Hertie-Institut
für klinische Hirnforschung

annual report 2008

center of neurology tübingen

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Department of Neurodegenerative Diseases

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Das Zentrum für Neurologie im Jahr 2008

Das Jahr 2008 war für das Zentrum für Neurologie eine Zeit des Übergangs.
Die Abteilung für Allgemeine Neurologie wurde seit dem Weggang von Prof. Weller zu Beginn des Jahres kommissarisch durch Prof. Arthur Melms geleitet. Dank des besonderen Engagements von Prof. Melms und aller ärztlichen Mitarbeiter war es möglich, die Leistung der Klinik in ihrer ganzen Breite aufrecht zu erhalten. Die Berufungsverhandlungen für die Nachfolge sind mittlerweile nahezu abgeschlossen, sodass wir mit großer Zuversicht in die weitere klinische und wissenschaftliche Zukunft des Zentrums für Neurologie sehen.
Gleichzeitig war das Zentrum auf wissenschaftlichem Gebiet auf „Expansionskurs".
Nach einer langen Vorbereitungsphase wurde im Dezember 2008 das Werner-Reichardt Zentrum für Integrative Neurowissenschaften (CIN), das bislang einzige eingeworbene Exzellenzcluster der Universität Tübingen, offiziell aus der Taufe gehoben. Eine ganze Reihe von Berufungsverfahren für Professuren und Nachwuchsgruppen konnten bereits erfolgreich abgeschlossen werden.
Eine besondere Bedeutung für die Zukunft des Zentrums kommt auch der erfolgreichen Bewerbung des HIH als Partnerstandort des in Gründung befindlichen „Deutschen Zentrums für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft, DZNE" zu. Die dadurch ermöglichte langfristige Sicherung von Forschungsmitteln wird den neurowissenschaftlichen Standort in Tübingen erheblich stärken. Die Gestaltung der Zusammenarbeit der neuen Professuren und Arbeitsgruppen des DZNE mit den bestehenden Strukturen des HIH und des CIN wird aber auch ganz neue Herausforderungen bringen.

▲ Abbildung:
Verleihung der Ehrensenatorwürde der Universität an Dr. Michael Endres, Vorstandsvorsitzender der Gemeinnützigen Hertie-Stiftung.

Zahlreiche erfolgreiche Drittmitteleinwerbungen, wie zum Beispiel im Rahmen des Nationalen Genomforschungsnetzes NGFNplus, einer der hochkompetitiven ERC Junior Research Awards für Dr. Marc Himmelbach von der Sektion Neuropsychologie, sowie zahlreicher DFG- und EU-Förderungen belegen darüber hinaus die wissenschaftliche Leistungsfähigkeit des Zentrums.
Die Vielfalt und der Erfolg der wissenschaftlichen Aktivitäten hat nach einer Evaluation der gemeinnützigen Hertie-Stiftung dazu geführt, dass das HIH inzwischen in die Spitzengruppe der europäischen Hirnforschungsinstitute vorstoßen konnte.
Die wichtige Rolle, die das HIH im Leben der Universität Tübingen spielt, fand seinen Ausdruck in der Verleihung der Ehrensenatorwürde der Universität an Dr. Michael Endres, den Vorstandsvorsitzenden der Gemeinnützigen Hertie-Stiftung.

Prof. Dr. Thomas Gasser, Prof. Dr. Mathias Jucker, Prof. Dr. Arthur Melms, Prof. Dr. Peter Thier

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 (Acting Director: Prof. Dr. A. Melms)
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 neuroimmunology, neurovascular diseases and neurooncology. This department also runs the stroke-unit/ICU, providing care for patients with acute stroke and other serious acute neurologic conditions.
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 21-bed ward for inpatients and through several outpatient specialty clinics.
The Department of Cognitive Neurology provides neuropsychological testing and diagnostic evaluations for patients with vestibular and neuroophtalmologic disorders for inpatients and outpatients of all clinical departments.
The fact that three of the four departments of the center actively 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 Parkinson's disease, multiple sclerosis, and brain tumors. However, the very tight interconnection of science and patient care is of eminent importance to all areas of disease-related neuroscience. It forms the very center of the Hertie concept and distinguishes the Hertie Institute from other institutions of neuroscientific research.

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 medizinischen 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 Institutionen, der Neurologischen Klinik und dem Hertie-Institut für klinische Hirnforschung (HIH).
Die Aufgaben des Zentrums liegen sowohl in der Krankenversorgung durch die Neurologische Klinik als auch in der wissenschaftlichen Arbeit der im HIH zusammengeschlossenen Forscher. Besonderer Wert wird auf die Heranbildung und Förderung des wissenschaftlichen Nachwuchses sowie auf den Wissenstransfer zwischen Forschung und Klinik gelegt.

Das Zentrum besteht derzeit aus vier Abteilungen:
Abteilung für Allgemeine Neurologie (Komm. Direktor: Prof. Dr. A. Melms)
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 Gefäßerkrankungen des Gehirns, die Neuroimmunologie und die Neuroonkologie. Die Abteilung betreibt die Schlaganfall- und Intensivstation der Klinik („Stroke-Unit“), in der Patienten mit akutem Schlaganfall und anderen schweren akuten neurologischen Krankheitsbildern behandelt werden.
Die Abteilung Neurologie mit Schwerpunkt Neurodegenerative Erkrankungen konzentriert sich in ihrem klinischen Bereich auf die Diagnostik und Therapie von neurodegenerativen Erkrankungen wie Morbus Parkinson, die Ataxien, spastische Spinalparalysen und Demenzen, aber auch von anderen Bewegungsstörungen wie den Dystonien oder dem Tremor. Für die Bewältigung dieser klinischen Aufgaben stehen der Abteilung eine Schwerpunktstation mit 21 Betten und mehrere Spezialambulanzen zur Verfügung.
Die Abteilung für kognitive Neurologie verfügt nicht über Betten, stellt jedoch die konsiliarische und ambulante neuropsychologische Versorgung und die Diagnostik im Bereich neurovestibulärer und neuroophthalmologischer Erkrankungen sicher.
Die Beteiligung dieser Abteilungen an allen Aspekten der klinischen Versorgung ist eine Grundlage der erfolgreichen klinischen Hirnforschung am Hertie-Institut. Dies gilt ganz offensichtlich für Medikamentenstudien, die am Zentrum zum Beispiel in der der Therapie der Parkinson-Krankheit und der Multiplen Sklerose sowie in der Hirntumorbehandlung 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.

Structure of the Clinical Departments

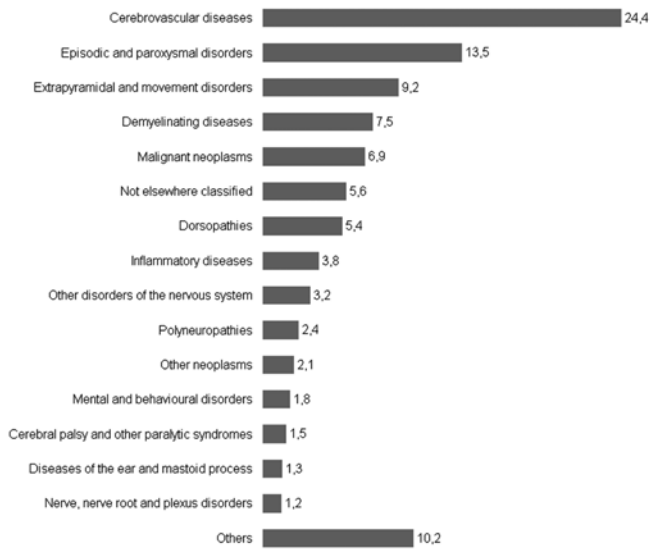
The Center of Neurology comprises three general neurological wards, one mixed neurological-neuro-surgical ward and an intensive care/stroke unit with a total of 73 beds.
The wards, 41 (ROSA), 42 (B5-Nord), 44 (B5-Süd, intensive care and stroke unit) and 45 (B5-Ost) are part of the Department of General Neurology. The ward 43 (B5-West) is part of the Department of Neurodegenerative Diseases. The general neurology wards 41 and 42 provide special care for brain tumor patients. Due to the primary care agreement of the University Medical Center and the district of Tübingen, the whole spectrum of neurological diseases including neurotrauma cases of the peripheral and central nervous system is referred to the Center of Neurology. The services are located in the CRONA hospital building. The central clinical laboratories, the Departments of Surgery (including Neurosurgery), Orthopedics, Radiology (including Neuroradiology), Radiooncology and Anesthesiology, as well as the Departments of Pediatrics and Internal Medicine are in close proximity.
By the end of 2008, after a period of reorganisation of the clinical structure and refurbishing, all neurological wards are located on the fifth floor of the B-tower of the CRONA building. This is expected to impove efficiency and the work flow within the Center of Neurology.
The neurological outpatient clinics primarily take care of patients referred from neurologists and in-patients from the other departments of the University Medical Center. Specialized outpatient clinics are open for patients seeking expert opinion in cerebrovascular disorders and stroke, neuroimmunology, neurodegenerative diseases, neurooncology, chronic neuropathic pain and epilepsy. For patients on intensive care units and for patients who are unable to be seen in the general neurological clinic, a neurological consult service is provided. This service also includes the Berufsgenossenschaftliche Unfallklinik and the Paul-Lechler-Krankenhaus in Tübingen as part of commitment to the interdisciplinary geriatric center.

Clinical Efficacy Data

Inpatient Care

The inpatient units of the University Hospital for Neurology treated more than 4.000 patients in 2008.

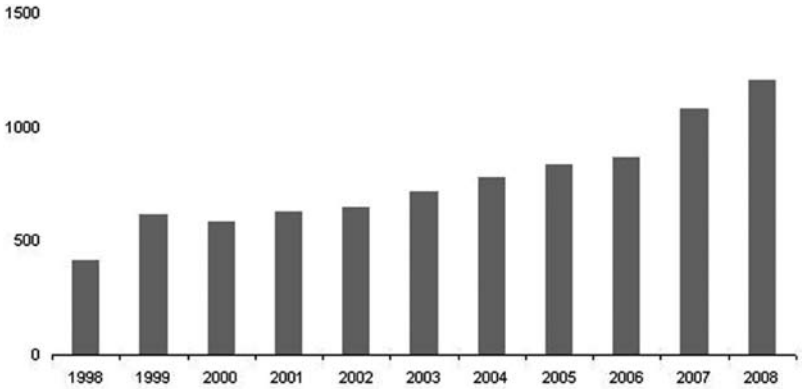
Number of admissions: 4.037 (2007: 4.272)
Length of stay: 5,4 days (2007: 5,3)
Case-Mix-Index: 1,63 (2007: 1,51)



◀ Figure 1:
In-patient Diagnosis Groups 2008 (%).

In 2008 we saw again an increase of admissions in the Stroke and Intensive Care Sector.

◀ Figure 2:
Admissions Stroke/ Intensive care Unit.



Outpatient Clinics

Neurooncology

This outpatient clinic sees more than 150 new patients each year and all visits add up to more than 800 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 and Tuesdays, but there are flexible appointments for urgent situations at any time. This outpatient clinic is run by C. Braun of the neurooncology team of the department, and supervised by Prof. Dr. A. Melms. 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 exchange between colleagues of the Departments of Neurosurgery, Radiooncology, Neuroradiology, Pediatrics and Oncology. Complex diagnostic or therapeutic issues are discussed in the Brain Tumor Board (Coordination by C. Braun and Prof. Dr. A. Melms) 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 and U. Küstner are study nurses involved in the organization of all outpatient clinics, multicenter trials and specific education of the patients.

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 iron metabolism of the brain using MRI and CSF examinations. Additionally, we collect DNA samples from patients with sporadic and familial RLS for genetic analysis.

Patients are seen by Dr. J. Godau and Prof. Dr. D. Berg.

Outpatient Clinics

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. M. Dengler (MS nurse) takes care of patients receiving IVIG or therapeutic antibodies like natalizumab. In 2008 the clinic was run by Dr. M. Albert, , PD Dr. Bischof, Dr. C. Frischholtz, and Dr. M. Pick, under the supervision of Prof. A. Melms.

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. 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.
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).

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 over 70 years of age, 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, speech therapy for aphasia and dysphagia, and occupational therapy for handicaps concerning activities of daily living. 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.
Scientific projects on the evaluation of geriatric problems include collaborative studies with the Department of Geriatric Medicine at the Robert-Bosch Hospital in Stuttgart (Dr. Globas, Dr. Maetzler, Prof. Becker) and with the Department of Psychiatry and Psychotherapy (Prof. Eschweiler, Dr. Leyhe). A monthly case-presentation of patients with dementias is organized by Dr. Leyhe.
Staff directly involved in the different services and projects include Prof. A. Melms, Prof. Berg, PD Dr. T. Haarmeier, Prof. R. Krüger, Dr. Globas, and Dr. Maetzler.

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, treatment planning, secondary prevention, and neurorehabilitation strategies. 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 potential. 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

Currently, there are approximately 150 patients who visit the clinic for patients with epilepsy 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

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 130 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 these patients, treatment may be optimized by intermittent or continuous apomorphine or duodopa 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 non-competitive mGlu5 receptor antagonist (AFQ056), the selective, reversible MAO-B Inhibitor safinamide, a partial D2/D3 and complete 5-HT1A agonist (Pardoprunox), and a combination of Levodopa, Carbidopa, and the COMT-inhibitor entacapone (Stalevo®), as well as observational studies of different medications. These activities are supported by the study nurses Ute Küstner, Gabriele Lutz and Marion Jeric, as well as the documentalist Tanja Riedl. 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. For patients with progressive supranculear palsy (PSP) an investigator initiated phase 2 open-label trial with the cholinesterase inhibitor rivastigmine® has been started as well as a 6 weeks audio-biofeedback training study with a movement sensor to improve postural control in cooperation with the Robert-Bosch-Hospital in 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 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 and regular teaching courses.
Appointments are scheduled daily in the outpatient clinic of the Center of Neurology. Patients are seen by Prof. T. Gasser, Prof. D. Berg, K. Brockmann; A. Di Santo; Dr. A. Gaenslen; Dr. J. Godau; H. Huber; K. Srulijes as well as the neuropsychologist Dr. rer nat. I. Liepelt.

Deep Brain Stimulation

Also known as "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 already in 1999. The concept of treatment and medical attendance developed by

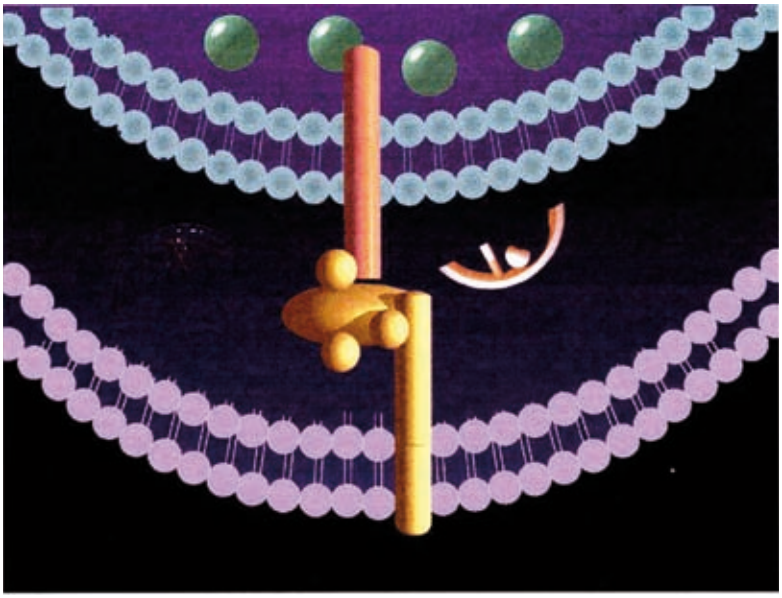
the network for deep brain stimulation of the University Clinic of Tübingen (BrainStimNet; www.brainstimnet.de) involves close interaction between neurologists, neurosurgeons, psychiatrists and physiotherapists. Patients are referred from outside neurologists as well as our own outpatient clinics for neurological movement disorders and psychiatric diseases. In 2008 interventions for DBS were performed on 45 patients including patients with Parkinson's disease, essential tremor, neuropathic tremor and dystonia. The growing relevance of Tübingen as a specialized center for deep brain stimulation was further recognized by its inclusion into the European EARLYSTIM-study group. Moreover based on own basic research in the identification of novel targets for DBS in Parkinson's disease, a study on the therapeutic effect of DBS in the pedunculopontine nucleus was implemented in Tuebingen.
Patients who are likely 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 outpatient 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 BrainStimNet Tübingen organizes regular conferences for patients and relatives in cooperation with the German Parkinson's disease Association (dPV).
Appointments are scheduled two days per week in the outpatient clinic for DBS.
Patients are seen by Dr. T. Wächter, Dr. S. Breit, D. Weiss and Prof. Dr. R. Krüger.

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 3-6 months. The clinic is a centre for "qualified botulinum toxin treatment" (Arbeitskreis Botulinumtoxin, German Neurological Society).
We are specialized on different forms of idiopathic, symptomatic and genetic dystonias with cranial, cervical, segmental and generalized distribution.
New treatment approaches for camptocormia or antecollis are translated form research to clinical pratice.
For patients with dystonias or spasticity BoNT treatment is optimized by EMG and ultrasound-guided injection techniques.
Our clinic participates in the collaborative Tuebingen BrainStimNet (www.brainstimnet.de). Patients with insufficient response to standard dystonia treatments are screened and evaluated for pallidal deep brain stimulation (DBS) at our centre.
Treatment evaluations also include physical and ergotherapeutic therapies. A specialized ergotherapeutic service for task-specific dystonias focussed on retraining is offered (Frau Wiesemeier, Therapiezentrum UKT). An increasing number of outpatients with spasticity have been managed with a combined treatment of BoNT injections and physiotherapy at the local MTR (Medical Training and Rehabiliation Centre, University of Tuebingen).
Basic courses in botulinum toxin injection therapy for cranial and cervical injections have been continued.

Outpatient Clinics

The tradition of expert meetings together with regional movement disorder experts has been continued. Meetings in 2008 were focussed on the practical use of dystonia genetics, the application of EMG and ultrasound for BoNT injections and presentation rounds for extraordinary patients from the regional clinics.



▲ Figure:
Molecular action of BoNT.

We have continued our strong collaboration with the dystonia clinic at the University of Innsbruck, Prof. Dr. J. Müller, and have detected worsening of cervical dystonia, so called "reverse sensory geste", in selected cervical dystonia patients from both clinics.
Appointments are scheduled every week on Wednesday and Thursday in the Outpatient Clinic of the Center of Neurology.
Medical Staff: Dr. F. Asmus (Head), Dr. M. Bauer, Dr. R. von Coelln, Dr. T. Lindig.

Neurologic Memory Clinic

Dementia is one of the most frequent problems of the elderly population and a major cause of disability and mortality. The most common forms of dementia are Alzheimer's disease and vascular dementia, and dementia associated with Parkinsonian syndromes (including idiopathic Parkinson's disease, diffuse Lewy body disease, progressive supranuclear palsy). The latter syndromes also represent the clinical and scientific focus of our memory clinic. Some of the dementive syndromes are treatable, and a minority of them (e.g. inflammation-associated dementias) are potentially curable. A thorough investigation with clinical, neuropsychological, biochemical and imaging methods of progressive cognitive deficits is therefore essential.
In a weekly memory outpatient clinic we offer such a program. In addition, multimodal therapeutic strategies including medication, memory training, and social counseling are provided, in co-operation with the memory clinic of the Department of Psychiatry.
A particular aim of our clinical and imaging studies are a better understanding of the differences / similarities between Alzheimer's disease and dementias associated with parkinsonism. Furthermore, we focus on the time course of disease progression and the efficacy of existing and new treatment options.
Clinicians: Dr. W. Maetzler, Prof. Dr. D. Berg
Neuropsychology: Dr. rer. nat. I. Liepelt.

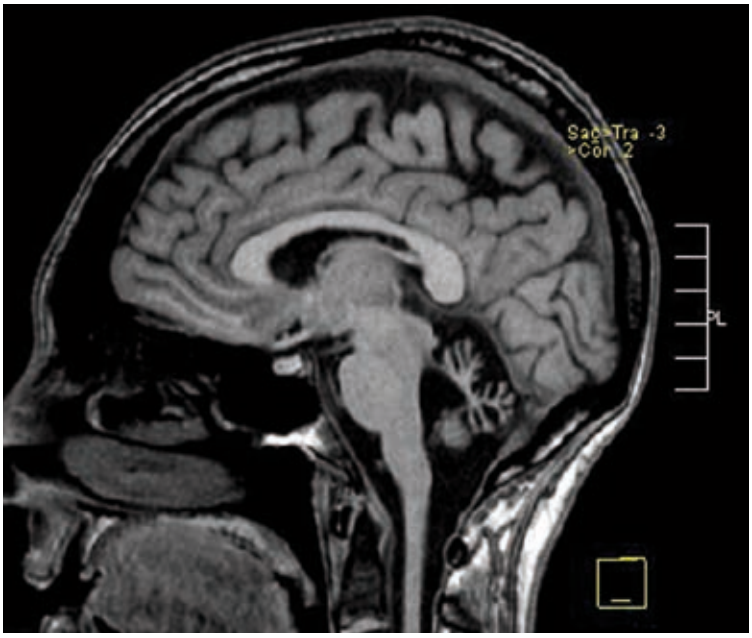
Outpatient Clinics

Spastic Paraplegias

The outpatient clinic for spastic paraplegias 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. Genetic diagnostics are offered for the most frequent subtypes. Additionally, new variants are genetically characterized on a research basis.
The clinic is run by Dr. R. Schüle and Dr. K. Karle and is supervised by Prof. Dr. L. Schöls.

Ataxia

The ataxia clinic provides tools to discover the cause of ataxia in close cooperation with the Department of Neuroradiology (MRT, MR-Spectroskopy) and the PET-center. In cooperation with the Institute of Medical Genetics we search for the genetic basis in patients and families with hereditary ataxias.
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 disease modifying factors of spinocerebellar ataxias in a prospective natural history study.
The clinic is run by Dr. M. Synofzik, Dr. Ch. Linnemann and Dr. T. Lindig and is supervised by Prof. Dr. L. Schöls.

Outpatient Clinics

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 detection. 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 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. Paraclinical tests include nerve conduction studies, electromyography, and evoked potentials. Additional diagnostic procedures (e. g. blood tests, lumbar puncture, and imaging of the brain and spinal cord) are necessary to exclude rare diseases mimicking ALS. Therefore, in most cases an in-patient treatment is required to confirm the diagnosis of ALS. Follow-up of patients as well as management of symptoms and complications are provided by the clinic.
The clinic is run by Dr. M. Synofzik, supervised by Prof. L. Schöls.

Neuropsychology

Strokes not only lead to motor and sensory impairment, 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 by Elisabeth Becker and supervised by Prof. Dr. Dr. H.-O. Karnath.

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.

Clinical 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 CO2 vasoreactivity tests are routinely performed.
The laboratory consists of a unit in the neurology outpatient clinic 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); supervisor and head of laboratory PD Dr. A Luft, Dr. B. Greve.

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 status epilepticus, or in various forms of coma. Each year, approximately 3,000 EEGs are recorded in outpatients and inpatients. The typical indications 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).

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).

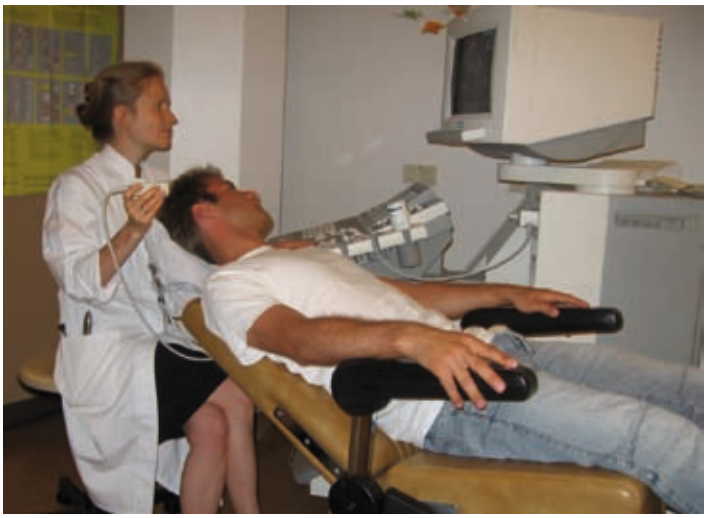
Clinical Laboratories

Transcranial B-mode sonography laboratory

The method to visualize morphological changes of the brain parenchyma in neurodegenerative disorders has been pioneered by Prof. G. Becker and Prof. D. Berg and is being continuously advanced and extended in its application by the group of D. Berg.

Patients with various movement and neurodegenerative disorders come from all over Germany to receive additional diagnostic information by this supplementary neuroimaging tool, which is especially helpful in the early and differential diagnosis of diseases.

Regular teaching courses as well as monthly individual training programs attended by medical doctors and scientists from all over the world are held to spread the method.



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 Mrs. A. Deutsch and Mrs. 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

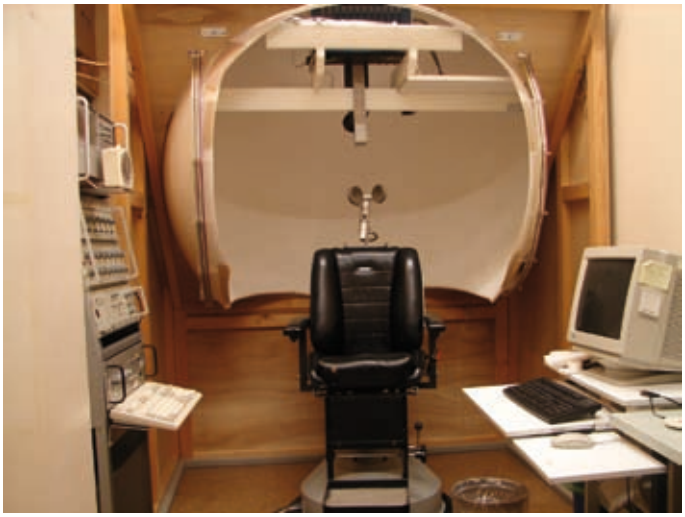
The EMG Laboratory offers all the standard electromyography and neurography procedures for the electrodiagnosis of neuromuscular diseases including polyneuropathies, entrapment neuropathies, traumatic nerve lesions, myopathies, myasthenic syndromes, and motor neuron diseases. In selected cases, polygraphic 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 2008, 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

Clinical Laboratories

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 2008, the EMG Laboratory was run by Dr. S. Jacob under the guidance of PD Dr. T. Haarmeier and Prof. A. Melms.

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 Mrs. C. Friedrich and analyzed by Dr. J. Pomper. For more complex questions, e. g., isolated testing of single canals, 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 non-invasive eye movements recording using video techniques (Scalar) and performs 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 Dr. J. Pomper and PD Dr. T. Haarmeier.



Clinical Chemistry Laboratory

The Clinical Chemistry Laboratory collects more than 2,000 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. Immunopathology includes the determination of a set of autoantibodies for the diagnosis of certain neuroimmunologi-

cal syndromes: autoantibodies to acetylcholine receptors, autoantibodies to muscle specific tyrosine kinase (MuSK), autoantibodies to titin for myasthenia gravis, and autoantibodies to gangliosides for immunoneuropathies. CSF-levels of amyloid peptide beta42, tau, and phospho-tau are measured to differentiate various forms of dementia. Cell populations in CSF and blood samples are examined by cytometry with a FACScalibur. The laboratory is supervised by Prof. Dr. A. Melms and PD Dr. Bischof.

Neurocardiology Laboratory

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, headed by cardiologist Dr. J. Erharhaghen. The laboratory is fully equipped with a modern multifunction 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 colour-coded Doppler and duplex investigation of the extracranial as well as intracranial vessels. This enables us to perform bedside vascular investigations and echocardiography of stroke patients on our 13-Bed ICU and Stroke Unit immediately after diagnosis.

Yearly, we perform approximately 1000 echocardiographic investigations, including M-Mode, 2-D mode, pulse-wave and continuous-wave 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 arrhythmia 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. Yearly, we record well over 900 24-hour ECGs and 700 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. Dr. Jite Erharhaghen is responsible for the neurocardiology laboratory.

Physical, Occupational & Speech Therapy

Physiotherapy

All neurological inpatients with sensory or motor deficits, movement disorders, pain syndromes, and degenerative spinal chord disease are allocated to individualized physiotherapy. Furthermore, group treatments are offered to Parkinson Patients. Currently nine physiotherapists are working within the "TherapieZentrum" responsible for the neurological wards.
The physiotherapist treatment is based on guidelines which have been worked out for special disease groups according to the current knowledge. This includes for example lumbar disc proplaps, stroke, ataxia and Parkinson's disease.
During the year 2008, 2.408 patients were seen.

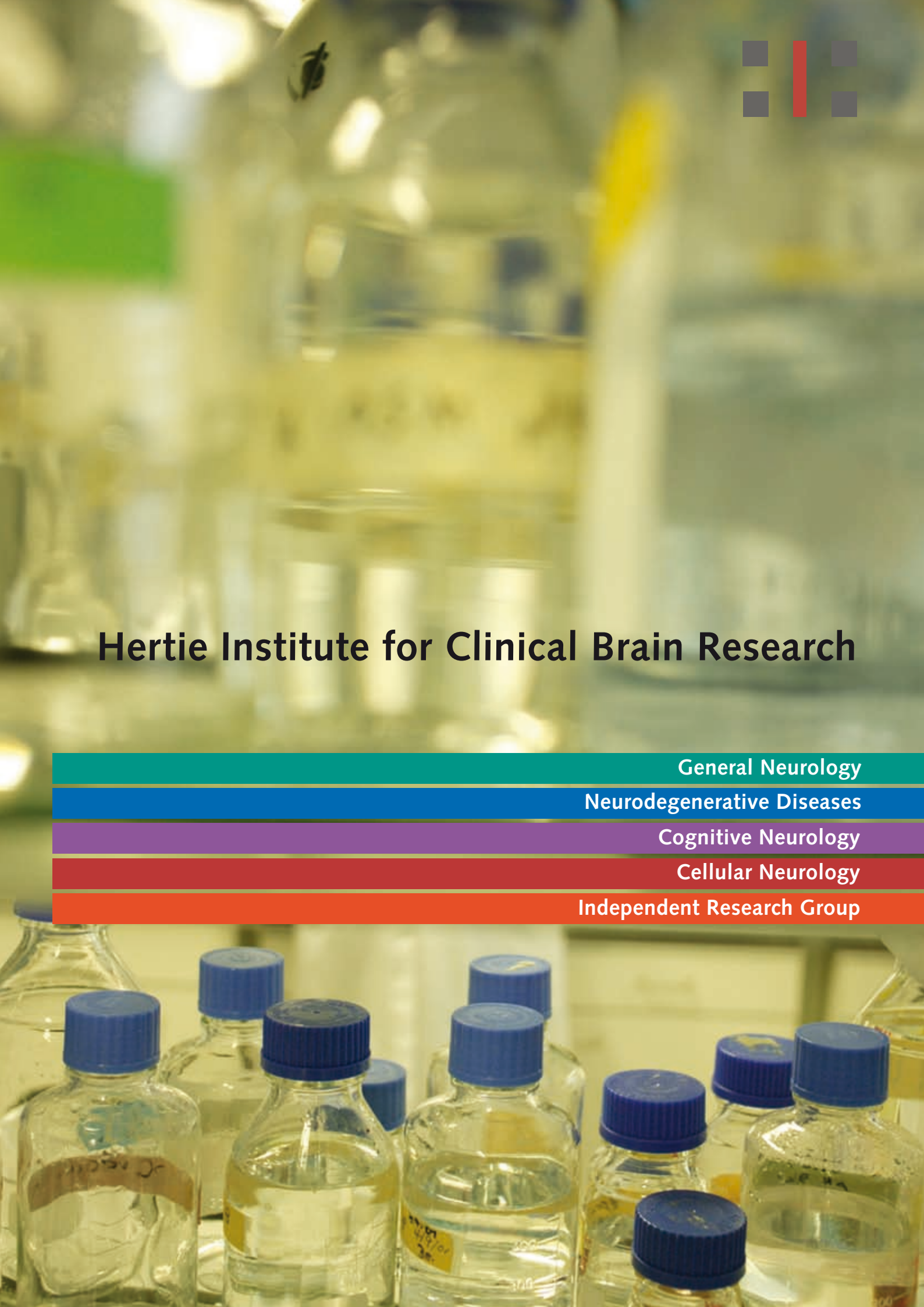
Occupational Therapy

Currently, four occupational therapists are working part-time in the department (I. Hartmann, A. Nölck, 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 2008, 917 patients were seen.
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 (approximately 1.132 patients in 2008).
Every acute stroke patient receives a bedside and, if necessary, a videoendoscopic or video-fluoroscopic swallowing examination. Therefore dysphagia can be recognized at an early stage, aspiration pneumonia can be prevented and specific therapy can be planned for every individual patient.
Additionally, in 2008 approximately 191 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 precendent 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 change their workplace: 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 and thus allow true "translational medicine", as it is often called today. But it is also demanding, as it calls for a higher degree of flexibility, cooperation and mutual understanding 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. The chairman reports to the assembly of research group leaders of the HIH on a monthly basis. Through this meeting, the (at latest count) eighteen 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 with a tenure track option. The first one, focussing on neuroregeneration in the spinal cord, has been established in 2006, a second group with a focus on synaptic plasticity in drosophila has been recently established. These groups are funded by a "research pool" for three to five years.

Twice a year, the board of directors presents the achievements 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 six years of its existence, the HIH has been growing rapidly. Its development is far from complete.

Groups at the HIH, under the leadership of Prof. P. Thier, have been instrumental in the successful bid of the university of Tübingen for a "cluster of excellence" within the excellence initiative of the German federal government. The "Werner Reichardt Centre for Integrative Neuroscience (CIN)" was formally founded in December of 2008. It will bring numerous new professorships and junior research groups to Tübingen, enriching neuroscience and providing new opportunities also for the HIH, particularly as the CIN made it possible to secure the construction of a second research building.

Finally, the HIH, together with the Medical Faculty, the University and the University Hospital successfully applied for a partner institute of the "German Center for Neurodegenerative Diseases within the Helmholtz-Association (DZNE).

All these developments will ensure the long-term success of the neuroscience community in Tübingen.

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 von HIH und Neurologischer Klinik in einer Zentrumsstruktur 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 gleichzeitig ein Vorteil, aber auch eine Herausforderung: sie soll in einer Weise, wie sie an traditionell aufgebauten Universitätskliniken kaum möglich ist, die patienten- und krankheitsorientierte Forschung fördern, und – um es mit einem heute gängigen Begriff auszudrücken– translationale Medizin ermöglichen. Diese Struktur ist aber auch eine Herausforderung, da sie mehr Flexibilität, Kooperationsbereitschaft und gegenseitiges Verständnis 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 achtzehn 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 der Untersuchung synaptischer Plastizität im Drosophila-Modell wurde Ende 2008 etabliert. Diese Gruppen werden für drei bis fünf Jahre aus dem zentralen Forschungspool des HIH finanziert.

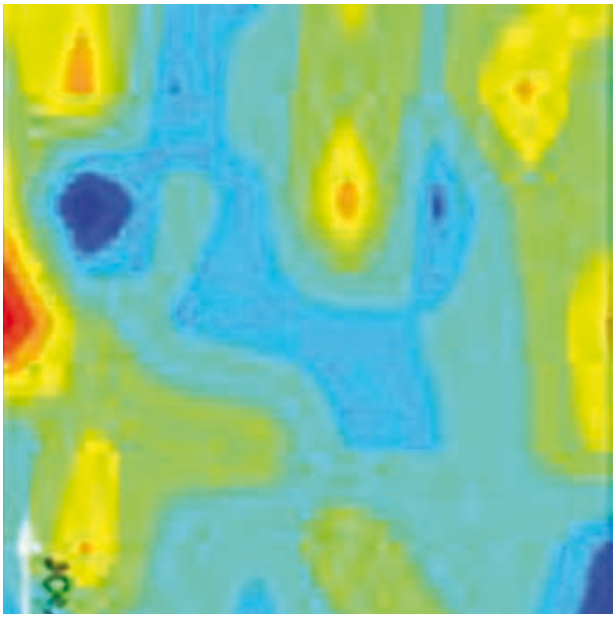
Zweimal im Jahr wird das HIH von seinem Kuratorium, das sich aus namhaften deutschen Neurowissenschaftlern zusammensetzt, besucht. Die Evaluationen dieses Gremiums sind dem Institut eine wertvolle Hilfe bei der weiteren Entwicklung.

Das Hertie-Institut ist in den sechs Jahren seiner Existenz rasch gewachsen. Seine Entwicklung ist noch lange nicht abgeschlossen.

Arbeitsgruppen des HIH waren unter Führung von Prof. P. Thier maßgeblich daran beteiligt, dass sich die Universität Tübingen erfolgreich um ein Exzellenzcluster im Rahmen des Exzellenzwettbewerbs der Bundesregierung bewerben konnte. Das dadurch geförderte „Werner-Reichardt Centrum für Integrative Neurowissenschaften (CIN)“ wurde im Dezember 2008 offiziell gegründet. Mit ihm werden eine Vielzahl von neuen Professuren und Nachwuchsgruppen die neurowissenschaftliche Landschaft in Tübingen bereichern und damit auch dem HIH neue Entfaltungsmöglichkeiten bieten, nicht zuletzt durch die Realisierung eines zweiten Forschungsgebäudes.

Darüberhinaus war das HIH zusammen mit Fakultät, Universität und Klinikum im Jahr 2008 auch mit seiner Bewerbung als Partnerstandort des „Deutschen Zentrums für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft“ (DZNE) erfolgreich. Diese erfreulichen Entwicklungen werden den Forschungsstandort Tübingen langfristig sichern und bereichern.

Acting Director: Prof. Dr. Arthur Melms



Department of General Neurology

Departmental Structure

The Department of General Neurology covers a wide spectrum of neurological diseases. It is part of the University Medical Center and also provides primary care in the district of Tübingen for patients with neurological disorders. Patients are referred from all over southern Germany as well as the neighbouring countries according to the clinical and scientific expertise of the Department, i.e., cerebrovascular diseases (ischemia, intracranial hemorrhage, vasculitis, vascular malformations), neuroimmunology (multiple sclerosis, myasthenia gravis and others), and neurooncology. Specialized neurooncology and stroke teams (stroke unit and early rehabilitation) provide multidisciplinary expert care for these disorders. As an integral part of the Comprehensive Cancer Centre (CCC), the Centre of Neurooncology is formed by the departments of neurology, neurosurgery, radiooncology, neuroradiology and brain pathology. Specialized outpatient clinics include a neuroimmunology clinic, and provide long term care for these patients. Other specialized clinics include epilepsy, headache and chronic pain syndromes. The aim of these outpatient clinics is not only to offer the best available therapy but also to provide the infrastructure for clinical studies and research. Specialized wards and outpatient clinics of the Department of General Neurology therefore provide the clinical basis for the research groups at the Hertie Institute of Clinical Brain Research. Internationally renowned research groups are active in neurooncology (Dr. Tabatabai, PD Dr. Naumann), cerebrovascular diseases, rehabilitation and neuroplasticity (Prof. Dr. Luft), neuroimmunology (Prof. Melms, PD Dr. Bischof, Dr. Greve) and brainstem/cerebellar systems neurophysiology (PD Dr. Haarmeier). These research groups are located in the immediate proximity of the clinical setting in the CRONA hospital building and the Hertie Institute for Clinical Brain Research. Close collaborations exist with the other departments and research groups at the Hertie Institute. The department also cooperates closely with the physiotherapy department at the University Medical Center (Therapiezentrum), which is focused on physiotherapy for low back pain and stroke rehabilitation.

The Department of General Neurology offers lectures for medical students, physicians in training, nursing staff, physiotherapists and and speech therapists. The grand round series welcomes internationally renowned clinical scientists giving state of the art lectures. The neurovascular lunch conference and the general neurology therapy seminar cover recent advances in neurology, internal medicine, neurosurgery, neuro-ophthalmology, neuroradiology and other areas relevant to the treatment of patients with neurological diseases. The lectures of basic and clinical neurology, the neurology seminar, the neuroexamination course and the intracranial pressure seminar are an integral part of the Medical School curriculum.

Arbeitsgruppe Neuro-Onkologie

Arbeitsgruppenleiter:
Ulrike Naumann, Ghazaleh Tabatabai

Die Arbeitsgruppe für Molekulare Neuro-Onkologie befasst sich mit verschiedenen Fragen der Biologie und Entwicklung neuer Therapiestrategie bösartiger Hirntumoren.

Forschungsschwerpunkte umfassen die Aufdeckung von Mechanismen, die zur Entstehung des Glioblastoms, des bösartigsten Hirntumors, führen und die Erforschung der Ursachen, warum diese Tumoren weitestgehend resistent gegenüber konventionellen Behandlungsmethoden wie Chemotherapie und Bestrahlung sind. Desweiteren werden neuartige Therapiestrategien entwickelt: Einige Ansätze zielen darauf, das körpereigene Immunsystem, das durch TGF-β, ein vom Gliom gebildetes Zytokin, gehemmt wird, wieder zu aktivieren. Nach einer derartigen Immuntherapie „reaktivierte“ 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: Ursprünglich krankheitserregende Viren können genetisch verändert und zur Tumorbekämpfung umfunktioniert werden. Diese veränderten, „krebsauflösenden“ (= onkolytischen) Viren befallen und vermehren sich ausschließlich in Tumorzellen. Durch die Vermehrung der Viren in der Tumorzelle wird diese lysiert, d.h. aufgelöst und die frei werdenden Viren befallen weitere, umliegende Krebszellen. Da das Virus ist nicht fähig ist, sich in „Nicht-Tumorzellen“ zu vermehren, bleiben normale Körperzellen unbeeinflusst. Andere Viren werden eingesetzt, um körpereigene Zellen (z.B. Stammzellen aus dem Blut) zu Transportsystemen umzufunktionieren. Diese veränderten Stammzellen wandern spezifisch zum Tumor und können daher als Transportvehikel genutzt werden, um therapierelevante Wirkstoffe oder Eiweiße gezielt zum Ort des Tumors zu 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 und wie diese Zellen sich gegen den Prozess des programmierten Zelltods (Apoptose) schützen. Ebenso werden in Kooperation mit pharmazeutischen Herstellern Hemmstoffe, sogenannte „small molecules“ hinsichtlich ihrer Einsetzbarkeit in der Gliomtherapie ausgetestet.

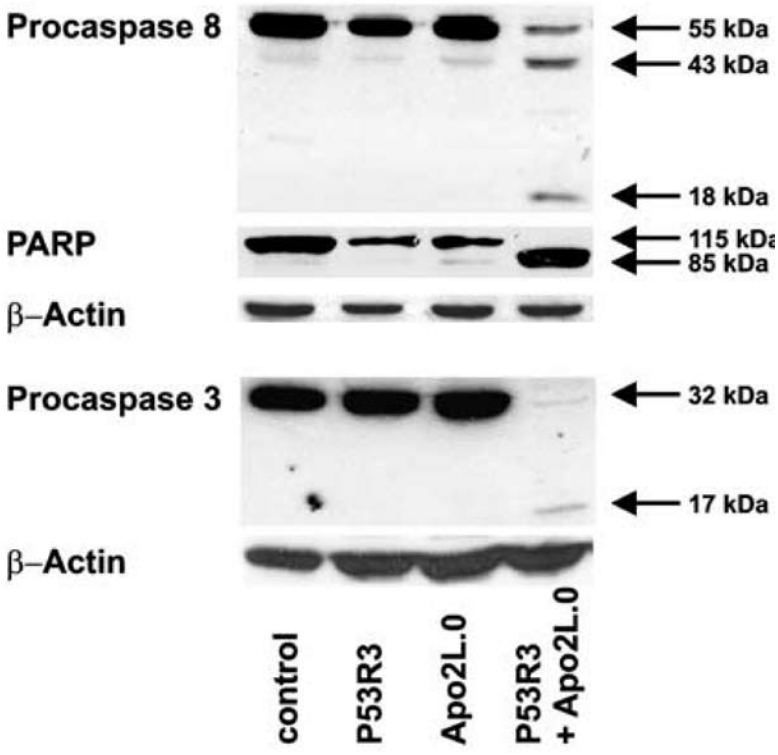
Neuro-Oncology

Group leaders:
Ulrike Naumann,
Ghazaleh Tabatabai

The Laboratory of Molecular Neuro-Oncology sets its focus on molecular, cell biological, metabolic and immunological aspects of malignant brain tumors leading to the development of new strategies for glioma therapy. The development of new therapies for malignant glioma involves viral therapy using oncolytic adenovirus as well as replication deficient adenovirus to express therapeutic genes, the identification of genes as putative new targets for glioma gene therapy, the mechanism of glioma tropisms of hematopoietic stem cells as well as in how far these cells can be used as a shuttle for the transportation of therapeutic genes. In addition, induction of cell death in glioma cells using small molecules is another focus of experimental glioma therapy.

Apoptosis (programmed cell death) is a well organized process of cellular suicide. Disorganization of this process leads to uncontrolled proliferation and survival, important processes in cancer development. We have tested whether adenoviruses coding for genes that regulate cell death are useful tools for future glioma gene therapy: CTS-1, a chimeric tumor suppressor, is based on the sequence of the tumor suppressor gene p53. This protein, also named "guardian of the genome", is mutated and therefore inactivated in more than 50% of tumors. Overexpression of CTS-1 in glioma cells induced cell death and blocked cell proliferation. To identify genes involved in CTS-1 mediated cell death in glioma, we generated a CTS-1-resistant glioma cell line. Whole genome expression array analysis showed differential expression of about 560 genes in parental and resistant cells. In a recent project, some of the genes identified so far were analyzed regarding their function in glioma. Future studies will analyze whether some of these genes are feasible as targets for glioma gene therapy. A second strategy to induce p53 activity in tumor cells sets the goal to reactivate mutant p53. Three "small molecule" p53 rescue compounds, P53R1, -R2 and -R3, restore the activity of mutant p53 proteins. These compounds induced p53 recruitment to target promoters in glioma cells, induced p53-dependent growth arrest and sensitized glioma cells to caspase-mediated apoptosis (Fig. 1). This study defines potentially effects of small molecules which open up new perspectives for cancer therapy.

