CENTER OF NEUROLOGY TÜBINGEN

Annual Report 2013

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The Center of Neurology
The Center of Neurology in 2013

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’s Clinical Neurology Department with the mission to promote excellence in research and patient care.

Presently, the center consists of four clinical departments (Neurology and Stroke, Epileptology, Neurodegeneration and Cognitive Neurology) and one basic science department (Cellular Neurology), which has recently installed an outpatient care unit in the field of Alzheimer’s disease. The 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 all departments of the center actively participate, albeit to a different degree, in the clinical care of patients with neurologic diseases is central to the concept of successful clinical brain research at the Hertie Institute. This is of course most obvious in clinical 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.


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

**NUMBER OF STAFF IN 2013**
Center of Neurology without nursing services (by headcount)

- 161
  - 46 % Third party funding
- 66
  - 19 % Hertie Institute
- 121
  - 35 % University Hospital of Neurology

**DEVELOPMENT OF STAFF**
Center of Neurology (by headcount)

- 2011: 350
- 2012: 345
- 2013: 348

**NUMBER OF PUBLICATIONS IMPACT FACTORS**
Center of Neurology (SCIE and SSCI / in 100 %)

- 2011: 157
- 2012: 184
- 2013: 259

**TOTAL FUNDINGS IN 2013**
Center of Neurology

- 6,774,500 €
  - 53 % Third party funding
- 2,900,000 €
  - 23 % Hertie Foundation
- 3,102,100 €
  - 24 % University Hospital of Neurology

**THIRD PARTY FUNDING**
Center of Neurology

- 2011: 4,837,767 €
- 2012: 6,359,309 €
- 2013: 6,774,484 €

**THIRD PARTY FUNDING IN 2013**
Center of Neurology

- Others: 34 %
  - 2,308,416 €
- EU: 19 %
  - 1,279,026 €
- BMBF: 24 %
  - 1,596,240 €
- DFG: 23 %
  - 1,561,492 €

Total: 6,745,174 €
University Hospital of Neurology
University Hospital of Neurology

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 12,000 (including diagnostic procedures) patients are examined and treated per year, many of them in specialty clinics which are directed by recognized specialists in the respective fields.

PATIENTENVERSORGUNG


In der neurologischen Poliklinik werden mehr als 12.000 Patienten pro Jahr ambulant betreut und Diagnosen durchgeführt, viele davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden.
Clinical Performance Data

INPATIENT CARE

The inpatient units of the University Hospital of Neurology treated more than 4,556 patients in 2013.

NUMBER OF ADMISSIONS | LENGTH OF STAY (IN DAYS)
--- | ---
4,556 | 5,4

INPATIENT DIAGNOSIS GROUPS

- Cerebrovascular diseases: 22.4%
- Episodic and paroxysmal disorders: 17.8%
- Extrapyramidal and movement disorders: 10.9%
- Other disorders of the nervous system: 4.7%
- Demyelinating diseases: 4.5%
- Malignant neoplasms: 4.5%
- Inflammatory diseases of the central nervous system: 3.9%
- Mental and behavioural disorders: 3.6%
- Diseases of the musculoskeletal system: 3.2%
- Polyneuropathies: 3.2%
- Other degenerative diseases of the nervous system: 2.3%
- Other neoplasms: 1.6%
- Nerve, nerve root and plexus disorders: 1.5%
- Others: 15.9%

OUTPATIENT CARE

NUMBER OF CONSULTATIONS
(including diagnostic procedures)

12,010

Close monitoring of patients at the intensive care unit.
Outpatient Clinics

ATAXIA

The ataxia clinic provides tools to discover the cause of ataxia in close cooperation with the Department of Neuroradiology (MRT, MR-Spectroscopy) and the Institute of Medical Genetics. Here we developed new tools to investigate the genetic basis of ataxias. To address the increasing number of genes causing ataxia we established gene panel diagnostics that allow parallel sequencing of all known ataxia genes. 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) we participate in a natural history study for spinocerebellar ataxias (SCA) as a prerequisite for interventional trials in the future. Special emphasis is given to early onset ataxias (EOA). With support of the EUROSCAR project funded by the EU we proposed a genetic screening program to determine the frequency of genetic subtypes and to discover new genes. In Friedreich’s ataxia the clinic participates in the European EFACTS project that aims to reveal the natural course of the disease and develop new biomarkers in preparation for new therapeutical approaches. 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) 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 conditions.
In 2013 the relevance of Tübingen as a specialized center for deep brain stimulation was underscored by its contribution to the European multicenter EARLYS TIM-study that proved for the first time an improved quality of life in patients undergoing DBS in early disease stages (Schuepback et al., NEJM, 2013). 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 were initiated. Here the first study on high frequent stimulation of the substantia nigra pars reticulata (SNr) as an add-on to the conventional subthalamic nucleus stimulation, was successfully accomplished and prove an effect on freezing of gait (Weiss et al., Brain, 2013). Thus we provide first means to address the major need for current therapy research due to 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 outpatient 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 were seen by Dr. T. Wächter, 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 unspecified 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.
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 patients 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 percent 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). 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 physio- 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 Tübingen).
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 and other clinical trials to explore novel treatment options. The inpatient unit with 28 beds (Wards 41/42 and 45), running under the supervision of Prof. Dr. Y. Weber, Dr. N. Focke and PD Dr. T. Freilinger, 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, Prof. Dr. Y. Weber and Dr. N. Focke) offers consulting and treatment in particular for difficult cases and specific questions including pregnancy under antiepileptic treatment and genetic aspects. Altogether we treat about 2,000 adult patients per year.

There is also a specialized ergotherapeutic service for taskspecific dystonias focused on retraining (S. Wiesemeier, Therapiezentrum UKT). Two to three 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 measures 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 G. Beck (technical assistant), Dr. K. Freitag and Prof. L. Schöls.
Outpatient Clinics

Neuro-geriatric patients receive physiotherapy for mobility training.

GERIATRICS

Geriatric patients are a special group of elderly people, usually over 70 years of age, who present with multiple and complex medical problems. In these patients, disabilities ranging from cerebrovascular to neurodegenerative diseases are most prevalent in combination with cardiovascular, respiratory, and metabolic disorders. Approximately 30% of the patients admitted to the Neurology department are older than 70 years and most of them fulfill the criteria of being a “geriatric patient”. Geriatric patients are often handicapped by a number of additional symptoms, such as incontinence, cognitive decline or dementia, and susceptibility to falls. These additional symptoms do not only complicate the convalescence process but also interfere, together with the primary disease, with functional outcome, daily activities and quality of life. It is thus our primary aim to identify quality of life-relevant functional deficits associated with the disease and comorbidities, using established geriatric assessment batteries. Affected patients receive goal-oriented physiotherapy for mobility training, neuropsychological training, speech therapy, and occupational therapy. Patients, spouses as well as family members receive specific information about community services and organization of geriatric rehabilitation. Staff directly involved in the different services includes Prof. W. Maetzler, Prof. R. Krüger, Markus Hobert and Dipl. Soz. Päd.-FH A. Steinhauser.

Scientific projects on the evaluation of geriatric topics are performed, e.g. with the Department of Geriatric Medicine at the Robert-Bosch Hospital in Stuttgart (Prof. Clemens Becker) and with the Department of Psychiatry and Psychotherapy (Prof. Eschweiler).

The Neurology Department is a member of the Center of Geriatric Medicine. This Center 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 Neurology Department provides a regular consult service for these institutions, and takes an active part in seminars, teaching, and training activities of the Center of Geriatric Medicine.
HEADACHE AND NEUROPATHIC PAIN

The outpatient unit is dedicated to neurological pain syndromes, including headache and facial pain as well as neuropathic pain syndromes. Patients may either be referred by neurologists or general practitioners. Appointments are available from Tuesday through Friday, and patients will be provided with mailed headache/pain diaries and questionnaires well before their scheduled appointment.

