workers

A study comprising a four-week randomised, double-blind, crossover comparison of Apomorphine Nasal Powder (2 and 4 mg) and Placebo Nasal Powder in the alleviation of acute episodes of motor symptoms associated with Parkinson's disease (phase II, recruitment ongoing)
Enrolled patients: 1 Investigators: D. Berg, J. Godau, A. Di Santo, and co-workers

Assessment of heartvalve fibrosis in patients with PD under dopaminergic treatment (recruitment ongoing)
Enrolled patients: 3 Investigators: D. Berg, K. Schweitzer, A. Gaenslen, and co-workers

An open, non-randomised, multinational, multicentre 6-week during study with direct switch to Stalevo in L-Dopa/DCCI-treated Parkinson´s disease Patients with early wearing. off to examine the efficacy and safety of Stalevo (phase IVb, recruitment ongoing)
Enrolled patients: 2 Investigators: D. Berg, A. Di Santo, J. Godau, A. Gaenslen, and co-workers

Neurodegenerative Diseases / Cognitive Neurology

Post marketing observational study on the effect of Rivastigmin in Parkinson's disease with dementia. Verlaufsbeobachtungsstudie Studie von Novartis (phase IVb, recruitment ongoing)
Enrolled patients: 3 Investigators: D. Berg, A.Di Santo, I Liepelt, and co-workers

Apomorphin - post marketing observational study in advanced Parkinson's disease (phase IVb, recruitment ongoing)
Enrolled patients: 5 Investigators: D. Berg, K.. Schweitzer, A. Gaenslen, and co-workers

Clinical Studies - Department of Cognitive Neurology

Learning-based quantitative analysis of neurological movement disorders (recruitment completed)
Enrolled patients: 60 Investigators: W. Ilg, H. Golla, M. Giese, P. Thier

An 80-week, randomized, multicenter, parallel-group, double-blind study of the efficacy and safety of atorvastatin 80 mg plus an acetylcholinesterase inhibitor versus an acetylcholinesterase inhibitor alone in the treatment of mild to moderate Alzheimer´s disease (phase II, recruitment ongoing)
Enrolled patients: 10 Investigators: H.-O. Karnath, T. Dehmer

Quantification of subtle movement changes in healthy subjects with increased echogenicity of the substantia nigra (phase I, recruitment ongoing)
Enrolled patients: 30 Investigators: W. Ilg, I. Liepelt, C. Urban, M. Giese, D. Berg

Third-Party Funding - Department of General Neurology

Cerebrale Mechanismen der auditiven Objekterkennung und der Sprachlautwahrnehmung: Funktionell-bildgebende Untersuchungen (SFB 550 B1)
Project leader H. Ackermann, W. Lutzenberger
Funding institution DFG
Funding period 01/06-12/08

Zerebrale Kontrolle der Sprechmotorik (fMRT) (AC 55/6-2, HA)
Project leader H. Ackermann
Funding institution DFG
Funding period 04/07-03/09

Neurorehabilitation
Project leader H. Ackermann
Funding institution Kooperationsvertrag Hohenurach
Funding period 01/07-12/11

Phonetische Fremdsprachenbegabung
Project leader H. Ackermann, W. Grodd
Funding institution DFG
Funding period 04/06-03/08

Charakterisierung autoreaktiver T-Zellen nach primärem und sekundärem Antigenkontakt (BI 603/5-1)
Project leader F. Bischof
Funding institution DFG
Funding period 11/05-10/07

Mechanisms of tolerance induction
Project leader F. Bischof, A. Melms
Funding institution Gemeinnützige Hertie-Stiftung
Funding period 05/04–04/06

Einfluss transkranieller Magnetstimulation auf Falschaussagen in der Tathergangsdiagnostik (BI 195/49-1)
Project leader N. Birbaumer, C. Gerloff, M. Lotze
Funding institution DFG
Funding period 12/04-11/06

The role of IKK2 in autoreactive lymphocytes: implications for the understanding of neurologic autoimmune diseases and therapeutic interventions (GR 1925/2-1)
Project leader B. Greve, R. Weissert
Funding institution DFG
Funding period 07/04–06/06

Cerebro-cerebelläre Kommunikation – Grundlage neurokognitiver Funktionen? (SFB 550, A2)
Project leader T. Haarmeier
Funding institution DFG
Funding period 01/06-12/08

General Neurology

Entwicklung neuronaler Repräsentationen nach Schlaganfall: Interaktion zwischen intakter und geschädigter Hemisphäre (SFB 550, C5)
Project leader Ch. Gerloff
Funding institution DFG
Funding period 01/06-03/06

Modulation interregionaler Kopplung - Neuronale Grundlagen visuomotorischer Integration und ihre Modulation durch neuronavigierte bifokale transkranielle Magnetstimulation (rTMS) (SFB 550, A13)
Project leader F. Hummel
Funding institution DFG
Funding period 01/06-12/08

Nachwuchsgruppe, Phosphatasen für motorisches Lernen
Project leader A. Luft
Funding institution IZKF
Funding period 03/05-03/08

Inhibitorische cortikale Mechanismen bei motorischem Lernen (SFB 550 C12)
Project leader A. Luft
Funding institution DFG
Funding period 01/06-12/08

Robotics for lower extremity rehabilitation
Project leader A. Luft
Funding institution VA, USA
Funding period 01/06-12/10

Procedural Learning after Stroke
Project leader A. Luft, O. Karnath
Funding institution Gemeinnützige Hertie-Stiftung
Funding period 10/06-09/07

Mechanismen der T-Zell-Toleranz und -Selektion im menschlichen Thymus
Project leader E. Tolosa
Funding institution Land BW Margarete v. Wrangell-Habilitations-programm für Frauen
Funding period 07/03-06/06

Checkpoints in the thymus for the control of autoimmunity: antigen processing and regulatory T cells (SFB 685 B5)
Project leader E. Tolosa, A. Melms
Funding institution DFG
Funding period 07/05-06/09

Heisenberg-Stipendium der DFG (WE 1947/4-1)
Project leader R. Weissert
Funding institution DFG
Funding period 08/02-07/07

General Neurology

Entwicklung einer Vakzine zur therapeutischen Induktion von T Helfer 2 Immunität bei Autoimmunerkrankungen (Verbundprojekt 1)
Project leader R. Weissert, F. Bischof
Funding institution IZKF
Funding period 07/04-06/07

Vakzinierung gegen Multiple Sklerose (Biochance Plus)
Project leader R. Weissert
Funding institution BMBF
Funding period 07/04-06/07

Immunogenicity and pathogenicity of self peptides eluted from central nervous system MHC molecules (WE 1947/5-1)
Project leader R. Weissert
Funding institution DFG
Funding period 12/04-11/07

Lentiviral transduzierte hämatopoietische Stammzellen als Vehikel für die Gentherapie experimenteller Gliome mit löslichen TGF-β-Rezeptoren (WE 1502/10-3)
Project leader M. Weller, W. Wick
Funding institution DFG
Funding period 10/04-09/06

IAP-Antagonismus als proapoptotisches Prinzip in der Behandlung maligner Gliome (10-2079-WE7)
Project leader M. Weller, U. Naumann
Funding institution Deutsche Krebshilfe
Funding period 10/03-09/06

CD70/CD27-abhängige Immunmodulation beim Glioblastom (2003.115.1)
Project leader M. Weller
Funding institution Wilhelm-Sander-Stiftung
Funding period 07/04-06/06

Novel targets for the molecular therapy of gliomas
Project leader M. Weller, W. Wick
Funding institution BMBF (NGFN2)
Funding period 09/04-08/06

Gliome. Molekulare Diagnostik und neue Therapieansätze
Project leader M. Weller
Funding institution Verbundprojekt der Deutschen Krebshilfe
Funding period 10/04-09/07

Etablierung adulter hämatopoetischer Stammzellen als Vehikel für die Therapie humaner Glioblastome
Project leader W. Wick, A. Wiesmann, M. Weller
Funding institution Verbundprojekt der Deutschen Krebshilfe
Funding period 06/03-05/08

General Neurology / Neurodegenerative Diseases

Glioblastomstammzellen
Project leader W. Wick
Funding institution Stiftung Sibylle Assmus
Funding period 10/05-09/06

Genetische Regulation von CTLA-4 und ICOS: Assoziation mit der Multiplen Sklerose (Fortüne 1392-1-0)
Project leader B. Greve
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 07/05-06/06

Die Bedeutung von Immunsemaphorinen für die Entstehung von Autoimmunerkrankungen im Zentralen Nervensystem (Fortüne 1311760)
Project leader F. Bischof
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 06/06-05/07

Characterization of the cystein protease cathepsin W and its functional role in cytotoxicity (Fortüne 1498-0-0)
Project leader E. Tolosa
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 03/06-02/07

Third-Party Funding - Department of Neurodegenerative Diseases

EST: Early-stage training: Molecular mechanisms of Neurodegeneration
Project leader T. Gasser
Funding institution EU
Funding period 04/06-03/08

German Network of Hereditary Movement Disorders (GeNeMove): Dystonia (01GM0304)
Project leader T. Gasser
Funding institution BMBF
Funding period 05/06-04/09

Competence Network Parkinson's diasease: DNA-Bank (01GI0401)
Project leader T. Gasser
Funding institution BMBF
Funding period 09/06-03/08

Neurodegenerative Diseases

Benchmarking-Depression in Parkinson's disease
Project leader T. Gasser, D. Berg
Funding institution BMBF
Funding period 03/05-02/07