Transforming growth factor-β (TGF-β) is abundantly expressed in malignant glioma and crucial for the tumor micromilieu. TGF-β not only enhances migration and invasion of glioma cells but also inhibits an effective anti-glioma immune response. TGF-β mediates its biologic effects through interactions with TGF-β receptors -II to -III. Soluble TGF-β recep-

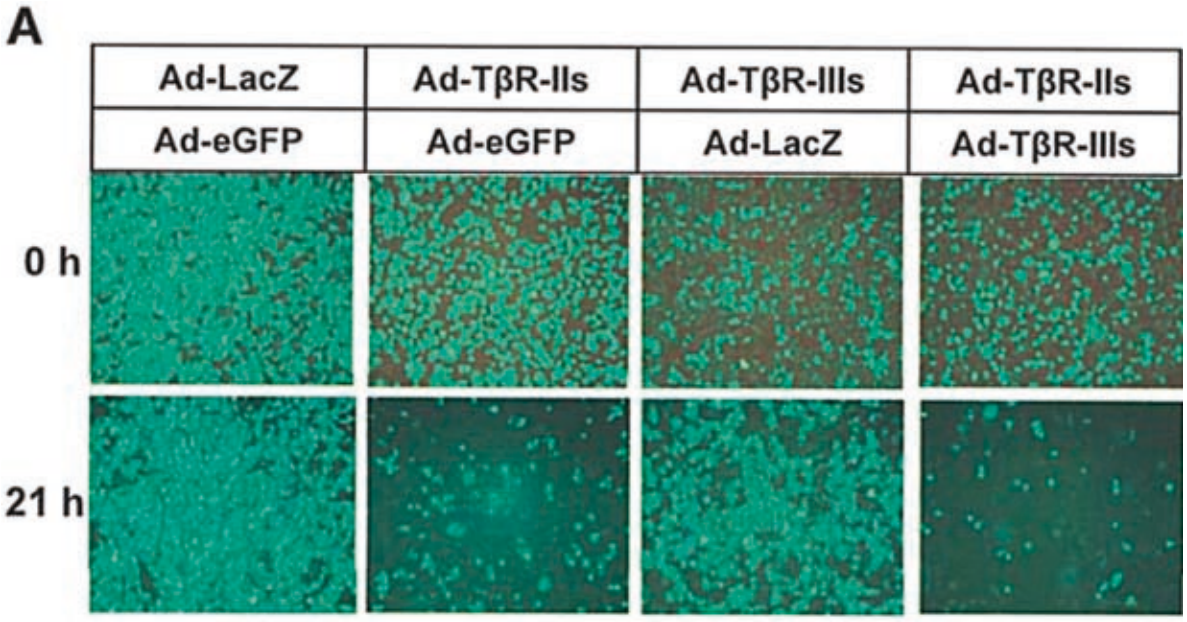


▼ Figure 1: P53R3 sensitises for Apo2L.0-induced apoptosis upstream of caspase activation. T98G cells were pretreated with P53R3 (20 mg/ml) for 24 h and co-treated with Apo2L.0 (100 ng/ml) for 6 h, lysed and analysed for the processing of caspases 8 and 3 and PARP by Immunoblot.

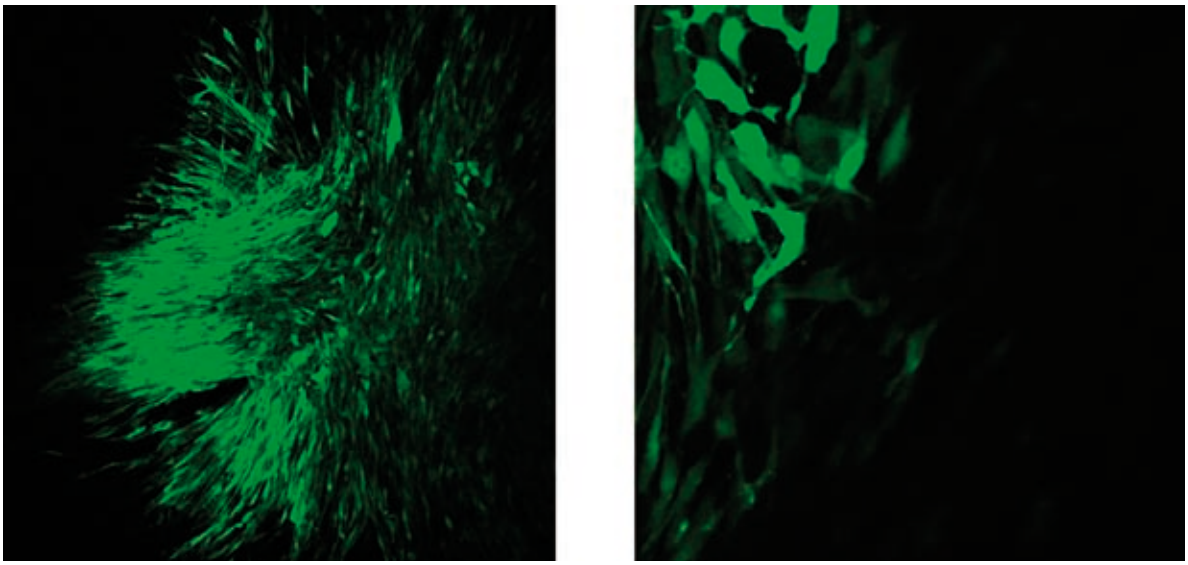
tors abrogate the TGF-β effect by competing for the binding of the ligand to its receptor. In an experimental glioma model we used adenoviral gene transfer to express soluble TGF-β receptors II and III in human glioma cell lines. The resulting data commend soluble TGF-β receptors as an immunotherapeutic tool since the lytic functions of natural killer cells were restored by the expression of soluble TGF-β receptors. In vivo, the transduction of glioma cells with soluble TGF-β receptors markedly prolonged survival of tumor bearing mice indicating that the expression of soluble TGF-β receptors could be used as a possible therapy of glioma (Fig. 2).

The development of oncolytic adenovirus for glioma virotherapy is another focus of interest. Viruses are known as inductors of disease. But not every virus induces sickness in man. For this, so called "oncolytic viruses" could be used to fight against cancer. These viruses identify and solely replicate in tumor cells. Non-neoplastic cells were infected, but the virus does not replicate. As a consequence of replication, the tumor cell is killed. In our studies we are testing an adenovirus (Ad-DELO) which exclusively replicates in chemoresistant tumor cells. As a side effect, infection of the cells with Ad-DELO leads to enhanced sensitivity towards chemotherapy. Armament of Ad-DELO with a shRNA against a DNA repair enzyme, MGMT, further sensitizes infected cells to chemotherapy. Treatment of glioma bearing mice showed prolonged median survival of mice having a combinatorial therapy with Ad-DELO and temozolomide, a chemotherapeutic drug.

Lentiviruses were used to transduce hematopoietic progenitor cells to express therapeutic genes. These infected hemotopoietic progenitor cells were directly targeted into the tumor mass and are therefore feasible shuttle vehicles for therapeutic molecules. Lentivirus could also be used to infect so called glioma stem cells (GSC). GSC, which are highly resistant to conventional cancer therapy, are presumably responsible for the generation of glioma recurrence. Therefore, GSC are highly interesting objects for new therapeutic approaches. To analyze the cell-cell interactions between tumor cells and transduced hematopoietic stem cells as well as to analyze mechanisms of tumor angiogenesis, we established, in cooperation with the department of cellular neurology, 2-Photon-Miscroscopy (Fig. 3).



▲ Figure 2:
Expression of soluble TGF-β receptors repress the inhibitory effects of TGF-β on the lytic activity of NK cells: GFP-positive LN-308 glioma cells were infected the indicated viruses and then irradiated with 30 Gy. After irradiation, human NK cells were added. Lysis of eGFP-positive glioma cells was assessed microscopically 24 h after co-culture.



▶ Figure 3: 2-Photon microscopic demonstration of intracerebrally GFP-transduced glioma cells (left panel: overview; 10-fold magnification; right panel: border area, 40-fold magnification).

In the Sonderforschungsprogramm "Therapeutic resistance of solid tumors" we are integrated in a network of scientific projects to analyse the molecular mechanisms responsible for resistance. Herein we are focussing to identify the role of the sphingolipid signaling pathways as well as of GSC.

homepage: http://www.hih-tuebingen.de/an/research0/neuro-onkologie/

Supported by: DFG, BMBF, Deutsche Krebshilfe, IZKF, Fortüne, SFB773, Bridging Grant Hertie-Stiftung

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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)

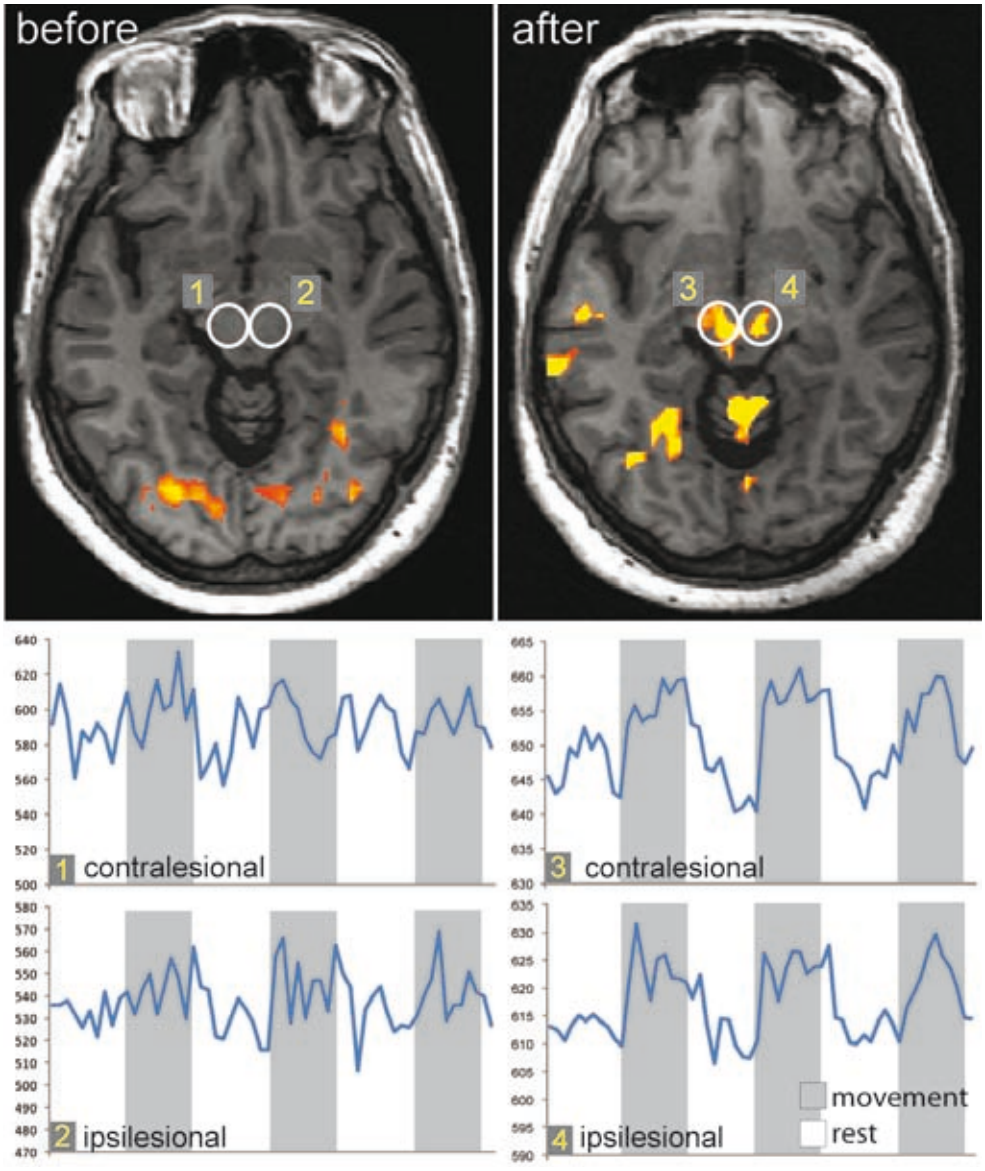
Clinical studies

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 capacity for 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 randomized controlled trials. Apart from 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.

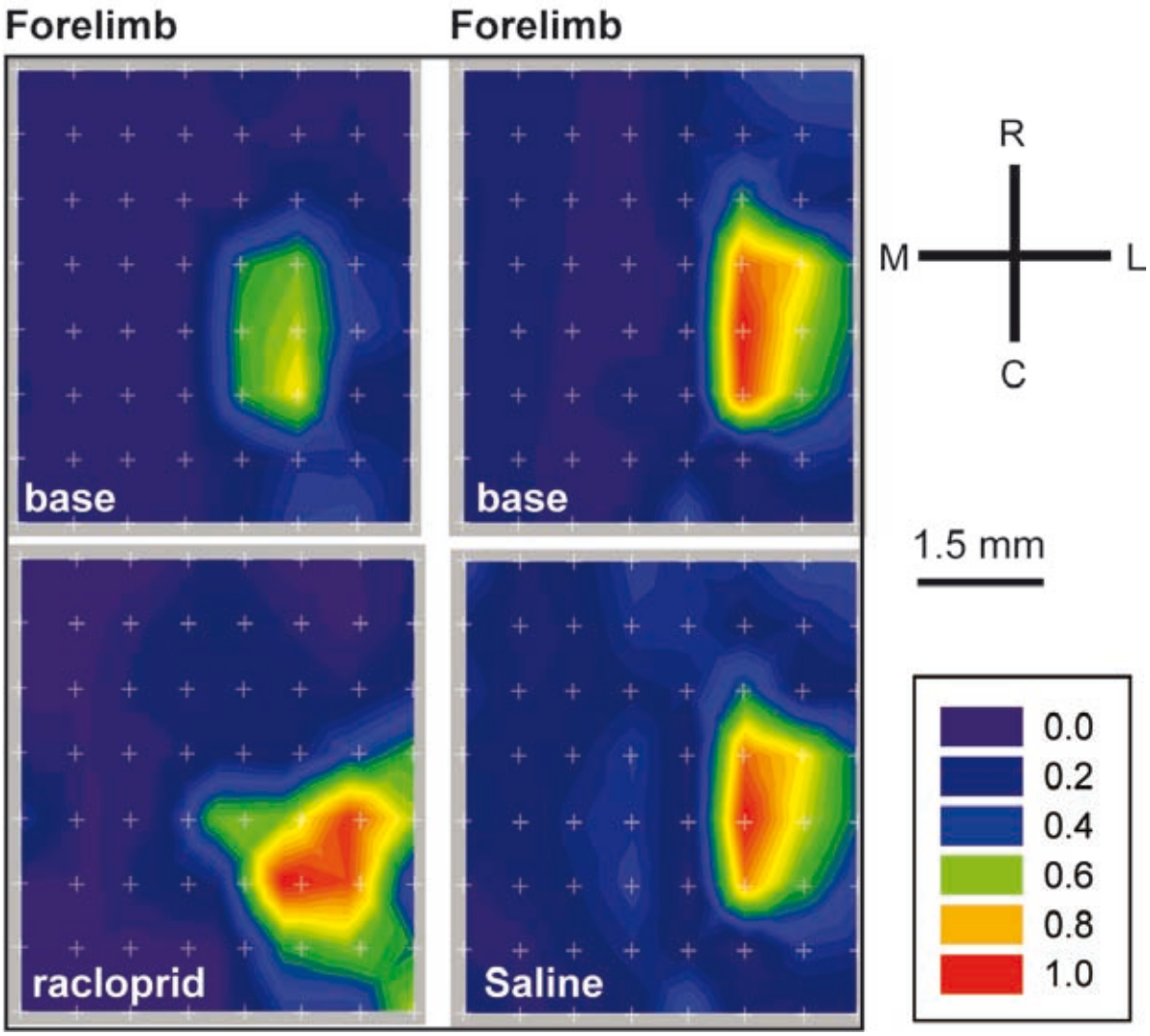
Projects

Bilateral arm training: We study whether humorous rewards (movies, smily faces) improve the therapeutic benefits of bilateral arm training (BATRAC) in stroke psurvivors with chronic hemiparesis. BATRAC is known to 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 (Luft et al, JAMA 2004, Whitall et al. Stroke, submitted). A randomized clinical study is currently recruiting at the University Hospital in Tübingen (recruitment in 2008 was 12 subjects).

Aerobic exercise training: 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 (see Figure 1). 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



◀ Figure 1:
Changes in brain activity after tradmill aerobic exercise are observed in brainstem and cerebellum.



◀ Figure 2: Somatosensory maps change and evoked potentials recorded using a thin film microelectrode array are enhanced after intracortical application of the D2-receptor antagonist reaclopride.

in neurorehabilitation and may provide further benefits to the patient. In collaboration with the Robert Bosch Hospital in Stuttgart, 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. The study has finished recruitment and will be completed by May 2009.

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 and synaptic plasticity within cortex indicating the existence of a dopaminergic system in motor cortex that supports learning and cortical plasticity. This system has been described morphologically 20 years ago, but no functional role had been found.

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. Modulation of dopaminergic transmission inside motor cortex alters cortical excitability and changes the somatosensory somatotopical map (Fig. 2).

Supported by: Deutsche Forschungsgemeinschaft (SFB 550, Lu 478/5), IZKF University of Tübingen, U.S. Veteran Affairs Administration.

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Staff:
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Arbeitsgruppe Neuroimmunologie

Arbeitsgruppenleiter: Arthur Melms, Felix Bischof

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-HirnSchranke 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.

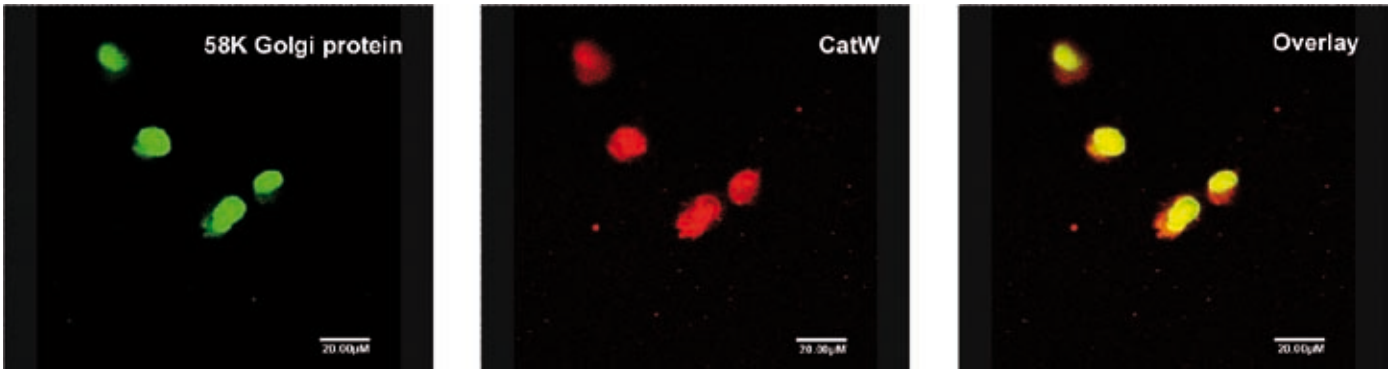
Neuroimmunology

(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.

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 in experimental autoimmune encephalomyelitis (EAE) an animal model of multiple sclerosis.

▼ Figure:
Cathepsin W (CatW) is present inside the Golgi apparatus. NKL cells were stained with antibody against the 58K Golgi protein (left panel, green), which stains the Golgi apparatus, and antibody against CatW (middle panel, red) and viewed with a confocal fluorescence microscope. The overlay of the two stainings is also shown (right panel).



Current projects address the following issues:

Selection of autoreactive T cells in the thymus and dysfunction of regulatory T cells in myasthenia gravis (C. Stoeckle).

Frequency, function and distribution of regulatory T cell populations in neuroimmunological diseases (C. Stoeckle, F. Bischof)

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 (C. Stoeckle)
- Modulation of antigen presentation as an experimental strategy to treat EAE (F. Bischof)
- Immunological memory and chronicity in autoimmunity (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 2008, our work was supported by grants from the DFG (SFB 685 and GK 794), the Gemeinützige Hertie Stiftung, and the intramural programs of the Medical Faculty of the University of Tübingen.

homepage: http://www.medizin.unituebigen.de/neurologie/0/NktaanD0_F_NIm.html)

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IZKF Nachwuchsgruppe Neuroimmunologie

Arbeitsgruppenleiter: Bernhard Greve

In der Arbeitsgruppe werden am Tiermodell der Multiplen Sklerose, der experimentellen autoimmunen Enzephalomyelitis (EAE), innovative Therapiestrategien getestet. Insbesondere wird versucht, mittels neuronaler Stammzellen immunmodulatorisch wirkende Botenstoffe gezielt in Entzündungsherde einzubringen. Damit soll die für die neurologische Symptomatik verantwortliche Inflammation im Zentralnervensystem vermindert werden.

Neuronale Stammzellen stellen einen neuen experimentellen Therapieansatz in der EAE dar: Zum einen können sie geschädigte Zellen, z.B. Oligodendrozyten, ersetzen. Zum anderen sezernieren sie per se Botenstoffe, die die Entzündungsreaktion beeinflussen. Neuronale Stammzellen haben einen ausgeprägten Pathotropismus, d.h. diese Zellen wandern selbständig innerhalb des Zentralnervensystems in Regionen ein, in den Entzündungsreaktionen oder sonstige Formen der Zellschädigung stattfinden. Wir machen uns diesen Tropismus zu Nutze, um gezielt immunmodulatorische Botenstoffe in die Regionen des Körpers zu bringen, in denen Entzündungsreaktionen stattfinden. Zu diesem Zweck setzten wir genetisch veränderte neuronale Stammzellen ein, die ein anti-inflammatorisch wirkendes Zytokin produzieren. Wir testen der Erfolg der Behandlung von an EAE erkrankten Tiere mit solchen Zellen und untersuchen darüber hinaus in vitro, wie solche Zellen mit Immunzellen interagieren.

Andere Projekte in unserer Gruppe beschäftigen sich mit der genetischen Regulation von Autoimmunerkrankungen. Hierzu werden gezielt Gene untersucht, die die Empfänglichkeit (Suszeptibilität) für MS/EAE oder auch immunologische Subphänotypen beeinflussen.

IZKF Junior Group Neuroimmunology

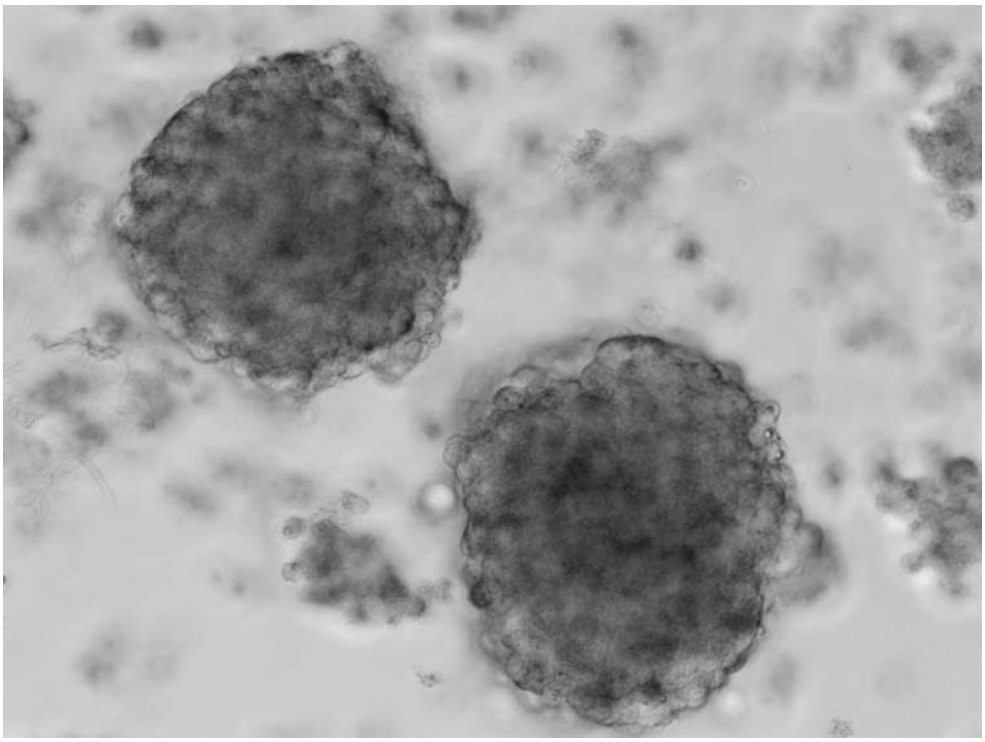
(Group leader: Bernhard Greve)

Multiple sclerosis (MS) is a disabling disease in which an autoimmune response directed against self antigens leads to damage of oligodendrocytes with subsequent demyelination and axonal damage. Current therapeutic approaches include multi-step, escalating immunomodulation and immunosuppression including corticosteroids, β-interferons, glatiramer acetate and immunosuppressants such as mitoxantron or cyclophosphamide. The recently established drug natalizumab is targeting the adhesion molecule very late antigen 4 (VLA-4) and inhibits the migration of immune cells into the central nervous system (CNS). Although current therapeutic approaches still focus on modulation or suppression of the immune system, recently the concept of remyelination and damage repair has been becoming more and more important.

The animal model of MS, experimental autoimmune encephalomyelitis (EAE), can be induced in different animal species, including rodents, by immunization with encephalitogenic CNS-associated proteins and immunodominant peptides. The pathology of EAE in mice and rats resembles in varying aspects the pathology of MS, including T cell and antibody responses, demyelination and axonal damage as well as clinical aspects such as occurrence of paralysis and different disease courses. Various therapeutic agents currently in clinical use or development have been discovered using animals models, the most prominent being glatiramer acetate and natalizumab. Therefore, EAE is a valuable model to investigate pathomechanisms as well as evaluating new therapeutics in MS.

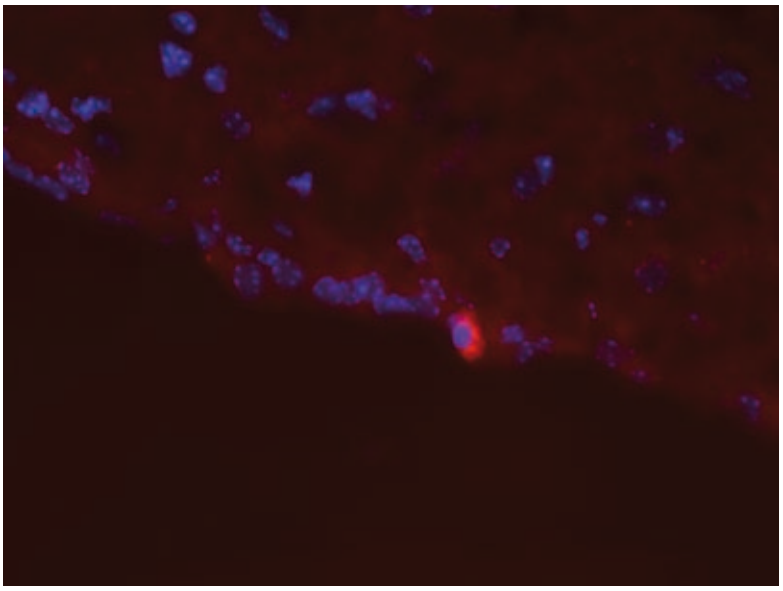
Auto-reactive CD4 T cells are a central component of the pathophysiology in MS and EAE although other cell types (CD8 T cells, B cells) have been implicated in CNS inflammation as well. The current concept of CD4 T cell lineage development include effector cells such as the classical T helper (Th) 1 and Th2 cells and, more recently, IL-17-producing Th17 T cells. Naïve precursor cells can be differentiated into IL-17-producing cells by TGF-β and IL-6. The central role of Th17 cells for the pathogenesis of chronic inflammation is currently being discovered.

On the other hand, effector CD4 T cells are controlled by various subsets of regulatory T cells (Treg). FoxP3-positive Treg may develop within the thymus or are induced in the periphery by TGF-β in absence of IL-6. FoxP3-negative Tr1 cells are induced by IL-10 and are themselves characterized by the production of this cytokine. IL-10 inhibits the production of a broad range of pro-inflammatory cytokines (e.g. TNF, IL-1) and chemokines as well as expression of MHC class II by antigen presenting cells, skews B cell function and can directly induce T cell anergy.



◀ Figure 1:
Murine neuronal stem cells (mNSC) grow in typical neurospheres in culture.

An emerging approach for a comprehensive therapy integrating various mechanisms of established and experimental therapies is the treatment with neural stem cells. Neural precursors, migrating to inflamed CNS tissue, may (i) decrease the levels of inflammatory mediators, (ii) enhance the number of new myelin-producing cells and regenerating neurons, (iii) produce growth factors promoting remyelination and (iv) reduce development of astrocyte scars.



◀ Figure 2:
After intravenous injection of PKH-labeled neuronal stem cells (red) into mice with EAE, the cells can be detected within the CNS.

▲ Figure 2:
After intravenous injection of PKH-labeled neuronal stem cells (red) into mice with EAE, the cells can be detected within the CNS.

In the mouse, multipotent neural stem cells are present in the subventricular zone (SVZ) of the lateral and third ventricle, in the hippocampus area and in the spinal cord ependymal layer. In vitro, they can be differentiated into different cell types including neurons, oligodendrocytes and astrocytes. During murine EAE, SVZ cells have been shown to be mobilized into the periventricular white and gray matter structures and some cells are found in demyelinating lesions. Recently, it has been shown that endogenous neural stem cells express B7 costimulatory molecules which enable them to interact with T cells. Cultured mouse neural precursor cells express VLA-4 and CD44 enabling them to interact with the blood brain barrier and to enter the CNS. Vascular endothelial growth factor (VEGF) is guiding the tumor-directed migration of human neural stem cells. Furthermore, it has been shown that neural precursor cells, when injected into mice or rats with EAE, home to areas of demyelination and axonal loss and are participating in remyelination processes. Neural precursors also accumulate in perivascular areas and survive repeated episodes of CNS inflammation. Coherent with these observations, it has been demonstrated that peripheral injection of neural precursors ameliorates clinical EAE, even if injected after disease onset.

Besides these intrinsic anti-inflammatory and repair-inducing properties, neural stem cells may be used for CNS delivery of disease-modifying factors. In contrast to other gene delivery methods (e.g. direct injection of adenoviral vectors into the CNS) this concept makes use of the unique pathotropism of neural stem cells which enables them not only to enter the CNS from the periphery but also directs their migration within the brain to sites of inflammation, demyelination, trauma or tumor growth. However, in most of the studies conducted so far using cell-based gene delivery, cell lines were injected directly into tumors or into the CNS.

In our project we make use of the pathotropism of neuronal stem cells by treating mice suffering from EAE with stem cells which are genetically modified to produce an anti-inflammatory cytokine. Therefore we use the intrinsic anti-inflammatory and regenerative abilities of neuronal stem cells and at the same time use them as a vehicle for delivery of an immune-modulating cytokine to sites of inflammation. Furthermore we study the interaction of neuronal stem cells with auto-reactive T cells in vitro under various experimental conditions. One additional aspect of our work is to inves-

tigate whether neuronal stems cells are able to induce regulatory T cells.

Further projects of our group focus on intracellular signaling pathways during autoimmune responses and the genetic regulation of autoimmune diseases. To this end we examine possible associations of specific candidate genes with MS/EAE or immunological sub-phenotypes of these diseases.

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Key Publications

Greve B, Hoffmann P, Vonthein R, Kun J, Lell B, Mycko MP, Selmaj KW, Berger K, **Weissert R**, Kremsner PG (2008) NCF1 gene and pseudogene pattern: association with parasitic infection and autoimmunity. Malar J 7:251

Greve B, Simonenko R, Illes Z, Peterfalvi A, **Hamdi N**, Mycko MP, Selmaj KW, Rozsa C, Rajczy K, Bauer P, Berger K, **Weissert R** (2008) Multiple sclerosis and the CTLA4 autoimmunity polymorphism CT60: no association in patients from Germany, Hungary and Poland. Mult Scler 14(2):153-8

Arbeitsgruppe Neurophonetik („neuro-speech“)

Arbeitsgruppenleiter: Hermann Ackermann

Unsere Arbeitsgruppe beschäftigt sich mit den zerebralen Grundlagen der Sprechmotorik und der Sprachlautwahrnehmung, eines nur den Menschen zur Verfügung stehenden „Kanals“ akustischer Kommunikation, der wiederum die Voraussetzung eines ebenfalls unserer Spezies vorbehaltenen verbalen Codes der Informationsverarbeitung darstellen dürfte. Zur Anwendung kommen (i) akustische und kinematische Analysen der Sprech- / Stimmstörungen bei „Modellerkrankungen“ des zentralmotorischen Systems, (ii) psychoakustische und –linguistische Experimente sowie (iii) funktionell-bildgebende Untersuchungen (funktionelle Kernspintomographie, fMRI; Ganzkopf-Magnetenzephalographie, MEG) zu den zerebralen Mechanismen der Verarbeitung von Lautsprache. Im vergangenen Jahr standen drei Fragestellungen im Vordergrund (gefördert von der Deutschen Forschungsgemeinschaft):

a. die Interaktionen des zentral-auditiven und zentral–visuellen Systems im Rahmen der Sprachlautwahrnehmung (SFB 550),

b. die funktionell-neuroanatomische Kompartimentalisierung des zerebralen Netzwerks der Sprechmotorikkontrolle (DFG AC 55/6-2),

c. die zerebralen Korrelate / Grundlagen von “Sprachtalenten“ wie der Fähigkeit des akzentfreien Gebrauchs von Fremdsprachen (DFG AC 55/7-1).

In den folgenden Absätzen soll der erstgenannte Forschungsschwerpunktetwas detaillierter dargestellt werden.

Mit Hilfe von fMRI und Ganzkopf-MEG werden die räumliche Verteilung hämodynamischer Aktivierungsmuster bzw. der Zeitverlauf evozierter Magnetfelder während der Verarbeitung audiovisueller Stimuluskonfigurationen erfasst. Die bisherigen MEG-Befunde weisen auf mehrere Schnittstellen von zentral-auditivem und –visuellem System hin, die sich (i) frühen Komponenten der Aufmerksamkeitslenkung, (ii) transmodalen „imagery“-Prozessen und schließlich (iii) der phonologischen Verrechnung sprachlich-kategorialer Informationseinheiten zuordnen lassen. Einerseits können diese Untersuchungen einen Beitrag zu der immer noch ungelösten Frage leisten, inwieweit audiovisuelle Illusionen wie z.B. der McGurk-Effekt an eine Signal-nahe oder eine eher abstrakt-kategoriale Ebene der Informationsverarbeitung gebunden sind, andererseits lassen sich durch die Analyse visueller Effekte auf die auditive Sprachwahrnehmung auch Modellvorstellungen der Linguistik zur Repräsentation sprachlicher Lautstrukturen überprüfen, z.B. die Annahme einer „phonologischen Zwischenebene“ der Wortverarbeitung.

Zumindest einige blinde Menschen sind in der Lage, ultra-schnelle verbale Äußerungen einer Silbenrate von bis 25 Silben pro Sekunde zu verstehen. Unter diesen Bedingungen ist Probanden ohne Visuseinschränkungen auditive Sprachwahrnehmung völlig unmöglich. Als ein weiterer Aspekt „audiovisueller Interaktionen“ sollen mit Hilfe funktionell-bildgebender Methoden die zerebralen Mechanismen dieser Fähigkeiten untersucht werden. Erste Ergebnisse deuten darauf hin, dass blinde Probanden offensichtlich Gyrus fusiformis und visuellen Kortex (!) zur Sprachlautwahrnehmung mit heranzuziehen vermögen.

Neurophonetics group

(Group leader:
Hermann Ackermann)

The "neuro-speech" group investigates the neural bases of speech communication - an unique capability of our species - based upon several approaches: (i) acoustic and kinematic analyses of speech motor deficits in patients with cerebral disorders / diseases, (ii) psychoacoustic and -linguistic experiments, and (iii) functional-imaging techniques (functional magnetic resonance imaging, fMRI; whole-head magnetoencephalography, MEG). At the moment, our scientific work focuses on three issues (supported by the German Research Foundation):

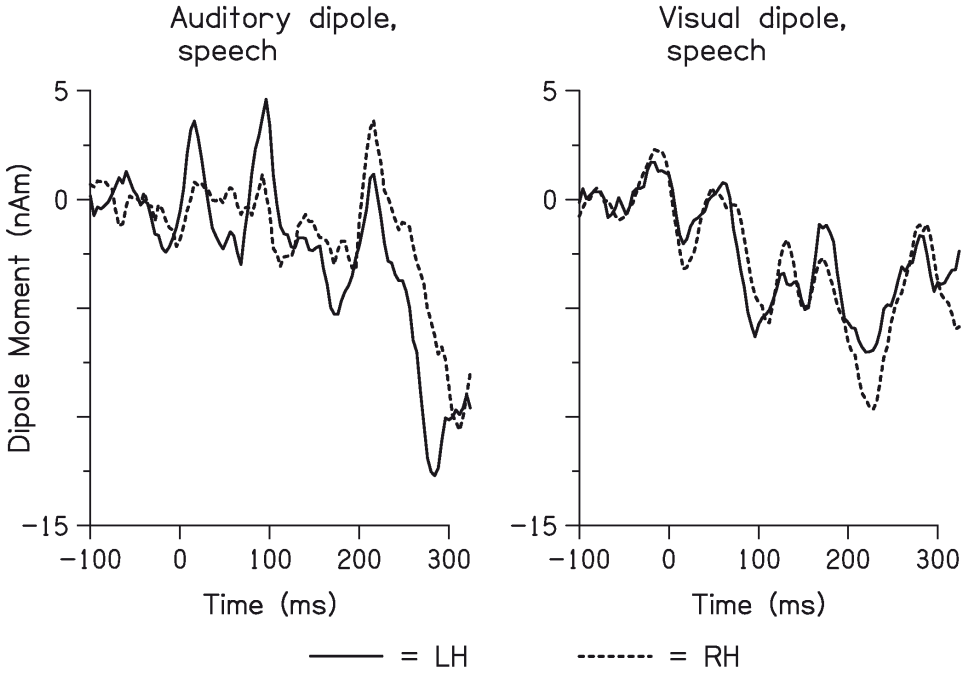
a. interactions of the central-auditory and -visual system during speech perception (SFB 550),

b. functional compartmentalization of the brain network of speech motor control (DFG AC 55/6-2),

c. cerebral correlates of "speech / language talents" (DFG AC 55/7-1).

The following paragraphs address the first of these research domains, i.e., the interactions of the central-auditory and –visual systems during speech perception.

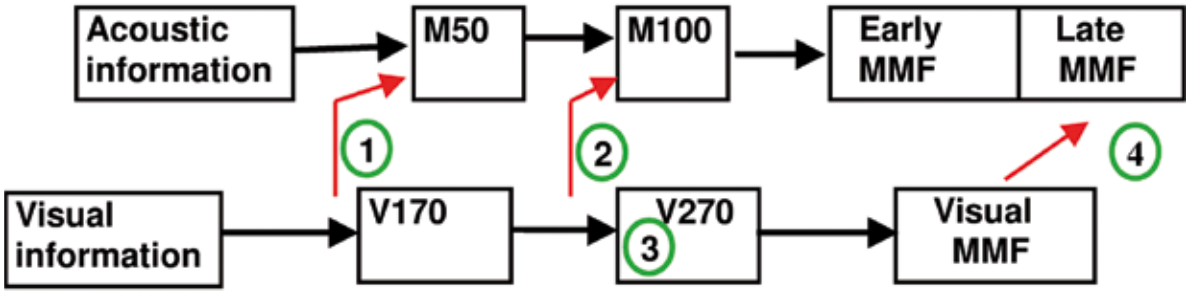
In case an auditory speech signal is synchronized with a video display of a speaking face, the visual channel may elicit auditory illusions – if the phonological information of the video is not congruent with the auditory input. The so-called McGurk effect, i.e., the perception of the phoneme /d/ if an acoustic /b/ is paired with a video of a speaker uttering /g/, represents a well-known example of such an illusion.



▼ Figure 1: Time course of mismatch responses to visual speech deviants (subspace projection onto bilateral dipole sources; RH = right, LH = left hemisphere) within the central- auditory system (left panel) and at a more posterior location (about 2 cm; right panel).

In our first whole-head MEG study addressing audiovisual interactions (Hertrich et al., Neuropsychologia 2007), we used an oddball design in order to elicit mismatch responses to rare stimuli differing from audiovisual standard /pa/ or /ta/ syllables (= frequent event) either in the acoustic or in the visual channel. This study revealed the latency of the mismatch response to visual deviants (> 200 ms) to be considerably prolonged as compared to acoustic deviants (180 ms). Furthermore, the visually-induced mismatch responses encompassed two components: the earlier one (ca. 220 ms) was bound to a source location posterior to the central-auditory system and lateralized to the right hemisphere whereas the later one, peaking at a latency of about 275 ms, could be assigned to a dipole source within left-hemisphere auditory cortex (see Figure 1). Among others, these findings clearly support a "late fusion" model of audiovisual speech perception. Conceivably, logical phonological operations act both upon visual and auditory features (e.g., the labial "place of articulation", derived from a visible bilabial gesture), giving rise to a perceptual (!) phoneme (re)construction (e.g., /p/). This suggestion is in line with a relatively broad temporal window for the integration of auditory and visual features (ca. 200 ms) as reported in earlier studies on the McGurk effect.

Apart from insights into audiovisual fusion processes during speech perception, the whole-head MEG study referred to

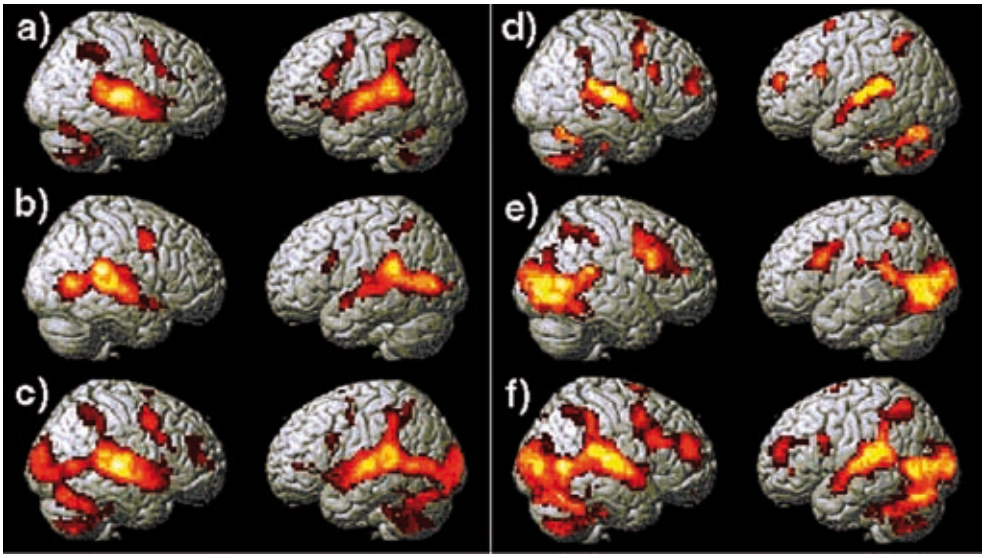


▲ Figure 2:
Sequence of interactions between the auditory and visual information "streams" as derived from the MEG data. The numbers within the green circles refer to different effects of visual motion upon evoked magnetic fields during AV speech perception:
(1) bilateral speech-unspecific attenuation of auditory evoked M50 fields (preparatory baseline shift),
(2) AV interactions at the level of the auditory evoked M100 component (differential pre-representational impact of visual speech and non-speech information; speech signals = hypoadditive M100 enhancement, non-speech signals = M100 attenuation),
(3) phonetic-linguistic coding ("weighting") of visual information outside the central-auditory system in terms of left-hemisphere suppression of /ta/-syllables,
(4) cross-modal sensory memory operations, developing into a fused phonetic percept, as indicated by a speech-specific visually induced left-lateralized late component (275 ms) of the mismatch field (MMF).

also revealed some interesting differential early effects of visual /pa/ and /ta/ stimuli on auditory evoked magnetic fields, even in case these videos were paired with acoustic non-speech tone signals. In order to further analyze these early encoding characteristics of visual speech features, a subsequent MEG investigation (Hertrich et al., Journal of Cognitive Neuroscience 2009) focused on pre-attentive processes within the temporal domain of the auditory M50 and M100 fields. This study revealed (i) supramodal visual motion effects within the M50 window of an opposite polarity to the auditory M50 during application both of speech (syllables) and non-speech stimuli (contraction/expansion of a circle pattern), (ii) a speech-specific hypoadditive impact of the speaking face upon the central-auditory system within the time domain of the auditory M100 field, and (iii) categorical (= all-or-nothing) effects of movement size of the speaking lips, conceivably, reflecting the transition of visual information from an analogue to a categorical representation. More specifically, responses to visual motion in case of /ta/ syllables appear to be suppressed, an operation that might be related to the phonological underspecification of coronal consonants in the mental lexicon.

Figure 2 displays the model of audiovisual speech perception processes derived from these results.

As a follow-up study to the second whole-head MEG experiment, the same stimulus configurations served as the test materials of an event-related fMRI study in order to obtain a more fine-grained cerebral localization of the various audiovisual processing stages of speech perception referred to. This investigation allows for two major conclusions (Hertrich et al., in preparation). First, the hypoadditive magnetic fields of the auditory cortex in response to visual speech stimuli - as documented in the preceding MEG study could be confirmed: silent visual speech motion, usually, gave



▼ Figure 3:
Functional magnetic resonance imaging (fMRI) during application of speech (a, b, c) and non-speech (d, e, f) stimuli (versus baseline, i.e., static visual stimuli); separate display of acoustic-only (a, d), visual-only (b, e), and AV trials (c, f; threshold: voxel-level $p < 0.001$, uncorrected; cluster-level $p < 0.05$, corrected).

rise to hemodynamic responses even in primary auditory cortex whereas, by contrast, non-speech control stimuli (circle patterns moving in a concentric fashion) did not activate the upper temporal lobe (Figure 3). In the presence of an acoustic speech signal, furthermore, visual motion did not elicit additional hemodynamic activation of the central auditory system. Second, visual motion yielded a distributed response pattern, encompassing inferior occipitotemporal areas, inferior frontal gyrus (IFG), and inferior parietal structures (IPG). At the level of occipitotemporal cortex, hemodynamic activation was approximately proportional to the perceived size of movement, indicating an analogue mode of stimulus encoding. In the absence of an acoustic signal, by contrast, the hemodynamic reaction of right IFG (pars triangularis) was characterized by overpropotional activation in response to visual /pa/ as compared to /ta/ syllables. Furthermore, left IFG as well as left IPG showed an interaction of motion size with the speech/nonspeech factor, indicating the range of speech (speaking face) and non-speech visual motion (moving geometric pattern) to be processed in a different manner.

As a further aspect of the interactions between the central-auditory and -visual system, our group has begun functional imaging studies in blind subjects capable to perceive ultra-fast synthetic speech of up to ca. 25 syllables per second. The cerebral mechanisms of this learned ability of blind patients have not yet been investigated so far. A first single-case study (Hertrich et al., Neurocase, in press) revealed hemodynamic activation of primary visual cortex and fusiform gyrus during auditory speech perception in this subject (Figure 4).