One major clinical focus is the diagnostic work-up and multimodal treatment of chronic headache disorders like chronic migraine (CM), medication-overuse headache or chronic tension-type headache. The unit further specializes in the diagnosis and treatment of rare primary headache syndromes like trigeminal autonomic cephalalgias (TACs; e.g. cluster headache, paroxysmal hemicrania or SUNCT syndrome) as well as rare monogenic migraine variants such as hemiplegic migraine. Finally, patients with neuropathic pain syndromes are diagnosed and treated in close collaboration with the Department of Anesthesiology, which organizes monthly interdisciplinary pain conferences.

Selected patients with otherwise refractory chronic headache disorders are offered access to new treatment modalities including botulinum toxin for CM or neurostimulation techniques (in collaboration with the Department of Neurosurgery), which are currently under evaluation. Inpatient treatment will be available in special cases (e.g. exacerbations of cluster headache, difficult cases of medication withdrawal). To address psychiatric comorbidities, which are highly prevalent and clinically relevant in chronic pain disorders, the unit is in close collaboration with both the Department of Psychosomatic Medicine and the Department of Psychiatry. The outpatient clinic is run by PD Dr. T. Freilinger together with Dr. N. Dammeier and Dr. S. Wolking.
Outpatient Clinics

LEUKODYSTROPHIES IN ADULTHOOD

Leukodystrophies are usually regarded as diseases that occur in infancy and childhood. However, for most leukodystrophies adult-onset forms have been identified but still frequently escape detection. The German Ministry of Education and Research (BMBF) supports a national research network for leukodystrophies (LeukoNet; 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.

NEUROIMMUNOLOGICAL DISORDERS

Patients with multiple sclerosis, immune-mediated neuropathies, and other neuroimmunological disorders are regularly seen in the outpatient-clinic for neuroimmunological diseases. Complex cases may be discussed in interdisciplinary conferences with colleagues from rheumatology, neuroophthalmology, neuroradiology, and neuropathology. The center of Neurology is certified by the German Multiple Sclerosis Association and a member of the Clinical Competence Network for Multiple Sclerosis and the Neuromyelitis Optica Study Group.

Patients with multiple sclerosis are referred from other institutions 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. A large number of patients participates in clinical trials which explore safety and efficacy of new treatments. Clinical trials are managed by a team of study nurses including U. Küstner, C. Ruth and B. Tolle. In 2013 the clinic was run by K. Friebe and L. Zeltner under the supervision of Prof. U. Ziemann and PD Dr. F. Bischof.

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. M. Synofzik, Dr. J. Müller vom Hagen, supervised by Prof. L. Schöls.
NEUROMUSCULAR DISORDERS

For the diagnosis of neuromuscular diseases the correct collection of medical history, including family history, is particularly important. In addition, the patients are examined neurologically and possibly electrophysiologically. In the clinic the indication to further necessary investigations such as MRI or muscle biopsy is provided. The therapy is tailored to the individual patient and his particular type of the disease and usually includes a medicated as well as physiotherapy regimen. The neuromuscular clinic is run by Dr. C. Schell.

NEUROLOGIC MEMORY OUTPATIENT 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 by Prof. W. Maetzler, M. Hobert, Dr. I. Liepelt-Scarfone and Dr. S. Graeber-Sultan.
Outpatient Clinics

NEURO-ONCOLOGY

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.

The outpatient clinic is run by Dr. C. Braun and M. Wolf and is supervised by Prof. U. Ziemann.

Being part of the Centre of Neurooncology Tübingen (ZNO) in the framework of the Tübingen Comprehensive Cancer Centre (CCC), the Neurooncology outpatient clinic has been rated „neurooncology module“ by the German Cancer Society (DKG). This rating is representing the highest level of excellence to be achieved. Besides the German Cancer Aid (DKH) is rating the CCC as Oncology centre of excellence.

This implies a thorough interaction with colleagues of the Departments of Neurosurgery, Radiooncology, Neuroradiology, Neuropathology, Pediatrics, and Oncology. Diagnostic as well as therapeutic decisions are routinely made by the Brain Tumor Board (Coordination Dr. C. Braun), taking place on a weekly basis at least. As neurooncology centre of international reputation the ZNO is represented within national and international organizations of significance. Dr. Braun is member of the following organizations: German Cancer Society (DKG), German Neuro-oncology Group (NOA), European Organisation for Research and Treatment of Cancer (EORTC). In connection with that the Neuro-oncology outpatient clinic is participating in a number of multicentre trials of the organisations mentioned above.

Besides a number of local trials is carried out as well. As a study nurse MS M. Jeric is entrusted with the organization, administration of multicentre trials and specific training of the patients.

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

NEUROVASCULAR DISEASES

The neurovascular outpatient clinic provides services for patients with neurovascular diseases including ischemic and hemorrhagic stroke, cerebral and cervical artery stenosis, microvessel disease, cerebral vein thrombosis, vascular malformations, and rare diseases such as cerebral vasculitis, endovascular lymphoma or arterial dissection. 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: Doppler and duplex ultrasound of cervical and intracranial vessels, transthoracic and transesophageal echocardiography, 24-hour Holter monitoring 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. Echocardiograms are performed by Dr. C. Zürn (cardiologist, shared appointment by the departments of neurology and stroke, and cardiology). In cooperation with the department of cardiology, event recorders are implanted in selected ischemic stroke patients with suspected atrial fibrillation.

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).
Outpatient Clinics

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 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 and the P-PPMI-(prodromal-PPMI) study, which follows individuals at high risk for PD to better understand the early phase of neurodegeneration. Both studies are 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 Parkinson’s disease but also atypical Parkinsonian syndromes offer the possibility to participate in new medical developments. Currently, we offer participation in studies involving a nicotine plaster in early PD, a selective adenosine A(2A) receptor antagonist as treatment for PD patients with motor fluctuations and dyskinesia, a new COMT-Inhibitor for patients with motor fluctuations, a polyphenol with antioxidative and neuroprotective capacities in the atypical Parkinsonian syndrome Multiple System Atrophy (MSA) as well as observational studies of different medications. Moreover, close cooperation with the outpatient rehabilitation center and the establishment of a Parkinson choir guarantee the involvement of additional therapeutic approaches.

These activities are supported by the study nurses K. Gauß, C. Haaga, and N. Runge as well as the documentalist T. Heger. 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, Dr. K. Brockmann, Dr. K. Srulijes and Dr. I Wurster as well as the neuropsychologists Dr. I. Lippelt-Scarfone, Dr. S. Gräber-Sultan and Marion Thierfelder. Our Parkinson’s nurse Ina Posner is engaged in the organization of the outpatient clinic, documentation, assessments and counselling of many aspects related to daily life.
SPASTIC PARAPLEGIAS

The outpatient clinic for hereditary spastic paraplegias (HSP) offers a specialist setting for the differential diagnostic workup and genetic characterization of patients with spastic paraplegia using the facilities of the Hertie Institute for Clinical Brain Research and cooperations with the Institute of Medical Genetics and the Department of Neuroradiology. Therapeutic options depend essentially on the underlying cause of the disease. Symptomatic treatment options include antispastic drugs, intrathecal application of Baclofen, local injections of Botulinum toxin and functional electrical stimulation. Tübingen is the disease coordinator for HSP in the NEUROMICS project funded by the EU that aims to discover new genes, gene modifiers as well as metabolic factors that cause or modify hereditary neurodegenerative diseases taking advantage of a broad spectrum of OMICS techniques like genomics, transcriptomics and lipidomics. The clinic is run by Dr. R. Schüle, Dr. K. Karle and Dr. T. Rattay 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.
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.

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, R. Mahle, Fr. Vohrer (staff technicians); Prof. 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. In 2013, 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.

The EMG Laboratory is organized by Mrs. J. Grimm who also performs nerve conduction studies with surface electrodes. In 2013, the EMG Laboratory was run by Dr. L. Zeltner und Dr. P. Martin under the guidance of Dr. Caroline Schell and Dr. Niels Focke.
Clinical Laboratories

**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 Dr. C. Schell and Dr. N. Focke. 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.

**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. C. Zürn. The laboratory is fully equipped with a modern multifunction ultrasound and echocardiography machine (Acuson Sequoia 512, Siemens) including probes for transthoracic and transesophageal investigations as well as abdominal and other soft tissue ultrasound (pleural, thyroid etc.). This allows to perform bedside echocardiography of stroke patients on the Stroke Unit immediately after diagnosis.

