

ANNUAL REPORT  
2011



# ANNUAL REPORT 2011

CENTER OF NEUROLOGY TÜBINGEN

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**THE CENTER OF NEUROLOGY**



*The Hertie-Institute for Clinical Brain Research with its modern architecture and up-to-date infrastructure is one of Germany's largest facilities for neurological research.*

## THE CENTER OF NEUROLOGY IN 2011

The Center of Neurology at the University of Tübingen was founded in 2001. It unites the Hertie-Institute for Clinical Brain Research (HIH) and the University Hospital for Neurology with the mission to promote excellence in research and patient care.

Presently, the center consists of four clinical departments (General Neurology, Epileptology, Neurodegeneration and Cognitive Neurology) and one basic science department (Cellular Neurology). The four clinical departments provide inpatient and outpatient care within the University Hospital, while their clinical and basic research groups are part of the Hertie-Institute.

The fact that four of the five 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, epilepsies and brain tumors. However, the intimate 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 Center of Neurology from other institutions of neuroscientific research.

2011

2011

## DAS ZENTRUM FÜR NEUROLOGIE IM JAHR 2011

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. Damit entstand 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. Das Zentrum besteht derzeit aus vier klinischen und einer grundlagenwissenschaftlichen Abteilung: Allgemeine Neurologie, Epilepsie, Neurodegenerative Erkrankungen, Kognitive Neurologie und Zellbiologie Neurologischer Erkrankungen.

Die besonders enge Verknüpfung von Klinik und Grundlagenforschung ist ein fundamentales Aspekt des Hertie-Konzepts und ein Alleinstellungsmerkmal gegenüber anderen Institutionen der Hirnforschung. Dies ist unter anderem die Grundlage für erfolgreiche Medikamenten-Studien, die am Zentrum zum Beispiel in der Therapie der Parkinson-Krankheit, der Epilepsien, der Multiplen Sklerose und auch in der Hirntumorbehandlung in erheblichem Umfang durchgeführt werden.

*The Department of Neurology is located on the premises of the Crona Hospitals.*



# 2011



*During her visit at the Center of Neurology in 2011, Prof. Annette Schavan, Federal Minister of Education and Research, is introduced to recent advances in clinical brain research. Here, Prof. Daniela Berg explains the use of ultrasound technology in the early detection of Parkinson's disease.*

# 2011

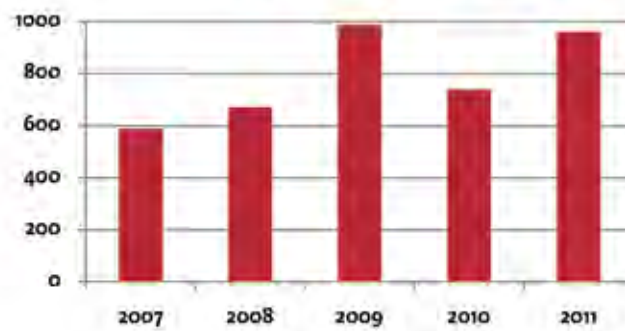
## FACTS & FIGURES



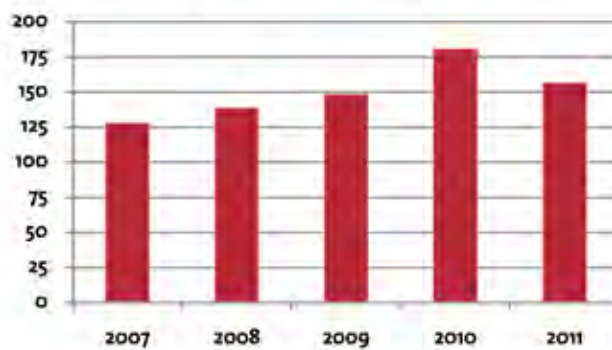
*The staff at the laboratories works eagerly on the elucidation of the mysteries of brain function.*

### PERFORMANCE DEVELOPMENT RESEARCH AND EDUCATION

Impact-Factors (SCIE and SSCI) (100%) (HIH)



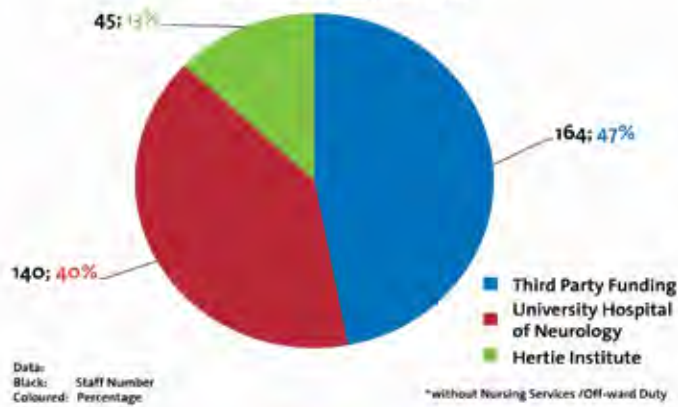
Number of Publications



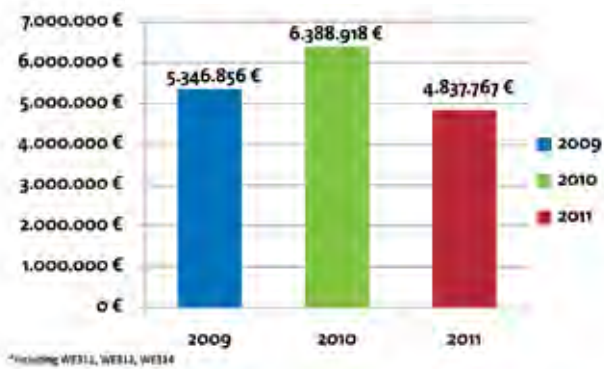




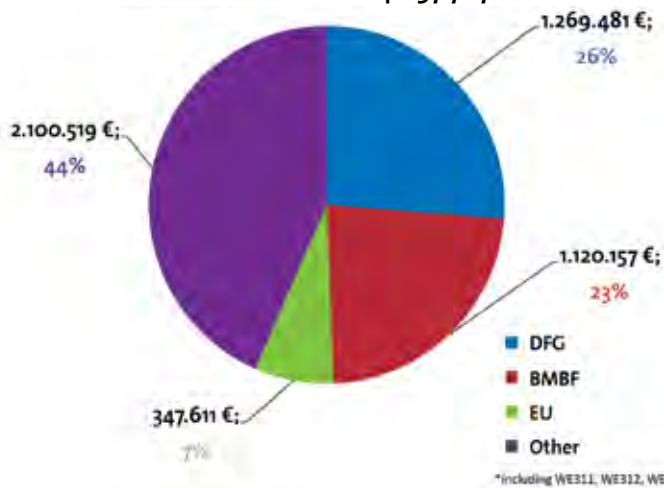
NUMBER OF STAFF (in 2011)

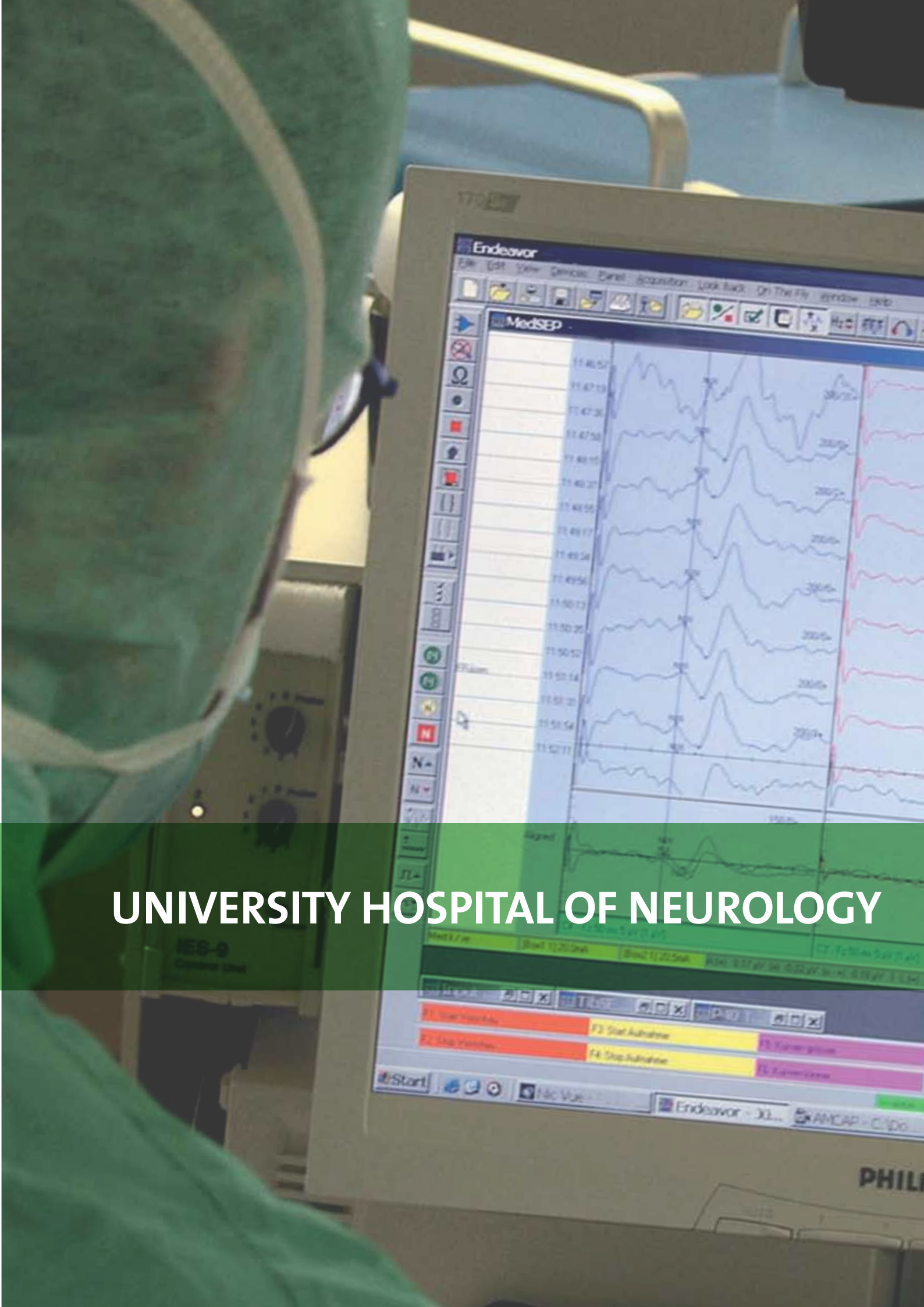


THIRD PARTY FUNDS  
from 2009 to 2011 (in €)



THIRD PARTY FUNDING  
Total in 2011: 4.837.767 €





# UNIVERSITY HOSPITAL OF NEUROLOGY



*Close monitoring of patients at the intensive care unit.*

## CLINICAL CARE

The clinical Department of Neurology of the University Hospital in Tübingen treats inpatients with the complete spectrum of neurologic diseases on four general wards. Patients with acute strokes are treated on a specialized stroke-unit which allows 24-hour surveillance and treatment. In addition, a specialized EEG-monitoring unit allows continuous long-term EEG recordings for patients with intractable epilepsies.



In the outpatient unit of the department, more than 3,000 patients are examined and treated per year, many of them in specialty clinics which are directed by recognized specialists in the respective fields.

**PATIENTENVERSORGUNG**

Die Neurologische Klinik am Universitätsklinikum Tübingen behandelt Patienten aus dem gesamten Spektrum neurologischer Erkrankungen auf vier Allgemeinstationen. Darüber hinaus werden Patienten mit akuten Schlaganfällen auf einer Schlaganfall-Spezialstation („Stroke-Unit“) behandelt, die rund um die Uhr die erforderlichen Überwachungs- und Therapiemaßnahmen erlaubt. Daneben gibt es eine spezielle Einheit zur kontinuierlichen Langzeit-EEG-Ableitung (EEG-

Monitoring) für Patienten mit schwer behandelbaren Epilepsien.

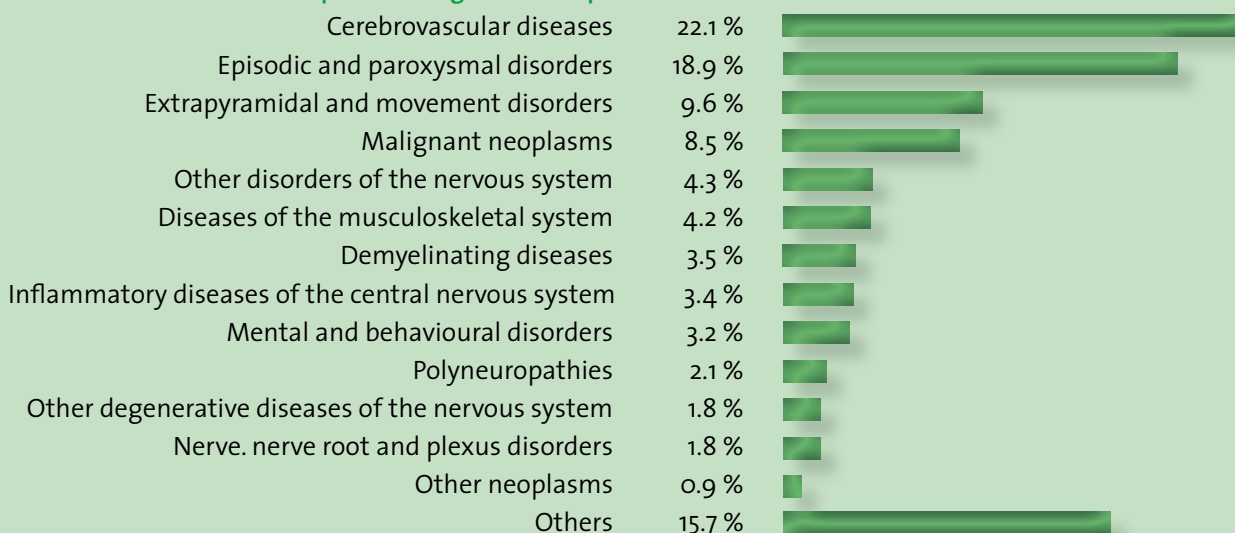
In der neurologischen Poliklinik werden mehr als 3.000 Patienten pro Jahr ambulant betreut, viele davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden.

**INPATIENT CARE**

The inpatient units of the University Hospital for Neurology treated more than 4,500 patients in 2011.

Number of admissions	4,525
Length of stay (in days)	5
Case-Mix-Index	1,36

**Inpatient Diagnosis Groups**



**OUTPATIENT CARE**

In 2011 we saw again an increase of admissions in the Stroke and Intensive Care Sector.

Number of consultations	14,800
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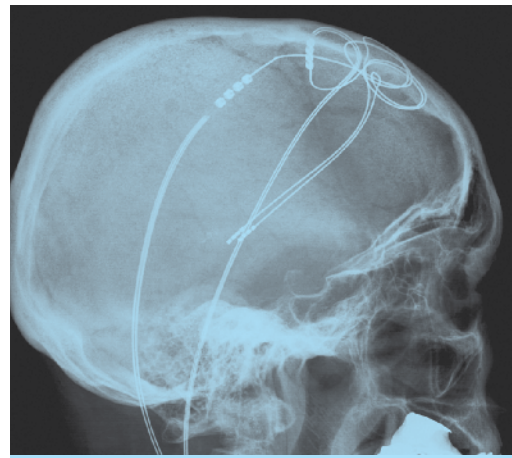
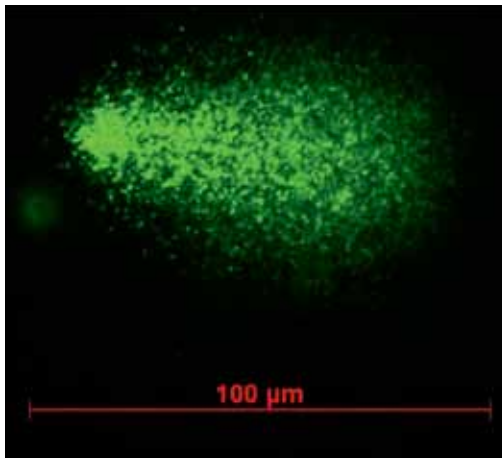
Left: Comet assay indicating impaired DNA repair in lymphoblastoids of patients with recessive ataxias.

Comet of DNA fragments in a lymphoblast with increased numbers of double strand breaks.

Right:

Deep brain stimulation for Parkinson's disease:

X-Ray image of an electrode inserted to the brain.



## ATAXIA

The ataxia clinic provides tools to discover the cause of ataxia in close cooperation with the Department of Neuro-radiology (MRT, MR-Spectroscopy) and the PET-center. In cooperation with the Institute of Medical Genetics the genetic basis in patients and families with hereditary ataxias are investigated.

Therapeutic options depend largely on the underlying cause of ataxia, the genetic defect, and concomitant symptoms. In cooperation with the Center of Physiotherapy, the experts 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 Ataxia Study Group ([www.ataxia-study-group.net](http://www.ataxia-study-group.net)) the Hospital of Neurology performs a natural history study for spinocerebellar ataxias (SCA) as a prerequisite for interventional trials in the future. Additionally, it participates in the RISCA project aiming at biomarkers that indicate the conversion of the preclinical state into disease manifestation in SCA mutation carriers. In Friedreich's ataxia the hospital conducts phase IIa and phase III trials with idebenone and an erythropoietin derivate that is supposed to increase frataxin levels.

The clinic is run by Dr. M. Synofzik, Dr. J. Schicks and Dr. J. Müller vom Hagen and is supervised by Prof. Dr. L. Schoels.

## 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](http://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 2011, interventions for DBS were performed on 75 patients including patients with Parkinson's disease, essential tremor, a variety of atypical tremor syndroms (neuropathic tremor, Holmes tremor, fragile X tremor ataxia syndrome) and dystonia. The growing relevance of Tübingen as a specialized center for deep brain stimulation was further recognized by its inclusion into the European multicenter EARLYSTIM-study group. Moreover, based on own basic research in the identification of novel targets for DBS in Parkinson's disease, two independent randomized controlled trials for unmet axial symptoms like 'freezing of gait' and 'imbalance and falls' in Parkinson's disease are on the way. Based on our recent research, neuromodulation of the so-called 'nigroponine locomotor loop'



provides the candidate target, using i) high-frequency stimulation of the substantia nigra pars reticulata (SNr) as an add-on to the conventional subthalamic nucleus stimulation, or ii) low-frequency stimulation of the pedunculopontine nucleus (PPN). This is of extraordinary need for current therapy research, as several independent long-term follow-up studies in Parkinson's disease underpinned the failure of established conventional pharmaco- and neurostimulation therapies concerning these highly incapacitating axial symptoms.

Patients who are likely to benefit from DBS undergo a detailed program of standardized neurological, neuropsychological, neuroradiological, and cardiological examinations on our ward for neurodegenerative 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 counseling 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, PD Dr. S. Breit, Dr. D. Weiss, Dr. C. Mielke, and Prof. Dr. R. Krüger.

## 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. It is 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 Dr. J. Pomper and Dr. L. Schwendemann.



*Over the last years, an increasing number of outpatients with spasticity have been managed with a combined treatment of BoNT injections and physiotherapy at the local Medical Training and Rehabilitation Center.*

## DYSTONIA AND BOTULINUM TOXIN TREATMENT

The outpatient clinic offers a comprehensive diagnostic work-up and the full range of treatment options for patients with different forms of dystonia, spasticity, and hyperkinetic movement disorders. In cooperation with the headache clinic (PD Dr. S. Schuh-Hofer), treatment with botulinum toxin injections for patient with chronic migraine is provided.

Approximately 450 to 500 patients are treated regularly with botulinum toxin (BoNT) injections in intervals of 3 to 6 months. Of those nearly 60% are treated for dystonia (including Blepharospasm and Meige-Syndrom as well as cervical, segmental, multifocal, generalized and task-specific dystonia) and facial hemispasm, 30% for spasticity and 10% for other indications (including migraine, hyperhidrosis, and hypersalivation).

For patients with dystonia or spasticity BoNT treatment is often optimized using EMG-, electro stimulation-, or ultrasound-guided injection techniques. Presently, the clinic is evaluating a new ultrasound-guided injection technique for the treatment of deep cervical muscles in cervical dystonia. The hospital also participates in several multicenter clinical studies to evaluate new preparations as well as new indications for BoNT treatment.

Dystonia patients with insufficient response to standard treatments can be treated with deep brain stimulation (DBS) of the internal pallidum in collaboration with the clinic for deep brain stimulation and the BrainStimNet ([www.brainstimnet.de](http://www.brainstimnet.de)).

The University Hospital of Neurology also contributes to different multicenter studies with the aim to evaluate and optimize pallidal DBS in dystonia patients.

Besides pharmacologic and surgical treatment, a wide range of physical and ergotherapeutic therapies are offered. Over the last years, 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 Rehabilitation Center, University of Tuebingen). There is also a specialized ergotherapeutic service for task-specific dystonias focused on retraining (S. Wiesemeier, Therapiezentrum UKT).

2 to 3 residents as well as host physicians are continually trained in both standardized and new injection techniques.

The tradition of expert meetings together with regional movement disorder experts has been continued. In a collaboration with four other botulinum toxin clinics in this area, a registry is presently set up which includes clinical features, life quality mea-



tures and treatment plans of approximately 1,300 patients seen regularly in these clinics. In a subgroup of dystonic patients of this registry we also collect DNA samples and capture clinical features for a European collaboration (European network for the study of dystonia syndromes, BMBS COST Action BM1101, headed by Prof. Alberto Albanese).

Appointments are scheduled every week on Wednesday and Thursday in the Outpatient Clinic of the Center of Neurology. The medical staff of this unit includes Dr. T. Wächter (Head), Dr. K. Brockmann, Dr. M. Engholm PhD, Dr. K. Schweizer, G. Beck (technical assistant).

## EPILEPSY

The Department of Neurology and Epileptology started its operations in November 2009. Since then, a large inpatient and outpatient clinic has been built offering the whole spectrum of modern diagnostic procedures and therapy of the epilepsies and all differential diagnoses of paroxysmal neurological disorders, such as syncope, dissociative disorders with pseudoseizures, migraine, transient ischemia, and also rare disorders, as episodic ataxias and paroxysmal movement disorders.

The epilepsy outpatient clinic offers consulting and treatment in particular for newly diagnosed, difficult-to-diagnose and difficult-to-treat cases, and for specific questions including women with epilepsy, pregnancy under antiepileptic treatment, and genetic aspects. The study center offers medical trials to explore novel treatment options. The inpatient clinic includes acute care for epileptic seizures and status epilepticus, longterm complex treatment for difficult cases (1-3 weeks), and a Video-EEG-Monitoring Unit which is operated in close cooperation with the Department of Neurosurgery. Within this unit, inpatients are continuously and simultaneously monitored with video and electroencephalography (EEG) for differential diagnostic and presurgical evaluations. Epilepsy surgery is a very effective treatment option for cases that are resistant to antiepileptic medication. Altogether we treat about 2,000 adult patients per year.

The in- and outpatient clinic is run by Prof. H. Lerche, PD Dr. Y. Weber, PD Dr. M. Dihné and Dr. S. Klamer.





*Neuro-geriatric patients receive physiotherapy for mobility training.*

## 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 are presented with multiple and complex medical problems. In these 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 pa-

tients. 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. Steinhäuser 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 (PD 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.

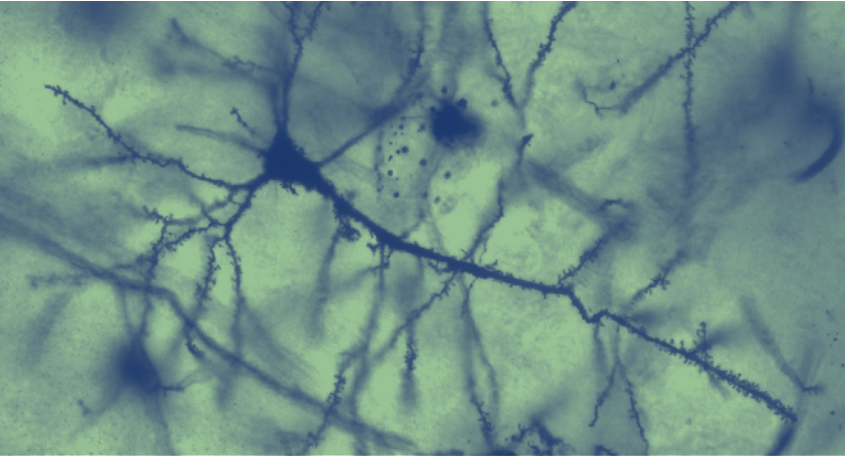
Staff directly involved in the different services and projects include Prof. D. Berg, Prof. T. Gasser, Prof. R. Krüger, PD Dr. W. Maetzler, and Prof. A. Melms.



## HEADACHE AND NEUROPATHIC PAIN

The outpatient unit focuses on neurological pain syndromes, including headache, facial pain and neuropathic pain syndromes. Patients may either be referred by general practitioners or neurologists. The unit is specialized in the diagnosis and treatment of rare primary headache disorders like cluster headache, hemicrania continua or SUNCT-syndrome. Another focus is the therapy of chronic headache disorders like chronic migraine, chronic tension type headache, and medication overuse headache. Patients with neuropathic pain syndromes are diagnosed and treated in close collaboration with the

Department of Anesthesiology which organizes interdisciplinary pain conferences. To address psychiatric comorbidities, which are frequent in chronic pain patients, the Department works in close cooperation with the Department of Psychosomatic Medicine and with the University Clinic for Psychiatry. The outpatient clinic is run by PD Dr. S. Schuh-Hofer and Dr. T. Ulrich.



*Pyramidal neuron in the hippocampus of an epileptic patient (40 times magnification).*

## 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; [www.leukonet.de](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. For an increasing number of these neurometabolic disorders treatment by enzyme replacement, substrate inhibition or stem cell transplantation become available.

Patients are seen by Dr. J. Müller vom Hagen and Prof. Dr. L. Schöls.

## MOTONEURON DISEASE

Motoneuron diseases are caused by the degeneration of motor neurons in the cerebral cortex (upper motor neuron) and/or 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 most cases ALS is a sporadic disease, but in about 10% of patients there is a familial background. 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 inpatient treatment is required to confirm the diagnosis of ALS. Treatment of respiratory problems is provided in close cooperation with the pulmonologists. Follow-up of patients as well as management of symptoms and complications are provided by the clinic.

The clinic is run by Dr. J. Müller vom Hagen, supervised by Prof. L. Schöls.

## 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 colleagues 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). M. Dengler and M. Jeric (study nurses) organize appointments and offer training for injection of interferons and copaxone. Patients interested to take part in clinical trials are interviewed, screened, and recruited after presentation in this clinic. Clinical trials are managed by U. Küstner.

In 2011 the clinic was run by O. Preische and L. Zeltner under the supervision of Prof. A. Melms and PD Dr. F. Bischof.

## 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, 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 dementia 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 such a program is offered.

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 the clinical and imaging studies are a better understanding of the differences/similarities between Alzheimer's disease and dementias associated with parkinsonism. Furthermore, the work focuses on the time course of disease progression and the efficacy of existing and new treatment options.

The Neurologic Memory Clinic is run PD Dr. W. Maetzler and Prof. Dr. D. Berg with support of Neuropsychologist Dr. I. Liepelt.

*Visualization of a DTI measurement of a human brain. Depicted are reconstructed fiber tracts that run through the mid-sagittal plane.*



## NEUROONCOLOGY

This outpatient clinic sees about 180 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 further 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. The outpatient clinic is run by Dr. C. Braun, M. Varga, and M. Wolf and is supervised by Prof. A. Melms.

The neurooncology outpatient clinic is an interdisciplinary clinic of the Center of Neurooncology at the Südwestdeutsche Tumorzentrum/Comprehensive Cancer Center Tübingen. This implies a regular dialogue with colleagues of the Departments of Neurosurgery, Radiooncology, Neuroradiology, Pediatrics and Oncology. Complex diagnostic or therapeutic decisions are routinely discussed by the Brain Tumor Board (Coordination Dr. C. Braun). Since October 2004, the German Cancer Council sponsors clinical neurooncology in Tübingen within the German Glioma Network ([www.gliomnetzwerk.de](http://www.gliomnetzwerk.de)).

M. Jeric and U. Küstner are study nurses involved in the organization of outpatient clinics, multicenter trials and specific training for the patients.

### 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 sensorimotor 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).

### 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 or whether signs of dementia emerge. It is also considered whether a patient 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 Piret Rebassoo, MSc, and supervised by Prof. Dr. Dr. H.-O. Karnath.

### NEUROVASCULAR DISEASES

The neurovascular outpatient clinic provides services for patients with neurovascular diseases including ischemic and hemorrhagic stroke, cerebral and cervical artery stenosis, microvascular disease, cerebral vein thrombosis, vascular malformations, and cerebral vasculitis. Its focus is on diagnosis, discussion and decision about treatments, secondary prevention, and neurorehabilitation strategies and schedules. Diagnostic tests performed as part of an outpatient visit include: duplex ultrasound of cervical and intracranial vessels, electrocardiogram, echocardiogram, and evaluation by a physiotherapist focusing on rehabilitation potentials. Computed tomography and magnetic resonance imaging are carried out in cooperation with the Department of Neuroradiology at the University of Tübingen. The neurovascular service is supervised by Prof. Dr. T. Haarmeier and Dr. J. Erharhagen (cardiologist).