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Key Publications

Ackermann H (2008) Cerebellar contributions to speech production and speech perception: psycholinguistic and neurobiological perspectives. Trends in Neurosciences 31:265-72

Hertrich I, Mathiak K, Lutzenberger W, **Ackermann H** (2009) Time course of early audiovisual interactions during speech and nonspeech central auditory processing: A magnetoencephalography study. Journal of Cognitive Neuroscience 21:259-74

Riecker A, **Brendel B**, Ziegler W, Erb M, **Ackermann H** (2008) The influence of syllable onset complexity and syllable frequency on speech motor control. Brain and Language 107:102-13

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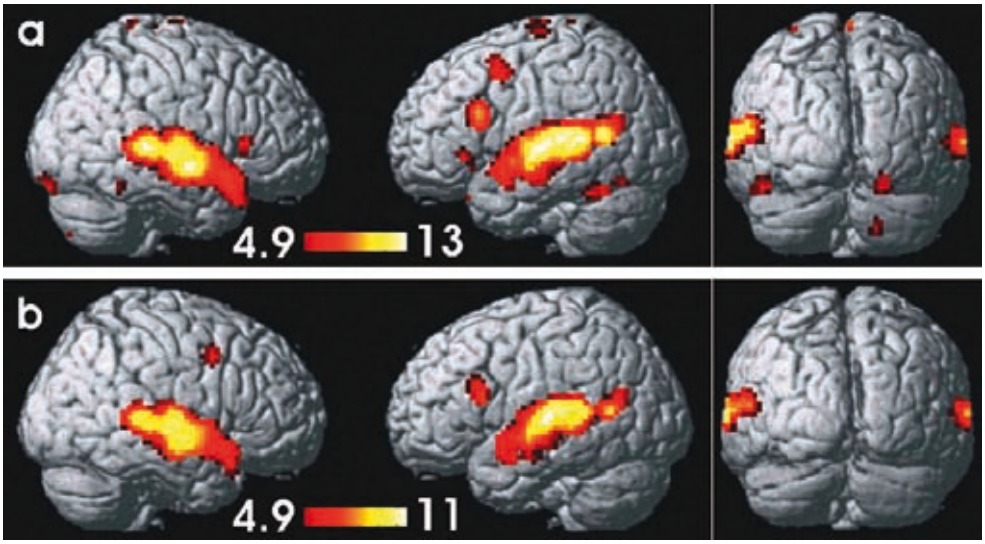
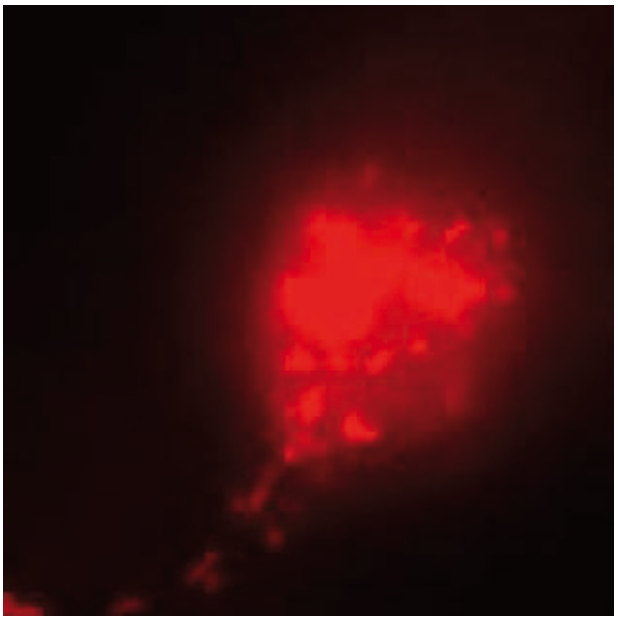
B. Brendel, M. Borutta, S. Dietrich, I. Hertrich, X. Hu, S. Reiterer



▶ Figure 4: Hemodynamic activation (fMRI; versus baseline) during perception of ultra-fast (upper panels) as compared to slow speech (lower panels) in a blind listener.

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 follows 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 and patient care.

Through its clinical division, the department treats patients with neurodegenerative diseases and movement disorders in one inpatient unit of 21 beds (Ward 43, under the supervision of Prof. Schöls and Prof. Krüger) and a number of specialized outpatient clinics. Diagnosis, differential diagnosis, and treatment of these disorders are carried out by specially trained staff on all levels, including nurses, physiotherapists, occupational and speech therapists, as well as 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, smell 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 Prof. Krüger in close collaboration with Dr. Garabaghi 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 Prof. Berg), dystonias, ataxias, spastic paraplegias, and neurogenetic disorders provides highly efficient patient management. The equally close interaction with basic research groups of the Hertie Institute for Clinical Brain Research, on the other hand, allows truly translational research with a rapid transfer of scientific progress into clinical practice.

This innovative concept includes active education and training of scientific and clinical junior staff.

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.

The basic research of the department was strengthened by the establishment of a "Section for Functional Neurogenetics" in 2006, headed by Prof. Kahle, who joined the department coming from Munich, and who provides 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 einem bestimmten Gen 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 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 konnten wir und andere zeigen, 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 Beschreibung des Verlaufs und des klinischen Erscheinungsbilds (Phänotyp), sowie die Suche nach Biomarkern und krankheitsmodifzierenden Faktoren im Vordergrund steht.

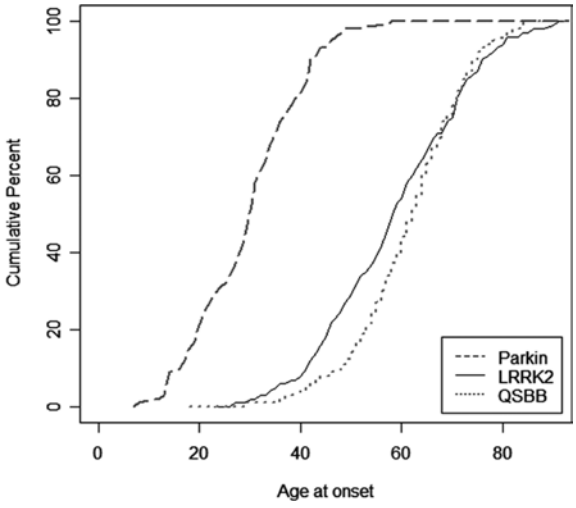
Aber auch andere „Parkinson-Gene" werden intensiv weiter untersucht, wie etwa das Gen für „α-Synuklein“, das "Parkin-Gen", das die häufigste rezessiv erbliche Form der Erkrankung verursacht, oder das erst vor Kurzem als Parkinson-Risikofaktor identifizierte Gen für die Glucocerebrosidase, das bislang nur als ursächlich für die seltene Gaucher-Erkrankung bekannt war. In grossen nationalen Konsortien, wie etwa dem Nationalen Genomforschungsnetz NGFNplus, der Helmholtz-Allianz, aber auch in vielen internationalen Kooperationen werden mit neuesten Methoden, etwa der „genomweiten Assoziationsuntersuchungen“ weitere genetische Risikofaktoren gesucht.

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.

Genetics of Parkinson's Disease and Other Movement Disorders

(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 diseases and movement disorders, such as the dystonias. Specific mutations in these genes cause rare familial forms of the respective conditions, whereas other, more common sequence variants, often called 'single nucleotide polymorphisms' or 'SNPs', are thought to increase susceptibility to the sporadic disorders. 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 and neurologic centers. DNA is isolated and data are entered into a comprehensive DNA-databank by Ann-Kathrin Hauser and Katja Hesse.



▲ Figure 1 Age of PD onset plotted against the cumulative proportion of the entire LRRK2 (black line), QSBB (Queen Square Brain Bank of idiopathic PD, dotted line) and parkin (dashed line) series respectively. LRRK2 develops at a younger age compared with sporadic iPD.

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 turned out to be clearly the most common cause for familial PD known to date, accounting for about 5 to 10% of familial and 1 to 5% of sporadic cases (in some isolated populations this number may reach 30 to 40%).

In a large collaborative effort with many groups around the world, we have conducted the largest survey to describe the clinical phenotype and penetrance of LRRK2-mutations. According to this study on more than 400 patients, the risk of developing PD, for a person inheriting the common G2019S mutation, is 28% at 59 years, 51% at 69 years and 74% at 79 years. The motor and non-motor symptoms of LRRK2-associated PD are a bit more benign than idiopathic PD (Healy et al., Lancet Neurology, fig. 1). In our own outpatient-unit, we are presently following more than 30 LRRK2-mutation carriers with and without overt symptoms of parkinsonism longitudinally, collecting clinical and imaging data as well as blood, serum and CSF, in order to identify biomarkers that might reflect the development and progression of the disease before overt clinical symptoms arise (Fig. 2).

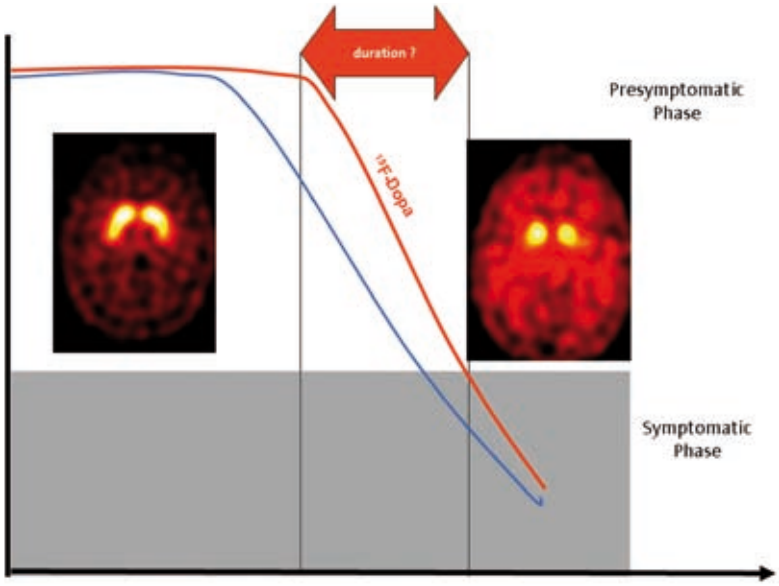
Other work regarding LRRK2 includes the characterization of a transgenic mouse model (PhD-student Marta Garcia Moralles, under the supervision of IZKF-group leader Dr. Dr. Saskia Biskup) and the establishment of patient-derived ex-vivo cellular models by Dr. Martina Wölfle and PhD-student Benjamin Schmid.

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 an E3 ubiquitin protein ligase. PhD-student Oliver Rothfuss and Dr. Nadja Patenge, in a project supported by the Fortüne-Programm, have identified another potentially important function of parkin: by chromatine-immuno-precipitation (CHIP), they have demonstrated that parkin interacts, directly or indirectly, with the mitochondrial genome and that it may promote protection and repair of mitochondrial DNA (Rothfuß et al., HMG submitted)

α-synuclein and Parkinson disease

The α-synuclein-gene (abbreviated as SNCA) is still the prototypical PD-gene, although



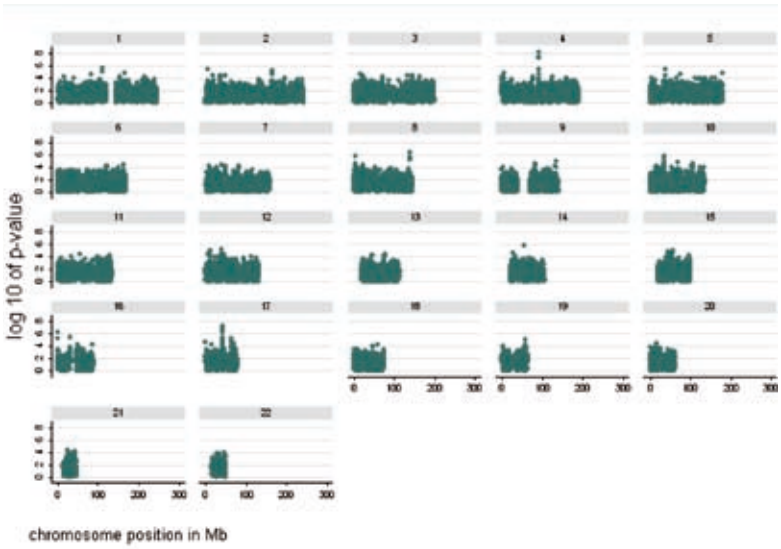
◀ Figure 2:
Imaging studies in presymptomatic LRRK2-mutation carriers may identify the time when neurodegeneration starts long before clinical symptoms appear. This is of eminent importance for the design of effective neuroprotection studies.

mutations in the coding region are much less common than those in LRRK2 or parkin, because the encoded protein is the major component of the Lewy-body, the characteristic protein aggregate found in 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.

While the causative role of SNCA point mutations and multiplications for familial PD is unchallenged, the possible role of SNCA-polymorphisms in the development of the sporadic disease reported by us and others has been much more controversial. In an attempt to identify new risk variants for the sporadic disease, PhD-student Claudia Schulte and Dr. Manu Sharma conducted a large genome-wide association study (GWAS), which was funded in part by the National Genome Network, NGFN2, in a collaboration with the Department of Medical Genetics of the University of Tübingen (Prof. O. Riess) and the laboratory for neurogenetics at the NIH (Dr. A. Singleton).

More than 1600 cases and 4000 controls were included in the exploratory phase, typing more than 500.000 single nucleotide polymorphisms (SNPs) using Illumina technology. The 384 top hits were then genotyped in a confirmatory sample of another 3500 cases and 4000 controls. Interestingly, only two clear risk loci were found: the genes for α-synuclein and for the microtubule associated protein tau (MAPTau) (Fig. 3). This study has now established SNCA beyond doubt as a risk factor for sporadic PD, a finding that has not come as a complete surprise, given the strong link on the pathologic level. Odds ratios are relatively small, about 1.3 in the heterozygous state, and 1.6 to 2 in the homozygous state, but as allele frequencies of the risk alleles are high, the population attributable risk is in the range of 10%.

By contrast, the finding of MAPTau as a major risk factor for sporadic idiopathic PD was surprising, as it appears to over-rule the long-held separation of neurodegenerative diseases in synucleinopathies (PD, dementia with Lewy-bodies, and multiple system atrophy (MSA)) and tauopathies (progressive supranuclear palsy



◀ Figure 3:
Results of a genome-wide association study (GWAS). Association with variants at two loci remained significant after stringent Bonferroni correction: SNCA (α-synuclein) on chromosome 4 and MAPtau (tau) on chromosome 17. Together these variants explain approximately 25% of the genetic variance of disease susceptibility.

(PSP), frontotemporal dementia (FTL-D) and others). Nevertheless, experimental evidence for an interaction of α-synuclein and tau has been accumulating over the last years, and our discovery will put those findings in a new and exciting clinico-genetic perspective.

What is the potential risk-conferring mechanism? In her PhD-work, Julia Fuchs was able to demonstrate that SNCA-risk variants lead to a higher gene expression when cloned into a luciferase reporter system (Fuchs et al., 2008), and that in vivo, high-risk variants are associated with a higher level of protein-expression in the blood, suggesting that the variants may act by causing a chronic, slight α-synuclein over-expression. Currently, intense efforts are pursuing this line of research, trying to identify the true causative variants as well as suitable read-outs of α-synuclein metabolism in blood and CSF.

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

Key Publications

Kamm C, Mayer P, **Sharma M**, Niemann G, **Gasser T** (2007) New family with paroxysmal exercise-induced dystonia and epilepsy. Mov Disord 22(6):873-877

Fuchs J, Tichopad A, Golub Y, Munz M, Schweitzer KJ, Wolf B, Berg D, Mueller JC, Gasser T (2008) Genetic variability in the SNCA gene influences alpha-synuclein levels in the blood and brain. Faseb J 22(5):1327-34

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Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Maljevic S, Margari L, **Kamm C**, Schneider SA, Huber SM, Pekrun A, Roebling R, Seebohm G, Koka S, Lang C, Kraft E, Blazevic D, Salvo-Vargas A, Fauler M, Mottaghy FM, Munchau A, Edwards MJ, Presicci A, Margari F, **Gasser T**, Lang F, Bhatia KP, Lehmann-Horn F, Lerche H (2008) GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. J Clin Invest 118(6):2157-68

Genes for the torsion dystonias

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 mutation causes the disease with reduced penetrance of about 30%. Christoph Kamm was able to demonstrate for the first time in a European population that the penetrance of the gene is strongly modified by a known polymorphism, D216H (Kamm et al., 2008). We were fortunate to be able to contribute to the discovery of a novel disease gene by the group of Holger Lerche in Ulm: we contributed one family characterized by Christoph Kamm (Kamm et al., 2007) to his study of paroxysmal exercise-induced dystonia (PED). This study identified mutations in the glucose transporter GLUT1 as causative in this rare disorder. This is of great significance as it immediately implies that a ketogenic diet is a simple and effective way to treat mutation carriers and not only to reduce the frequency of their episodes of dystonia, but also to avoid long-term deleterious complications (Weber et al., J Clin Invest, 2008).

Neuroinflammation in Parkinson's and Alzheimer's disease

Lars Stolze and PhD-student Christian Thetard continued their work on the influence of the cellular immune response on protein aggregation in AD and PD. An aggregation of CD11+ microglial cells in the brains of transgenic animals with protein aggregation in the vicinity of aggregates, supporting earlier observations of a role of cell mediated immunity in neurodegenerative diseases.

Other Projects

In his continued studies on the genetic basis of amyotrophic lateral sclerosis (ALS), PhD-student Rubén Fernández Santiago could strengthen the evidence for a role of the vascular endothelial growth factor (VEGF) gene by contributing his data to a large multicenter meta-analysis.

Staff:
R. v. Coelln, R. Fernández Santiago, M. Garcia Miralles, A. Hauser, K. Hesse, C. Kamm, C. Klein, N. Patenge, O. Rothfuss, B. Schmid, C. Schulte, M. Sharma, C. Thetard, M. Wölfle

Parkinsonsyndrome, Demenzen und RLS: Ursachen, Früherkennung und Therapiestrategien

Arbeitsgruppenleiterin: Daniela Berg

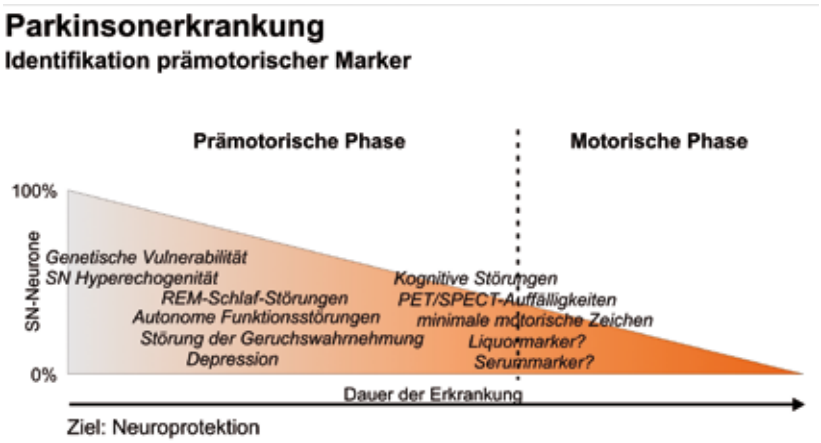
Obwohl es sich bei der Parkinsonerkrankung, den neurodegenerativen Demenzen (z.B. Alzheimer Demenz, Parkinson-Demenz, Lewy-Körperchen-Demenz) und dem Restless-Legs-Syndrom (RLS – Bewegungsunruhe der Beine) aufgrund des häufigen Vorkommens um „Volkskrankheiten" handelt, ist die sichere Diagnose insbesondere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

Bei den neurodegenerativen Erkrankungen sind bei Auftreten erster sichtbarer Symptome 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 von einer nervenzellschützenden Therapie profitieren könnten.

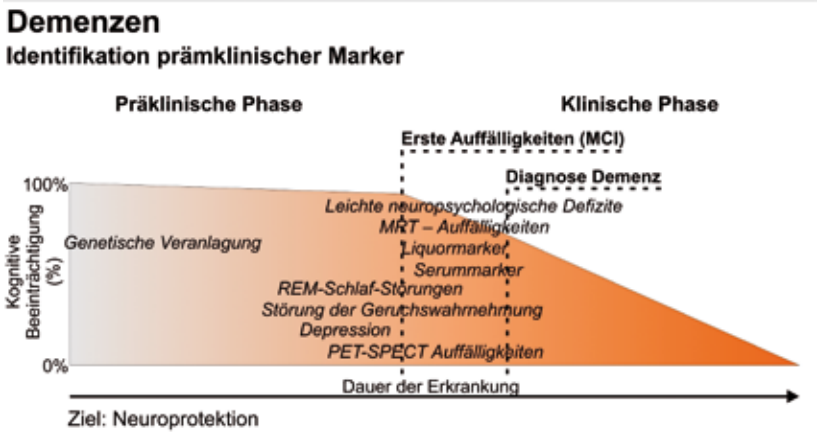
Darüber hinaus wird der Ursache verschiedener Marker nachgegangen – z.B. SN-Hyperechogenität (=vermehrte Helligkeit der Substantia nigra im Ultraschall des Gehirns), für die eine Assoziation mit einem vermehrten Eisengehalt und Mikrogliaaktivierung bereits gezeigt werden konnte.

▼ Abbildung:
In den Abbildungen sind verschiedene Auffälligkeiten, die der Parkinsonerkrankung und Demenzen vorangehen können, dargestellt. In großen prospektiven Kohortenstudien wird die Bedeutung dieser Marker bezüglich einer Krankheitsentwicklung und ihre Veränderungen im Verlauf untersucht.

Die Signalausdehnung der Substantia nigra ist nicht nur für die Parkinsonerkrankung von Bedeutung. Wir konnten zeigen, dass sich bei RLS-Patienten eine verminderte Echogenität der Substantia nigra findet, die in Kernspinuntersuchungen mit einem verminderter Eisengehalt in dieser Region und weiteren Strukturen des Gehirns assoziiert ist. Diese Entdeckung kann zukünftig nicht nur zur besseren Diagnostik, sondern auch zum besseren Verständnis der Erkrankung und zur Entwicklung weiterer Therapien beitragen.



Ein neuer Schwerpunkt der Arbeitsgruppe ist die Suche von klinischen, bildgebenden und Liquor-/Blut-Markern für die Progressive supranukleäre Blickparese, und die Etablierung von sensitiven Messmethoden für veränderte Körperbewegungen. Davon ist ein besseres Verständnis für derartige neurodegenerative Bewegungsstörungen und Erkenntnisse, z. B. über den Ablauf von Stürzen, zu erwarten.



Parkinsonism, dementia and RLS: Causes, early diagnosis and therapeutic strategies

(Group leader: Daniela Berg)

I. Parkinson's disease (Brockmann; Di Santo; Fruhmann-Berger; Gaenslen; Godau; Groeger; Huber; Liepelt; Srulijes)

With a prevalence of about 2% in the population older than 60 years, Parkinson's disease is one of the most common neurodegenerative disorders.

"Hyperechogenicity of the substantia nigra (SN)", known to be present in more than 90% of Parkinson's disease (PD) patients was shown to constitute a valuable biomarker for the very early diagnosis of PD and differential diagnosis of Parkinsonian syndromes in a prospective study supported by the Michael J. Fox Foundation. Moreover, in yet healthy subjects displaying this ultrasound feature, a striking association with risk and premotor markers such as positive family history for PD, slight neuropsychological and motor impairment as well as REM Sleep Behaviour Disorder (RBD) could be found. First analyses of a large tricenter (Universities of Tübingen, Homburg, Innsbruck) cross-sectional study, including more than 1800 healthy subjects aged 50 years and older showed a marked association of SN hyperechogenicity and a variety of premotor makers singularily and in combination. Ongoing follow-up examinations, also supported by the Michael J. Fox Foundation, will show the value of single and/or combined markers as predictors for the development of PD.

As the reason for SN hyperechogenicity is still unknown and as there exists a genetic vulnerability for the ultrasound sign, search for genes possibly accounting for the ultrasound sign are carried on, supported by the National Genome Research Network (NGFN).

To validate effective therapeutic strategies, progression markers for the neurodegenerative process in PD are essential – both before and after motor manifestation. With funding of Johnson&Johnson Pharmaceutical Research a longitudinal study could be initiated, aiming to identify progression markers in subjects defined as high risk (by co-occurrence of a number of premotor markers) and early PD patients in comparison to controls.

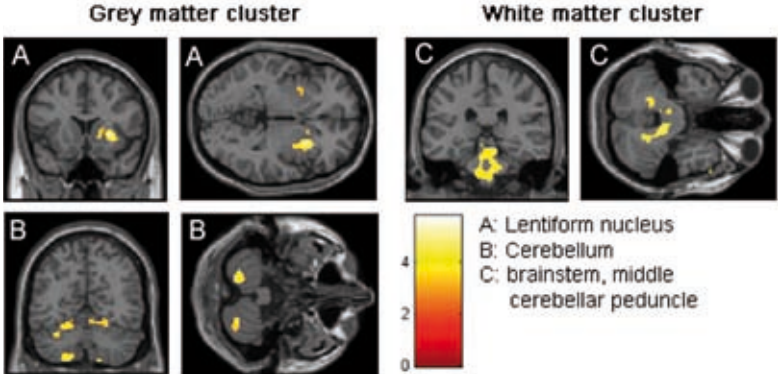
A specific search for disease and progression markers is being carried on in a longitudinal study on LRRK2 patients and mutation carriers using clinical, neuropsychological, neuroimaging as well as blood and CSF markers.

The desire to develop broad therapeutic concepts has lead to three different approaches:

(i) In a number of clinical studies, phase II to IV, new drugs could be evaluated.

(ii) With support of the German Parkinson association (dPV) the hypothesis that proper nutrition may have a positive effect on disease manifestation and progression was reviewed and condensed as an advisory broschure for patients.

(iii) Physical therapy and specific exercise play an important role in the treatment of PD in all disease stages. In collaboration with the Sports Departments of the Universities of Tübingen and Stuttgart we investigated the effect of



▶ Figure 1:
Changes in brain morphology of patients with idiopathic Parkinson's disease induced by a disease specific 3 months motor training. Coloured areas mark regions where significant differences in grey / white matter volume could be observed when comparing T1w-3D MRI images of pre-training and post-training condition between all patients. Changes seen in the brainstem and the cerebellum were associated with a regain of motor function, indicating that even the brain of neurodegeneratively diseased subjects shows plasticity and can be trained.

specific exercise on the brain grey and white matter. It could be demonstrated that even in the diseased brain certain functions could be recovered by specific training. Further effort is put on the evaluation of different forms of exercise to meet the specific needs of PD patients in different disease stages. (Figure 1)

II. Progressive supranuclear palsy – an atypical Parkinsonian syndrome (Srulijes, Maetzler)

Progressive supranuclear palsy (PSP) is a rare, severe neurodegenerative disease. So far, no effective therapy is known. Recently two subgroups of the disease have been defined. As the differentiation of PSP in the two subtypes is based on retrospective, neuropathological data, a study was designed to define the PSP subtypes intra vitam and to search for additional in-vivo markers which have the potential to differentiate the given subtypes. Despite the low prevalence of the disease a large group of almost 30 PSP patients could be recruited and is currently being investigated by neuroimaging (MRI and FDG-PET), neuropsychological testing, electrooculography, nystagmography, accelerometry, an acuity paradigm, and blood and cerebrospinal fluid analyses. The demographic analysis of the first 25 patients shows that our PSP subgroups are basically comparable with those proposed. Analyses of these comprehensive data will enable a deeper inside into the pathological mechanisms of this devastating disease, with the option to define more specific therapeutic targets.

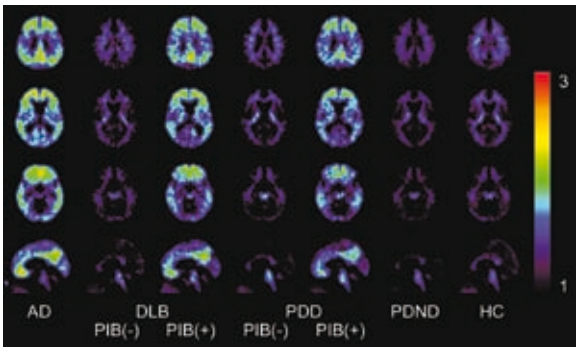
New therapeutic options are followed with two strategie:

1. Subjects with PSP often suffer from cognitive deficits. Based on promising preliminary observations, a phase 2 open-label trial with the cholinesterase inhibitor Rivastigmine® has been started. The efficacy of cholinergic treatment on specific cognitive functions, motor performance and the occurrence of side effects in PSP-related dementia will be measured. Preliminary results point to a positive effect of the drug on distinct cognitive deficits.

2. In collaboration with the Geriatric Department of the Robert-Bosch-Hospital in Stuttgart (Head PD Dr. C. Becker) we started a 6 weeks training study on PSP subjects with a movement sensor on the lower back connected with audio-biofeedback to improve postural control.

III. Dementias in Lewy body diseases (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. Moreover, there exists no clear categorization of dementias in Lewy body diseases.



▲ Figure 2: Positron emission tomography images of a beta-amyloid-detecting substance (PIB, mean uptake ratios, cerebellum = 1) of patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), Parkinson disease with dementia (PDD), Parkinson disease without dementia (PDND), and of healthy controls (HC) demonstrate that AD-like amyloid pathology is present in a relevant percentage of demented Lewy body disease patients.

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.

Due to abnormal neuronal α-synuclein inclusions (Lewy bodies, LB), dementia with Lewy bodies (DLB), Parkinson disease with dementia (PDD) and Parkinson disease without dementia (PDND) are subsumed under the term "Lewy body diseases", LBD, as they share a large number of similarities. Furthermore, similar neuropathologic and biochemical changes in LBD and Alzheimer's disease (AD) suggest that there is also some overlap between these two most frequent neurodegenerative diseases. With a positron emission tomography paradigm detecting β-amyloid as AD-typic changes (Figure 2), we were able to show that cognitive decline In LBD is to a large extent independent from AD-type changes. However, about one quarter of LBD patients do show these AD-type changes paralleled by further signs and symptoms associated with AD, indicating that these patients may rather suffer from a subtype of AD than from classical Parkinson disease. Actually

there is a focus on the investigation of body fluid markers which may serve as pathophysiologically relevant biomarkers for the progression of LBD subjects.

IV. Restless-Legs-Syndrome (Godau)

Restless-Legs-Syndrome (RLS) is a very common sensorimotor disorder affecting about 10% of the German population. However little is known about the pathophysiological changes underlying the development of RLS and tools to objectively diagnose RLS are to be developed.

Using transcranial B-Mode sonography it could be demonstrated in large cohorts that decreased echogenicity of the substantia nigra (SN) is a valuable sonographical marker for RLS with very good sensitivity, specificity and predictive values. Additionally, other abnormalities could be found, including brain regions like the red nucleus and the brainstem midline raphe. Those are correlated with common comorbidities such as periodic limb movements and depression, which may have a major impact on the quality of life even in sufficiently treated patients.

Using MRI, an association of RLS with reduced tissue iron content of the whole brain was found. Further MRI and CSF studies are currently performed for a better understanding of the pathophysiologic role of impaired iron metabolism in the development of RLS. Moreover, also in patients with other disorders such as polyneuropathy similar abnormalities of brain structures on transcranial sonography have been found. These new insights may help to better understand changes of brain structure and function which may promote development of RLS.

Additionally, in epidemiological studies, occurrence of symptoms, comorbidities and long-term effects of treatment are investigated, aiming to improve the understanding and treatment of RLS. For example, we found that rotigotine, a new dopamine agonist is most effective in the reduction of augmentation, one of the most feared side effects of RLS medication.

homepage: http://hih.med.uni-tuebingen.de/nd/research/parkinsonsyndrome-demenzen-und-rls-ursachen-frueherkennung-und-therapiestrategien/

Staff:
K. Brockmann, A. Di Santo, M. Fruhmann-Berger, A. Gaenslen, J. Godau A. Groeger, H. Huber, I. Liepelt, K. Srulijes; W. Maetzler (associated staff)

Key Publications

Berg D, et al. (2008) Transcranial sonography in movement disorders. Lancet Neurol 7(11):1044-55

Berg D (2008) Biomarkers for the early detection of Parkinson's and Alzheimer's disease. Neurodegener Dis 5:133-6

Gaenslen A, **Gasser T, Berg D** (2008) Nutrition and the risk for Parkinson's disease: review of the literature. J Neural Transm. 2008 115(5):703-13

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Godau J et al. (2008) Multiregional brain iron deficiency in restless legs syndrome, Mov Disord 23(8):1184-7

Godau J, et al. (2008) Sonographic abnormalities of brainstem structures in restless legs syndrome. Sleep Med 9(7):782-9

Liepelt I, et al. (2008) Substantia nigra hyperechogenicity assessed by Transcranial Sonography is related to neuropsychological impairment in the elderly population. J Neural Transm 115(7):993-9

Maetzler W, et al. (2008) Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. Neurobiol Dis [Epub ahead of print]

Maetzler W, et al. (2008) [11C]PIB binding in Parkinson's disease dementia. Neuroimage 39:1027-33

Arbeitsgruppe Funktionelle Neurogenomik

Arbeitsgruppenleiter: Rejko Krüger

Noch vor 15 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 viele 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 hat in den letzten Jahren erfolgreich zur Entdeckung von neuen Krankheitsgenen bei der Parkinson-Krankheit beigetragen und ist spezialisiert auf die Untersuchung neu gefundener Gen-Mutationen hinsichtlich ihrer Auswirkungen auf den Überleben von Nervenzellen bei der Parkinson-Krankheit. Hierzu werden neben molekulargenetischen Methoden zur Mutationssuche in Kandidatengenen auch genetische Zellkultur- und Tiermodelle eingesetzt, um möglichst genau die Signalwege, über die krankheitsverursachende Mutationen, die Nervenzellen schädigen, zu untersuchen. Dabei kommen neben biochemischen Methoden zur Untersuchung von Protein-Bindungen auch Funktionstests zur Messung der Energiegewinnung der Zelle, der Veränderung von Zellorganellen und des Zellüberlebens unter Stress zum Einsatz.

Beispielhaft haben wir im Jahre 2008 eine Veränderung in einem Bindungspartner des Parkinson-assoziierten Proteins Synphilin-1 als Risiko für die Parkinson-Krankheit bei der DNA Untersuchung von mehr als 500 Parkinson Patienten identifiziert (Wahl et al., 2008; Bonin et al., 2008). Das von uns gefundene Omi/HtrA2 (PARK13) Gen verursacht eine sehr seltene Ursache der Parkinson-Krankheit, wie wir in einer internationalen Studie an über 15.000 Probanden aus 17 Ländern von 4 Kontinenten zeigen konnten (Strauss et al, 2005; Krüger et al., 2009; Abstract). Aktuelle Arbeiten weisen auf eine besondere Bedeutung der Kraftwerke der Nervenzelle, der Mitochondrien, im Rahmen der Entstehung der Parkinson-Krankheit hin. Wir konnten erstmals zeigen, dass bestimmte bei der Parkinson-Krankheit mutierte Proteine, Omi/HtrA2 und DJ-1, eine direkte Wirkung auf die Mitochondrien-Form und –Funktion haben und einen Abbau geschädigter Mitochondrien beeinflussen (Krebiehl et al., 2008; Kieper et al., 2009; Abstracts).

Ziel der Arbeiten ist die Entdeckung 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.

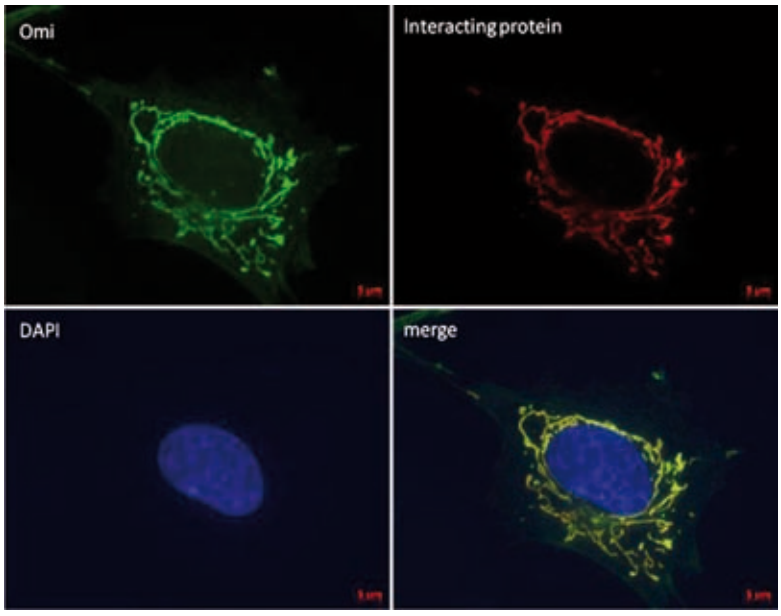
Functional Neurogenomics Laboratory

(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. As a major focus our group intensively studies the functional consequences of 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, analyses of mitochondrial function and dynamics, and the effects of cell viability in cellular and transgenic animal models of the disease. These studies aim at the development of novel neuroprotective therapeutic strategies in the treatment of PD as the most common neurodegenerative movement disorder.

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

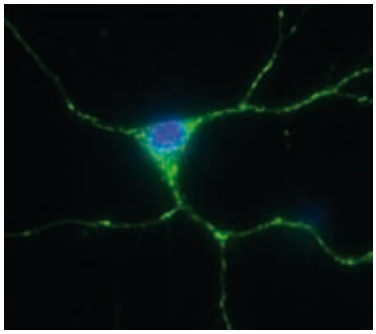
We identified the first mutations in the Omi/HtrA2 gene in PD, two heterozygous amino acid substitutions (A141S and G399S; Strauss et al., 2005). Based on cell culture models derived from Omi/HtrA2 knockout mice our experiments focus on the further characterization of Omi/HtrA2 mutations regarding mitochondrial function, protease activity and differential substrate binding (DFG-supported project KR2119/3-1). We describe a role of Omi/HtrA2 in protein quality control in the mitochondria (Radke et al., 2008). We used fibroblasts from knockout mice and observed the differences in the mitochondrial potential and the levels of reactive oxygen species (ROS) that lead to characteristic alterations in mitochondrial dynamics shown by life cell imaging (Kieper et al., submitted). Moreover we generated 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. Another strategy to define the role of Omi/HtrA2 in neurodegeneration is to identify novel interactors. Using GST pulldown assays with physiological and mutant Omi/HtrA2 and subsequent mass spectroscopy we identified an intramitochondrial target of Omi/HtrA2, that we named OIP-2. Current experiments focus on the functional significance of this interaction for protein quality control in the mitochondria. (see fig. 1)



▶ Figure 1: Using fluorescence microscopy with ApoTome technique (Zeiss, Germany), we confirmed the subcellular co-localistation of Omi and a new interacting protein in mitochondria.

Characterization of DJ-1-mediated neurodegeneration

Based on a DJ-1 knockout (KO) mouse model we describe a novel role of DJ-1 in the regulation of mitochondrial morphology in mouse embryonic fibroblasts (Krebiehl et al., 2008, Abstract). Loss of DJ-1 was related to an accumulation of intramitochondrial reactive oxygen species (ROS) and disturbed mitochondrial membrane potential. Using live cell imaging and automated assessment of mitochondrial



◀ Figure 2:
Analyses of mitochondrial morphology and dynamics in primary cortical neurons of DJ-1 knockout mice using Mitotracker (Molecular Probes, USA) as a dye.

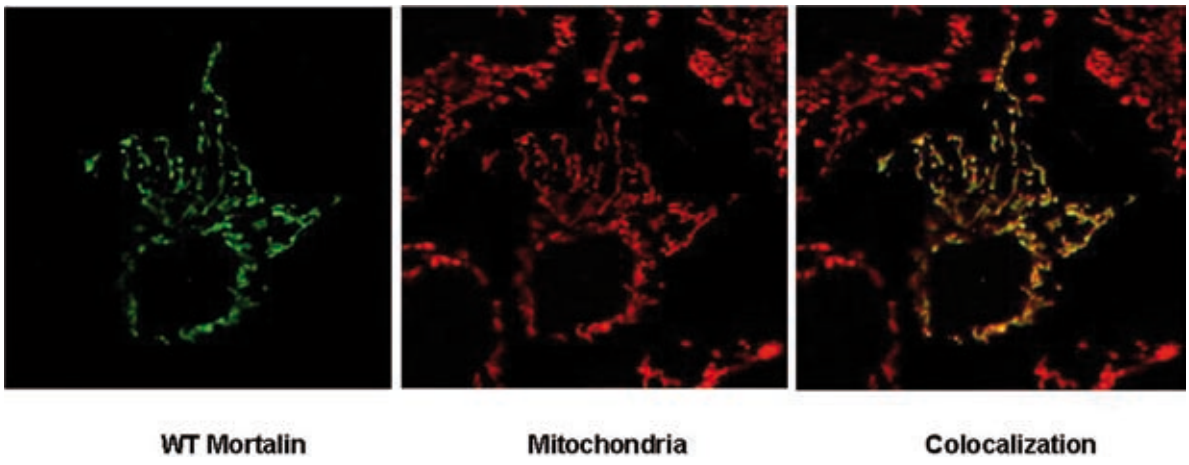
morphology we found characteristic alterations of mitochondrial dynamics in DJ-1 KO cells. ROS production in the mitochondria is a fundamental regulatory event in autophagy which ultrastructural analyses revealed disrupted lysosomal degradation pathways in DJ-1 KO cells. Indeed we found dysregulation of autophagy in cells lacking physiological DJ-1 protein. (see fig. 2)

The role of Mortalin in neurodegeneration in Parkinson's disease

To understand the function and potential signalling pathways of DJ-1-mediated neurodegeneration, we performed GST pulldown assays with DJ-1 and subsequent mass spectroscopy and identified Mortalin/Grp75 as a novel interactor. Mortalin/Grp75, an intramitochondrial stress response protein, plays a crucial role for mitochondrial homeostasis. It has been linked to Parkinson's disease due to reduced levels of mortalin/Grp75 in affected brain regions of PD patients. Mortalin/Grp75 is involved in mitochondrial import, stress response and cell death related to aging. We screened for mutations in the Mortalin gene in a large number of PD patients and found a novel variant only present in one PD patient. The functional characterization of this mutation is of major interest to define mechanisms of susceptibility to cellular stress (Burbulla et al., 2009; Abstract). (see fig. 3)

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

Synphilin–1 is linked to abnormal protein degradation in PD. Using high troughput mutation screening we identified the first mutation in the synphilin-1 gene in PD and defined a role of the TGF-beta mediated pathway in synphilin-1-mediated toxicity using Microarray analysis of (Marx et al., 2003; Bonin et al., 2008). Our group identifed a novel specific interaction of synphilin-1 with the regulatory proteasomal protein S6 ATPase (tbp7; Marx et al., FASEB J, 2007). To define a possible role of S6 ATPase in PD pathogenesis, we performed a genetic screening in a large sample of German PD patients. We identified a novel rare variant acting as a risk to develop sporadic PD (Wahl et al., 2008). Synphilin-1 aggregates display the key features of the so called "aggresomes" due to their perinuclear localization. Recent evidence suggested that autophagy (i.e. the active transport and degradation of intracellular components, proteins and organelles



◀ Figure 3:
Studies of the subcellular localisation of overexpressed wildtype and mutant Mortalin in HEK293 cells reveals mitochondrial import of the wildtype protein.

in lysosomes) may be involved in aggresomal clearance. The aim of our work is to assess, if the pharmacological activation of autophagy is effective in the clearance of SYPH1 aggregates and whether this modulation of autophagic pathways is able to rescue cells from death. For this purpose, we perform treatments with combinations of stressors and activators of autophagy on GFP-tagged SYPH1 overexpressing cultured cells, and then we evaluate aggregates by fluorescence microscopy and cell viability using biochemical assays (see fig. 4).

Key Publications

Bonin M, **Marx FP, Kautzmann S**, Riess O, **Krüger R** (2008) Microarray expression analysis reveals genetic pathways implicated in C621 Synphilin-1-mediated toxicity. J Neural Transm 115:941-58

Marx FP, Soehn AS, Berg D, Melle C, **Schiesling C, Lang M, Kautzmann S, Strauss KM**, Franck T, Engelender S, Pahnke J, Dawson S, von Eggeling F, Schulz JB, Riess O, **Krüger R** (2007) The proteasomal subunit S6 ATPase is a novel synphilin-1 interacting protein – implications for Parkinson's disease. FASEB J 21:1759-67

Radke S, Chander H, Schäfer P, Meiss G, **Krüger R**, Schulz JB, Germain D (2008) Mitochondrial protein quality control by the proteasome involves ubiquitination and the protease Omi. J Biol Chem 283:12681-5

Wahl C, Kautzmann S, Strauss KM, Lang M, Schiessling C, Woitalla D, Müller T, Berger K, Niewar M, Bauer P, Riess O, **Krüger R** (2008) A comprehensive genetic study of the proteasomal subunit S6 ATPase in German Parkinson's disease patients. J Neural Transm 115:1141-8

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

homepage: http://www.hih-tuebingen.de/abteilungen/nd/research/gen/

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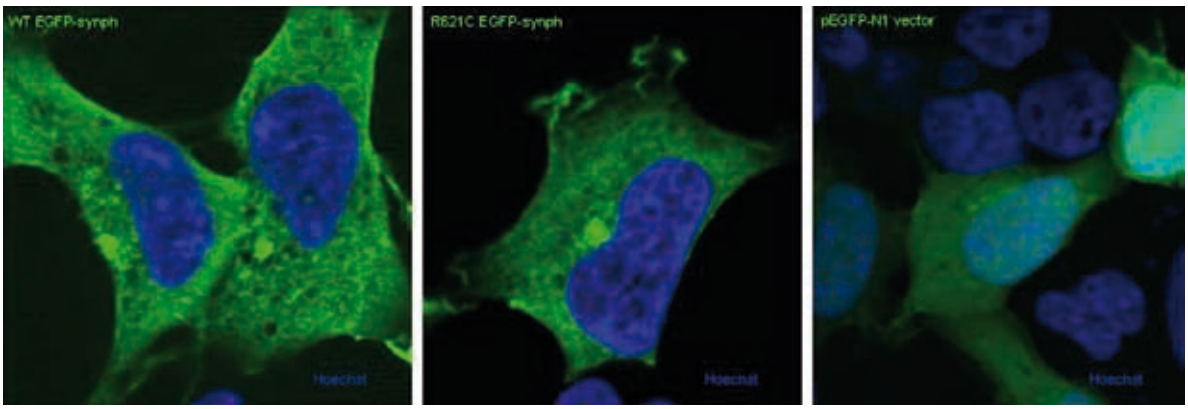


▶ Figure 4: Analyses of synphilin-1 aggregates that display the key features of the so called "aggresomes" due to their perinuclear localization in HEK293 cells overexpressing wildtype and mutant synphilin-1-EGFP-fusion protein.

Arbeitsgruppe Genetik 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 (phasische, repetitive) 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 den Dystonie-Plus Syndromen, der dopa-responsiven Dystonie (DRD, DYT5), der Myoklonus-Dystonie (M-D, DYT11) und den genetisch heterogenen, nicht neurodegenerativen Dystonie-Parkinson-Syndromen (RDP, DYT12, DYT16). Durch die genetischen Arbeiten unserer Gruppe sollen neben der Erforschung der Dystonie-Plus Syndrome selbst durch die Entdeckung neuer dystonie-assoziierter Pathways auch das Verständnis der idiopatischen, sporadischen Dystonien verbessert werden.

- „Assoziations-Studien“. Bei diesem Studientyp werden genetische Varianten untersucht, welche die Erkrankungsentstehung begünstigen.Historisch waren Assoziationsstudien auf das Vorliegen sog. Kandidatenhypothesen angewiesen. Ergebnisse pathohistologischer oder biochemischer Studien bei Menschen oder häufiger in Tiermodellen wurden auf ihre Gültigkeit bei Patienten untersucht. Methodisch bedingt konnten bei diesen Studien bislang nur bekannte Genvarianten, z.B. im TorsinA-Gen (DYT1), auf die Entstehung und die Ausbreitung fokaler oder segmentaler Dystonien untersucht werden. Unsere Arbeitsgruppe bereitet im Rahmen einer nationalen und internationalen Kooperation eine genomweite Assozationsstudie bei verschiedenen idiopathischen Dystonien vor. Diese Untersuchungstechnik erlaubt erstmals rein methodenbasiert (= statistischer Vergleich von 500‘000 single nucleotide Polymorphismen (SNP) über das gesamte Genom), die Erstellung einer Assozationsanalyse. Mit dieser Technik verknüpft ist die Erwartung des Aufdeckens neuer Gene, die an der Entstehung von Dystonien mitwirken. Dies gelang bislang schon bei anderen Erkrankungen, z.B. dem Restless Legs Syndrom, bei denen klassische genetische Methoden auch keine relevanten Erkenntnisse zeigten.