Yearly, we conduct approximately 1,500 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 1000 24-hour (Holter) ECGs and 800 24-hour ambulatory blood pressure measurements are recorded. In high-risk patients event recorders are implanted to accelerate the detection of atrial fibrillation.
NEUROSONOLOGY LABORATORY

The neurosonology laboratory is equipped with two color-coded Duplex sonography systems: a Toshiba Aplio and a Philips Epiq7. Furthermore, we have two portable CW/PW Doppler systems: a DWL Multi-Dop pro and a DWL Multi-Dop T digital. The neurosonological examinations are performed by the ultrasound assistants Mrs. Nathalie Vetter and Mrs. Yvonne Schütz under the supervision of Dr. Sven Poli, consultant stroke neurologist and neurointensivist.

The laboratory consists of a unit in the outpatient department of the Dept. of Neurology mainly for non-acute or elective ultrasound examinations of in- and outpatients as well as a mobile unit located directly on our Stroke Unit allowing the full range of neurosonological examinations at the bedside immediately after admission.

Routine diagnostic tests include Duplex imaging of carotid, vertebral, and subclavian arteries, as well as the Circle of Willis (with and without contrast). Furthermore, functional testing for vertebral steal, bubble test for right to left shunts (e.g. persistent foramen ovale), and continuous doppler monitoring of the cerebral blood flow (e.g. before, during and after neuroradiological interventions) or for detection of cerebral microembolisms (high-intensity transient signals) are routinely performed.

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.

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.

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 2013, approximately 1,000 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 proplaps, stroke, ataxia, Parkinson’s disease. Within the year 2013 approximately 2,500 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 1,000 patients in 2013).

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 2013 approximately 500 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.
The Hertie Institute for Clinical Brain Research
In 13 years of its existence, the Hertie Institute has grown to more than 350 employees of all levels, from technicians to 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 Neurology and Stroke, 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 has been a pure basic science department, focusing on Alzheimer’s disease. In the year 2012 it has recently installed an outpatient care unit in the field of Alzheimer’s disease.

The institute is home to a total of 28 research groups, 25 of them within the aforementioned departments, three as independent junior research groups. The first of these independent groups, which has been established in 2006, has successfully passed its evaluation by the scientific advisory board of the Hertie Institute as an independent group status. In the year 2013 the head of this independent research group accepted the offer of a chair in restorative neuroscience at Imperial College in London, but he still runs his independent research unit at HIH. In 2013, scientists at the Center of Neurology have obtained more than 6.0 million Euro in third party funding and have published 250 papers in peer reviewed journals. As a primary care institution, all clinical departments together treat patients with the complete spectrum of neurological diseases. To strengthen the interactions
between clinical and basic research the “Hertie Grand Rounds” have been established as novel seminar series that reflects an initiative to allow both, clinicians and basic researchers, to comprehensively discuss exemplary diseases of our research focuses at the Center of Neurology and Hertie Institute. Silke Jakobi has become the new head of communications in October 2012. She is responsible for all HIH communication and public outreach activities. She will also support the fundraising activities.

Since 2012 the new research building for the “Werner Reichardt Centre for Integrative Neuroscience (CIN)” on the Schnarrenberg neuroscience campus, which also houses HIH groups, has been completed, and the scientific work has begun. The construction for the new building of the Tübingen site of the “German Center for Neurodegenerative Diseases (DZNE)” within the Helmholtz Association is making progress as well as the setting up of DZNE Tübingen.

Finally, the Hertie Institute for Clinical Brain Research and the entire Neuroscience Community in Tübingen set up the Hertie Lecture in Brain Research. The first Hertie Lecture in Brain Research will initiate a yearly series of highly visible neuroscience lectures and will act as a crystallization core for neuroscientists and the public in Tübingen. The entire Neuroscience Community in Tübingen has actively participated by nominating internationally renowned scientists of the highest level as candidates for speakers.

All these developments will ensure the long term success of the neuroscience community in Tübingen.
Das Hertie-Institut für klinische Hirnforschung (HIH)

13 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.


Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Peter Thier
Prof. Dr. Ulf Ziemann
Department of Neurology and Stroke
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The Department of Neurology and Stroke 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 neurovascular diseases (ischemia, intracranial hemorrhage, vasculitis, vascular malformations, rare neurovascular diseases such as endovascular lymphoma, paraneoplastic coagulopathy, or reversible cerebral vasoconstriction syndrome), neuroimmunology (multiple sclerosis, myasthenia gravis and others), and brain tumors. Specialized teams in stroke medicine (stroke unit and rehabilitation), neuroimmunology and neurooncology provide expert multidisciplinary care for patients with these disorders. As an integral part of the Comprehensive Cancer Center (CCC), the Departments of Neurology, Neurosurgery, Radiooncology, Neuroradiology and Neuropathology form the Center of Neurooncology.

Prof. Dr. Ulf Ziemann is head of the Department of Neurology and Stroke Neurology.
Specialized outpatient clinics in Neurovascular Diseases, Neuroimmunology and Neurooncology offer the best available therapy and provide the infrastructure for clinical trials and investigator initiated research.

The Department of Neurology and Stroke provides the clinical basis for its Research Groups at the Hertie Institute for Clinical Brain Research. All Research Groups have strong interest in bridging neuroscience and health care in translational research concepts. Currently, five Research Groups exist that are active in brain networks and plasticity (Prof. Dr. Ulf Ziemann), stroke and neuroprotection (Dr. Sven Poli), neuroimmunology (PD Dr. Felix Bischof), neuro-oncology (Prof. Dr. Ulrike Naumann) and speech disorders (Prof. Dr. Hermann Ackermann). The Research Groups are located in the immediate proximity of the clinical setting in the CRONA hospital building or in 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 (Zentrum für ambulante Rehabilitation), which is focused on physiotherapy for stroke rehabilitation.

The Department of Neurology and Stroke 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 neurology therapy seminar gives up-to-date overviews on recent advances in neurology, internal 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, and the training course on neurological examination skills are integral parts of the Medical School curriculum and are usually honored by the evaluation of the students.
The human brain has an amazing capacity to reorganize, which ensures functional adaptation in an ever-changing environment. This capacity for neural plasticity becomes even more important for rehabilitation after cerebral injury such as stroke. Interest in our group focuses on understanding principles of neural plasticity in the human cortex. In particular, we are interested how mechanisms of neural plasticity underlie learning in the healthy brain and re-learning in the injured brain. What rules govern learning? How do brain networks change after brain injury to compensate for and regain lost functionality? And can this knowledge be used to predict and facilitate rehabilitation after brain injury? We address these questions by imaging (fMRI, DTI) and electrophysiological (EMG, EEG, MEG) methods in combination with non-invasive brain stimulation (TMS, tDCS) and pharmacology. Our goal is to develop new rehabilitative strategies and make meaningful advances in the clinical practice of patients with brain diseases.

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Combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG) constitutes a powerful tool to directly assess human cortical excitability and connectivity. TMS of the primary motor cortex elicits a sequence of TMS-evoked EEG potentials (TEPs). It is thought that inhibitory neurotransmission through GABA-A receptors (GABAAR) modulates early TEPs (< 50ms after TMS), whereas GABA-B receptors (GABABR) play a role for later TEPs (at around 100ms after TMS). However, the physiological underpinnings of TEPs have not been clearly elucidated yet. Here, we studied the role of GABAA/B-ergic neurotransmission for TEPs in healthy subjects using a pharmaco-TMS-EEG approach. In a first experiment, we tested the effects of a single oral dose of alprazolam.
(a classical benzodiazepine acting as allosteric positive modulator at α1, α2, α3 and α5 subunit-containing GABAARs) and zolpidem (a positive modulator mainly at the α1 GABAAR) in a double-blind, placebo controlled, crossover study. In a second experiment, we tested the influence of baclofen (a GABABR agonist) and diazepam (a classical benzodiazepine) vs. placebo on TEPs. Alprazolam and diazepam increased the amplitude of the negative potential at 45ms after stimulation (N45) and decreased the negative component at 100ms (N100), whereas zolpidem increased only the N45. In contrast, baclofen specifically increased the N100 amplitude.