BioProfile: Generation of Neuronal Stem Cells (0313700)
Project leader T. Gasser
Funding institution BMBF
Funding period 10/05-09/07

National Genome Research Network (NGFN2): Identification of Genetic Risk Factors for Parkinson's Disease (01GI0201)
Project leader T. Gasser / D. Berg
Funding institution BMBF
Funding period 08/04-07/07

Ausbildungsstipendium Klinische Parkinsonforschung
Project leader T. Gasser, D. Berg
Funding institution Deutsche Parkinsonvereinigung
Funding period 02/04-10/07

Biomarker Award
Project leader D. Berg
Funding institution Michael J. Fox Foundation
Funding period 06/05-05/07

Rivastigmin (Exelon®) zur Behandlung der Demenz bei Patienten mit Progressiver Supranukleärer Blickparese
Project leader D. Berg
Funding institution Novartis
Funding period 12/06-12/07

Bildgebung von Amyloid-Ablagerung im Gehirn von PatienInnen mit Alzheimer Erkrankung, Lewykörper-Demenz, Parkinson-Erkrankung mit Demenz oder Zerebraler Amyloidangiopathie in vivo mittels Positronen-Emissions-Tomographie
Project leader W. Maetzler, D. Berg
Funding institution AKF, Nr. 201-0-0
Funding period 12/06-12/07

Identifizierung und Validierung von Parkinson-Genen mit funktioneller Genomik in Zellkultur und Tiermodellen (N1NV-S31T09)
Project leader P. Kahle
Funding institution BMBF
Funding period 08/04-07/07

Neurodegenerative Diseases

Transgenic α-Synuclein Expression in Oligodendrocytes: In vivo Models of Multiple System Atrophy (SFB596 TP A01)
Project leader P. Kahle
Funding institution DFG
Funding period 07/04-09/07

Animal Models for Recessive Hereditary Parkinson's Disease Caused by DJ-1 Mutations (SFB596 TP A12)
Project leader W. Wurst / P. Kahle
Funding institution DFG
Funding period 07/04-06/08

Congruent Mechanisms of Neuroprotection Mediated by Recessive Parkinson's Disease Genes
Project leader P. Kahle
Funding institution Novartis Pharma
Funding period 08/06-07/08

Funktionelle Charakterisierung der pathogenetischen Bedeutung von Mutationen im Neurofilament-M und –H Gen beim idiopathischen Parkinson-Syndrome (KR 2119/1-1)
Project leader R. Krüger
Funding institution DFG
Funding period 05/04-04/06

Generierung transgener Omi/HtrA2-Mauslinien (Fortüne 1311743)
Project leader R. Krüger
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 12/05-12/06

Funktionelle Charakterisierung von Mutationen im Omi/HtrA2 Gen beim Parkinson-Syndrom (KR 2119/3-1)
Project leader R. Krüger
Funding institution DFG
Funding period 09/06-08/08

Generierung transgener Mauslinien zur funktionellen Charaktierisierung einer neu identifizierten G399S Mutation im Omi/HtrA2 Gen bei der Parkinson-Krankheit (F1311743)
Project leader R. Krüger
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 09/06-08/08

LEAPS Validation study
Project leader R. Krüger, T. Gasser, O. Riess
Funding institution Michael J. Fox Foundation
Funding period 08/05-03/06

Neurodegenerative Diseases

Deciphering molecular pathways of monogenic forms of Parkinson disease by cell culture and animal models (01GS0468_TP 8.2.2)
Project leader R. Krüger, O. Riess, J.B. Schulz
Funding institution BMBF (NGFN2)
Funding period 09/04-08/07

GeNeMove: Hereditary Spastic Paraplegia (01GM0304)
Project leader L. Schöls
Funding institution BMBF
Funding period 10/03-09/08

Leukonet: Clinical, neurophysiological and neuroradiological characterization of leukodystrophies in adulthood (01GM0309)
Project leader L. Schöls
Funding institution BMBF
Funding period 10/03-09/08

EUROSCA: SpinoCerebellar Ataxia Registry (EUROSCA-R) and Core Assessment for Interventional Therapies (CAPIT-SCA) (LSHM-CT-2004-503304)
Project leader L. Schöls
Funding institution EU
Funding period 01/04-12/08

Subprocesses of human executive functions and their relation to genotypes in the dopaminergic system (I/80711)
Project leader L. Schöls
Funding institution Volkswagen Foundation
Funding period 07/05-06/07

Funktionelle und strukturelle Charakterisierung der Basalganglien bei den Spinozerebellären Ataxien Typ 2 und Typ 3 (Sch0754/3-1)
Project leader L. Schöls
Funding institution DFG
Funding period 09/05-08/07

Klonierung des Gens für eine neue Form der autosomal dominanten spastischen Spinalparalyse (Sch0754/4-1)
Project leader L. Schöls
Funding institution DFG
Funding period 07/06-06/08

Anästhesie bei Ataxie-Erkrankungen
Project leader L. Schöls
Funding institution Deutsche Heredo-Ataxie-Gesellschaft (DHAG)
Funding period 01/06-12/06

Cognitive Neurology

Third-Party Funding - Department of Cognitive Neurology

Action representation and learning (I/76 556)
Project leader M. Giese
Funding institution VW Foundation
Funding period 06/01-05/07

Quantitative assessment and theoretical modeling of the visual tuning properties of canonical and mirror neurons in the monkey cortical premotor area F5 (SFB 550, C10)
Project leaders M. Giese, P. Thier
Funding institution DFG
Funding period 01/06-12/08

The expression of emotions through bodily movements (RGP54/2004)
Project leader M. Giese
Funding institution HFSO
Funding period 10/04-09/07

Learning of structured trajectory models with high flexibility for computer animation (GI 305/2-1)
Project leader M. Giese
Funding institution DFG
Funding period 01/06-12/07

Peract: Marie Curie Training Site "Perception and action in space." Project: Sensorimotor integration (MEST-CT-2004-504321)
Project leader U. Ilg
Funding institution EC
Funding period 08/04-07/08

Geschwindigkeitsillusion und deren zentralnervöse Grundlagen (IL 34/6-1)
Project leader U. Ilg
Funding institution DFG
Funding period 09/06-08/08

Störungen motorischen Handelns nach Schädigungen des parietalen und des temporalen Cortex beim Menschen (SFB 550, A4)
Project leader H.-O. Karnath
Funding institution DFG
Funding period 01/00-12/08

Peract: Marie Curie Training Site "Perception and action in space." Project: Spatial reference frames (MEST-CT-2004-504321)
Project leader H.-O. Karnath
Funding institution EC
Funding period 08/04-07/08

Neural correlates of spatio-temporal impairments of conscious visual processing (d/05/54042)
Project leader H.-O. Karnath
Funding institution DAAD Vigoni-Program
Funding period 01/06-12/07

Cognitive Neurology

Neuronale Mechanismen der Bildung numerischer Kategorien und Konzepte bei Affen (SFB 550, C11)
Project leader A. Nieder
Funding institution DFG
Funding period 01/03-12/08

Career Development Award (CDA 0038/2004-C)
Project leader A. Nieder
Funding institution HFSO
Funding period 01/05-12/07

The neural coding of numerical, spatial and sensory magnitudes in the human and non-human primate brain (I/81 035)
Project leader A. Nieder
Funding institution VW Foundation
Funding period 12/05-11/08

Kontrolle von Armbewegungen bei Kindern und der Zusammenhang zur Entwicklung visuell-räumlicher Fähigkeiten (RI 1215/2-1)
Project leader S. Richter
Funding institution DFG
Funding period 04/05-03/07

Aktive Bewegung als Grundlage der Texturdiskrimination. Psychophysikalische und elektrophysiologische Untersuchungen der bewegungsabhängigen Modulation von taktiler Wahrnehmung im Vibrissensystem der Ratte (SFB 550, B11)
Project leader C. Schwarz
Funding institution DFG
Funding period 01/06-12/08

Mikrostimulationsgetriggertes fMRI als Werkzeug zur Charakterisierung cerebello-cerebraler Schleifen (SFB 550, A9)
Project leader F. Sultan
Funding institution DFG
Funding period 01/03-12/08

Setup and maintenance of the Dept. Cognitive Neurology (TS 013/01.184/98)
Project leader P. Thier
Funding institution Schilling Foundation
Funding period 07/00-06/10

Ponto-cerebelläre Grundlagen zielgerichteten Agierens im Raum (SFB 550, A7)
Project leader P. Thier
Funding institution DFG
Funding period 01/00-12/08

Service and special functions (SFB 550, D1)
Project leader P. Thier
Funding institution DFG
Funding period 01/00-12/08

Cognitive Neurology

Peract: Marie Curie Training Site "Perception and action in space." Project: Cortico-cerebellar interplay (MEST-CT-2004-504321)
Project leader P. Thier
Funding institution EC
Funding period 08/04-07/08

Sensoprim: Marie Curie Training Site "Sensory information processing in non-human primates." (MEST-CT-2004-07825)
Project leader P. Thier
Funding institution EC
Funding period 07/04-06/08

3 Ts magnetic resonance scanner for functional imaging (Th 812/1-1)
Project leader P. Thier
Funding institution DFG
Funding period as of 2002

Von Helmholtz's missing reference signals: Do they reflect an adapting action of the cerebellum on the cerebral cortex? (I80 727)
Project leader P. Thier
Funding institution VW Foundation
Funding period 09/05-08/08

Die Bedeutung der Blickrichtung für soziale Kognition: Die neurobiologische Basis für Autismus (01GA0503)
Project leader P. Thier
Funding institution BMBF
Funding period 07/05-06/08