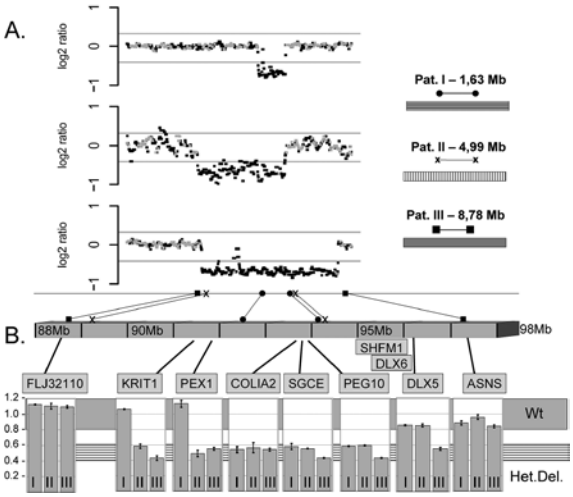
Genetics of Dystonia

(Group leader:
Friedrich Asmus)

We have continued and extended our efforts in the genetic characterisation of dystonia-plus syndromes.

In Myoclonus-Dystonia (M-D), over 20 novel and recurrent mutations of the SGCE gene were identified. For the first time, a heterozygous deletion in exon 10 of the SGCE gene was detected in a patient with a typical M-D phenotype. The vast majority of SGCE mutations published to date reside in the "extracellular" exons 1 to 8. In an Irish girl with M-D, a deletion of exon 10 was detected, introducing a putative frameshift of the translational reading frame. Therefore, mutated mRNA species might either be removed by nonsense-mediated mRNA decay or translated mRNA might lack important intracellular interaction motifs.

We assessed the phenotypic spectrum in patients with SGCE mutations. In three patients megabase deletions of the 7q21 region were correlated with the clinical presentation. The deletion size was determined by the novel technique of assessment of copy number variation (CNV) with single nucleotide polymorphism (SNP) chip arrays[1]. Here, over 100'000 SNPs are genotyped and analysed for CNVs genome wide (see figure). Beside obvious phenotypic features like M-D or split hand/split foot malformation with sensorineural hearing loss (SHFM1D, OMIM 220600), subtle alterations were observed like mild joint laxity related to heterozygosity for COL1A2, the causative gene for dominant osteogenesis imperfecta. Of even greater importance for genetic counselling, one patient's deletion of the KRIT1 gene caused cerebral cavernous malformations type IV, which had been overlooked before the availability of the test result, but need further imaging follow-up.



◀ Figure:
Correlation of clinical phenotype and size of heterozygous megabase deletions in the 7q21 region around the SGCE gene. (A) Results of genome wide copy number analysis using Affymetrix 100K SNP arrays. Reduced Log2 ratios in the 7q21.11 to 7q21.3 region indicate heterozygous genomic deletions of differing size (1.63Mb-8.78Mb).(B) Heterozygous deletions of pathogenic genes in humans were confirmed by qPCR experiments. For clinical details see text. (from Asmus et al.).

Phenotypic characteristics for the differentiation of Myoclonus-Dystonia and Benign Hereditary Chorea caused by TITF-1 mutations had been suggested after the assessment of mutation-positive index patients[2]. We have confirmed these criteria in a previously undiagnosed cohort of paediatric patients with childhood-onset "jerky" movement disorders. Only BHC displayed continuous choreatic limb movements. Only SGCE mutation carriers displayed lightning-like myoclonic jerks rarely seen at rest but consistently aggravated by action. Two further categories emerged: myoclonic dystonia, characterised by prevailing dystonia and jerks limited to the body regions of active dystonia and a novel category "Dystonia with poly-mini myoclonus (D-PMM)"[3]. This hyperkinetic movement disorder is characterized by a paediatric-onset, limb dystonia (i.e. writer's cramp) and myoclonus of low amplitude limited to the arms and pectoralis muscles. D-PMM is inherited in an autosomal-recessive inheritance mode and will be further studied genetically.

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

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Key Publications

Asmus F, Hjermind LE, Dupont E, et al. (2007) Genomic deletion size at the epsilon-sarcoglycan locus determines the clinical phenotype. Brain 130:2736-45

Asmus F, Devlin A, Munz M, Zimprich A, **Gasser T**, Chinnery PF (2007) Clinical differentiation of genetically proven benign hereditary chorea and myoclonus-dystonia. Mov Disord 22:2104-9

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Sektion Klinische Neurogenetik

Sektionsleiter: Ludger Schöls

Neurogenetische Forschung ermöglicht vielfältige neue Einblicke in pathophysiologische Prozesse und die Genese neurodegenerativer Erkrankungen. Die Möglichkeit, über die Identifizierung des ursächlichen Gendefekts Krankheiten von ihrer primären Ursache her zu untersuchen, bietet einzigartige Chancen, die zugrunde liegenden Krankheitsmechanismen zu erforschen und Strategien zu entwickeln, um korrigierend in diese einzugreifen. So werden neurogenetische Krnakheiten trotz ihrer Seltenheit zu Modellen für häufige neurodegenerative Erkrankungen, wie z. B. den Morbus Parkinson oder Alzheimer. Die Sektion Klinische Neurogenetik untersucht genetische Grundlagen und Krankheitsmechanismen bei erblichen Bewegungsstörungen und Stoffwechselveränderungen des Gehirns. Besondere Schwerpunkte bilden die Ataxien und Spastischen Spinalparalysen.

Bei den Ataxien kommt es durch eine Degeneration des Kleinhirns zu Koordinationsstörungen mit unsicher-schwankendem Gang, Ungeschicklichkeit der Hände, undeutlichem Sprechen und Augenbewegungsstörungen. Ataxien weisen trotz ihrer Seltenheit viele verschiedene genetische Ursachen auf. Für die häufigsten, autosomal dominant vererbten Formen, die Spinocerebellären Ataxien (SCA) Typ 1, Typ 2, Typ 3 und Typ 6 wird in einem von der EU geförderten Projekt der natürliche Erkrankungsverlauf untersucht. Ein genaues Wissen über das Fortschreiten der Erkrankung ist eine unverzichtbare Voraussetzung für die Planung zukünftiger Therapiestudien. Für die häufigste Form der rezessiv vererbten Ataxien, die Friedreich-Ataxie, läuft derzeit eine multizentrische Studie, in der verschiedene Dosierungen von Idebenone gegen Placebo getestet werden. In Kooperation mit der Medizinischen Genetik in Tübingen und der Arbeitsgruppe von Michel Koenig in Strasbourg suchen wir nach Ursachen früh beginnender Ataxien, bei denen Symptome bereits vor dem 25. Lebensjahr auftreten.

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 verlässliches Maß für die Schwere einer HSP entwickelt und erarbeiten in einer Untersuchung des natürlichen Erkrankungsverlaufs essentielle Daten für zukünftige Therapiestudien. In dem europäischen Netzwerk EUROSPA streben wir eine Verbesserung der genetischen Diagnostik für HSP-Patienten an.

Jüngst konnten wir in einer deutschen Familie mit dominant vererbter HSP einen neuen Genort (SPG36) identifizieren und arbeiten derzeit an der Identifizierung des krankheitsverursachenden Gens. Da die motorischen Nervenzellen (Motoneurone) für die Beinmuskeln sehr lange Fortsätze (Axone) benötigen, um die Steuerungsimpulse von der Hirnrinde bis zum Ausgang des Rückenmarks zu leiten, sind sie besonders anfällig für Störungen des axonalen Transports. Dies ist vermutlich ein häufiger Pathomechanismus bei der HSP, den wir in Zellkulturen von Motoneuronen sowie in einem transgenen Fliegenmodell untersuchen. Diese Fliegen tragen dieselben Mutationen in ihrem Motor für den axonalen Transport (Kinesin, verantwortlich für SPG10) wie einige unserer Patienten. Ziel ist ein besseres Verständnis der zur HSP führenden Krankheitsprozesse und langfristig die Entwicklung neuer therapeutischer Strategien.

Weitere Erkrankungen, an denen die Klinische Neurogenetik am Hertie-Institut arbeitet sind die Leukodystrophien im Erwachsenenalter, Erkrankungen der Mitochondrien, die Amyotrophe Lateralsklerose und der essentielle Tremor.

Clinical Neurogenetics

(Group leader:
Ludger Schöls)

The Section of Clinical Neurogenetics focuses on hereditary movement disorders and neurometabolic diseases with special interest in ataxia and spastic paraplegia. The work is dedicated to translational research taking advantage of the close cross-linking of the Hertie-Institute and the University Clinic. To this end we have established a network of clinical and laboratory research. At the Department of Neurodegenerative Diseases we run outpatient clinics specialised in ataxia, spastic paraplegia, amyotrophic lateral sclerosis, leukodystrophies and neurogenetic diseases. National and international registries of patients with these rare disorders help to assemble a critical number of patients for clinical studies. We run natural history studies since prospective analyses of the natural progression are missing in most neurogenetic diseases although such data are essential to design therapeutic studies. In imaging studies and electrophysiological analyses we aim to establish biomarkers of disease activity. Biomaterials like DNA, RNA, CSF, lymphoblasts and fibroblasts are gathered for rare neurogenetic diseases and stored in the biobank at the HIH. They serve as essential tools for the identification of new disease genes, functional analyses and cell culture models. Transgenic drosophila carrying mutations found in our patients help to a better understanding of pathogenesis in motor neuron degeneration and may serve as a screening tool for potential therapeutical compounds.

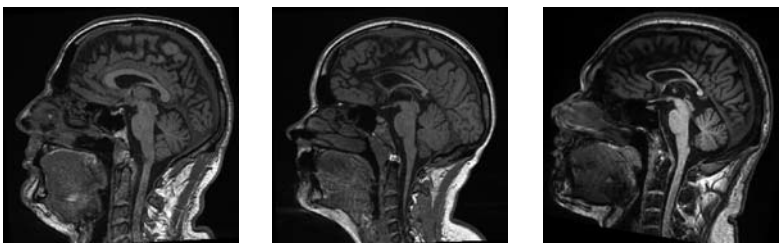
Ataxia
(Matthis Synofzik, Christoph Linnemann, Tobias Lindig)

Cerebellar ataxias divide 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 the EUROSCA consortium supported by the European Union (http://www.eurosca.org/) we set up a European registry for SCA with more than 3.000 patients suffering from this rare disease. In preparation for upcoming intervention studies we generate data on the progression of SCA in an international natural history study and aim to establish electrophysiological parameters as biomarkers of disease progression.

Early onset ataxia (EOA) frequently shows autosomal recessive inheritance and is caused by loss of function mutations in mitochondrial proteins like in Friedreich's ataxia, the most frequent recessive ataxia in the western world. Other pathogenic mechanisms in EOA include impaired protection to oxidative stress and impaired DNA repair mechanisms. We identified mutations in the mitochondrial polymerase gamma (POLG) as the second most frequent cause of EOA in our cohort. Sensory neuropathy and external ophthalmoplegia are clinical hallmarks suggesting POLG mutations in EOA patients.

Although physiotherapy is regarded as most important in ataxia, specific therapeutical concepts are scarce and not evaluated. In cooperation with Doris Brötz and Winfried Ilg we developed an ataxia training program focussing on coordinative exercises and evaluated it by clinical rating scales and computerized gait analysis. Patients with cerebellar ataxia who regularly performed this training improved their movment control to an amount that equals the natural progression of two or more years. Longterm follow-up of these patients is on the way.

In Friedreich's ataxia we participate in a phase III trial with idebenone. Preliminary data suggests that idebenone may by its antioxidative potency and function as OXPHOS enhancer improve not only cardiac hypertrophy but also neurological



A B C

▶ Figure 1: MRI in SPG4 (A), SPG11 (B) and SPG 15 (C). In SPG11 and SPG15 the corpus callosum is thin especially in the anterior parts.

deficits at least at high doses in early stages of the disease.

Hereditary spastic paraplegia (HSP) (Rebecca Schüle, Kathrin Karle)

HSP is characterized by degeneration of the corticospinal tract. Clinically, HSP presents as slowly progressive gait disorder with spasticity restricted to or pronounced in the lower limbs. Since motor neurons to the legs have among the longest axons of the nervous system it is likely that HSP is primarily an axonal disease with factors like axonal transport being crucial in pathogenesis.

In a BMBF-supported project (GeNeMove; http://www.genemove.de) we set up a national network of spastic paraplegia clinics including more than 400 patients with this rare disease. Here we developed the spastic paraplegia rating scale (SPRS) as a measure of disease severity in HSP. With the help of this scale and an inventory of complicating signs and symptoms we analyse the clinical spectrum of HSP and assess disease progression in a natural history study.

Genetically HSP is highly heterogeneous with about 40 genes and loci identified so far. Most recently three new genes for autosomal recessive HSP have been cloned. Spastic paraplegia with thin corpus callosum, mental retardation and axonal neuropathy comprise the clinical characteristics of both, SPG11 and SPG15 (figure 1), while SPG5 presents as pure spastic paraplegia.

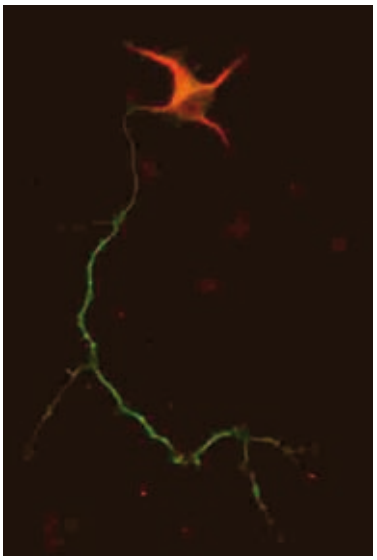
In a European network (EUROSPA) with partners in Paris, Rome and Jerusalem we aim to identify new genes for autosomal dominant HSP. Recently, we mapped a new locus for adHSP in a German family (SPG36). Currently, we work intensively in cloning the responsible gene.

Primary motor neuron culture allows to anylse axonal outgrowth in mouse models of HSP (figure 2). At the HIH we assess axonal transport of mitochondria in motor neurons using live cell imaging. In cooperation with Tobias Rasse we developed a transgenic drosophila model of SPG10 with kinesin mutations found in our HSP families. This model will be used to further study pathogenesis and screen for effective interventional strategies.

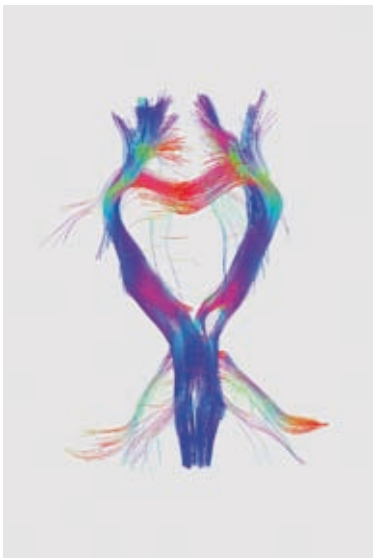
Tobias Lindig evaluates MRI tools for the assessment and quantification of spinal cord degeneration. Beside 3D imaging for volumetric analyses he assesses the corticospinal tract in diffusion tensor images (figure 3). Comparison of cerebral and spinal seeds will help to clarify whether HSP is primarily an axonal or rather a neuronal disease.

Leukodystrophies and neurometabolic disorders in adulthood

Leukodystrophies are commonly regarded as diseases of infancy although for most



◀ Figure 2: Motor neuron in culture.

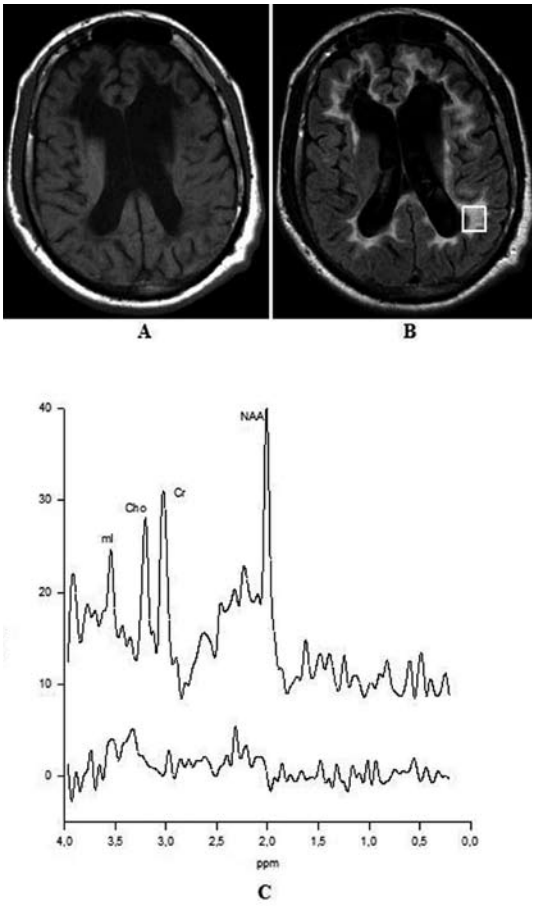


A

B

◀ Figure 3: Fibre tracking of pyramidal tracts with seading in the internal capsule in spastic paraplegia patients with moderate (A) and severe (B) disability.

leukodystrophies adult-onset forms have been defined. In the BMBF supported national leukodystrophy network (http://www.leukonet.de/) we analyze the natural course of leukodystrophies in adulthood as an essential prerequisite for therapeutical studies. Neuroimaging including MRI and MR spectroscopy helps to identify patterns characteristic for the underlying disease e.g. in vanishing white matter disease (figure 4).



▲ Figure 4: MRI in vanishing white matter disease demonstrating cystic degeneration predominantly in the frontal white matter in T1- (A) and FLAIR-weighted images (B). Characteristic decline of all metabolites such as N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myo-inositol (ml) in MR spectroscopy (C).

homepage:
http://hih.med.uni-tuebingen.de/nd/research/sektion-klinische-neurogenetik/

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 disorders like cerebrotendinosis xanthomatosa or Refsum disease metabolic abnormalities can be improved by restrictive diets or supplementary therapy. In an increasing number of leukodystrophies substrate inhibition, enzyme substitution or hematopoetic stem cell transplantation are upcoming new therapeutic options.

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 students from the University of Barcelona is analyzed for polymorphisms in four genes (DRD4, COMT, MAO, DAT) known to modulate dopaminergic function. Influence of genotypes on executive function is studied in a multimodal approach including an extensive neuropsychological test battery, event-related brain potentials and functional MRI. Polymorphisms of the genes for the D4 dopamine receptor and COMT were shown to be associated with distinct differences in error monitoring and response inhibition. Furthermore, the same polymorphisms were shown to modulate the response to monetary gains and losses in a gambling task. These studies have been supported by the Volkswagen foundation.

Key Publications

Beetz C, **Schüle R**, Deconinck T, Tran-Viet KN, Zhu H, Kremer BP, Frints SG, van Zelst-Stams WA, Byrne P, Otto S, Nygren AO, Baets J, Smets K, Ceulemans B, Dan B, Nagan N, Kassubek J, Klimpe S, Klopstock T, Stolze H, Smeets HJ, Schrander-Stumpel CT, Hutchinson M, van de Warrenburg BP, Braastad C, Deufel T, Pericak-Vance M, **Schöls L**, de Jonghe P, Zuchner S (2008) REEP1 mutation spectrum and genotype/phenotype correlation in hereditary spastic paraplegia type 31. Brain 131:1078-86

Ebbing B, Mann K, Starosta A, Jaud J, **Schöls L, Schüle R**, Woehlke G (2008) Effect of spastic paraplegia mutations in KIF5A kinesin on transport activity. Hum Mol Genet 17:1245-52

Riecker A, Nagele T, Henneke M, **Schöls L** (2007) Late onset vanishing white matter disease. J Neurol 254:544-5

Kramer UM, Cunillera T, Camara E, Marco-Pallares J, Cucurell D, Nager W, Bauer P, **Schüle R, Schöls L**, Rodriguez-Fornells A, Munte TF (2007) The impact of catechol-O-methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. J Neurosci 27:14190-8

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Arbeitsgruppe Funktionelle Neurogenetik

Arbeitsgruppenleiter: Philipp Kahle

In heutigen Zeiten erhöhter Lebenserwartung stellen altersabhängige neurodegenerative Erkrankungen eine zunehmende Belastung nicht nur für den einzelnen Patienten, sondern auch für die gesamte Gesellschaft dar. Alle diese chronisch fortschreitenden Erkrankungen wie Morbus Parkinson und Lewykörper-Demenz sowie frontotemporale Demenzen und amyotrophe Lateralsklerose sind durch intrazelluläre Eiweiß-Ablagerungen und Neuronenverlust charakterisiert. Auf zellulärer Ebene, und vom klinischen Bild einmal abgesehen, unterscheiden sich diese Krankheiten somit lediglich durch die Identität des jeweiligen zur Ablagerung neigenden Proteins, der subzellulären Lokalisation der entstehenden Aggregate, sowie letztendlich durch den Zelltod verschiedener neuronaler Subpopulationen.

Die Arbeitsgruppe beschäftigt sich im Bereich der Proteopathien hauptsächlich mit dem Parkinson-verursachenden synaptischen Protein α-Synuklein. Wir haben schon vor einiger Zeit ein α-Synuklein transgenes Mausmodell geschaffen, welches die menschliche Neuropathologie hervorragend abbildet (siehe Kahle (2008) Acta. Neuropathol. 115:87). Erstaunlicherweise ist in Nagetieren das für Parkinson-Symptome verantwortliche nigrostriatale Dopaminsystem kaum durch α-Synukleinopathie beeinträchtigt, wohl aber Bereiche im Grosshirn, die auch im Menschen bei Lewykörper-Demenz betroffen sind, insbesondere der Mandelkern (Amygdala), interessanterweise bei zunehmendem Alter (Freichel et al. (2007) Neurobiol. Aging 28:1421). In kombinierten Lernverhaltensversuchen und histologischen Untersuchungen erforschen wir nun die kognitiven Nervenbahnen in alternden transgenen Mäusen, um die Auswirkungen von α-Synuklein Veränderungen (Fehlfaltung, abnorme Phosphorylierung, etc.) auf kognitive Neurotransmission zu verstehen (Schell et al. im Druck; Mbefo et al. eingereicht). Molekulare und zelluläre Aspekte von α-Synukleinopathie werden weiter in einfacheren Modellsystemen wie *Caenorhabditis elegans* und Zellkulturen studiert.

Die Arbeitsgruppe ist weltweit führend bei der Erforschung von Mausmodellen für Lewykörper-Demenz. So wurde der 1. Internationale Workshop „α-Synuclein in Health and Disease“ in Lausanne/Schweiz am 24.-26. 9. 2008 auch mit Unterstützung der Gemeinnützigen Hertie-Stiftung organisiert. Diese Forschung wurde zunächst mit einem Hertie-Bridging Grant anfinanziert und konnte im Jahr 2008 erfolgreich in die Helmholtz-Allianz “Mental Health in an Aging Society” eingebracht werden.

Nicht nur die Erforschung der proteopathischen Eiweisse, sondern auch die zellulären Verteidigungsmechanismen tragen entscheidend zum Krankheitsverständnis bei. Man vermutet, dass die rezessiven Parkinson-Gene hier wirken. Wir konnten zeigen, dass das weitaus häufigste Parkinson-Genprodukt Parkin, welches fehlgefaltete Eiweisse steuert, in einem neuartigen Parkinson-Zellkulturmodell neuroprotektiv wirkt, und den Wirkmechanismus auf die Unterdrückung von Stress-aktivierten Kinasen zurückführen (Hasegawa et al. (2008) J. Neurochem. 105:1700). Diese Veröffentlichung bildete den erfolgreichen Abschluss eines Humboldt-Stipendiaten (Dr. Takafumi Hasegawa), und zusammen mit der intensiven Erforschung der Regulation von Zelltod-vermittelnden Kinase-Wegen durch ein zweites rezessives Parkinson-Gen, DJ-1 (Görner et al. (2007) J. Biol. Chem. 282, 13680-13691; Waak et al. im Druck), die Grundlage für das Einwerben eines weiteren grösseren Grants im Rahmen des Nationalen Genomforschungsnetzes (NGFNplus). Auch das wichtige dominante Parkinson-Gen LRRK2 spielt eine Rolle als direkter Auslöser von Kinase-Wegen. Diese Forschung führte zu 2 Dissertationsabschlüssen (Susanne Weber, Dr. med. magna cum laude; Christian Klein, Dr. rer. nat. magna cum laude).

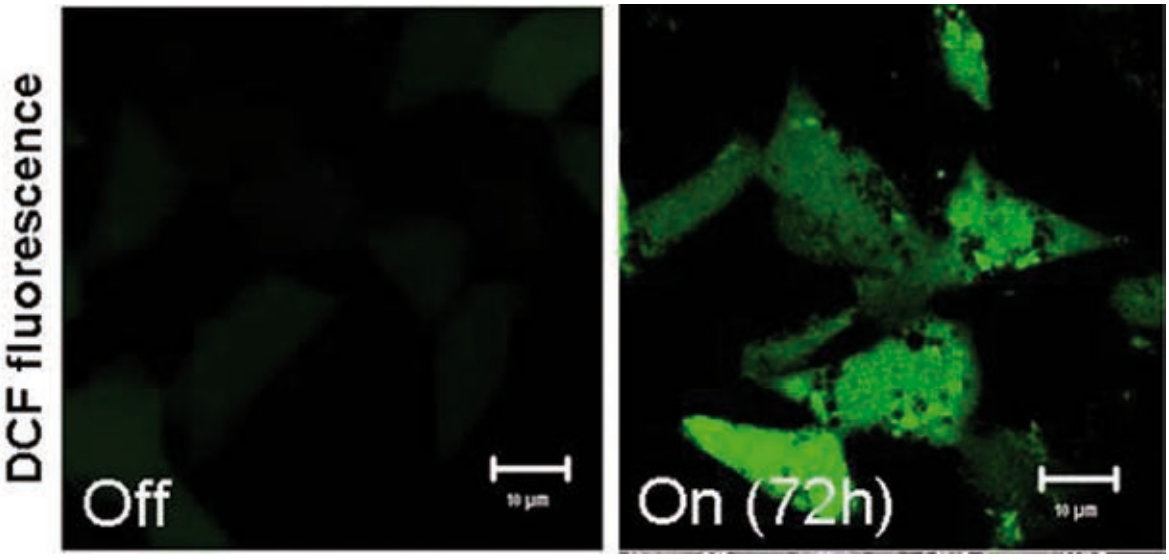
Functional Neurogenetics

(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, Omi/HtrA2, 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 Kahle (2008) Acta. Neuropathol. 115:87).

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. The dopaminergic system of αSYN transgenic mice is remarkably spared, but cognition of aged (Thy1)-h[A30P]αSYN mice is severely impaired, most likely due to their amygdala neuropathology (Freichel et al., (2007) Neurobiol. Aging 28:1421). 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. Susann Horn together with Elena Hausherr are studying the use of viral models of α-synucleinopathy. This work is supported by the Helmholtz Alliance for Mental Health in an Aging Society.



▶ Figure: Intracellular ROS formation triggered by tyrosinase.

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 together with Susanne Weber has 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. Furthermore, Christian Klein is investigating the mode of activation of LRRK2 and other members of this so-called ROCO kinase family. This work is supported by the Hertie Foundation.

Cytoprotective Role of Parkin on Dopaminergic Neurodegeneration

Mutations in the PARK2/PARKIN gene account for most cases of recessive parkinsonism, and may genetically predispose to PD. Parkin is a broadly functional cytoprotective enzyme with E3 ubiqutin ligase activity. However, it is not understood how parkin protects the PD affected dopaminergic (DAergic) neurons. To investigate the molecular and cellular mechanisms of DA neurotoxicity and their modulation by PD-associated genes, Dr. Takafumi Hasegawa has developed novel neuronal cell lines co-expressing human PD-associated genes together with transcriptionally regulated tyrosinase. 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. Massive intracellular production of reactive oxygen species occurs as a by-product, which leads to the activation of apoptotic pathways. Using this cell culture model of PD-relevant oxidative DA neurotoxicity, Hasegawa, Treis, et al. (2008) could demonstrate that parkin suppresses apoptotic stress-activated protein kinase signaling. We are currently identifying the regulatory parkin effector proteins, and their exact ubiquitin modification(s).

Regulation and Modulation of the E3 Ubiquitin Ligase Parkin

Many 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 together with Sven Geisler and Nicole Springer / Diana Skujat investigate 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 fortüne program.

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 together with Stephanie Weber 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 (Görner et al., 2007). This work is supported by the German National Genome Research Network (NGFNplus), 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 and Marlene Anderson are 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. This work is supported by the German Competence Net „Neurodegenerative Dementias".

Staff:
M. Anderson, I. Carballo Carbajal, F. Fiesel, S. Geisler, T. Hasegawa, E. Hausherr, K. Holmström, S. Horn, C. Klein, H. Schell, D. Skujat, N. Springer, W. Springer, A. Treis, J. Waak, S. Weber, S. Weber-Endress

Key Publications

Hasegawa T, **Treis A**, Patenge N, **Fiesel FC**, **Springer W, Kahle PJ** (2008) Parkin protects against tyrosinase-mediated dopamine neurotoxicity by suppressing stress-activated protein kinase pathways. J Neurochem 105: 1700-15

Görner K, Holtorf E, **Waak J**, Pham TT, Vogt-Weisenhorn DM, Wurst W, Haass C, **Kahle PJ** (2007) Structural determinants of the C-terminal helix-kink-helix motif essential for protein stability and survival-promoting activity of DJ-1. J Biol Chem 282:13680-91

Freichel C, Neumann M, Ballard T, Müller V, Woolley M, Ozmen L, Borroni E, Kretzschmar HA, Haass C, Spooren W, **Kahle PJ** (2007) Age-dependent cognitive decline and amygdala pathology in α-synuclein transgenic mice. Neurobiol Aging 28:1421-35

Springer W, Kahle PJ (2006) Mechanisms and models of α-synuclein-related neurodegeneration. Curr Neurol Neurosci Rep 6:432-436

Kahle PJ (2008) α-Synucleinopathy models and human neuropathology: similarities and differences. Acta Neuropathol 115:87-95

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

Projektgruppe C. elegans

Projektgruppenleiter: Wolfdieter Springer

Der äußerst simple und nur 1mm lange (Ø 70µm) Fadenwurm Caenorhabditis elegans, kurz C. elegans lebt normalerweise in der Blumenerde und ernährt sich dort von Bakterien. Da er dennoch eine enorme Konservierung biochemischer und zellulärer Komplexität zeigt ist er mittlerweile zum best untersuchten Organismus und auch zu einem vollwertigen Modellsystem der biomedizinischen Forschung avanciert. Es findet sich nämlich zu rund 65% aller bislang identifizierten humanen Krankheitsgene ein entsprechendes Homolog im Genom des Wurms. Die Nachwuchsgruppe verwendet den Wurm nicht trotz, sondern gerade wegen seiner Einfachheit, um Gene die mit der Parkinson'schen Erkrankung (PD) oder auch frontotemporalen Demenzen (FTD) assoziiert sind, zu untersuchen. Dabei liegt das Augenmerk auf der Charakterisierung der physiologischen bzw. pathophysiologischen Funktionen der entsprechenden gesunden bzw. mutierten Genprodukte.

Im Jahr 2008 erhielten C. elegans Forscher bereits zum dritten Mal den Nobelpreis für ihre grundlegenden Arbeiten an diesem Wurm, die sich sämtlich auf höhere Organismen übertragen ließen. Erst wurde der Preis 2002 an Sidney Brenner verliehen. Seine Arbeitsgruppe entdeckte den programmierten Zelltod und beschrieb erstmals alle Zellteilungen und Differenzierungen eines vollständigen Organismus vom befruchteten Ei bis hin zum adulten Tier. C. elegans zeichnet sich durch eine konstante Zellzahl von exakt 959 Zellen aus. 302 dieser, also fast 1/3 aller Zellen, sind Neurone die aufgrund ihrer Verschaltungen und ihres chemischen Inhalts 118 verschiedenen neuronalen Klassen zugeordnet werden können. Von besonderem Interesse der Nachwuchsgruppe sind die lediglich 8 Dopamin-enthaltende Neurone (Abb. 1) sowie die Muskel-innervierenden Motorneurone (Abb. 2) deren Zellkörper und Fortsätze sich in vivo untersuchen lassen.

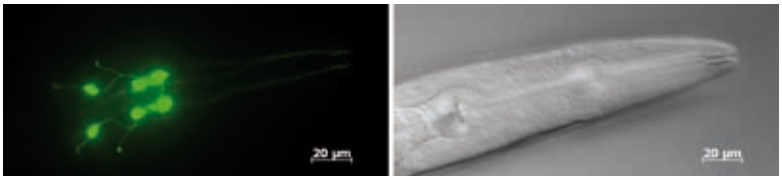
Im Jahr 2006 wurde dann die Entdeckung der RNA-Interferenz (RNAi) und die daraus resultierende Methodik des „gene silcening" geehrt. Bei C. elegans lassen sich seine rund 19.000 Gene gezielt und ganz einfach durch „Füttern" entsprechender dsRNA-produzierender Bakterien manipulieren. Seine einfache Haltung und kurze Generationszeit (2,5 Tage bei 25°C) sowie seine enorm große Reproduktionsfähigkeit (bis zu 100.000 pro Woche ausgehend von einem einzelnen Hermaphrodit) vereinfachen dies weiterhin. In Kombination mit biochemischen Methoden konnte die Nachwuchsgruppe 2008 ein umfassendes Netzwerk genetischer wie auch physikalischer Interaktoren erstellen und somit neue weiterführende Signalwege identifizieren.

Dieses Jahr wurde der Nobelpreis erneut an C. elegans Forscher verliehen, diesmal für die Einführung des grün fluoreszierenden Proteins (GFP). Aufgrund seiner einmaligen Transparenz lassen sich intrazelluläre Prozesse an einem lebenden Organismus studieren. 2008 erhielt die Projektgruppe die Möglichkeit, eigene transgene Linien mittels Mikroinjektion herzustellen. Daraufhin wurden zahlreiche transgene Wurmstämme generiert um die bereits identifizierten Interaktionen und Signalwege auch in vivo im zellulären Kontext eines Organismus studieren zu können. Dabei wurden u.a. auch „humanisierte Würmer" generiert die das gesunde menschliche Gen oder auch die Krankheits-verursachenden mutierten Formen produzieren. Die so generierten transgenen Tierstämme sind Gegenstand der momentanen Forschung.

C. elegans Group

(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 (Springer and Kahle, 2006). We are particularly interested in the elucidation of molecular and cellular pathogenic mechanisms resulting in Parkinson's disease (PD) or frontotemporal dementia (FTD).



▶ Figure 1: Transgenic GFP lines used for visualization of the 6 DA neurons and their processes in the head region of C. elegans.

Regulation and Modulation of the Parkin E3 Ubiquitin Ligase Activity

We are studying the physical and genetic interactions of Parkin with genes involved in the ubiquitin de-/conjugation system (Springer et al., 2005). In 2008 we have identified novel co-factors of Parkin and thus have established a comprehensive interaction network by a directed and hypothesis-driven combinatorial approach of C. elegans RNAi and Yeast-two-hybrid screening. The knowledge of all putative co-factors provides the essential basis in order to fully understand the complex multilayer control of the E3 ubiquitin ligase activity. Currently we are assessing the effects of co-factor selection on type and mode of ubiquitin conjugation mediated by Parkin.

▲ Figure 2: Molecules differentially labeled with fluorescent proteins (EGFP or mCherry) are being co-expressed to study their functional consequences in vivo.

Autophagic/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 proteasome has been studied, whereas the contribution of the autophagic/lysosomal pathway remains enigmatic. Impaired autophagy as well as 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 protein metabolism, we are investigating the autophagic/lysosomal involvement as well as cell death routes deriving from these organelles. This work is ongoing and supported by the fortüne-Programm.

Cell Biology of the Frontotemporal Dementia Associated Genes

In 2008 the group started to phenotypically characterize deletion mutants of the C. elegans TDP-43 and Progranulin homologs. As a complement to the knock-out strains we have already generated various transgenic C. elegans lines ectopically expressing the respective worm or human genes which are currently analyzed in detail. Similar to the human situation, TDP-43 can be forced to aggregate when expressed in specific neuronal subpopulations of C. elegans.

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

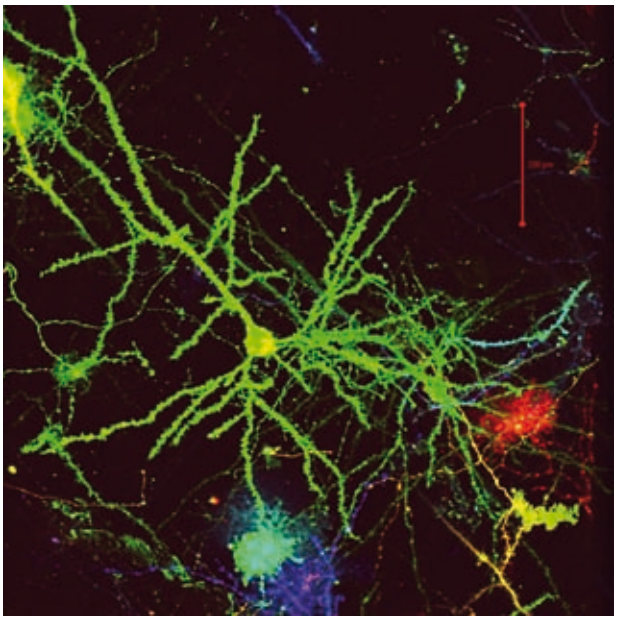
Staff:
S. Geisler, N. Springer/D. Skujat, A. Treis

Key Publications

Springer W, Hoppe T, Schmidt E, Baumeister R (2005) A Caenorhabditis elegans Parkin mutant with altered solubility couples alpha-synuclein aggregation to proteotoxic stress. Hum Mol Genet 14:3407-23

Springer W, Kahle PJ (2006) Mechanisms and models of alpha-synuclein-related neurodegeneration. Curr Neurol Neurosci Rep 6, 432-6

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 University Hospital 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. In summer 2008 the Section on Computational Sensomotorics, headed by Prof. Dr. M. Giese, newly appointed W3-professor, and funded by the German Research Council within the framework of the Excellence Cluster "Centre for Integrative Neuroscience", was installed at the department.

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 analyzed using classical neuropsychological techniques in conjunction with state-of-the-art psychophysical, behavioral and brain imaging 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 (SFB) 550: "Recognizing, localizing, acting: Neurocognitive mechanisms and their flexibility", supported by the German Research Council (DFG) and coordinated by P. Thier.

Two former young investigator groups changed their status in 2008: the first one is the young investigator group on "Neuronal mechanisms of numerical categories and concept formation", set up within the framework of the SFB 550 and headed by Prof. Dr. A. Nieder, who became chairman of the Department of Animal Physiology at the University of Tübingen and moved his group to the Institute of Zoology. The second one on the "Representation of action and learning", headed by Prof. Dr. M. Giese and funded by the Volkswagen Foundation until 2007, turned into the Section on Computational Sensomotorics funded by the DFG within the framework of the Excellence Cluster "Werner Reichardt Centre for Integrative Neuroscience (CIN)". Another 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 International Graduate School for Neural and Behavioural Sciences. Further teaching is deployed at the Faculties of Biology (Prof. Dr. U. Ilg) and Informatics (Prof. Dr. M. Giese and Dr. W. Ilg) and, of course, at Tübingen Medical School. In 2008 Prof. Dr. U. Ilg became Director of the newly established Competence Center of Neuroscience that provides unique training opportunities for high school students and their teachers.

MRI-Labor

Arbeitsgruppenleiter: Fahad Sultan, Peter Dicke

Diese Arbeitsgruppe nutzt kernspintomographische Techniken, um Einblicke in die Architektur und die Arbeitsweise des Gehirns zu gewinnen 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 auch 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 der nichtverbalen sozialen Kommunikation. Weiterhin werden die neuronalen Grundlagen der verdeckten visuellen Suche erforscht. 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 eine Herstellung passgenauer Implantate ermöglichen. Diese Implantate werden aufgrund der des guten Formschlusses 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

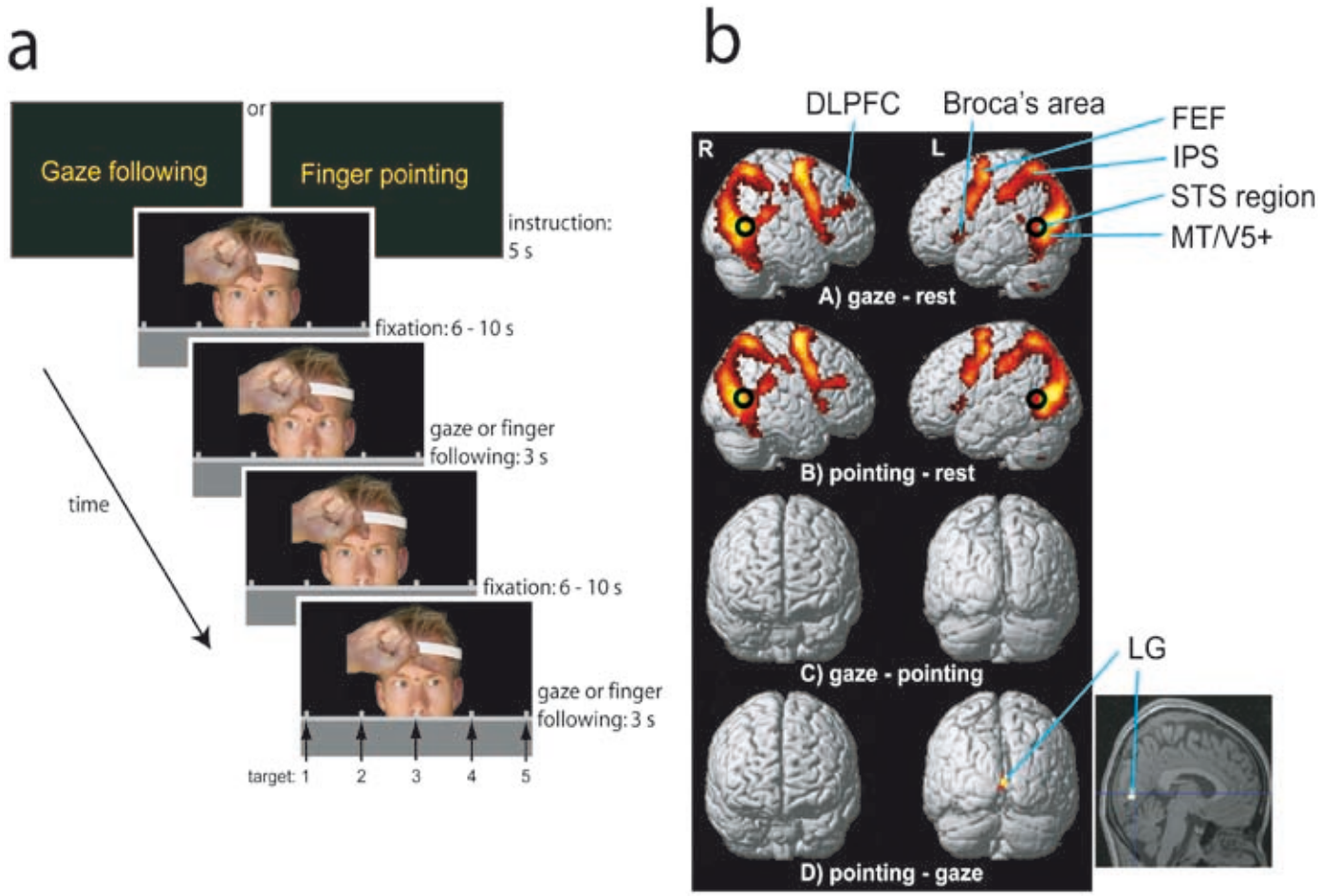
(Group leaders:
Fahad Sultan, Peter Dicke)

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 incomparable 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. On the one hand, we use 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. N. Logothetis from the Max Planck Institute for Biological Cybernetics we use invasive techniques such as electrical stimulation in animals to utilize the unique 3D capabilities of MRI to image the brain's functional connectivity.

Correlative human and monkey fMRI (Peter Dicke)

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 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 (gray value of the iris) to make an eye movement towards an object in space. Our results (Materna et al. 2008a) 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. In a following study we could furthermore show that the posterior STS is as well able to extract non-eye specific spatial information from body parts as a pointing finger to direct the gaze of a viewer to the target of interest (Materna et al. 2008b) (see fig. 1). 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.

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 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



▲ Figure 1:
Figure 1a: Example of the pictures presented in both conditions: gaze following and finger pointing. **Figure 1b:** Group data (n=17) showing the activation patterns for A: the gaze following– rest contrast, B: the finger pointing – rest contrast, C: the gaze following– finger pointing contrast and D: the finger pointing – gaze following contrast superimposed on a SPM brain template. A, B: lateral view, C, D: anterior and posterior view. D: additional overlay on a sagittal T1 image of one of the subjects, $P < 0.001$ uncorrected. R, right hemisphere; L, left hemisphere; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; IPS, intraparietal sulcus; STS, superior temporal sulcus; MT/V5+, medial temporal area; LG, lingual gyrus.

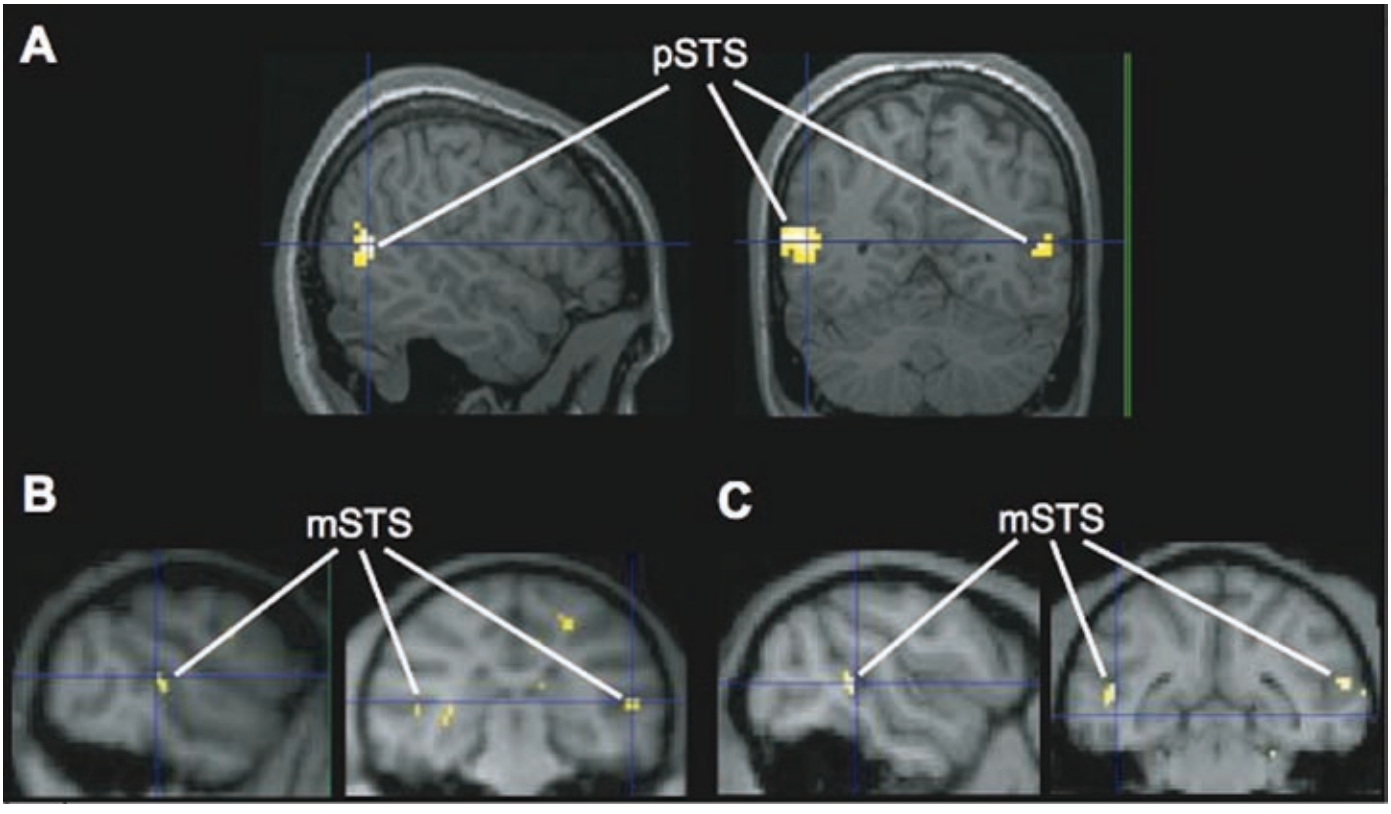
using this approach to analyze the neuronal underpinnings of gaze direction processing. Rhesus monkeys have been successfully trained to use gaze direction as offered by portraits of other monkeys in order to reallocate their attention to particular objects in space. Two of the animals trained have been 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 study resulting on 18 subjects suggest separate regions

in the STS for the processing of eye gaze and head gaze respectively

The function of the dorsal frontoparietal network during covert visual search: Visual scenes explored covertly are initially represented in a retinal frame of reference (FOR), but it seems likely that "later" stages of the cortical network use non-retinal or eye centered representations as they may ease the integration of different sensory modalities for the formation of supramodal representations of space. We tested if the cortical elements involved in covert attention are based on eye-centered or non-eye-centered coding by using fMRI. Subjects were scanned while detecting a target item (a normally oriented "L") amidst a set of distractors (rotated "L"s). The array was centered either 5° right or left of the fixation point, independent of eye-gaze orientation, which was varied in 3 steps, straight relative to the head, 10° left or 10° right. A quantitative comparison of the BOLD responses for the 3 eye-gaze orientations revealed higher activations for the right intraparietal sulcus (IPS) and the right frontal eye field (FEF) for search directed to the contralateral eye-centered space, independent of whether the array was located in the right or left (head-centered) hemispace. The corresponding areas in the left hemisphere showed the reverse pattern, i.e. an activation by search in the right eye centered hemispace. In other words, the IPS and FEF, members of the cortical network underlying covert search, operate in an oculocentric FOR. We started the training of monkeys executing a similar task to locate the functional equivalent regions for a more detailed investigation on the level of single units.