These results provide strong evidence that the N45 represents activity of α1-subunit containing GABAARs, while the N100 represents activity of GABABRs. Findings open a novel window of opportunity to study alteration of GABAA-/GABAB-related inhibition in disorders such as epilepsy, schizophre-nia, or after ischemic stroke.

Enhancing effect size of non-invasive brain stimulation on plasticity and learning by brain polarization

Another project has just started and will investigate the possibility to increase the size effect of non-invasive brain stimulation (cortico-cortical paired associative TMS) by concurrent brain polarization by transcranial direct current stimulation (tDCS), according to the following rationale and project plan: Voluntary movements of the hand are associated with coordinated neuronal activity in a distributed large-scale cortical motor network. Task-dependent increases in effective connectivity, in particular the connection between supplementary motor area (SMA) and primary motor cortex (M1), funnel driving activity into the voluntarily active M1. Stroke patients with hand paresis typically show impairments of this task-dependent increase of SMA-M1 connectivity and activation of the ipsilesional M1. The degree of these abnormalities correlates with motor clinical deficits of the paretic hand.

Here we propose a novel MR-navigated paired associative transcranial magnetic stimulation (PAS) technique in combination with transcranial direct current stimulation (tDCS) to induce cooperative spike-timing dependent plasticity (STDP)-like. We will specifically target the SMA-M1 connection to strengthen task-dependent increases in effective connectivity of this pathway. We expect that strengthening of the SMA-M1 pathway will enhance motor performances and motor learning processes. In a first step, the experiments will be performed in young healthy subjects with a high potential for plastic change to explore the effects of combined SMA-M1 PAS and M1-tDCS on motor performance and learning. In a second step, successful protocols will be applied to elderly healthy subjects with an expected reduced potential for plastic change, with the ultimate translational aim to apply these protocols (in an extension of this project) to stroke patients with the intention to improve function of their paretic hand.

Sonification of arm/hand movements to improve neurorehabilitation of stroke patients.

Finally, we are currently starting a first clinical neurorehabilitation trial, using sonification of hand/arm movements to improve rehabilitation of hand/arm function in stroke patients. We will use sensors attached to the hand and arm that allow real-time sonification (translation into music) of arm movements in 3D-space. We expect that musical encoding of arm movements will help to improve motor control of impaired arm movements in stroke patients. We plan, together with Prof. Altenmüller at the Hannover Medical School (MHH) to recruit 90 stroke patients with arm/hand paresis into a randomized study with three arms: arm movement training in 3D space (1) with sonification using classical music; (2) with sonification using pop music; (3) without sonification.

The patients will be training in 15 sessions à 20 minutes over a period of 3 weeks. We will test performance in several standardized motor tests and evaluate quality of life in a standardized questionnaire prior to and after the training period. In addition, EEG will be used to explore intervention-induced changes in cortico-cortical networks.

SELECTED PUBLICATIONS


Lately, we assessed whether CNS-directed autoimmunity can be suppressed by intravenous injection of neural stem/progenitor cells (NSPC), which were genetically modified to overexpress the immunomodulatory cytokine Interleukin-10 (IL-10) and which have the ability to directly migrate into the CNS and to replace damaged CNS cells. We established techniques to isolate, cultivate and analyze recently identified lymphocyte populations including murine and human T helper type nine (Th9) cells and terminally differentiated B lymphocyte populations. The interaction of Th9 cells and neurons was assessed using primary neuronal cultures, immunofluorescence microscopy and time-lapsed phase contrast microscopy.

In addition, we assessed whether carbohydrate residues on the surface of immune cells are involved in regulating autoimmunity within the CNS. We demonstrated that during the development of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis, immune cells alter surface expression of N-linked carbohydrate residues.
N-glycosylation of CD4+FoxP3+ regulatory T cells was increased during the induction-phase of EAE and this increased N-glycosylation was related to a higher immunosuppressive capacity of regulatory T cells. In parallel, we assessed surface glycosylation of immune cells in patients with MS and discovered that Interferon beta-1a treatment leads to reduced alpha-2,3-sialylation of non-activated helper T cells. Alpha-2,3-sialylated residues were predominantly expressed by effector T cells while only a small fraction of regulatory T cells displayed alpha-2,3-sialylated residues. T cells without alpha-2,3-sialylation displayed a reduced capacity to proliferate after polyclonal stimulation. Collectively, these data indicate a new mechanism of action of Interferon beta-1a in RRMS.

As a possible new treatment option for patients with progressive multifocal leukoencephalopathy (PML), an often devastating inflammatory disease of the CNS, we assessed efficacy and immunological consequences of continuous infusions of the CD4 T cell stimulating cytokine interleukin-2.

SELECTED PUBLICATIONS


*shared senior authorship


Glioblastoma (GBM) is the most common and lethal brain neoplasm with a median patient survival after standard therapy of 12 to 15 months. 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. In our recent project, we investigate the role of CPE in cell signaling pathways associated with cell motility and cell proliferation as well as its capability to reduce the invasive growth of GBM cells in vivo using a mouse GBM model.

In Europe, cancer patients widely use mistletoe extracts for complementary cancer therapy. We could demonstrate that mistle lectins (ML) enforce immune cells to attack and to kill GBM cells. Beside its immune stimulatory effect, mistle extracts 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 mistle extracts also delayed tumor growth in mice. ML showing multiple positive effects in the treatment of GBM, may therefore hold promise for concomitant treatment of human GBM. In our present experiments we are interested if ML are able to inhibit GBM-induced neovascularization and if these lectins, especially the recombinant ML I, work in synergy with chemo- or radiotherapy.

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, NFkappaB activation was mandatory for Ad-CTS-1 induced cell death. Our results were in contrast to other groups who demonstrated that activation of NFkappaB protected GBM cells. This has important implications for the role of NFkappaB as a player involved in tumor progression and should also be kept in mind when using NFkappaB-specific inhibitors in the therapy of cancer, especially in the therapy of GBM. In our recent project we are interested to unravel the role of IkappaB, an untypical inhibitor of NFkappaB known to be a transcription factor per se, but also a modulator of NFkappaB transcriptional activity, in the growth and cell death resistance of GBM cells.

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.

**SELECTED PUBLICATIONS**


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). Based on a previous functional magnetic resonance imaging (fMRI) study in a group of blind subjects (Dietrich et al. 2013a, Hertrich et al. 2013a), a training experiment is currently under way to further support the notion that the recruitment of a “visual” strategy underlies both in early – as well as late-blind subjects the acquisition of this exceptional skill (Dietrich et al. 2013b). Against the background of our preceding fMRI as well as magnetoencephalography (MEG) investigations, we assume, more specifically, that blind people use auditory-afferent information via an audiovisual pathway (pulvinar) to record prosodic speech events within right-hemispheric visual cortex. Presumably, this signal-related event structure is then transmitted to the frontal speech processing network via subcortical structures and rostral parts of the supplementary motor area (pre-SMA) – a region considered an important timing interface (Hertrich et al. 2013b). We now have begun to apply the technique of Transcranial Magnetic Stimulation (TMS) in healthy and in blind subjects to further determine in how far the various brain regions involved in time-critical aspects of speech processing contribute (in a causal manner) to ultra-fast speech perception (in cooperation with the Brain Networks & Plasticity (BNP) Lab, see above).

Studies in Neurophonetics

Following an invitation by Wiley’s Interdisciplinary Reviews, the scope of the – relatively new – research area “Neurophonetics” as been delineated in a review paper (Hertrich & Ackermann 2013). Furthermore, a dissertation project could be finished in 2013 that investigated the neural underpinnings of the perception of the categorical vowel length contrast in German subjects, based upon psychoacoustic tests and MEG measurements (Tomaschek et al. 2013).

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. Schölß, M. Synofzik and T. Lindig, Center for Neurology, University of Tübingen, 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 analysed so far. Reduced speaking rate and voice irregularities were found specifically related to ataxia in other domains (Brendel et al. 2013). 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 circuits, 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”). An elaborated account of this model has been accepted as a target article in Behavioral and Brain Sciences (Ackermann H, Hage SR, Ziegler W. Brain mechanisms of acoustic communication in humans and nonhuman primates: An evolutionary perspective) and will be printed together with 30 commentaries and a response of the authors.