## PARKINSON'S DISEASE

The Center of Neurology at the University of Tübingen runs the largest outpatient clinic for patients with Parkinson syndromes in Southern Germany. More than 120 patients are seen every month. A major focus of the clinic is the early differential diagnosis of different Parkinson 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 Parkinson syndromes who may obtain genetic counseling in cooperation with the Department of Medical Genetics.

The Department of Neurodegeneration is one of the two German centers that participate in the international Parkinson Progression Marker Initiative (PPMI), a 5 years follow-up of de novo Parkinson patients to better understand etiology and disease progression. This study is supported by the Michael J Fox Foundation. Additionally, large scale longitudinal studies are being performed to better understand the different phases of neurodegeneration as well as symptom development and progression to finally enable more specific, individualized therapies.

Another 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 in co-operation with the Ward for Neurodegenerative Diseases 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).

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 the nicotinic acetylcholine receptor (nAChR)  $\alpha 7$  partial agonist AQW051, a new COMT-Inhibitor, an oral neurotrophic factor inducing drug as well as observational studies of different medications. These activities are supported by the study

nurses K. Gauß, C. Haaga, T. König, as well as the documentalist T. Heger. For patients with progressive supranuclear palsy (PSP) an investigator initiated phase 2 open label trial with the cholinesterase inhibitor rivastigmine® is being conducted and a 6 weeks audio-bio-feedback training study with a movement sensor to improve postural control has been successfully completed 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 (Deutsche Parkinson Vereinigung, dPV) are organized. Moreover, visitors from all over the world are trained in the technique of transcranial sonography in regular teaching courses.

Appointments are scheduled daily in the outpatient clinic of the Center of Neurology. Patients are seen by Prof. D. Berg, K. Brockmann; Dr. A. Gaenslen; Dr. J. Godau; Dr. K. Srulijes, Dr. I Wurster as well as the neuropsychologists Dr. I. Liepelt-Scarfone and Dr. S. Gräber-Sultan.





## RESTLESS LEGS SYNDROME

Restless Legs Syndrome (RLS) affects more than 4 million people in Germany. Although RLS is one of the most common neurological disorders, it 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 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 patients' 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).

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. In this context it was found that poor treatment success regarding improvement of RLS symptoms and quality of life is primarily related to the presence of neuropsychiatric comorbidities. This finding has been received internationally with great interest as it directly affects treatment strategies.

Moreover, patients can take part in medical studies. Beyond this, the clinic collects DNA samples from patients with sporadic and familial RLS for genetic analysis.

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



## 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 Neuro-radiology.

Therapeutic options depend essentially on the underlying cause of the disease. Symptomatic treatment options include antispastic drugs, intrathecal application of Baclofen, local injections of Botulinum toxin and functional electrical stimulation.

Tübingen is the German partner in a European network for hereditary spastic paraplegia research (EUROSPA) funded by the EU and the German Ministry of Education and Research (BMBF). This project aims to decipher the genetic causes underlying HSP. In this network the research on autosomal dominant HSP is coordinated in Tübingen.

The clinic is run by Dr. R. Schüle, Dr. K. Karle and Dr. S. Wiethoff and is supervised by Prof. Dr. L. Schöls.

## TREMOR-SYNDROMES

Although essential tremor is with a prevalence of 1 to 5% the most frequent movement disorders, diagnosis and especially differential diagnosis is often challenging. In the outpatient clinic for tremor a thorough standardized assessment battery has been established to facilitate diagnosis and decision for therapeutic strategies. Using this battery specific tremor subgroups have been characterized. Close cooperation with the clinic for DBS (deep brain stimulation, head Prof. R. Krüger) ensures the inclusion of this highly effective treatment option into decision making. Moreover, research on etiology and pathophysiology is pursued in national and international cooperations.

Patients are seen by Dr. I. Wurster and Prof. Dr. D. Berg.





*Subject ready for EEG recording. The typical indications for this procedure are epilepsy, brain tumors, stroke, brain injury, neurodegenerative disorders, and coma or milder forms of altered consciousness.*

### CLINICAL CHEMISTRY LABORATORY

The Clinical Chemistry Laboratory collects more than 1,500 samples of cerebrospinal fluid (CSF) per year throughout the University Medical Center. Routine parameters include cell count, glucose, lactate and protein analysis, i. e., albumin and IgG in serum and CSF. Oligoclonal bands in CSF and serum are detected by isoelectric focusing and silver staining. Cytology of CSF is analyzed on cytopins 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 neuroimmunological syndromes: autoantibodies to acetylcholine receptors, autoantibodies to muscle specific tyrosine kinase (MuSK), autoantibodies associated with neurological paraneoplastic syndromes (Anti-Hu, Anti-Yo, Anti-Ri, and subspecifications), autoantibodies to aquaporin-4, and autoantibodies to gangliosides for immunoneuropathies. Cell populations in CSF and blood samples are examined by cytometry with a FACScalibur. More recently, CSF-levels of amyloid peptide beta42, tau, and phospho-tau are measured to differentiate various forms of dementia.

The laboratory is supervised by Prof. Dr. A. Melms.

### EEG LABORATORY

The electroencephalography (EEG) laboratory is equipped with 4 mobile digital and 2 stationary recording places (IT-Med). For analysis, 6 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. On the neurological intermediate care and 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, coma or milder forms of altered consciousness, and the differential diagnoses of brain tumors, stroke, brain injury, and neurodegenerative disorders. EEG training is conducted according to the guidelines of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN). The EEG training course lasts for 6 months and is provided for 4 neurological residents at a time. Laboratory staff: B. Wörner, M. Harder and R. Mahle (staff technicians); PD Dr. Y. Weber (head of the laboratory).



## EMG 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 (Dantec Keypoint G4). 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 2011, more than 3,000 patients were seen and more than 20,000 recordings were done. In most cases (approximate 70%), a combination of neurography and electromyography is requested. In addition, a Neurosoft Evidence 9000MS stimulator is available for transcortical magnetic stimulation and recording of motor cortex-evoked potentials in approximately 800 patients per year.



*Transcranial magnetic stimulation for testing integrity of the central motor system*

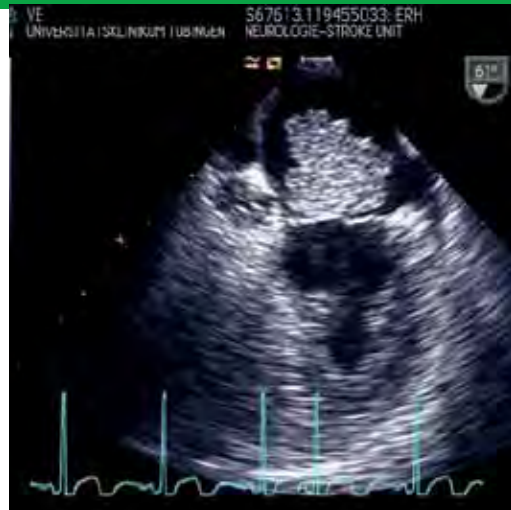
The EMG Laboratory is organized by Mrs. J. Grimm who also performs nerve conduction studies with surface electrodes. In 2011, the EMG Laboratory was run by Dr. B. Liske under the guidance of Prof. Dr. T. Haar-meier, Prof. Dr. A. Melms and Dr. C. Frischholz.

## ENG LABORATORY

Approximately 250 patients suffering from otoneurological or neuro-ophthalmological problems are examined each year using electronystagmography (ENG) and a variety of complementary techniques. 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 offline. 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 vestibuloocular (VOR) reflex (caloric and rotation tests).

The recordings are performed by C. Friedrich and analyzed by Dr. J. Pomper and L. Schwendemann. 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 (Chronos) and performs otolith testing such as the measurement of the subjective visual vertical and vestibular evoked myogenic potentials (VEMP). The laboratory is supervised by L. Schwendemann and Dr. J. Pomper.

*Transesophageal echocardiogram (TEE) showing a left atrial myxoma protruding through the mitral valves in a young patient with multiple embolic strokes*



## 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 A. Deutsch and J. Grimm who are supervised by Prof. Dr. T. Haarmeier and PD Dr. F. Bischof. 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 the clinic who attend for at least one year, colleagues from the Departments of Neurosurgery and Neuropediatrics make use of this continuing training.

## NEUROCARDIOLOGY LABORATORY

Cardiovascular and cerebrovascular diseases represent the leading causes of death in the Western industrialized world. This is mainly due to ischemic heart disease. The Dutch TIA Study demonstrated that patients with a transitory ischemic attack (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 up to 25% of all strokes and usually cause territorial apoplexies. After an acute stroke, cardiac investigations are urgently required to find potential cardiac causes, in order to reduce the risk of stroke recurrence within days or weeks after the first stroke.

At the University Hospital there is a department with its own neurocardiology laboratory, headed by cardiologist Dr. J. Erharhagen. 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 color coded Doppler and duplex investigation of the extracranial as well as intracranial vessels. This allows to perform bedside vascular investigations and echocardiography of stroke patients on the 13-Bed ICU and Stroke Unit immediately after diagnosis.

Yearly, we conduct approximately 1,000 echocardiographic examinations, 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. Younger patients are regularly examined 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 Societies 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 the stroke unit, there is a completely equipped long term registration unit consisting of 24-hour ECG (Holter ECG), 24-hour ambulatory blood pressure measurement, and in cooperation with the cardiology unit of the department of internal medicine, 7-day event recorders and implantable event recorders. Yearly, well over 900 24-hour (Holter) ECGs and 700 24-hour ambulatory blood pressure measurements are recorded. In order to find the underlying causes of syncope, tilt table investigations are conducted. To identify a hypersensitive carotid bulb, carotid pressure testing is performed.



*Transcranial B-mode sonography procedure: The probe is placed at the temporal bone window in a patient in supine position to assess the brain in standardized scanning planes.*

## NEUROSONOLOGY AND ECHOCARDIOGRAPHY LABORATORY

The ultrasound laboratory is equipped with a Toshiba Aplio 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 without contrast). Functional testing for vertebral steal, persistent foramen ovale, and cerebral microembolism (HITS) are routinely performed.

The laboratory consists of a unit in the neurology outpatient department focusing mainly on neurosonology of extracranial and intracranial arteries. The ultrasound unit in close proximity to the stroke unit is run by Dr. Erharhaghen, a cardiologist and intensive care specialist who performs 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, approximately 4,000 examinations of extracranial arteries and approximately 3,000 transcranial Doppler or color-coded Duplex exams are conducted

in the laboratory. Dr. Erharhaghen performs approximately 1,000 transthoracic and 200 transesophageal echocardiographies each year.

## 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 and far beyond 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 attended by medical doctors and scientists from all over the world are continuously overbooked. Meanwhile the method is being applied in many countries on all continents.

### OCCUPATIONAL THERAPY

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 2011, approximately 859 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.

### PHYSIOTHERAPY

All neurological inpatients with sensory or motor deficits, movement disorders, pain syndromes, and degenerative spinal column disease are allocated to individualized physiotherapy. Currently 10 physiotherapists are working within the "TherapieZentrum" responsible for the neurological wards.

The physiotherapist treatment is based on guidelines which had been worked out for special disease groups according to the current knowledge. This includes for example lumbar disc prolaps, stroke, ataxia, Parkinson's disease.

Within the year 2011 approximately 2,207 patients were seen.



*Fiberoptic endoscopic evaluation of swallowing (FEES) of a patient with dysphagia*

### SPEECH THERAPY

Neurological patients with swallowing and speech-/language disorders receive speech therapy while staying in hospital.

The emphasis within the team of five speech therapists is the treatment of patients with dysphagia (approximately 940 patients in 2011).

Every acute stroke patient receives a bedside and, if necessary, a videoendoscopic or videofluoroscopic swallowing examination. Therefore dysphagia can be recognized at an early stage, an aspiration pneumonia can be prevented and a specific therapy can be planned for every individual patient.

Every acute stroke patient also receives a bedside speech- and language examination. Additionally, in 2011 approximately 404 patients with aphasia and dysarthria received an intensive speech- and language treatment. The aim of the speech therapy with these patients is to improve their communication ability.

*Stair climbing with the physiotherapist*



# HERTIE-INSTITUTE FOR CLINICAL BRAIN RESEARCH

General Neurology  
Neurology and Epileptology  
Neurodegenerative Diseases  
Cognitive Neurology  
Cellular Neurology  
Independent Research Groups



## THE HERTIE-INSTITUTE FOR CLINICAL BRAIN RESEARCH (HIH)

In less than 10 years of its existence, the Hertie-Institute has grown to more than 200 scientists of all levels, from PhD students to full professors. Outstanding achievements of the institute are discoveries related to the molecular, genetic and physiological basis of a number of major neurologic diseases.

The institute presently consists of four clinical and one basic science department: the Departments for General Neurology, for Epileptology, for Neurodegenerative Disorders and for Cognitive Neurology all share inpatient related research as well as patient care, while the Department of Cellular Neurology is a pure basic science department, focusing on Alzheimer's disease.

The institute is home to a total of 25 research groups, 22 of them within the aforementioned departments, three as junior research groups. The first of these independent groups, which has been established in 2006, has just successfully passed its evaluation by the scientific advisory board of the Hertie-Institute and has been promoted from a "junior" to "independent" group status. The second group established in 2008 was also successfully evaluated and will be continued.

In 2010, scientists at the Center of Neurology have obtained more than 4.8 million Euro in third party funding and have published 175 papers in peer reviewed journals.

The new Department of Neurology with focus on Epileptology has started operations in November 2009 and has quickly become a visible component of the center. It attracts

a growing number of in- and outpatients with paroxysmal neurological disorders, in particular those with difficult to treat epilepsies, but also pain and muscle disorders. An electroencephalography (EEG) -monitoring unit for presurgical work-up of pharmacoresistant epilepsies and differential diagnosis of episodic disorders has been successfully established. The unit is run in close cooperation with the neurosurgery department. The research is focused on the genetics, pharmacogenetics and pathophysiological mechanisms of epilepsies and related disorders.

The new head of the Department for Neurovascular Diseases (previously Department of General Neurology) will join the institute in spring 2012. The Department for Neurovascular Diseases runs the large stroke unit of the University Hospital. As a primary care institution, all clinical departments together treat patients with the complete spectrum of neurological diseases.

Dr. Astrid Proksch has become the new managing director of the Hertie-Institute in spring 2011. To celebrate the 10<sup>th</sup> anniversary more than 800 guests joined the anniversary lecture held by Nobel laureate Prof. Dr. Eric R. Kandel together with his wife Prof. Dr. Denise B. Kandel. Scientifically the anniversary was celebrated with an international symposium on "Perspectives in Brain Research". This symposium was intended to discuss a wide range of exciting and timely topics of the neurosciences.

The new research building for the "Werner Reichardt Centre for Integrative Neuroscience (CIN)" on the Schnarrenberg neuroscience campus, which will also house HIH groups, has nearly been completed. 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 (DZNE) within the Helmholtz Association. All these developments will ensure the long term success of the neuroscience community in Tübingen.

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





## DAS HERTIE-INSTITUT FÜR KLINISCHE HIRNFORSCHUNG (HIH)

### DAS HERTIE-INSTITUT FÜR KLINISCHE HIRNFORSCHUNG (HIH)

Zehn Jahre nach seiner Gründung durch die Gemeinnützige Hertie-Stiftung, die Universität Tübingen und das Universitätsklinikum Tübingen gehört das HIH auf dem Gebiet der klinischen Hirnforschung zum Spitzenfeld europäischer Forschungseinrichtungen. Herausragende Forschungsergebnisse haben das Institut auch über die Grenzen Europas hinaus bekannt gemacht. Seine Arbeitsschwerpunkte liegen im Bereich neurodegenerativer und entzündlicher Hirnerkrankungen, der Schlaganfallforschung, Epilepsien und der Erforschung der Grundlagen und Störungen von Wahrnehmung, Motorik und Lernen. Zu den bedeutenden Forschungserfolgen des HIH zählen die Entdeckung wichtiger genetischer und molekularer Grundlagen der Entstehung und Progression neurologischer Erkrankungen.

In den Abteilungen sind zurzeit 18 Professoren und etwa 350 Mitarbeiter in 25 Arbeitsgruppen tätig. Die Gemeinnützige Hertie-Stiftung wendete bisher rund 30 Millionen Euro für das HIH auf und wird ihre Förderung fortsetzen.

Im November 2009 hat die neue Abteilung mit dem Schwerpunkt Epileptologie ihre Arbeit aufgenommen und sich in kurzer Zeit zu einer wichtigen Komponente des Zentrums entwickelt. So wird von den dort tätigen Ärzten beispielsweise in Kooperation mit der neurochirurgischen Klinik eine Video-EEG-Monitoring Einheit betrieben, in der bei Patienten gleichzeitig und kontinuierlich ein

Video und die Hirnströme aufgezeichnet werden. Die Forschungsschwerpunkte der Abteilung sind die Genetik und Pathophysiologie erblicher Epilepsiesyndrome und verwandter neurologischer Erkrankungen.

Im Frühjahr 2012 wird der neue Leiter der Abteilung Vaskuläre Neurologie (bisher Abteilung für Allgemeine Neurologie) seine Arbeit aufnehmen. Die Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen betreibt die große Schlaganfallstation der Klinik. Als Einrichtungen der Primärversorgung versorgen alle Abteilungen zusammen Patienten aus dem gesamten Spektrum neurologischer Erkrankungen. Dr. Astrid Proksch übernahm im Frühjahr 2011 die Geschäftsführung des Hertie-Instituts.

Im Oktober 2011 kamen 800 Gäste aus Wissenschaft und Politik anlässlich des zehnjährigen Bestehens des HIH zur Festveranstaltung in die Universität Tübingen. Den Festvortrag hielt Medizin-Nobelpreisträger Prof. Dr. Eric R. Kandel gemeinsam mit seiner Frau Prof. Dr. Denise B. Kandel. Im Rahmen dieser Feierlichkeiten öffnet das Hertie-Institut für klinische Hirnforschung seine Türen für die Öffentlichkeit: Wissenschaftler stellten aktuelle Forschungsergebnisse vor und führten durch die Labore. Außerdem fanden Vorträge über neue Entwicklungen aus Forschung und Therapie zu den Krankheiten Multiple Sklerose, Alzheimer, Epilepsie und Parkinson statt. Der Tag der offenen Tür wurde außerordentlich gut von der breiten Öffentlichkeit angenommen.

Wissenschaftlich wurden die „Zehn Jahre HIH“ auch in einem Symposium zu Perspektiven der Hirnforschung gewürdigt. Weltweit



Celebrating the 10<sup>th</sup> anniversary of the Hertie-Institute in a select company: Dr. Michael Endres, Director of the Hertie-Foundation, with Nobel laureate Prof. Dr. Eric R. Kandel, his wife Prof. Dr. Denise B. Kandel, Prof. Bernd Engler, President of Tübingen University, and Prof. Michael Bamberg, Chairman of the Board of the University Hospital.



*The Parkinson Laboratory at the Hertie-Institute for Clinical Brain Research in Tübingen: Fragmented DNA material is analyzed by electrophoretic means.*

*renommierte Neurowissenschaftler kamen zu einer Diskussion über die neuesten Entwicklungen und Forschungsrichtungen zusammen.*

*Das HIH, ein Modellprojekt für Public Private Partnership, hat auch im Jahr 2011 mehr als 4,8 Millionen Euro an Drittmitteln eingeworben und 175 Veröffentlichungen in wissenschaftlichen Fachzeitschriften publiziert. Diese Zahlen belegen u. a. die wissenschaftliche Leistungsfähigkeit des Zentrums. Die wichtige Rolle, die das HIH im Leben der Universität Tübingen spielt, wurde auch durch die intensive Beteiligung am Konzept der Universität im Exzellenz-Wettbewerb deutlich.*

*Auch strukturell geht das HIH neue Wege. Die Reformansätze gelten vor allem drei Schwerpunkten: Die Einrichtung einer Department-Struktur, die Einrichtung eines Pools von flexibel und kurzfristig einsetzbaren Fördermitteln und der Aufbau eines Modells für einen leistungsabhängigen Gehaltszuschlag für alle Mitarbeiter. 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 und 2010 aufbauend*

*auf einer erfolgreichen internationalen Evaluierung in eine selbständige Arbeitsgruppe umgewandelt. Die zweite Gruppe mit Fokus auf der Untersuchung synaptischer Plastizität im Drosophila-Modell wurde Ende 2008 etabliert und im Rahmen einer internationalen Evaluation 2011 verlängert.*

*Eine besondere Bedeutung für die Zukunft des Zentrums kommt auch seiner Beteiligung an der erfolgreichen Bewerbung von Tübingen als Partnerstandort des „Deutschen Zentrums für Neurodegenerative Erkrankungen, DZNE“ zu. Die Etablierung dieses Partnerstandortes ermöglicht die langfristige Sicherung von Forschungsmitteln und führt zu einer erheblichen Stärkung des neurowissenschaftlichen Standorts.*

*Nach einer dreijährigen Bauphase konnte Ende 2011 der Neubau des Werner-Reichardt Zentrums für Integrative Neurowissenschaften (CIN), das direkt gegenüber dem HIH liegt, weitgehend fertig gestellt werden. Auch Forschungsgruppen des HIH werden in diesem Forschungsbau ihre Arbeit aufnehmen.*

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



**DEPARTMENT OF  
GENERAL NEUROLOGY**





## DEPARTMENTAL STRUCTURE

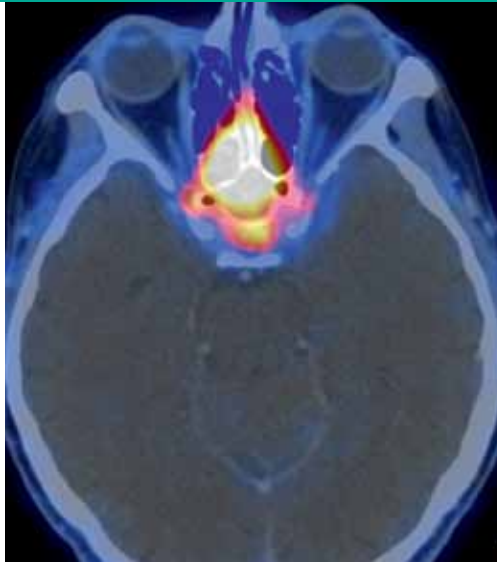
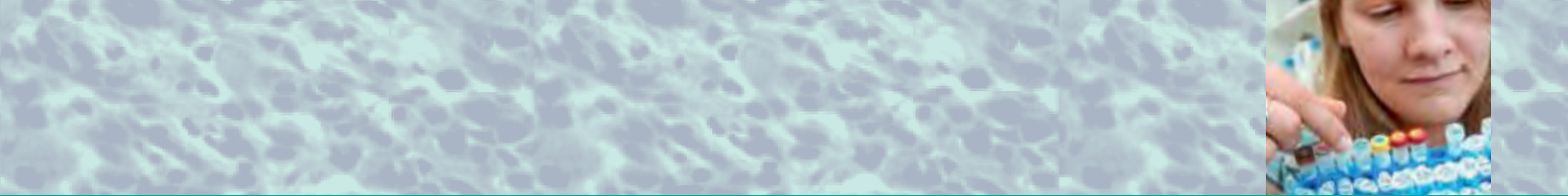


*Prof. Dr. Arthur Melms is head of the Department of General Neurology*

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 neighboring countries according to the clinical and scientific expertise of the Department, including complex cerebrovascular diseases (ischemia, intracranial hemorrhage, vasculitis, vascular malformations), neuroimmunology (multiple sclerosis, myasthenia gravis and others), and brain tumors. Specialized teams in neurooncology and stroke medicine (stroke unit and rehabilitation) provide expert multidisciplinary care for patient with these disorders. As an integral part of the Comprehensive Cancer Center (CCC), the Center of Neurooncology is formed by the Departments of Neurology, Neurosurgery, Radiooncology, Neuroradiology and Brain Pathology.

The aim of the 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. Renowned research groups are active in neuroimmunology (Prof. Dr. Arthur Melms), neurooncology (PD Dr. Ulrike Naumann), neurophysiology of perception (Prof. Thomas Haarmeier) and speech disorders (Prof. Dr. Hermann Ackermann). 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.



*Meningioma of a 70 year old patient, visualized by PET/CT, a combination of positron emission tomography and computer tomography.*

The Department of General Neurology offers lectures for medical students, physicians in training, nursing staff, physiotherapists 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, inter-

nal medicine, neurosurgery, neuroophthalmology, neuroradiology and other areas relevant to the treatment of patients with neurological diseases. The lectures of basic and clinical neurology, the seminar on neurology, the training course on neurological examination skills are an integral part of the Medical School curriculum and are usually honored by the evaluation of the students.



## NEUROIMMUNOLOGY

**Head:** Prof. Dr. Arthur Melms

**Team:** 5 members

**Key words:** neuroimmunology  
myasthenia gravis  
multiple sclerosis  
neuromyelitis optica  
regulatory T cells, T<sub>regs</sub>  
antigen presentation

[www.hih-tuebingen.de/neuro-immunologie/](http://www.hih-tuebingen.de/neuro-immunologie/)

*We investigate T and B cell biology in diseases like multiple sclerosis (MS), neuromyelitis optica and myasthenia gravis (MG). These neuroimmunological diseases are mediated by autoreactive T and B lymphocytes. The prerequisites for an autoimmune response are the failure of tolerance mechanisms and the display of epitopes recognised by autoreactive T cells in a non-tolerogenic context. In the case of autoreactive T cells some autoantigens can be detected not only in patients but also in healthy subjects. This shows that central tolerance is not perfect, underscoring the importance of peripheral tolerance mechanisms such as regulatory T cells (T<sub>regs</sub>). The comparison of the suppressive capability of T<sub>regs</sub> in MS and MG patients with that in healthy individuals revealed an impairment of T<sub>regs</sub> in the patient group. Understanding the loss of T<sub>reg</sub> function might be a first step in developing new therapeutic approaches against neuroimmunological diseases.*

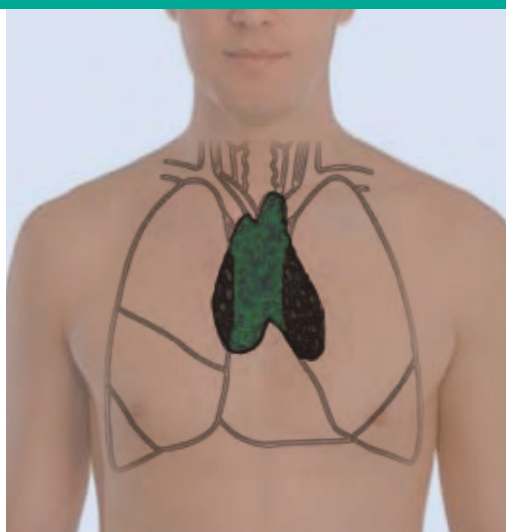
*Wir beschäftigen uns mit Krankheiten wie der Multiplen Sklerose, der Neuromyelitis optica und der Myasthenia gravis. Diese neuroimmunologischen Erkrankungen werden durch T- und B-Lymphozyten hervorgerufen, die die körpereigenen Nervenstrukturen angreifen. Diese Immunzellen kommen im Abwehrsystem jedes Individuums vor, befinden sich aber normalerweise in einem nicht-aktivierten Zustand. Ein wichtiges Instrument zur Unterdrückung unerwünschter Immunreaktionen sind regulatorische T-Lymphozyten (T<sub>regs</sub>), die sich aufgrund bestimmter Oberflächenmerkmale von anderen Lymphozytenarten unterscheiden lassen. Der Vergleich regulatorischer T-Lymphozyten von gesunden Probanden und Patienten mit Multipler Sklerose oder Myasthenia gravis ergab, dass T<sub>regs</sub> bei beiden Gruppen zwar in ähnlicher Häufigkeit vorkommen, aber bei Patienten mit neuroimmunologischen Krankheiten eine Funktionsstörung aufweisen. Verlaufsuntersuchungen zeigten, dass dieses Defizit durch eine Immuntherapie teilweise korrigiert werden kann. Die Aufklärung dieser Funktionsstörung sollte es ermöglichen, neue Behandlungsansätze für neuroimmunologische Erkrankungen zu entwickeln.*

One of our research focuses, in recent years, deals with different aspects of thymic and peripheral antigen processing and presentation, especially with respect to the role of lysosomal proteases like the cathepsins (Cat) and asparagine endopeptidase (AEP). The action of lysosomal proteases is required for releasing T cell epitopes from proteins processed in the MHC II pathway. Earlier studies from our group revealed different signatures of lysosomal proteases in primary dendritic cells, monocytes, B lymphocytes, thymic epithelial cells, and myoblasts.