▼ Figure 2:
Comparison between the significant (p<0.001, uncorrected) Bold response pattern for the eye gaze following > color matching contrast in humans (a) and the head gaze following > color matching contrast in monkey M1 (b) and M2(c). pSTS: posterior superior temporal sulcus: mSTS. Middle superior temporal sulcus; r: right hemisphere.



In-vivo imaging of the monkey brain's connectivity with fMRI and electrical stimulation (Fahad Sultan)

Revealing excitable subcortical networks by microstimulation-fMRI of the deep cerebellar nuclei: Electrical stimulation, combined with functional magnetic resonance imaging (es-fMRI), is proving to be an important tool to study the functional properties of spatially distributed neuronal networks of the brain. In this subproject, we want to understand how information is propagated between the two major cortices of the primate brain, the neocortex and the cerebellar cortex. Methods to study widely distributed networks of the brain functionally have been rather limited up to now. Our initial experiments showed that the evoked blood oxygen level-dependant (BOLD) responses were due to the stimulation of pyramidal axons (Tolias and Sultan et al., Neuron 48:901-911, 2005). Furthermore, es-fMRI revealed the primary projection sites of the stimulated areas. However, irrespective of the stimulation parameters, there was no indication of transsynaptic propagation of the activity within the neocortex. In this project we want to electrically stimulate the deep cerebellar nuclei to see whether es-fMRI can be a useful in-vivo polysynaptic tracing tool. Experiments were performed on three rhesus monkeys. Chambers were centred on the deep cerebellar nuclei (DCN) by the stereological coordinates obtained from a pre-surgery high resolution MR scan. So far we have electrically stimulated 19 different sites in different parts of the deep cerebellar nuclei. Electrical stimulation of the DCN leads to reliable transsynaptic responses in the neocortex. Surprisingly, the BOLD responses can be observed in multiple neocortical sites extending beyond classical cerebellar targets (such as primary motor cortex) and also extending to the hemisphere ipsilateral to the stimulation site. An analysis of the BOLD amplitude in cortical and subcortical structures indicated that the bilateral spread of activity is already present at subcortical levels, i.e. the thalamus. Currently we cannot exclude the possibility that we stimulated fibres of passage that then activated the contralateral DCN and hence contributed to the bilateral neocortical activation patterns. However, the observation of wide-spread BOLD responses in thalamic regions outside the known thalamic termination sites of the DCN indicates that the DCN are able to drive brainstem circuits effectively that then reach neocortex through several thalamic nuclei. These results indicate that, apart from the direct DCN -thalamic projection, indirect routes exist by which the cerebellum can mediate information to the neocortex that may be equally important and effective despite requiring the additional passage through synapses in met- and mesencephalic structures.

Flattened representation of the neocortical areas of Macaca mulatta: The macaque cerebral cortex corresponds to a disk of roughly 130 mm diameter and constitutes of possibly over one hundred different areas as described by a wealth of anatomical, electrophysiological and neurochemical studies. Based on the recently published MRI and histology atlas (Saleem and Logothetis, A combined MRI and histology atlas of the rhesus monkey brain in stereotaxic coordinates. London: Academic Press; 2007) we provide a flattened representation of these areas using techniques implemented in the mrVISTA software suite (Wandel et al., J Cogn Neurosci 12, 739-752, 2000). For this we segmented 125 areas of the neocortex on MR sections based on corresponding histological sections of the same monkey. The border between white and grey matter was also marked and used for surface mesh and flat map generation. The segmented areas were then projected onto the flat maps. Our results showed that the surface areas on these flat maps were in good agreement with previously published data for areas such as V1, V2 and also for the total neocortex. The differences in these cases ranged between 3 and 6%. The average size of an area was 140 mm^2 and the seven largest areas were V1, V2, V4,1-2, 3a-b, and F1. These results confirm previous work that in the macaques the largest brain regions are devoted to vision, followed by regions devoted to somatosensation and motor control.

Comparative anatomy: In another project of the MRI laboratory we study the com-

parative anatomy of the cerebellum. A part of the brain that shows some marked variations in size and shape in the primate order. To understand the complex position of the cerebellum in the mammalian evolution we decided to take a closer look at the much simpler cerebellum of birds to search for correlation of cerebellar size and behavioural specialization. So far the analysis of the cerebellum of 24 bird families showed that some birds with large brains (crows, parrots and woodpeckers) have a specially enlarged cerebellum (Sultan, Current Biology, 15:R649-650, 2005). The enlarged region of the cerebellum receives trigeminal and visual inputs and is likely related to the birds' ability to use their beaks to manipulate their environment, very similar to the primates' usage of their hands. Together with Mark Augath and Nikos Logothetis (Max Planck Institute for Biological Cybernetics) we have employed structural MRI to analyze non-invasively the morphology of bird brains obtained from the Naturhistorisches Museum Basel (Portmann collection) and from the Zoological Museum of Amsterdam. So far we have successfully imaged two species of hornbills (one species dated from the year 1888) and reconstructed the cerebellar surface of one.

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

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Key Publications and References

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Sektion Neuropsychologie

Sektionsleiter: Hans-Otto Karnath

Arbeitsschwerpunkte der Sektion Neuropsychologie sind die Untersuchung der Raumorientierung und des Objekterkennens des Menschen. An Patienten mit Hirnschädigungen und an gesunden Versuchspersonen werden unter Einsatz funktioneller Bildgebung (fMRT), transkranieller Magnetstimulation (TMS) und der Registrierung von Augen- und Handbewegungen die Mechanismen unserer Wahrnehmung der Körperorientierung, Prozesse der Aufmerksamkeit und Raumexploration sowie die visuomotorischen Koordinationsprozesse beim Zeigen und Greifen untersucht. Die übergeordnete Frage, die der Arbeit der Sektion Neuropsychologie zugrunde liegt, ist die Frage danach wie Organismen sensomotorische Koordinationsleistungen erbringen. Zur Generierung eines sinnvollen motorischen Handelns, z.B. bei der Exploration und der Orientierung im Raum oder dem Ausführen von Ziel- und Greifbewegungen, ist die Nutzung und Abstimmung einer Vielzahl sensorischer Informationen erforderlich, die in unterschiedlichen Koordinatensystemen vorliegen und sich ständig verändern. Wie unser Gehirn diese Aufgabe bewältigt stellt ein Grundproblem der Kognitiven Neurowissenschaften dar. Die Erkenntnisse erlauben uns nicht nur die grundlagenwissenschaftlichen Fragen besser zu verstehen, sondern auch neue Strategien für die Behandlung von Patienten zu entwickeln, die nach einer Hirnschädigung Störungen in diesen Bereichen aufweisen.

Section for Neuropsychology

(Section Head: Hans-Otto Karnath)

The Section for Neuropsychology focuses on the investigation of spatial cognition and object recognition in humans. The current issues of our work comprise the perception of body orientation, spatial attention and exploration, and visuomotor coordination in grasping and pointing movements. We investigate patients with brain lesions as well as healthy subjects using functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and eye- and hand movement recordings. These approaches aim to elucidate the integration processes of perceptual information from different modalities and their use in the control of action. To accomplish the initiation and execution of adequate motor behavior, e.g. during exploration of space or grasping an object, a continuous updating and alignment of incoming sensory information is required as this information is coded in different coordinate systems and changes fast in our environment. A better understanding of these processes not only allows us new insights into normal brain functions, but also enables us to develop new approaches for the treatment of patients with brain lesions and their functional disorders.

Current research topics are related to:

- Anosognosia
- Action control and sensorimotor coordination
- Auditory localization in space
- Comparative studies in human and non-human primates
- Exploration of space
- Extinction
- Object perception
- Pusher-Syndrome
- Pure alexia
- Visual integration and simultanagnosia

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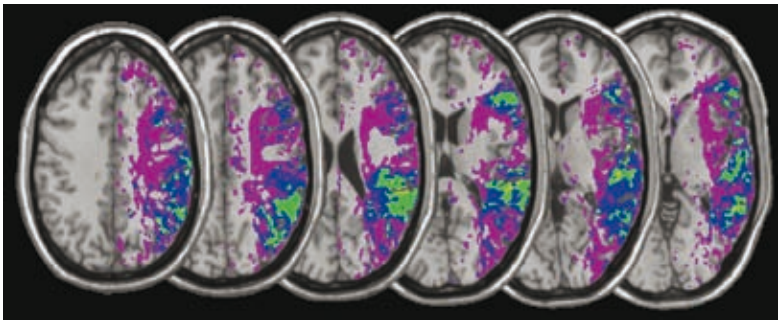


▶ Figure 2: Normalized Perfusion-Weighted Imaging (PWI). In patients with stroke lesions, we use PWI to identify the abnormally perfused brain area(s) that receive enough blood supply to remain structurally intact, but not enough to function normally. In order to recognize these common areas in groups 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.

Okulomotorik Labor

Arbeitsgruppenleiter: Uwe J. Ilg

Die Arbeitsgruppe versucht, die Mechanismen und das neuronale Substrat der sensorischen Integration aufzuklären.

Die Wahrnehmung unserer Umwelt basiert nicht nur auf der Verarbeitung von Informationen aus unseren Sinnesorganen. Verfolgt ein Zuschauer zum Beispiel die halsbrecherische Fahrt eines Abfahrtsskiläufers, so bewegt sich das Bild des Skifahrers auf der Netzhaut dank exakt angepasster Augengeschwindigkeit überhaupt nicht. Trotz der Abwesenheit einer Bewegung im Netzhautbild ist sich der Zuschauer jederzeit darüber bewusst, dass der Skifahrer mit vielleicht mehr als 100 km/h zu Tale braust. In dieser Situation wird die Information über die Ausführung einer Augenbewegung für die subjektive Bewegungsempfindung benutzt.

Die Arbeitsgruppe bedient sich wichtiger Methoden moderner kognitiver Hirnforschung. So werden einerseits in psychophysischen Untersuchungen die Wahrnehmungen von gesunden Versuchspersonen analysiert. Beispielhaft für zielgerichtetes Verhalten werden Augen- und Handbewegungen registriert und analysiert. Andererseits wird das neuronale Entladungsmuster von Nervenzellen im Gehirn von Rhesusaffen während der Ausführung von zielgerichtetem Verhalten oder während der subjektiven Wahrnehmung aufgezeichnet und analysiert.

Es wurden zwei unterschiedliche Bereiche im Gehirn lokalisiert, die entscheidend zur Verrechnung von Information über die Bewegung in der Netzhaut und über die Bewegung der Augen beitragen. Ein Bereich (Frontales Augenbewegungsfeld) liegt im Stirnlappen, die andere Region (Area MT und MST) am Übergang vom Hinterhauptlappen in den Scheitellappen.

In einer weiteren Studie konnten wir zeigen, dass Neurone in einer frühen Stufe der Informationsverarbeitung entscheidend zu einer Misswahrnehmung der Geschwindigkeit eines Reizes beitragen. Wird eine Versuchsperson gebeten, die Geschwindigkeit einer Punktwolke einzuschätzen, so werden konsistente Fehler in der Einschätzung der Geschwindigkeit durch die Größe der Punktwolke verursacht. Die Geschwindigkeit einer kleinen Punktwolke wird höher als die Geschwindigkeit einer großen Punktwolke eingeschätzt, selbst wenn beide Punktwolken sich exakt gleich schnell bewegen. Einzelne Nervenzellen im mittleren temporalen Areal (MT) zeigen in ihrer Kodierung für die Geschwindigkeit genau diese Abhängigkeit von der Größe eines Reizes.

Die erzielten Resultate helfen, die Funktionsweise unserer eigenen Großhirnrinde besser zu verstehen und legen damit die Grundlage für ein profundes Verständnis der Ausfälle nach Schädigungen dieser Hirnbezirke. Die Grundlagen der tierexperimentellen Methodik helfen entscheidend, angewandte bio-medizinische Therapiemöglichkeiten wie die tiefe Hirnstimulation oder die technischen Implantate der Hörschnecke oder der Netzhaut zu verbessern.

Oculomotor Laboratory

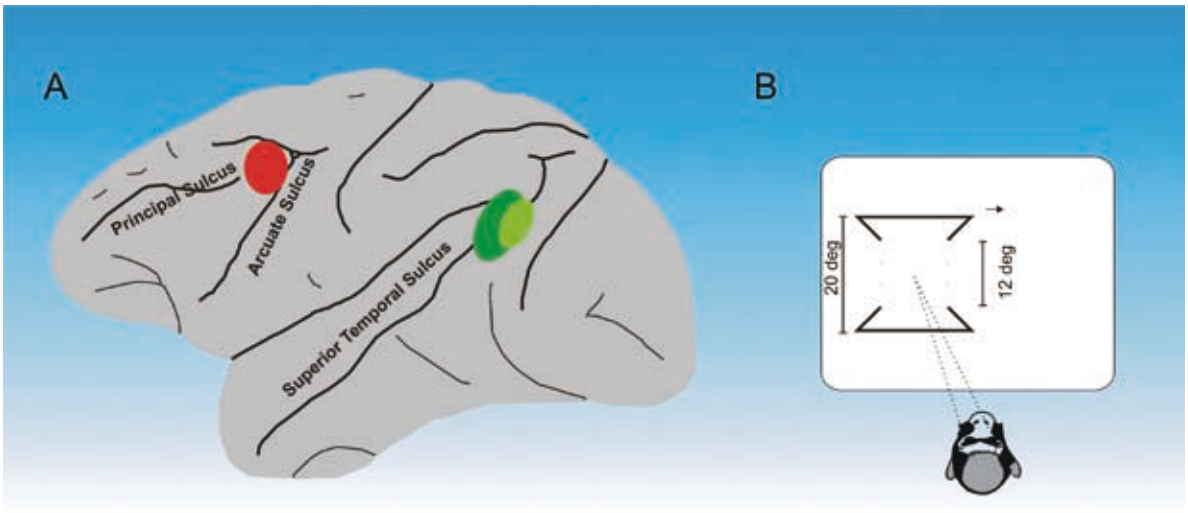
(Group Leader: Uwe J. Ilg)

The basic mechanisms underlying the execution of goal-directed behavior (action) as well as perception are the key interest of the oculomotor lab. Therefore, psychophysical studies as well as behavioral experiments focusing on the execution of hand and eye movements with normal human subjects are preformed. The results of these studies are compared with the insights from experiments on awake and trained rhesus monkeys performing similar paradigms. These insights are based on the analysis of behavioral parameters such as the details of goal-directed hand and eye movements, psychophysical results, single-unit activity patterns as well as the consequences of artificial activation or inhibition of specific brain areas. The brain areas under examination are the middle temporal area (MT, light green in Fig. 1), the medial superior temporal area (MST, dark green in Fig. 1) and the frontal eye field (FEF, red in Fig. 1).

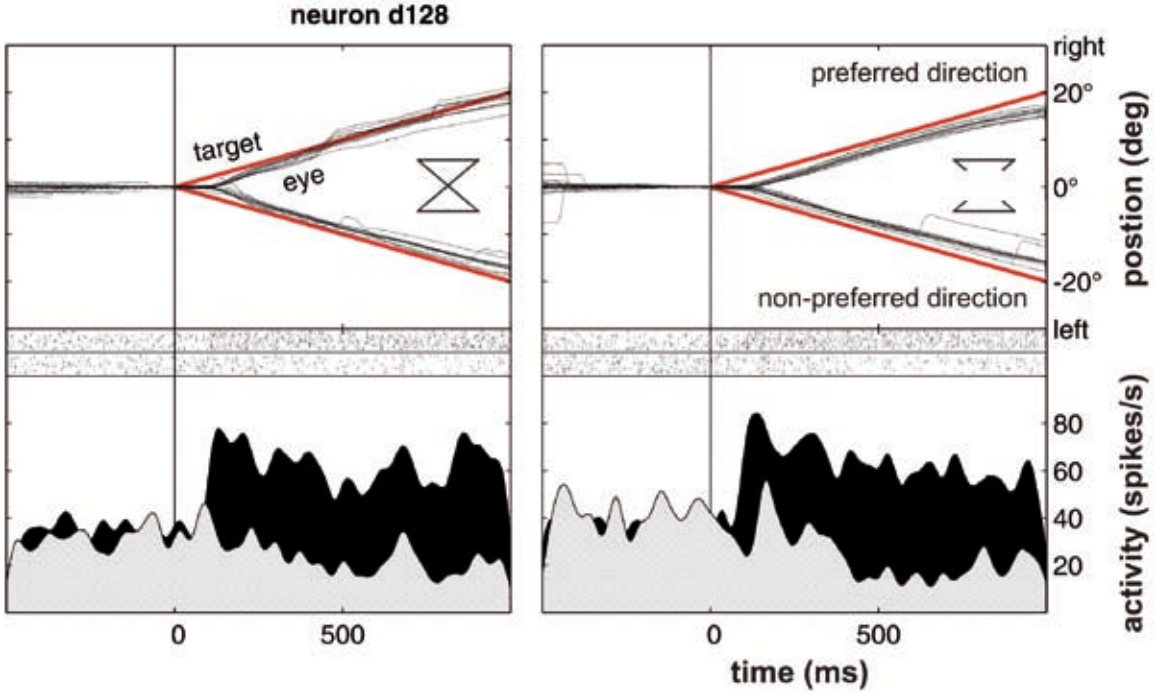
Recently, we focused on the issue whether and how the FEF contributes to the generation of smooth pursuit. The first question we tried to answer was the question whether pursuit-related activity recorded from the FEF was dominated by retinal image slip signals. The existence of extra-retinal signals related to the ongoing eye movements can be documented using the "imaginary" pursuit target. This target does not provide stimulation of the central visual field.

If the pursuit-related activity during pursuit of the real and "imaginary" target is similar, the interpretation is that the neuron receives extra-retinal signals related to eye speed in addition to the retinal image slip signals. Figure 2 gives the eye movements and the firing pattern of a typical neuron recorded from the FEF.

The pursuit-related activity during tracking of a real and "imaginary" target is very similar. This result is very robust, the similarity can not only be seen in individual neurons but also in the population response of all recorded neurons. It is important to note that we used a fixed initial fixation period of 500 ms during each trial in these studies. Therefore, it is possible to assume that the monkeys developed a prediction of the end of this time interval and consequently expected precisely the onset of the pursuit target. The change in the firing pattern towards a more regular pattern might be taken as an argument for this notion.

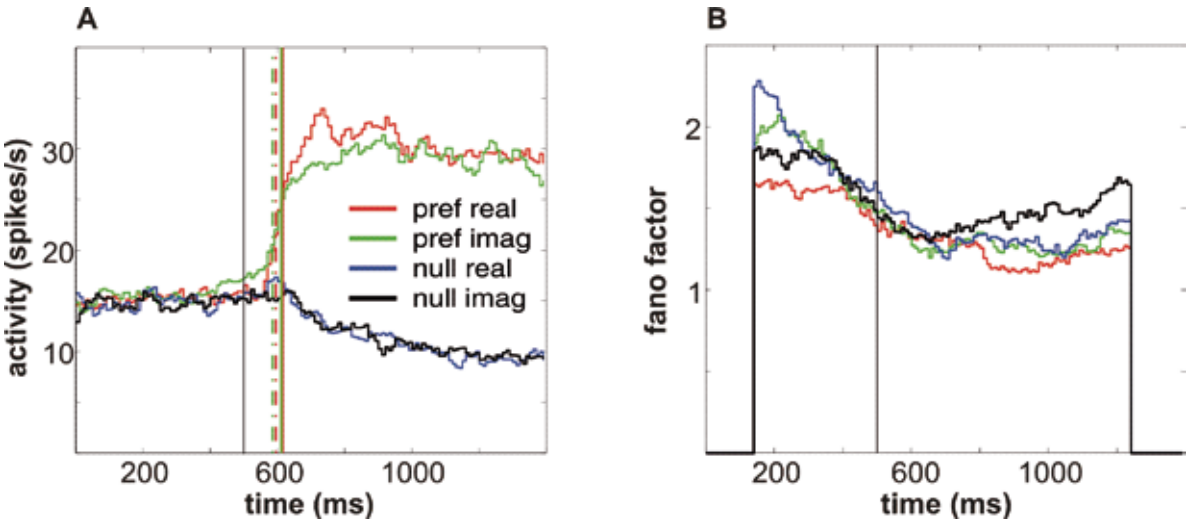


▲ Figure 1:
A gives a side view of a simplified monkey brain. The three marked areas, i.e. the frontal eye field (FEF, red), the middle temporal area (MT, light green) and the medial superior temporal area (MST, dark green) are known to be important with respect of the generation of smooth pursuit as well as for the perception of visual motion. B gives an idea of the "imaginary" pursuit target used in several studies. The monkeys are trained to track the invisible intersection of diagonals. This stimulus makes it possible to elicit smooth pursuit eye movements without retinal image slip in the central visual field.



Having this first hint towards the contribution of the FEF to prediction in mind, we thought about an eye movement paradigm to address this question in detail. Eye movements provide the ground to quantify experimentally the ability to predict future events. As a first step, we documented that the ability of rhesus monkeys to produce anticipatory eye movements is very similar to the ability of a human subject.

▲ Figure 2:
shows the eye movements and the neuronal discharge of a single neuron recorded from the frontal eye field. It is important to note that the eye movements directed towards the real target (left panel) are very similar to the eye movements elicited by the "imaginary" target (right panel). Similarly, the neuronal responses do not show differences. Therefore, this pursuit-related activity can not be explained as the consequence of retinal image slip processing (modified from Ilg and Thier 2008).



▲ Figure 3:
A gives the population response of 58 neurons recorded from the frontal eye field. The vertical black line gives the onset of pursuit target. The dotted vertical lines give the latencies of the neuronal responses; the solid vertical lines give the latency of the eye movement. Importantly, the neuronal responses precede the eye movement onset, absolutely necessary for a causal relationship of the FEF in the generation of pursuit. In addition, a slight increase of activity during the initial 500 ms fixation period can be observed. This increase might be taken as a hint to the fact that this neuron contributes to anticipation. This is further supported by the change of the firing pattern towards a regular pattern expressed by a decrease of the Fano-Factor shown in B (modified from Ilg and Thier 2008).

In short, we used a 500 ms gap period during which the target moved invisible for the subject. During this period, predictive smooth eye movements were generated. We calculated V500 as a measure for these eye movements. When we performed single-unit recordings, we found neurons in the FEF which increased their firing rate during the gap period. Interestingly, these neurons increased their activity exclusively if the monkey expected the upcoming target movement in the preferred direction of the recorded neuron.

Now, we have detailed information about the processing within the two very different brain areas, i.e. the frontal eye field and the medial superior temporal area. In future studies, we will concentrate on the specific interactions between these two cortical areas.

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

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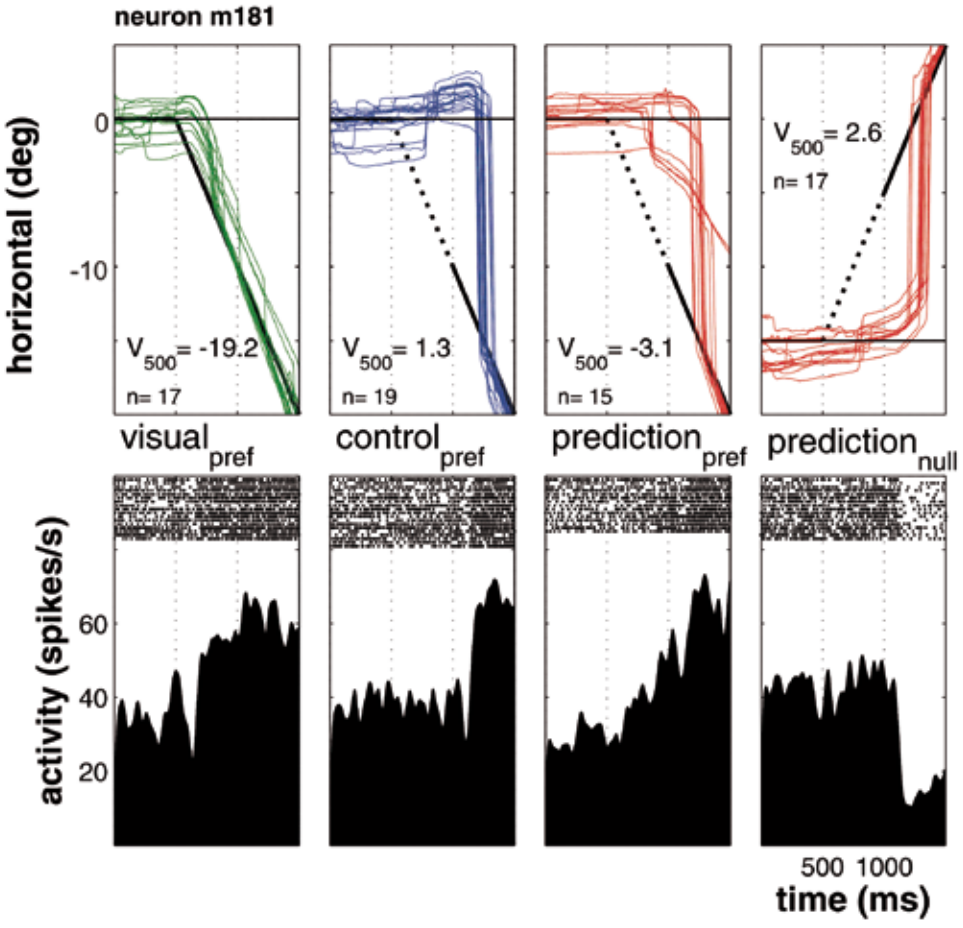

▶ Figure 4: Response of a typical FEF neuron in four different conditions with different amounts of anticipation. The V500 values are given in deg/s. The leftmost panel (green) gives the visual control situation, the target was continuously visible. The blue traces represent the control condition in which the monkey could not predict the upcoming target movement. The red traces inform about the anticipation trials. However, this neuron increased its activity only if the monkey anticipated the upcoming target movement in the preferred direction.

Labor PrimatenNeurokognition

Arbeitsgruppenleiter: Andreas Nieder

Seit 2003 untersucht die DFG-Nachwuchsgruppe PrimatenNeurokognition am HIH die neuronalen Grundlagen numerischer Kategorien und Konzepte an verhaltenstrainierten Rhesusaffen und menschlichen Probanden mittels kombinierter psychophysischer und neurophysiologischer Studien. Sprachliches Zählvermögen beim Menschen tritt nicht de novo in der Evolution auf, sondern entsteht aus biologischen Vorläufern. Nichtsprachliche Anzahl-Repräsentationen bei Affen sind aufgrund der relativen Ähnlichkeit von Menschen- und Affengehirn von besonderem Interesse. Schwerpunktmäßig werden der Präfrontalkortex und der hintere Parietalkortex untersucht, klassische Assoziationskortizes, die eine dominante Rolle bei der Kodierung numerischer Information und abstrakter Denkleistungen allgemein spielen. Hinsichtlich nichtsprachlicher Quantifizierungsleistungen weisen unsere Studien klar auf Homologien zwischen dem Menschen- und Affengehirn hin und verdeutlichen den Nutzen nichtmenschlicher Primaten als Modellsystem. Künftig werden diese Erkenntnisse erlauben, experimentellen Zugang zu zellulären Substraten und Mechanismen zu ermöglichen, die mit anderen hochentwickelten kognitiven Fähigkeiten, wie etwa syntaktische, semantische und arithmetische Leistungen, in Verbindung stehen.

Mit dem Ruf des Arbeitsgruppenleiters an den Lehrstuhl für Tierphysiologie an der Universität Tübingen im Jahre 2008 endet die Tätigkeit der Arbeitsgruppe am HIH. Für die erfolgreiche Umsetzung der Experimente war die hervorragende Infrastruktur innerhalb des Hertie-Instituts für Klinische Hirnforschung entscheidend. Zum einen muss die verantwortungsvolle Arbeit mit nichthumanen Primaten höchsten Anforderungen bezüglich Unterbringung, tierärztlicher Versorgung und operativer Ausstattung genügen. Diese Anforderungen waren innerhalb der Abteilung Kognitive Neurologie des HIH beispielhaft gegeben. Zum andern erlaubte uns die hervorragende apparative Ausstattung am Universitätsklinikum, unser Forschungsprogramm zu erweitern und mittels funktioneller Bildgebung den Brückenschlag zur numerischen Kognition am Menschen anzugehen. Die Mitglieder der Arbeitsgruppe PrimatenNeurokognition bedanken sich sehr herzlich für die exzellenten Arbeitsbedingungen in den vergangenen fünf Jahren am Hertie-Institut für Klinische Hirnforschung in Tübingen.

Primate NeuroCognition Laboratory

(Group Leader: Andreas Nieder)

The DFG-junior research group PrimateNeurocognition investigates since 2003 at the HIH the neuronal foundations of numerical categories and concepts in behaviorally-trained rhesus monkey and human subjects via a combination of psychophysical and neurophysiological methodologies. Verbal numerical competence in humans does not emerge de novo in humans, but builds on biological precursors. Because of the relative similarities between the human and monkey brain, non-linguistic numerosity representations in monkeys are of special interest. Research focuses on the prefrontal and the posterior parietal cortices, classical association cortices that play a dominant role in coding numerical information and abstract thinking in general. Within the realm of nonverbal quantification capabilities, our studies showed clear homologies between human and monkey brains and thus demonstrate the need for nonhuman primates as model systems. In the future, these findings will enable us to tackle the cellular substrates and mechanisms that are related to high-level cognitive skills, such as syntactic, semantic and arithmetic capabilities.

The work of the junior research group at the HIH ended in 2008 after the head of the group accepted an offer as full professor at the Dept. Animal Physiology, University of Tübingen. To accomplish the experiments over the last years successfully, the excellent infrastructure of the Hertie-Institute for Clinical Brain Research was of paramount importance. On the one hand, responsible experiments in nonhuman primates rely on the best housing facilities, veterinary treatment and surgical equipment. These requirements were ideally fulfilled at the Department of Cognitive Neurology. On the other hand, the excellent technical equipment at the University Hospital allowed us to extend our research program to better bridge findings between nonhuman and human primates by including human functional imaging. The members of the research group PrimateNeurocognition are very grateful to the Hertie Insitute for Clinical Brain Research in Tübingen for providing excellent research conditions over the past five years.

homepages: http://www.hih-tuebingen.de/kn/forschung0/labor-primatenneurokognition/

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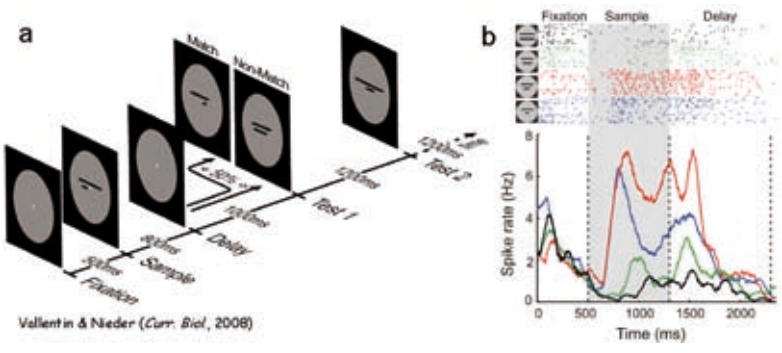
▼ Figure: Coding of spatial proportions in primate prefrontal cortex. (A) Delayed match to proportion task. To start a trial the monkey had to grasp a lever and maintain fixation. If the sample and test display showed the same proportion, i.e. the same length ratio between a reference and test line, the monkey had to release the lever. The monkey had to continue holding the lever until the second test appeared (which was always a match) if the sample and test display showed different proportions (probability of match/non-match condition = 0.5). (B) Responses of a proportion-selective neuron. In the top panel, the neuronal responses are plotted as dot-raster histograms (each dot represents an action potential, spike trains are sorted and color-coded according to the sample proportion illustrated by example stimuli on the left). Middle panels show spike density functions (activity to a given proportion averaged over all trials and smoothed by a 150 ms Gaussian kernel). The first 500 ms represent the fixation period followed by a 800 ms sample and a 1000 ms delay phase (separated by vertical dotted lines). Data from Vallentin & Nieder (Curr. Biol., 2008).



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Labor für Aktive Wahrnehmung

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 sowohl 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 Arbeiten in den letzten Jahren konzentrierten sich auf die Schaffung von zuverlässigen psychometrischen Verfahren (Stüttgen et al., 2006; Gerdjikov et al. 2008). Diese wurden dann eingesetzt um die psychometrische Empfindlichkeit des gesamtem Tieres mit der Empfindlichkeit einzelner Neurone zu vergleichen. Es stellte sich heraus, dass die Detektionsleistung des Tieres sich durch 5 gleichzeitige Aktionspotentiale in 5 Neuronen des primären somatosensorischen Kortex erklären lässt (Stüttgen und Schwarz, 2008).

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. Hierzu wurden die detaillierten neuronalen Antworten auf Mikrostimulation in verschiedenen Stimulussituationen untersucht (Butovas und Schwarz, 2007). Es liegen erste Ergebnisse vor, die zeigen, dass eingeprägte Signale in verschiedenen Verhaltenssituationen (aktiv vs. passiv) unterschiedliche Wahrnehmungsschwellen aufweisen (Butovas und Schwarz, 2008).

Active Perception Lab

(Group Leader:
Cornelius Schwarz)

Active perception in the rat's whisker system

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 somatosensory body map is laid out in great resolution along the entire tactile pathway. In addition, 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. Previous work shows that a movement-dependent signal, presumably originating in primary motor cortex switches the characteristics of tactile processing in barrel cortex (Haiss and Schwarz, 2005; Hentschke et al., 2006).

Methods: Recording and stimulation via chronically implanted multielectrode arrays are combined with precise tracking of the fine vibrissae. Active vibrissae movements in head-fixed rats are operantly conditioned. The perception of the animal is measured using go/no go detection and discrimination tasks.

Results: To establish the measurements of the animal's perception 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). We have extended this work to precise comparison of psychometric performance with neurometric sensitivities of barrel cortex neurons. Using a likelihood model of population firing, we have found that 5 action potentials in 5 barrel cortex neurons are sufficient to explain the detection performance of the animal (Stüttgen and Schwarz, 2008). In a next step a vibrotactile discrimination task was established. A first study provided evidence that the contribution of intensity cues predominates other physical vibration parameters like kinematic features and frequency and is encoded in spike frequency of primary afferents rather than in spike timing (Gerdjikov et al., 2008). Furthermore, we elucidated specific activation modes of the whisker-related tactile system (Stüttgen et al., 2008).

Perspectives. The next step will be to work out the differences of active vs. passive touch. To this end, we will, firstly, compare psychophysical measurements under conditions of active and passive touch. Secondly, we will measure the strategy with which the animals solve the discrimination in different ranges of stimulus parameters, and ask in how far such adaptive behavior and its electrophysiological reflections optimize perception.

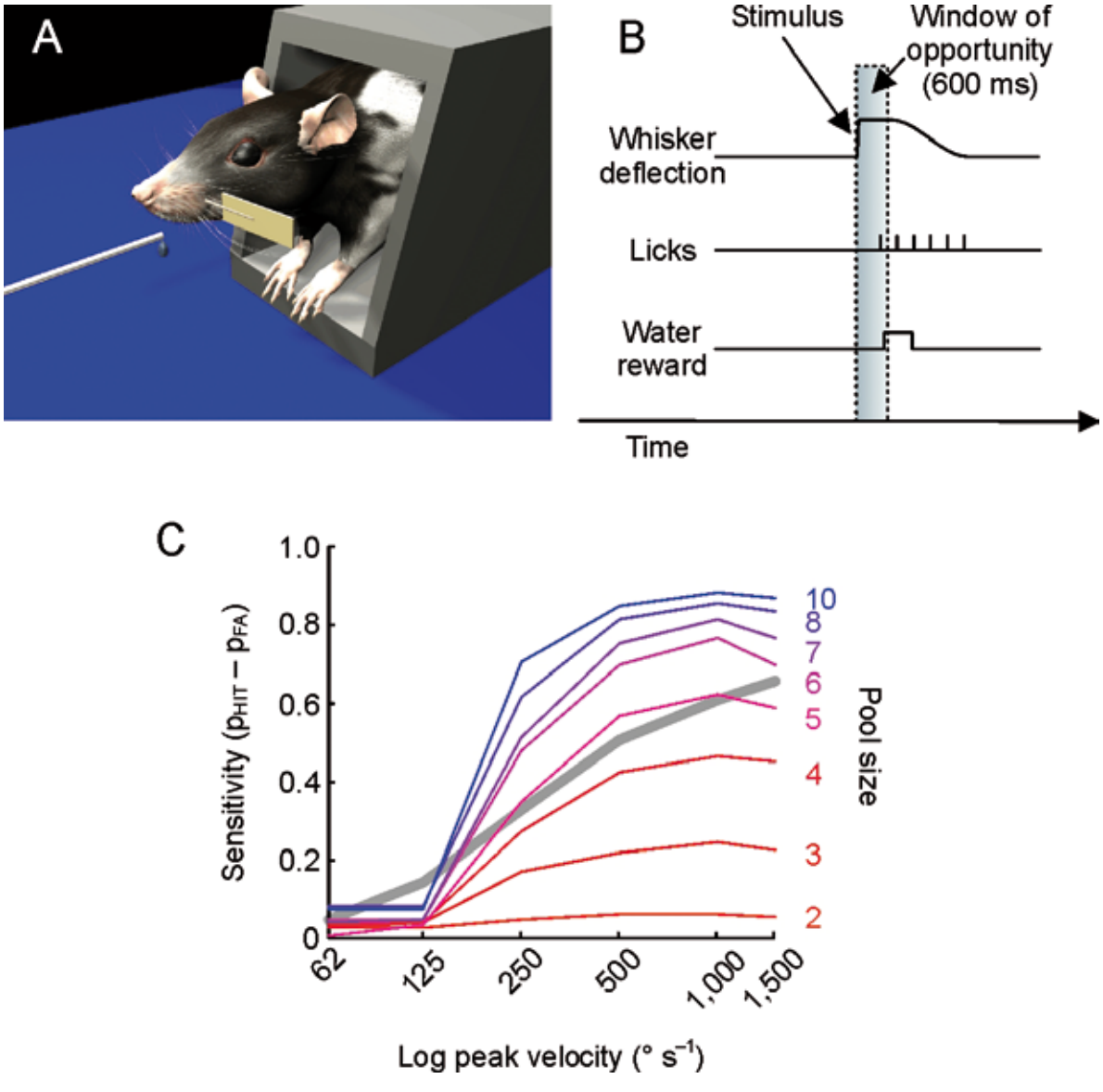
Dynamic microstimulation/ Central machine-brain interface

Background. We hypothesize that the input-output function of a central machine-brain interface changes dynamically due to functional context (i.e. the spatiotemporal pulse pattern into which a specific pulse is embedded, and the functional state of the neuronal structure).

Results. Using a psychophysical detection task, we have shown that series of repetitive pulses of intracortical microstimulation are detected better than single pulses. In comparison to independent pulses, however, only double pulses, but not longer pulse series, yielded superior access to perception (Butovas and Schwarz, 2007). Using the model system of active perception, we have obtained preliminary evidence that electrophysiological responses to single pulses

and detection performance are distinct for passive vs. active touch (Butovas and Schwarz, 2008). In cooperation with the Department of Technical Informatics University Leipzig, we have designed an algorithm that uses electrophysiological measurement of local field potentials to extract contextual information, and to adapt stimulation parameters in real time. It is hoped that the precision with which information can be imprinted into cortical circuits via a machine-brain interface can be improved using this technique (Brugger et al., 2008).

▼ Figure:
A: Set-Up. The schematic shows the position of the rat and a piezo-actuator that contacts one of its whiskers. Reward is a drop of water that can be licked off a spout.
B: Psychophysical paradigm. After a stimulus is given to the whisker via the piezo-actuator (here a sigmoidal step) the rat has 600 ms time to indicate detection by emitting a lick at the spout. The indicator lick is detected and leads to a water reward.
C: Comparison of sensitivity of the rat and its neurons in barrel cortex. Results of a data based Monte-Carlo simulation assessing the match between psychometric (gray) and neurometric curves. Five of the most sensitive neurons in barrel cortex perform as well as the rat observer under conditions of temporal uncertainty (i.e. rat/neuron observer do not know when exactly the stimulus will appear) (Stüttgen and Schwarz, 2008).



Cellular mechanisms determining the deep cerebellar nuclei spike-output.

(Group leader: Christine M. Pedroarena)

Background: The cerebellum is involved in motor coordination and the control of movement timing, as is demonstrated by loss of these functions with cerebellar diseases. Within the cerebellar circuits, the neurons of the deep cerebellar nuclei (DCNs) are key elements because, firstly, they are the main target of the cerebellar cortex, secondly, they receive copies of all cerebellar afferent information, and thirdly, they are the sole output of the cerebellum signal to its target structures. The present project asks how intrinsic and synaptic mechanisms determine and control DCN spike frequency and timing.

Results: A first project focused on intra-nuclear circuits. At least, three different types of DCNs can be distinguished based on their neurotransmitter content and projection patterns: glutamatergic, GABAergic and glycinergic neurons. These different types of DCNs are known to be locally interconnected but the synaptic effects of such pathways are not clear. Our studies showed that glycinergic synapses were developmentally regulated and were activated in animals older than 18 days. Glycinergic synapses display fast kinetics compatible with a role in timing of the synaptic output of the principal glutamatergic DCNs (Pedroarena & Kamphausen, 2008). A second project investigates the role of different potassium channels in regulating timing of spontaneous and evoked DCNs firing. We found that large calcium dependent potassium channels (BK) control mainly the interspike membrane potential during spontaneous firing and only indirectly the repolarization of action potentials. As a consequence, BK channels regulate the spontaneous firing rate but have minor effects on the activity evoked by depolarizing steps and the input/output curves. These effects contrast with the role of BK channels in neurons of other brain structures and with the effect of other voltage dependent potassium channels expressed by DCNs' (Pedroarena, 2007).

homepage: http://www.hih-tuebingen.de/en/kn/forschung0/active-perception-lab/

Key Publications

Stüttgen MC, Schwarz C (2008) Psychophysical and neurometric detection performance under stimulus uncertainty. Nat Neurosci 11:1091-99

Stüttgen MC, Kullmann S, Schwarz C (2008) Responses of rat trigeminal ganglion neurons to longitudinal whisker stimulation. J Neurophysiol 100:1879-94.

Butovas S, Schwarz C (2008) State dependent LFP responses to intracortical microstimulation in rats' barrel cortex. Soc Neurosci 863.3

Brugger D, **Butovas S**, Bogdan M, **Schwarz C**, Rosenstiel W (2008) Direct and inverse solution for a stimulus adaptation problem using SVR. ESANN Proceedings: 397-402

Gerdjikov T, Bergner C, Schwarz C (2008) Barrel cortex frequency encoding and behavioral discrimination in the rat whisker system. Soc Neurosci 858.11

Pedroarena CM, Kamphausen S (2008) Glycinergic synaptic currents in the deep cerebellar nuclei. Neuropharmacology 54:784-95

Pedroarena CM (2007) Pharmacological investigations indicate that BK channels control spontaneous and repetitive firing of deep cerebellar nuclear neurons. Soc Neurosci 245.2

Butovas S, Schwarz C (2007) Intracortical microstimulation in barrel cortex of awake, head-restraint rats: assessment of detection thresholds. Eur J Neurosci 25:2161-69

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

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Labor Sensomotorik

Arbeitsgruppenleiter: Hans-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.

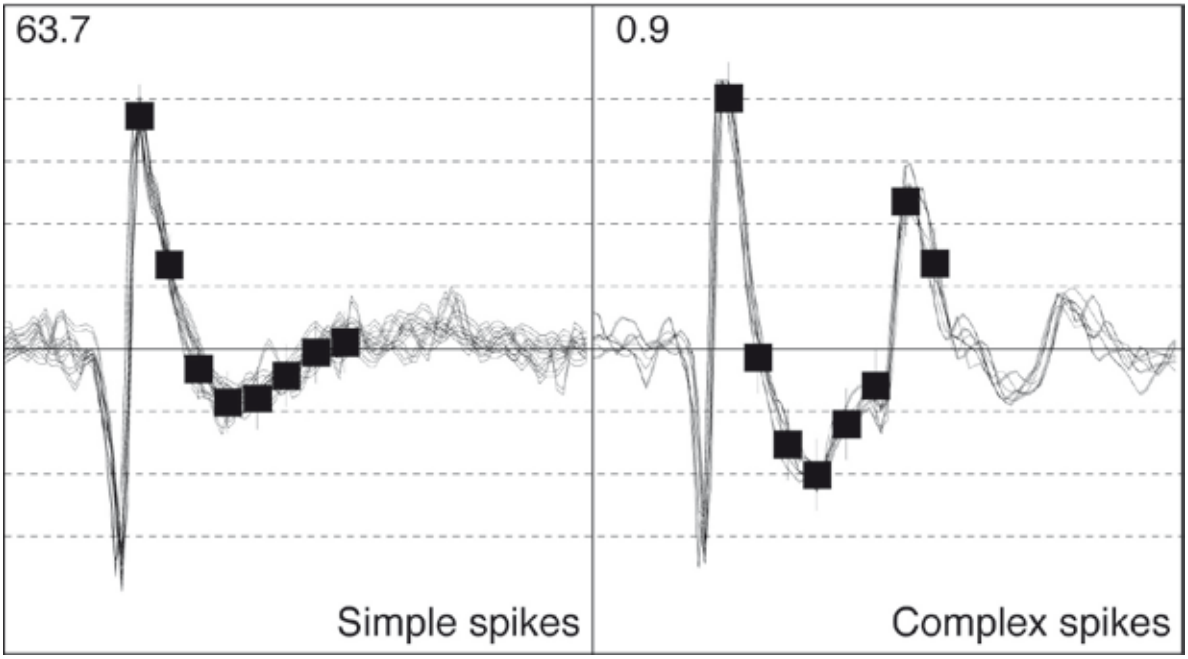
In den zurückliegenden Jahren hat sich die Arbeitsgruppe schwerpunktmäßig mit der Rolle des Kleinhirns befasst, eines Teiles des Gehirns, der den wesentlichen Teil der von ihm verarbeiteten Informationen unter Vermittlung der Brückenkerne aus der Großhirnrinde bezieht und seinerseits über die Kleinhirnkerne 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 erforscht. 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 Modells der Sakkadeneffektoren bzw. ganz generell der motorischen Peripherie betrachtet werden, wie es von manchen theoretischen Konzepten zur motorischen Kontrolle gefordert wird.