* cooperation with E. Zrenner and A. Bernd, Center for Ophthalmology, University of Tübingen
** cooperation with S. Hage, Department of Biology, University of Tübingen, and W. Ziegler, Clinical Neuropsychology Research Group, Munich

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”.

**SELECTED PUBLICATIONS**


The research focus of our Stroke & Neuroprotection Laboratory is to find new and to optimize existing neuroprotective strategies that can help to minimize brain damage after stroke. Furthermore, we aim to study and characterize molecular mechanisms involved in ischemic-hypoxic damage and reperfusion-reoxygenation-induced neuronal death. Our current projects evaluate the effects of selective brain hypothermia combined with normobaric and hyperbaric hyperoxygenation. Our goal is to provide translational research with a close link to clinical application.


**SELECTED PUBLICATIONS**


**Purrucker J, Hametner C, Engelbrecht A, Bruckner T, Popp E, Poli S.** Comparison of stroke scores in the prehospital and intrahospital emergency settings. Stroke, submitted


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The Department of Neurology and 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. Beside epileptology other foci are pain disorders, particularly headache and neuromuscular diseases. The clinic offers the whole spectrum of modern diagnostic and therapeutic procedures. The inpatient unit with 28 beds (Wards 41/42 and 45), running under the supervision of Prof. Dr. Y. Weber, Dr. N. Focke and PD Dr. T. Freilinger, 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

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

Departmental Structure

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For electrophysiological recordings of neuronal activity in brain slices, a glass micropipette with a very fine tip (left) is brought in tight contact with a neuronal cell under microscopic control (middle). 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 (right).
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 recruiting well-defined cohorts of patients with epilepsies and related disorders (see group on Clinical Genetics of Paroxysmal Neurological Diseases), 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.

Epilepsy affects up to 3% of people during their lifetime, with a genetic component playing a major pathophysiological role in almost 50% of cases. To analyze the genetic architecture of epilepsy we have been involved in national (National Genome Network, NGFNPplus and German Network of Neurological and Ophthalmological Ion Channel Disorders, IonNeurONet) and international (FP6: Epicure, ESF: EuroEPINOMICS, FP7: EpiPGX) research networks confined to the recruitment of large cohorts of affected individuals and/or families and their genetic analyses. As an example, within the EuroEpinomics consortium we recently identified mutations in GRIN2A encoding the NR2A subunit of the NMDA receptor in two large independent cohorts comprising the whole spectrum of genetic focal epilepsies (Lemke et al, 2013).

Detected genetic variants are subjected to functional analysis in different heterologous systems. Using an automated two-voltage clamp system in Xenopus laevis oocytes, we showed that newly detected GABA(A) receptor variants reduce GABA-induced currents, which can explain the occurrence of seizures via reduced inhibition in brain. Furthermore, our analysis of seven KCNQ2 mutations associated with severe epileptic encephalopathy with pharmacoresistant
seizures and mental retardation suggested a dramatic loss-of-function with prominent dominant-negative effects on WT channels as a common pathophysiological mechanism of these mutations (Orhan et al, 2013). Expressing a number of SCN2A mutations affecting the sodium NaV1.2 channel in a mammalian cell line revealed a gain-of-function pathomechanism (Lauxmann et al. 2013).

Functional implications of selected mutations are further examined in neuronal expression systems, such as transfected murine primary neurons and genetically-altered animal models. Electrophysiological methods, including single cell patch clamp or multielectrode array (MEA) technique to analyze neuronal network activity are employed. Such studies revealed for instance a hyperexcitability of single neurons and neuronal networks caused by two disease-causing KCNQ2 mutations (Füll et al., in preparation). We further characterized a knock-in mouse carrying a SCN1A mutation associated with generalized epilepsy with febrile seizures plus (GEFS+) and found a reduced excitability of inhibitory neurons in all examined brain regions. SCN1A is coding for the voltage-gated sodium NaV1.1 channel expressed in inhibitory neurons and our findings indicate disinhibition as a mechanism of seizure generation in this model. To better understand these mechanisms we also assessed network dysfunction on MEAs, in thalamocortical field recordings and by using Ca2+ imaging of the hippocampus (Hedrich et al. submitted). In contrast, in a SCN2A mouse model, which is currently analyzed in cooperation with D. Isbrandt (Hamburg) and H. Beck (Bonn), epilepsy is driven by an intrinsic hyperexcitability of excitatory pyramidal neurons (ongoing work by Liu et al.). We also started collaborations on in vivo multi-electrode array analysis with C. Schwarz (Systems Physiology group) and on 2-photon Ca2+ imaging of the cortex with O. Garaschuk (Inst. Physiology II). Furthermore, in cooperation with the groups of T. Gasser and S. Liebau (Institute of Neuronatomy), we have been generating induced pluripotent stem (iPS) cells from fibroblasts and keratinocytes of patients with epilepsy and differentiating them into neurons in order to establish human disease models to examine mechanisms of epileptogenesis.

An additional research interest is structural and functional brain imaging. We are establishing novel 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. Moreover, we also use fMRI to characterize and better understand these effects, in particular episodic memory processes generated in the hippocampus.

The newly established research group of PD Dr. T. Freilinger aims at understanding the molecular pathophysiology of primary headache disorders with a special focus on migraine. As a monogenic model disease we are studying familial hemiplegic migraine (FHM), which is caused by mutations in cerebral ion channels and transporters. Complementary to ongoing genetic studies in this field, a major focus will be the multimodal clinical and electrophysiological characterization of a newly generated transgenic mouse model for FHM.

**SELECTED PUBLICATIONS**


*corresponding authors


Paroxysmal neurological disorders include a broad spectrum of clinical entities such as migraine, episodic ataxia or myotonia. The research group is focused on the clinical genetics of epilepsies and paroxysmal dyskinesias, paroxysmal neurological disorders with overlapping clinical and pathophysiological features.

Epilepsy is a very common neurological disease with a life time incidence of up to 3% in the general population. Epilepsies are divided in focal and generalized forms as well as in lesional (induced by e.g. scars, dysplasias or strokes) and genetic (idiopathic) forms looking from a pathophysiological point of view. Up to 30% of epilepsies are genetically determined but only 1-2% are monogenic with a single mutation leading to the clinical syndrome. Most of the genetic epilepsies follow a complex-genetic trait in which only a combination of genetic changes lead to the phenotype. Important groups of genetic epilepsies are the following:

(i) idiopathic generalized epilepsies (IGE) like the absence epilepsies with childhood (CAE) and juvenile onset (JAE) or juvenile myoclonic epilepsy (JME)
(ii) the idiopathic focal epilepsies such as the Rolandic epilepsies, nocturnal frontal lobe epilepsy (ADNFLE) or familial temporal lobe epilepsies (TLE)
(iii) the benign syndromes of early childhood such as the benign familial neonatal (BFNS), infantile (BFIS) and the infantile-neonatal (BFINS) forms and
(iv) the epileptic encephalopathies such as the Dravet syndrome (SMEI, severe myoclonic epilepsy of infancy) or Othahara syndrome.

Epilepsies are related to paroxysmal dyskinesias (PD) since both diseases can be found in the same family and can be based on the same genetic defect. Paroxysmal dyskinesias can be symptomatic (e.g. multiple sclerosis lesions found in the basal ganglia), but most of the described cases are of idiopathic/genetic origin. The genetic forms are divided in the following three subtypes:

(i) non-kinesigenic dyskinesia (PNKD)
(ii) kinesigenic dysinesia (PKD)
(iii) exertion-induced dyskinesia (PED)

The observed episodic dyskinesias include choreatic, ballistic, athetotic and dystonic features. They can be induced by different stimuli: In PNKD by stress or alcohol but not by movements, in PKD by sudden voluntary movements, and in PED after prolonged periods of exercise (10-30 min) in the exercised muscle groups.