Geschwindigkeitsillusion und deren zentralnervöse Grundlagen (fortüne 1312030)
Project leader U. Ilg
Funding institution Medical Faculty
Funding period 07/06-09/06

Third-Party Funding - Department of Cellular Neurology

APOPIS
Project leader M. Jucker
Funding institution EU-FP6/BBW
Funding period 01/04-12/06

NGFN-2 - Functional Genome Research for Human Health (01GS0468)
Project leader M. Jucker
Funding institution BMBF / DLR
Funding period 08/04-05/08

Generation of APP transgenic mice
Project leader M. Jucker
Funding institution Koesler
Funding period 01/05-12/07

Anti beta-amyloid 'anticalins' as a promising therapeutic and specific approach to treat Alzheimer's disease ARREST-AD (01GU0522)
Project leader M. Jucker
Funding institution BMBF / DLR
Funding period 10/05-09/08

Autophagie und chronische Erkrankungen
Project leader M. Jucker, L. Stoltze
Funding institution FSP des Landes Baden-Württemberg
Funding period 03/06–02/08

Exogenous induction of cerebral amyloidogenesis (ZEN-06-27341)
Project leader M. Jucker
Funding institution Alzheimer's Association USA
Funding period 08/06 – 07/08

Two-photon microscopy for in vivo application
Project leader M. Jucker, M. Calhoun
Funding institution Leica Microsystems
Funding period 01/06–12/08

Learning-related gene expression in cortical systems: the impact of vascular and parenchymal amyloid (CA 477/1-2)
Project leader M. Calhoun
Funding institution DFG
Funding period 06/05-10/07

Relational memory and learning-related gene induction in AD mouse models (IRG-05-13464)
Project leader M. Calhoun
Funding institution Alzheimer's Association USA
Funding period 10/05-09/08

Cellular Neurology

A new model for investigating the role of the human immune system in Alzheimer's disease (Thyssen 10.05.2.193)
Project leader L. Stoltze
Funding institution Fritz Thyssen Stiftung
Funding period 11/05-10/07

Charakterisierung der Rolle von T-Zellen in der Alzheimer-Erkrankung (Fortüne 1516-0-0)
Project leader L. Stoltze
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 12/05-11/06

Regulation der Genexpression durch die APP-interzell. Domäne (AICD) und Fe65 (Fortüne 1495-0-0)
Project leader E. Kilger
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 11/05-10/06

Molecular mechanisms controlling synaptic stability (Fortüne 1314025)
Project leader T. Rasse
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 11/06-02/07

Lern-assoziierte Genexpression in transgenen Mausmodellen der Alzheimer Krankheit (scholarship)
Project leader B. Wegenast-Braun
Funding institution Studienstiftung des deutschen Volkes
Funding period 06/05-06/07

Modelling AD in mice with human immune system (scholarship)
Project leader D. Lindau
Funding institution Boehringer Ingelheim
Funding period 08/05-07/07

Alzheimer: 100 Years and Beyond Symposium
Project leader M. Jucker
Funding institution Fondation Ipsen, Breuer-Stiftung, Gemeinnützige Hertie-Stiftung
Funding period 11/05-11/06

Alzheimer: 100 Years and Beyond Symposium
Project leader M. Jucker
Funding institution DFG
Funding period 11/05-11/06

Alzheimer: 100 Years and Beyond Symposium
Project leader M. Jucker
Funding institution Abbott, Boehringer Ingelheim, Eisai/Pfizer, Elan Pharmaceuticals, Hoffmann-La Roche, Novartis
Funding period 11/05-11/06

Publications - Department of General Neurology

Original Articles

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General Neurology

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Neurodegenerative Diseases

Publications - Department of Neurodegenerative Diseases

Original Articles

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Cognitive Neurology / Cellular Neurology

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Original Articles

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Herzig MC, van Nostrand WE, **Jucker M** (2006) Mechanism of cerebral ß-amyloid angiopathy: Murine and cellular models. Brain Pathol 16:40-54

Meyer-Luehmann M, Coomaraswamy J, Bolmont T, Kaeser S, Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret J, Paganetti P, Walsh DM, Mathews P, Ghiso J, Staufenbiel M, Walker L, **Jucker M** (2006) Exogenous induction of Ab-amyloidogenesis is governed by agent and host. Science 313:1781-4

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Pickford F, **Coomaraswamy J, Jucker M**, McGowan E (2006) Modeling familial British dementia in transgenic mice. Brain Pathol 16:80-5

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Jucker M (2006) The neuronal origin hypothesis of cerebral amyloid angiopathy. In: Jucker M, Beyreuther K, Haass C, Nitsch R, Christen Y (eds) Alzheimer: 100 Years and Beyond. Springer Verlag Berlin Heidelberg, 220-3

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Review

Di Giovanni S (2006) Regeneration following Spinal Cord Injury, from experimental models to humans: where are we? Expert Opinion on Therapeutic Targets. 10(3):363-76.

General Neurology

Awards - Department of General Neurology

A. Luft
Alois-Kornmüller Award, Deutsche Gesellschaft für Klinische Neurophysiologie

A. Luft
Commerzbank-Preis

F. Bischof
TEVA Neuroscience Award FOCIS, San Francisco

Habilitations

A. Luft
General Neurology – Plasticity of the Motor System as Basis for Recovery of Motor Function after Stroke

Appointments

C. Gerloff
W3-Professorship, Hamburg

U. Herrlinger
W2-Professorship, Bonn

R. Weissert
W2-Professorship, Düsseldorf; offer declined

W. Wick
W3-Professorship, Heidelberg

PhD Theses

M.M. Buitrago
Cortical Mechanisms of Motor Learning: behavioral, molecular and electrophysiological studies
(Faculty of Biology)
Supervisor: A. Luft

P. Schnorrer
Characterization of crosspresentation and Cystatin C biology in dendritic cells
(Faculty of Biology)
Supervisors: A. Melms, H-G. Rammensee

C. Luther
Impaired function of CD4+ FOXP3+ regulatory T cells in patients with myasthenia gravis
(Faculty of Biology)
Supervisors: A. Melms, H-G. Rammensee

General Neurology / Neurodegenerative Diseases

U. Feger
Phenotypische und funktionelle Charakterisierung HLA-G-exprimierender T-Zellen
(Faculty of Biology)
Supervisors: A. Melms, H-G. Rammensee

Medical Thesis

Janna-Carolin Fischer
Die PCV-Polychemotherapie bei Rezidiven maligner Gliome- eine retrospektive Analyse von 122 Krankheitsverläufen
(Medical Faculty)
Supervisor: M. Weller

Diploma

C. Netzer
Die Bedeutung von immunologischem Gedächtnis für die Entwicklung von Autoimmunität im Zentralen Nervensystem
Supervisor: F. Bischof

M. Rautenberg
Generierung und Testung von DNA Vakzinen bei der experimentellen autoimmunen Enzephalomyelitis
Supervisor: R. Weissert

K. Steinbach
Immunosemaphorine in der Entstehung von Autoimmunität im ZNS
Supervisors: F. Bischof, S. Stevanovic

Kerstin Stuck
Virale Infektionen bei der MS
Supervisor: R. Weissert

Awards - Department of Neurodegenerative Diseases

T. Hasegawa
Postdoctoral Fellowship, Alexander von Humboldt Foundation

K. Holmström
Graduate Fellowship, NEUROTRAIN European Early Stage Research Training Programme

N. Klatt
Educational Stipend, Stiftung Begabtenförderungswerk für berufliche Bildung, German Ministry for Education and Research

J. Waak
Travel Award, International Brain Research Organisation, World Congress of Neuroschience, Melbourne, Australia

Neurodegenerative Disease / Cognitive Neurology

Patents

R. Krüger
Deutsche Patenterteilung Nr. 102004004924, Antrag vom 28.01.2004,
Bezeichnung: A141S und G399S Mutationen im Omi/HtrA2 Protein bei Morbus Parkinson

Appointments

T. Gasser
Chair of the Department of Neurology, Technical University, Munich; offer declined.

Medical Theses

C. Siefker
Echogenicity of the Substantia nigra assessed by Transcranial Sonography in Elderly People and Parkinson Patients: Correlation with Clinical and Epidemiological Data
(Medical Faculty)
Supervisor: Daniela Berg

N. Akbas
Mutationsanalysis of the HFE-Gene using DHPLC in Patients with Hemochromatosis and Parkinson's Disease
(Medical Faculty)
Supervisor: Daniela Berg

Awards - Department of Cognitive Neurology

U. Ilg
Teaching Award 2006 of the Graduate School of Neural and Behavioural Sciences

E. Huberle, K. Seymour, C. Altmann, H-O. Karnath
Poster Award of the Deutsche Gesellschaft für Neurologie

E. Huberle
Carl Liebermeister Award of the Medical Faculty, Tübingen and the Interdisciplinary Center for Clinical Research

Habilitations

M. Giese
Informatics (University of Ulm) – Learning-based Representations of Complex Body Movements: Studies in Brains and Machines

Cognitive Neurology

Appointments

M. Giese
Senior Lecturer, University of Wales, Bangor

H.-O. Karnath
Chair of the Department of Medical Psychology, University of Düsseldorf, Düsseldorf; offer declined

PhD Theses

N. Catz
Cerebellar mechanisms underlying saccadic plasticity
(Graduate School for Neural and Behavioural Sciences)
Supervisor: P. Thier

H. Dietrich
Functional magnetic resonance imaging in alert behaving monkeys
(Graduate School for Neural and Behavioural Sciences)
Supervisor: P. Thier