Sensorimotor Laboratory

(Group Leader: Hans-Peter Thier)

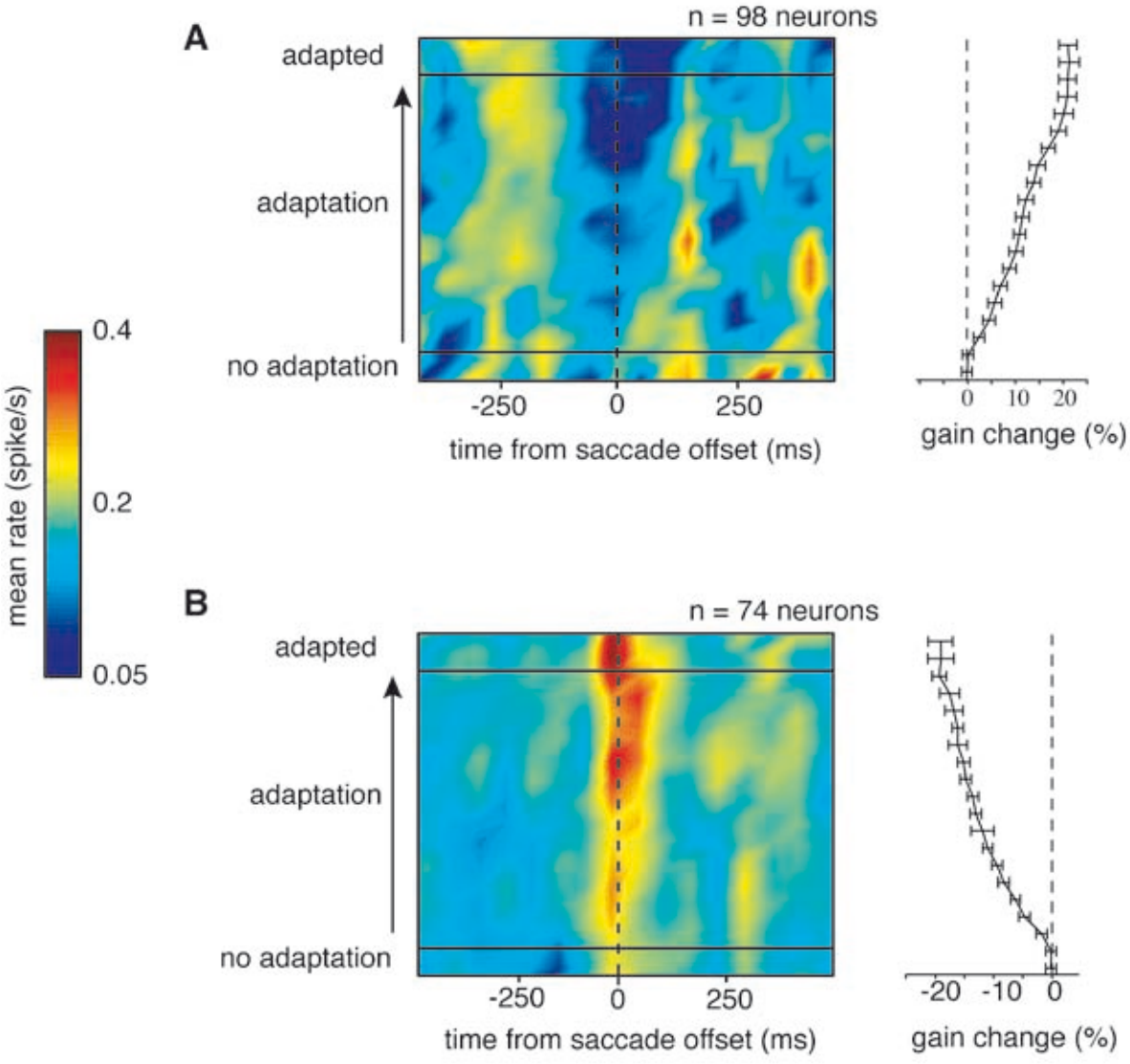
Work in this group is guided by the conviction that any attempt to understand the function of cerebral cortex, the most „humane" part of our brains, will only be successful if we take into account its interactions with a number of subcortical structures supported by extensive fiber systems connecting 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



▶ 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.

spike (CS), characterized by conspicuously low discharge rates (1-2 Hz). (see Fig. 1)

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



▲ 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 color 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.

spikes fired 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 precise 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. In as yet unpublished experiments we recently demonstrated that this is indeed the case.

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 fig. 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.

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/

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Key Publications

Catz N, Dicke PW, Thier P (2008) Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. PNAS 105(20):7309-7314

Catz N, Dicke PW, Thier P (2005) Cerebellar complex spike firing is suitable to induce as well as stabilize motor learning. Curr Biol 15:2179-2189

Thier P, Dicke PW, Haas R, Barash S (2000) Encoding of movement time by populations of cerebellar Purkinje cells. Nature 405:72-76

Neuropsychologie der Handlungskontrolle

Arbeitsgruppenleiter: Marc Himmelbach

Im Jahr 2008 ist diese Arbeitsgruppe durch die Einwerbung umfangreicher Drittmittel aus der Sektion Neuropsychologie (AG Karnath) hervorgegangen. Als Forschungsdisziplin versucht die Neuropsychologie durch die Untersuchung und Beschreibung von Verhaltensstörungen nach einer lokalen Schädigung des Gehirns die Funktionsweise des intakten menschlichen Gehirns zu erschließen.

Drei Störungsbilder sind im Kontext der visuellen Handlungskontrolle von besonderer Bedeutung, die visuelle Agnosie, die optische Ataxie und die Gliedmaßenapraxie. Jedes dieser Störungsbilder steht mit einem Verarbeitungsschritt bei der Planung und Umsetzung von Handlungen in engem Zusammenhang. Patienten mit visueller Agnosie können Gegenstände ihrer Umgebung zwar sehen, jedoch nicht mehr erkennen. Ist in diesem Fall auch ein Erkennen der Handlungsmöglichkeiten, die ein Objekt bietet, unmöglich? Patienten mit optischer Ataxie erkennen Gegenstände und Objekte, zeigen jedoch grobe Fehler bei der Kontrolle der Richtung ihrer Handbewegungen und der Steuerung der Handöffnung beim Ergreifen. Ist diese Beeinträchtigung von der folgenden Benutzung der Objekte unabhängig? Kann ein intaktes Wissen um den korrekten Gebrauch eines Gegenstandes die Defizite reduzieren? Schließlich zeigen Patienten mit einer Gliedmaßenapraxie ein fehlerhaftes Wissen um die Benutzung eines Objektes und grobe Fehler, wenn sie Handlungen anderer nachahmen sollen.

Es erscheint uns offensichtlich, dass Erkennen (visuelle Agnosie), visuomotorische Kontrolle (optische Ataxie) und das Wissen um und das Erkennen von Handlungen (Apraxie) eng miteinander verbunden sind und sich gegenseitig beeinflussen. Die Existenz dieser Patienten wurde dagegen immer als Hinweis auf klar abgegrenzte, serielle Verarbeitungsschritte gewertet. Im Fokus der Arbeitsgruppe stehen vergleichende Untersuchungen der visuellen und motorischen Leistungen dieser Patienten. Die Patienten sollen Gegenstände erkennen, Greifbewegungen ausführen und den Gebrauch von Objekten demonstrieren. Dabei wird die ihnen zur Verfügung stehende Information im Verlauf der Untersuchungen manipuliert, so dass Gemeinsamkeiten und Unterschiede der einzelnen Störungsbilder dargestellt werden können. Diese neuropsychologischen Untersuchungen werden ergänzt durch die funktionelle Bildgebung des intakten Gehirns bei der Ausführung möglichst ähnlicher Aufgaben. So wird der ursächlichen Beschreibung im Falle der Patientenuntersuchungen eine räumlich präzise Lokalisation einzelner Verarbeitungsschritte und der Interaktionen zwischen neuronalen Strukturen zur Seite gestellt. Ziel dieser Arbeit ist eine Beschreibung des verzweigten Weges der Informationsverarbeitung vom Erkennen eines Objektes bis zur Ausführung einer zielorientierten Handlung. Die vergleichende Arbeit mit unterschiedlichen Patientengruppen kann dabei bisher nicht bekannte Potentiale für eine Kompensation oder sogar Restitution der jeweils beeinträchtigten Funktion aufdecken.

Neuropsychology of Action

(Group Leader: Marc Himmelbach)

Three neuropsychological disorders are of outstanding importance in the context of human action control: visual agnosia, optic ataxia, and limb apraxia. Patients suffering from visual agnosia can see but not recognize objects in their environment. Patients suffering from optic ataxia successfully recognize objects but demonstrate gross misreaching and impaired grip formation. Patients with apraxia demonstrate impaired knowledge about object usage and deficient pantomime or imitation of actions.

Obviously, recognition, sensorimotor control, and action knowledge are interdependent processes. However, in the two recent decades neuropsychological approaches primarily aimed at functional segregation. An outstanding example is the two visual streams model in its various formulations. E.g. one version authored by Milner and Goodale proposed that an occipito-temporal visual pathway is primarily dedicated to visual processing for perception and memory, while a dorsal occipito-parietal pathway shall be dedicated to visual processing for action control. One crucial assumption of this model is a dependency of delayed actions on the intact occipito-temporal system with an immediate loss of parietal involvement once an action is delayed. In a behavioral study we demonstrated that this assumption must be wrong. Recently, we additionally showed that intact parts of a patient's damaged parietal cortex participate in the control of delayed actions.

Our current projects explore the interaction between visual perception, action knowledge, and the execution of appropriate actions especially in patients with optic ataxia. These patients' visuomotor deficits seem to be restricted to objects with less action affordances in comparison to familiar everyday objects. Our studies comprise measurements of reaching and grasping movements and fMRI experiments implementing similar behavioral paradigms for the examination of healthy humans and neurological patients. The comparison of healthy participants and brain-damaged patients in neuroimaging studies provides a powerful tool to describe undisturbed information processing on the one hand and cortical reorganisation in brain-damaged patients on the other hand.

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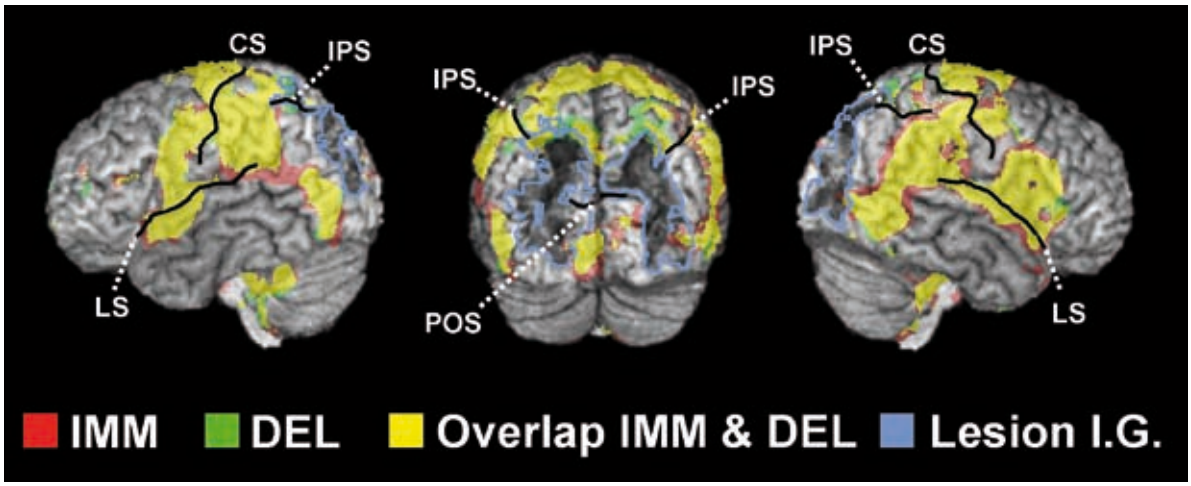


▶ Figure: Functional magnetic resonance imaging of immediate (IMM) and delayed (DEL) action execution in a patient with optic ataxia due to a bilateral damage of the occipito-parietal cortices. In stark contrast to healthy humans, this patient is more accurate in delayed than in immediate actions. Our results show that this behavioural difference is not due to topographical changes of the residual activation pattern.

Key Publication

Himmelbach M, Nau M, **Zündorf I**, Erb M, Perenin M-T, **Karnath H-O** (in press) Brain activation during immediate and delayed reaching in optic ataxia. Neuropsychologia, doi: 10.1016/j.neuropsychologia.2009.01.033

Sektion Theoretische Sensomotorik

Sektionsleiter: Martin Giese

Die Sektion für Theoretische Sensomotorik befasst sich mit theoretischen Fragestellungen in der Neurologie und in den Neurowissenschaften und technischen Anwendungen. Sie ist Teil des Hertie Institutes für klinische Hirnforschung und des Centrums für Integrative Neurowissenschaften (CIN).

Die Sektion bearbeitet drei Forschungsbereiche:

1. Kontrolle von komplexen Körperbewegungen bei gesunden Probanden und neurologischen Patienten. Ein Beispiel ist die Messung winziger Bewegungsveränderungen, die bei der Erkennung vorklinischer Symptome der Parkinsonschen Erkrankung helfen können. Ein anders Beispiel ist die Untersuchung der adaptiven Anpassung von Bewegungen bei Patienten mit Kleinhirnstörungen.

2. Entwicklung und Testung neuronaler Modelle für höhere visuelle Funktionen, insbesondere für die Erkennung von komplexen Bewegungen und Handlungen. Ein Beispiel ist die Entwicklung physiologisch plausibler neuronaler Netzwerkmodelle, die erklären wie ‚Spiegelneurone' zur visuellen Erkennung von zielgerichteten Handlungen beitragen könnten. In diesem Zusammenhang arbeitet die Sektion eng mit Experimentalisten in den Bereichen Elektrophysiologie und funktionelle Bildgebung zusammen.

3. Technische Anwendungen in Medizintechnik und biologisch inspirierte technische Systeme. Beispiele sind technische Systeme für die Bewegungsmessung sowie die Unterstützung und Optimierung von Rehabilitation (Physiotherapie). Ein weiteres Beispiel sind biologisch inspirierte Verfahren zur Simulation komplexer Körperbewegungen mit Anwendungen in den Bereichen Computeranimation und Robotik.

Die Sektion für Theoretische Sensomotorik arbeitet eng mit dem Zentrum für Neurologie und anderen Gruppen des Hertie-Institutes und des CIN 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), der Ecole Polytechnique Fédérale de Lausanne (Schweiz), und dem Collège de France (Paris).

Section Computational Sensomotorics

(Section Head: Martin Giese)

The Section for Computational Sensomotorics works on theoretical problems in the context of neurology and neuroscience and technical applications. It is part of the Hertie Institute, the Centre for Integrative Neuroscience (CIN) and the medical faculty of the University of Tübingen. The Section provides access to advanced facilities for movement analysis, including a motion capture laboratory with two VICON motion capture systems, data gloves, facilities for stimulus presentation in Virtual Reality, EMG, etc. (Fig. 1).

▼ Figure 1: Motion laboratory of the Section for Computational Sensomotorics.

Research is organized within three main areas:

1) Control and measurement of complex body movements in healthy people and neurological patients;

2) development and testing of neural theories for high-level vision, and specifically the recognition of body movements and actions;

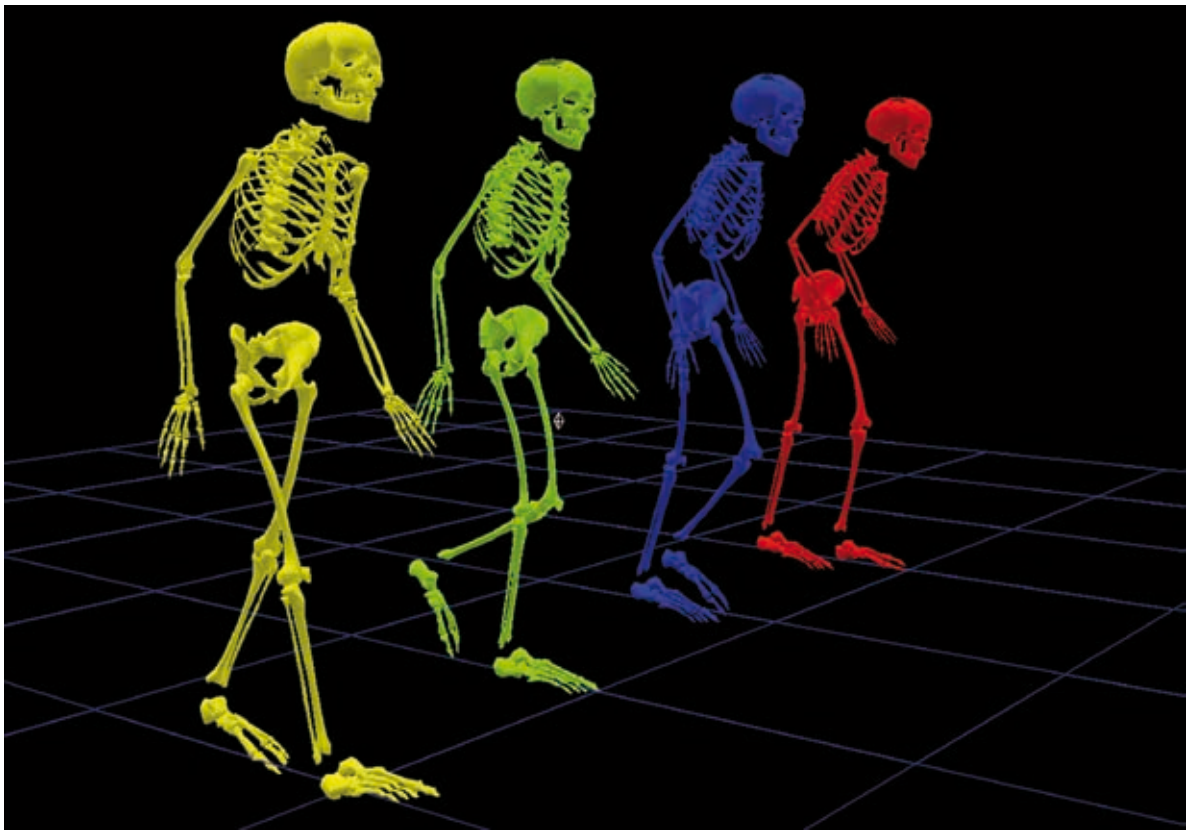
3) biomedical engineering and biologically-inspired technical applications.

1) Control and measurement of complex body movements

Core topics in this area are theoretical methods for the study of complex body movements and the underling neural control processes. Examples are the development of sensitive measures for subtle movement deficits that are characteristic for pre-clinical stages of Parkinson's disease (Fig. 2) or novel methods for the accurate modelling and quantification of subtle coordination deficits in cerebellar ataxia, suitable for the differentiation of different classes of symptoms in gait patterns and other complex movements. Another problem is the development of technical methods that are suitable for the validation and improvement of rehabilitation and physiotherapy. Such experiments are performed in collaboration with several clinical groups in the Hertie Institute and the Centre of Neurology. At the same time, the Section develops own experiments on the motor control and adaptation of complex body movements investigating patients and healthy controls.

2) Neural theories for high-level vision and action recognition

The second research focus of the section is the development and testing of theoretical physiologically plausible neural models. A particular focus of this work has been the investigation of the recognition of biological motion and actions. This involves, on the one hand, computer simulations of hierarchical dynamic neural models whose components reproduce detailed properties of neurons in human and monkey visual, parietal and premotor cortex.

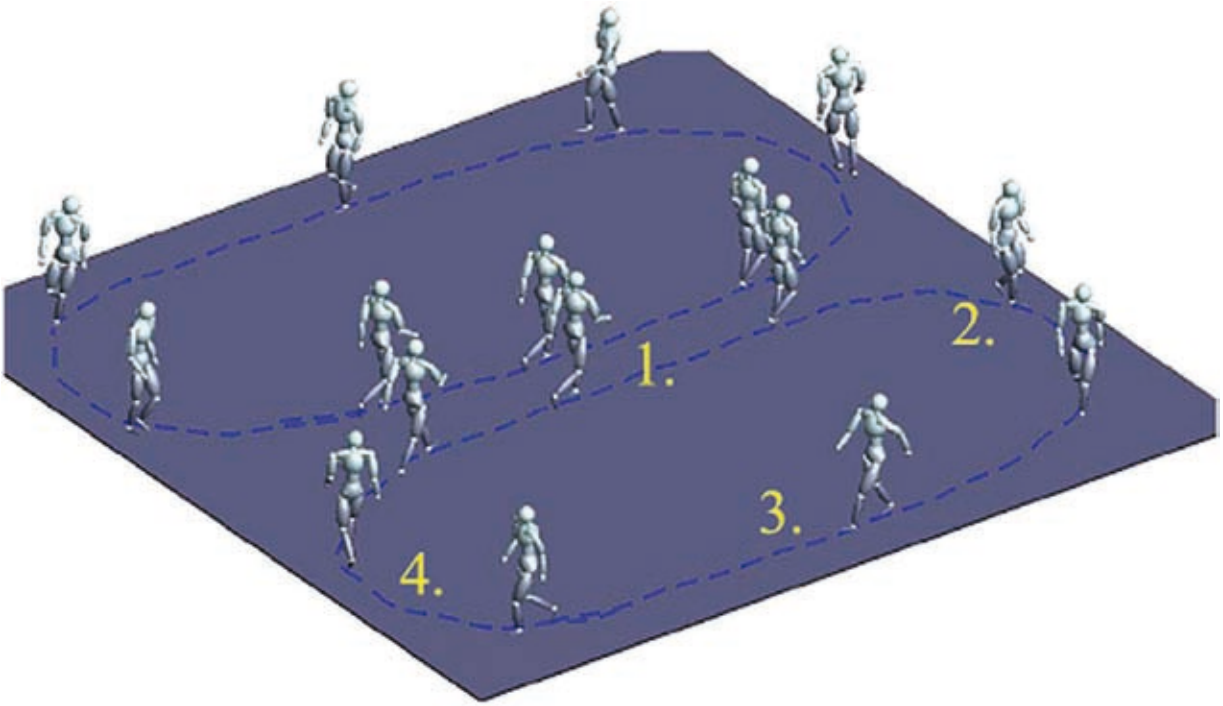


◀ Figure 2: Recorded postures representing characteristic changes that are typical for different levels of Parkinson's disease.

On the other hand, the Section also realizes psychophysical experiments to test specific predictions from such neural theories. In addition, the group collaborates closely with other experimental groups on functional imaging and electrophysiological experiments on motion and action recognition. An example is the investigation of the 'mirror neuron system' in premotor cortex in a joint SFB project with the laboratories of P. Thier (HIH) and G. Rizzolatti (Univ. Parma). A specific focus of this work is to investigate how purely visual representations interact with motor representations in the recognition of complex movement patterns that are relevant, or not relevant for motor execution. A variety of experiments suggests a critical role of learning in the processing of complex movements and actions. The investigation of learning processes and the interaction between motor and visual learning is thus a central topic in this domain. Going beyond a localization of relevant brain areas, the ultimate goal of this work is the identification of specific detailed neural circuits that are suitable for the realization of the computational functions that are required for the processing of complex movements and actions.

3) Biomedical engineering and technical applications

A core interest in technical applications is the development of tools and methods that support diagnostics and rehabilitation in neurology. Examples are devices for the measurement and quantification of movement deficits outside the laboratory, specifically in situations that are relevant for everyday life. Another topic in this area, that will be a focus of future research are robotics tools that are suitable for supporting the quantification of motor behaviour and physiotherapy. Other projects in this domain try to realize technical systems, e.g. in computer vision and computer graphics, exploiting biologically motivated concepts. An example is the development of learning-based highly flexible representations for human movements that are suitable for real-time applications, e.g. in computer animation and robotics. At the same time, these technically motivated models are useful to study interactive behavior, for example in human crowds (Fig. 3). Another example is the development of biologically motivated computer vision



▲ Figure 3:
Recorded postures representing characteristic changes that are typical for different levels of Parkinson's disease.

systems for the recognition of complex movement patterns, e.g. in surveillance applications.

The Section is collaborating with a variety of national and international partners. National cooperation includes the Max Planck Institute for Biological Cybernetics (Tübingen), University of Ulm, Fraunhofer Institutes (St. Augustin and Stuttgart). Close international partners are the Massachusetts Institute of Technology (Cambridge, MA), Weizmann Institute (Rehovot, Israel), Collège de France (Paris, France), and Harvard Medical School (Boston, MA).

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Key Publications

Roether CL, **Omlor L**, **Giese MA** (2008) Lateral asymmetry of bodily emotion expression. Current Biology 18(8):R329-30

Ilg W, Golla H, **Thier P**, **Giese MA** (2007) Specific influences of cerebellar dysfunctions on gait. Brain 130:786-98

Omlor L, **Giese MA** (2007) Blind source separation for over-determined delayed mixtures. Advances in Neural Information Processing Systems 19:1049-56

Casile A, **Giese MA** (2006) Non-visual motor learning influences the recognition of biological motion. Current Biology 16(1):69-74

Leopold, D A, Bondar I V, **Giese MA** (2006) Norm-based face encoding by single neurons in the monkey inferotemporal cortex. Nature 442(7102):572-5

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, Elektroenzephalographie, funktionelle Kernspintomographie) oder mittels Stimulationstechniken (transkranielle Magnetstimulation, DC-Stimulation).

Aktuelle Projekte bearbeiten folgende Fragen:

a. Ziel fortlaufender 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 zugrunde liegen, 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 von Stimulationsexperimenten (TMS, tDCS) ist es, Stimulationstechniken zu entwickeln, welche bei Gesunden und Patienten helfen können, visuelle Diskriminationsleistungen zu verbessern.

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, electroencephalography, functional magnetic resonance imaging), and transcranial magnetic or direct current stimulation (TMS, tDCS) of human subjects.

Current studies focus on the following topics. In ongoing 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 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. The goal of stimulation experiments applying TMS and tDCS techniques is the development of new stimulation protocols that may allow to improve visual discrimination.

Key Publications

Golla H, Tziridis K, **Haarmeier T**, Catz N, Barash S, **Thier P** (2008) Reduced saccadic resilience and impaired saccadic adaptation due to midline cerebellar disease. Eur J Neurosci 27(1):132-44

Händel B, Lutzenberger W, **Thier P, Haarmeier T** (2008) Selective attention increases the dependency of neuromagnetic responses on visual motion coherence. Cerebral Cortex 18:2902—8

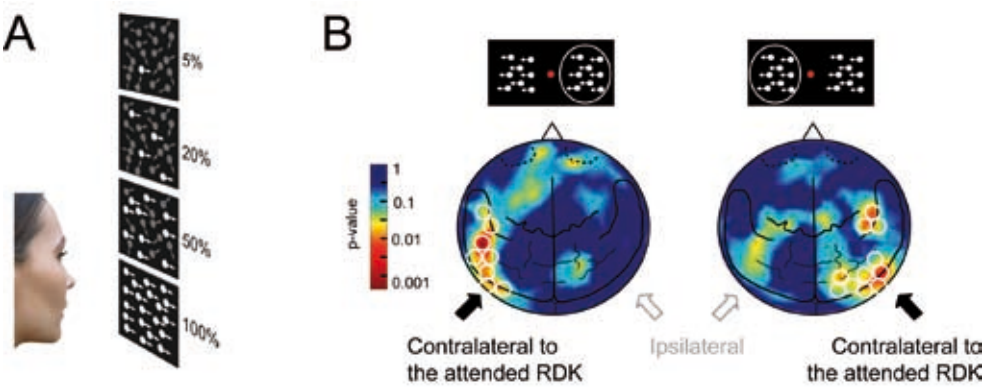
Becker HGT, Erb M, **Haarmeier T** (2008) Differential dependency on motion coherence in subregions of the human MT+ complex. Eur J Neurosci 28:1674-85

Händel B, Haarmeier T (2008). Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination. NeuroImage doi:10.1016/j.neuroimage.2008.12.013

Händel B, Lutzenberger W, **Thier P, Haarmeier T** (2007) Inverse dependencies on visual motion coherence of area MT+ and early visual cortex. Cerebral Cortex 17(7):1542-9

Haarmeier T, Thier P (2007) The attentive cerebellum – myth or reality? Cerebellum 6(3): 177-83

Tikhonov A, **Händel B, Haarmeier T**, Lutzenberger W, **Thier P** (2007) Gamma oscillations underlying the visual motion after-effect. NeuroImage 38(4):708-19

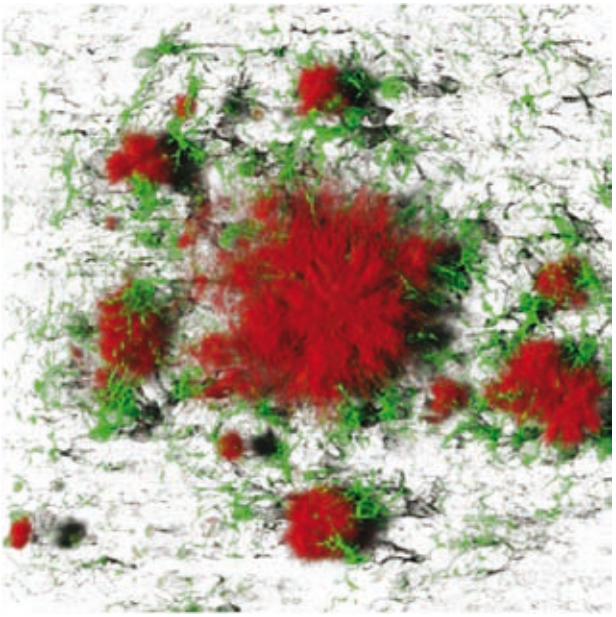


▼ Figure 1: Influences of spatial attention on visual motion processing as assessed by MEG in normal human subjects. A - Sketch of visual motion stimuli presented. B – Cortical responses induced by visual motion reflect the strength of visual motion (motion coherence) only if spatial attention is directed to the stimulus, see also Händel et al., 2008.

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

Staff:
H. Becker, B. Händel, P. Koertvelyessy, L. Zizlsperger

Director: Prof. Dr. Mathias Jucker



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 four research groups: The Neuropathology group uses transgenic mouse models to study the mechanisms of brain aging and in particular cerebral amyloidosis. 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 2008 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, Romania, 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.

Arbeitsgruppe 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, welche 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

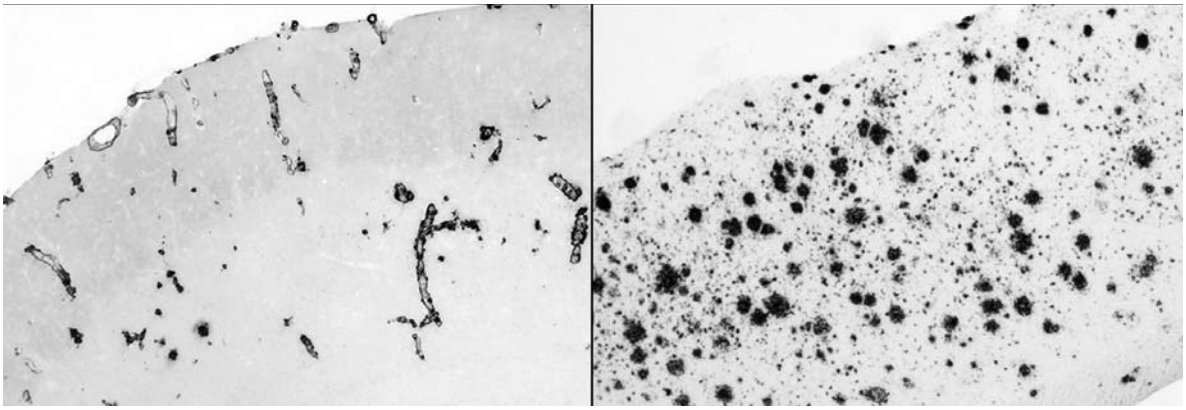
We are interested in studying the mechanism and therapy of cerebral amyloidosis. In particular, the following objectives are pursued:

(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.

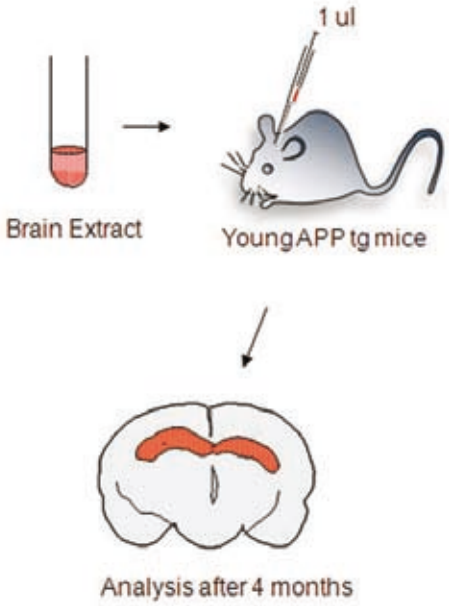
(III) Aβ-amyloidosis targeted immunotherapies have been developed but remain confined to patients that lack significant CAA due to the possibility of CAA-induced hemorrhage as a side effect. Can similar immunotherapies be developed for CAA and non-Aβ amyloidoses and what is the mechanism of amyloid induction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

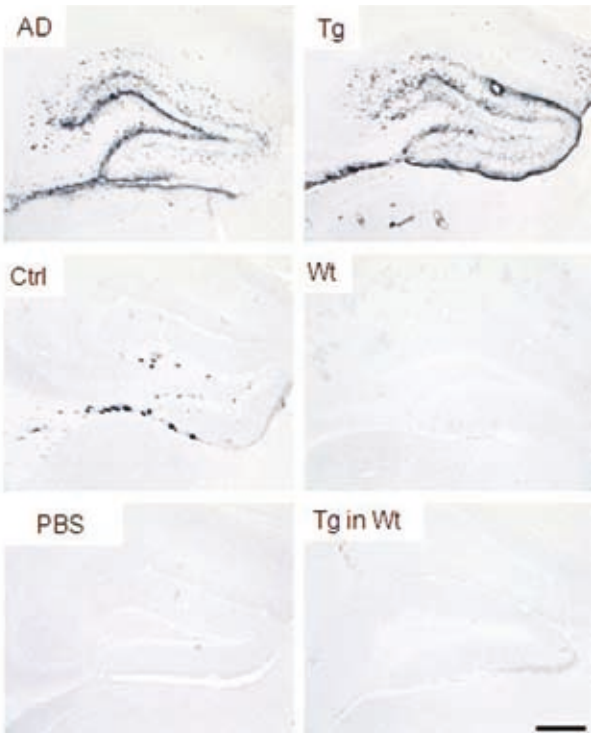
▼ Figure 1:
APPDutch transgenic mice (left) develop cerebral amyloid angiopathy (CAA) in the absence of parenchymal amyloid, while APPPS1 mice (right) develop predominately parenchymal amyloid (amyloid plaques). Shown is the Aβ-immunostained neocortex.



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 APP-Dutch 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 transmis-





◀ 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.

sible 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).

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 (Käser et al., 2007), 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

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

Kaeser S, Herzig M, Coomaraswamy J, Kilger E, Selenica ML, Winkler D, Staufenbiel M, Levy E, Grubb A, **Jucker M** (2007) Cystatin C modulates cerebral ß-amyloidosis. Nature Genetics 39:1437-9

homepage: www.hih-tuebingen.de/zellbiologie/forschungsgruppen/neuropathologie/

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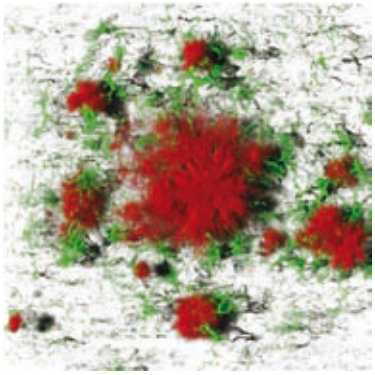


▲ Figure 3:
Microglia (green) surrounding an amyloid plaque (red)

Arbeitsgruppe Molekularbiologie

Arbeitsgruppenleiterin: Ellen Kilger

Das Amyloid Precursor Protein (APP) spielt eine wichtige Rolle bei der Entstehung der Alzheimer Demenz (AD). Seine Spaltung durch verschiedene Proteasen führt neben weiteren Produkten auch zur Entstehung von Aβ Peptiden, 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. So wird z.B. versucht, Inhibitoren für die beteiligten Proteasen γ-Sekretase und BACE-1 zu entwickeln. Jedoch sind bis heute die Regulationsmechanismen der APP Prozessierung nicht bis ins Detail aufgeklärt. Der Fokus der Arbeitsgruppe liegt auf der Erforschung von Faktoren, die an der Spaltung von APP sowie der Entstehung und Ablagerung von Aβ beteiligt sind, mit dem Ziel neue Ansatzmöglichkeiten zur Entwicklung von Medikamenten zu finden. In diesem Zusammenhang konnten bereits neue Erkenntnisse zur Wirkung des Tyrosinkinase Inhibitors Gleevec als Basis zur Entwicklung möglicher Aβ senkender Therapeutika gewonnen werden.

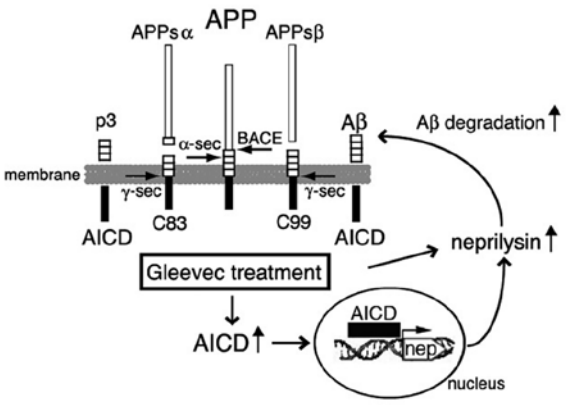
Neuere Studien weisen darauf hin, dass das Membranprotein Bri2 mit APP interagieren und die APP Prozessierung beeinflussen kann. So bewirkte die Überexpression von Bri2 in APP-transgenen Mäusen eine Reduktion der Amyloidablagerungen im Gehirn. Mutationen des Bri2-Gens verursachen ähnlich wie Mutationen im APP Gen eine neurodegenerative Erkrankung, die Familiäre Britische Demenz (FBD) und die Familiäre Dänische Demenz (FDD), ebenfalls mit charakteristischen Amyloidablagerungen. In der Arbeitsgruppe wurde untersucht, auf welche Weise Bri2 und dessen mutierte Formen ADanPP und ABriPP die Prozessierung von APP und die Enstehung von Aβ beeinflussen. Sowohl Bri2 als auch ADanPP zeigten eine deutliche Reduktion von sekretiertem Aβ in Zellkultur Experimenten. APP transgene Mäuse, die mit ADanPP exprimierenden Mäusen gekreuzt wurden, wiesen eine deutliche Reduktion der Amyloidablagerungen im Gehirn auf. Weitere Untersuchungen zur Interaktion zwischen APP und Bri2 werden weitere Aufschlüsse über die Regulation der APP Prozessierung liefern. Darüber hinaus wird untersucht, ob Bri2-, ABri- oder ADan-Peptide mit Aβinteragieren und dessen Aggregation oder Degradation verändern. Diese Ergebnisse werden zu einem besseren Verständnis dessen führen, wie man für therapeutische Stratetegien gezielt auf die APP-Prozessierung einwirken kann. Darüberhinaus werden sie unser Wissen erweitern, wie die Interaktion von Bri2 und APP möglicherweise zur Entstehung zerebraler Amyloidose und Demenz beiträgt.

In der Arbeitsgruppe wurden zur Untersuchung von Amyloidablagerungen zusätzlich zwei neue transgene Mausmodelle generiert. Mäuse mit transgener Expression von APPswe und PS1L166P unter der Kontrolle des GFAP Promoters sollen Aufschluss darüber geben, ob von Astrocyten produziertes Aβ ebenfalls zur Ablagerung von Amyloid führen kann, oder im Gegensatz der neuronale Ursprung für die Amyloidbildung Voraussetzung ist. Ein zweites Mausmodell mit gezielter Bildung des amyloidogenen Aβ42 in vaskulären glatten Muskelzellen wird als Modell für vaskuläre Amyloidablagerungen etabliert.

Molecular Biology

(Group leader: Ellen Kilger)

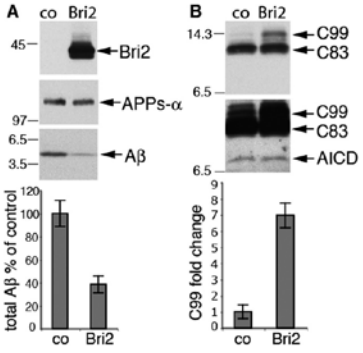
The major focus of the molecular biology group is the processing and cellular function of the amyloid precursor protein (APP). APP is one of the major proteins involved in Alzheimer's disease (AD), but its physiological function remains elusive. The group concentrates on the regulation of APP processing, with the aim to find new pathways to decrease the amount of amyloid-beta (Aβ) peptides as a therapeutical strategy for AD. Thereby new insights into the mechanism of Gleevec, a known tyrosine kinase inhibitor, could be provided (Fig.1), which may serve as basis for potential Aβ lowering drugs (Eisele et al. 2007). 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.



▲ Figure 1: APP processing and working model of Gleevec mechanism. Gleevec treatment increases AICD levels via a slowed turnover of AICD. Neprilysin expression is increased by Gleevec, mediated by transcriptional activation, which probably involves AICD signaling. Increased neprilysin expression may lower Aβ levels by enhanced degradation. α-sec: α-secretase, γ-sec: γ-secretase, nep: neprilysin gene.

The APP and the Bri2 protein are both genetically linked to specific forms of dementia. Mutations in the Bri2 gene cause Familial British Dementia (FBD) and Familial Danish Dementia (FDD). Both, APP and Bri2 are processed by several proteases, giving rise to small peptides, which aggregate and accumulate in plaques and vascular deposits in the brains of patients. In AD, oligomerisation and aggregation of Aβ peptides are thought to be causative to the disease. Recent in vitro results suggest a direct interaction of Bri2 with APP which leads to altered APP processing and decreased Aβ secretion. However the underlying mechanisms have not yet been satisfactorily elucidated.

To test a potential influence of Bri2, we analyzed the processing of APP after overexpression of Bri2 in different APP expressing cell lines. In agreement with published results (Fotinopoulou et al. 2005; Matsuda et al. 2005), we found that overexpression of Bri2 leads to a significant decrease in total secreted Aβ and increase in C99 fragments (Fig.2). Different from published results no significant changes in the levels of C83 or APPs-α were found. Also levels of AICD remained unchanged, although C99 showed a strong increase (Fig.2B). These results clearly confirm that Bri2 influences the processing of APP in cells, reducing Aβ while probably not affecting APP signaling via AICD. Similar to Bri2, also the mutant form ADanPP lead to a significant decrease in secreted Aβ. In addition, by crossing ADanPP transgenic mice with APP transgenic mice, a significant reduction in plaque load was observed in double transgenic mice. Based on these results we are currently further investigating the mechanism of how Bri2 interferes with APP processing, Aβ generation and/or degradation.



◀ Figure 2: Bri2 overexpression leads to changes in APP processing in HEK293-APPwt cells. A: Total secreted Aβ is reduced to 38% of controls (n=4, p=0.0007), while APPs-α levels remain unchanged. B: C99 is strongly increased but APP and AICD levels show no significant changes.

Key Publications

Eisele YS, Baumann M, Klebl B, **Nordhammer C**, **Jucker M**, **Kilger E** (2007) Gleevec increases levels of the amyloid precursor protein intracellular domain and of the amyloid-beta degrading enzyme neprilysin. Mol Biol Cell 18(9):3591-600

Hamid R, **Kilger E**, Willem M, Vassallo N, Kostka M, Bornhoevd C, Reichert AS, Kretzschmar HA, Haass C, Herms J (2007). Amyloid precursor protein intracellular domain modulates cellular calcium homeostasis and ATP content. J Neurochem 102:1264-75

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

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.

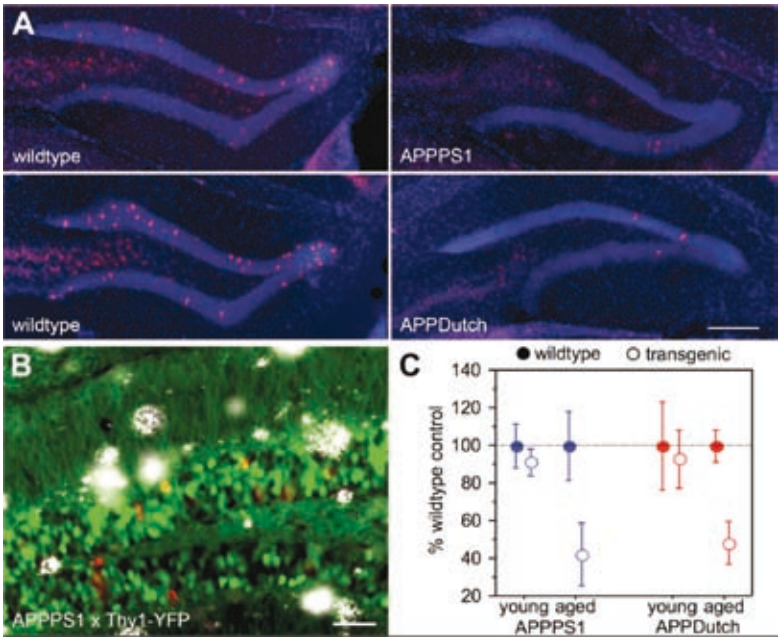
Für all diese Techniken sind hochspezialisierte analytische und computergesteuerte Auswertungsmodule erforderlich. Daher liegt ein weiterer wichtiger Schwerpunkt unserer Arbeitsgruppe auf der Softwareentwicklung zur vier-dimensionalen Visualisierung und Quantifizierung neuronaler Strukturen. Ein Projekt,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

Molecular Imaging

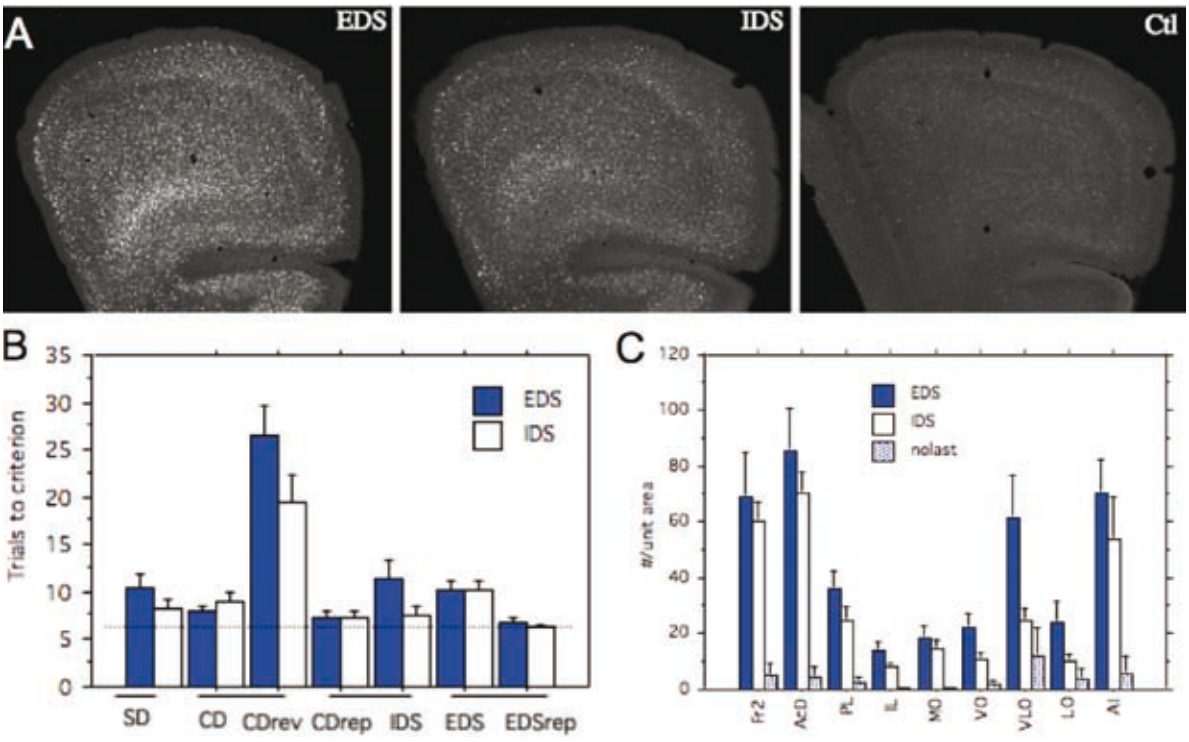
(Group leader:
Michael Calhoun)

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.