PNKD has been associated with idiopathic generalized epilepsies with mutations found in the potassium channel gene KCNMA1, PKD with the benign familial infantile seizures (BFIS) with mutations found in PRRT2 (proline rich transmembrane protein), and PED with different forms of absence epilepsies (mutations found in SLC2A1 coding for the glucose transporter type 1, Glut1).

Glut1 is the most relevant glucose transporter of the brain since it delivers glucose across the blood brain barrier. The Glut1 syndromes include a variety of clinical features with a huge variability in phenotypes. The first mutations in PED were described in 2008. The mutations lead to a functionally relevant reduction in the glucose uptake which can well explain the episodic character of the symptoms under exertion (Weber et al. 2008). Mutations in SLC2A1 were also found in early-onset absence epilepsy (EOAE, Suls et al. 2009) and childhood absence epilepsy (CAE, Striano et al. 2012). All Glut1 syndromes respond well to a ketogenic diet which bypasses the defective glucose metabolism by providing ketones.

The syndrome of benign familial infantile seizures (BFIS) is characterized by a cluster of seizures with an onset between 3 and 12 months of age. The seizures can be treated well by common antiepileptic medications or disappear spontaneously. Most of the patients never develop seizures in adult ages and have a normal psychomotor development. Up to 40% of patients also suffer from PKD which can be also treated by...
common antiepileptic drugs. Since many years, it was clear that both syndromes are linked to a huge region on chromosome 16 (Weber et al. 2006, Weber et al. 2008) but an underlying gene could not be detected for a long time. Recently, mutations in the gene PRRT2 were described as the main cause of BFIs, ICCA and PKD by our and many other groups (Schubert et al. 2012, Becker et al. 2013). The resulting protein might be functionally relevant in the vesicle synaptic metabolism of neurons.

We are furthermore interested in the genetics of epileptic encephalopathies. A trio sequencing approach has been applied by the EuroEPINOMICS-RES consortium (see Experimental Epileptology group) as a valuable tool for detecting the underlying genetic causes of these severe disorders. De novo loss-of-function variants were detected in CHD2 (encoding chromo-domain helicase DNA binding protein 2) in a cohort of severely affected children with a fever-sensitive myoclonic epileptic encephalopathy very similar to Dravet syndrome. The functional relevance of CHD2 haploinsufficiency was assessed in a zebrafish in vivo model system, in which knocking down chd2 revealed epileptiform discharges similar to seizures in affected persons and altered locomotor activity (Suls et al., 2013).

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Expression of the glucose transporter type 1 (Glut1) in Xenopus laevis oocytes.
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 maturation processes. These processes were accompanied by an increasing density of presynaptic vesicles. Furthermore, we demonstrated that ES cell-derived network activity was sensitive to synthetically 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 invitro neuronal network activity

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

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 piagial 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. Functionally 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 invitro neuronal network activity (ivNN A) recorded by multielectrode arrays measuring synchronously bursting neural populations. Functionally relevant substances in pathologically altered CSF were biochemically identified, and ivNN A 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 ivNN A. 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 ivNN A 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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The Department of Neurodegenerative Diseases was founded with the support of the Charitable Hertie Foundation and started operations on September 1, 2002. The department pursues a comprehensive approach towards basic and clinical research in the field of neurodegenerative diseases and movement disorders, from their genetic basis and early diagnosis to innovative treatment and patient care. Through its clinical division, the department cares for patients with neurodegenerative diseases and movement disorders in one inpatient unit of 21 beds (Ward 43, under the supervision of Prof. L. Schöls and Prof. R. Krüger) and several specialized outpatient clinics. The clinical work is carried out by specially trained staff on all levels, including nurses, physiotherapists, occupational and speech therapists, as well as neurologists and neuropsychologists.

The department offers specialized and up-to-date diagnostic procedures for neurodegenerative diseases, including 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. In 2013, the clinical department was named as one of Germany’s Top Ten hospital departments in Parkinson’s Disease by the Magazine Focus.

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. Kähles 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. Dr. S. Biskup leads a research group on LRRK2-biology, but also a highly successful company that offers innovative methods of genetic diagnosis. Prof. W. Maetzler focusses on neurogeriatrics and gait disorders in Parkinson’s disease and dementias.

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.

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

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).
Specific mutations in some genes can cause rare inherited forms of Parkinson’s disease (PD). Mutations in the LRK2-gene, causing the most prevalent autosomal-dominant form of PD, was discovered by us and collaborators in 2004 (Zimprich et al., Neuron 2004). A contribution of more common genetic sequence variants, often called single nucleotide polymorphisms (SNPs), in the etiology of the much more common sporadic (= non-familial) is now equally well established.

In an attempt to identify these risk variants for the sporadic disease, we have conducted the first large genome-wide association study (GWAS), funded in part by the National Genome Network, NGFN2, in a collaboration with the laboratory for neurogenetics of the National Institutes of Health (NIH). This landmark study, which used material from more than 5,000 patients and 8,000 control individuals, identified two major genetic risk loci for sporadic PD: SNCA, encoding α-synuclein and MAPT, containing the gene for the microtubule associated protein tau (Simon-Sanchez et al., Nat Genet 2009). Both genes had already been known to play an important role in familial PD and frontotemporal dementia, and the findings have now been confirmed by numerous other studies.

Although most patients with Parkinson’s disease (PD) do not have affected parents or siblings, it is becoming increasingly clear that genetic factors greatly 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 betroffen 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.
Since this initial study, we have worked with numerous collaborators who had performed similar studies to re-analyze the data, now based on a total sample size of almost 20,000 cases and 95,000 controls. This latest meta-analysis resulted in the confirmation of a total of 28 risk loci with genome wide significance (Nalls et al., Lancet 2011; Nalls et al., submitted). These variants can also influence the course of the disease (Brockmann et al., Mov Disord 2013).

As genome-wide association studies only capture relatively common variants, a significant proportion of the total genetic risk remains to be discovered. This is sometimes called the “missing heritability”, and thought to be conferred mainly by rare genetic variants of moderate effect size. In order to identify the relevant variants, we are conducting whole-exome sequencing studies.

Knowing the genetic underpinnings of a complex neurodegenerative disorder such as PD is important, but it does not yet answer the question how these 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” into so-called “induced pluripotent stem cells” (iPSC) has opened up a whole new research area: The iPSCs can be differentiated into practically any cell type of the body, including nerve cells. We have successfully used this technology and have generated numerous iPSC-lines with specific PD-related mutations. These cells allow us to study the consequences of PD causing mutations in their “natural” surrounding. We have been able to demonstrate that iPSC-derived neurons from patients with LRRK2-mutations have specific abnormalities which can be rescued by correcting the gene mutation using highly specific molecular tools (Reinhardt et al., Cell Stem Cell, 2013).

**SELECTED PUBLICATIONS**

Dystonia is the third most common movement disorder, and mutations in a growing number of genes have been identified as causes for hereditary forms in many cases. The aim of the group, which brings together clinical experience in the diagnosis and treatment of the dystonias with expertise in molecular genetics, is to define the role of known genes in the etiology of dystonia, but especially to find new genes and therefore gain novel insight into the molecular pathogenesis of the disorder.

Patient recruitment is based on the departmental outpatient clinic for botulinum toxin treatment led by Prof. Schöls, on international collaborations but also on the work of Dr. E. Lohmann, who is presently working at the University of Istanbul, supported by a Margarete von Wrangell-stipend. As Turkey is a country with a high rate consanguinity, the prevalence of hereditary recessive diseases is greatly increased. Building on an existing cohort of patients with dystonia from consanguineous families in Turkey, detailed phenotyping and a thorough work-up of the families will provide the basis for future genetic analyses.

**SELECTED PUBLICATIONS**

We are elucidating the molecular mechanisms of neurodegeneration and physiological roles of genes linked to Parkinson’s disease (PD) as well as the neuropathological disease entities characterized by the nucleic acid binding proteins TDP-43 and FUS, causing frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). We are doing basic research using biochemical, molecular and cell biological methods, fly and mouse models, and patient-derived biomaterials.