J. Jastorff
Neural mechanisms for the learning of biological motion and actions
(Graduate School for Neural and Behavioural Sciences)
Supervisor: M. Giese

L. Johannsen
Disordered perception of own body orientation and postural control in stroke patients
(Graduate School for Neural and Behavioural Sciences)
Supervisor: H.-O. Karnath

A. Tikhonov
MEG correlates of perceptual stability in man
(Graduate School for Neural and Behavioural Sciences)
Supervisor: P. Thier

Medical Theses

E. Huberle
Spatial and temporal properties of shape processing in the human visual cortex
(Medical Faculty)
Supervisor: H.-O. Karnath

S. Kamphausen
Functional architecture of the cerebellar nuclei: Investigations of membrane physiology, morphology, and glycinergic synaptic transmission of cerebellar nuclei neurons
(Medical Faculty)
Supervisor: C. Schwarz

Cognitive Neurology / Cellular Neurology

Diploma

U. Biber
Initiierung von Augenfolgebewegungen
Supervisor: U. Ilg

A. Mandler
Augenbewegungen beim Lesen bewegter Texte
Supervisor: U. Ilg

Awards

M. Jucker
Deutschland – 365 Orte im Land der Ideen
100 Jahre Alzheimerforschung – 2. November 2006

M. Jucker
ZENITH Award 2006, Alzheimer Association USA

PhD Thesis

Tristan Bolmont
Mechanisms underlying the initiation of cerebral betaamyloidosis and neurofibrillary tau pathology: New insights from transgenic mice
(Faculty of Philosophy, University of Basel)
Supervisor: M. Jucker

Diploma

J. Salih
Analysen des Ubiquitin-Proteasom-Systems in einem transgenen Mausmodell der Alzheimer Krankheit
Supervisor: M. Jucker

Zhenyu-Gao
Hippocampal aging in mice: Modifier loci control occurrence of granular inclusion bodies in aged mice
Supervisor: M. Jucker

Uli Pfeiffer
The orbital prefrontal cortex of the mouse mediates extradimensional set-shifting: comparison of activation profiles of the immediate early gene Arc across subregions of the prefrontal cortex
Supervisor: M. Calhoun

Lectures

Lectures - Summer Term 2006

Principles of Neurology
Medical School
Prof. M. Weller, PD Dr. W. Wick

Introduction to Clinical Neurology
Medical School
Prof. M. Weller

Curriculum "Intracranial Pressure"
Medical School
Prof. A. Melms, PD Dr. A. Luft, PD Dr. J. Steinbach, Prof. M. Meyermann, PD Dr. T. Nägele, PD Dr. B. Will

Genetic and Molecular Basis of Neural Disease
Graduate School for Neural and Behavioural Sciences
Prof. M. Jucker, Prof. T. Gasser, PD Dr. A. Luft, Prof. M. Weller

Cellular and Molecular Biology of Neurons
Graduate School for Neural and Behavioural Sciences
Dr. N. Patenge

Methods in Molecular Neurobiology
Graduate School for Neural and Behavioural Sciences
Dr. F. Asmus, Dr. C. Kamm, Dr. N. Patenge

Behaviour and Cognition: Communication and Social Cognition
Graduate School for Neural and Behavioural Sciences
Dr. A. Nieder

Behaviour and Cognition: Visual Perception
Graduate School for Neural and Behavioural Sciences
Dr. M. Giese

Behaviour and Cognition: Neuropsychology
Graduate School for Neural and Behavioural Sciences
Prof. H.-O. Karnath

Fundamentals of Sensorimotor Integration
Faculty of Biology and Graduate School for Neural and Behavioural Sciences
Prof. Dr. U. Ilg

Neurodegenerative Disorders
Contribution to interdisciplinary lecture series: "Medicine of aging"
Prof. Dr. T. Gasser

Lectures / Seminars and Courses

Lectures - Winter Term 2006/2007

Principles of Neurology
Medical School
Prof. M. Weller, PD Dr. W. Wick

Introduction to Clinical Neurology
Medical School
Prof. M. Weller

Molecular and Cellular Biology
Graduate School for Neural and Behavioural Sciences
Dr. N. Patenge

Motor Systems
Graduate School for Neural and Behavioural Sciences
Prof. P. Thier

Neurophysiology
Graduate School for Neural and Behavioural Sciences
PD Dr. C. Schwarz, Dr. N. Pedroarena

Nerve Regeneration and Repair
Graduate School for Neural and Behavioural Sciences
Dr. S. Di Giovanni

Seminars and Courses - Summer Term 2006

Neurological Examination
Medical School
Prof. M. Weller, Prof. W. Wick, PD Dr. T. Haarmeier
and staff of the Departments of General Neurology and Neurodegenerative Diseases

Neurology Seminar and Bedside Teaching
Medical School
Prof. T. Gasser, Prof. L. Schöls, PD Dr. T. Haarmeier, Prof. M. Wick

Introduction to Clinical Medicine
Medical School
Prof. A. Melms, PD Dr. J. Steinbach

Contributions to i-KliC „Intracranial Pressure/Stroke“
Medical School
Prof. A. Melms, PD Dr. A. Luft, PD Dr. W. Wick

Seminars and Courses

Contributions to i-KliC „Hepatology, Infectious Diseases and Rheumatology"
Medical School
Prof. A. Melms

TüKliS „Treatment of Neurological Disorders/Case Presentations"
Medical School
PD Dr. D. Berg, PD Dr. T. Haarmeier, PD Dr. R. Krüger, Prof. A. Melms, Prof. L. Schöls, PD Dr. J. Steinbach, Prof. M. Weller, Prof. W. Wick

TüKliS "Bedside Teaching"
Medical School
Prof. A. Melms

TüKliS "Imaging Techniques in Neurosciences"
Medical School
PD Dr. D. Berg

TüKliS „Movement Disorders"
Medical School
Prof. T. Gasser, PD Dr. D. Berg, Prof. L. Schöls

TüKliF „Trinucleotide Repeat Disorders"
Medical School
Prof. L. Schöls, Dr. T. Schmidt, Dr. P. Bauer

TüKliF „Immune Status of the Brain"
Medical School
Prof. R. Weissert

Current Problems in Diagnosis and Treatment of Neurodegenerative Disorders
Medical School
Prof. T. Gasser, Prof. L. Schöls

Current Trends in Neuro-oncology
Medical School
PD Dr. U. Naumann, Prof. M. Weller

Interdisciplinary Brain Tumor Seminar (in cooperation with the Departments for Neurosurgery, Neuroradiology, and Radiooncology)
Medical School
PD Dr. J. Steinbach, Prof. M. Weller, Prof. W. Wick

Neuroscience Lecture Series
Medical School
Prof. M. Weller, Prof. W. Wick

Neuropathological Case Presentation (in cooperation with the Institute for Brain Research)
Medical School
PD Dr. J. Steinbach, Prof. M. Weller

Seminars and Courses

Interdisciplinary Pain Seminar (in cooperation with the Clinic for Anaethesiology and Clinic for Neurosurgery)
Medical School
PD Dr. J. Steinbach

Research Seminar Experimental Neuroimmunology
Medical School
Prof. R. Weissert

Journal Club Neuroimmunology
Medical School
Dr. K. de Graaf, Prof. A. Melms, Dr. E. Tolosa, Prof. R. Weissert

Research Seminar Experimental Neurogenetics
Medical School
Prof. T. Gasser, Prof. L. Schöls, PD Dr. D. Berg, Dr. F. Asmus, Dr. N. Patenge

Neurobiologisches Montagskolloquium
Medical School
Prof. U. Ilg, Prof. P. Thier

Current Problems of Sensorimotor Integration
Medical School
Prof. U. Ilg, PD Dr. J. Schwarz, Prof. P. Thier

Current Problems in Neuropsychology
Medical School
Prof. H.-O. Karnath

Neurobiology of the Cerebellum
Medical School
Dr. P. Dicke, PD Dr. C. Schwarz, Prof. P. Thier

Executive Functions and the Frontal Lobe
Graduate School for Neural and Behavioural Sciences
Dr. A. Nieder

Brain Slices as Tools in Neurobiology
Graduate School for Neural and Behavioural Sciences
PD Dr. C. Schwarz, Prof. P. Thier, Dr. C. Pedroarena

GKKN Graduate Research Training Program on Cognitive Neurobiology
Graduate Research Training Program on Cognitive Neurobiology
Prof. H.-P. Karnath

Neurokolloquium Tübingen
SFB 550, Hertie Institute for Clinical Brain Research, MPI for Biological Cybernetics, Graduate School for Neural and Behavioural Sciences
Prof. P. Thier

Seminars and Courses

Current Concepts in Oculomotor Function
Faculty of Biology
Prof. U. Ilg

Tierphysiologischer Kurs Bioinformatik
Faculty of Biology
Prof. U. Ilg

Pharmacotherapy of Parkinson's Disease
Contribution to interdisciplinary lecture series: "Pharmacology"
Prof. L. Schöls

Seminars and Courses - Winter Term 2006/2007

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TüKliS "Bedside Teaching"
Medical School
Prof. A. Melms

TüKliS "Imaging Techniques in Neurosciences"
Medical School
PD Dr. D. Berg

TüKliS „Clinical Neurogenetics"
Medical School
Prof. L. Schöls, PD Dr. D. Berg, Prof. T. Gasser

Seminars and Courses

TüKliF „Immune Status of the Brain"
Medical School
Prof. R. Weissert

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Prof. T. Gasser, Prof. L. Schöls