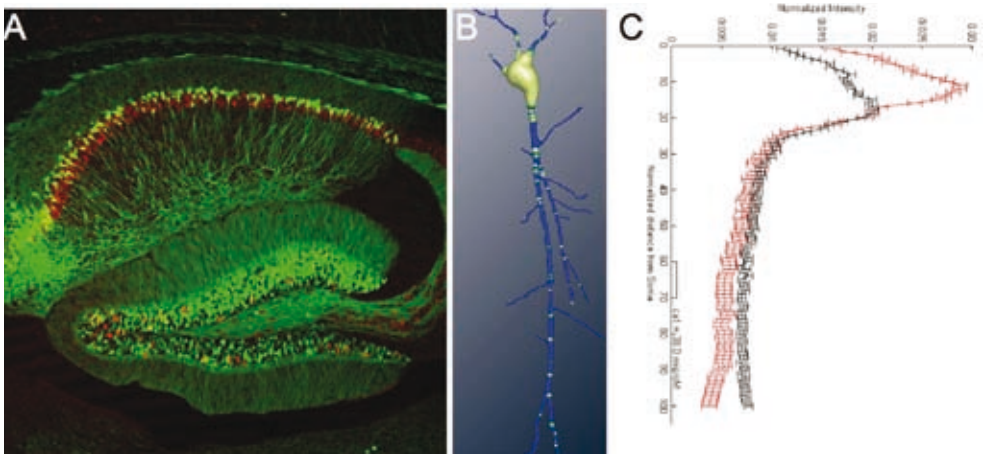


▼ Figure 2:
Increased expression of Arc in specific PFC subregions following EDS.

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



◀ 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.

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 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., Journal of Neuroscience, 2008). (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

Calhoun ME, Fletcher BR, Yi S, Zentko DC, Gallagher M, Rapp PR (2008) Age-related spatial learning impairment is unrelated to spinophilin immunoreactive spine number and protein levels in rat hippocampus. Neurobiol Aging 29(8):1256-64

Bolmont T, Haiss F, Eicke D, **Radde R**, Mathis CA, Klunk WE, Kohsaka S, **Jucker M**, **Calhoun ME** (2008) Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci 28(16):4283-92

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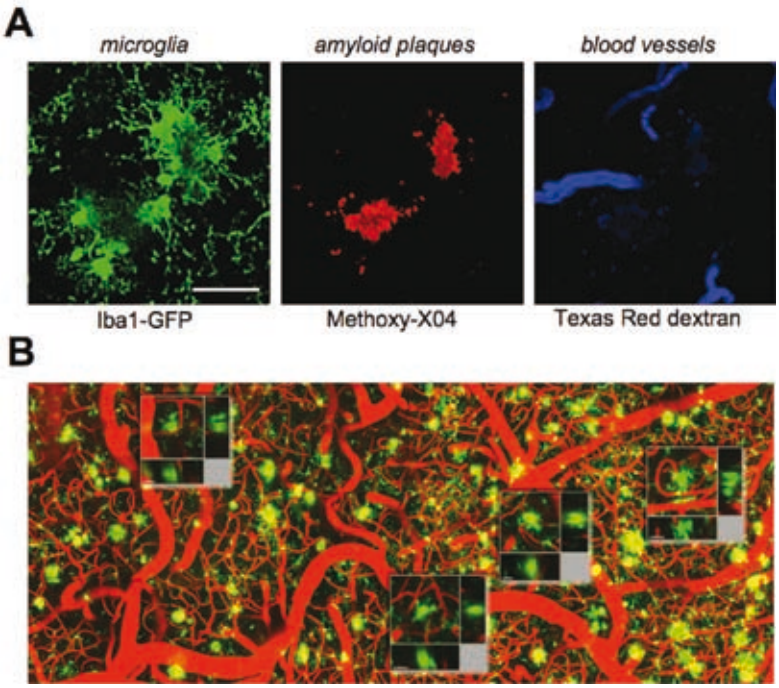

▶ Figure 4: Visualization of microglia and amyloid plaques in a living Iba1-GFP x APPPS1 mouse.

Arbeitsgruppe Drosophila

Arbeitsgruppenleiter: 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

(Group 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.

homepage: http://www.hih-tuebingen.de/synaptic-plasticity

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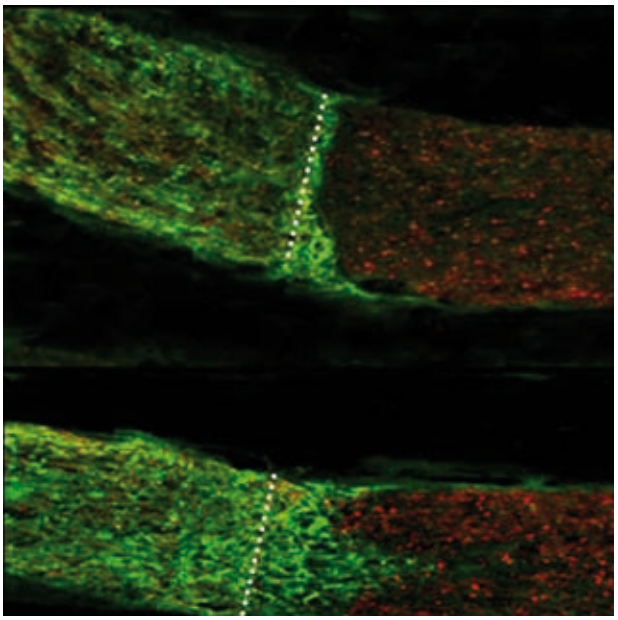
Key Publications

Füger P, **Behrends LB**, Mertel S, Sigrist SJ, and **Rasse TM** (2007) Live imaging of synapse development and measuring protein dynamics using two-colour fluorescence recovery after photo-bleaching at Drosophila synapses. Nature Protocols 2 (12):3285-98

Group leader: Dr. 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 Rückenmarks- und Hirnverletzungen ein.

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 Retinolsäure und TSA. Diese Präparate erhöhen die Aktivität von Genen wie p53, von dem wir zeigen konnten, dass es das Wachstum und die Regeneration von Axonen fördert. Wir gehen davon aus, dass die Anwendung dieser Präparate und die Regulierung spezifischer molekularer Abläufe der Einleitung von Regenerationsprozessen bei Verletzungen des Nervensystems förderlich sind und zu besserer Regeneration bei Patienten mit neurodegenerativen Erkrankungen führen können.

Sollte sich unser Ansatz unter den Versuchsbedingungen als erfolgreich erweisen, so hoffen wir, ihn auf klinische Studien mit Patienten, die von Schlafanfall, Wirbelsäulen- und Hirntrauma betroffen sind, übertragen zu können.

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. A degree of axon sprouting does 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.

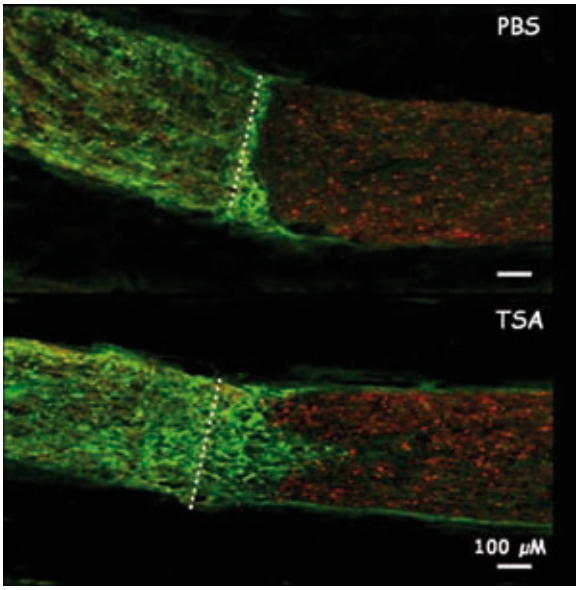
Therefore, the success of the reparative processes depends upon factors able to:

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;

▼ Figure 1: Regeneration in the optic nerve. GAP-43 immunohistochemistry (green) and counterstaining with α-NF-200 (red). Many more axons cross the crush site (dotted line) up to 0,4 mm following TSA delivery as opposed to vehicle. Scale bar: 100 µM.



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 from 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 use models of Spinal Cord Injury and Optic Nerve Crush 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.

More specifically, our lab focuses on how transcription can affect cytoskeleton remodeling in neurite/axon outgrowth and axon regeneration. Therefore, the main 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.

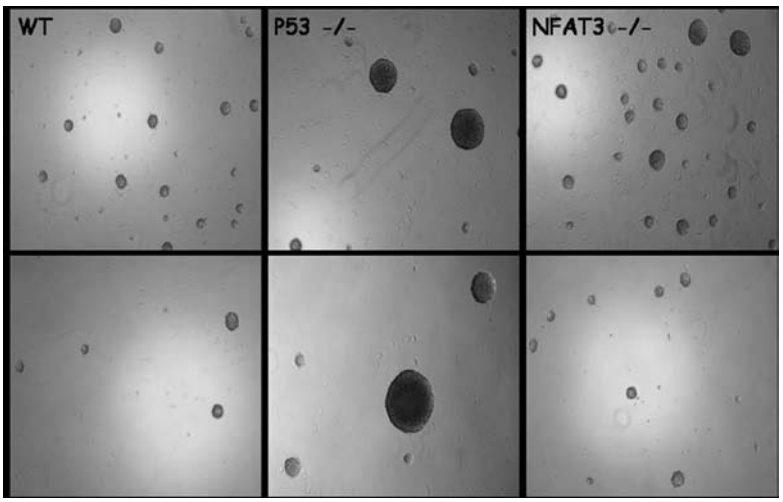
Taking advantage from data obtained from our microarrays time series study in Spinal Cord and Brain injury (see publications), and using a series of bioinformatics approaches (including Genomatix software for promoter analysis), we have recently defined a putative transcriptional cascade between upstream transcription factors and downstream cytoskeleton related gene targets functionally related to axonal plasticity and regeneration.

Transcription factors of interests include p53, NFAT, and the role of DNA and histone modifying enzymes that affect the status of chromatin and make it more or less transcriptionally active.

Current Projects include:

1. The role of the tumor suppressor p53 in axon outgrowth 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; Tedeschi et al., CDD, 2008). 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 (Tedeschi et al., CDD, 2008). This project aims at defining novel patterns of p53 signaling and new downstream p53 targets that are important for axon growth and regeneration following spinal and brain injuries (Andrea Tedeschi: andrea.tedeschi@medizin.uni-tuebingen.de)

2. 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 affect transcription of crucial factors that promote axon outgrowth (Nguyen and Di Giovanni, IJDN, 2008; Nguyen et al., under review). We therefore hypothesize that NFAT might promote axon growth also following SCI. To this end, we have generated NFAT transgenic mice and crossed 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. 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 hopefully open opportunities for a specifically-targeted therapeutic approach for axon regeneration. (Tuan Nguyen: tuan.nguyen@medizin.uni-tuebingen.de)



◀ Figure 2: E13 embryonic neural stem cells (NSC). P53 and NFAT-3 NSC regulate the size and the proliferation of NSC.

3. Retinoic acid and acetyl transferases-dependent pathways in neuronal differentiation and axon regeneration: Acetylation increases gene expression and protect neurons from cell death. We have recently shown that acetylation of specific transcription factors can promote also axon outgrowth through specific histone modifying enzymes dependent pathways (Gaub et al., under review). 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. Currently the effects of retinoic acid and acetylation pathways on axon regeneration are under investigation in SCI and ONC in vivo models of axonal injury. (Perrine Gaub: perrine.gaub@medizin.uni-tuebingen.de and Radhika Puttagunta: Radhika.puttagunta@medizin.uni-tuebingen.de)

4. Chromatin status and axon regeneration: Chromatin status profoundly affects transcription. DNA methylation and histone post-translational modifications are largely responsible to determine favorable chromatin conditions for specific occupancy of promoters by transcription factors and for transcription to work properly. Efficient and specific transcription is required for axon outgrowth and may play a role to promote axonal regeneration. We study the role of histone modifications and DNA methylation in in vivo models of axonal injury and regeneration taking advantage of the dorsal root ganglia system, at the cross road between the peripheral and the central nervous system (Elisa Floriddia: elisa.floriddia@hotmail.it and Ricco Linder: riccolindner@gmx.de)

5. Transcriptional regulation in neural stem cells: Transcriptional control is essential to regulate neural progenitor cells proliferation and differentiation. Clarification of the molecular mechanisms of neural differentiation can help understanding some pro-regenerative molecular changes in the adult injured neurons that partially recapitulate development. Last, but not least, fostering neural differentiation could be useful to promote functional recovery following a variety of neurological disorders characterized by neuronal loss and damage. The roles of P53 and NFAT in neural stem cells proliferation and differentiation are currently been investigated (Kirsi Forsberg: kirsi.forsberg@medizin.uni-tuebingen.de)

homepage: http://www.hih-tuebingen.de/neuroregeneration_repair/

Staff:
H. Beck, E. Floriddia, K. Forsberg, P. Gaub, R. Linder, T. Nguyen, R. Puttagunta, A. Tedeschi, A. Wüttke

Key Publications

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

Knights CD, Catania J, **Di Giovanni S**, Muratoglu S, Perez R, Swartzbeck A et al. (2006) Distinct p53 acetylation cassettes differentially influence gene-expression patterns and cell fate. J Cell Biol 173:533–44.

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

Byrnes K, Stoica BA, Fricke S, **Di Giovanni S**, Faden AI. (2007) Cell Cycle Activation Contributes to Post-Mitotic Cell Death and Secondary Damage after Spinal Cord Injury. Brain 130 (Pt 11):2977-92

Nguyen T, Di Giovanni S. (2008) NFAT signaling in neural development and axon growth. Int J Dev Neurosci 26(2):141-5

Tedeschi A, **Nguyen T**, **Puttagunta R, Gaub P**, **Di Giovanni S** (2008) A p53-CBP/p300 transcription module is required for GAP-43 expression, axon outgrowth, and regeneration. Cell Death Differ [Epub ahead of print]

General Neurology

Head of the Department of General Neurology

Prof. Dr. A. Melms (Acting-Chairman)

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Dr. J. Erharhaghen (neuro-cardiology)
Dr. B. Greve (since 10/2008)
PD Dr. T. Haarmeier
PD Dr. A. Luft (until 8/2008)
Dr. J. Rieger (until 3/3008)
Dr. F. Schmidt (until 1/2008)
PD Dr. S. Schuh-Hofer (since 2/2008)
Dr. R. v. Coelln (until 12/2008)

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Dr. Huberle
H. Kiesewetter
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M. Varga
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Dipl. Inf. H. Rapp
G. Hipp

Professorship for Neurorehabilitation

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

Neurodegenerative Diseases / Cognitive Neurology

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Prof. Dr. L. Schöls (Vice-Chairman, Section Head)

Attending physicians

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Prof. Dr. D. Berg

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Dr. R. von Coelln
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Dr. C. Linnemann
Dr. M. Synofzik

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Station 42

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General Neurology

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Neurodegenerative Diseases

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Cellular Neurology

Director of the Department of Cellular Neurology

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B. Wegenast-Braun
H. Wölfing

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B. Graus
I. Guhl (maternity leave)
C. Krüger
U. Obermüller
C. Schäfer

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A. Humburg
M. Knopp
S. Kramer
V. Olik
S. Ott
N. Rupp
A. Wiedenbusch
Y. Zhang

Independent Junior Research Group / Hertie Institute Administration

Independent Junior Research Group Leader

Dr. Dr. S. Di Giovanni

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E. Floriddia
P. Gaub
A. Tedeschi
Dr. T. Nguyen
R. Linder

Technical staff / Administration

A. Wüttke

Medical Doctoral Students / Master Students

A. Schmandke
T. Schmandke

Hertie Institute Administration

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

General Neurology

Clinical Studies - Department of General Neurology

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: 44 Investigator: C. Braun (previously W. Wick)

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: 8 Investigator: C. Braun (previously F. Schmidt)

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, recruitment completed)
Enrolled patients: 7 Investigator: G. Tabatabai

NOA05 Phase II-Studie zur Chemotherapie und Strahlentherapie der Gliomatosis cerebri
Enrolled patients: 11 Investigator: C. Braun (previously U. Herrlinger)

OSAG101 Multizentrische Phase III-Studie zur randomisierten Prüfung der Kombination aus Bestrahlung + Temodal + OSAG 101 versus Bestrahlung + Temodal
Enrolled patients: 9 Investigator: A. Melms (previously J. Steinbach)

ENZASTAURIN II Enzastaurin und Radiotherapie in der Primärbehandlung von Patienten mit neu diagnostiziertem Glioblastom ohne Methylierung von des MGMT Promotors
Enrolled patients: 1 Investigator: G. Tabatabai

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 closed)
Enrolled patients: 7 Investigators: A. Melms

TRANSFORMS (CFTY720D2302): A 12-month double-blind, randomized, multicenter, activecontrolled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis. (phase III, recruitment closed)
Enrolled patients: 1 Investigator: A. Melms

Neurodegenerative Diseases

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 completed)
Enrolled patients: 18 Investigators: L. Schöls, Ch. Linnemann, K. Karle, T. Lindig

Effectiveness of coordinative training in cerebellar and afferent ataxia (recruitment completed)
Enrolled patients: 16 Investigators: L. Schöls, M. Synofzik

Parkinson's disease

The Effect of Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) on Quality of Life in Comparison to Best Medical Treatment in Patients with Complicated Parkinson's Disease and Preserved Psychosocial Competence (EARLYSTIM-study)
Enrolled patients: 2 Investigators: R. Krüger, A. Gharabaghi, S. Breit, T. Wächter, D. Weiss

Auswirkungen der Tiefen Hirnstimulation auf prozedurale Lernprozesse bei idiopathischen Parkinson Patienten – Analyse von zentralen Kohärenzmustern
Enrolled patients: 26 Investigators: R. Krüger, T. Wächter, D. Weiss, J. Lin Lam

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: 11 Investigators: D. Berg, A. Di Santo, H. Huber 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. Di Santo, H. Huber 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: 16 Investigators: D. Berg, A. Di Santo, and co-workers

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: 4 Investigators: D. Berg, K. Srulijes 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

Neurodegenerative Diseases / Cognitive Neurology

A multi-centre, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration study in patients with Parkinson's disease to assess the efficacy of AFQ056 in reducing L-dopa induced dyskinesias, and the safety and tolerability of AFQ056 in combination with L-dopa (phase IIa with Tübingen as leading center, recruitment for first part completed)
Enrolled patients : 10 Investigators: D. Berg, J. Godau, and co-workers

Trust (Transdermal Rotigotine User Surveillance Study): A naturalistic, multisite, observational study of Rotigotine Transdermal Patch and other currently prescribed therapies in patients with Idiopathic Parkinson's Disease (recruitment ongoing)
Enrolled patients: 5 Investigators: D. Berg, H. Huber, K. Srulijes

Relevant (Registry to Evaluate Advanced PD Treatment): a prospective, multi-center, multi-national, structured data collection initiative compiling data on the treatment of patients with Advanced Parkinson's Disease. (recruitment ongoing)
Enrolled patients: 4 Investigators: T. Gasser, D. Berg, R. Krüger, K. Srulijes, H. Huber, D. Weiss

Collection and analysis of biological fluids obtained from pre- and symptomatic patients carrying pathogenic LRRK2 mutations: Establishment of a correlation between Parkinson's Disease symptoms and selected, quantifiable markers in those fluids
Enrolled patients: 72 Investigators: T. Gasser, K. Brockmann, A. di Santo, D. Berg

Clinical Studies - Department of Cognitive Neurology

Quantification of subtle movement changes in healthy subjects with increased echogenicity of the substantia nigra (phase II, recruitment completed)
Enrolled patients: 100 Investigators: W. Ilg, I. Liepelt, C. Urban, M. A. Giese, D. Berg

Motor learning in patients suffering from cerebellar ataxia (phase II, recruitment completed)
Enrolled patients: 15 Investigators: W. Ilg, M. Synofzik, S. Burkhard, D. Brötz, M. A. Giese, L. Schöls

Emotion perception from gait pattern in idiopathic Parkinson's disease and spinocerebellar ataxia (phase I, recruitment ongoing)
Enrolled patients: 51 Investigators: C. L. Roether, C. Linnemann, S. U. Steele, A. Gaenslen, D. Berg, L. Schöls, P. Thier, M. A. Giese

General Neurology

Third-Party Funding - Department of General Neurology

Ongoing Grants

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

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

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

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

Ausschaltung der autokrinen Effekte des Zytokins TGFbeta auf Gliomzellen durch Expression eines dominant-negativen TGFbeta Rezeptors (fortüne F1311816)
Project leader G. Eisele
Funding institution Medical Faculty Univ. Tübingen
Funding period 07/07-06/08

Neural stem cell-based gene delivery in experimental autoimmune encephalomyelitis (1685-0-0)
Project leaders B. Greve
Funding institution IZFK Tübingen
Funding period 05/07-04/09

Dopamin im Motorkortex und motorisches Lernen (Lu 748/5-1)
Project leader A. Luft
Funding institution DFG
Funding period 10/07-09/09

Inhibitorische Mechanismen in der Konsolidierungsphase motorischer Fertigkeiten (SFB 550, C12)
Project leaders A. Luft
Funding institution DFG
Funding period 01/06-12/08

General Neurology

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

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

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

Clinical studies
Project leader A. Melms, A.Luft, and co-workers
Funding institution Pharmaceutical industry
Funding period 01/08-12/08

p53-basierte experimentelle Therapie maligner Gliome (NA 770/1)
Project leader U. Naumann, M. Weller
Funding institution DFG
Funding period 01/07-12/09

XIAP-basierte experimentelle Therapie maligner Gliome (107553)
Project leader U. Naumann, M. Weller
Funding institution Deutsche Krebshilfe
Funding period 08/07-01/2010

Präklinische Untersuchungen zum Potential einer Therapie mit YB-1-abhängigen onkolytischen Adenoviren zur Therapie von Gehirntumoren (01GU0614)
Project leader U. Naumann, M. Weller
Funding institution BMBF
Funding period 01/07-12/09

Die Rolle von TRAIL-induzierten, nicht-apoptotischen Signalwegen bei Migration und Apoptoseresistenz (fortüne F1311794)
Project leader J. Rieger
Funding institution Medical Faculty Univ. Tübingen
Funding period 10/07-09/08

General Neurology / Neurodegenerative Diseases

New Grants

Zerebrale Mechanismen der auditiven Objekterkennung und der Sprachlautwahrnehmung: Funktionell-bildgebende Untersuchungen (SFB 550/B1)

Project leader	H. Ackermann
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Investigation of the effect of GA on the dynamics of autoreactive T cell populations using MHC class II Tetramers

Project leader	F. Bischof
Funding institution	TEVA Pharma
Funding period	01/08 – 03/10
Awarded on	Mar 19, 2008

Erforschung der molekularen Mechanismen einer ISCADOR-Behandlung im Gliobastom

Project leader	U. Naumann
Funding institution	Hans Sauer Foundation
Funding period	01/09 – 12/10
Awarded on	Dec 4, 2008

Therapieresistenz solider Tumoren und ihre Überwindung (SFB 773)

Project leader	G. Tabatabai
Funding institution	DFG
Funding period	07/08 - 06/12
Awarded on	Jun 6, 2008

Third-Party Funding - Department of Neurodegenerative Diseases

Ongoing Grants

Rivastigmin (Exelon®) zur Behandlung der Demenz bei Patienten mit Progressiver Supranukleärer Blickparese

Project leader	D. Berg
Funding institution	Novartis
Funding period	12/06-12/09

Bewegungstherapie bei Morbus Parkinson – Korrelation von morphologischen Veränderungen und positiven Effekten auf Motorik und Alltagsbewältigung

Project leader	D. Berg
Funding institution	Medical Faculty Univ. Tübingen
Funding period	08/07-08/08

Neurodegenerative Diseases

Study in patients with Parkinson's disease to assess the efficacy of AFQ056
Project leader D. Berg
Funding institution Novartis Pharma AG
Funding period 10/07-06/08

Prospective validation of risk markers for the development of Parkinson's disease
Project leader D. Berg
Funding institution Michael J. Fox Foundation for Parkinson's Research
Funding period 12/07-05/09

Evaluation von Standards zur Diagnostik der Demenz bei Morbus Parkinson
Project leader I. Liepelt, D. Berg
Funding institution Dr. Werner Jackstädt Foundation
Funding period 01/06-10/08

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 12/06-02/09

Parkinsonism as a prototypical geriatric disease: gaining new insight into the pathophysiology, dual tasking capacity and gerontechnological approaches for Parkinson's disease patients (Nr 32.5.1141.0019.0)
Project leader: W. Maetzler
Funding institution: Robert Bosch Foundation
Funding period: 01/08-12/11

Identification of Genetic Risk Factors for Parkinson's Disease (01GS0468)
Project leader T. Gasser, D. Berg
Funding institution BMBF (NGFN2 und NGFN2 Aufstockung)
Funding period 08/04-05/08

Functional Genomics of Parkinson's Disease: Genomics of Parkinson's disease
Project leader T. Gasser, D. Berg
Funding institution BMBF/DLR
Funding period 06/08-05/11

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

Neurodegenerative Diseases

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

Identifizierung und Validierung von Parkinson-Genen mit funktioneller Genomik in Zellkultur und Tiermodellen (N1NV-S31T09, NGFN-2 Aufstockung)
Project leader P. Kahle
Funding institution BMBF
Funding period 08/07-05/08

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 von Mutationen im Omi/HtrA2 Gen beim Parkinson-Syndrom (KR 2119/3-1)
Project leader R. Krüger
Funding institution DFG
Funding period 09/06-10/09

Charakterisierung von Mortalin als neues DJ-1-interagierendes Protein (F1313061)
Project leader R. Krüger
Funding institution Medical Faculty Univ. Tübingen
Funding period 11/07-10/08

Deciphering molecular pathways of monogenic forms of Parkinson disease by cell culture and animal models (01GS0468)
Project leader R. Krüger, O. Riess, J.B. Schulz
Funding institution BMBF (NGFN2 und NGFN2-Aufstockung)
Funding period 09/04-05/08

GeNeMove: Hereditary Spastic Paraplegia (01GM0603)
Project leader L. Schöls
Funding institution BMBF
Funding period 10/03-03/09

Leukonet: Clinical, neurophysiological and neuroradiological characterization of leukodystrophies in adulthood (01GM0838)
Project leader L. Schöls
Funding institution BMBF
Funding period 10/03-12/11

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 01/04-12/09

Neurodegenerative Diseases

Klonierung des Gens für eine neue Form der autosomal dominanten spastischen Spinalparalyse (Scho754/4-1)

Project leader	L. Schöls
Funding institution	DFG
Funding period	07/06-08/09

EUROSPA: European and Mediterranean network on spastic paraplegias (01GM0807)

Project leader	L. Schöls
Funding institution	EU
Funding period	05/08-04/11

RISCA – Prospective study of individuals at risk for spinacerebellar ataxia (01GM0820)

Project leader	L. Schöls
Funding institution	EU
Funding period	04/08-03/11

Functional Characterization of a Novel Parkin-Cathepsin Interaction (fortüne 1667-0-0)

Project leader	W. Springer
Funding Institution	Medical Faculty, Univ. Tübingen
Funding period	06/07-05/09

New Grants

Prävalenz der Osteoporose bei Patienten mit Morbus Parkinson

Project leader	D. Berg
Funding institution	Novartis
Funding period	12/08-10/09
Awarded on	Dec 2, 2008

Transkranielle Sonographie (TCS) bei Bewegungsstörungen – Methodik und klinische Relevanz

Project leader	D. Berg
Funding institution	Boehringer
Funding period	06/08
Awarded on	Jun 11, 2008

Progression markers in the suspected premotor phase and early Parkinson's disease

Project leader	D. Berg
Funding institution	Janssen Pharma
Funding period	12/08-12/11
Awarded on	Nov 28, 2008

Hertie-Stipendienprogramm Neurowissenschaften

Project leader	L. Burbulla
Funding institution	Hertie Foundation
Funding period	12/08 - 11/11
Awarded on	Nov 4, 2008

Neurodenerative Diseases

NGFN Plus Parkinson Network: Scientific Administrative Office (01GS08134 TP1)

Project leader	T. Gasser
Funding institution	BMBF
Funding period	06/08 – 05/11
Awarded on	Jul 7, 2008

NGFN Plus Parkinson Network: Genomics of Parkinson's disease (01GS08134 TP2)

Project leader	T. Gasser / D. Berg
Funding institution	BMBF
Funding period	06/08 – 05/11
Awarded on	Jul 7, 2008

Helmholtz alliance for mental health in an aging society: Subproject: Clinics and genetics of Parkinson's disease (HelMA)

Project leader	T. Gasser
Funding institution	BMBF, Helmholtz-Association
Funding period	07/08 – 06/11
Awarded on	May 5, 2008

Schaffung und bildgebende Untersuchung von Zellkultur und Tiermodellen für TDP Pathologie (01 GI 0705/ TP)

Project leader	P. Kahle
Funding institution	BMBF
Funding period	10/07 – 09/10
Awarded on	Jan 10, 2008

Regulation of apoptosis signal regulating kinase pathways by DJ-1 and Parkin (01GS08134-9)

Project leader	P. Kahle
Funding institution	BMBF / DLR
Funding period	06/08 – 05/11
Awarded on	Jul 7, 2008

Auswirkungen der Tiefen Hirnstimulation auf prozedurale Lernprozesse bei idiopathischen Parkinson Patienten – Analyse von zentralen Kohärenzmustern

Project leader	R. Krüger
Funding institution	Medtronic
Funding period	04/08 – 03/09
Awarded on	Apr 24, 2008

Mitochondrial stress response in neurodegeneration and aging – dissection of Omi/HtrA2 and DJ-1 mediated signalling pathways (01GS08134-10)

Project leader	R. Krüger
Funding institution	BMBF / DLR
Funding period	07/08 – 06/11
Awarded on	Jul 7, 2008

Neurodegenerative Diseases / Cognitive Neurology

Internationales Netzwerk für spinozerebelläre Ataxien (RISCA) (01 GM0820/TP)

Project leader	L. Schöls
Funding institution	BMBF / DLR
Funding period	04/08 – 03/11
Awarded on	Apr 30, 2008

Internationales Netzwerk zur spastischen Paraplegie (EUROSPA) (01 GM0807/TP)

Project leader	L. Schöls
Funding institution	BMBF / DLR
Funding period	05/08 – 04/11
Awarded on	Jun 13, 2008

mitoNet-German Network for Mitochondrial Diseases (TP A2)

Project leader	L. Schöls
Funding institution	BMBF / DLR
Funding period	02/09 – 01/12
Awarded on	Sep 3, 2008

Third-Party Funding - Department of Cognitive Neurology

Ongoing Grants

Promotionsstipendium: Contributions of the superior colliculus in sensorimotor integration in humans (SFB 550, Integriertes Graduiertenkolleg)

Project leader	S. Borchers
Funding institution	DFG
Funding period	07/08-06/09

Action representation and learning (I/76 556)

Project leader	M. Giese
Funding institution	VW Foundation
Funding period	06/01-02/08

Quantitative Messung und theoretische Modellierung der visuellen Tuning-Eigenschaften von Mirrorneuronen im prämotorischen Kortex (Area F5) von Affen (SFB 550, C10)

Project leaders	M. Giese, P. Thier
Funding institution	DFG
Funding period	01/06-12/08

Cognitive Neurology

The expression of emotions through bodily movements (RGP54/2004)
Project leader M. Giese
Funding institution HFSO
Funding period 10/04-03/08

Learning of structured trajectory models with high flexibility for computer animation (GI 305/2-1)
Project leader M. Giese
Funding institution DFG
Funding period 04/06-12/08

Communication with emotional body language (COBOL) (NEST-043403)
Project leader M. Giese
Funding institution EC
Funding period 11/06-10/09

Zerebro-zerebelläre Kommunikation - Grundlage neurokognitiver Funktionen? (SFB 550, A2)
Project leader T. Haarmeier
Funding institution DFG
Funding period 01/00-12/08

Beteiligung der Colliculi superiores an der räumlichen Planung und Ausführung von visuell gesteuerten Handbewegungen (HI 1371/1-1)
Project leaders M. Himmelbach, H.-O. Karnath
Funding institution DFG
Funding period 09/08-08/11

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 09/06-02/09

Alterungsprozesse der auditiven und multisensorischen Raumwahrnehmung (KA 1258/7-1)
Project leader H.-O. Karnath
Funding institution DFG
Funding period 10/07-09/09

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

Cognitive Neurology

Verbundprojekt Visuo-räumliche Kognition: TP 5 "Higher order integration of space and gist in the human parietal cortex" (01GW0654)
Project leader H.-O. Karnath
Funding institution BMBF
Funding period 01/07-12/09

Verbundprojekt Räumliche Orientierung: TP 1 "Fractionating disorders of spatial orientation and attention in brain-damaged patients with spatial neglect and extinction" (01GW0641)
Project leader H.-O. Karnath
Funding institution BMBF
Funding period 01/07-12/09

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

European Research Network for Investigating Human Sensorimotor Function in Health and Disease (05RNP089 ERNI-HSF)
Project leader H.-O. Karnath
Funding institution ESF
Funding period 01/07-12/11

Kinematische Analyse komplexer Armbewegungen bei Schlaganfallpatienten (fortüne 1443-0-0)
Project leaders H.-O. Karnath, M. Giese
Funding institution Medical Faculty Univ. Tübingen
Funding period 04/07-03/09

Procedural learning deficits in patients with subcortical stroke (HIH S.07.00058)
Project leaders A. Luft, H.-O. Karnath
Funding institution Hertie Foundation
Funding period 01/07-12/11

Promotionsstipendium: Rolle der elektrischen Synapsen in der inferioren Olive im Tiermodell (SFB 550, Integriertes Graduiertenkolleg)
Project leader J. R. Müller
Funding institution DFG
Funding period 02/08-10/08

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

Cognitive Neurology

Career Development Award (CDA 0038/2004-C)
Project leader A. Nieder
Funding institution HFSO
Funding period 01/05-12/08

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 06/06-05/09

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

Context-dependent changes of signal transfer at a central machine-brain interface. A study using multielectrode stimulation and recording in barrel cortex of awake rats during active and passive touch (SCHW 577/7-1)
Project leader C. Schwarz
Funding institution DFG
Funding period 01/07-12/08

Analyse der zerebralen Wirkungen von Benzodiazepinen mit Hilfe von Knock-in-Mäusen: Welche Subtypen des GABAA-Rezeptors sind beteiligt? (SCHW 577/8-1)
Project leader C. Schwarz
Funding institution DFG
Funding period 10/07-09/10

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

Cognitive Neurology

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

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 09/05-12/09

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

Verbundprojekt Räumliche Orientierung: TP 2 "Towards the neuronal basis of spatial updating" (01GW0641)
Project leader P. Thier
Funding institution BMBF
Funding period 01/07-12/09

Sachbeihilfe Competence Centre Neuroscience (35.5.8051.0149.0/MA01)
Project leader P. Thier
Funding institution Robert Bosch Foundation
Funding period 01/08-11/10

Cognitive Neurology

New Grants

Encoding of action kinematics and dynamics in the responses of mirror neurons in monkey premotor area F5 (SFB 550/TP C10)

Project leader	M. Giese
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Zerebro-zerebelläre Kommunikation – Grundlage neurokognitiver Funktionen? (SFB 550/A2)

Project leader	T. Haarmeier
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Human reaching and grasping – cognitive networks of visual action control (211078)

Project leader	M. Himmelbach
Funding institution	ERC
Funding period	09/08-08/13
Awarded on	Aug 4, 2008

Schülerlabor Neurowissenschaften (00.139.2008)

Project leader	U. Ilg
Funding institution	Tschira Foundation
Funding period	01/09-12/11
Awarded on	Sep 3, 2008

Störungen motorischen Handelns nach Schädigungen des parietalen und des temporalen Kortex beim Menschen (SFB 550/A4)

Project leader	H.-O. Karnath
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Role of structural and functional brain damage on spatial cognition – combined DT tractrography and perfusion MRI studies (EXC 307-CIN)

Project leader	H.-O. Karnath
Funding institution	DFG
Funding period	01/09 -12/10
Awarded on	Nov 25, 2008

4. Statussymposium "Dynamik und Adaptivität neuronaler Systeme" (I/83 638)

Project leader	A. Nieder
Funding institution	VW Foundation
Funding period	02/08-08/08
Awarded on	Feb 20, 2008

Cognitive Neurology

Aktive Bewegung als Grundlage der Texturdiskrimination. Psychophysikalische und elektrophysiologische untersuchen der bewegungsabhängigen Modulation von taktiler Wahrnehmung im Vibrissensystem der Ratte (SFB 550/TP B11)

Project leader	C. Schwarz
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Unravelling functional connectivity of widely distributed networks of the non-human primate brain (SFB 550/TP A9)

Project leader	F. Sultan
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Sekretariat und Computerpool (SFB 550, D1)

Project leader	P. Thier
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Sachkostenbeihilfe Gastwissenschaftler Halim Hicheur (3.3-FRAU/1128930 STP)

Project leader	P. Thier
Funding institution	Humboldt Foundation
Funding period	05/08-04/10
Awarded on	Apr 8, 2008

Schülerlabor Competence Centre Neuroscience (1.03.1/08/008)

Project leader	P. Thier
Funding institution	Hertie Foundation
Funding period	07/08 – 06/09
Awarded on	Jul 4, 2008

Die zerebellären Grundlagen motorischen Lernens (SFB 550, A7)

Project leader	P. Thier
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Cellular Neurology

Third-Party Funding - Department of Cellular Neurology

Ongoing Grants

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

Transgene Mausmodelle von familiärer britischer und dänischer Demenz: der Einfluss von nicht-A beta zerebraler Amyloidose und Angiopathie (JU 655/3-1)
Project leader J. Coomaraswamy, M. Jucker
Funding institution DFG
Funding period 01/08-12/10

Hertie-Stipendienprogramm Neurowissenschaften
Project leader C. Duma
Funding institution Hertie Foundation
Funding period 03/07-08/08

NGFN-2 extension - Functional Genome Research for Human Health (01GS0468)
Project leader M. Jucker
Funding institution BMBF / DLR
Funding period 08/07-05/08

Autophagie und chronische Erkrankungen (32-7532.22-28-18/3)
Project leader M. Jucker, L. Stoltze
Funding institution FSP des Landes Baden-Württemberg
Funding period 03/06–12/08

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 07/06-06/09

Exogenous induction of cerebral amyloidogenesis (ZEN-06-27341)
Project leader M. Jucker
Funding institution Alzheimer's Association USA
Funding period 09/06 – 10/08

Kompetenznetz degenerative Demenzen, KNDD (01GI0705)
Project leader M. Jucker
Funding institution BMBF / DLR
Funding period 10/07-09/10

Cellular Neurology

Generation of APP transgenic mice
Project leader M. Jucker
Funding institution Koesler
Funding period 01/05-12/09

NGFN-Plus: Pathomechanism of Cerebral Amyloid Angiopathy
Project leader M. Jucker
Funding institution BMBF/DLR
Funding period 06/08-05/11

Scholarships for Alzheimer Research
Project leader M. Jucker
Funding institution Anonymous private donator
Funding period 01/08

Systematische Untersuchung von Signalwegen, die die Stabilisierungs von Synapsen regulieren (21-655.023/572)
Project leader T. Rasse
Funding institution Eliteprogramm Landesstiftung Baden Württemberg
Funding period 03/07-12/08

APP fragments regulating synapse formation and elimination (AFI 07851)
Project leader T. Rasse
Funding institution Alzheimer Forschung Initiative e. V.
Funding period 01/08-10/09

Charakterisierung der Rolle von T-Zellen in der Alzheimer-Erkrankung (fortüne 1516-0-1)
Project leader L. Stoltze
Funding institution Medizinische Fakultät, Universität Tübingen
Funding period 07/07-08/08

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 Foundation
Funding period 11/05-04/08

New Grants

Transgene Mausmodelle für die familiäre britische und dänische Demenz: Rolle der Amyloidose für Neurodegeneration und Dysfunktion
Project leader J. Coomaraswamy
Funding institution Carl-Zeiss Foundation
Funding period: 02/09 - 01/11
Awarded on Dec 18, 2008

Cellular Neurology / Independent Junior Research Group

Hertie-Stipendienprogramm Neurowissenschaften

Project leader	J. Hefendehl
Funding institution	Hertie Foundation
Funding period	12/08 - 11/11
Awarded on	Nov 4, 2008

Generation of APP transgenic mice

Project leader	M. Jucker
Funding institution	Koesler
Funding period	01/09 - 12/09
Awarded on	Jan 2, 2008

ERA-Net „NEURON“ Transfer of misfolded protein as a pathogenetic mechanism in neurodegenerative disease

Project leader	M. Jucker
Funding institution	BMBF / DLR
Funding period	02/09 - 01/12
Awarded on	Sep 29, 2008

Verbundprojekt Kompetenznetz Demenzen - Neurodegeneration - Teilprojekt: Aß and Tau aggregation: Initiation, modulation and imaging (addition) (01 GI 0705)

Project leader:	M. Jucker
Funding institution:	BMBF / DLR
Funding period:	10/07 - 09/10
Awarded on:	Sep 11, 2008

Third-Party Funding - Independent Junior Research Group

Ongoing Grants

The role of p53 tumor suppressor pathways in axon growth (fortüne F.1311786)

Project leader	S. Di Giovanni
Funding institution	Medical Faculty Univ. Tübingen
Funding period	01/07-12/08

MDM2-p53 antagonists in axonal regeneration (1R21 NS052640-01A2)

Project leader	S. Di Giovanni
Funding institution	NIH
Funding period	03/07-02/09

Enhancement of p53 activity (IRP-D-021/07)

Project leader	S. Di Giovanni
Funding institution	IRP Foundation
Funding period	08/07-07/09

Independent Junior Research Group

The regulation of the transcription factor p53 in neurite outgrowth and neuron differentiation (DI 1497/1-1)

Project leader	S. Di Giovanni
Funding institution	DFG
Funding period	03/07-02/10

New Grants

Hertie-Stipendienprogramm Neurowissenschaften

Project leader	H. Beck
Funding institution	Hertie Foundation
Funding period	12/08 – 11/11
Awarded on	Nov 4, 2008

Cortical dopamine for the improvement of motor function after stroke (SFB 550-C12)

Project leader	S. Di Giovanni
Funding institution	DFG
Funding period	01/09 – 12/09
Awarded on	Dec 3, 2008

Carbon-Nanotube-Elektroden auf mikrosystemtechnischen Implantatkomponenten für Neuromonitoring und –stimulation

Project leader	S. Di Giovanni
Funding institution	Landesstiftung Baden-Württemberg
Funding period	10/10 – 12/11
Awarded on	Sep 26, 2008

Enhancement of transcription by deacetylase inhibition as a novel therapeutic strategy for spinal cord injury

Project leader	S. Di Giovanni
Funding institution	IRG-CIN
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General Neurology

Publications – Department of General Neurology

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Publications - Department of Neurodegenerative Diseases

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von Coelln R, Raible A, **Gasser T, Asmus F** (2008) Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. Movement Disorders 23(6):889-92

Wahl C, Kautzmann S, **Krebiehl G, Strauss K**, Woitalla D, Müller T, Bauer P, Riess O, **Krüger R** (2008) A comprehensive genetic study of the proteasomal subunit S6 ATPase in German Parkinson's disease patients. Journal of Neural Transmission 115(8):1141-8

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Reviews

Berg D (2008) Biomarkers for the early detection of Parkinson's and Alzheimer's disease. Neuro-Degenerative Diseases 5(3-4):133-6

Berg D, Godau J, Walter U (2008) Transcranial sonography in movement disorders. Lancet Neurology 7(11):1044-55

Biskup S, Gerlach M, Kupsch A, Reichmann H, Riederer P, Vieregge P, Wüllner U, **Gasser T** (2008) Genes associated with Parkinson syndrome. Journal of Neurology 255 Suppl 5:8-17

Gaenslen A, **Gasser T, Berg D** (2008) Nutrition and the risk for Parkinson's disease: review of the literature. Journal of Neural Transmission (Vienna, Austria: 1996) 115(5):703-13

Kahle PJ (2008) alpha-Synucleinopathy models and human neuropathology: similarities and differences. Acta Neuropathologica 115(1):87-95

Schiesling C, Kieper N, Seidel K, **Krüger R** (2008) Review: Familial Parkinson's disease--genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. Neuropathology and Applied Neurobiology 34(3):255-71

Neurodegenerative Diseases / Cognitive Neurology

Books, book chapters, and proceedings

Gasser T (2008) Biomarker für neurodegenerative Erkrankungen. In: Schmitz G, Endres S, Götte D (eds): Biomarker: Bedeutung für medizinischen Fortschritt und Nutzenbewertung. Schattauer Verlag, Stuttgart, New York, 156-168

Publications - Department of Cognitive Neurology

Original Articles

Baier B, Karnath H-O (2008) Tight link between our sense of limb ownership and self-awareness of actions. Stroke 39:486-8

Becker HGT, Erb M, **Haarmeier T** (2008) Differential dependency on motion coherence in subregions of the human MT+ complex. European Journal of Neuroscience 28:1674-85

Biber U, Ilg UJ (2008) Initiation of smooth-pursuit eye movements by real and illusory contours. Vision Research 48:1002-13

Bock S, **Dicke PW, Thier P** (2008) How precise is gaze following in humans? Vision Research 48:946-57

Catz N, Dicke PW, Thier P (2008) Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. PNAS 105(20):7309-14

Daddaoua N, Dicke PW, Thier P (2008) The subjective visual vertical in a nonhuman primate. Journal of Vision 8(3):19, 1–8, http://journalofvision.org/8/3/19/, doi:10.1167/8.3.19.