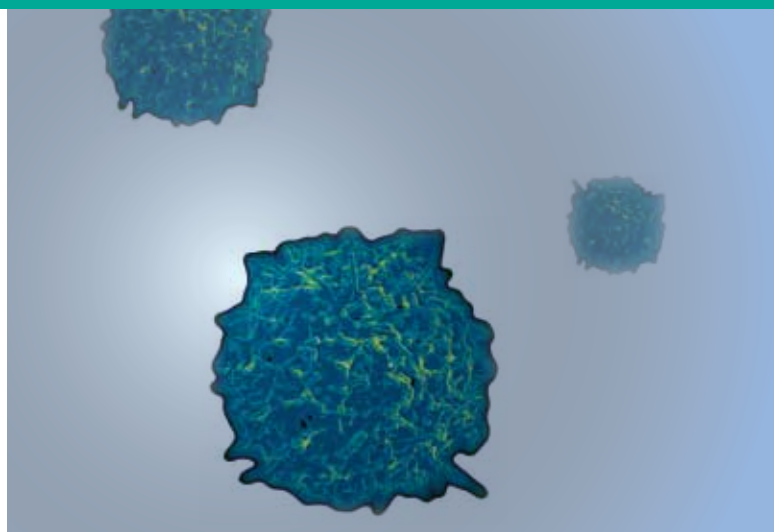
In the context of myasthenia gravis, we found selective overexpression of Cat V in thymic tissue. These findings suggested that skewed T cell selection due to altered antigen processing in the thymic APC might promote the development of this autoimmune disease. Knowing how thymic APC handle proteins to create the self-peptide matrix on which T cells are selected, is crucial for understanding the mechanisms underlying self-tolerance and autoimmunity. Extending these earlier findings, we determined the expression and localization of proteases known to be involved in antigen processing in the human thymus.

We have established a method to isolate different APC subsets and different approaches including RT-PCR, active site labeling, in vitro digests with lysosomal extracts are used to study the MHC II antigen processing machinery and autoantigen processing in the human thymus. We find that each type of thymic APC expresses a different signature of lysosomal proteases, providing indirect evidence that positive and negative selection of CD4<sup>+</sup> T cells might occur on different sets of peptides. Modulation of antigen processing may offer a novel approach to interfere with the activation of autoimmune T lymphocytes.

Currently, we have expanded this topic with a project aiming to explore the human thymus MHC peptide ligandome. Until today, direct evidence on the naturally presented peptides, derived from self-proteins that actually contribute to negative selection of thymocytes under physiological conditions in the human is missing. To this end,



Anatomic position of the human thymus (black/green). Self tolerance and autoimmunity are dependent on a complex selection process in this organ.



Human T lymphocytes

the most direct approach is the elution of peptides from isolated thymic APC and their characterisation by mass spectrometry. We have been successful in sequencing MHC class I- and MHC class II-bound peptides from ex vivo isolated thymic CD11c+ DC as well as non-DC APCs from healthy donors. Insight into the natural peptide repertoire will pave the way for a comprehensive understanding of the regulation of self-tolerance and could lead to better design of therapeutic interventions.

Our second field of interest is  $T_{reg}$  cells, a particular subset of T cells with the ability to suppress unwanted immune reactions. A loss of  $T_{regs}$  is usually associated with complex autoimmune syndromes. We have shown that the peripheral frequency of  $T_{reg}$  cells in MG patients is unaltered when compared with age-matched healthy donors. However, we have more recently demonstrated that the suppressive capability of peripheral blood  $T_{reg}$  in untreated MG patients is profoundly impaired. This has also been observed in patients with MS, suggesting a more common dysfunction in autoimmune diseases. Immunosuppressive treatment with prednisolone showed a considerable improvement of  $T_{reg}$  cell function in MG patients. At present we are trying to understand whether signals involved in the tuning of  $T_{regs}$  can be exploited to develop new tools for cell therapy in autoimmune diseases.

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**MOLECULAR NEURO-ONCOLOGY****Head:** PD Dr. Ulrike Naumann**Team:** 5 members**Key words:** brain tumor  
glioblastoma  
virotherapy  
gene therapy[www.hih-tuebingen.de/neuro-onkologie](http://www.hih-tuebingen.de/neuro-onkologie)

*The Research Group Molecular Neuro-Oncology investigates various aspects of the biology of glioblastomas (GBM), the most frequent and lethal human brain tumor. Characteristics of this tumor are its rapid, destructive and invasive growth into the healthy brain, its capability to suppress immune cells to attack the tumor as well as its resistance to chemotherapeutic drugs and radiation therapy. To know the biology of GBM in detail is important for the development of novel therapeutic strategies. We examine the effects of natural substances, "small molecule" inhibitors, secreted cellular factors and so called "oncolytic" viruses.*

*Die Arbeitsgruppe für Molekulare Neuro-Onkologie befasst sich mit Fragestellungen zur Tumorbiologie des Glioblastoms (GBM), dem häufigsten und bösartigsten Hirntumor des Menschen mit einer mittleren Überlebenszeit von nur 12 bis 15 Monaten. Die Bösartigkeit dieser Tumorart basiert darauf, dass GBM schnell und invasiv in gesundes Hirngewebe einwachsen; nach operativer Entfernung können Sekundärtumoren innerhalb kurzer Zeit sogar in der bislang gesunden Gehirnhälfte entstehen. Glioblastome hindern zudem Immunzellen daran, Krebszellen zu attackieren, und sind größtenteils resistent gegenüber Standardtherapien wie Bestrahlung oder Chemotherapie. Die Biologie des GBM zu kennen ist deshalb die Grundvoraussetzung, um neue Behandlungsverfahren entwickeln zu können. Wir arbeiten daran, das invasive Wachstum von GBM-Zellen zu verhindern, und versuchen Tumorzellen wieder für Standard-Therapieansätze zu sensibilisieren. Zudem beschäftigen wir uns mit der Entwicklung von „onkolytischen“ Adenoviren, die für die GBM-Therapie eingesetzt werden können.*

Glioblastoma (GBM) is the most common and lethal brain neoplasm with a median patient survival after standard therapy of 12 to 15 month. Only few therapeutic regimens provide a short increase in survival. The failure of effective therapy regimens is associated with the GBM malignant characteristics meaning that GBM are mainly cell death resistant, possess immunosuppressive function and show a highly invasive and migratory growth. We set our research to get more information concerning the immunology, the molecular and cell biology of GBM. To know the biology of GBM in detail is important for the development of novel therapeutic strategies, a second section of our research.

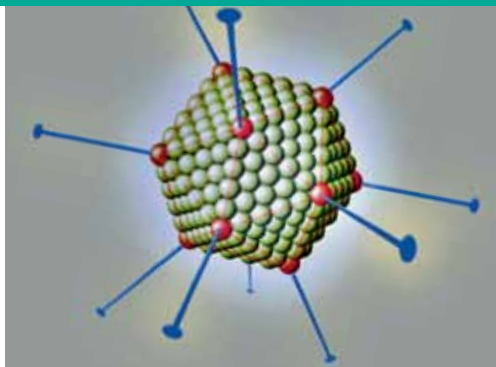
Drivers of GBM motility include cytokines, protein modifiers altering the extracellular matrix, cytoskeleton members and regulators of adhesion. Inhibiting migration by novel therapeutic strategies might therefore be an important treatment strategy for GBM. In collaboration with Prof. Mittelbronn (Frankfurt) we have shown that the neuropeptide processor carboxypeptidase E (CPE) plays a central role in tumor cell motility. Reduced CPE in a cell death resistant GBM cell line and lower CPE expression levels in a cohort of GBM samples compared to healthy brain prompted us to analyze the function of CPE as a putative tumor suppressor. Indeed, CPE loss was associated with worse prognosis. CPE expression reduced, whereas inhibition enhanced GBM cell motility. Decreased migration following CPE expression was paralleled by altered cellular morphology, promoting more stable adhesion contact sites to the ECM. Our findings indicate an anti-migratory role of CPE in GBM with prognostic impact for patient survival.

Mithramycin A (MitA) is used in the therapy of several cancers. In experimental tumors, MitA mediates the expression of genes involved in tumor progression, immunosurveillance, cell motility and cell death. In GBM cells, MitA reduced the secretion and activity of migration-involved genes, paralleled by a significant reduction of GBM cell migration. MitA, besides killing GBM cells, might also reduce the migration of residual cells and, in consequence, suppress or delay GBM recurrence. For this, MitA might be a hopeful agent for GBM treatment.





Extracts from the mistletoe plant reduce tumor growth in mice.



In mice, the oncolytic adenovirus Ad-Delo3-RGD is capable of inducing death of glioblastoma cells.

In Europe, cancer patients widely use mistletoe extracts such as ISCADOR Q for complementary cancer therapy. We could demonstrate that ISCADOR Q enforces immune cells to attack and to kill GBM cells. Beside its immune stimulatory effect, ISCADOR mitigated GBM cell motility, paralleled by decreased expression of genes known to push and by enhanced expression of genes known to delimitate cancer progression. Treatment of GBM with ISCADOR Q also delayed tumor growth in mice. ISCADOR Q, showing multiple positive effects in the treatment of GBM, may therefore hold promise for concomitant treatment of human GBM.

The tumor suppressor p53 is inactive in more than 50% of all human tumors, including GBM. We have explored the therapeutic potency of a synthetic, p53-based chimeric protein named CTS-1. CTS-1 expression induced growth arrest and cell death in cancer cell lines. Modulation of gene expression is responsible for the antitumor properties of CTS-1. Interestingly, NFκB activation was mandatory for Ad-CTS-1 induced cell death. Our results were in contrast to other groups who demonstrated that activation of NFκB protected GBM cells. This has important implications for the role of NFκB as a player involved in tumor progression and should also be kept in mind when using NFκB-specific inhibitors in the therapy of cancer, especially in the therapy of GBM.

Oncolytic adenoviruses (OAV) that replicate selectively in tumor cells and not in normal cells are used as agents to fight cancer. These viruses have displayed potential to efficiently kill not only cancer cells, but also cancer stem cells. In collaboration with

Dr. Holm (TU Munich) we have analyzed the antitumoral effects of an OAV. We have demonstrated that *in vitro* OAV works synergistically with the GBM standard chemotherapeutic temozolomide (TMZ). *In vivo* in a mouse model using highly resistant GBM stem cells, intratumoral injection of OAV induced tumor lysis and prolonged survival of tumor bearing mice.

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## NEUROPHONETICS

**Head:** Prof. Dr. Hermann Ackermann

**Team:** 6 members

**Key words:** speech production and perception  
neurobiology of language  
acoustic communication

[www.hih-tuebingen.de/neurophonetik](http://www.hih-tuebingen.de/neurophonetik)

*The neurophonetics-group investigates the neural bases of speech communication – an unique capability of our species – based upon psycholinguistic methods and functional-imaging technology.*

*Die Arbeitsgruppe untersucht die neurobiologischen Grundlagen von Sprechmotorik und Sprachwahrnehmung insbesondere unter Verwendung funktionell-bildgebender Methoden.*

### Blind subjects deploy visual cortex in order to better understand spoken language \*

Blind individuals may learn to comprehend ultra-fast synthetic speech at a rate of up to about 22 syllables per second (syl/s), exceeding by far the maximum performance level of normal-sighted listeners (8-10 syl/s). Using functional magnetic resonance imaging (fMRI), we were able to demonstrate for the first time that this exceptional skill correlates significantly with hemodynamic activation of several components of the central-visual system, including right-hemisphere primary visual cortex (V1) (Hertrich et al. 2009, Dietrich et al., submitted).



*Whole-head fMRI analyses (14 blind, 12 sighted subjects) revealed activation clusters in right-hemisphere primary-visual cortex (V1), left fusiform gyrus (FG), bilateral pulvinar (Pv) – not visible – and supplementary motor area (SMA), in addition to perisylvian “language zones”.*

Magnetoencephalography (MEG) could further corroborate the suggestion of a crucial contribution of right-hemisphere V1 to this perceptual skill: cross-correlation analyses (see Hertrich et al. 2012) revealed enhanced phase-locking of MEG signals to syllable onsets during comprehension of ultra-fast speech in blind subjects (Hertrich et al., submitted).

### Speech motor deficits in disorders of the cerebellum

Cerebellar disorders may give rise to a distinct syndrome of speech motor deficits, called ataxic dysarthria. In cooperation with L. Schöls, M. Synofzik and T. Lindig, Center for Neurology, University of Tuebingen, we try to clarify whether the syndrome of ataxic dysarthria separates into various subtypes, depending upon which component of the



cerebellum is predominantly compromised. Patients with Friedreich ataxia or spinocerebellar ataxia (SCA3, SCA6) have been analyzed so far. Reduced speaking rate and voice irregularities were found specifically related to ataxia in other domains (Brendel et al., submitted). In SCA-patients, by contrast, articulatory problems emerged as a predictor for ataxia severity.

### An evolutionary perspective on spoken language: vocal continuity between non-human and human primates \*\*

Any account of what is special about the human brain must specify the neural bases of our unique trait of articulate speech – and the evolution of these remarkable skills in the first place. Analyses of the disorders of acoustic communication following cerebral lesions/diseases as well as functional imaging studies in healthy subjects throw – together with paleoanthropological data – some light on the phylogenetic emergence of spoken language, pointing at a two-stage model of the evolution of articulate speech:

- (i) monosynaptic refinement of the projections of motor cortex to the brainstem nuclei steering laryngeal muscles (brain size-associated phylogenetic trend), and a
- (ii) subsequent “vocal-laryngeal elaboration” of cortico-basal ganglia circuitries, driven by human-specific FOXP2 mutations.

A more extensive representation of laryngeal muscles within the basal ganglia should have allowed for the deployment of the vocal folds – beyond sound generation (“voice box”) – as an “articulatory organ” which can be pieced together with orofacial gestures into holistic “motor plans”, controlling syllable-sized movement sequences. Among other things, this concept

- (i) elucidates the deep entrenchment of articulate speech into a nonverbal matrix of vocal affect expression (emotive prosody) which “gestural-origin theories” fail to account for, and

- (ii) points at age-dependent interactions between the basal ganglia and their cortical targets similar to vocal learning in songbirds.

Thus, the emergence of articulate speech – often considered a sign of human superiority within the animal kingdom – appears to have involved the “renaissance” of an ancestral organizational principle (“evolutionary tinkering”) (Ackermann H, Hage SR, Ziegler W. Brain mechanisms of acoustic communication in humans and nonhuman primates: An evolutionary perspective, submitted).

\* cooperation with E. Zrenner and A. Bernd, Center for Ophthalmology, University of Tuebingen

\*\* cooperation with S. Hage, Department of Biology, University of Tuebingen, and W. Ziegler, Clinical Neuropsychology Research Group, Munich

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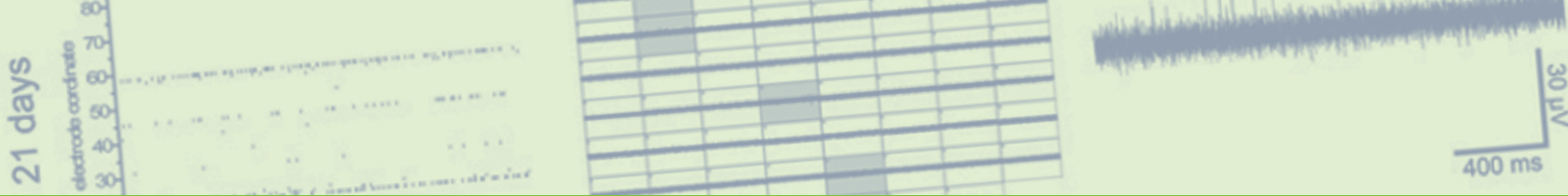
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**Hertie Institute**  
for Clinical Brain Research

**DEPARTMENT OF  
NEUROLOGY AND EPILEPTOLOGY**





## DEPARTMENTAL STRUCTURE



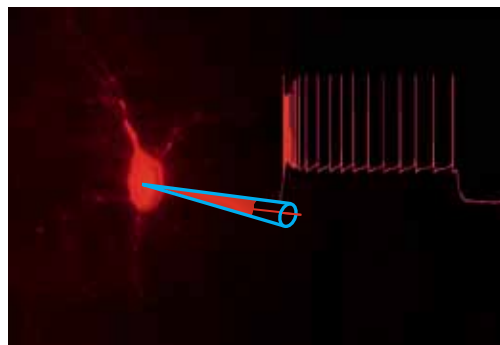
*Prof. Dr. Holger Lerche heads the Department of Neurology and Epileptology*

The Department of Epileptology was founded with the generous support of the Charitable Hertie Foundation and started its activities in November 2009. As part of the Center of Neurology and together with the other Neurological Departments, the Department of Epileptology is responsible for the clinical care of all neurological patients at the University Clinic Tübingen. A team of nurses, therapists and physicians trained for neurological disorders is available for the inpatient and outpatient clinics. The initial operations of the department have been focusing on establishing an effective structure to successfully support basic and clinical research in the field of epileptology and associated paroxysmal neurological disorders and provide excellence in patient care.

The clinic offers the whole spectrum of modern diagnostic and therapeutic procedures. The inpatient unit with 19 beds (Wards 41 and 42), running under the supervision of PD Dr. Y. Weber and PD Dr. M. Dihné, includes acute care for epileptic seizures and status epilepticus, longterm complex treatment for difficult cases, and a Video-EEG-Monitoring Unit which is operated in cooperation with the Department of Neurosurgery. Within this unit, inpatients are continuously and simultaneously monitored with video and electroencephalography (EEG) for differential diagnostic and presurgical evaluations. Epilepsy

surgery, an effective treatment for patients resistant to anticonvulsive medication, deep brain stimulation of the thalamus and vagal nerve stimulation are provided in close cooperation with the Department of Neurosurgery (Dr. S. Rona, Prof. Dr. J. Honegger, Prof. Dr. A. Garabaghi). The epilepsy outpatient clinic (Prof. Dr. H. Lerche and PD Dr. Y. Weber) offers consulting and treatment in particular for difficult cases and specific questions including pregnancy under antiepileptic treatment and genetic aspects. Other outpatient clinics are focused on headache and neuropathic pain (PD Dr. S. Schuh-Hofer and PD Dr. T. Schmidt-Wilcke), on neuromuscular diseases (PD Dr. T. Schmidt-Wilcke), and genetically determined paroxysmal neurological and ion channel disorders (Prof. Dr. H. Lerche and PD Dr. Y. Weber). Specific genetic diagnostic testing using parallel next generation sequencing of all known epilepsy genes in one step (also available for other neurological disorders) has been established together with PD Dr. S. Biskup who founded the company CEGAT in Tübingen.

The department's study center has been involved in diverse medical trials to explore novel treatment options. The department supports the medical and neuroscientific education at the University of Tübingen by providing a comprehensive offer of lectures, seminars and courses.



For electrophysiological recordings of neuronal activity in brain slices, a glass micropipette with a very fine tip (left page) is brought in tight contact with a neuronal cell under microscopic control (this page, left). Recorded neurons are labelled with fluorescent dyes (red) to identify them after recordings; the picture shows a collage with a symbolized pipette and an original recording of a series of action potentials (this page, right).

The department stimulates synergies between physicians in the Neurological Clinic and basic research groups in the Hertie-Institute with the aim to work on clinically driven basic research questions and rapidly transfer scientific progress into clinical practice. Our main research topics are

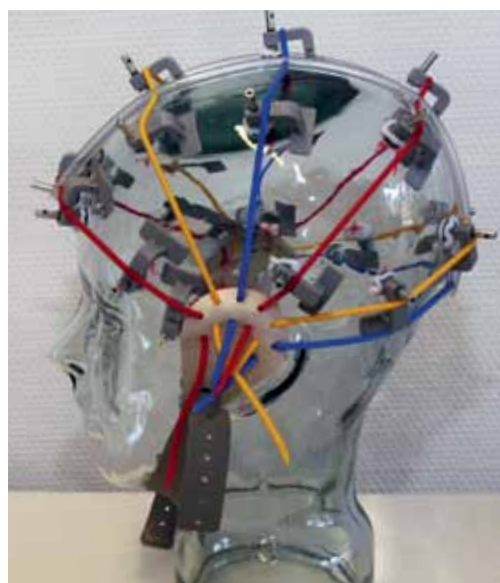
- (i) the genetics and pathophysiology of hereditary epilepsy syndromes and related neurological disorders,
- (ii) the closely related mechanisms of the excitability of nerve cells and neuronal networks and
- (iii) the molecular function, pharmacology and localization of ion channels and transporters, which are membrane proteins that regulate neuronal excitability.
- (iv) structural and functional brain imaging to detect epileptogenic lesions and foci, and to characterize memory processes.

This latter work is performed in close cooperation with the MEG Center and the Departments of Neuroradiology, Neuroimaging and Neurosurgery and was joined in 2011 by PD Dr. Tobias Schmidt-Wilcke with a focus on functional pain networks.

The Experimental Epileptology was complemented in 2011 by the independent group of PD Dr. Marcel Dihné. Their work is

focused on the analysis of neuronal network activities of cultured neurons on multielectrode arrays under different pathophysiological conditions including networks of embryonic and induced pluripotent stem cells.

*Electroencephalography (EEG) is used to record the spontaneous electrical activity of the brain by multiple electrodes placed on the scalp in a standardized manner. Abnormalities in EEG due to epileptiform brain activity represent the major diagnostic feature of epilepsy.*





**EXPERIMENTAL EPILEPTOLOGY**

**Head:** Prof. Dr. Holger Lerche

**Team:** 25 members

**Key words:** channelopathies  
genetics  
seizures  
imaging  
neuronal networks

[www.hih-tuebingen.de/de/experimental-epileptology](http://www.hih-tuebingen.de/de/experimental-epileptology)

We are analyzing different mouse models for genetic epilepsy, such as SCN1A knock-in or KCNQ2 knock-out mice.



The goal of our research is to link the molecular mechanisms of mainly genetic, neurological diseases caused by disturbed neuronal excitability to their clinical symptoms. We are collecting well-defined cohorts of patients with epilepsies and related disorders, searching for disease-causing genetic defects with modern sequencing techniques, particularly in ion channels or transporters, and analyzing their functional consequences to understand the pathomechanisms and improve therapy. To study mechanisms of neuronal hyperexcitability on the molecular, cellular and network level, we use non-neuronal screening tools such as automated electrophysiology in oocytes and mammalian cells, neuronal expression systems including neurons derived from induced pluripotent stem cells, and gene-targeted mouse models. To understand the processes of the human brain underlying seizure activity, we use structural and functional brain imaging strategies.

Das Ziel unserer Forschung ist es, die molekularen Mechanismen vor allem genetischer, neurologischer Krankheiten mit einer gestörten neuronalen Erregbarkeit mit ihren klinischen Symptomen zu verknüpfen. Wir rekrutieren gut definierte Kohorten von Patienten mit Epilepsien und verwandten Krankheiten, suchen nach den genetischen Defekten mit modernen Sequenziermethoden, insbesondere in Ionenkanälen oder -transportern, und untersuchen deren funktionelle Auswirkungen, um die Pathomechanismen zu verstehen und die Therapie zu verbessern. Darüber hinaus untersuchen wir die Mechanismen neuronaler Übererregbarkeit auf molekularer, zellulärer und Netzwerkebene mit Screening-Methoden, wie automatisierter Elektrophysiologie in Oozyten oder Säugierzellen, in neuronalen Expressionssystemen einschließlich induzierter pluripotenter Stammzellen, und in genetisch veränderten Mausmodellen. Um die Prozesse epileptischer Aktivität im menschlichen Gehirn zu verstehen, verwenden wir strukturelle und funktionelle bildgebende Verfahren.



Mutations of GLUT1, the primary molecule to deliver glucose across the blood-brain barrier, have been associated with a spectrum of neurological disorders

Epilepsy affects up to 3% of people during their life time. In almost 50%, a genetic component plays a major pathophysiological role. Since ion channels form the basis of neuronal excitability, genetic mutations affecting channels may drive networks into synchrony to promote seizures. Indeed, most of the mutations identified so far in inherited epilepsy syndromes affect ion channel genes. To analyze the genetic architecture of epilepsy we have been involved in different national (National Genome Network, NGFNplus) and international (FP6: Epicure, ESF: EuroEPINOMICS, FP7: EpiPGX) research networks confined to recruit large cohorts of affected individuals and/or families subjected to genetic analyses. In the Epicure project, a number of novel variants have been

detected using candidate gene sequencing in families with idiopathic generalized epilepsy. New variants were found in genes coding for the glucose transporter type 1, different GABA(A) receptor subunits, K<sup>+</sup> and Na<sup>+</sup> channel subunits. Detected genetic variants undergo a functional analysis to understand the mechanisms of neuronal hyperexcitability. Using an automated two-voltage clamp system in oocytes, we could show that several novel GABA(A) receptor variants dramatically reduce GABA-induced currents which could reduce inhibition in brain and explain the occurrence of seizures. One of our focuses is on KCNQ2 channels. Their gating or transport to the membrane are altered in a neonatal form of epilepsy and they are the target of a recently released novel antiepi-

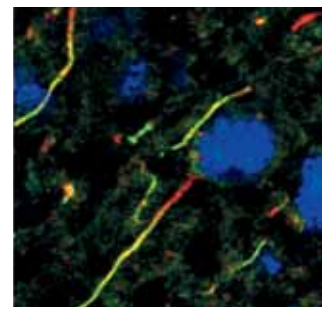


leptic drug, retigabine. We have been analyzing a cohort of KCNQ2 mutations associated with severe epileptic encephalopathy, and in contrast to the benign neonatal seizures, we observed a dramatic loss-of-function with dominant-negative effects on WT channels which correlate to the severe clinical picture. Furthermore, we are one of the first groups reporting that the mutations within the pre-synaptic protein PRRT2 are a common cause of benign familial infantile seizures (BFIS).

To examine the functional implications of disease-related mutations in neurons, we use transfected mouse neuronal cultures and genetically-altered animal models. We assess the subcellular localization of the affected molecules, their targeting mechanisms, and provide the functional analysis of single neurons and neuronal networks *in vitro* by employing immunohistochemistry and electrophysiological methods. We have been examining neuronal firing properties in acute brain slices from epileptic mouse models. Our ongoing study of a knock-in mouse carrying a mutation in the *SCN1A* gene associated with generalized epilepsy with febrile seizures plus (GEFS+) revealed a reduced excitability of inhibitory neurons in all examined brain regions, namely thalamus, cortex and hippocampus. *SCN1A* is coding for the Na<sup>+</sup> channel Na<sub>v</sub>1.1 expressed in inhibitory neurons and our findings indicate dysinhibition as a mechanism of seizure generation in this model. The perspectives with such animals are to understand how epileptic activity is generated in neuronal networks on the basis of molecular defects, which will be studied for example in cooperation with Prof. Olga Garaschuk (Inst. Physiology II, Tübingen) using 2-photon *in vivo* Ca<sup>2+</sup> imaging of the cortex. Furthermore, in cooperation with the group of Prof. Gasser, we have been establishing protocols for generation of induced pluripotent stem (iPS) cells from fibroblasts of patients affected with epilepsy. The iPS cells will be differentiated into neurons and their functional analysis used as a human disease model to examine mechanisms of epileptogenesis.

An additional research interest of the department is structural and functional brain imaging. In drug-resistant focal epilepsies, it is important to identify the epileptogenic foci and lesions for surgery, which cannot always be detected with standard

magnetic resonance imaging (MRI). We are establishing further methods, in particular the use of EEG combined with functional MRI, high-density EEG and magnetoencephalography (MEG). The combination of these methods may emerge as strong tool to localize epileptic activity and identify pathological networks. We also intend to use these methods to understand pathological networks in genetically determined epilepsies and correlate the molecular defects to network dysfunction. Since memory functions are often affected in epilepsy patients, we also use fMRI to characterize and better understand in particular episodic memory processes generated in the hippocampus.



Staining of mouse brain cryosections: the yellow lines reveal the co-localization of the Kv7.2 (green) and Na<sub>v</sub>1.2 channels (red) in cortical pyramidal neurons (blue: nuclei).

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## FUNCTIONAL NEURONAL NETWORK AND NEURAL STEM CELLS

**Head:** PD Dr. Marcel Dihné

**Team:** 3 members

**Key words:** stem cells  
functional neuronal networks

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### Development and pharmacological modulation of embryonic stem cell-derived neuronal network activity

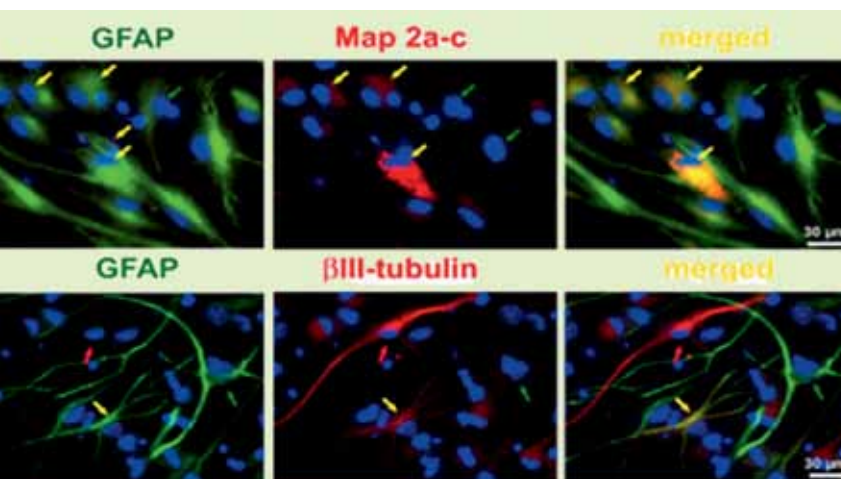
Neuronal network activity can be assessed by the microelectrode array (MEA) technology that allows simultaneous recording of the electrical activity exhibited by entire populations of neurons over several weeks or months *in vitro*. We demonstrated that ES cell-derived neural precursors cultured on MEAs for 5 to 6 weeks develop functional neuronal networks with oscillating and synchronous spike/burst patterns via distinct states of activity and towards late maturational processes. These processes were accompanied by an increasing density of presynaptic vesicles. Furthermore, we demonstrated that ES cell-derived network activity was sensitive to synaptically acting drugs indicating that pharmacologically susceptible neuronal networks were generated. Thus, the MEA technology represents a powerful tool to describe the temporal progression of stem cell-derived neural populations towards mature, functioning neuronal networks that can also be applied to investigate pharmacologically active compounds. Actually, we are generating human functional neuronal networks from both native human embryonic and induced pluripotent stem cells.