Current Trends in Neuro-Oncology
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Interdisciplinary Brain Tumor Seminar
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Medical School
Prof. R. Weissert

Journal Club Neuroimmunology
Medical School
Dr. K. de Graaf, Prof. A. Melms, Dr. E. Tolosa, Prof. R. Weissert

Research Seminar Experimental Neurogenetics
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Prof. T. Gasser, Prof. L. Schöls, PD Dr. D. Berg, Dr. F. Asmus, Dr. N. Patenge

Neurobiologisches Montagskolloquium
Medical School
Prof. U. Ilg, Prof. P. Thier

Current Problems of Sensorimotor Integration
Medical School
Prof. U. Ilg, PD Dr. J. Schwarz, Prof. P. Thier

Seminars and Courses / Lab Rotations

Current Problems in Neuropsychology
Medical School
Prof. H.-O. Karnath

Neurobiology of the Cerebellum
Medical School
Dr. P. Dicke, PD Dr. C. Schwarz, Prof. P. Thier

Clinical Neuropsychology
Medical school
Prof. H.-O. Karnath

Practical Course 'Sensomotorik'
Medical School, Graduate School for Neural and Behavioural Sciences
Dr. C. Braun, Prof. U. Ilg, Dr. A. Nieder, Prof. P. Thier, Dr. A. Werner

Practical Course 'Motor Unit'
Graduate School for Neural and Behavioural Sciences
Dr. Beykirch, Prof. U. Ilg, PD. Dr. C. Schwarz, Prof. P. Thier

Neurokolloquium Tübingen
SFB 550, Hertie Institute for Clinical Brain Research, MPI for Biological Cybernetics, Graduate School for Neural and Behavioural Sciences
Prof. P. Thier

Current Concepts in Oculomotor Function
Faculty of Biology
Prof. U. Ilg

Practical Course 'Animal Physiology'
Faculty of Biology
Prof. U. Ilg, Dr. A. Nieder

Lab Rotations - Summer Term 2006

Graduate School for Neural and Behavioural Sciences
Dr. F. Asmus, Dr. M. Giese, Dr. C. Kamm, Dr. A. Luft, Dr. N. Patenge, Dr. C. Pedroarena

Faculty of Biology
Prof. R. Weissert

Lab Rotations - Winter Term 2006/2007

Graduate School for Neural and Behavioural Sciences
Dr. F. Asmus, Dr. C. Kamm, Dr. N. Patenge, Dr. C. Pedroarena

Faculty of Biology
Prof. R. Weissert

Scientific Conferences - Department of General Neurology

3. Tübinger Tagung: Therapie maligner Gliome - Standards und Perspektiven
Tübingen, March 17-18, 2006
M. Weller, W. Wick

Multiple Sclerosis - Pathogenesis and Novel Therapeutic Strategies
Tübingen, May 17, 2006
A. Melms, M. Platten, R. Weissert, W. Wick

The Neurobiology of Eye Movements - Looking Back and Forth
Tübingen, July 28, 2006
T. Haarmeier

Erkennen, Lokalisieren, Handeln
Tübingen, October 1-3, 2006
A. Luft, L. Schöls, M. Giese, D. F. Hanley

Scientific Conference - Department of Neurodegenerative Diseases

Kyoto, 2006: Transcranial echosonography
Skills Workshop at the 10th International Congress of Parkinson's Disease and Movement Disorders;
D. Berg

Scientific Conferences - Department of Cognitive Neurology

The Legacy of Santiago Ramón y Cajal: Different kinds of grey matter and their functional significance.
Tübingen, June 17-19, 2006
N. Logothetis, A. Schüz, F. Sultan

Numerical competence in primates: from non-verbal precursors to symbolic representations.
Vienna, Symposium at the Forum of European Neuroscience (FENS), July 8-12, 2006
A. Nieder

Dynamical motion processing: new insights into the neuronal machinery.
Vienna, Symposium at the Forum of European Neuroscience (FENS), July 8-12, 2006
U. Ilg, G. Masson

Was leisten moderne Neuroimaging-Verfahren?
Mannheim, Symposium at the 79. Kongress der Deutschen Gesellschaft für Neurologie (DGN), 2006
H-O Karnath, C. Büchel

Scientific Conference - Department of Cellular Neurology

Alzheimer: 100 Years and Beyond
Tübingen, November 2-5, 2006
M. Jucker, S. Eberle

Leitung

Prof. Dr. med. M. Weller
PD Dr. med. W. Wick

Anmeldung

PD Dr. Wolfgang Wick
Abteilung für Allgemeine Neurologie
Hertie-Institut für Klinische Hirnforschung
Universität Tübingen
Hoppe-Seyler-Str. 3
72076 Tübingen
Telefon: + 49 (70 71) 29-8 21 41 (Zentrale)
+ 49 (70 71) 29-8 04 16 (Büro)
+ 49 (70 71) 29-8 20 49 (Sekretariat, Frau Marterer)

Veranstaltungsort

CRONA Klinikum Schnarrenberg
Grosser Hörsaal (HS 210)
Hoppe-Seyler-Str. 3
72076 Tübingen

Datum

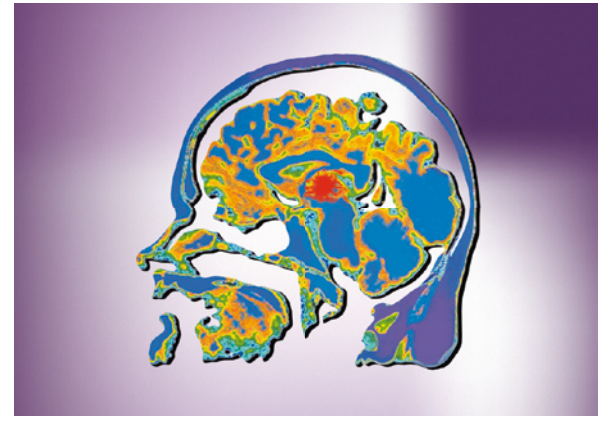
Beginn: Freitag, 17. März 2006, 14:00
Ende: Samstag, 18. März 2006, 13:00

Mit freundlicher Unterstützung der
***essex** pharma* GmbH

essex pharma

Vorläufiges Programm

3. Tübinger Tagung
Therapie maligner Gliome



Standards und Perspektiven
State of the Art Symposium

17.–18. März 2006
in Tübingen

Eberhard-Karls-Universität UKT Universitätsklinikum Tübingen

Südwestdeutsches Tumorzentrum
Comprehensive Cancer Center Tübingen

Freitag, 17. März 2006

Grundlagen
Vorsitz: R. Meyermann

14:00 Begrüßung
M. Weller

14:10–14:40 WHO-Klassifikation der Gliome: was muss in der nächsten Revision geändert werden?
G. Reifenberger

14:40–15:00 Klinische Strategien der EGFR Inhibition: wer sollte behandelt werden?
J. Steinbach

15:00–15:20 Alkylierende Chemotherapie: Resistenzmechanismen und ihre Überwindung
B. Kaina

15:20–15:30 Diskussion

Posterbegehung und Pause

Niedrig-gradige Gliome
Vorsitz: M. Mehdorn

16:30–16:45 Operative Therapie
J.C. Tonn

16:45–17:00 Strahlentherapie
R.D. Kortmann

17:00–17:15 Chemotherapie
R. Stupp

17:15–17:30 Keine Therapie
U. Schlegel

17:30–17:45 Diskussion

17:45–18:15 Highlights der Postersitzung und Posterpreise
M. Mehdorn et al.

Samstag, 18. März 2006

Anaplastische Gliome
Vorsitz: G. Schackert

9:00–9:30 Löst die molekulargenetische Diagnostik die Histopathologie ab?
A. v. Deimling

9:30–10:00 Aktuelle Studienergebnisse und neue Konzepte für Intergroup-Konzepte
W. Wick

Glioblastome: Optimierung der Standardtherapie
Vorsitz: J. Honegger

10:00–10:20 Gibt es eine Renaissance der Glioblastomchirurgie?
W. Stummer

10:20–10:40 Ist die Dosiseskalation bei der Bestrahlung sinnvoll?
J. Debus

10:40–11:00 Ist die Dosiseskalation bei Temozolomid sinnvoll?
M. Weller

Pause

Glioblastom: Experimentelle Therapie
Vorsitz: R. Engenhardt-Cabillic

11:30–11:50 Lokale Chemotherapie: sind die Gliadel-Studien positiv?
tba

11:50–12:10 Hat Angiogenesehemmung noch eine Zukunft?
P. Vajcoczy

12.10–12:30 Stammzellbasierte Strategien
G. Nikkhah

12.30–12:50 Immuntherapie
U. Bogdahn

The Legacy of Santiago Ramón y Cajal:

Different kinds of grey matter and their functional significance

Organizers:
Nikos Logothetis
(MPI für biologische Kybernetik, TÜ)
Almut Schüz
(MPI für biologische Kybernetik, TÜ)
Fahad Sultan
(Hertie Institute for Clinical Brain Research, TÜ)

Date:
June 17-19, 2006
Location:
Lecture hall of the Max-Planck-Guesthouse, Spemannstr. 36, TÜ

Valentin Braitenberg (at the symposium on his 80th birthday) and Kevin Martin

Schedule

Saturday, June 17th

	Speaker	**Chairman**
9:15am:	Nikos Logothetis Welcome and overview	
9:30-10:20am:	Javier DeFelipe (Madrid) „The pyramidal neuron in cognition“	N. Logothetis
10:20-11:10am:	Kevan Martin (Zürich) “A rough guide to cortical circuits”	N. Logothetis
11:45-12:35noon:	Ed Callaway (La Jolla) “Unraveling fine-scale and cell-type specificity of visual cortical circuits”	G. Palm
2:30-3:20pm:	Stefan Rotter (Freiburg) “A random graph approach to neocortical networks”	G. Palm