In the past year, we completed a structure/function study on novel DJ-1 variants discovered in Dutch patients with early-onset PD by the group of Peter Heutink (now DZNE Tübingen). While the A179T substitution showed no defects, the P158del mutation led to protein destabilization and loss of neuroprotective functions of DJ-1 (Rannikko et al. JNC). In the course of these studies, we started to collaborate with Poul Henning Jensen (Univ. Aarhus, Danmark) in the context of the EU Training Consortium NEURASYN. We used their cell culture model of MSA and demonstrated neuroprotective effects of DJ-1 in this model. Moreover, we found that the cell death receptor Fas plays a role in MSA a-synucleinopathy (Kragh et al. PONE).

We were active in contributing antibody expertise to a local biomarker study on selected publications


The Section of Clinical Neurogenetics is dedicated to rare neurodegenerative disorders like ataxias, spastic paraplegias, amyotrophic lateral sclerosis, fronto-temporal dementia, mitochondrialopathies 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.

Ataxia

In preparation for interventional trials in spinocerebellar ataxias (SCA) we participated in the EUROSCA consortium supported by the European Union (www.eurosca.org) and set up a European registry with more than 3,000 patients suffering from this rare disease. We extended the SCA cohort to individuals at risk to develop SCA, i.e. first degree relatives of a patients who carry a 50 % risk to inherit the mutation. In this RISCA cohort we could show early changes in eye movements and in MR imaging before onset of ataxia. This allows to apply future therapies in a presymptomatic stage and raises the chance to modify disease progression (Jacobi et al Lancet Neurol 2013).

Early onset ataxias are a major challenge to physicians as they divide into numerous genetic subtypes, almost all of them being extremely rare. To gather a representative cohort of such patients we established a national network for early onset ataxias and set-up standards for diagnostic work-up and clinical characterization. All patients are registered in a newly created web based databank. This database is also open for European partners including paediatricians.

The complex genetics of early onset ataxias leave most patients without a molecular diagnosis. To overcome this problem we developed an ataxia gene panel tool using next generation sequencing techniques to analyse all known ataxia genes and several neurometabolic ataxia-mimics in one single approach by massive parallel sequencing. With this new tool we identified several patients with very rare ataxia subtypes including ARSCAS, Niemann Pick Type C and LBSL (leucencaphalopathy with brainstem and spinal cord involvement and increased lactate) (Synofzik et al. Orphanet J 2013, Schicks et al. Neurology 2013a, Schicks et al. Neurology 2013b).

Families negative for all known ataxia genes underwent whole exome sequencing to search for new genes. By this approach we identified two new genes for autosomal recessive ataxia. WWOX is responsible for recessive ataxia with generalized tonic-clonic epilepsy and mental retardation (Synofzik et al. Brain 2013 epub). PNPLA6 causes ataxia with hypogonadism, a syndrome known as Gordon Holmes syndrome.
or as Boucher-Neuhauser syndrome if ataxia and hypogonadism are accompanied by chorioretinal dystrophy (Synofzik et al. Brain 2013, epub).

In terms of therapy we have shown that active coordinative training is effective to reduce ataxia especially if performed on regular basis. Motivation and frustration frequently hinders every day training sessions especially in young patients. To address this problem we aimed to combine coordinative training with a fun factor and used whole-body controlled video game technology for highly interactive and motivational coordinative training for children with ataxia. Despite progressive cerebellar degeneration, children were able to improve motor performance by intensive coordination training. We could show that whole-body controlled video games present a highly motivational, cost-efficient, and home-based rehabilitation strategy to train dynamic balance and interaction with dynamic environments in kids (Ilg et al. Neurology 2012).

**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. In two HSP mouse models we revealed molecular mechanisms for such a length dependent axonopathy. SPG10 is caused by mutations in the kinesin KIF5a, the motor of anterograde axonal transport. In a knockout model we found axonal transport to be affected but not only in anterograde but also in retrograde direction suggesting an essential interplay between both (Karle et al., Neurogenetics 2013). In a mouse model of SPG15 generated by the group of Hübner in Jena we could show that lack of SPASTIN leads to endolysosomal abnormalities and impaired axonal outgrowth (Khundadze et al. PLoS Genet 2013).

Rapid progress in genetic technologies allows for time- and cost-effective analyses of whole exomes providing sequencing data of all coding regions of a genome within weeks. This turns out to become a highly efficient tool in the analysis of so far undefined genetic diseases. Using whole exome sequencing we found seven new genes causing HSP within 2 years: Reticulon 2 (RTN2) causing SPG12 (Montenegro et al. JCI 2012), B4GALNT1 causing SPG26 (AJHG 2013), DDHD1 causing SPG28 (AJHG 2012), GBA2 causing SPG46 (AJHG 2013), adaptor protein complex 4 (AP4B1) causing SPG47 (Bauer et al. Neurogenetics 2012), CYP2U1 causing SPG49 (AJHG 2012) and DDHD2 causing SPG54 (Schüle et al. Eur J Hum Genet 2013). This success in gene discovery became possible because of longstanding set-up of a large HSP cohort in national and European networks and close cooperation with the patient support groups.

Further effort is made to coin improved understanding of the molecular pathogenesis of HSP into therapeutic progress. Here we focus on SPG5, a subtype of HSP caused by mutations in CYP7B1. Lack of CYP7B1 leads to the accumulation of oxysterols (especially 27-OH sterol) in serum and even more pronounced in CSF (Schüle et al, J Lipid Res 2010). In cell cultures we could show that 27-OH sterol levels similar to concentrations in CSF of patients impair motoneuron-like cells. First results from a pilot trial with the cholesterol-lowering drug atorvastatin indicated lowering of 27-OH sterol in patients with SPG5.

**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. After successful set-up of the consortium more than 50 families have been identified in Israel and the West Jordan land. Microarray based homozygosity mapping and high-throughput sequencing approaches allow for the identification of the molecular cause of the disease in an increasing number of families including the identification of new genes (Bauer et al. Neurogenetics 2012, Mallaret et al. Brain 2013, epub).

**SELECTED PUBLICATIONS**


With the aging society the prevalence of Parkinson’s disease (PD) and neurodegenerative dementias increases 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 for an objective, individualized understanding and description of disease progression. Additionally novel medication and conservative therapeutic strategies are offered in numerous studies.

**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, as well as 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. Moreover, a special focus is being put on the identification and better understanding of subgroups of PD, i.e. monogenetic forms or forms in which specific pathophysiological aspects play a major role – e.g. inflammation, mitochondrial dysfunction. Another focus is dementia in PD, especially the early diagnosis with the intention to intervene at a stage at which a greater benefit for patients and caregivers may be achieved. As a substantial impact on the activities of daily living function is mandatory for diagnosis of dementia varying scales and objective measurements are evaluated which might serve as diagnostic tools even in the pre-stage of dementia.

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 20 times increased risk to develop PD within five years,
(ii) evaluation of progression markers in the pre-diagnostic phase of PD is feasible by assessing individuals with various combinations of risk and prodromal markers
(iii) the neurodegenerative process in GBA-PD is associated with alterations of membrane phospholipid metabolism which might be also involved in abnormal α-synuclein aggregation
(iv) Plasma ceramide and glucosylceramide metabolism is altered in sporadic Parkinson’s disease and associated with cognitive impairment
A further focus of the group is standardization of assessments in collaboration with other experts. In cooperation with Prof. Walter Maetzler and colleagues simple to apply, non-invasive accelerometer-based measurement systems as well as devices to test fine motor function are applied in many of the cohort studies to objectively assess subtle motor deficits.

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.

**Atypical Parkinsonian syndromes**

Major effort has been put into 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 180 subjects with clinically defined idiopathic PD the cognitive, neurobehavioral, motor and blood marker profile is being monitored longitudinally to discover factors which are associated with a more rapid cognitive decline. Further projects are followed in national and international cooperations.

**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 variance. Thus a large cohort of tremor patients is currently being characterized with thorough quantitative assessment 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.

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The functional neurogeriatrics group is dedicated to investigations of movement control of the elderly and individuals with prodromal and early stages of neurodegenerative disorders such as Parkinson’s disease. Quantitative ambulatory assessment of axial and distal movements is performed with state-of-the-art measurement and investigation techniques. We are focusing on the association of movement deficits with quality of life in particular in chronic progressive diseases such as Parkinson’s disease, and to give direct feedback to the user about movement deficits and resources to increase self-empowerment.