### Effects of inflammatory cytokines on neural stem cells

Primary and secondary inflammatory processes are playing a role in nearly all brain pathologies. As endogenous neural stem cells supply the brain throughout life with new functional cells, it is important to verify the effect of inflammatory processes that include e.g. the up-regulation of cytokines on neural stem cells.

### Epilepsy-associated alterations of *in-vitro* neuronal network activity

The impact of epilepsy-associated mutation in genes encoding for ion channels on neuronal network activity is currently under investigation.

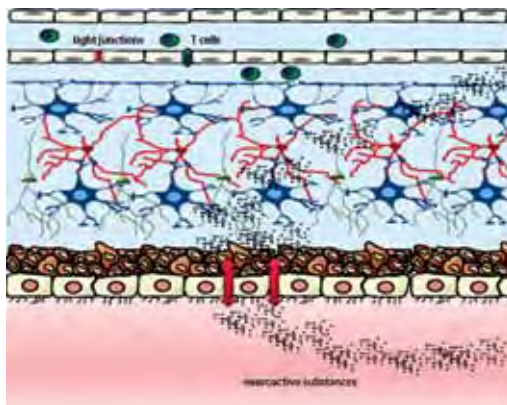


Cell type-specific marker expression after IFN $\gamma$  treatment under proliferative conditions.



## Volume transmission-mediated encephalopathies

There is strong evidence that the composition of cerebrospinal fluid (CSF) influences brain development, neurogenesis and behavior. The bi-directional exchange of CSF and interstitial fluid (ISF) across the ependymal and pia-glial membranes is required for these phenomena to occur. Because ISF surrounds the parenchymal compartment, neuroactive substances in the CSF and ISF can influence neuronal activity. Function-



*In vivo* situation of neuropil with astrocytes (blue) and different kinds of neurons (red, green). The lateral ventricle (pale red) contains cerebrospinal fluid with neuroactive substances.

ally important neuroactive substances are distributed to distant sites of the central nervous system by the convection and diffusion of CSF and ISF, a process known as volume transmission. It has recently been shown that pathologically altered CSF from patients with acute traumatic brain injury suppresses *in vitro* neuronal network activity (ivNNA) recorded by multielectrode arrays measuring synchronously bursting neural populations. Functionally relevant substances in pathologically altered CSF were biochemically identified, and ivNNA was partially recovered by pharmacological intervention. When considering the concept of volume transmission, it remains unclear whether the *in vivo* parenchymal compartment remains unaffected by pathologically altered CSF that significantly impairs ivNNA. We hypothesize that the relevance of pathological CSF alterations goes far beyond the passive indication of brain

diseases and that it includes the active and direct evocation of functional disturbances in global brain activity through the distribution of neuroactive substances, for instance, secondary to focal neurological disease. For this mechanism, we propose the new term “volume transmission-mediated encephalopathies” (VTE). Recording ivNNA in the presence of pure human CSF could help to identify, monitor and potentially suggest means for antagonizing functionally relevant CSF alterations that direct result in VTEs.

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**Hertie Institute**  
for Clinical Brain Research



**DEPARTMENT OF  
NEURODEGENERATIVE DISEASES**





*Insertion of an electrode during deep brain stimulation for Parkinson's disease.*

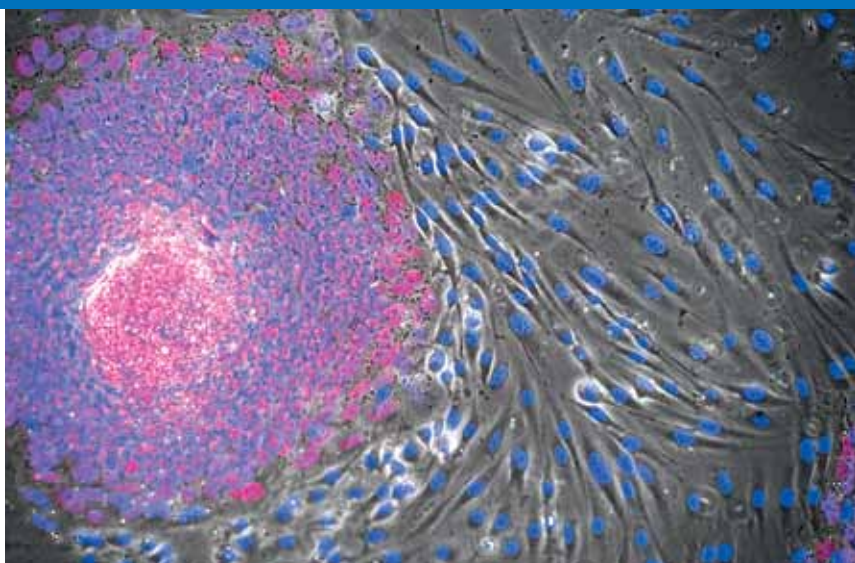
## DEPARTMENTAL STRUCTURE



*Prof. Dr. Thomas Gasser is Chairman of the Department of Neurodegenerative Diseases*

The Department of Neurodegenerative Diseases was founded with the 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 20 beds (Ward 43, under the supervision of Prof. L. Schöls and Prof. R. 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 and neuropsychologists.

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 and genetic testing. Innovative treatment for patients with Parkinson's disease (PD) and other movement disorders include deep brain stimulation (in close collaboration with the Department of Neurosurgery), but also continuous apomorphine or levodopa infusion 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 PD, dementias and restless legs syndrome, dystonias, motor neuron diseases, ataxias, spastic paraplegias, and neurogenetic disorders allows highly efficient patient management. The equally close interaction of clinicians with basic and clinical scientists within the Hertie-Institute for Clinical Brain Research, on the other hand, allows truly translational research. This innovative concept includes active education and training of scientific and clinical junior staff.



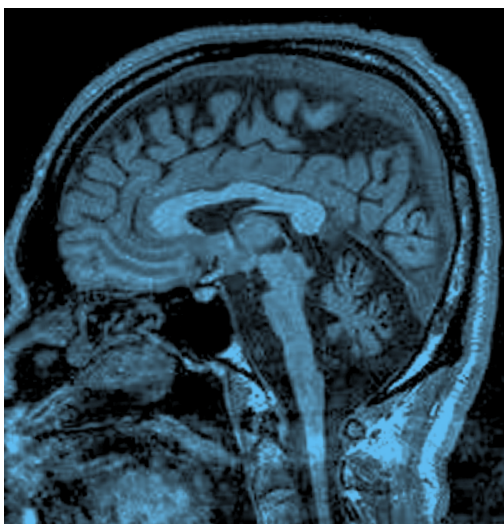
*To study the effects of mutations related to Parkinson's disease, induced pluripotent stem cells (iPSC) with specific genetic alterations have been generated (red: iPSC, co-cultured with embryonic connective tissue (blue) from mice).*

Research is currently organized within 7 research groups, headed by group leaders. The group of Prof. T. Gasser investigates the genetic basis of Parkinson's disease and other movement disorders with classic positional cloning and also high throughput array and next generation sequencing techniques. The group works closely with the team of Prof. D. Berg (Clinical Parkinson's Research) with its focus on clinical cohort studies, phenotyping and neuroimaging. Some members of the group of Prof. R. Krüger develop and test novel stimulation paradigms of deep brain stimulation, while others are interested in fundamental mechanisms of neurodegeneration in PD, with a particular focus on mitochondrial function and dysfunction. Prof. P. Kahles group (section of Functional Neurogenetics) investigates also

fundamental aspects of neurodegeneration in PD, while Prof. L. Schöls and his team (Section for Clinical Neurogenetics) focusses on clinical and fundamental aspects of inherited ataxias, spastic paraplegias, motor neuron diseases and other rare neurogenetic conditions.

Two additional scientists have become group leaders in 2011: Dr. Dr. Saskia Biskup, who leads a research group on LRRK2-biology, but also has founded a company that offers innovative methods of genetic diagnosis, and PD Dr. Walter Maetzler, who focusses on neurogeriatrics and gait disorders.

Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with Parkinson's disease and other neurodegenerative diseases



*Both, fundamental mechanisms of neurodegeneration in Parkinson's disease and the effects of deep brain stimulation are investigated in Professor Krüger's group.*

## PARKINSON GENETICS

**Head:** Prof. Dr. Thomas Gasser

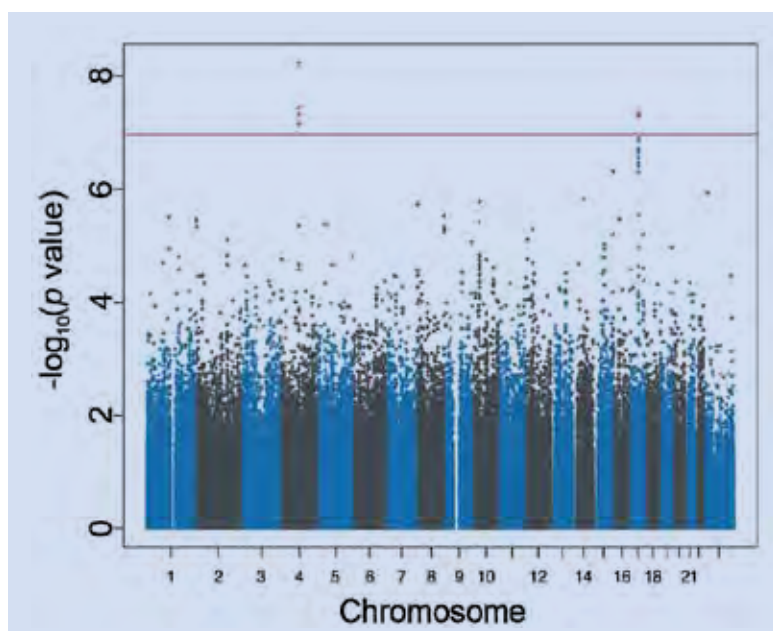
**Team:** 12 members

**Key words:** Parkinson`s disease  
genetics  
association studies  
GWAS  
mutation

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*Although most patients with Parkinson's disease (PD) do not have affected parents or siblings, it is becoming increasingly clear that genetic factors nevertheless influence the risk to develop the disease and determine its course. As members of an international consortium, we are striving to identify these genetic variants by state-of-the-art high throughput techniques in conjunction with in depth clinical analyses.*

*Obwohl bei den meisten Parkinson-Patienten keine weiteren Familienmitglieder von dieser Erkrankung betroffenen sind, wird immer klarer, dass genetische Faktoren dennoch das Erkrankungsrisiko und den Verlauf beeinflussen. Innerhalb eines großen internationalen Konsortiums arbeiten wir mit modernen Hochdurchsatzmethoden verbunden mit genauen klinischen Analysen daran, diese genetische Varianten zu identifizieren.*



*A large genome-wide study identified two genetic risk loci for sporadic PD. One is SNCA, containing the gene for the microtubule associated protein tau.*

It is well established that specific mutations in some genes can cause rare inherited forms of Parkinson's disease. A contribution of more common genetic sequence variants, often called single nucleotide polymorphisms (SNPs), in the etiology of the typical sporadic (= non-familial) form of the disease is suspected, but less well understood.

In an attempt to identify these risk variants for the sporadic disease, we have conducted a large genome-wide association study (GWAS), which was funded in part by the National Genome Network, NGFN2, in a collaboration with the laboratory for neurogenetics at the National Institutes of Health (NIH). This landmark study, which used material from more than 5,000 patients and 8,000 control individuals, identified only two major genetic risk loci for sporadic PD: SNCA, encoding  $\alpha$ -synuclein and MAPT, containing the gene for the microtubule associated protein tau. Both genes had already been known to play an important role in PD and other neurodegenerative diseases, and the findings have now been confirmed by numerous other studies.

It was somewhat surprising that even a study of this size failed to identify any further risk loci. We therefore proceeded to share our findings with five other research groups from different countries, who had performed similar studies, and re-analyzed the data, now based on a total sample size of more than 12,000 cases and 20,000 controls. This reanalysis resulted in the identification of as many as 9 additional risk loci with genome wide significance, and genotyping a further 1,920 variants that had provided suggestive, but not significant evidence for association in the initial exploratory phase of the study produced another 5 risk genes (IPDGC).

Based on these results, we are now designing a custom array that will allow to interrogate the entire known genetic risk for PD (and other neurodegenerative diseases) at an affordable cost, thereby creating a tool to be used for the stratification of patient populations according to genetic risks.

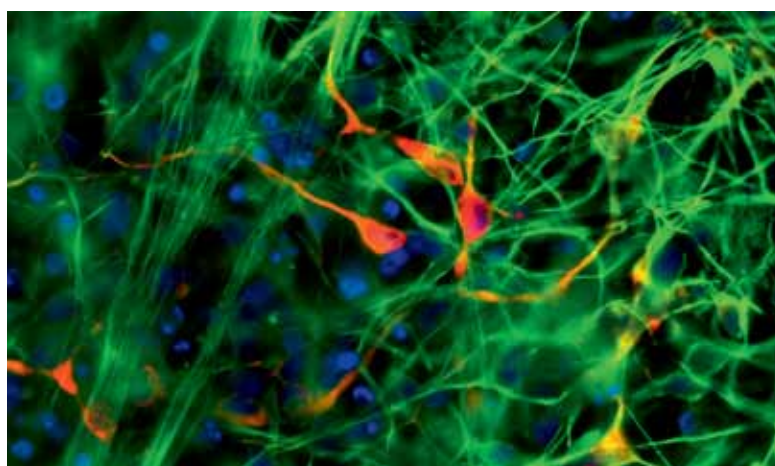
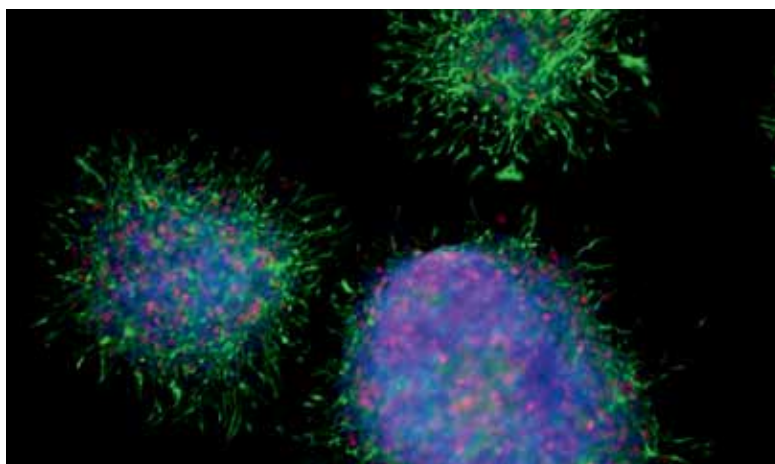
Underlying genetic variants do not only influence disease risk, but also the clinical features of the disease. In two studies we could demonstrate that clinical and neuroimaging characteristics of patients with two



right, top: Neuronal progenitor cells derived from reprogrammed epithelial cells of a Parkinson patient: In contrast to iPSC cells or embryonic stem cells the differentiation potential of these cells is restricted to neuronal cells which are direct precursors of dopaminergic neurons (right, bottom: red dye).

genetically determined forms of PD, namely those with heterozygous mutations in the LRRK2 and glucocerebrosidase (GBA) gene, respectively, differ from a group of PD patients without known genetic risk variants.

Knowing the genetic underpinnings of a complex neurodegenerative disorder such as PD is important, but it does not yet answer the question how this genetic abnormalities damage a specific population of neurons and lead to disease. Until recently, studies on gene function have only been possible in animal and cellular models, which often just have provided a rather artificial environment, not capturing the specific features of human neurons. The revolutionary technology of reprogramming cells has opened up a whole new research area: Tissue, for example derived from the skin of an adult human being, can be turned into so called “induced pluripotent stem cells” (iPSC) that closely resemble embryonic stem cells. The iPSCs can be differentiated into practically any cell type of the body, including neuronal phenotypes. We have begun to establish this technology and have generated numerous iPSC-lines with specific PD-related mutations. These cells will allow us to study the consequences of PD causing mutations in their “natural” surrounding. First experiments have shown that iPSC-derived neurons from patients with an LRRK2-mutation have specific abnormalities which can be rescued by correcting the gene mutation using highly specific molecular tools.



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## CLINICAL NEURODEGENERATION

**Head:** Prof. Dr. Daniela Berg

**Team:** 24 members

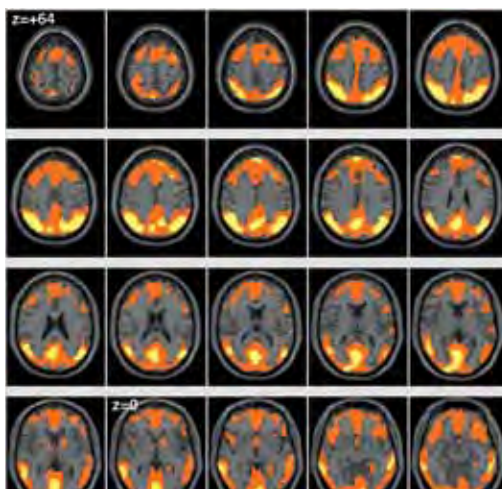
**Key words:** Parkinson's disease  
Alzheimer's disease  
Lewy-Body disease  
diagnostic and prognostic markers  
imaging  
prospective cohort studies

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*With the aging society the prevalence of Parkinson's disease (PD) and neurodegenerative dementias increase steadily. Notably, neurodegenerative processes underlying these diseases start years before clinical diagnosis, and have progressed by large when therapy starts. Therefore, the group Clinical Neurodegeneration follows large cohorts of patients and yet healthy individuals with an increased risk for neurodegenerative diseases to identify markers for an earlier diagnosis and objective description of disease progression. Additionally novel medication and conservative therapeutic strategies are offered in numerous studies.*

*In der immer älter werdenden Bevölkerung nimmt die Zahl an Patienten, die von Parkinson oder neurodegenerativen Demenzen betroffen sind, stetig zu. Gleichwohl sind noch viele Fragen bezüglich Ursachen, Entstehung und Verlauf dieser „Volkskrankheiten“ unklar. Von besonderer Bedeutung ist, dass der Nervenzelluntergang schon Jahre vor Auftreten der zur Diagnose führenden Symptome wie den typischen Bewegungsauffälligkeiten oder einer Demenz beginnt und zum Diagnosezeitpunkt schon fortgeschritten ist. Die AG Klinische Neurodegeneration untersucht deshalb in großen prospektiven Kohortenstudien charakteristische Veränderungen, die als diagnostische und prognostische Marker dienen können. Auffälligkeiten des Gehirns in bildgebenden Verfahren wie Ultraschall und MRT, klinische Veränderungen (z. B. bei bestimmten Bewegungsmustern oder beim Denken) sowie Marker im Nervenwasser wurden bereits als Diagnose- und Verlaufsmarker identifiziert. Zudem werden neue medikamentöse und konservative Therapiestrategien im Rahmen von Studien angeboten.*

*PET imaging in non-demented patients with Parkinson's disease. Highlighted regions indicate brain areas with hypometabolism which was found to be primarily associated with cognitive impairment and dementia.*



## Parkinson's disease

With a prevalence of about 2% in the population older than 60 years, Parkinson's disease (PD) is one of the most common neurodegenerative disorders. As there is still a substantial lack of knowledge with regard to the correct and early diagnosis, the course and etiology of PD, the group Clinical Neurodegeneration is conducting a number of large prospective longitudinal studies in national and international cooperations in patients and individuals at risk for the disease. Selected examples of recent findings are

- (i) substantia nigra hyperechogenicity in healthy individuals older than 50 years determined by transcranial sonography indicates a more than 17 times increased risk to develop PD within three years,
- (ii) elevated levels of the Insuline Growth Factor 1 (IGF-1) can be a marker for PD and putatively for individuals at risk for PD,
- (iii) increased gray matter volume of different anatomical structures on MRI in asymptomatic LRRK2 mutation carriers indicates compensatory mechanisms,
- (iv) changes in the metaboliteratio of the substantia nigra determined by MRI-Spectroscopy implies a PD specific alteration.

A further focus of the group is standardization of assessments in collaboration with other experts. Dr. Maetzler and colleagues developed an assessment battery for axial motor deficits (such as gait and sway deficits) by use of a simple to apply, unobtrusive accelerometer-based measurement system worn at the lower back for quantitative detection of subtle motor deficits. Further quantitative assessments are a device testing fine motor function, and a device for autonomic dysfunction. Inclusion of these techniques will allow new insights into the pathophysiology and progression of symptoms in symptomatic but also presymptomatic stages of neurodegeneration.

In collaboration with the group of Prof. Thomas Gasser the group Clinical Neurodegeneration has been crucially involved in the development and maintenance of the Hertie-biobank which is currently the basis for many national and international cooperations, promoting effective research in PD and other neurodegenerative disorders.



Moreover, based on the desire to improve therapy, the group has expanded its involvement in a number of mono- and multicenter clinical studies, phase II to IV, for all stages of PD. As an example it could be shown that the new compound AFQ056 (a subtype selective inhibitor of mGluR5) has a clinically relevant and significant antidyskinetic effect without changing the antiparkinsonian effects of dopaminergic therapy.

### Atypical Parkinsonian syndromes

Major effort has been put in the characterization of progressive supranuclear palsy (PSP) by use of clinical, biochemical and neuroimaging parameters. As an example Richardson-type PSP-patients were found to have thalamic and frontal hypometabolism in FDG-PET examinations, compared to parkinsonism-type patients who tended to have putaminal hypometabolism. These findings are the basis for a better understanding of these subgroups, and for future therapeutic interventions.

### Dementias with Lewy-bodies

With the demand for an early, individualised, and better treatment, one focus of the group is to identify patients with a potentially higher risk of dementia. In a cohort comprising 140 subjects with clinically defined idiopathic PD the profile of different cognitive phenotypes as well as cognitive worsening is being monitored longitudinally to enable the evaluation of factors which are associated with a more rapid cognitive decline.

### Tremor

With a prevalence of 1 to 5% essential tremor is the most frequent movement disorder. Understanding of the etiology is limited, which is at least in part due to a great phenotypic. Thus a large cohort of tremor patients is currently being characterized with thorough quantitative assessments batteries to better understand subtypes and facilitate differential diagnosis. In cooperation with national and international groups standardized protocols are being established and GWAS (genome-wide association studies) are being performed to disclose the secrets of this common movement disorder.

### Restless-Legs-Syndrome

The Restless-Legs-Syndrome (RLS) is a sensorimotor disorder affecting about 10% of the German population. The observation that treatment effect is often very limited led to a large study, which revealed that poor treatment success, regarding improvement of RLS symptoms, quality of life and number of RLS related physician contacts is primarily related to the presence of neuropsychiatric comorbidities. This finding has been internationally received with great interest as it directly affects treatment strategies.

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## FUNCTIONAL NEUROGENETICS

**Head:** Prof. Dr. Philipp Kahle**Team:** 12 members**Key words:** Parkinson's Disease  
amyotrophic lateral sclerosis  
frontotemporal dementia  
synuclein  
RNA-binding proteins  
mitochondria  
signal transductions[www.hih-tuebingen.de/funct-neurogenet](http://www.hih-tuebingen.de/funct-neurogenet)

*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], dementia with Lewy bodies [DLB], Alzheimer's disease, frontotemporal dementias [FTD], amyotrophic lateral sclerosis [ALS], etc.) are characterized by intracellular protein inclusions that are specific for each of these diseases. We investigate the protein structural, molecular, cellular, and histopathological mechanisms underlying dysfunction of the PD/DLB-causing synaptic protein  $\alpha$ -synuclein and other PD gene products as well as the FTD/ALS-associated RNA-binding proteins TDP-43 and FUS/TLS. Novel RNA targets of TDP-43 and FUS/TLS are screened with high throughput, and are validated structurally and functionally in cell cultures and animal models.*

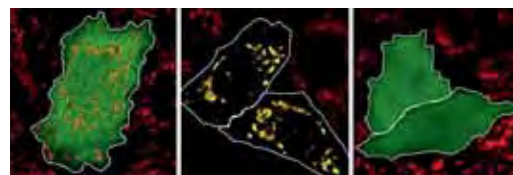
*Altersbedingte neurodegenerative Krankheiten entwickeln sich zu einer besorgniserregenden Belastung unserer immer älter werdenden Bevölkerung. Die meisten chronischen neurodegenerativen Krankheiten (Morbus Parkinson, PD; Demenz mit Lewy-Körperchen, DLB; Morbus Alzheimer; frontotemporale Demenzen, FTD; amyotrophe Lateralsklerose, ALS, etc.) weisen Proteineinschlüsse innerhalb der Zelle auf – und zwar in charakteristischer Weise für die jeweilige Krankheit. Auf der Ebene von Proteinstruktur, Molekular- und Zellbiologie und Histopathologie erforschen wir die Ursachen für die gestörte Funktion des synaptischen Proteins  $\alpha$ -Synuklein, das PD/DLB- verursacht, sowie weiterer PD-Genprodukte. Für die FTD/ALS-assozierten RNA-bindenden Proteine TDP-43 und FUS/TLS fahnden wir mit Hochdurchsatzverfahren nach neuen RNA-Zielmolekülen, die in Zellkulturen und Tiermodellen strukturell und funktionell bewertet werden.*

Effects of Mutant  $\alpha$ -Synuclein on Cognitive Behaviour of Transgenic Mice

We are using transgenic mice expressing human mutant A30P  $\alpha$ -synuclein under the control of a Thy1 promoter, which recapitulate human  $\alpha$ -synucleinopathy down to the ultrastructural level. Cognitive behavior of (Thy1)-h[A30P] $\alpha$ SYN mice is impaired in an age-dependent manner, most likely due to development of neuropathology within the amygdala circuitry. 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. We are analyzing and characterizing the effects of  $\alpha$ -synuclein modifications (with emphasis on phosphorylation) and aggregation on neuronal dysfunction and behavioural impairments in these (Schell et al. submitted) and novel  $\alpha$ -synuclein transgenic mice (Rieker et al. 2011). This work is supported by the Helmholtz Alliance for Mental Health in an Aging Society (HelMA) and the German Center for Neurodegenerative Diseases (DZNE).

## Regulation and Cellular Effects of Parkin E3 Ubiquitin Ligase Activities

Most of the familial PD cases are caused by recessive mutations in the PARK2/PARKIN gene, which may also be a genetic risk factor for sporadic PD. The PARKIN gene product functions as an E3 ubiquitin protein ligase for a variety of unrelated substrate proteins. Lysine-48 linked polyubiquitination leads to protein targeting to the proteasome and subsequent degradation. Furthermore, ad-



*Parkin-mediated mitophagy. Under basal conditions (left), parkin (green) is distributed throughout the cytosol. Two hours after addition of the mitochondrial uncoupler CCCP (middle), parkin is recruited to mitochondria (yellow overlay), which begin to cluster. After 24h (right), mitochondria are eliminated in the parkin-transfected cells.*

ditional specific linkages with ubiquitin and ubiquitin-like modifiers, further complex regulatory functions and cellular effects. To shed light on the diverse effects of parkin-mediated ubiquitin protein modifications, we investigate its regulation in cell-free assays and cell culture. Special emphasis is on the role of parkin in the autophagic degradation of damaged mitochondria. Parkin is recruited to experimentally depolarized mitochondria in a PINK1-dependent manner, which is differentially affected by PD mutations in both genes (Geisler et al. 2010a and 2010b; Springer & Kahle, 2011). We discovered that parkin mediates a new kind of K27-linked ubiquitylation of the outer mitochondrial membrane protein VDAC1. RNAi experiments provided evidence for the importance of PINK1/parkin-mediated mitophagy, identified involved autophagy mediators, and are currently expanded to further understand how parkin and PINK1 regulate mitochondrial turnover. This work is supported by the German National Genome Research Network NGFNplus and the EU FP7 Consortium MEdelian FOrms of Parkinsonism (MEFOPA).

### Cell Biology of the FTD/ALS Associated Nuclear Splice Factor TDP-43

TDP-43 in cytosolic and nuclear inclusions was recently identified as neuropathological hallmark of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). It is to show now if the cytosolic aggregates are actively neurotoxic or if their cytosolic sequestration of these nuclear proteins deprives neurons of vital RNA processing factors. To identify novel target genes, we conduct expression profiling studies after RNA interference. We have identified the intracellular transport protein histone deacetylase 6 (HDAC6) and the exon junction complex component SKAR as novel TDP-43 target mRNAs and validated them structurally and functionally in non-neuronal and neuronal cells treated with siRNA and lentiviral shRNA vectors as well as in TDP-43 mutant animal models (Fiesel et al. 2010 and 2011b). The involvement of HDAC6 in neurite outgrowth impairments of TDP-43 deficient neuronal cells could be



demonstrated (Fiesel et al. 2011a). We are now also validating novel yeast 2-hybrid interactors of TDP-43. This work is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBWF) Competence Network "Degenerative Dementias" (KNDD) and the German Center for Neurodegenerative Disease (DZNE).