4-4:50pm:	Almut Schüz (Tübingen) "Quantitative aspects of cortico-cortical connections"	F. Pulvermüller
4:50-5:40pm:	Moshe Abeles (Ramat-Gan)	F. Pulvermüller

Sunday, June 18th

9:30-10:20am:	Harvey Karten (LaJolla) "Cognition in Dinosaurs: Evolution of Computational Circuits in the Forebrain"	H. Luksch
10:20-11:10am:	Catherine Carr (College Park) "Sound localization circuits"	H. Luksch
11:45-12:35noon:	Fahad Sultan (TÜ) "The cerebellum and the evolution of the avian and mammalian brain"	A. Aertsen
2:30-3:20pm:	Detlef Heck (Memphis, TN) "Structure and function of the cerebellar cortex"	A. Aertsen
4-4:50pm:	Harald Luksch (Aachen) "The avian optic tectum: Cells, circuits and concepts"	K. Kirschfeld
4:50-5:40pm:	Christian Wehrhahn (TÜ) "When fly, cat and man see vehicles"	K. Kirschfeld

Monday, June 19th

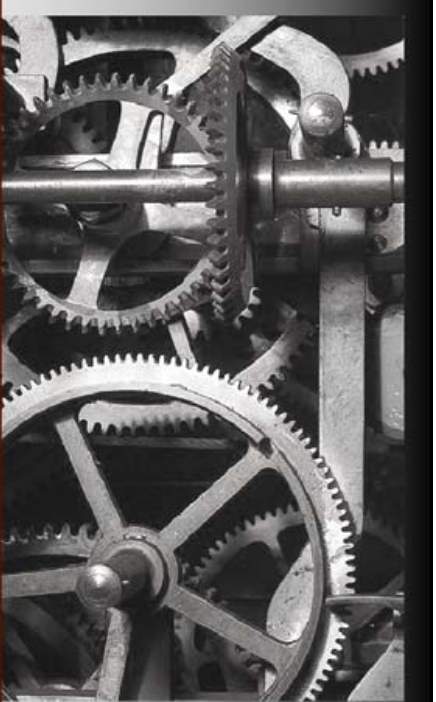
9:30-10:20am:	Heinz Wässle (Frankfurt) "Color coding in the mammalian retina"	V. Braitenberg
10:20-11:10am:	Zoltan F. Kisvárday (Debrecen) " Organization principles of horizontal connections in the visual cortex: implications for perceptual interactions"	V. Braitenberg
11:45-12:35noon:	Jonathan C. Horton (San Francisco) "Ocular dominance without ocular dominance columns"	V. Braitenberg
12:35-1:15pm:	Afterthoughts	

The Neurobiology of Eye Movements - Looking Back and Forth

International Symposium supported by the
Hertie Institute for Clinical Brain Research (HIH)

in honor of

Prof. Dr. Johannes Dichgans



Hertie-Institut
für klinische Hirnforschung

UKT

July, 28th, 2006
University of Tübingen

8:15 am - 5:00 pm, Lecture Hall, Children's Hospital, building 410, Floor C3, Hoppe-Seyler-Str. 1, Tübingen

Friday, July 28, 2006

08:15-08:50 REGISTRATION

08:50-09:00 **Johannes Noth**
(Aachen, Germany; President of the German Neurological Society)
Welcome address

09:00-09:40 **Michael Fetter**
(Karlsbad-Langensteinbach, Germany)
3-dimensional eye movement analysis – from bench to bedside

09:40-10:20 **David Zee**
(Johns Hopkins University School of Medicine, Baltimore, MD, USA)
The molecular biology of saccadic oscillations

10:20-10:50 *Coffee break*

10:50-11:30 **Thomas Brandt**
(Ludwig-Maximilians-University, Munich, Germany)
A technical eye inspired by biology

11:30-12:10 **Peter Thier**
(University of Tübingen, Germany)
The cerebellar control of oculomotor learning

12:10-13:30 *Lunch*

13:30-14:10 **Thomas Haarmeier**
(University of Tübingen, Germany)
Contributions of the cerebellum to visual perception

14:10-14:50 **Richard Sylvester**
(University College London, UK)
Oculomotor signals in visual cortex

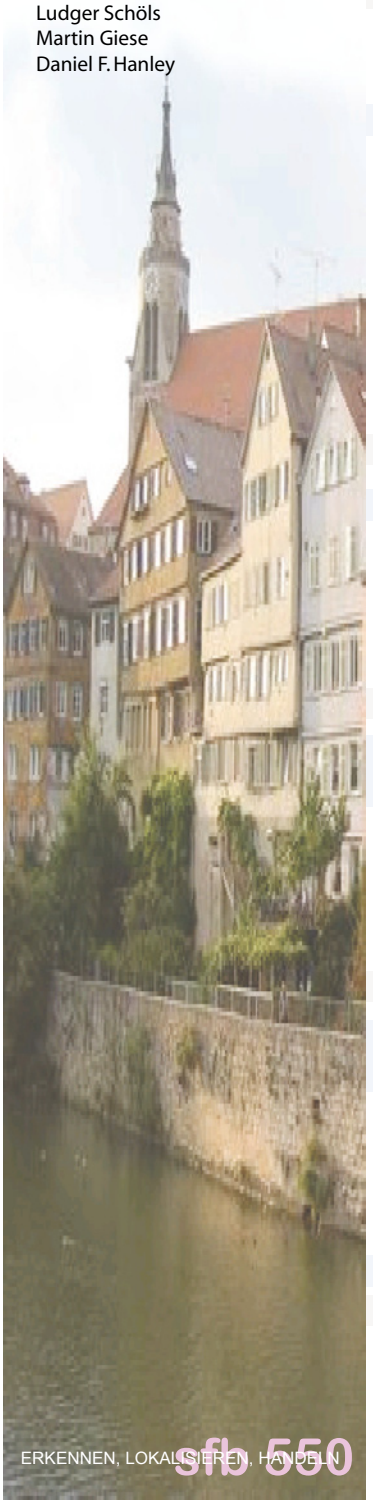
14:50-15:20 *Coffee break*

15:20-16:00 **Marianne Dieterich**
(University of Mainz, Germany)
Brain imaging and the vestibular system

16:00-16:40 **Alain Berthoz**
(CNRS and Collège de France, Paris, France)
Neural mechanisms of saccadic gaze control. Studies with fMRI and intracranial recordings

Hertie Institut
Für klinische Hirnforschung

Organizers
Andreas R. Luft
Ludger Schöls
Martin Giese
Daniel F. Hanley



Program

Sunday, October 1, 2006

Arrival, sightseeing tour, dinner at local restaurant

Monday, October 2, 2006

8:30 - 8:40	Welcome and Introduction
8:40 - 9:20	Daniel F. Hanley "Bringing task-specific training to clinical trials"
PART 1:	**Sensory Input (Chairs: S. McCombe-Waller, H.O. Karnath)**
9:20 - 10:00	Leonard Cohen "Influence of somatosensory input on motor function and recovery after stroke"
10:00 - 10:40	Chris Miall "Motor learning in eye-hand coordination tasks"
10:40 - 11:20	Joachim Liepert "Hypaesthesia, motor excitability and some implications for recovery"
11:20 - 11:40	Coffee break (posters)
PART 2:	**Motor Output (Chairs: L. Forrester, L. Johanssen)**
11:40 - 12:20	Jim Ashe "Motor sequence learning"
12:20 - 13:00	Jill Whitall "Motor sequences in rehabilitation"
13:00 - 14:50	Lunch break (posters)
PART 3:	**Mechanisms of Network Reorganization (Chairs: S. Di Giovanni, N. Birbaumer)**
14:50 - 15:30	Mengia S. Rioult-Pedotti "Structural plasticity and motor learning"
15:30 - 16:10	Randolph Nudo "Cortical electrophysiology of stroke recovery"
16:10 - 16:30	Coffee break (posters)
PART 4:	**Future of Rehabilitation Science (Chairs: S. Knecht, Ch. Gerloff)**
16:30 - 17:10	Agnes Flöel "Pharmacological enhancement of recovery"
17:10 - 17:50	Friedhelm Hummel "Brain stimulation and recovery"
17:50	**Plenary Session (Chairs: E. König, A. R. Luft)**
19:30	Dinner for Invited Speakers