De Haan B, Morgan PS, Rorden C (2008) Covert orienting of attention and overt eye movements activate identical brain regions. Brain Research 1204:102-11

Dicke PW, Chakraborty S, **Thier P** (2008) Neuronal correlates of perceptual stability during eye movements. European Journal of Neuroscience 27:991-1002

Frank B, Schoch B, Hein Kropp C, Hövel M, Gizewski ER, **Karnath H-O**, Timmann D (2008) Aphasia, neglect and extinction are no prominent clinical signs in children and adolescents with acute surgical cerebellar lesions. Experimental Brain Research 184:511-9

Freyberg S, Ilg UJ (2008) Anticipatory smooth-pursuit eye movements in man and monkey. Experimental Brain Research 186(2):203-14

Fruhmann Berger M, Johannsen L, **Karnath H-O** (2008). Time course of eye and head deviation in spatial neglect. Neuropsychology 22:697-702

Giese MA, Thornton IM, Edelman S (2008) Metrics of the perception of body movement. Journal of Vision 8(9):13:1-18, http://journalofvision.org/8/9/13/, doi:10.1167/8.9.13.

Cognitive Neurology

Golla H, **Tziridis K, Haarmeier T, Catz N**, Barash S, **Thier P** (2008) Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. European Journal of Neuroscience 27:132-44

Händel B, Lutzenberger W, **Thier P, Haarmeier T** (2008) Selective attention increases the dependency of neuromagnetic responses on visual motion coherence. Cerebral Cortex 18:2902-8

Ilg UJ (2008) The role of areas MT and MST in coding of visual motion underlying the execution of smooth pursuit. Vision Research 48:2062-9

Ilg UJ, Thier P (2008) The neural basis of smooth pursuit eye movements in the rhesus monkey brain. Brain and Cognition 68:229-40

Ilg W, Giese MA, Gizewski ER, Schoch B, Timmann D (2008). The influence of focal cerebellar lesions on the control and adaptation of gait. Brain 131:2913-27

Jacob SN, **Nieder A** (2008) The ABC's of cardinal and ordinal number representations. Trends in Cognitive Sciences 12:41-43

Jones RW, Kivipelto M, Feldman H, Sparks L, Doody R, Waters DD, Hey-Hadavi J, Breazna A, Schindler RJ, Ramos H, LEADe investigators* (2008) The Atorvastatin/Donepezil in Alzheimer's disease study: Design and baseline characteristics. Alzheimer's and Dementia 4:145-53. * **Karnath H-O** = LEAD investigator

Karnath H-O, Suchan J, Johannsen L (2008) Pusher syndrome after ACA territory infarction. European Journal of Neurology 15:e84-e85

Materna S, Dicke PW, Thier P (2008) Dissociable roles of the superior temporal sulcus and the intraparietal sulcus in joint attention: an fMRI study. Journal of Cognitive Neuroscience 20:108-19

Materna S, Dicke PW, Thier P (2008) The posterior superior temporal sulcus is involved in social communication not specific for the eyes. Neuropsychologia 46:2759-65

Merten K, Nieder A (2008) Compressed scaling of abstract numerosity representations in adult humans and monkeys. Journal of Cognitive Neuroscience 21:333-46

Papageorgiou E, **Ticini LF**, Hardiess G, Schaeffel F, Wiethoelter H, Mallot HA, Bahlo S, Wilhelm B, Vonthein R, Schiefer U, **Karnath H-O** (2008) The pupillary light reflex pathway: Cytoarchitectonic probabilistic maps in hemianopic patients. Neurology 70:956-63

Pedroarena CM, Kamphausen S (2008) Glycinergic synaptic currents in the deep cerebellar nuclei. Neuropharmacology 54:784-95

Roether CL, Omlor L, Giese MA (2008) Lateral asymmetry of bodily emotion expression. Current Biology 18(8):R329-30

Seymour K, **Karnath H-O**, **Himmelbach M** (2008). Perceptual grouping in the human brain: common processing of different cues. Neuroreport 19:1769-72

Cognitive Neurology

Staudt M, **Ticini LF**, Grodd W, Krägeloh-Mann I, **Karnath H-O** (2008) Functional topography of early periventricular brain lesions in relation to cytoarchitectonic probabilistic maps. Brain and Language 106:177-183

Stüttgen MC, Kullmann S, **Schwarz C** (2008) Responses of rat trigeminal ganglion neurons to longitudinal whisker stimulation. Journal of Neurophysiology 100:1879-84

Stüttgen MC, Schwarz C (2008) Psychophysical and neurometric detection performance under stimulus uncertainty. Nature Neuroscience 11:1091-9

Synofzik M, Lindner A, Thier P (2008) The cerebellum updates predictions about the visual consequences of one's behavior. Current Biology 18(11):814-8

Synofzik M, Vosgerau G, Newen A (2008) Beyond the comparator model: A multifactorial two-step account of agency. Consciousness and Cognition 17(1):219-39

Synofzik M, Vosgerau G, Newen A (2008) I move, therefore I am: a new theoretical framework to investigate agency and ownership. Consciousness and Cognition 17(2):411-24

Timmann D, Brandauer B, Hermsdörfer J, **Ilg W**, Konczak J, Gizewski ER, Schoch B (2008). Lesion-symptom mapping of the human cerebellum. Cerebellum 7(4):602-6

Wick W, Stupp R, Beule A-C, Bromberg J, Wick A, Ernemann U, Platten M, Marosi C, Mason WP, van den Bent M, Weller M, Rorden C, **Karnath H-O**, The European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada Clinical Trails Group. (2008). A novel tool to analyse MRI recurrence patterns in glioblastoma. Neuro-Oncology 10:1019-24

Books, book chapters, and proceedings

Brugger D, **Butovas S**, Bogdan M, **Schwarz C**, Rosenstiel W (2008) Direct and inverse solution for a stimulus adaptation problem using SVR. ESANN Proceedings 2008, 397-402

Curio C, **Giese MA**, Breidt M, Kleiner M, Bülthoff HH (2008) Probing dynamic human facial action recognition from the other side of the mean. ACM Symposium on Applied Perception in Graphics and Visualization. ACM Press, New York, 59-66

Fleischer F, **Casile A, Giese MA** (2008) Neural Model for the Visual Recognition of Goal-directed Movements. In: Kurkova V, Neruda R, Koutnik J (eds.). ICANN 2008, Part II, LNCS 5164, 939-48

Karnath H-O (2008) Neglect. In: Gauggel S, Herrmann M (eds). Handbuch der Psychologie - Handbuch der Neuro- und Biopsychologie. Hogrefe, Göttingen, 547-56

Karnath H-O, Zihl J (2008) Rehabilitation bei Störungen der Raumkognition. In: Diener HC, Putzki N et al. (eds). Leitlinien für Diagnostik und Therapie in der Neurologie. 4. Auflage. Thieme, Stuttgart, 953-9

Karnath H-O (2008) Neglect. Aktuelle Neurologie. Sonderband "Neurologie 2008". Thieme, Stuttgart, 528-9

Cognitive Neurology / Cellular Neurology

Karnath H-O (2008) Pusher-Syndrom. Aktuelle Neurologie. Sonderband "Neurologie 2008". Thieme, Stuttgart, 530-1

Park A, Mukovskiy A, Omlor L, Giese MA (2008) Synthesis of character behaviour by dynamic interaction of synergies learned from motion capture data. In: Skala V (ed) Proceedings of the 16th International Conference in Central Europe on Computer Graphics, Visualization and Computer Vision (WSCG), Plzen, Czech Republic, 9-16

Publications – Department of Cellular Neurology

Original Articles

Bolmont T, Haiss F, **Eicke D, Radde R**, Mathis CA, Klunk WE, Kohsaka S, **Jucker M, Calhoun ME** (2008) Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci 28:4283-92

Calhoun ME, Fletcher BR, Yi S, Zentko DC, Gallagher M, Rapp PR (2008) Age-related spatial learning impairment is unrelated to spinophilin immunoreactive spine number and protein levels in rat hippocampus. Neurobiol Aging 29:1256-64

Ermini FV, Grathwohl S, Radde R, Yamaguchi M, Staufenbiel M, Palmer TD, **Jucker M** (2008) Neurogenesis and alterations of neural stem cells in mouse models of cerebral amyloidosis. Am J Pathol 172:1520-28

Jucker M, Heppner FL (2008) Cerebral and peripheral amyloid phagocytes - an old liaison with a new twist. Neuron 59:8-10

Radde R, Duma C, Goedert M, **Jucker M** (2008) The value of incomplete mouse models of Alzheimer's disease. Eur J Nucl Med Mol I 35:S70-S74

Independent Junior Research Group

Publications – Independent Junior Research Group

Original Article

Nguyen T, Di Giovanni S (2008) NFAT signaling in neural development and axon growth. Int J Dev Neurosci 26(2): 141-145

Book Chapter

Di Giovanni S (2008) The role of gene expression dependent molecular pathways in axon plasticity and neuron repair following acute CNS injury. In : Müller H (ed) Neural Degeneration and Repair – Gene Expression Profiling, Proteomics, Glycomics and Systems Biology. Wiley Publishers, Weinheim 2008: 105-124

General Neurology

Awards - Department of General Neurology

B. Amend
Carl-Liebermeister-Preis der Medizinischen Fakultät

S. Wintterle
Dietrich-Plester-Preis der Medizinischen Fakultät

C. Stoeckle
International Society of Neuroimmunology Travel Grant, Fort Worth, TX, USA

Habilitations

S. Schuh-Hofer
General Neurology – Pathophysiologie von Migräne und Clusterkopfschmerz: Periphere und zentrale Pathomechanismen

Appointments

A. Luft
Assistant Professorship, Zürich

Medical Thesis

B. Amend
Mechanismen zur Entstehung von Autoimmunität im Zentralnervensystem
(Medical Faculty)
Supervisors: A. Melms, F. Bischof

J. Erharhaghen
Bedeutung der Perfusions-Computertomographie beim akuten ischämischen Insult
(Medical Faculty)
Supervisor: A. Luft

C. Lange
Untersuchung autoreaktiver T-Helferzellen mit MCH Klasse II Tetrameren während antigen-spezifischer Toleranzindukiton mit rekombinierten Invarianten Ketten im Tiermodell der multiplen Sklerose
(Medical Faculty)
Supervisors: A. Melms, F. Bischof

S. Wintterle
Die Rolle neuer Kostimulationsmoleküle der B7-Familie in der Immunantwort
(Medical Faculty)
Supervisors: A. Melms, H. Wiendl

General Neurology / Neurodegenerative Diseases

Diploma

S. Csacsko
Antigen-spezifische Toleranzinduktion durch genetisch modifizierte Invariante Ketten
(Faculty of Biology)
Supervisors: F. Bischof, S. Stevanovic

S. Stehling
Oberflächenglykosylierungen auf murinen Immunzellen in gesunden Tieren und in der Entstehung von Autoimmunität
(Faculty of Biology)
Supervisors: F. Bischof, S. Stevanovic

A. Wuttke
Verhaltensbiologische Untersuchungen bei der experimentellen autoimmunen Enzephalomyelits
(Faculty of Biology)
Supervisors: R. Weissert, HA Mallot, A. von Ameln-Mayerhofer

Awards - Department of Neurodegenerative Diseases

K. Karle
Promotionspreis der Julius-Maximilians-Universität Würzburg

K. Karle
Preis der Unterfränkischen Gedenkjahrstiftung für Wissenschaft

O. Rothfuss
Poster Award of the German Society of Neurogenetics

A. Seibel
Poster Award of the German Society of Neurogenetics

H. Schell
Travel Award, International Workshop „a-Synuclein in Health and Disease“, Lausanne, Switzerland

R. Schüle
Poster Award of the German Society of Neurogenetics

J. Waak
Travel Award, 14th Annual Meeting of the German Society of Neurogenetics, Lübeck

Habilitations

S. Breit
Funktionelle Rolle des Nucleus pedunculopontinus in der Pathophysiologie der Basalganglien
Supervisor: T. Gasser

Neurodegenerative Diseases

Medical Theses

C. Wahl
Mutationsscreening und Assoziationsstudien der proteasomalen Untereinheit S6-ATPase bei Patienten mit Parkinsonscher Erkrankung
Supervisor: R. Krüger

J. Godau
Transcranial sonography in the diagnosis of restless legs syndrome
(Medical Faculty)
Supervisor: D. Berg

S. Weber-Endreß
Molekulare und zellbiologische Charakterisierung der Parkinson-assoziierten Leuzin-reichen Repeat-Kinase 2
Supervisor: P. Kahle

A. Wolpert
Determination of CSI-spectroscopic norm values in the basal ganglia and thalamus
(Medical Faculty)
Supervisor: D. Berg

PhD Theses

J. Fuchs
Genetic Risk Factors and their functional Duplication in Parkinson`s Disease
Supervisor: T. Gasser

C. Klein
Functional characterization of leucine-rich repeat kinase 2 dimerization
Supervisor: P. Kahle

C. Schiesling
Bedeutung von DJ-1 (PARK7) in der Parkinson-Krankheit –
Funktionelle Charakterisierung und Identifikation von neuen interagierenden Proteinen
Supervisor: R. Krüger

M. Sharma
Genetic Epidemiology of Parkinson Disease
Supervisor: T. Gasser

Diploma

M. Anderson
Cellular Effects of TDP Expression and Silencing
Biology, external Univ. Oldenburg
Supervisor: Philipp Kahle

Neurodegenerative Diseases / Cognitive Neurology

E. Hausherr
Post-translational Modifications Regulating α-Synuclein Aggregation and Transport
(biology)
Supervisor: Philipp Kahle

A. Treis
Regulation of the E3 Ubiquitin Ligase Parkin
(biology)
Supervisor: Philipp Kahle

Awards - Department of Cognitive Neurology

I. Diester
Hertie Reseach Prize 2008

T. Haarmeier
Felgenhauer Award, Deutsche Gesellschaft für Neurologie

M. Himmelbach
European Research Council Starting Grant

Appointments

M. Giese
W3 Professorship, University of Bochum, declined
W3 Professorship, University of Tübingen, accepted

A. Nieder
Chair, Department of Animal Physiology, University of Tübingen, accepted

C. Schwarz
Associate Professor, University of Maryland, declined

PhD Theses

I. Diester
Representational formats of numerical information in the monkey cortex
(Graduate School for Neural and Behavioural Sciences)
Supervisor: A. Nieder

M. Fruhmann Berger
On the relation between active and passive behaviour in patients with spatial neglect - Insigths from acute stroke and the course of recovery
(Faculty of Information and Cognitive Science)
Supervisor: H.-O. Karnath, R. Ulrich

Cognitive Neurology

B. Händel
Functional correlates of the physical and perceptual properties of coherent visual motion in humans
(Faculty of Biology/Medical School)
Supervisor: T. Haarmeier

S. Kamphuis
Toward the neuronal basis of gaze following, using fMRI in humans and monkeys
(Graduate School for Neural and Behavioural Sciences)
Supervisor: P. Thier

Medical Theses

M. Berner
Störung der visuell-räumlichen Wahrnehmung nach Kleinhirnläsion?
(Medical School)
Supervisor: H.-O. Karnath, S. Richter

P. Thümmler
Blickdeviation nach linkshemisphärischem Schlaganfall
(Medical School)
Supervisor: H.-O. Karnath

M. Synofzik
Die Rolle interner Modelle bei der Wahrnehmung von Eigenbewegungen
(Medical School)
Supervisor: P. Thier, A. Lindner

Diploma/Masters

P. F. Benz
Erstellung einer Software zur partiellen Virtualisierung von Experimentierumgebungen für die perzeptionelle Blickrichtungsbestimmung
Supervisor: P. Dicke, P. Thier

S. Borchers
The role of the human superior colliculus in visual search - an fMRI study
Supervisor: M. Himmelbach

P. Georgieva
Selective microstimulation in rat neocortex - An explorative study
Supervisor: C. Schwarz

C. V. B. Hübner
Erstellung einer Software zum Design virtueller Experimentumgebungen: Bestimmung des Referenzsystems der visuellen Verarbeitung artifizieller Blicke
Supervisor: P. Dicke, P. Thier

Cognitive Neurology / Cellular Neurology

W. Linzenbold
Untersuchung der Augenbewegung beim Lesen von bewegten und statischen Texten
Supervisor: U. J. Ilg

T. Wiestler
Modellierung motorischer Adaptionsprozesse bei Beinbewegungen unter dem Einfluss cerebellärer Dysfunktion
Supervisors: W. Ilg, P. Thier, A. Zell

Awards – Department of Cellular Neurology

J. Coomaraswamy
Fellowship, Carl-Zeiss-Stiftung, Postdoktorandenförderung

J. Hefendehl
Fellowship, Hertie-Stipendienprogramm Neurowissenschaften, Promotionsstipendium

Diploma

L. Behrends
Der Einfluss von APPL auf Bildung und Stabilisierung von Synapsen
Supervisor: T. Rasse / M. Jucker

S. Kramer
Kartierung und Charakterisierung der Mutante fluglotse
Supervisor: T. Rasse / M. Jucker

M. Knopp
Systematische Identifizierung von Genen, die zur Stabilisierung von Synapsen beitragen
Supervisor: T. Rasse / M. Jucker

A. K. M. Langenbruch
Active Zone Precursor Vesikel
Supervisor: T. Rasse / M. Jucker

Lectures

Lectures - Summer Term 2008

Principles of Neurology
Medical School
Prof. T. Gasser, Prof. A. Melms

Introduction to Clinical Neurology
Medical School
Prof. D. Berg, PD Dr. T. Haarmeier

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

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"
Medical School
Prof. T. Gasser

Lectures - Winter Term 2008/2009

Principles of Neurology
Medical School
Prof. T. Gasser, Prof. A. Melms

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

Introduction to Clinical Neurology
Medical School
Prof. D. Berg, PD Dr. T. Haarmeier

Genetic and Molecular Basis of Neural Disease
Graduate School for Cellular and Molecular Neurosciences
Prof. M. Jucker, Prof. T. Gasser, Prof. Schöls

Lectures / Seminars and Courses

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

Neurochemistry and Neurotransmitters
Graduate School of Cellular and Molecular Neuroscience
Prof. P. Kahle

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. C. Pedroarena

Methods in Neuropsychology
Graduate School for Neural and Behavioural Sciences
Dr. M. Himmelbach

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

Seminars and Courses - Summer Term 2008

Neurological Examination
Medical School
Prof. T. Gasser, Prof. A. Melms, PD Dr. T. Haarmeier,
and staff of the Departments of General Neurology and Neurodegenerative Diseases

Neurology Seminar and Bedside Teaching
Medical School
Prof. D. Berg, PD Dr. T. Haarmeier, Prof. R. Krüger, Prof. A. Melms, Prof. L. Schöls

Introduction to Clinical Medicine
Medical School
PD Dr. F. Bischof

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

Contributions to i-KliC „ Infectious Diseases, Clinical Oncology and Emergency Medicine "
Medical School
Prof. A. Melms

Seminars and Courses

Lunch Conference: Critical Care Neurology
Medical School
PD Dr. A. Luft, Dr. J. Erharhaghen

TüKliS „Treatment of Neurological Disorders/Case Presentations"
Medical School
Prof. D. Berg, PD Dr. Bischof, PD Dr. T. Haarmeier, PD Dr. A. Luft, Prof. R. Krüger, Prof. A. Melms, Prof. L. Schöls

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

TüKliS "Dr House – neurological cases"
Medical School
Dr. F. Asmus

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

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

Current Trends in Neuro-oncology
Medical School
PD Dr. U. Naumann

Neuroscience Lecture Series
Medical School
Prof. T. Gasser, Prof. A. Melms, PD Dr. T. Haarmeier

Clinical Neuropathology QB5 (in cooperation with the Institute for Brain Research)
Medical School
Prof. A. Melms, Prof. R.. Meyermann, PD Dr. Will

Interdisciplinary Pain Seminar (in cooperation with the Clinic for Anaethesiology and Clinic for Neurosurgery)
Medical School
PD Dr. S. Schuh-Hofer

Journal Club Neuroimmunology
Medical School
Dr. B. Greve, Dr. C. Stoeckle

Seminars and Courses

Research Seminar Experimental Neurogenetics
Medical School
Prof. T. Gasser, Prof. L. Schöls, Prof. 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. C. 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

Clinical Neuropsychology
Medical School
Prof. H.-P. Karnath

PERACT Colloquium
Medical School
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, Centre for Integrative Neuroscience
Prof. P. Thier

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

Neuroprosthetics
Graduate School for Neural and Behavioural Sciences
Prof. U. Ilg

Tierphysiologischer Kurs Bioinformatik
Faculty of Biology
Prof. U. Ilg

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

Seminars and Courses

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

Seminars and Courses - Winter Term 2008/2009

Neurological Examination
Medical School
Prof. T. Gasser, Prof. A. Melms, PD Dr. T. Haarmeier
and staff of the Departments of General Neurology and Neurodegenerative Diseases

Neurology Seminar and Bedside Teaching
Medical School
Prof. L. Schöls, Prof. A. Melms, Prof. D. Berg, Prof. R. Krüger, PD Dr. T. Haarmeier

Introduction to Clinical Medicine
Medical School
PD Dr. F. Bischof

TüKliS "Intracranial Pressure"
Medical School
Dr. J. Erharhaghen, Prof. A. Melms, Prof. M. Meyermann, Dr. B. Will

Treatment of Neurological Disorders/Case Presentations
Medical School
Prof. D. Berg, PD Dr. F. Bischof, Dr. B. Greve, PD Dr. T. Haarmeier, Prof. R. Krüger, Prof. A. Melms, Prof. L. Schöls

Lunch Conference: Critical Care Neurology
Medical School
Dr. J. Erharhaghen, PD Dr. T. Haarmeier, Dr. B. Greve

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

TüKliS "Dr House – neurological cases"
Medical School
Dr. F. Asmus

TüKliS "Advanced neurological examination"
Medical School
Prof. L. Schöls, Prof. T. Gasser

Seminars and Courses

Current Trends in Neuro-Oncology
Medical School
PD Dr. U. Naumann

Clinical Neuropathology (in cooperation with the Institute for Brain Research)
Medical School
Prof. A. Melms, Prof. R. Meyermann, PD Dr. Will

Interdisciplinary Brain Tumor Seminar
(in cooperation with the Departments for Neurosurgery, Neuroradiology, and Radiooncology)
Medical School
C. Braun

Neuroscience Lecture Series
Medical School
Prof. T. Gasser, Prof. A. Melms, PD Dr. T. Haarmeier

Neuropathological Case Presentation (in cooperation with the Institute for Brain Research)
Medical School
C. Braun, Prof. A. Melms, Prof. R.. Meyermann

Clinical Neuropathology QB5 (in cooperation with the Institute for Brain Research)
Medical School
Prof. A. Melms, Prof. R. Meyermann, PD Dr. Will

Interdisciplinary Pain Seminar
(in cooperation with the Clinic for Anaethesiology and Clinic for Neurosurgery)
Medical School
PD Dr. S. Schuh-Hofer

Journal Club Neuroimmunology
Medical School
Dr. B. Greve, Dr. C. Stoeckle

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

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

Current Problems of Sensorimotor Integration
Medical School
Prof. U. Ilg, PD Dr. C. 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
Prof. M. Giese, Dr. M. Himmelbach, Dr. Winfried Ilg, Dr. A. Lindner, Prof. P. Thier

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

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

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

Lab Rotations - Summer Term 2008

Graduate School for Neural and Behavioural Sciences
Dr. F. Asmus, Dr. A. Luft, Dr. N. Patenge

Lab Rotations - Winter Term 2008/2009

Graduate School for Neural and Behavioural Sciences
Prof. U. Ilg, Prof. H.-O. Karnath, PD Dr. C. Schwarz

Graduate School for Molecular and Cellular Neuroscience
Prof. M. Jucker, Prof. P. Kahle, Dr. S. Di Giovanni

General Neurology / Neurodegenerative Diseases

Therapie neurologischer Erkrankungen - 24. Gemeinsame Fortbildungsveranstaltung der Neurologischen Universitätskliniken München und Tübingen
Tübingen, April 19, 2008
A. Luft (Tübingen), Th. Klopstock (München)

Conferences - Department of General Neurology

Aktuelle Therapie der Multiplen Sklerose
Tübingen, October 8, 2008
A. Melms, F. Bischof, B. Greve, M. Albert

Conferences - Department of Neurodegenerative Diseases

DGKN Symposium: B-mode sonography for neurological diseases
Magedeburg, April 12, 2008
D. Berg

Workshop: Current practice and new developments in deep brain stimulation
Tübingen, April 24-25, 2008
R. Krüger

Workshop: Transkranial sonography in movement disorders
Tübingen, June 7, 2008
D. Berg

DGN Minisymposium: Application of transcranial sonography and MRI for the intra- and postoperative monitoring of electrode positions in patients with DBS
Hamburg, September 13, 2008
D. Berg

International Workshop „α-Synuclein in Health and Disease"
Lausanne, Switzerland, September 24-26, 2008
P. Kahle

Cognitive Neurology

Conferences - Department of Cognitive Neurology

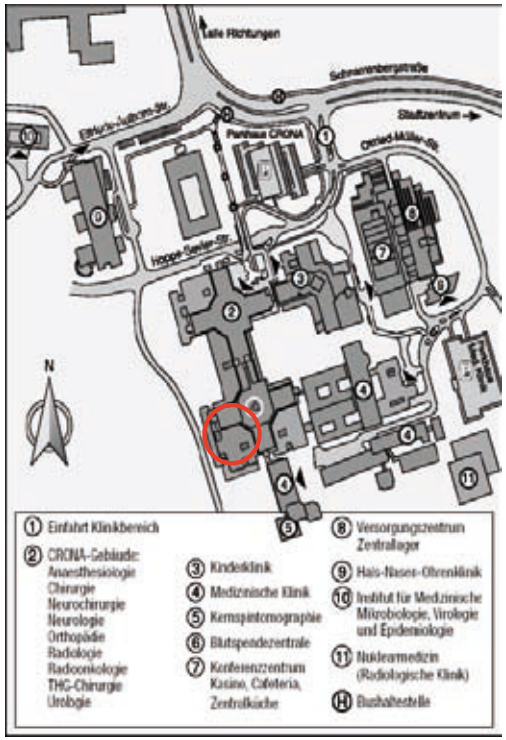
1st Annual Conference "PrimateNeurobiology"
Tübingen, February 27-29, 2008
P. Thier

4th Status Conference "Dynamics and Adaptivity of Neuronal Systems: Integrative Approaches to Analyse Cognitive Functions"
Tübingen, March 12-14, 2008
A. Nieder

23rd Annual Conference of the Society for Neuropsychology (GNP) 2008
Tübingen, October 9-12, 2008
H.-O. Karnath

Veranstaltungsort:
CRONA Klinikum
Großer Hörsaal CRONA, Ebene B3,
Hoppe-Seyler-Str. 3
72076 Tübingen

Dienstag, 23.09.2008
Beginn: 14.00 Uhr



Veranstalter:
Prof. Dr. med. T. Gasser, Abteilung Neurologie mit Schwerpunkt Neurodegenerative Erkrankungen, Zentrum für Neurologie und Hertie-Institut für Klinische Hirnforschung, Universität Tübingen

Kontaktadresse und Anmeldung:

6. Tübinger Infotag
'Parkinson-Therapie'
Parkinson-Ambulanz und Ambulanz für Tiefe Hirnstimulation
Hoppe-Seyler-Str. 3
72076 Tübingen
Tel.: 07071-29-85165

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Organisation:
PD Dr. med. R. Krüger
Leiter der Ambulanz für Tiefe Hirnstimulation
Neurologische Klinik
Universität Tübingen
Hoppe-Seyler-Str. 3
72076 Tübingen
Tel.: 07071-29-82141
Fax: 07071-29-5260

Zentrum für Neurologie und Hertie-Institut für Klinische Hirnforschung, Universitätsklinikum Tübingen

Eberhard-Karls-Universität UKT Universitätsklinikum Tübingen

Hertie-Institut für klinische Hirnforschung

6. Tübinger Infotag

'Parkinson-Therapie'

Behandlungsmöglichkeiten bei fortgeschrittener Parkinson-Krankheit

Beispiele und Diskussion
Dienstag, 23.09.2008

Referenten und Moderatoren

Dr. F. Asmus, Tübingen
PD Dr. K. Bötzel, München
Prof. Dr. Th. Brandt, München
Dr. R. von Coelln, Tübingen
Prof. Dr. U. Ernemann, Tübingen
Dr. J. Erharhaghen, Tübingen
PD Dr. G. Eschweiler, Tübingen
Dr. D. Eser, München
Dr. B. Feddersen, München
Prof. Dr. Th. Gasser, Tübingen
Dr. B. Greve, Tübingen
Dr. E. Huberle, Tübingen
Dr. Ch. Kamm, Tübingen
Prof. Dr. Th Klopstock, München
PD Dr. R. Krüger, Tübingen
PD Dr. S. Lorenzl, München
PD Dr. A. Luft, Tübingen
Dr. W. Mätzler, Tübingen
Prof. Dr. A. Melms, Tübingen
Dr. Ch. Opherk, München
Dr. H. Pellkofer, München
Dr. S. Rona, Tübingen
PD Dr. F. Roser, Tübingen
Dr. M. Voss, Tübingen
Dr. J. Wagner, München

Für die freundliche Unterstützung bedanken wir uns bei

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Organisation:
Prof. Dr. Th. Klopstock, München
PD Dr. A. Luft, Tübingen

Auskunft:
PD Dr. A. Luft, Tel. 07071/29 82049
aluft@jhu.edu

ZENTRUM FÜR NEUROLOGIE
Prof. Dr. med. Thomas Gasser
Prof. Dr. med. Arthur Melms
Prof. Dr. med. Peter Thier
Klinikum der Universität Tübingen
Hoppe-Seyler-Str. 3
72076 Tübingen

THERAPIE NEUROLOGISCHER ERKRANKUNGEN

24. Gemeinsame
Fortbildungsveranstaltung der
Neurologischen Universitätskliniken
München und Tübingen

Samstag, 19. April 2008
9:00 bis 16:30 Uhr

Hörsaal des HNO-Klinikums
Elfriede-Aulhorn-Straße 5, 72076
Tübingen

Zeit und Ort:
Samstag, 19. April 2008, 9:00-16:30 Uhr
Hörsaal des HNO-Klinikums
Elfriede-Aulhorn-Straße 5, 72076 Tübingen

Eine Teilnahmegebühr wird nicht erhoben.
Anmeldung ist nicht erforderlich.

Für die Veranstaltung sind 8 Fortbildungspunkte von der Landesärztekammer Baden-Württemberg veranschlagt.

Anreise mit öffentlichen Verkehrsmitteln:
Vom Tübinger Hauptbahnhof fahren die Busse der Linien 5 (10min Takt), 13, 18 und 19 zu den Kliniken auf dem Schnarrenberg. Von den Bushaltestellen ist es nur ein kurzer Fußweg zur HNO-Klinik (türkisfarbenes Gebäude).

Mit dem Auto
Auf dem Schnarrenberg parken Sie am besten im Parkhaus der „Crona Kliniken“ und gehen am Institut für Biochemie vorbei zur HNO-Klinik (türkisfarbenes Gebäude).

PROGRAMM

9:00 –9:15 Begrüßung und Einführung
Th. Gasser

EPILEPSIE
(Vorsitz: Th. Klopstock)

9:15-9:30	Vagusstimulation bei Epilepsie *B. Feddersen, München*
9:30-9:45	Epilepsie-Monitoring *S. Rona, Tübingen*
9:45-10:55	Kasuistik I *J. Wagner, München*
10:55-10:15	Update I: Multiple Sklerose *H. Pellkofer, München*

10:15-10:45 Pause

KOGNITION UND DEMENZ
(Vorsitz: Th. Brandt)

10:45-11:00	Sinn und Unsinn von Liquordiagnostik bei Demenz *W. Mätzler, Tübingen*
11:00-11:15	Behandlungsstrategien bei Alzheimer-Demenz *G. Eschweiler, Tübingen*
11:15-11:30	Posteriore kortikale Atrophie *E. Huberle, Tübingen*
11:30-11:45	Behandlungsstrategien bei progressiver supranukleärer Blickparese *S. Lorenzl, München*
11:45-11:55	Kasuistik II *M. Voss, Tübingen*
11:55-12:15	Update II: Guillain Barré-Syndrom *B. Greve, Tübingen*

12:15-13:15 Mittagspause

BEWEGUNGSSTÖRUNGEN & NEUROSTIMULATION
(Vorsitz: A. Melms)

13:15-13:30	Camptocormie - Syndrom, Ätiologien und Behandlung *R. v. Coelln, Tübingen*
13:30-13:45	Neue Therapieoptionen beim fortgeschrittenen Parkinson-Syndrom *R. Krüger, Tübingen*
13:45 -14:00	Neurostimulation für Tics, Depression und Schmerzen *K. Bötzel, München*
14:00-14:10	Kasuistik III *D. Eser, München*
14:10-14:30	Syringomyelie *F. Roser, Tübingen*

14:30 – 15:00 Pause

VASKULÄRE NEUROLOGIE
(Vorsitz: A. Luft)

15:00-15:15	Stenosen der extra- und intrakraniellen Arterien *U. Ernemann, Tübingen*
15:15-15:30	Neues zur TIA *Ch. Opherk, München*
15:30-15:45	Medikamentöse Sekundärprävention *J. Erharhaghen, Tübingen*
15:45-16:00	Botulinumtoxin nach Schlaganfall *F. Asmus, Tübingen*
16:00-16:10	Kasuistik IV *Ch. Kamm, Tübingen*
16:10-16:30	Medikamenten-induzierte Myopathien *Th. Klopstock, München*

Anmeldung und Fragen

Frau C. Riegraf
Sekretariat der Abteilung Allgemeine Neurologie
Zentrum für Neurologie
Hoppe-Seyler-Str. 3
72076 Tübingen

Telefon: 0 70 71/29-8 20 49
e-mail:
christine.riegraf@med.uni-tuebingen.de

oder

PD Dr. F. Bischof
Felix.Bischof@uni-tuebingen.de

Die Veranstaltung ist durch die Landesärztekammer Baden-Württemberg mit 2 Fortbildungspunkten anerkannt

Veranstaltungsort

Konferenzzentrum – Kliniken Berg,
Ottfried-Müller-Straße 6
1. OG
Gebäude 520, Raum I und II

Neurologische Universitätsklinik
Hertie-Institut für klinische Hirnforschung

Eberhard-Karls-Universität
UKT
Universitätsklinikum Tübingen

Fortbildung

Aktuelle Therapie der Multiplen Sklerose

08.10.2008
18.00 Uhr

Sehr geehrte Kolleginnen und Kollegen,

die Therapie der Multiplen Sklerose hat sich im Verlauf der letzten Jahre enorm gewandelt und es ist klar, dass dieser Trend weiter anhalten wird. Damit steigen die Anforderungen an den behandelnden Neurologen, der seine Patienten optimal versorgen möchte und gleichzeitig zum wirtschaftlichen Einsatz der Mittel verpflichtet ist.

Diese Fortbildungsveranstaltung soll den aktuellen Stand und die unmittelbar anstehenden Veränderungen der Immuntherapie der MS aufzeigen und ein Forum bieten für den Dialog zwischen den an der ambulanten und klinischen Versorgung tätigen Kollegen.

Über Ihr Kommen würden wir uns sehr freuen.

Prof. Dr. A. Melms

Programm

18.00 Uhr Begrüßung
A. Melms

18.10 Uhr
Aktuelle Aspekte der Basistherapie: Interferone - Glatiramerazetat - Natalizumab.
B. Greve

18.30 Uhr
Was kommt als nächstes? Laufende Therapiestudien.
F. Bischof

18.50 Uhr
Auf dem Weg zur individualisierten Therapie: Beispiele aus der Praxis.
A. Melms, M. Albert

19.10 Uhr Diskussion

Referenten

Dr. Dr. M. Albert
PD Dr. F. Bischof
Dr.med. B. Greve
Prof. Dr. A. Melms

Abteilung Allgemeine Neurologie
Neurologische Universitätsklinik
Zentrum für Neurologie
Hoppe-Seyler-Straße 3
72076 Tübingen

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Sanofi-Aventis

Poster Session

1 Bareyt A, Lefèvre P, Missal M, de Hamptinne C
Consequences of changing expectations on anticipatory pursuit

2 Biber U, Ilg UJ
Action and perception are similarly influenced by the motion after-effect

3 Carrozzini C, Raffi M, Maioli MG, Squatrito S
Pre-saccadic and eye position signal coding in area PEc of the behaving monkey

4 Diester I, Nieder A
Correlated discharges of different cell types in the monkey prefrontal cortex during a numerosity discrimination task

5 Fize D, Richard G, Jouffrais C, Fabre-Thorpe M
EEG in head-free monkeys engaged in a rapid visual categorisation task

6 Freyberg S, Ilg UJ
Anticipatory smooth-pursuit eye movements in man and monkey

7 Goossens J
to be announced

8 Guerrasio L, Goffart L, Buettner U
The role of fastigial nuclei during fixation

9 Heinzle J, Hepp K, Martin KAC
An anatomically constrained model of the layered local circuit of the primate frontal eye fields

10 Hugues S, Fleuriet J, Masson G, Goffart L
Effects of target size on fixational saccades in the head restrained monkey

11 Kaping D
Task-specific attentional modulation of MT responses

12 Klaes C, Westendorff S, Gail A
Memory encoding of spatial motor-goals in the fronto-parietal reach network

13 Klingenhoefer S, Wittenberg M, Wachtler T, Bremmer F
Receptive field shifts in macaque primary visual cortex induced by saccade adaptation

14 Kozyrev V, Lochte A, Treue S
Non-multiplicative attentional modulation of responses in macaque area MT to bidirectional motion

15 Kruse W, Dannenberg S, Gieselmann A, Hoffmann K-P
Microstimulation in area MT impairs visually guided hand movements

16 Baumann M, Fluet M-C, Scherberger H
Hand grasping representation in parietal and premotor cortex in macaque monkeys

17 Lindner A, Iyer A, Kagan I, Andersen RA
Expected reward magnitude modulates fMRI-activity in monkey ventral and dorsal cortical streams and the striatum during a goal-directed saccade task

18 Oliynyk A, Gesierich B, Canto R, Fadiga G, Caselli L, Fadiga L
An optimized approach for long-term single neurons recordings in behaving monkeys

19 Rothé M
Behavioral shifts and actions valuation in the anterior cingulate cortex

20 Self M, Super H, Roelfsema P
The laminar distribution of figure-ground modulation in macaque primary visual cortex

21 Thomassen JS, Hess BJM
Do eye-head movement responses in monkeys during passive whole body or optokinetic full field rotations reflect the illusion of "looking where one is going?

22 Townsend B, Subasi E, Lehmann S, Scherberger H
Decoding hand-grasping signals from primate premotor and parietal cortex

23 Trigo-Damas I, Biber U, Ilg UJ
Visual motion processing: illusions of speed

24 Vallentin D, Nieder A
Primates understand proportionality

25 Westendorff S, Klaes C, Gail A
Dynamic integration of space and context for the encoding of motor-goals in reaching

26 Wittenberg M, Teichert T, Eckhorn R, Bremmer F, Wachtler T
Presaccadic activity enhancement in primary visual cortex is not feature-specific

Conference Center
Schnarrenberg
Building 520
Otfried-Müller-Str. 6
72076 Tübingen

Conference office

Dagmar Heller-Schmerold

☏ +49 (0)7071 29 85662, schmerold@uni-tuebingen.de

☏ +49 (0)7071 29 80460 at the conference centre from February 27-29

Wednesday, February 27

12:00 REGISTRATION

13:50 WELCOME ADDRESS

14:00 Kevan Martin (Zürich)
Connecting primate neocortex: Patterns and principles

14:30 Fahad Sultan (Tübingen)
Revealing excitable subcortical networks by microstimulation-fMRI of the deep cerebellar nuclei

15:00 Leonardo Fogassi (Parma)
Neurons of ventral premotor cortex of macaque monkey play a role in the voluntary control of vocalization

15:30 COFFEE BREAK

16:15 Luciano Fadiga (Ferrara)
Visual feedback from the own acting hand modulates the activity of grasping motor neurons in monkey premotor area F5

16:45 Ben Townsend (Zürich)
Coding and decoding of hand grasping in parietal and premotor cortex

17:15 Alexander Gail (Göttingen)
Movement planning in the fronto-parietal reach network

17:45 Luca Bonini (Parma)
Chaining motor acts into goal directed actions: the role of the inferior parietal convexity

18:30 OPENING RECEPTION

Thursday, February 28

9:00 Yves Trotter (Toulouse)
Implication of primate area V1 in neural 3-D spatial localization processing

9:30 Lionel Nowak (Toulouse)
Orientation tuning, when examined with briefly flashed stimuli, is not contrast invariant in area V1 of a primate, the common marmoset

10:00 COFFEE BREAK

10:45 Francisco Gonzalez (Santiago de Compostela)
Orientation and direction sensitivity to stereobars in the visual cortex of the monkey

11:15 Michael Brosch (Magdeburg)
Tone sequence analysis in auditory cortex

12:00 LUNCH

13:15 Kristian Folta (Göttingen)
The role of acoustic and visual gaps in monkey interval timing: Evidence against stop/reset mechanisms

13:45 Jean Laurens (Zürich)
Integration of semicircular canal and otolith signals subserves dynamic spatial orientation

14:15 Suryadeep Dash (Tübingen)
Specific vermal complex spike responses build up during the course of smooth pursuit adaptation, paralleling the decrease of performance error

14:45 Laurent Goffart (Marseille)
Neural mechanisms for orienting the fovea toward a visual object

15:30 **POSTER SESSION** & COFFEE

18:30 WORKING DINNER

Friday, February 29

9:00 Marcus Missal (Leuven)
Neuronal bases of directional expectation and anticipatory pursuit

9:30 Simone Materna (Tübingen)
Neuronal substrates of gaze following in monkeys: an fMRI study

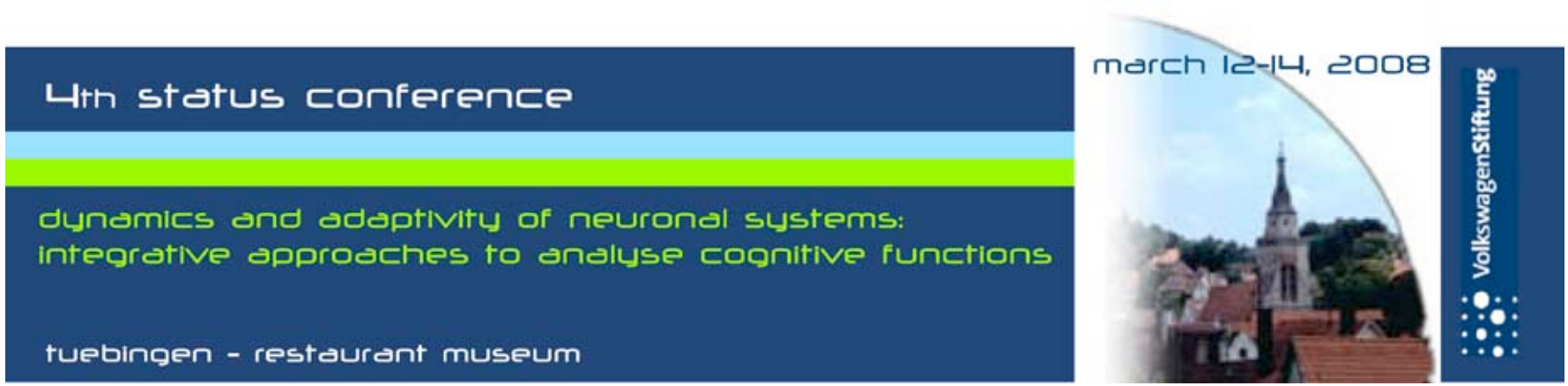
10:00 COFFEE BREAK

10:45 Björg Kilavik (Marseille)
Motor cortical LFPs are modulated during temporal attention and movement preparation

11:15 Alexa Riehle (Marseille)
While waiting to move: the complementarity of precise spike synchrony and firing rate in monkey motor cortex

11:45 Jerome Sallet (Bron)
Neural implementation of branching and interference resolution in the anterior cingulate cortex

12:30 LUNCH



Wednesday, March 12, 2008

WELCOME ADDRESS (Henrike Hartmann & Indra Wilms-Hoff, VW Foundation)

Sonja Grün (Wako-Shi, Japan)
Coordinated neuronal activity in visual cortex of monkey freely viewing natural scenes

Udo Ernst (Bremen, Germany)
Predicting human contour detection

Petra Stoerig (Düsseldorf, Germany)
Learning to recognize objects with an image-to-sound conversion-based sensory substitution system

Alexander Münchau (Hamburg, Germany)
Observing biological movements distinctly affects auditorily cued motor responses

Peter Thier (Tübingen, Germany)
Self-motion and perception

Dominik Heyers (Oldenburg, Germany)
Do migratory birds "see" the magnetic field? Vision as neuronal substrate for magnetic orientation

Plenary Lecture
Stanislas Dehaene (Saclay, France)
Intuitions of number and space

Thursday, March 13, 2008

Plenary Lecture
Nicola S. Clayton (Cambridge, UK)
What do crows know about other minds and other times?

Bernhard Ronacher (Berlin, Germany)
3-D orientation in desert ants

Carsten T. Wotjak (München, Germany)
Towards an animal model of PTSD

Bertram Gerber (Würzburg, Germany)
Outcome expectations drive learned behaviour in larval Drosophila

Peer Wulff (Aberdeen, UK)
From synapse to behaviour: rapid modulation of defined neuronal populations through engineered GABAa receptors

Andreas Lüthi (Basel, Switzerland)
Pathway-specific function for different AMPA receptor subunits in amygdala long-term potentiation and fear conditioning

Menahem Segal (Rehovot, Israel)
Morphological and functional plasticity of dendritic spines in hippocampal neurons

Plenary Lecture
Daniel Margoliash (Chicago, USA)
Early events in bird song learning; coupling sensory and sensorimotor learning

Hermann Wagner (Aachen, Germany)
Correlates of binaural masking-level difference in the barn owl

Henning Scheich (Magdeburg, Germany)
Categorical decision making in primate auditory cortex

Stefan Treue (Göttingen, Germany)
Non-multiplicative attentional modulation of responses in macaque area MT to bidirectional motion

Xiao-Jing Wang (New Haven, USA)
An integrated microcircuit model of attentional processing in the neocortex

Susan J. Sara (Paris, France)
Cortical spindles and hippocampal ripples in tune with activity of locus coeruleus neurons during sleep after learning: players on the off-line memory consolidation scene?

Thomas Knöpfel (Wako-Shi, Japan)
Involvement of protein synthesis and degradation in long-term potentiation of Schaffer collateral CA1 synapses

Plenary Lecture
Nikos K. Logothetis (Tübingen, Germany)
On the interpretation of neural and hemodynamic signals

Friday, March 14, 2008

Plenary Lecture
Robert J. Zatorre (Montreal, Canada)
Anatomical and functional plasticity in human auditory cortex: pitch, speech, and cross-modal reorganization

Merav Ahissar (Jerusalem, Israel)
Speech perception and the efficiency of integrating spatial cues

Christian Dobel (Münster, Germany)
Cognitive and neural correlates of second language acquisition

Marcus Meinzer (Münster, Germany)
Neural correlates of immediate and delayed intense language training success in chronic aphasia

Thomas Münte (Magdeburg, Germany)
The impact of COMT and DRD4 genotypes on neurophysiological markers of performance monitoring

Hartwig Siebner (Kiel, Germany)
Ultra-focal transcranial magnetic stimulation of the left primary motor and dorsal premotor cortices can probe premotor-to-motor connectivity in the intact human brain

Oliver Bosch (Regensburg, Germany)
Early life stress: Opposite effects on adult stress coping depend on the genetic background

Organisation: Andreas Nieder

Impressum: Center of Neurology
University Hospital of Neurology
Hoppe-Seyler-Straße 3 and
Hertie Institute for Clinical Brain Research
Otfried-Müller-Straße 27
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