*Neurodegenerative diseases in elderly people become an increasingly worrisome burden in our society.*

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## DEEP BRAIN STIMULATION

**Head:** Prof. Dr. Rejko Krüger

**Team:** 11 members

**Key words:** unmet symptoms  
motor networks  
freezing of gait  
falls  
learning

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*Our group on “Deep brain stimulation” works on deciphering the pathophysiological correlates of gait disturbances. Pathological hypersynchronisation of antagonist muscles was currently identified as a key mechanism of Parkinsonian motor impairment that is predominantly transmitted on nigropontine routes. This major novel pathophysiological insight translates into two separate randomized controlled trials in order to modulate the ‘nigropontine locomotor loop’ on the level of i) the substantia nigra pars reticulata or ii) the pedunculopontine nucleus for unmet axial symptoms in Parkinson’s disease.*

*Die Arbeitsgruppe „Tiefe Hirnstimulation“ untersucht krankheits-assoziierte Zusammenhänge bei Gangstörungen mit dem Ziel, diese translational in neue Therapiekonzepte der Neurostimulation zu übertragen. Die krankhafte Hypersynchronisation entgegengesetzt wirkender Muskeln hat sich als Schlüsselmechanismus für Bewegungsstörungen bei Parkinson erwiesen und wird über absteigende „nigropontine“ Bahnen vermittelt. Innerhalb zweier unabhängiger randomisierter kontrollierter Studien werden diese nigropontinen Schleifen auf Ebene i) der Substantia nigra pars reticulata oder ii) des pedunculopontinen Kerns zur Therapie von Gangstörungen moduliert. Diese Therapiestudien sind im Hinblick auf die Autonomie und Lebensqualität des Parkinson-Patienten von außerordentlicher Bedeutung, zumal gewöhnliche Therapien bei Gangstörungen und Stürzen nur unzureichend wirken.*

D. Weiss has a special expertise on long-range motor network connectivity as a pathophysiological substrate of Parkinsonian bradykinesia and freezing phenomena. Based on current findings, an exaggerated drive of descending subcortical ‘nigropontine’ motor output to the spinal  $\alpha$ -motoneurons (without entraining the primary motor cortex) is likely to contribute to slowness and freezing phenomena of movement in PD. We find hypersynchronicity between antagonist muscles related to the dopaminergic ‘off-state’ in Parkinson’s disease during finger movements that also presents during episodes of upper-limb freezing.

Our simultaneous intra- and perioperative analyses of motor network connectivity based on simultaneous LFP, EEG, and EMG recordings favor a loss of efferent cortical mo-



*With regard to the hitherto unmet therapeutic need on gait disturbances and falls we want to develop novel treatment strategies.*

tor control and unselective hypersynchronous nigropontine drives to antagonist muscles, whereas L-Dopa and subthalamic stimulation facilitate the efferent cortical motor drive in parallel to motor improvement. Due to the recent technological advancement, first pilot recordings of wireless EEG-EMG data acquisition were performed in walking PD patients exhibiting freezing of gait. These innovative recordings parallel the findings of hypersynchronicity in antagonist muscles similar to upper limb freezing. Based on this novel pathophysiological insight, we aim to translate the knowledge on segregate functional basal ganglia circuitries into novel therapeutic strategies for the hitherto unmet therapeutic need on gait disturbances and falls. Therefore, we consider co-stimulation of the Substantia nigra pars reticulata (SNr) additional to the conventional subthalamic stimulation for gait disturbances in advanced Parkinson's disease. The first double-blind randomised controlled clinical trial on SNr stimulation for axial symptoms was registered and we expect the final results in 2012.

S. Breit is working on animal models of Parkinson's disease, using electrophysiological methods for assessing modulation of basal ganglia network activity in the context of selective lesioning or high-frequency stimulation paradigms. The results of his experimental animal studies suggested that the pedunculopontine nucleus might be a valuable new target for deep brain stimulation, particularly in the treatment of axial parkinsonian symptoms. Following a translational approach, S. Breit initiated the worldwide first randomized double-blinded study assessing the efficacy and safety of deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease patients with severe gait disorder.

The scientific work of Dr. Tobias Wächter is focused on the function of the basal ganglia in planning, execution and learning of motor behavior and particularly the influence of feedback (reward and punishment) on these motor functions. Current imaging work using fMRI demonstrates the importance of the basal ganglia on learning from feedback in stroke survivors. Furthermore behavioral and imaging studies on healthy

controls show implicit learning from feedback to change over a lifetime with age. Presently, behavioral studies on patients with deep brain stimulation of different subcortical regions (STN, SNR, PPN) are ongoing to examine the function of different subcortical regions on learning and processing of negative and positive feedback.

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## CLINICAL NEUROGENETICS

**Head:** Prof. Dr. Ludger Schöls  
**Team:** 12 members  
**Key words:** ataxias  
 spastic paraplegias  
 rare neurogenetic diseases  
 axonal transport  
 translational medicine  
 clinical trials

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*The Section of Clinical Neurogenetics is dedicated to rare neurodegenerative disorders like ataxias, spastic paraplegias, amyotrophic lateral sclerosis, mitochondriopathies and leukodystrophies. Focusing on the genetic basis of these diseases and defining the disease causing mutations helps us to decipher the underlying pathogenesis of neurodegeneration from its very beginning. The close interplay of clinical work at the Department of Neurology and basic research at the HIH enables us to address essential clinical questions to the lab and in return to bring back cutting edge results from the bench to the patient and run early clinical trials.*

*Die Sektion Klinische Neurogenetik widmet sich seltenen neurodegenerativen Erkrankungen wie Ataxien, spastischen Spinalparalysen, der Amyotrophen Lateralsklerose, Mitochondriopathien sowie Leukodystrophien. Durch die Erforschung des genetischen Hintergrunds dieser Erkrankungen und der krankheitsverursachenden Mutationen versuchen wir die zugrundeliegenden Krankheitsmechanismen aufzudecken und die neurodegenerativen Prozesse von ihrem Ursprung her zu verstehen. Die enge Vernetzung von Patientenbetreuung in der Klinik für Neurologie einerseits mit der Grundlagenforschung am Hertie-Institut für Hirnforschung andererseits ermöglicht es uns, essentielle klinische Fragen in der experimentellen Laborforschung zu berücksichtigen. Umgekehrt können neueste Ergebnisse der Grundlagenforschung schnell vom Labor in die Anwendung gelangen und in klinische Studien einbezogen werden.*

## Ataxia

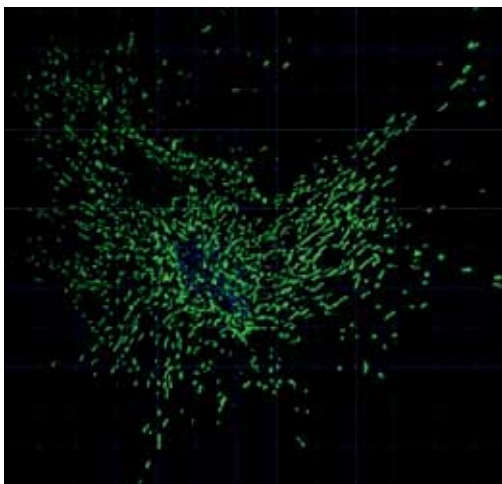
In preparation for interventional studies in spinocerebellar ataxias (SCA) we participated in the EUROSCA consortium supported by the European Union ([www.euroasca.org](http://www.euroasca.org)) and set up a European registry with more than 3,000 patients suffering from this rare disease. The EUROSCA natural history study revealed a comprehensive quantitative account of disease progression that is essential to calculate study duration and number of participants in trials in the future. Furthermore, this study identified factors that specifically affect disease progression (Jacobi et al 2011).

Since identification of the genetic cause is a prerequisite for meaningful research into pathogenesis and causative therapy of ataxias we performed large scale mutation screens. We found almost 9% of SCA families negative for common repeat expansions to be caused by macro deletions of the ITPR1 gene (SCA15) whereas none of our families had PDYN mutations (SCA23) (Synofzik et al. 2011a; Schicks et al. 2011a). Furthermore, we identified DARS2 mutations as a cause of episodic ataxia that can be treated successfully with acetazolamide (Synofzik et al. 2011b).

In Friedreich's ataxia (FA) we participated in several phase II and III trials with the antioxidant idebenone and the erythropoietin analogue CEPO. Additionally, we could show that restless legs syndrome is frequent in FA and goes along with hypoechogenicity of the substantia nigra suggesting reduced iron content (Synofzik et al. 2011c).

Although physiotherapy is regarded as most important in ataxia, specific therapeutic 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 movement control to an amount that equals the natural progression of two or more years. Longterm follow-up showed that improvements of motor performance and achievements for activities of daily life persisted after 1 year with best results obtained in patients who continued regular training at home (Ilg et al. 2010).

*Fragmented mitochondria in fibroblasts of a patient with OPA1 mutations causing defects of mitochondrial fission and fusion dynamics*



## Hereditary spastic paraplegia (HSP)

HSP is characterized by mostly selective degeneration of the corticospinal tract. Thereby the longest axons to the legs are much more severely affected than the relatively shorter axons to the arms suggesting a length dependent axonopathy. In SPG10, a dominantly inherited subtype of HSP, we found human mutations to affect axonal transport of mitochondria and to impair axonal outgrowth. This makes sense since mutations causing SPG10 are located in the kinesin heavy chain (KIF5a), the motor of axonal transport. Interestingly, transport is affected in both directions, anterograde and retrograde suggesting an essential interplay between both (Karle et al., in press).

Rapid progress in genetic technologies allows for rapid and cost-effective analyses of whole exomes providing for sequencing data of all coding regions of a genome. This turns out to become a highly efficient tool in the analysis of so far undefined genetic diseases. Using whole exome sequencing we found mutations in the adaptor protein complex 4 (AP4B1) to cause SPG47, a new recessive subtype of HSP (Bauer et al. in press). Moreover we used this technique to investigate in close cooperation with the Institute of Human Genetics in Tübingen, the Helmholtz Institute in Munich and the John P. Hussman Institute for Human Genomics in Miami large numbers of HSP exoms which are currently under analysis. Within the EUROSPA network funded by the EU we screened large cohorts of HSP patients for mutation in HSP genes SPG5, SPG7, SPG11, SPG15 and SPG42 and deciphered unexpected phenotypic variants using high throughput techniques (e.g. Schicks et al. 2011b).

While the progress in the molecular understanding of HSP not yet paved the way for new therapeutic interventions, we started a study to improve spastic gait in HSP patients by functional electrical stimulation (FES) of peripheral nerves to improve foot dorsiflexion and prevent stumbling by an external device that sends impulses to the peroneal nerve triggered by sensor registering foot movements during the gait cycle. In a controlled trial using timed walking, video docu-

mentation and computerized movement analyses we aim to prove FES as an effective tool to improve gait in patients with HSP.

## Trilateral project in Arab societies

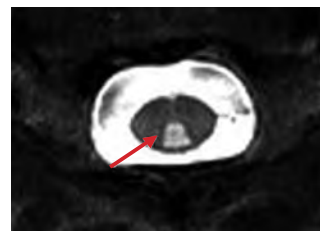
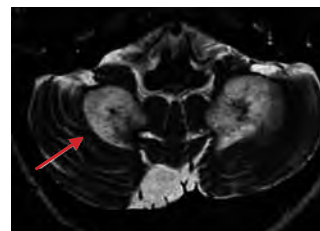
In 2011 we started a new trilateral DFG project involving Israeli, Palestinian and German groups in the discovery of new genetic diseases in consanguineous families of the Arab population. The Kick-off meeting took place in Tübingen in May 2011 and more than 15 families have been investigated and visited since in Israel and the West Jordan land, most of them with so far undefined disorders.

## Center of Rare Diseases Tübingen (ZSE)

In 2010 we funded the first German Center of Rare Diseases in Tübingen with Eva Luise Köhler attending the opening ceremony. In the mean time 9 centers for subspecialties have been established. Disease registers, a central rare disease guide, interdisciplinary conferences for unsolved cases and psycho-social consulting are key achievements reached so far. Furthermore, the group is engaged in several national and international rare disease networks like Leukonet, mitoNET, RISCA and EUROSPA.

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MRT lesions typical for leukodystrophy with brainstem (top) and spinal cord lesions (bottom) due to DARS2 mutations



**Hertie Institute**  
for Clinical Brain Research



**DEPARTMENT OF  
COGNITIVE NEUROLOGY**







*The displayed system allows the application of external mechanical perturbations to the body in order to study the motor control during complex walking*

## DEPARTMENTAL STRUCTURE



*Prof. Dr. Peter Thier heads the Department of Cognitive Neurology.*

The Department of Cognitive Neurology (DCN) was founded in the year 2000 with support from the program “C4-Department of Neuroscience at Neurology Clinics“ of the Hermann and Lilly-Schilling Foundation. In the year 2002, in which the Neurology Clinic was reorganized, the DCN became a constitutional part of the newly founded twin institutions, namely the Center of Neurology and the Hertie-Institute for Clinical Brain Research. In the beginning of 2004, it was reinforced by the formation of a Section on Neuropsychology associated with a professorship for neuropsychology both taken over by Hans-Otto Karnath. In summer 2008 the Section on Computational Sensomotorics, headed by the newly appointed professor Martin Giese and funded co-jointly by the Hertie Foundation and the German Research Council within the framework of the Excellence Cluster “Centre for Integrative Neuroscience” (CIN), was installed at the department. In 2009 Cornelius Schwarz was appointed professor and head of the research group on Systems Neurophysiology within the CIN. This group was integrated into the DCN.

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, non-human 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 perception and learning. In close collaboration with the interdisciplinary centers for magnetoencephalography and magnetic resonance imaging (MRI) at the Medical Faculty, functioning imaging experiments

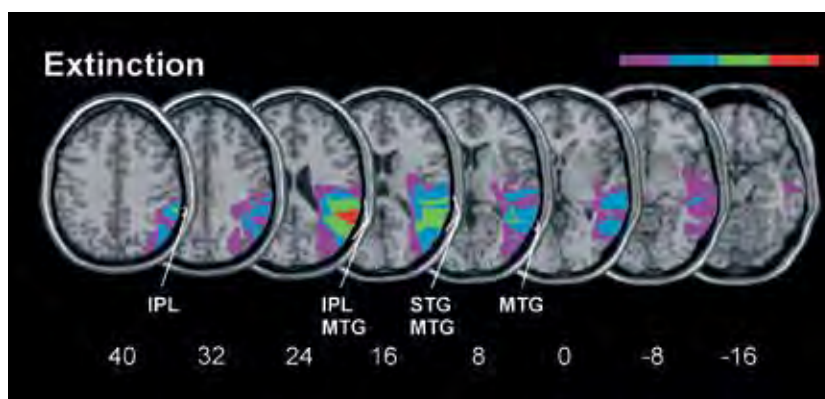


are carried out that tie up the behavioral experiments on patients with brain lesions, on the one hand, and experiments on animal models, on the other hand.

Several members of the DCN were engaged in the neuroscientific Collaborative Research Center (Sonderforschungsbereich SFB) 550: "Recognizing, Localizing, Acting: Neurocognitive Mechanisms and their Flexibility", that ended in December 2009 and was coordinated by Peter Thier. Several of them are now among the applicants of an emerging SFB initiative on "The Neural Basis of Cognitive Control", which is currently under evaluation. This initiative is coordinated by Andreas Nieder, former junior research group leader at the DCN and now head of the Department of Animal Physiology. Many members of the DCN are also part of the ongoing excellence cluster "Werner Reichardt Centre for Integrative Neuroscience (CIN)", for which a renewal application was submitted in 2011. The CIN is coordinated by Peter Thier.

All members of the DCN contribute significantly to research-oriented teaching at the Graduate Training Center of Neuroscience, which currently involves the International Graduate School for Neural and Behavioural Sciences and the Graduate School of Cellular and Molecular Neuroscience.

Martin Giese has been instrumental in helping to set up yet a third Graduate School on Theoretical Neuroscience, which started in October 2011. Further teaching is deployed at the Faculties of Biology (Uwe Ilg) and Informatics (Martin Giese and Winfried Ilg) and, of course, at Tübingen Medical School.



*Extinction patients can detect a single stimulus at any spatial location. However, when two stimuli are presented simultaneously, subjects are impaired at perceiving the contralesional item. In the Department of Cognitive Neurology both neurologically healthy subjects and neurological patients are studied with the aid of methods like TMS, fMRI, lesion mapping and behavioural studies to resolve questions concerning the anatomy and the underlying mechanisms of extinction.*

**SENSORIMOTOR LABORATORY****Head:** Prof. Dr. Peter Thier**Team:** 8 members**Key words:** mirror neurons  
attention  
autism  
social cognition  
motor learning  
fatigue  
ataxia[www.hih-tuebingen.de/sensomotorik-labor](http://www.hih-tuebingen.de/sensomotorik-labor)

*The lab works on the underpinnings of social interactions and the mechanisms underlying motor learning and their disturbances due to disease.*

*Das Labor befasst sich mit den neuronalen Grundlagen sozialer Interaktionen und denen motorischen Lernens sowie deren krankheitsbedingter Störungen.*



*Mirror neurons are activated by the execution of specific types of goal-directed motor acts such as grasping a piece of apple in order to eat it as well as by the observation of such motor acts carried out by others.*

One of the key interests of the sensorimotor laboratory concerns the underpinnings of social interactions and their disturbances due to disease such as in schizophrenia or autism: how is it possible to understand the intentions, the desires and beliefs of others, in other words to develop a theory of (the other one's) mind (TOM)?

Establishing a TOM requires the identification of the focus of attention of another person as well as an understanding of the purpose of her/his actions. Attention allows us to select particular aspects of information impinging on our sensory systems, to bring them to consciousness and to choose appropriate behavioural responses. Social signals such as eye or head or body orientation are a particularly powerful class of sensory cues attracting attention to objects of interest to the other one. The sensorimotor laboratory tries to unravel the neuronal mechanisms affording joint attention. The working hypothesis, supported by previous and ongoing work of the lab, is that joint attention is based on specific parts of cerebral cortex (areas in the superior temporal sulcus [STS]), extracting the relevant visual features, allowing the characterization of eye and head gaze direction and converting them into spatial coordinates, taking the prevailing geometrical relationships into account. The lab hypothesizes that malfunction of these areas may actually underlie the inability of patients with autism to efficiently exploit gaze cues when interacting with others.

Complementary work on the underpinnings of social cognition addresses the role of the mirror neuron system in pre-motor cortex in action understanding. Mirror neurons are a class of neurons in pre-motor cortex of monkeys that are activated by specific types of goal-directed motor acts such as grasping a piece of apple in order to eat it. Unlike typical motor neurons, mirror neurons are also activated, if the animal observes somebody unfolding similar behaviour. This basic finding has suggested that we may understand the actions of others by mapping observed actions onto our motor repertoire, an idea that is varyingly referred to as simulation or resonance theory.



*Mirror neurons, a class of neurons in premotor cortex of monkeys, are driven not only by the observation of naturalistic actions but also by filmed actions. In both cases, the same neurons show similar responses.*

Although these ideas have received wide attention, way beyond the confines of the neurosciences, the major tenet of the mirror neuron concept has never been rigorously tested. In an attempt to better understand the complex features of mirror neurons and ultimately to put the simulation theory to a critical test, our lab is carrying out experiments on premotor cortical area F5. In a nutshell, these experiments show that this particular area has access to streams of information which are obviously very important for the evaluation of actions of others such as information on the operational distance between actor and observer or the subjective value, the observed action has for the observer. Moreover, recent work of the lab clearly shows that observation-related responses of mirror neurons are to some extent view-point invariant. This is important as the perspective under which we see the actions of others is of course not fixed.

A second key interest of the sensorimotor laboratory pertains to the role of the cerebellum in motor control. Using short-term saccadic adaptation as a model of motor learning, the sensorimotor lab has been able to develop a detailed model of the neuronal underpinnings of cerebellum based learning. Its central idea is that a climbing fibre signal, representing information on the adequacy of the behaviour prunes a simple spike population signal, which in turn, controls the behaviour. A distinctive feature of cerebellum based learning, worked out by the group is its extreme speed, accommodating behavioural adjustments within seconds, allowing the cerebellum to compensate imperfections of movements due to fatigue. The notion that the biological purpose of cerebellum based learning is the

compensation of motor or cognitive fatigue has also allowed the group to suggest a new perspective on cerebellar ataxia, the key deficit of patients suffering from cerebellar disease. Ataxia, characterized by the lack of precision, reduced velocity and increased variance is an inevitable consequence of the motor system inability to compensate fatigue. In perceptual disturbances from cerebellar disease the group has worked on similar principles accounting for the perceptual deficits of patients.

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## THEORETICAL SENSOMOTORICS

**Head:** Prof. Dr. Martin Giese  
**Team:** 10 members  
**Key words:** sensorimotor control  
 neural modeling  
 movement quantification  
 motor training and adaptation  
 biologically-motivated machine learning

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*The Section for Theoretical Sensomotorics investigates theoretical principles in the perception and control of motor actions. Research is organized around three main topics: 1) Clinical movement control and rehabilitation, 2) neural mechanisms of action perception and sensorimotor coupling; 3) technical applications in biomedical engineering and biologically inspired machine learning. Research includes psychophysical and clinical experiments on sensorimotor functions and the development of mathematical models for neural circuits in the brain. In addition, the section works on technical systems that exploit brain-inspired principles and which support the accurate diagnosis and rehabilitation training in neurological diseases.*

*Die Sektion Theoretische Sensomotorik erforscht die theoretischen Prinzipien der Erkennung und Steuerung motorischer Handlungen. Die Forschungsarbeiten des Institutes gruppieren sich um drei Hauptthemen: 1) Klinische Forschung zur Bewegungskontrolle und Rehabilitation; 2) neuronale Mechanismen der Bewegungserkennung und Bewegungssteuerung; 3) technische Anwendungen in Medizintechnik und biologisch-inspiriertes maschinelles Lernen. Die eingesetzten Methoden umfassen psychophysische und klinische Experimente zu sensomotorischen Funktionen und die Entwicklung mathematischer Modelle für neuronale Mechanismen. Außerdem entwickelt die Sektion technische Systeme, die Prinzipien der Informationsrepräsentation im Gehirn nutzen und eine genaue Diagnose sowie die Rehabilitation bei neurologischen Erkrankungen unterstützen.*

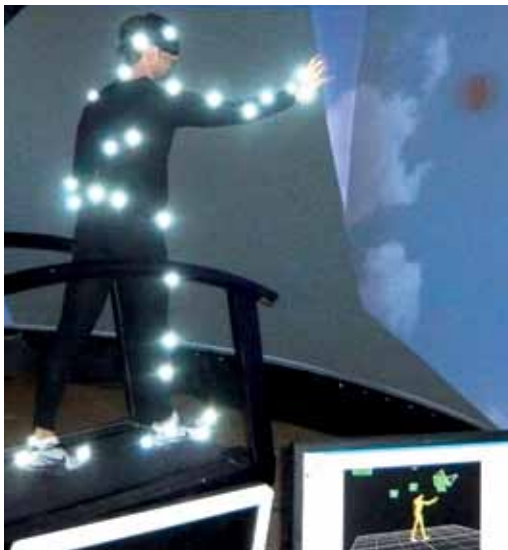
## Clinical movement control and rehabilitation

Many neurological disorders, such as Parkinson's disease, are associated with characteristic movement deficits. Their detailed quantitative characterization can help to understand underlying neural mechanisms and improve the differential diagnosis of such disorders. In addition, it supports the very early diagnosis of such diseases. We exploit advanced methods for movement analysis, motion capture, machine learning, computer animation, and robotics in order to quantify and study changes in movement behavior.

In recent projects, we were able to show that physiotherapeutical training induces beneficial long-term effects in cerebellar ataxia patients, contrasting the common opinion that cerebellar patients do not profit from motor training. Using computer games (Kinect platform) in collaboration with L. Schöls (Dept. Neurodegeneration) we devised novel training paradigms for children with cerebellar ataxia. Developing advanced mathematical methods for the analysis of coordination patterns, we were able to dissociate different deficits in the control of walking and to associate them with specific cerebellar lesion sites (in collaboration with D. Timmann, Uniklinik Essen). We also study how motion perception is influenced by the simultaneous execution of movements and how this interaction is influenced by cerebellar lesions. Advanced mathematical analysis techniques also are the basis of work in collaboration with D. Berg (Dept. Neurodegeneration), where based on very subtle movement deficits we were able to predict the clinical manifestation of Parkinson's disease several years in advance. Together with the Fraunhofer Institute for Manufacturing Engineering and Automation (IPA) in Stuttgart we have developed a prototype of a robot that supports rehabilitation training of free walking tasks. In addition, the system allows the application of external mechanical perturbations to the body in order to study the motor control during complex walking.

## Neural mechanisms of action perception and sensorimotor coupling

Recent research provides strong evidence that neural representations for the perception and motor control of actions are tightly interacting. We investigate the neural mechanisms that form the basis of this coupling combining neural modeling, psychophysical and fMRI experiments, and in collaboration with P. Thier's group also electrophysiology in non-human primates. Physiologically plausible models, e.g. for the recognition of goal-directed hand actions, help to motivate questions for physiological experiments that investigate the computational basis of the processing of action stimuli and facial movements. Body movements are also important for the expression of emotions, and the perception of emotions is impaired, e.g. in schizophrenic patients. We



We have developed a novel virtual reality setup for the recording of arm movements which at the same time have to be coordinated with walking movements.

study such impairments collaborating also with the Dept. Psychiatry (A. Fallgatter). We also develop mathematical methods for the accurate modeling of complex body movements based on 'movement primitives' for application in computer graphics and robotics, and we study experimentally how such primitives interact for complex tasks, e.g. walking and reaching, using Virtual Reality setups.

## Technical applications and biologically inspired machine learning

Representations of information in technical systems, such as robots or computer vision systems, still lack the flexibility and degree of generalization that is accomplished by biological organisms. Inspired by the principles of the representation of complex actions in biological systems, we develop novel algorithms that recognize and synthesize highly realistic body movements and that link them to high-level semantic representations. This work combines advanced methods from machine learning (e.g. Gaussian process models and graphical models), computer vision and computer graphics. We validate the performance of such technical systems by psychophysical experiments in close collaboration with expert users, e.g. in surveillance applications.

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## NEUROPSYCHOLOGY OF ACTION

**Head:** Dr. Marc Himmelbach

**Team:** 9 members

**Key words:** reaching  
grasping  
optic ataxia  
apraxia  
visual agnosia

[www.hih-tuebingen.de/en/neuropsychology-of-action](http://www.hih-tuebingen.de/en/neuropsychology-of-action)

*The Research Group “Neuropsychology of Action” is dedicated to investigations of human action control. Our work combines neuropsychological examinations of brain-damaged patients with state-of-the-art techniques for behavioural and brain activity measurements (functional neuroimaging; transcranial magnetic stimulation; motion and eye tracking systems).*

*Die Forschungsgruppe „Neuropsychologie der Handlungskontrolle“ widmet sich der Erforschung motorischer Kontrollprozesse beim Menschen. Unsere Arbeit kombiniert neuropsychologische Untersuchungen hirngeschädigter Patienten mit modernsten experimentellen Methoden der Verhaltens- und Hirnaktivitätsmessung.*

Our work addresses higher order motor control deficits. With ‘higher order’ we want to express that these deficits are not simply caused by a loss of muscular strength. Our individual research projects investigate the neural and functional foundations and conditions that are associated with such disorders.

### The impact of object knowledge on visual motor control

We grasp a screwdriver in a specific way if we are about to use it and in a very different way if we just want to put it aside. Despite of such quite obvious dependencies of visual motor control on object recognition, many researchers believe that the actual control of human grasping depends almost entirely on the direct visual information about object sizes irrespective of any stored knowledge in our memory. In contrast, we demonstrated that well established associations, build through a long-term learning process, are powerful enough to change visual motor control. Interestingly, we also observed some patients with impairments in the control of grasping who apparently exploited such associations for an individual improvement: they are better in grasping very familiar in comparison to neutral geometrical objects. Our work suggests that the role of object familiarity on the control of movements was dramatically underestimated in the past.

### The human superior colliculi – a small big player in the human brain?

The superior colliculi are located at the upper brainstem of humans. They are considered as a primarily oculomotor and sensory structure. In fact, for many ‘lower’ animals the superior colliculus represents the essential visual system. In contrast, in humans it seems to be only a small player in the context of large cortical networks. Through the last decade research in non-human primates demonstrated that the superior colliculi are capable of doing more than just detecting a stimulus and executing a saccade. However, we have almost no



Brain activity during a pointing movement can be monitored by magnetic resonance imaging. The subject gets some last instructions before the recording starts.

idea whether similar functional properties could be present in the human colliculi as the brainstem structures are very difficult to measure in humans. We have not only mastered the task of functional neuroimaging of the superior colliculi in humans, but in our most recent studies also found surprising evidence for its role in the control of arm movements. A precise and conclusive functional mapping of the colliculi in living humans might reveal that this concise structure could be good candidate regions in the framework of neuroprosthetics and brain stimulation in the future.