Tuesday, October 3, 2006

Satelite Symposium: Modern stroke physical therapy

Alzheimer: 100 Years and Beyond

Centenary Meeting

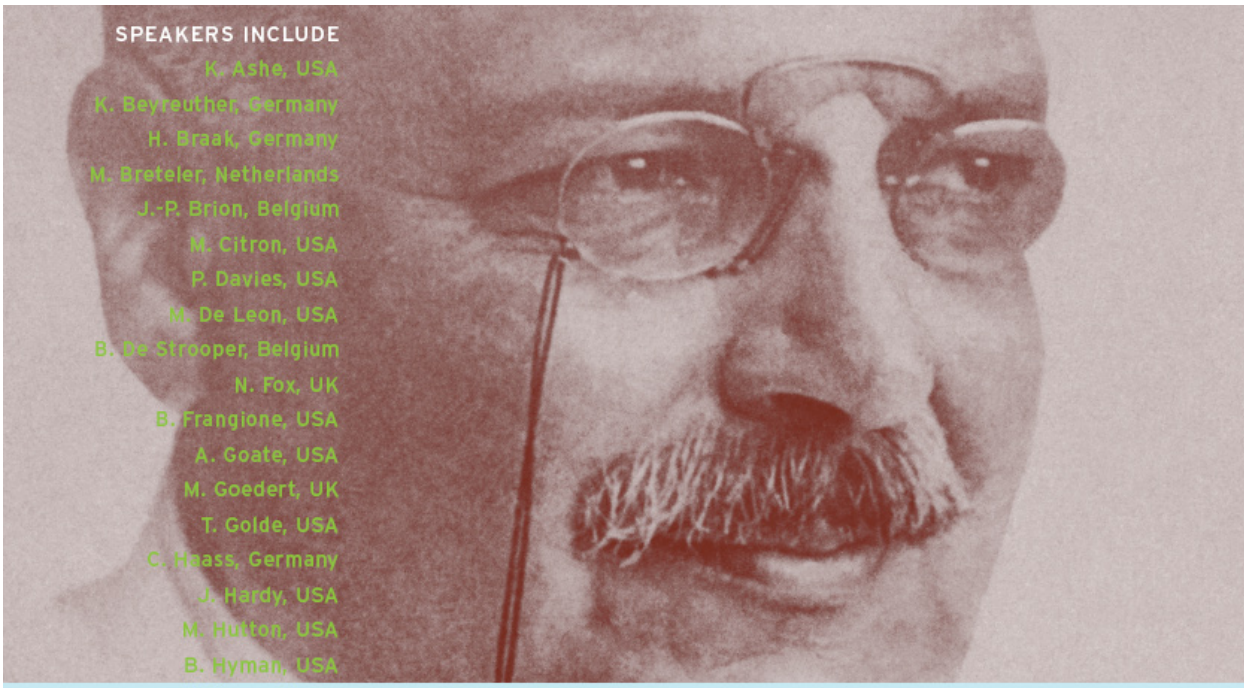
November 2 - 5, 2007 in Tübingen

On November 3, 1906 Alois Alzheimer traveled to the university city of Tübingen, Germany, to present an unusual case of dementia at the "37. Jahresversammlung südwestdeutscher Irrenärzte". Auguste D. would become known as the first documented case of Alzheimer's disease. Alzheimer described the pathological characteristics of the disease in the auditorium of the Institute of Psychiatry at the University of Tübingen. Exactly 100 years later the centenary meeting *Alzheimer: 100 Years and Beyond* took place at the very same location. On this occasion, *Science* magazine selected the 100 years anniversary for its cover page of the Nov 3 issue and referred to the event in Tübingen.

An opening event was celebrated for the public in the Festsaal of the Neue Aula on November 2, where speakers from various fields presented their point of view on aging and Alzheimer to about 500 guests. This event was also elected as one of the 365 Places 2006 in the Land of Ideas, an initiative supported by the German government.

The scientific meeting took place on November 3 and 4 in the Institute of Psychiatry. A Scientific Advisory Board had been appointed whose 62 members were invited to vote for worldwide leading scientists to speak in three different sessions. The meeting started on November 3, 2006 with a retrospective featuring "Pioneers" who contributed to Alzheimer's disease research over the last 100 years. On November 4, "Current Concepts" were presented in the morning and in the afternoon "Challenges" for the new century were discussed. In Session 1 speakers included: Robert Terry, Khalid Iqbal, Peter Davies, Cai'ne Wong, Colin Masters, Jean-Pierre Brion, Konrad Beyreuther, Dmitry Goldgaber, Rudy Tanzi, Yasuo Ihara, Michel Goedert, Mony de Leon, Sangram Sisodia, Bruce Yankner, Blas Frangione, Peter St George-Hyslop, Heiko Braak, Alison Goate, Gerard D. Schellenberg, Christian Haas, Allen Roses (on video), Steven Younkin, Karen Ashe, Mike Hutton, Martin Citron, and Dale Schenk; in Session 2: Christine van Broeckhoven, Bradley Hyman, Takaomi Saido, Bart de Strooper, Michael Wolfe, Eckard Mandelkow, Virginia Lee, William Klunk, John Morris, and Roger Nietsch; in Session 3: Monique Breteler, Nick Fox, Todd E. Golde, John Hardy, Takeshi Iwatsubo, Zaven Khachaturian, David Holtzman, Don Price, Dennis Selkoe, Leon Thal, John Trojanowski, and Bengt Winblad.

As space was very limited in the historic building only about 190 scientists could participate. To make this extraordinary meeting accessible to a wider audience the scientific part was broadcasted as a live video stream via the Internet and which was followed by many viewers around the world. All 48 talks including discussions can now be enjoyed one by one on a set of 4 DVDs providing a powerful retrospective of the scientific progress in the field as well as a number of daring outlooks which may or may not become reality in the near future. These DVDs are available via our homepage www.alz100.de where further information on the event can also be found.



SPEAKERS INCLUDE
K. Ashe, USA
K. Beyreuther, Germany
H. Braak, Germany
M. Breteler, Netherlands
J.-P. Brion, Belgium
M. Citron, USA
P. Davies, USA
M. De Leon, USA
B. De Strooper, Belgium
N. Fox, UK
B. Frangione, USA
A. Goate, USA
M. Goedert, UK
T. Golde, USA
C. Haass, Germany
J. Hardy, USA
M. Hutton, USA
B. Hyman, USA
Y. Ihara, Japan
K. Iqbal, USA
T. Iwatsubo, Japan
Z. Khachaturian, USA
W. Klunk, USA
V. Lee, USA
E. Mandelkow, Germany
C. Masters, Australia
J. Morris, USA
R. Nitsch, Switzerland
S. Paul, USA
D. Price, USA
A. Roses, USA
T. Saido, Japan
G. Schellenberg,USA
D. Schenk, USA
D. Selkoe, USA
S. Sisodia, USA
P. St George-Hyslop, Canada
R. Tanzi, USA
R. Terry, USA
L. Thal, USA
J. Trojanowski, USA
C. Van Broeckhoven, Belgium
B. Winblad, Sweden
M. Wolfe, USA
C. Wong, USA
B. Yankner, USA
S. Younkin, USA

alzheimer *100 years* and beyond

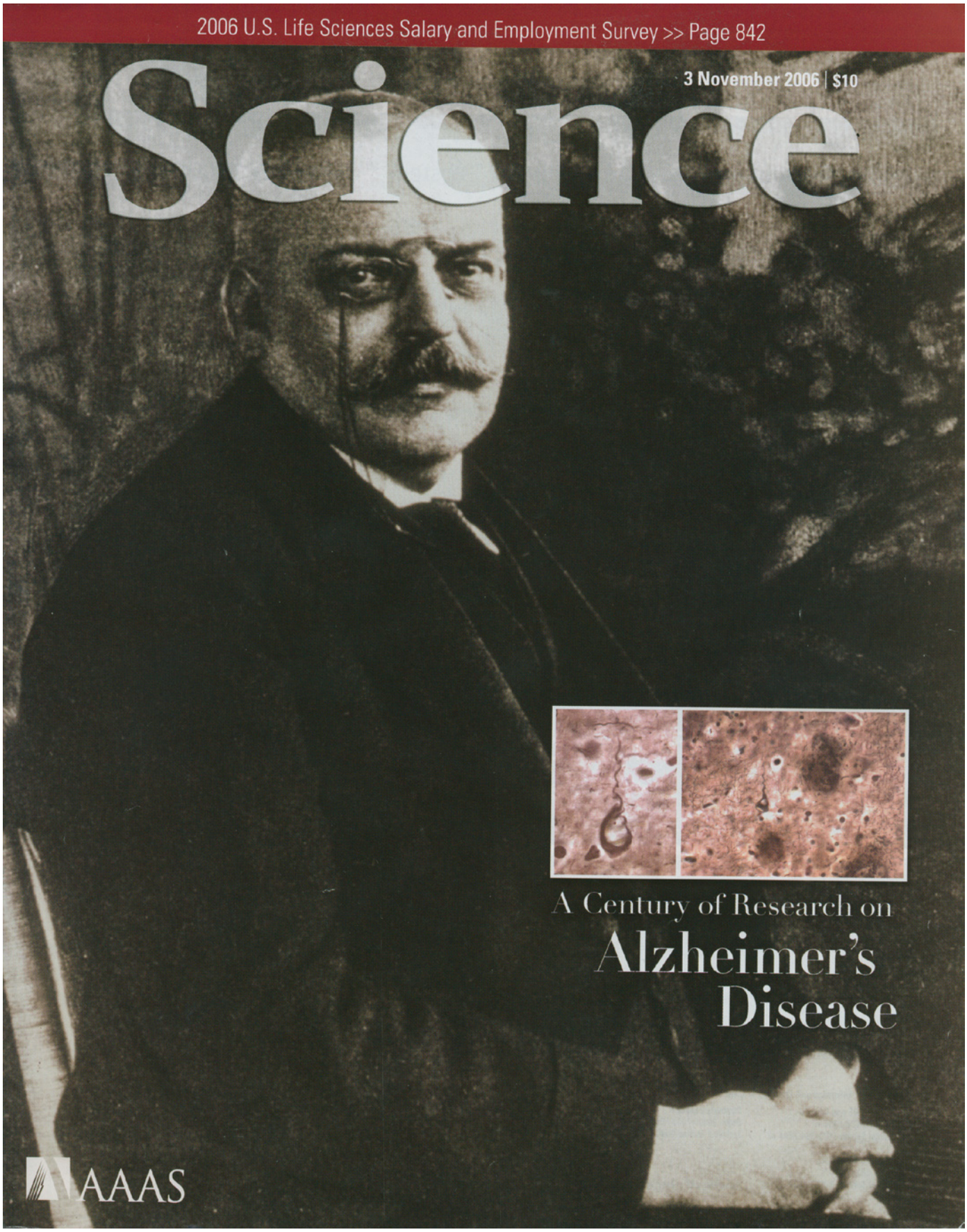
centenary meeting

november 2 – 5, 2006 tübingen, germany

ORGANIZED BY M. Jucker, K. Beyreuther, G. Buchkremer, Y. Christen, C. Haass, K. Maurer, J. Mervaillie, R. Nitsch