### The impact of proprioceptive deficits on visuomotor coordination in neurological patients

We take it for granted that we can feel our own body, the position and movements of our own limbs. But soon we realise that it is pretty difficult to explore in more detail the current feedback from our body sensors. In fact, this is also true for experimental and clinical measures of proprioception. In this project we are faced with the same problem, as we want to investigate the actual impact of a flawed feedback of body information on the control and execution of hand movements. There are very few investigations of the influence of an impaired proprioceptive input on visually guided movements in patient populations using trustworthy measurements of proprioception. The widely used clinical screenings are

very insensitive, whereas more precise measures require unacceptable examination durations and procedures. We currently establish technically simple and straightforward, but nevertheless sensitive and reliable procedures to elucidate proprioceptive impairments where these were previously overlooked. These procedures will then allow us to really determine the role of proprioceptive deficits in the occurrence of visuomotor disorders like, for example, optic ataxia.

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## OCULOMOTOR LABORATORY

**Head:** Prof. Dr. Uwe Ilg

**Team:** 4 members

**Key words:** eye movements  
saccades  
smooth pursuit eye movements  
parietal cortex  
frontal cortex  
attention

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*The reaction times as well as the speed of very fast eye movements correlate with a person's daily amount of computer games: People who play more than 1 hr per day video games tend to show shorter saccadic reaction times on one hand and increased maximal eye speed on the other. Surprisingly, the error rates in specific oculomotor tasks are not different between players and non-players. Our findings are absolutely novel and extend classical work on cognitive versus reflexive control of saccades by others. Our data clearly demonstrate that playing video games does not produce a loss of executive control function, at least with respect to oculomotor control systems.*

*Sowohl Reaktionszeiten wie auch die Maximalgeschwindigkeit von sehr schnellen Augenbewegungen korrelieren mit der Dauer, die ein Mensch mit Spielen am Computer verbringt: Menschen, die mehr als eine Stunde pro Tag am Computer spielen, zeigen einerseits kürzere Reaktionszeiten und andererseits höhere Augengeschwindigkeiten als Menschen, die weniger als eine Stunde oder gar nicht am Computer spielen. Überraschenderweise sind die Fehlerquoten zwischen Spielern und Nichtspielern nicht unterschiedlich. Unsere Ergebnisse sind absolut neu und erweitern unser aktuelles Wissen über die kognitive und reflexhafte Kontrolle unserer Augenbewegungen. Sie zeigen sehr klar, dass das Spielen von Computerspielen nicht dazu führt, dass die exekutive Kontrolle abnimmt, zumindest nicht im Zusammenhang mit der Ausführung von Augenbewegungen.*

## Possible effects of video games on eye movement and saccadic reaction time

Saccades are fast gaze shifts between two phases of fixation that move a given detail of our visual periphery into the central field of vision characterized by a superior spatial resolution. The selection of the target of the upcoming saccade includes suppression of other visual stimuli. The interplay between selection and suppression can be studied perfectly in the anti-saccade paradigm: subjects are asked to perform eye movements opposite to the presentation of a visual target. If a target is presented left of the fixation dot, the subject is asked to perform a gaze shift to the right.

Nowadays, video games are an omnipresent medium. In Germany, a recent study showed, that over 46% of the teenagers between 12 and 19 are consuming video games on a daily basis. Despite this strong prevalence the effects of video game consumption are still under debate.

In most of these studies the effects of video games on attention are addressed by indirect measurements and may be influenced by the motivation of the test subjects. We decided to examine possible effects of video games in a simple oculomotor task: the anti-saccade task. The subject has to perform a cognitively driven saccade to the mirror position of a visual target (*anti-saccade*). In some cases, the subject is not able to suppress the gaze shift towards the target, triggered by a reflexive shift of attention towards the target. These saccades are called *pro-saccades*. There is wide agreement that the fast visual orienting responses are generated by the superior colliculus in the midbrain whereas the cognitively driven anti-saccades are mediated by the frontal eye field in the frontal cortex. So the frequency of erroneous pro-saccades can be used as a measure for the strength of the executive control function of the frontal cortex.

As basis for our experiment we tested a total of 55 subjects aged 15 to 31 years. All subjects were classified in three groups in regard to their daily gaming time: non-VGPs played less than one hour per day (n=25),

whereas video game players (VGPs) were divided into intermediate VGPs if they played one to two hours per day and strong VGPs played more than two hours per day.

### VGPs show shorter reaction times

Firstly, we analyzed the saccadic reaction times of our subjects. A general finding was that the erroneous pro-saccades had about 100 ms shorter reaction times than the correctly executed anti-saccades. More strikingly, the reaction times of both saccades were decreased for approximately 10 ms in VGPs compared to non-players.

### VGPs have higher peak velocities

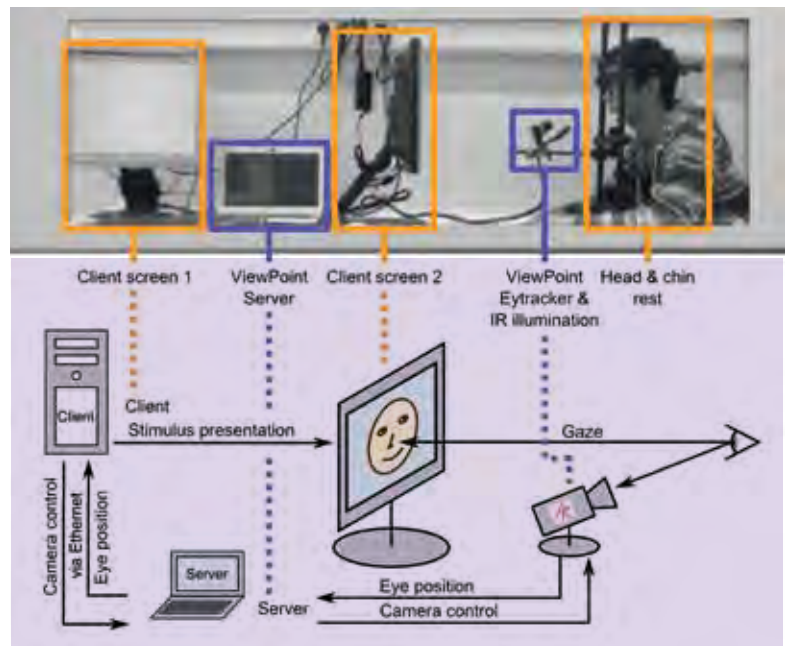
The eye speed during gaze shifts reaches very high values. In our data, the maximal velocity of the eye is between 350 and 400 degrees/second. In other words, if the eyes could rotate without limitations, a complete rotation would occur within one second. As reported by others, pro-saccades reach higher peak velocities than anti-saccades. Surprisingly, both types of saccades of VGPs reach higher peak velocities as gaze shifts executed by non-VGPs.

### No differences in error rates

To examine the cognitive control function, we examined the frequency of erroneous pro-saccades in the anti-saccade task. VGPs as well as non-players showed an error rate of approximately 40%, there was no difference between players and non-players.

### Do shorter saccadic reaction times account for faster attentional processing?

The decrease of reaction times in VGPs may be attributed to faster attentional processing. This is consistent with the reports from other studies, which analyzed the effects of video gaming on attention and found a similar reduction of reaction times in VGPs. It seems that VGPs are especially better in endogenous controlled shifts of attention compared to reflexive shifts of attention.



### No different error rate indicates functioning cognitive control

In general, there is a speed-accuracy trade-off during the execution of anti-saccades. Subjects with short reaction times tend to show higher error rates than subjects with longer latencies. Despite this general relationship, we fail to find an increased amount of errors in VGPs compared to non-players. Since the frequency of pro-saccades is a direct measure for the amount of executive control function, our results show that this function is not impaired in VGPs compared to non-VGPs. Therefore, we conclude that playing video games does not produce negative effects on the control function of the frontal lobe.

*We examined possible effects of video games in a simple oculomotor task: the subject has to perform a cognitively driven saccade to the mirror position of a visual target (anti-saccade).*

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## NEUROPSYCHOLOGY

**Head:** Prof. Dr. Dr. Hans-Otto Karnath

**Team:** 24 members

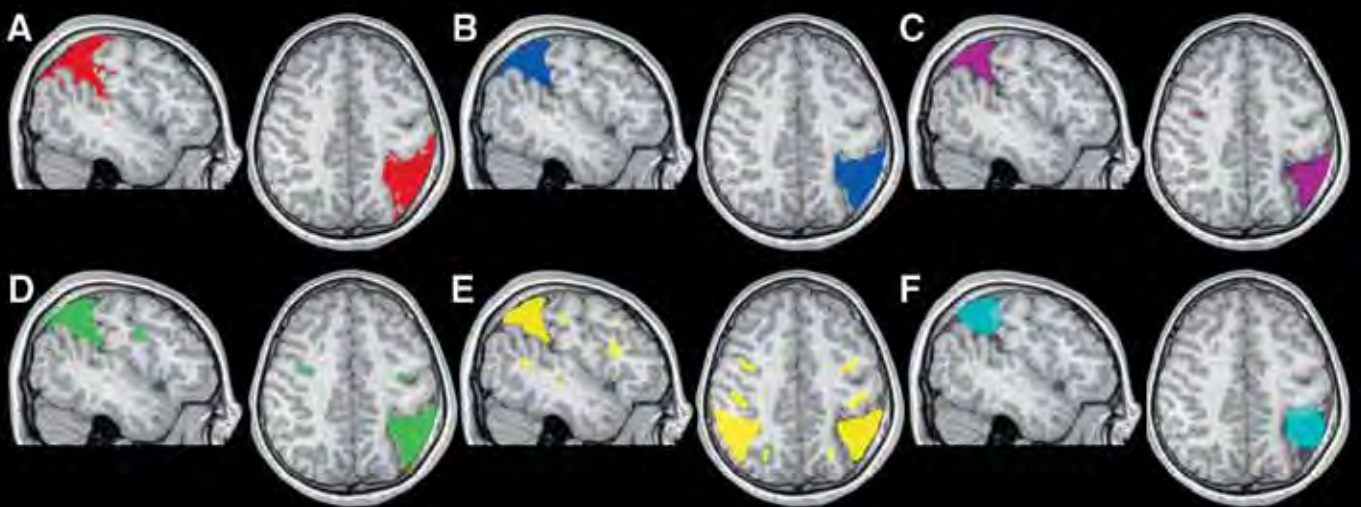
**Key words:** cognitive neuroscience  
neuropsychology

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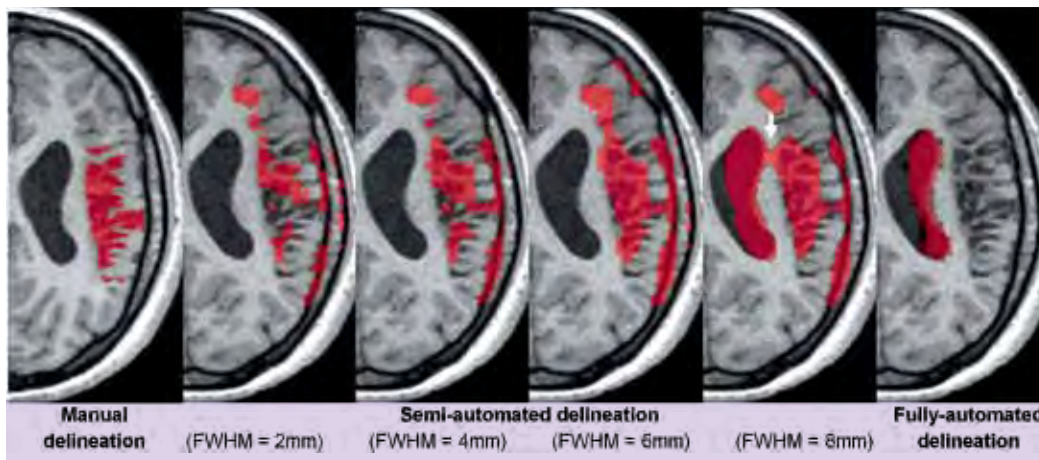
*The Section for Neuropsychology focuses on the investigation of spatial cognition and object recognition in humans. The current issues of our work comprise the action control and sensorimotor coordination, object identification, perception of body orientation, spatial attention and exploration, grasping and pointing movements, and auditory localization in space.*

*Die Sektion Neuropsychologie ist Teil des Themengebiets Kognitive Neurowissenschaften. Zu den Arbeitsschwerpunkten der Sektion gehören die Raumorientierung des Menschen, seine Fähigkeit, Objekte zu erkennen sowie die Wahrnehmung der eigenen Körperorientierung. Darüber hinaus werden Prozesse der Aufmerksamkeit und Raumexploration, die visuomotorischen Koordinationsprozesse beim Zeigen und Greifen sowie die akustische Raumorientierung untersucht.*

The Division of Neuropsychology's main areas of research are the study of spatial orientation and object perception in humans. To this end, techniques such as functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), eye tracking, and the motion capture of hand and arm movements in both patients with brain-damage and healthy subjects are employed. Additionally, the mechanisms and processes of human perception of objects, attention, the exploration of space, as well as visuomotor coordination during pointing, grasping and object interaction/manipulation are examined.



*Manual, semi-automated, and automated delineation of chronic brain lesions: a comparison of methods.*



Manual, semi-automated, and automated delineation of chronic brain lesions: a comparison of methods.

However, the greater question driving the Division of Neuropsychology's research is "How do organisms perform sensorimotor coordination processes?". For example, in order to generate successful motor actions (e.g. pointing or grasping movements) we must actively deal with the problem of spatial exploration and orientation. In order to do this it is necessary to process a multitude of sensorimotor information that is derived from constantly changing coordination systems. Another major focus of Cognitive Neurosciences is to investigate how this task is accomplished by the human brain.

The answers to our research questions do not only allow for a better basic scientific understanding of these processes but will also guide us to develop new strategies for the treatment of patients with brain-damage who show deficits in these areas.

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**MRI LABORATORY****Head:** PD Dr. Fahad Sultan, Dr. Peter Dicke**Team:** 6 members**Key words:** functional magnetic resonance imaging  
social attention  
subcortical networks  
brain evolution  
electrical stimulation[www.hih-tuebingen.de/mri-labor](http://www.hih-tuebingen.de/mri-labor)

*The unparalleled expansion of the human brain following an evolutionary process underlies many of our higher cognitive abilities. This increase was accompanied by a number of adaptations that we share with our fellow primates. Understanding the evolutionary adaptations that occurred and relating them to the human cognitive abilities that emerged is important for several diseases of the human brain (e.g., autism). In this lab-unit we for instance compare non-human primates with the human ability for gaze following and map the brain with functional magnetic resonance imaging (fMRI) to identify regions relevant for social interactions. In another project we compare subcortical regions in the cerebellum in primates and relate these to specializations in network architecture of the human brain. Together with Nikos K. Logothetis from the Max Planck Institute for Biological Cybernetics we use electrical stimulation to study the output of these specialized networks with fMRI and show that these subcortical regions target wide-spread cortical networks.*

*Unsere höheren Hirnleistungen sind in einem evolutionären Prozess erworben worden und basieren auf einigen Spezialisierungen in der Netzwerkarchitektur unserer Gehirne. Viele dieser evolutionären Anpassungen teilen wir mit den uns nächsten Verwandten, den Primaten. Das Verständnis dieser Anpassungen und ihrer Beziehung zu unseren Hirnleistungen könnte für das Erfassen zahlreicher Erkrankungen (z. B. Autismus) entscheidend sein. In unserem Labor untersuchen wir u. a. die Fähigkeiten von nicht-humanen Primaten und von Menschen, verschiedenen Blickrichtungen folgen zu können, sowie die diesen Fähigkeiten zugrunde liegenden Netzwerkstruktur des Großhirns mittels funktioneller Magnetresonanztomographie (fMRT). Ein weiterer Fokus unserer Forschung ist die Spezialisierung der Netzwerkarchitektur tieferer Hirnstrukturen. Diesem Aspekt wurde bisher nur sehr wenig Beachtung geschenkt. In Zusammenarbeit mit Nikos K. Logothetis vom Max-Planck-Institut für biologische Kybernetik in Tübingen untersuchen wir mittels elektrischer Stimulation und fMRT die Verbindungen der tiefen Hirnstrukturen zum Großhirn. Unsere Ergebnisse zeigen erstmalig, dass diese tiefen Hirnstrukturen einen bedeutenden Einfluss auf weitreichende Großhirnnetzwerke haben.*

**Correlated human and monkey fMRI**

**fMRI of gaze following in humans:** The direction of a person's gaze indicates what object he or she is paying attention to and a shift in gaze direction indicates a change of the object of attention. Hence, gaze direction may serve as a key to developing an understanding of the other one's interests and possible intentions. Indeed, humans make use of eye-gaze, i.e. the orientation of someone else's eyes relative to objects in the world, very early during development and impaired processing of gaze information may be the basis of disturbances of social communication such as autism. The substrates and the principles underlying gaze directions are only insufficiently understood. We have used fMRI to delineate the relevant areas in the human brain and 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 (grey value of the iris) to make an eye movement towards an object in space. Our results show that the posterior part of the STS region and the cuneus are specifically involved in extracting and using detailed directional information from the eyes of another person to redirect one's own gaze and establish joint attention.

**fMRI of gaze following in monkeys:** For monkey-fMRI we are using a standard clinical 3T scanner (TimTrio Siemens). Visual stimuli are projected onto a fronto-parallel screen. Eye movements are tracked using a homemade, MRI-compatible eye tracker. The principal aim of this project is the identification of areas in the monkey brain that are functionally equivalent to those of humans, allowing one to use results obtained by electrophysiologically exploring the activated areas in the monkey brain in order to draw inferences on the properties of the activated areas in the human brain. We are currently using this approach to

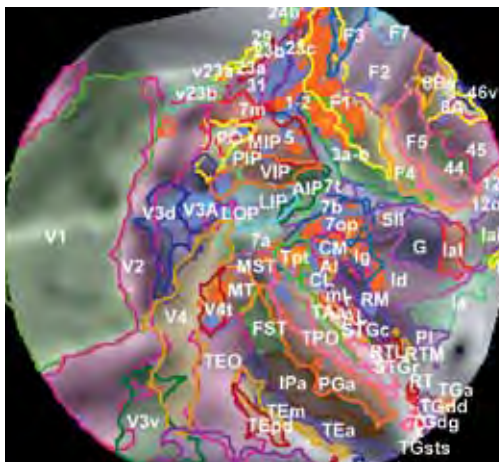
analyze the neuronal underpinnings of gaze direction processing. Rhesus monkeys have been successfully trained to use gaze direction as offered by portraits of other monkeys in order to reallocate their attention to particular objects in space.

### In-vivo imaging of the monkey brain's connectivity

**Unravelling a cerebellar high-frequency pathway targeting extensive motor, sensory and parietal cortical networks:** Electrical stimulation of the gateway of the cerebellar output, the deep cerebellar nuclei (DCN), leads to reliable transsynaptic responses in the neocortex. There is a striking difference between our previous results by electrical stimulation of striate and extrastriate neocortex and our current DCN stimulation results. Differences in inhibition probably constitute a crucial factor.

Stimulation of the neocortex revealed the presence of strong inhibition, thus preventing the propagation of electrically-induced activation over multi-synaptic pathways. Stimulating the DCN we observed stimulation-induced BOLD activity in classical cerebellar receiving regions such as primary motor cortex, as well as in a number of additional areas in insular, parietal and occipital cortex, including all major sensory cortical representations. Independent of the specific cerebral area activated, responses were strongest for very high stimulation frequencies ( $\Rightarrow$  400Hz), suggesting a projection system optimized to mediate fast and temporarily precise information.

In conclusion, both the topography of the stimulation effects as well as its emphasis on temporal precision is in full accordance with the notion of cerebellar forward model information modulating cerebro-cortical processing.



Electrical stimulation of the gateway of the cerebellar output, the deep cerebellar nuclei (DCN), leads to reliable transsynaptic responses in the neocortex.

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## SYSTEMS NEUROPHYSIOLOGY

**Head:** Prof. Dr. Cornelius Schwarz

**Team:** 10 members

**Key words:** neocortex  
multiple neuron recordings  
active touch  
cognitive control  
perception  
sensory detection  
sensory discrimination

[www.hih-tuebingen.de/en/systems-neurophysiology](http://www.hih-tuebingen.de/en/systems-neurophysiology)

*We study the operating principles of the neocortex using modern multi-neuron electrophysiology and optical methods. We have established methods to observe tactile sensorimotor behavior in rodents that let us study neocortical function during highly defined and precisely monitored behavior. The similarity of neocortex in animals and humans suggests that the results can be transferred easily to research on human disease (Alzheimer's, Parkinson's, schizophrenia, and depression).*

*Wir erforschen die Funktion des Großhirns (Neokortex) mithilfe moderner Multineuronen-Elektrophysiologie und bildgebender Verfahren auf zellulärer Ebene. Dazu haben wir neuartige Methoden entwickelt, mit denen wir beobachten können, wie Nagetiere ihren Tastsinn einsetzen. Damit sind wir in der Lage, funktionelle Aspekte der Großhirnfunktion für genau definiertes und präzise vermessenes Verhalten zu untersuchen. Die Ähnlichkeit des Neokortex bei Tieren und Menschen legt nahe, dass unsere Resultate sehr einfach auf die Erforschung von Dysfunktion bei menschlichen Großhirnerkrankungen übertragbar sein werden (Alzheimer, Parkinson, Schizophrenie und Depression).*

## Associative coupling in the neocortex

The overarching goal of our work is to understand the operating principles of the neocortex, a unique brain structure which mainly evolved in mammals. There is clear evidence that the neocortex, in the broadest sense, endows the subject with cognitive capabilities. The big mystery is, how the vast diversity of neocortex-dependent behaviors are generated by a structure that shows nearly identical neural architecture across species (mouse, rat, monkey, human) and functional systems (sensory, motor, cognition): The neocortex is a quasi-two dimensional sheet of neural tissue, which is composed of repetitive neuronal elements and network connections. Even an expert can hardly decide on the basis of a microscopic image of neocortex, whether it was prepared from a mouse, rat, monkey or human.

The generality of neuronal architecture related to vastly diverse functions renders it likely that, beyond specific signal processing, there must be a generic function common to all cortical areas in animals and humans. We hypothesize that the neocortex is a giant associative storage device, which handles flexible combinations of sensory, motor and cognitive functions that the individual has learned in his/her life.

To verify this hypothesis, we firstly need to clarify how signals are represented within neocortical networks and what role the confusing multitude of neuronal components plays (e.g. the six neocortical layers, or the various types of excitatory and inhibitory neurons). Second, it must be resolved how separate areas are linked and whether the link and concurrent signal processing make use of the same neural elements and activities, or whether they can be separated.

This research therefore requires the combination of a macroscopic and microscopic view – i.e. the study of representation of memories on the cellular level locally and their linkage between cortical areas globally. We employ modern methods of multiple neuron electrophysiology and optical imaging and combine it with behavioral observation at highest precision. Our model for studying these questions is the sensorimo-



*Active tactile exploration of the environment using vibrissa*



tor vibrissal system (vibrissae = whiskers) of rodents. These animals use an ‘active’ strategy of sampling tactile information about their immediate environment by actively moving their vibrissae across objects in their vicinity. We examine tactile representations, how they are formed into a percept, and how they are coupled to motor representations to optimize tactile exploration. In addition, we have begun to study coupling of other areas, e.g. sensory and so-called higher cortical areas, during decisions making.

Regarding the close similarity of neocortex in animals and humans it is very likely that basic scientific knowledge that we gain in animals can be generalized very easily to understand also principles of function or dysfunction in humans and patients. Of course, future applications for the better of humans suffering from neocortical diseases such as Alzheimer’s and Parkinson’s disease, schizophrenia, or depression, need future progress in applied and translational neuroscience. However, before this can happen, a thorough understanding of the bases of neocortical function has to be reached. This is the purpose of our research.

Beyond the goal to understand the function of the neocortex we have started to direct our research toward possible future applications. We work toward the establishment of cortical sensory neuroprostheses, that in the future might help those help patients, who lost a sense due to a disease of the central nervous system. A major problem is that percepts produced by electrical activation of cortical networks depend

very much on the sensory and behavioral context. Our solution to this problem is to establish intelligent implants that measure neural activity to assess information about contexts (i.e. the associative state of the cortical tissue to be activated) and use this to increase precision with which sensory signals can be imprinted into central neuronal structures and reach perception.

*Rodents deploy their whiskers to explore their environment.*

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**Hertie Institute**  
for Clinical Brain Research



**DEPARTMENT OF  
CELLULAR NEUROLOGY**



Alois Alzheimer, born in 1864, is credited with identifying the first published case of “presenile dementia”, later identified as Alzheimer’s disease.

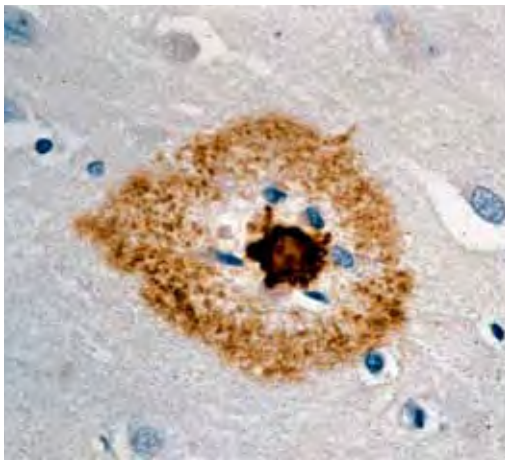
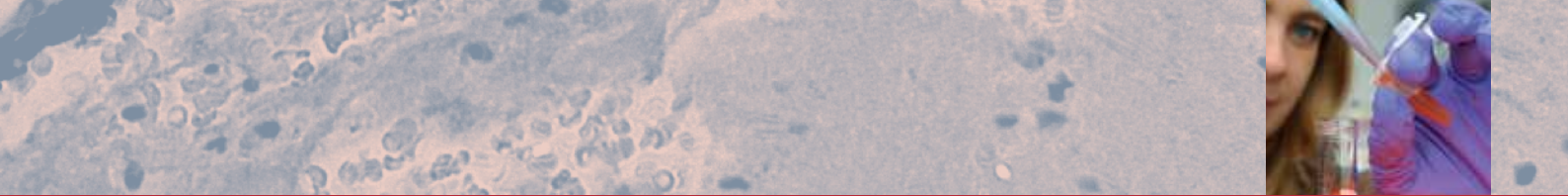
## DEPARTMENTAL STRUCTURE



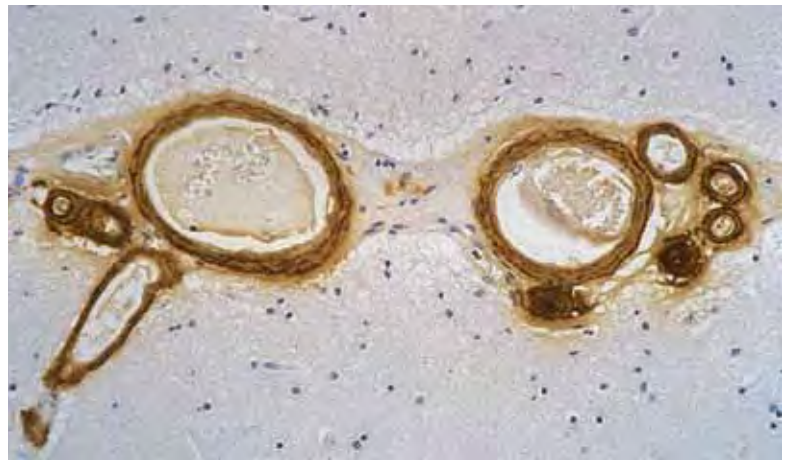
Prof. Mathias Jucker is head of the Department of Cellular Neurology

The Department was founded in 2003. The research focus is on the cellular and molecular mechanisms of brain aging and age-related neurodegenerative diseases with a special emphasis on the pathogenesis of Alzheimer’s disease and cerebral amyloid angiopathy. Alzheimer’s disease is the most frequently occurring age-related dementia with more than one million people affected in Germany. It was in Tübingen that Alois Alzheimer described the disease in 1906 for the first time to his colleagues.

Currently our department is composed of four research groups and one core unit: The group of Molecular Biology studies the processing and metabolism of the pathogenic proteins that are involved in Alzheimer’s disease and related dementias. The Neuropathology group uses primarily transgenic mouse models to study the pathomechanisms of Alzheimer’s disease and cerebral amyloid angiopathies. The Neuroimmunology group works on aspects of innate immunity in the aging brain and neurodegenerative diseases with a special focus on therapy. Finally, the group of Molecular Imaging studies how Alzheimer’s disease lesions and neurodegeneration develops over time using *in vivo* multiphoton microscopy. The core unit supports the department primarily with mouse genotyping, ELISA measurements, and other technical and administrative support.



*Amyloid plaque (A $\beta$  immunocytochemistry) in an Alzheimer brain*



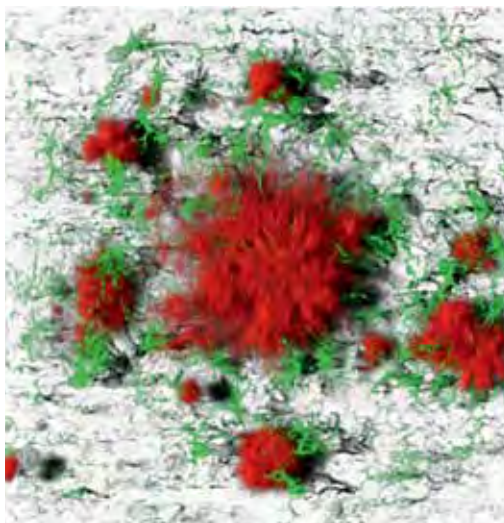
*Vascular amyloid (cerebral amyloid angiopathy) in an Alzheimer brain.*

Our department hosts scientists from more than 10 nations ranging from short-term fellows, master students, PhD/MD students to postdocs and group leaders. The department includes two open W3 professor positions that will be filled in the coming years. For one position it is planned to recruit a more clinically oriented scientist 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 extramurally highly competitive and intramurally socially attractive for coworkers.

**ALZHEIMER'S DISEASE****Head:** Prof. Dr. Mathias Jucker**Team:** 18 members**Key words:** cellular neurology  
Alzheimer's disease  
cerebral amyloid angiopathy[www.hih-tuebingen.de/zb](http://www.hih-tuebingen.de/zb)

*Our objective is to understand the pathogenic mechanism of Alzheimer's disease and related amyloidoses and to develop therapeutic interventions.*

*Unser Ziel ist, den Pathomechanismus der Alzheimer-Erkrankung und verwandter Amyloiderkrankungen zu verstehen und therapeutische Interventionen zu entwickeln.*



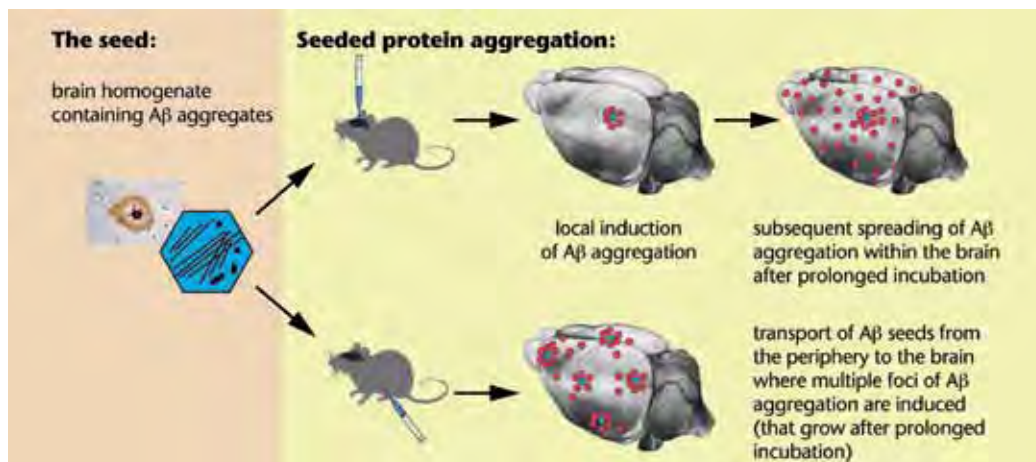
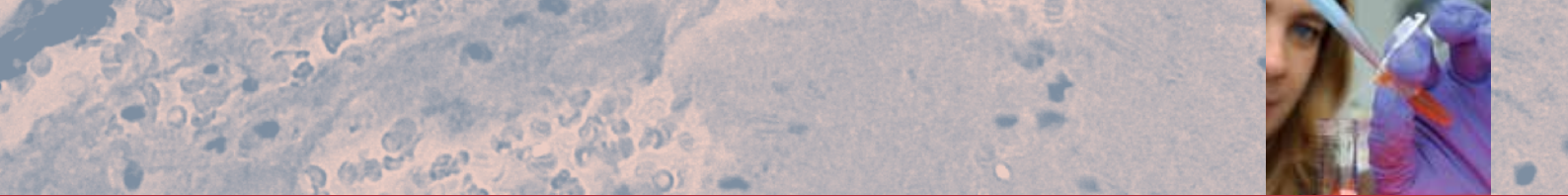
*Microglia (green) surrounding an amyloid plaque (red)*

Misfolded proteins are the cause of many neurodegenerative diseases. How these proteins misfold and what the initial trigger is for the misfolding and their subsequent aggregation is, however, largely unknown. Furthermore, it remains unclear why the aging brain is a risk factor for neurodegenerative diseases.

In Alzheimer's disease aggregated  $\beta$ -amyloid ( $A\beta$ ) protein is deposited extracellularly in so-called amyloid plaques. Aggregated  $A\beta$  leads to a miscommunication between the cells and in a second stage to neuron death. The same  $A\beta$  protein can also build up in blood vessels which will cause amyloid angiopathy with potential vessel wall rupture and fatal cerebral bleedings.

In the past few years we have managed to generate transgenic mouse models that either mirror Alzheimer's pathology by developing  $A\beta$  plaques or serve as a model for cerebral amyloid angiopathy by depositing  $A\beta$  protein in blood vessels. With the help of these models we have been able to show that  $\beta$ -amyloid aggregation can be induced exogenously by inoculations of mice with brain extracts from deceased Alzheimer patients or from aged transgenic mice with  $A\beta$  deposition. The amyloid-inducing agent in the extract is probably the misfolded  $A\beta$  protein itself. Thereby, soluble proteinase K (PK)-sensitive  $A\beta$  species have been found to reveal the highest  $\beta$ -amyloid-inducing activity.

These observations are mechanistically reminiscent of prion diseases and are now used to develop new therapeutic approaches



*$\beta$ -amyloid containing brain extracts which are intracerebrally or intraperitoneally injected in young APP transgenic mice induce A $\beta$ -aggregation and deposition in the animals.*

for Alzheimer's disease and other amyloidoses. First immunotherapy trials in transgenic mice are promising and show that  $\beta$ -amyloid aggregation can be reduced by targeting the initial proteopathic A $\beta$  seeds. Microglia appear to play a crucial role in A $\beta$  immunotherapy.

It is important to translate therapy success in mice into clinical settings. Moreover, it is essential to detect and prevent A $\beta$  aggregation in mice and men before it leads to the destruction of neurons as seen in Alzheimer's disease. To this end we use *in vivo* 2-photon microscopy to track initial A $\beta$  aggregation and analyze A $\beta$  levels in mouse cerebrospinal fluid as an early biomarker of Alzheimer's disease.

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## MOLECULAR BIOLOGY

**Head:** Dr. Frank Baumann; Dr. Ellen Kilger

**Team:** 4 members

**Key words:** molecular mechanisms of neurodegeneration

[www.hih-tuebingen.de/molekularbiologie](http://www.hih-tuebingen.de/molekularbiologie)

*We study mechanisms of neurodegeneration in Alzheimer's Disease. We use molecular and cell biology techniques to identify key processes and potential steps of intervention.*

*Wir untersuchen Mechanismen der Neurodegeneration bei der Alzheimer-Erkrankung. Dabei nutzen wir Methoden der Molekular- und Zellbiologie, um Schlüsselschritte und Interventionspunkte zu finden.*

The Molecular Biology group has its focus in four major areas:

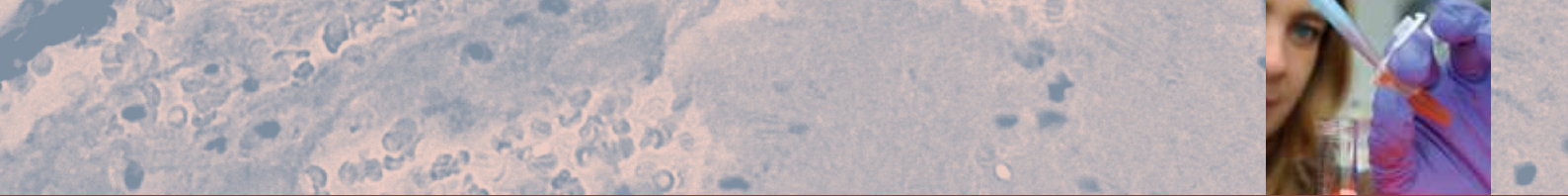
- (i) Processing and cellular function of the amyloid precursor protein (APP)
- (ii) Intervention strategies to lower the amount of A $\beta$  liberated from APP
- (iii) Uptake and spreading of protein aggregates
- (iv) Neurotoxic mechanism underlying proteopathies.

APP is one of the major proteins involved in Alzheimer's disease (AD) but its physiological function remains elusive. Sequential cleavage of APP by  $\beta$ - and  $\gamma$ -secretase leads to generation of amyloid-beta (A $\beta$ ) peptides, the major components of amyloid plaques in the brain of patients with AD. In addition, also a c-terminal fragment (AICD) is liberated whose cellular function is not yet understood. In the past the group has concentrated on processes that regulate APP processing with the aim to find new pathways to decrease the amount of A $\beta$  peptides as a therapeutic strategy for

AD. Profound insights into the mechanism of Gleevec, a known tyrosine kinase inhibitor, were gained.

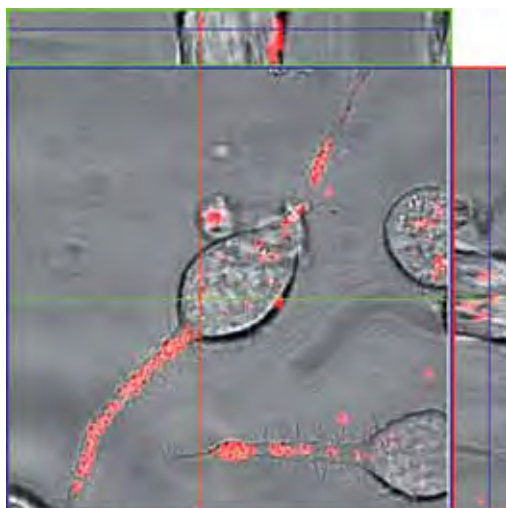
Recently another protein Briz came into focus. APP and Briz are both genetically linked to specific forms of dementia. Mutations in the Briz gene cause Familial British Dementia (FBD) and Familial Danish Dementia (FDD). One similarity is that both APP and Briz have to undergo proteolytic processing to liberate small aggregation prone peptides. These are in turn the building blocks of extracellular deposits formed either as plaques or around blood vessels in brains of patients. Like in AD models a recently established FDD-model recapitulates the main histologic features. Recent *in vitro* results suggested a direct interaction of Briz with APP which lead to altered APP processing and decreased A $\beta$  secretion. Our further in depth analysis revealed a new mechanism of interaction. In agreement with previous results we found that overexpression of Briz leads to a significant decrease in total secreted A $\beta$  and an increase in other c-terminal fragments. Furthermore, we could identify the upregulation of secreted insulin degrading enzyme (IDE), a major degradation protease, under these conditions. This was independent of the processing of Briz and also worked in a truncated version of the protein. We suggest now that Briz might act as a receptor that regulates IDE levels which in turn affects A $\beta$  levels by influencing APP metabolism. Therefore the regulation of IDE activity may be a new promising therapeutic approach.

A $\beta$  deposition has long been associated with neurodegeneration. However, animal models that succeeded to mimic plaque formation failed to display neurodegeneration or neuronal loss. Isolated neuronal cells are, however, very sensitive to oligomeric forms of A $\beta$  though never forming plaque-like aggregates. To understand this discrepancy we started to investigate uptake and spreading of A $\beta$  in cultured cells. Preliminary results suggest a prominent role of APP in the process of uptake yet it remains unclear whether it acts as a receptor or whether APP associated modifications have an indirect influence on internalization. Uptake and intracellular production of A $\beta$  may result



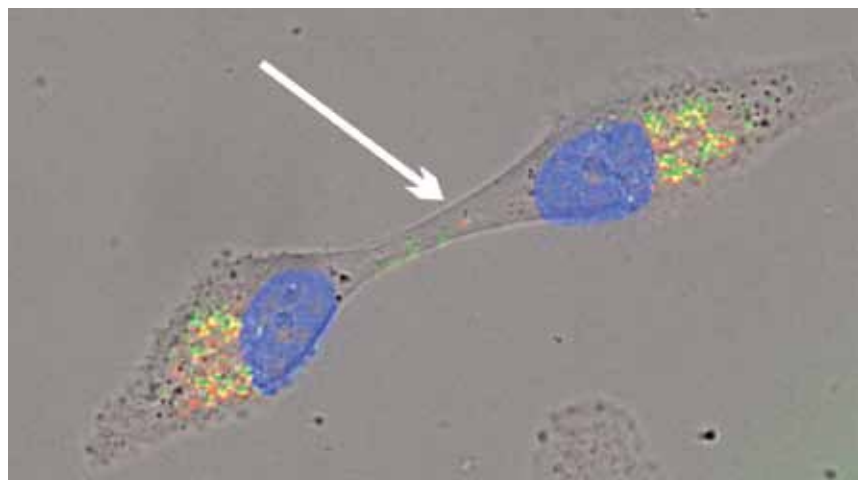
in the accumulation of A $\beta$  also within cells and organelles. Previous reports have drawn attention to the accumulation of A $\beta$  within mitochondria. With a novel *in vivo* targeting approach based on previous studies we established the exclusive sorting of A $\beta$  to mitochondria and are currently investigating metabolic consequences.

A $\beta$  aggregation has been studied extensively *in vitro*. Recently lipids have come into focus as a key component for aggregation of infectious prion protein aggregates. Furthermore, membranes and membrane anchoring proved to be key features for neurotoxic-



Uptake and intracellular aggregation of fluorescently labeled (red) A $\beta$  particles in N2A-neuroblastoma cell line (3D reconstructed confocal image with 2D Projections; X/Y-plane: blue box, Z/Y: red box, Z/X: green box).

ity in prion diseases. To investigate whether similarly membrane association of A $\beta$  would promote both aggregation and neurotoxicity *in vivo* we have modified the A $\beta$  peptide. Using previous expression methods we established membrane anchored A $\beta$  with an artificial C-terminal membrane anchor. Preliminary results indicate that A $\beta$  can indeed be stably expressed on cell surfaces both in cell culture models and in transgenic mice. Membrane anchored A $\beta$  also promotes plaque deposition *in vivo* when co-expressed with soluble A $\beta$  in mice. Future work will utilize this model to understand the role of membrane anchored A $\beta$  intermediates in initiation of A $\beta$  aggregation and neurotoxicity.



Live image of A $\beta$  (green) spreading between two cells. Arrow indicates an intracellular moving aggregate. (Lysosomes red, nuclei blue, lysosomal A $\beta$  yellow)

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**Hertie Institute**  
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**INDEPENDENT  
RESEARCH GROUPS**



## NEUROREGENERATION AND REPAIR

**Head:** Dr. Simone Di Giovanni

**Team:** 8 members

**Key words:** synaptic plasticity  
spinal cord injury  
stroke  
axonal regeneration  
neurogenesis  
transcription

[www.hih-tuebingen.de/neuroregeneration-re](http://www.hih-tuebingen.de/neuroregeneration-re)

*Following acute central nervous system (CNS) injury, axonal regeneration is limited, due to a lack of neuronal intrinsic competence and the presence of extrinsic inhibitory signals. Injury fragments the myelin insulating layer, releasing extrinsic inhibitory molecules. We show here that a neuronal transcriptional pathway can interfere with extrinsic inhibitory myelin-dependent signaling, thereby promoting neurite outgrowth. Our findings identify a novel link between pro-axonal outgrowth and inhibitory signaling, thus allowing for the development of molecular strategies to enhance axonal regeneration following CNS injury.*

*Bei einer akuten Verletzung des zentralen Nervensystems (ZNS) haben Nervenfasern von Natur aus nur eine eingeschränkte Fähigkeit, sich zu erneuern. Hinzu kommt, dass durch die Verletzung der isolierenden Myelinschicht Moleküle freigesetzt werden, die über einen membranständigen Rezeptorkomplex die Regeneration der Nervenzellen verhindern. Wir haben die molekularen Komponenten eines Mechanismus identifiziert, der in diese Blockade eingreift und damit letztlich das erneute Auswachsen von Nervenfasern unterstützt. Auf der Basis dieser Erkenntnisse können wir nun neue molekulare Strategien entwickeln, die die Nervenregeneration nach einer Verletzung verbessern.*

### RA-RAR $\beta$ counteracts myelin-dependent inhibition of neurite outgrowth

The neuronal insulating layer, myelin, is fragmented following a spinal lesion, releasing the extrinsic inhibitory molecules, MAG, Nogo and OMgp that inhibit axonal outgrowth and functional recovery following injury. These myelin proteins signal through the neuronal membrane bound Nogo Receptor (NgR) complex, which includes NgR1, Lingo-1, and p75<sup>NTR</sup> or TROY. Myelin protein engagement of the NgR complex activates RhoA, which induces ROCK-dependent phosphorylation of cofilin, thus actin depolymerization and growth cone collapse.

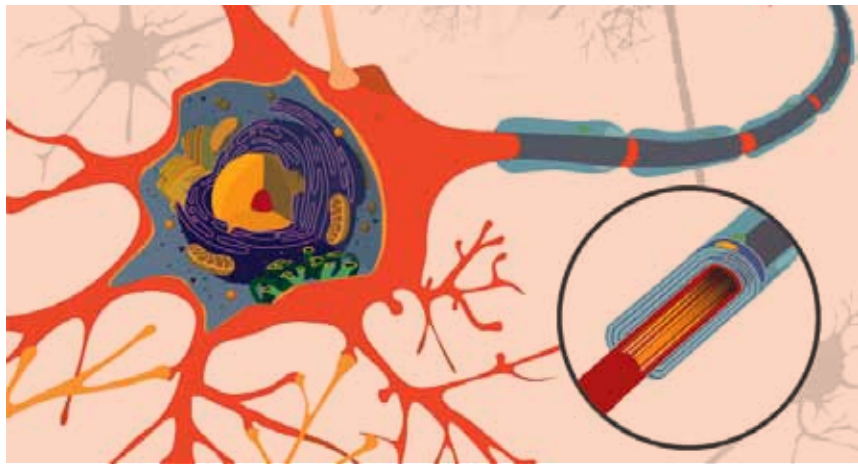
Overexpression of the transcription factor, retinoic acid (RA) receptor beta 2 (RAR $\beta$ 2) promotes neurite outgrowth in primary neurons cultured on inhibitory substrates and induces axonal regeneration via neuronal intrinsic pathways *in vivo* following a spinal lesion. More recently, phosphorylated AKT, a serine/threonine kinase, was associated with the beneficial effects of RAR $\beta$ 2, however, so far no direct transcriptional targets for RAR $\beta$ 2 that promote neurite outgrowth on inhibitory substrates have been identified.

Importantly, transcriptional pro-neurite outgrowth and extrinsic inhibitory pathways have not been previously shown to directly intersect or form a unique signaling cascade. Specifically, we show for the first time that myelin strongly inhibits the recruitment of RAR $\beta$  to the RARE1 in the Lingo-1 promoter and that RA treatment allows RAR $\beta$  to occupy the RARE1 of the Lingo-1 promoter thereby inhibiting its expression in response to myelin. Furthermore, Lingo-1 gene silencing experiments, which repressed Lingo-1 expression at both the mRNA and protein level, enhanced neurite outgrowth similar to that of RA treatment alone. These data confirm that the protective role of RA-RAR $\beta$  in neurite outgrowth on an inhibitory myelin substrate involves Lingo-1 inhibition.

It has been established that inhibition of Lingo-1 or RhoA activation as well as overexpression of RAR $\beta$ 2 or administration of a RAR $\beta$  agonist all promote axonal sprouting and functional recovery following SCI. Inter-

estingly, the administration of RA not only activates the transcription factor RAR $\beta$  but also increases its gene expression. What remains to be determined is whether RA will repress Lingo-1 expression following SCI, as this would have relevant implications for the described pro-regenerative role of RA-RAR $\beta$  pathways. We show that Lingo-1 expression is repressed by RA treatment (5mg/kg daily via IP injection) versus vehicle (DMSO) following a dorsal overhemisection. Underlining the importance of Lingo-1 repression is the fact that the presence of all three members of the NgR complex is necessary for RhoA activation. Moreover, Lingo-1 repression is not observed in RAR $\beta$   $-/-$  mice. This *in vivo* data provides physiological relevance to the novel molecular mechanism we have elucidated *in vitro*.

Our findings identify for the first time a direct link between the neuronal pro-neurite outgrowth RA-RAR $\beta$  pathway and extrinsic inhibitory NgR complex-dependent signaling. We show that RA bound RAR $\beta$  occupies a novel RARE on the Lingo-1 promoter, transcriptionally repressing Lingo-1 gene activation and thus RhoA activation, culminating in neurite outgrowth. This is the first report of transcriptional regulation of a NgR complex member, suggesting that transcriptional control plays a critical functional role for at least one NgR complex member, Lingo-1. Furthermore, we demonstrate that Lingo-1 expression is required for RA-RAR $\beta$  to counteract myelin-dependent inhibition of neurite outgrowth. Finally, we provide physiological confirmation that RA represses Lingo-1 expression *in vivo* following SCI in a RAR $\beta$ -dependent manner. These findings are consistent with, yet further develop, earlier reports that showed a role for RAR $\beta$ 2 in promoting axonal regeneration following SCI. Given that RA and the regenerative molecule cyclic AMP induce expression of RAR $\beta$ , it will be of interest to determine their combined regenerative effect. Understanding the precise mechanism involved in induction of neuronal regeneration by RA-RAR $\beta$  signaling may allow for more comprehensive combinatorial therapies with clinically available RA, for example with the CSPG inhibitor chondroitinase ABC, for the treatment of SCI.



A spinal lesion may lead to a fragmentation of the neuronal insulating layer, myelin. We identified molecular components that counteract the inhibitors of axonal outgrowth and functional recovery.

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## PHYSIOLOGY OF LEARNING AND MEMORY

**Head:** Dr. Ingrid Ehrlich

**Team:** 6 members

**Key words:** synaptic plasticity  
amygdala  
fear learning  
extinction  
anxiety disorders

[www.hih-tuebingen.de/learning-and-memory](http://www.hih-tuebingen.de/learning-and-memory)

*We study learning and memory processes using associative fear conditioning and extinction in rodents. We apply physiological techniques to decipher cellular and synaptic processes in neural circuits of the amygdala and related areas. This allows to understand how learning modifies brain circuits and how these processes may be dysregulated in anxiety disorders.*

*Wir untersuchen Lern- und Gedächtnisprozesse anhand von klassischer Furchtkonditionierung und Extinktionslernen. Dabei verwenden wir vor allem physiologische Methoden, um die zellulären und synaptischen Veränderungen in den neuronalen Schaltkreisen der Amygdala zu ergründen. Dies gibt uns Aufschluss darüber, wie Lernprozesse im Gehirn umgesetzt werden, aber auch wie eine Fehlsteuerung dieser Prozesse zu Angststörungen führen kann.*



Organisms continuously adapt their behavior to survive. Such experience-driven adaptations are mediated by modifications in brain function. We study changes in brain function by investigating fear conditioning and extinction of fear in mice, a powerful model for associative learning and memory. Our goal is to elucidate the molecular, synaptic and cellular changes in neural circuits that process fear-related information. We combine several techniques, including slice electrophysiology, imaging, histology, viral gene transfer *in vivo*, and behavioral analysis.

The amygdala, a brain structure in the temporal lobe, is a key structure for storing fear memories. Fear memories can be modified by a second learning process called extinction, where the individual learns that certain stimuli are not fearful anymore in a specific setting. Extinction depends on a larger brain network comprising the amygdala, the hippocampus (a structure important for different forms of memory and processing of spatial information) and the medial prefrontal cortex (a structure associated with the control of actions), as well as interactions between them. To date, some of the strongest links between neural plasticity and behavioral learning come from studies of fear memory in the amygdala. Changes can be detected *ex vivo* in recordings from brain slices obtained from trained animals. Our research hinges on using this approach. While plastic changes of sensory inputs (from thalamus and cortex) to excitatory cells in the amygdala are well understood, inputs from other structures as well as intra-amygdala inhibitory elements may also undergo plasticity. Our goal is to identify and investigate novel changes in these networks.

One line of research aims to understand properties and function of a specific set of inhibitory neurons in the amygdala, the intercalated cells. These cells have recently received much attention, as they become activated during fear behaviors and are crit-

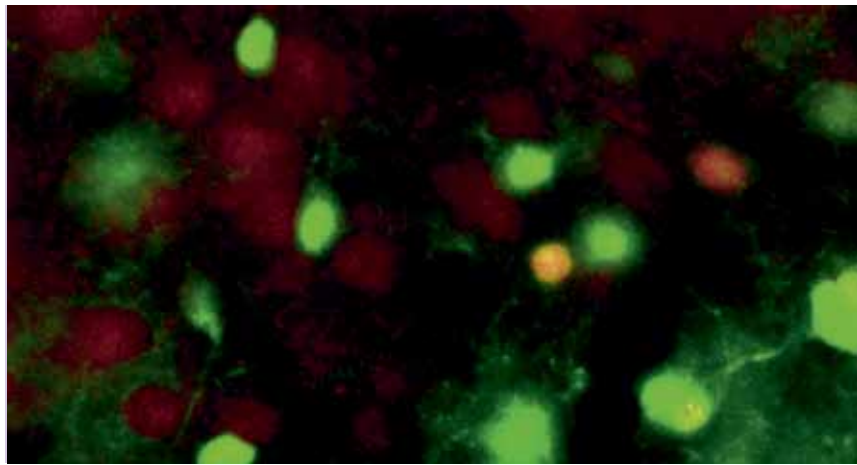
*Lab member Daniel Bosch working on the patch clamp setup recording amygdala neurons in live brain slices.*

ical for extinction. However, little is known about their properties and connectivity. We combine electrophysiological and anatomical techniques to understand how they are integrated and process information within amygdala networks. Our findings indicate that most of these cells receive sensory thalamic and cortical inputs. Morphological analysis reveals subclasses of these neurons with diverse outputs to different amygdala regions. Our future goal is to combine recordings with two photon imaging to investigate plasticity at individual synapses onto these inhibitory cells and learning-driven changes in their inputs and morphology.

A second line of research investigates interactions of amygdala, hippocampus, and prefrontal cortex at the cellular level, which are critical for understanding extinction mechanisms. To do so, we developed targeted stimulation of long-range inputs to the amygdala using viral-driven expression of light-activatable channels for simultaneous visualization and optical stimulation. We started to characterize specific inputs from subregions of the prefrontal cortex to selected target cells (identified in transgenic mice) in the amygdala of naïve animals. Our next goal is to address how synaptic communication between these brain areas changes in animals subjected to fear and extinction learning.

A third line of research addresses developmental processes in amygdala circuits that could underlie developmental differences in learning behavior. The ability to learn fear first emerges in infancy and changes into adulthood. Extinction learning emerges in juveniles, but is different from adults. While extinction in adults depends on multiple brain areas and appears to suppress fear memory, extinction in juveniles depends on the amygdala and appears to erase fear memory. We are currently investigating developmental changes particularly in amygdala inhibitory networks that occur between infancy and adulthood. Our future goal is to elucidate the underlying mechanisms and ultimately to see if they are linked to differences in learning behavior.

Studying mechanisms of fear and extinction memory not only provides insights



Fluorescent image of the amygdala of transgenic mice expressing green fluorescent protein (green) in inhibitory interneurons, costained with the calcium binding protein Calretinin (red) which weakly labels excitatory neurons and some interneurons (yellow).

into general principles of memory formation, but also into neural dysfunction during inappropriate control of fear in conditions such as human anxiety disorders.

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**SYNAPTIC PLASTICITY****Head:** Dr. Tobias Rasse**Team:** 13 members**Key words:** Drosophila  
synapse  
axonal transport  
in vivo imaging[www.hih-tuebingen.de/synaptic-plasticity](http://www.hih-tuebingen.de/synaptic-plasticity)

*Our research focuses on regulatory mechanisms controlling neuronal communication. We want to unravel the nature of neuronal communication breakdown that leads to neurodegeneration. Drosophila larvae are used to trace individual neuronal contacts (synapses) to detect structural modifications in them that lead to changes in larva and adult fly behaviour. A time course study of cellular alterations occurring during neurodegeneration progression provides a valuable insight into the mechanisms underlying biological processes of loss of neuronal connections and cell death.*

*Im Verlauf vieler neurodegenerativen Krankheiten sterben Nervenzellen und Nerven-Zellkontakten werden aufgelöst. Um dies näher zu untersuchen, bedienen wir uns einer selbst entwickelten Methode, die es uns erlaubt, in lebenden Fruchtfliegenlarven die Bedingungen zur Bildung von synaptischen Verbindungen zu untersuchen. 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.*

**In vivo imaging**

Recently we described a microscopy technique applicable to the analysis of synapse assembly in intact *Drosophila* larvae. The assay is useful for studying the dynamics of the formation of new synapses. Using this technique we were able to prove that the disruption of active zone development is accompanied by abnormal postsynaptic development. While the formation of synapses is a comparatively slow biological process, axonal transport and the delivery of cargo occurs much faster.

Recent modifications of the imaging setup allow for the monitoring of both fast and slow processes. To analyze stability, turnover and redistribution of proteins possibly involved in stabilizing synapses fluorescence recovery after photo-bleaching (FRAP) or photo-activation can be combined in vivo imaging. Two prerequisites are required for applying this method to study the turnover of any protein of interest. The protein subjected for analysis must be tagged with two different fluorophores, e.g. GFP and mCherry, and has to be expressed in two independent transgenic constructs. Flies carrying GFP constructs are crossed with mCherry carriers to give a progeny expressing two fractions of the protein of interest: the mCherry-tagged protein and the other one labeled with GFP. The mCherry signal can be selectively bleached, while the GFP fluorescence will serve as a reference. This type of bleaching does not affect the function of the protein as it was exemplified previously by examining a GFP-tagged glutamate receptor.