THE SCIENTIFIC ADVISORY BOARD Karen Ashe, Konrad Beyreuther, Heiko Braak, Jean-Pierre Brion, Yves Christen, Martin Citron, Carl Cotman, Mony De Leon, Bart De Strooper, Monica Di Luca, Karen Duff, Falk Fahrenholz, Blas Frangione, Dora Games, Sam Gandy, Michel Goedert, Paul Greengard, John Growdon, Christian Haass, John Hardy, Jean-Jacques Hauw, David Holtzman, Michael Hutton, Bradley Hyman, Yasuo Ihara, Khalid Iqbal, Takeshi Iwatsubo, Mathias Jucker, Zaven Khachaturian, June Kinoshita, Eddie Koo, Frank LaFerla, Peter Lansbury, Lars Lannfelt, Virginia Lee, Eva Mandelkow, Eckard Mandelkow, Eliezer Masliah, Colin Masters, Mark Mattson, Konrad Maurer, Patrick McGeer, Roger Nitsch, Margaret Pericak-Vance, George Perry, Don Price, Allen Roses, Gerard Schellenberg, Dale Schenk, Dennis Selkoe, Sam Sisodia, Peter St George-Hyslop, Gabrielle Strobel, Rudy Tanzi, Robert Terry, Leon Thal, John Trojanowski, Christine Van Broeckhoven, Bengt Winblad, Michael Wolfe, Bruce Yankner, Steve Younkin

live video stream available at www.alz100.de


2006 U.S. Life Sciences Salary and Employment Survey >> Page 842
Science
3 November 2006 | $10
A Century of Research on
Alzheimer's Disease
AAAS

»Altern und Alzheimer« wurde von der Initiative »365 Orte im Land der Ideen« der Bundesregierung ausgezeichnet. Sie stellt die Auftaktveranstaltung zum internationalen wissenschaftlichen Symposium »Alzheimer: 100 Years and Beyond« dar, zu dem die wichtigsten Alzheimerforscher weltweit erwartet werden. Dieses wird von Prof. Dr. Mathias Jucker vom Hertie-Institut für klinische Hirnforschung organisiert und findet am 3. und 4. November in der Psychiatrischen Klinik Tübingen an demselben Ort, an dem Alois Alzheimer bereits vor 100 Jahren sprach, statt.

Anfahrt

Am Nachmittag des 2. November finden Stadtführungen rund um das Thema »Wissenschaft« statt. In der Klinik für Psychiatrie können Sie eine kleine Ausstellung zur Geschichte der Mikroskopie in der Alzheimerforschung besichtigen. Mehr dazu unter www.alz100.de

Deutschland
Land der Ideen

Mit dem Auto

Aus Richtung Stuttgart/A 8: B 27 in Richtung Tübingen/ Reutlingen. In Tübingen Stadtausfahrt in Richtung Zentrum/Herrenberg, B 28. Den Hinweisschildern in Richtung Zentrum folgen.
Aus Richtung Singen/A 81: Autobahnausfahrt Herrenberg. In Tübingen den Hinweisschildern in Richtung Zentrum/Alle Richtungen folgen. In der Wilhelmstraße 7 befindet sich die Neue Aula nach ca. 500 m auf der linken Seite.

Mit öffentlichen Verkehrsmitteln

Die Bus-Linien 1, 2, 3, 4, 6, 7, 17 fahren im 5-Minuten-Takt direkt zur Neuen Aula.

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für klinische Hirnforschung

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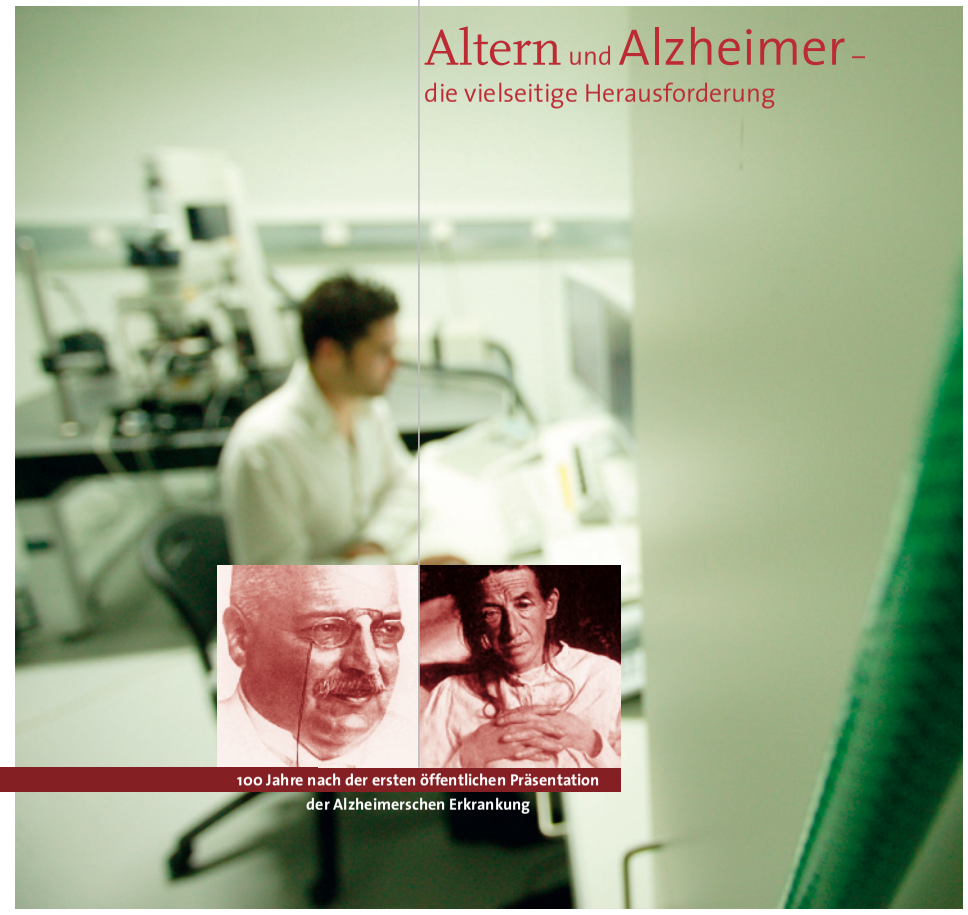
Hertie-Institut
für klinische Hirnforschung

Einladung

Altern und Alzheimer –
die vielseitige Herausforderung



100 Jahre nach der ersten öffentlichen Präsentation der Alzheimerschen Erkrankung

Vor 100 Jahren hat Professor Alois Alzheimer in Tübingen die Krankheit seiner Patientin Auguste D. zum ersten Mal öffentlich vorgestellt. Kaum jemand nahm damals Notiz davon.

Altern und Alzheimer – die vielseitige Herausforderung

Seitdem hat sich die Alzheimersche Erkrankung durch die steigende Lebenserwartung zu einer gesellschaftlichen Herausforderung entwickelt.

Heute ist die Erforschung des Morbus Alzheimer weltweit eine der am nachdrücklichsten verfolgten Aufgaben in den Neurowissenschaften.

Das Hertie-Institut für klinische Hirnforschung wurde im Jahre 2001 von der Gemeinnützigen Hertie-Stiftung errichtet. Es zählt zu den weltweit führenden Forschungseinrichtungen im Kampf gegen die Alzheimersche Erkrankung.

Donnerstag, 2. November 2006
18.00 Uhr (Einlass ab 17.00 Uhr)

Festsaal der Neuen Aula
Wilhemstraße 7
72076 Tübingen

100 Jahre nach der ersten öffentlichen Präsentation der Alzheimerschen Erkrankung lädt das **Hertie-Institut für klinische Hirnforschung** herzlich dazu ein, die Thematik Altern und Alzheimer aus verschiedensten Richtungen in den Blick zu nehmen.

Im Anschluss, gegen 20.00 Uhr, bitten wir zu einem kleinen Empfang im Foyer.

Um 21.00 Uhr besteht im Hörsaal des Anatomischen Instituts (Österbergstraße 3) die Gelegenheit zum Besuch des Theaterstücks »Die Akte der Auguste D.« von Konrad und Ulrike Maurer in der Inszenierung der Intendantin des LTT, Simone Sterr. Eintrittskarten sind am 2. 11. 2006 gegen eine Schutzgebühr von € 3 zwischen 9.00 und 16.30 Uhr in der Buchhandlung Osiander in der Wilhelmstraße und zwischen 17 und 20.30 Uhr im Foyer der Neuen Aula erhältlich.

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Eberhard-Karls-Universität Tübingen

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Erwin Teufel
ehem. Ministerpräsident
des Landes Baden-Württemberg

der historische Blick
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der künstlerische Blick
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Autor u. a. von Small World

der theologische Blick
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em. Professor für ökumenische Theologie
Eberhard-Karls-Universität Tübingen
Präsident der Stiftung Weltethos

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