Alternatively, local protein turnover, transport and delivery can be determined directly by tracing a photo-labeled population of proteins. Thereby, photo-labeling can either be achieved by photo-activation, i.e. the conversion of non-fluorescent protein such as photoactivatable-GFP into the activated fluorescent state by illumination with 400 nm laser light, or by photo-conversion, i.e. the switching of a convertible fluorescent molecule (i.e. dendraz). The photo-conversion is preferable since it allows us to trace non-converted and converted protein populations simultaneously. We are currently establishing a new transgenic stock

and microscopy assays to measure protein turnover at the NMJ directly.

### Behavioral Assays

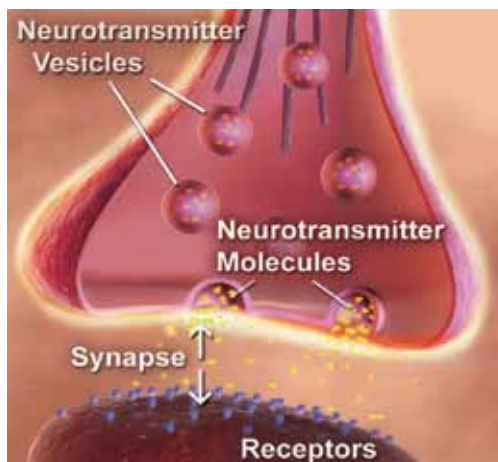
The custom-build software *Animal tracer* coordinates quantification of subtle changes in larval locomotion. It provides a functional readout of synaptic pathology at the neuromuscular synaptic terminal. Thus, we showed that the motoneuron-specific expression of a mutated protein initially identified in hereditary spastic paraplegia patients is sufficient to impair *Drosophila* larval locomotion. We found that these pathological impairments in locomotion are correlated with the size and age of *Drosophila*, something analogous to observations in human patients.

### High-throughput screening

*Drosophila melanogaster* has been extensively used for genetic screens. Moreover it has also emerged as an efficient whole animal model for high-throughput drug screens. The great advantage of using *Drosophila* in such screens is a perspective of testing and characterizing drugs that can take effects only in the context of a multi-cellular organism to target neurodegenerative disorders.

### Future directions

Synapse formation and maturation critically depends on kinesin-based fast axonal transport. Kinesin motors mediate the anterograde transport of synaptic cargoes along microtubule tracks. The depletion of axonal transport cargoes from synapses contributes to the pathology associated with both neurodegenerative and neurodevelopmental disorders such as hereditary spastic paraplegia (HSP), Morbus Parkinson (PD), Fronto-temporal dementia (FTD), Fragile X Syndrome, Angelman's Syndrome, Autism, Down's Syndrome, Rett's Syndrome and Schizophrenia. Synaptic cargoes that are inadequately transported in neurodegenerative and neurodevelopmental disorder include: mitochondria, RNA, proteins important for stability and dynamics of the



In normal cells, synapses mediate the communication between neurons. A loss of these neuronal connections is closely linked with neurodegenerative disorders.

cytoskeleton and structural proteins important for the formation of new active zones.

Our laboratory is interested in the mechanisms that regulate intracellular transport. Furthermore we want to understand how synapses are affected in a background compromised for supply of transport cargoes. Our research aims to clarify whether a synaptic "deficit" is caused by direct defects in the molecular motors or by induced disturbances in microtubule tracks.

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## **IMPRINT**

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*Insertion of an electrode during deep brain stimulation for Parkinson's disease.*

## DEPARTMENTAL STRUCTURE

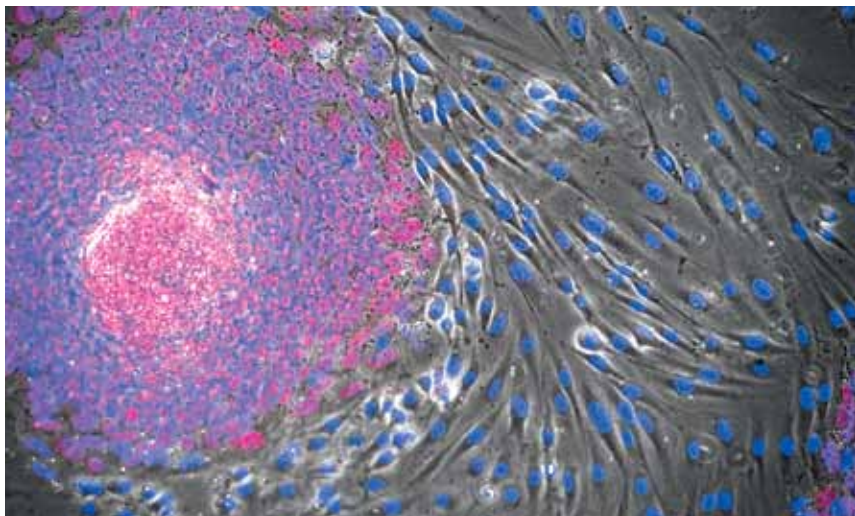


*Prof. Dr. Thomas Gasser is Chairman of the Department of Neurodegenerative Diseases*

The Department of Neurodegenerative Diseases was founded with the 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 20 beds (Ward 43, under the supervision of Prof. L. Schöls and Prof. R. 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 and neuropsychologists.

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 and genetic testing. Innovative treatment for patients with Parkinson's disease and other movement disorders include deep brain stimulation (in close collaboration with the Department of Neurosurgery), but also continuous apomorphine or levodopa infusion 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, dystonias, motor neuron diseases, ataxias, spastic paraplegias, and neurogenetic disorders allows highly efficient patient management. The equally close interaction of clinicians with basic and clinical scientists within the Hertie-Institute for Clinical Brain Research, on the other hand, allows truly translational research. This innovative concept includes active education and training of scientific and clinical junior staff.





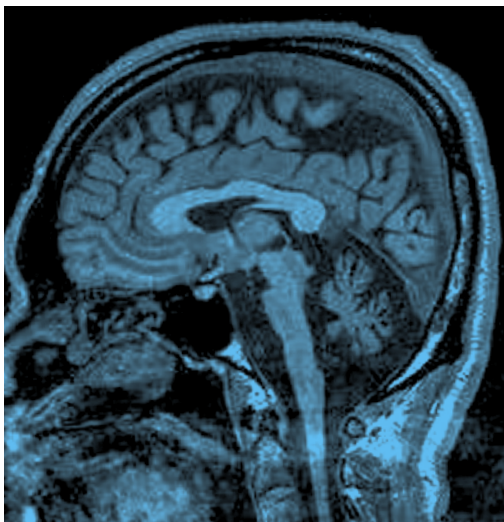
*To study the effects of mutations related to Parkinson's Disease induced pluripotent stem cells (iPSC) with specific genetic alterations have been generated (red: iPSC, co-cultured with embryonal connective tissue (blue) from mice).*

Research is currently organized within 7 research groups, headed by group leaders. The group of Prof. T. Gasser investigates the genetic basis of Parkinson's disease and other movement disorders with classic positional cloning and also high throughput array and next generation sequencing techniques. The group works closely with the team of Prof. D. Berg (Clinical Parkinson's Research) with its focus on clinical cohort studies, phenotyping and neuroimaging. Some members of the group of Prof. R. Krüger develop and test novel stimulation paradigms of deep brain stimulation, while others are interested in fundamental mechanisms of neurodegeneration in PD, with a particular focus on mitochondrial function and dysfunction. Prof. P. Kahles group (section of Functional Neurogenetics) investigates also

fundamental aspects of neurodegeneration in PD, while Prof. L. Schöls and his team (Section for Clinical Neurogenetics) focusses on clinical and fundamental aspects of inherited ataxias, spastic paraplegias, motor neuron diseases and other rare neurogenetic conditions.

Two additional have become group leaders in 2011: Dr. Dr. Saskia Biskup, who leads a research group on LRRK2-biology, but also has founded a company that offers innovative methods of genetic diagnosis, and PD Dr. Walter Maetzler, who focusses on neurogeriatrics and gait disorders.

Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with PD and other neurodegenerative diseases



*Both, fundamental mechanisms of neurodegeneration in Parkinson's Disease and the effects of deep brain stimulation are investigated in Professor Krüger's group.*

## CELLULAR NEUROPHYSIOLOGY

**Head:** Dr. Christine M. Pedroarena

**Team:** 2 members

**Key words:** synaptic plasticity  
intrinsic membrane properties  
neural network computations  
cerebellum  
learning

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*Animal behavior, ranging from simple motor tasks to cognitive processes are assured by the computations that distinct neural networks perform, which in turn, are determined by their characteristic neuronal connectivity and the particular set of synaptic and membrane properties displayed by its neuronal components. Understanding how these very basic cellular mechanisms build up to finally determine specific neural functions is one of the major questions of neurosciences today and the long-term research interest of this laboratory. Our studies address this issue focusing on the cerebellum, a structure well known to control the coordination and timing of movements as revealed by the severe deficits observed in cerebellar ataxic diseases. Our special emphasis is on the neuronal network responsible for generating the cerebellar output signal, the cerebellar nuclei.*

*Verhaltensmuster von Tieren, angefangen bei einfachen Bewegungsabläufen bis hin zu kognitiven Leistungen, werden bestimmt von der Signalverarbeitung in neuronalen Netzen, die ihrerseits von der charakteristischen Verschaltung der Nervenbahnen und den spezifischen Eigenschaften der Synapsen und Membranen geprägt sind. Zu verstehen, wie aus diesen sehr einfachen zellulären Mechanismen schließlich ein Gebilde komplexer neuronaler Funktionen entsteht, ist eine der zentralen Fragen der Neurowissenschaften in der Gegenwart, die wir zur langfristigen Richtschnur unserer Forschung gemacht haben. Unsere wissenschaftliche Arbeit konzentriert sich dabei auf das Kleinhirn, eine Struktur, die dafür bekannt ist, die räumliche und zeitliche Koordination von Bewegungen zu kontrollieren. Dies manifestiert sich etwa in den motorischen Ausfallerscheinungen bei Erkrankungen des Kleinhirns. Der Schwerpunkt unserer Forschung liegt auf den Kernregionen des Kleinhirns, die für ausgehende Signale aus diesem Gehirnareal zuständig sind.*

## Cellular mechanisms of deep cerebellar nuclei neuron network function

Neurons of the deep cerebellar nuclei (DCNs) are critical elements of the cerebellar circuits: first, their axons form the output of the cerebellum to other brain areas, second, they are the main target of the cerebellar cortex (CCx) and finally, they receive copies of all types of cerebellar afferents. Despite this central position and recent evidence that this might be the locus of some important forms of cerebellar learning, the functional characteristics of DCNs and the circuits in which these neurons take part are still poorly understood. Our research, focused on the synaptic and intrinsic membrane mechanisms that support this network performance, seeks to shed light on the basis of cerebellar function in normal and pathological conditions.

## Transfer of information using inhibitory signals

The cerebellar cortex has been attributed the major computational role in cerebellar function. Interestingly, all the output of this structure is carried exclusively via the inhibitory pathway formed by the axons of the GABAergic Purkinje cell (PC). One project of our laboratory investigates the cellular mechanisms that support transfer of signals from the cerebellar cortex (CCx) to the DCN neurons using inhibitory synapses and how this function could be affected under different physiological or pathological conditions. We previously determined that rebound excitation, an intrinsic property of DCNs, is an efficient mechanism to transfer transient PC signals to DCN spike output (Pedroarena, 2010). Due to the lack of specific and potent blockers of the putative ionic channels responsible for rebound excitation, the identity of the channels responsible for this type of response was the subject of intense debate. In a collaborative effort with scientists that developed a new compound that selectively and potently blocked T-type calcium channels (TTA-P2) we demonstrated that these channels are at the basis of rebound firing in DCNs. Interestingly, T-type

channels seem to be involved in two different forms of rebounds that may have different roles in signal encoding. Future studies are planned to investigate the mechanisms that support these two different types of rebounds and how deficit of rebound firing affects cerebellar function.

### Control of DCNs tonic firing.

DCNs show pacemaking type of firing, relevant for detecting inhibitory inputs from the cerebellar cortex and continuously influencing target structures. We hypothesized that in spontaneously firing neurons, action potential activated potassium channels must have an important role in setting the basal membrane potential and tonic firing rate. In particular, we analyzed the role of BK channels, a type of channel usually involved in repolarizing action potentials. We discovered a new role for BK channels in large DCN: instead of repolarizing the action potentials they contribute to set the membrane potential and tonic firing rate. This unusual role is determined by the interplay with other channels with faster kinetics, like the Kv3 type of channels. The results also showed how BK channels gain a new role in the repolarization of action potentials if Kv3 channel function is experimentally depressed. Thus, DCN-BK channels might be a natural target for therapeutic interventions tending to compensate the loss of function caused by pathological deficits of Kv3 channels, such as those observed in some forms of hereditary ataxia. Results from the same study also provided evidence that the therapeutic effect of 4-Aminopyridine, a compound that has been used to treat some forms of episodic ataxia, likely depends on the effect of this drug on DCN-Kv3.1 channels, opening new avenues for rational therapeutic interventions.



A student, Rebecca Böhme, performing patch clamp recordings of cerebellar nuclei neurons in live brain slices.

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## NEUROBIOLOGY OF DECISION MAKING LABORATORY

**Head:** Dr. Axel Lindner

**Team:** 10 members

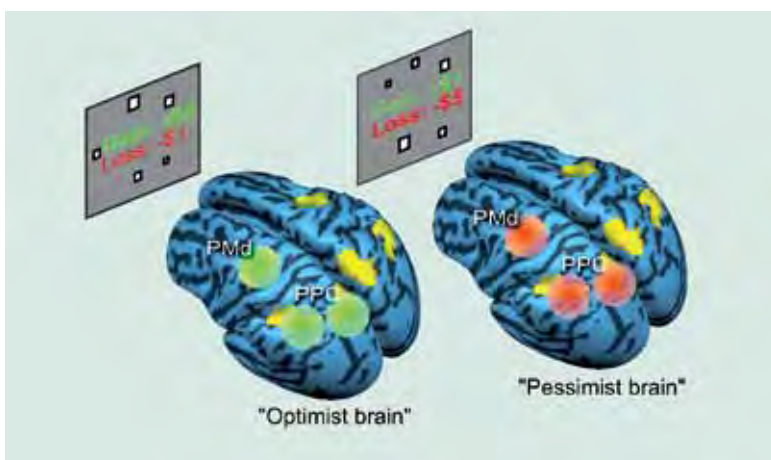
**Key words:** decision making  
awareness of action  
motor preparation  
schizophrenia  
cerebellum  
parietal cortex  
fMRI

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*We study the neuronal basis and pathological changes of the cognitive processes that enable us to choose, generate and optimize behavior, and that predict its consequences.*

*Wir erforschen die neuronalen Grundlagen und pathologischen Störungen der kognitiven Prozesse, mittels derer wir unser Verhalten wählen, generieren und optimieren, sowie dessen Folgen vorhersagen.*

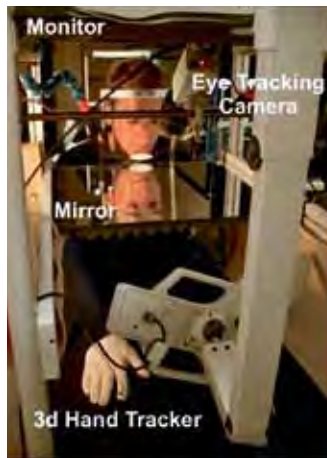
Given the vast number of behavioral options that are usually available in a given situation, how do we – and thus our brain – decide which option to go for? How is the selected behavior generated and optimized? And how does our brain predict the consequences of that behavior, allowing us to distinguish things that we cause from externally produced events? Our interdisciplinary research aims to give answers to such questions and, moreover, tries to explain specific symptoms of neurological and psychiatric diseases that reflect a disorder of the underlying cognitive processes. To this end, we perform psychophysical experiments and functional imaging studies (functional magnetic resonance imaging, fMRI; simultaneous electroencephalography, EEG; magnetoencephalography, MEG) in healthy subjects and specific patient populations. We also develop advanced analytical tools for the detection of distributed information and hierarchical processes in electrophysiological recordings (local field potentials LFP in non-human primates, human MEG) and fMRI data. These approaches allow us to get a more comprehensive understanding of how cortical and sub-cortical functional networks in both humans and non-human primates subserve the cognitive functions of interest. Our empirical research is thereby not only grounded in systems neuroscience. It also is inspired and validated by methods and concepts of our collaborators, namely computational modeling, philosophical analysis and economic (decision) theory.



*Motor planning activity (yellow region) is highest for large expected gains in subjects who believe that they perform well (green region); conversely, activity is highest for large expected losses in subjects who think that they perform poorly (red region).*

Using fMRI, we demonstrated that regions within posterior parietal and premotor cortex play a major role in the preparation of goal-directed eye- and reaching-movements (Lindner et al. 2010; Kagan et al. 2010). Parietal and premotor preparatory brain activity was thereby modulated by subjects' engagement in a behavioral plan, which varied as a function of the amount of reward and punishment subjects associated with the upcoming behavior (Iyer et al. 2010). Our ongoing experiments currently ask, whether parietal and premotor activity is thereby confined to the planning of a selected behavior only, or whether this activity also reflects the way we represent alternative behavioral options, how much we are engaged in each of these options and how we ultimately select between them. In other words, we currently try to uncover the neuronal underpinnings of decision processes that underlie goal-directed behavior of healthy individuals. We also try to predict and validate related dysfunctions of these processes as a consequence of brain damage.

Given that we ultimately decided and performed a goal-directed behavior – how are we able to tell whether we are causally responsible for this behavior and its consequences? And how can we distinguish these consequences from events originating from our environment? The import of these questions gets immediately obvious when considering schizophrenia patients: certain patients show a deficit in predicting the consequences of their own actions, which they (therefore) do not feel causally responsible for (Lindner et al. 2005; Synofzik et al. 2010). Obviously, these patients tend to falsely reject agency for their own behavior and its consequences. Instead, they often form delusional beliefs that “external forces” make them think, speak or even move arms and legs – a symptom that correlated with our experimentally described deficits. Currently, we aim to identify the neuronal mechanisms that allow healthy individuals to predict the sensory consequences of their behavior and that allow them to causally attribute events to their own agency. We also investigate related disorders of self-agency attribution due to brain lesions, for instance



associated with the cerebellum (compare Lindner et al. 2006; Synofzik et al. 2008). Moreover, we try to unravel the reasons why such self-attribution fails in many Schizophrenia patients.

*Using this 2D Virtual Reality Setup we study how subjects are able to tell whether they are causally responsible for the visual consequences of their pointing movements.*

## SELECTED PUBLICATIONS

- Lindner A, Thier P, Kircher TT, Haarmeier T, Leube DT (2005) Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. *Current Biology* 15(12):1119-24.
- Lindner A, Haarmeier T, Erb M, Grodd W, Thier P (2006) Cerebro-cerebellar circuits for the perceptual cancellation of eye movement-induced retinal image motion. *Journal of Cognitive Neuroscience* 18(11):1899-1912.
- Synofzik M\*, Lindner A\*, Thier P (2008) Linking perception with action: The cerebellum updates expectancies about the sensory consequences of our behavior. *Current Biology* 18(11):814-8.  
\*authors contributed equally
- Synofzik M, Thier P, Leube DT, Schlotterbeck P, Lindner A (2010) Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. *Brain* 133(1):262-71.
- Iyer A, Lindner A, Kagan I, Andersen RA (2010) Motor preparatory activity in posterior parietal cortex is modulated by subjective absolute value. *PLoS Biology* 8(8):e1000444.
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**NEURO-VESTIBULAR DIAGNOSTICS****Head:** Dr. Jörn Pomper**Team:** 4 members**Key words:** dizziness  
vertigo  
oculomotor disorders  
vestibular system  
stable perception[www.hih-tuebingen.de/sensomotorik-labor/neuro-vestibular-diagnostics](http://www.hih-tuebingen.de/sensomotorik-labor/neuro-vestibular-diagnostics)

*Our aim is to apply and improve state-of-the-art neurovestibular diagnostics to understand how diseases impair the perception of a stable world experienced as dizziness.*

*Unser Ziel besteht darin, die neurovestibuläre Diagnostik zu verbessern und einzusetzen, um den Einfluss von Erkrankungen auf die stabile Raumwahrnehmung und damit die Entstehung von Schwindel zu erforschen*

**DIZZINESS**

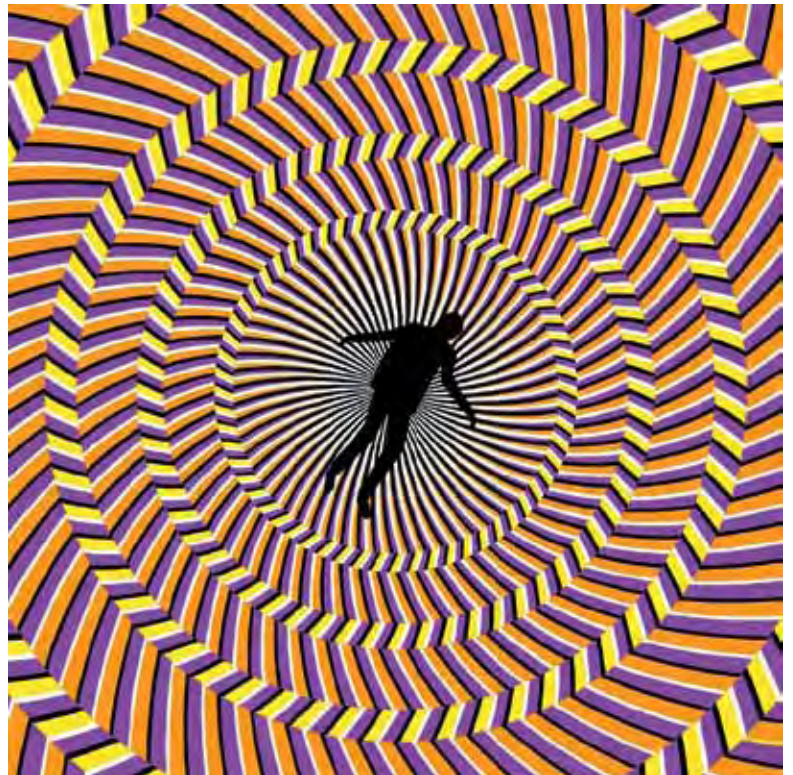
The complaint of dizziness is highly prevalent but remains often an enigma to the physician in daily practice. Serious diseases potentially accompanied by dizziness like stroke, multiple sclerosis or brain tumors can easily be identified by brain imaging or other standard neurological techniques without the necessity to understand how dizziness evolves. The treatment of the underlying disease mostly relieves dizziness. The majority of patients suffering from dizziness, however, do not have an observable lesion. Here, the aim is to understand and to treat the underlying deficits within a pathophysiological framework of dizziness.

Basically, we consider a disturbance of the perception of one's own orientation relative to the outside world as the core pathologic correlate of the subjective experience of dizziness. Hence, affections of any neural system contributing to this perceptual stability would, in principle, be capable to elicit dizziness.

Traditionally, emphasis has been placed on the vestibular system that is reflected in the current diagnostic repertoire. The integrity of semicircular canals, primary afferents, and the vestibulocerebellum is evaluated by vestibular stimulation and the recording of eye movements dependent on vestibular stimulation. Currently used stimulation methods encompass caloric and rotatory stimuli with distinct accelerations (chair rotation, head-impulse-test). Eye movements are recorded by means of electrooculography, videooculography or search coils dependent on the problem to clarify. The integrity of otolith organs and their central connections is examined by applying acoustic or vibratory stimuli and evaluating evoked myogenic potentials of neck or facial muscles (cVEMP, oVEMP). Quantitative head-impulse-measurements using search coils and both VEMPs constitute innovative techniques that have extended our diagnostic repertoire and provided new explanations of some forms of previously mysterious forms of dizziness.



*The picture might give a sense for the experience of dizziness as a consequence of an instable perception of space. Here the visual surrounding is characterized by conflicting spatial cues evoking a foretaste of disorientation and unsteadiness as patients with dizziness suffer from.*

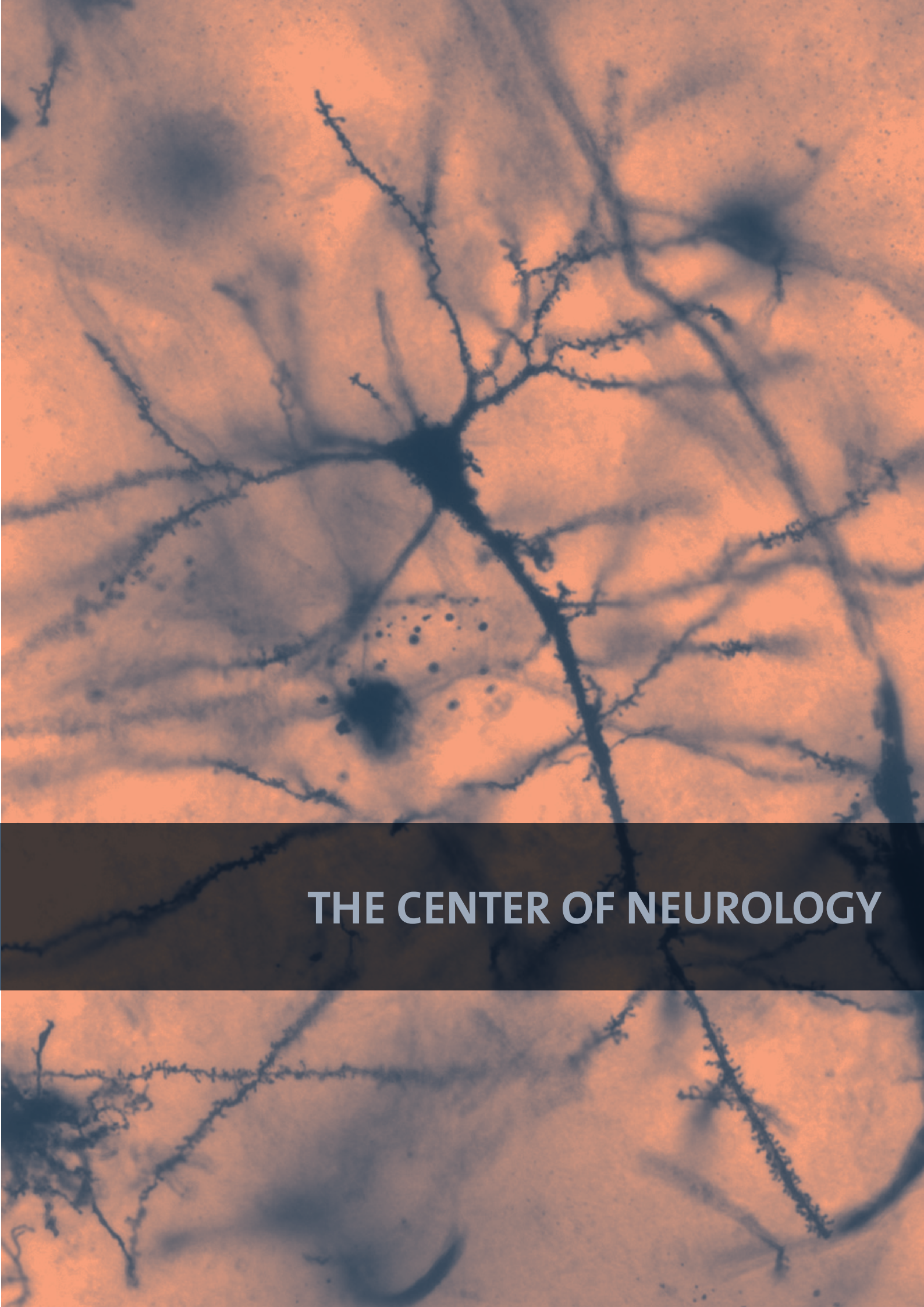


The usage of these up-to-date techniques in the evaluation of patients suffering from dizziness is one of our group's interests. To this end, we have established normative data over the last years. These new tests have allowed us to increase the percentage of patients in whom specific forms of dizziness can be diagnosed. On the other hand, a significant group of patients remains, in whom the dizziness remains „idiopathic“, i.e. unexplained. Objective measurements of deficits or proven concepts are scarce. Psychogenic origins and circumscribed deficiencies in sensorimotor processing are discussed but remain controversial. In order to make headway, the laboratory explores the possibility that some forms of idiopathic dizziness may be a consequence of dysfunctional sensorimotor processing related to perceptual stability. We apply and extend psychophysical techniques, many of them developed at the DCN during the last years. Psychophysical data are compared with validated questionnaires to infer their potential relevance for dizziness and their

relationships to psychopathological conditions. For example, we conducted a study in patients with chronic dizziness in which we could not verify one of the widely assumed hypotheses of a maladjusted efference copy involved in visual perception.

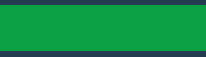
### SELECTED PUBLICATIONS

- Pomper JK, Wilhelm H, Tayebati SK, Asmus F, Schüle R, Sievert KD, Haensch CA, Melms A, Haarmeier T (2011) A novel clinical syndrome revealing a deficiency of the muscarinic M<sub>3</sub> receptor. *Neurology* 76(5):451-5.
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