Empowering patients with chronic diseases to manage their own health and disease can result in improving health outcomes, encouraging patients to remain so, and in increased quality of life (Maetzler, Domingos, et al., 2013). Moreover, it most probably leads to more cost-effective healthcare systems. The value of these activities is increasingly recognized not only by the patients and their doctors but also by stakeholders and funding agencies.

Our group is centrally involved in the development of a multimodal sensor information system for individuals with Parkinson’s disease which exactly focuses on self-empowerment of the users. This system will be used in the home environment of patients with Parkinson’s disease, and will be modular, extendible, adaptive and minimally obtrusive. Partners from England, Germany, Norway and Portugal contribute to this EU-funded ICT project (FP7, SENSE-PARK).

Example of movement detection in the home environment: Angular velocity of a gyroscope fixed on an iron while used by a patient with Parkinson’s disease (top) and a healthy control (bottom), for ironing a shirt. Note also the 6 Hertz waves in the inset, representing action tremor.
Another focus of our group is the investigation of quality of life aspects in Parkinson’s disease. This disease has a major impact on the quality of life because it affects physical, mental and social life. Since there are many factors contributing to a patient’s quality of life, it is essential for clinicians and scientists to measure these as objectively as possible (Maetzler, 2014). In the EU-funded ITN project Moving beyond we aim at defining a conceptual framework that will quantitate quality of life in patients with Parkinson’s disease, using both cross-sectional and longitudinal objective measures generated in local study populations. Apart from this focus, the Moving beyond project spans the spectrum from basic understanding of mechanisms, over diagnostics to therapeutic applications of supraspinal motor control deficits (Maetzler et al., 2012; Maetzler, Nieuwhof, et al., 2013).

**Effects of Protein clearance deficits on Parkinson’s disease:**
Together with the groups of Prof. Daniela Berg and Prof. Thomas Gasser, our group is centrally involved in a structured and continuous development and maintenance of a local Neuro Biobank. In this context, our group aims at investigating the association of biochemical markers – such as markers of protein clearance – with symptoms and signs of Parkinson’s disease.

Protein clearance is critical for the maintenance of the integrity of neuronal cells, and there is accumulating evidence that in Parkinson’s disease impaired protein clearance fundamentally contributes to functional and structural alterations eventually leading to clinical symptoms. Particular focus is put on amyloid precursors such as APP (Vijayaraghavan et al., 2013), and astrocytic and microglial responses (Sathe et al., 2012).

**SELECTED PUBLICATIONS**


Maetzler W. Why do nondopaminergic features in Parkinson disease matter? Neurology 2014


The Functional Neurogenomics Group is focused on the elucidation of molecular signaling pathways leading to neurodegeneration in Parkinson’s disease (PD). We intensively study functional consequences of the identified mutations involved in pathogenesis of PD by investigating the underlying molecular signaling cascades. Here we have access to a unique collection of patient-based cellular models, including carriers of the A30P mutation in the alpha-synuclein gene (Krüger et al., 2001) and the ‘E64D’ mutation in the DJ-1 gene (Hering et al., 2004). Using patient fibroblasts to study mitochondrial function and dynamics the group pioneered in the field of mitochondrial pathologies in Parkinson’s disease and defined first mitochondrial phenotypes related to mutations in the DJ-1 and the mortalin gene (Krebiehl et al., 2010; Burbulla et al., 2010). Most interestingly characteristic mitochondrial alterations were already observed in cells from presymptomatic human mutation carriers indicating a potential role as a biomarker of the disease (Burbulla et al., 2010). Recent studies aim at the identification shared pathways of different PD-associated proteins linked to mitochondrial quality control. Here we found that PINK1/Parkin-mediated increase in mitophagy can rescue the loss of mortalin function phenotype characterized by intramitochondrial proteolytic stress (Burbulla et al., in press). Moreover in collaboration with T. Rasse we confirmed a role of mortalin in neurodegeneration in flies in vivo (Zhu et al., 2013). Reduced levels of mortalin caused a Parkinsonian locomotor phenotype in flies that was related to a loss of synaptic mitochondria. We further extended our research on the characterization of neuron-specific phenotypes based on induced pluripotent stem cells (Reinhard et al., 2013) and are currently developing first individualized treatment strategies. After the identification of a novel mechanism for c.192G>C mutant DJ-1 that leads to complete protein loss due to defective splicing, we are currently applying targeted approaches for rescuing the correct splicing and restituting DJ-1 protein levels in neurons derived from stem cells of affected mutation carriers (Obermaier et al., 2013; Abstract).

The Deep Brain Stimulation Group represents the clinical focus on advanced stages of Parkinson’s disease, dystonia and tremor. Here the interdisciplinary BrainStimNet Tübingen (Neurosurgery, Prof. Gharabaghi; Psychiatry, Prof. Plewnia; Ethics, Prof. Wiesing) developed into one of the leading centers in Germany during the last 5 years. This is reflected by the integration into large international multi-center studies, where Tübingen substantially contributed to the EarlyStim Study, that revealed a significant gain in quality of life in PD patients with early motor fluctuations and will change treatment algorithms for PD in the future (Schüpbach et al., 2013). Moreover the group translated electrophysiological
With regard to the hitherto unmet therapeutic need on gait disturbances and falls we want to develop novel treatment strategies.

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DEPARTMENT OF COGNITIVE NEUROLOGY

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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 “Werner Reichardt 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.

Prof. Dr. Peter Thier heads the Department of Cognitive Neurology.
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 are currently engaged in an initiative to set up a Collaborative Research Center (SFB) on "Perception-Action and Social Interaction – Neural Encoding and Computations." This initiative is coordinated by Martin Giese, leader of the research group 'Computational Sensomotorics' at the DCN and the pre-proposal will be evaluated in May 2014. Many members of the DCN are also part of the ongoing excellence cluster "Werner Reichardt Centre for Integrative Neuroscience (CIN)", which is now in its second funding period. The CIN is coordinated by Peter Thier. In October 2013 the DFG-funded trans-regional Research Unit (FOR1847) 'The Physiology of Distributed Computing Underlying Higher Brain Functions in Non-Human Primates' was granted and will be fully operational in March 2014. It brings together research groups from Göttingen, Marburg, Frankfurt and Tübingen working with non-human primates. The Research Unit is coordinated co-jointly by Peter Thier and Stefan Treue of the German Primate Center Göttingen.

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, the Graduate School of Cellular and Molecular Neuroscience and the Graduate School for Neural Information Processing. Martin Giese has been instrumental in helping to set up the latter, which started in October 2011. Uwe Ilg heads the ‘Schülerlabor Neurowissenschaften’ (Pupils’ Lab Neurosciences) funded by the CIN, that aims at making senior pupils familiar with neuroscientific topics. 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.
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 behavioral 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 premotor cortex in action understanding. Mirror neurons are a class of neurons in premotor 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 behavior. 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.

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 viewpoint invariant. This is important as the perspective under which we see the actions of others is of course not fixed.

A second major 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 fiber signal, representing information on the adequacy of the behavior prunes a simple spike population signal, which in turn, controls the behavior. A distinctive feature of cerebellum-based learning worked out by the group, is its extreme speed, accommodating behavioral 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’s inability to compensate fatigue. Based on studies of perceptual disturbances from cerebellar disease, the group has been able to provide evidence for the notion that such disturbances are a consequence of a loss of the ability to generate fast, optimized predictions of the consequences of movements, deploying the same neuronal principles that enable short-term motor learning and fatigue compensation. Maladapted sensory predictions may lead to dizziness but also to disturbances of agency attribution, the latter arguably a key disturbance in schizophrenia. These pathophysiological concepts are pursued in patient studies.

**SELECTED PUBLICATIONS**


Clinical movement control and rehabilitation

Many neurological disorders, such as cerebellar ataxia, 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 pre-clinical diagnosis of such diseases as well as the quantification of therapeutic benefits, which is extremely difficult for complex body movements with relevance for every-day life. We exploit advanced methods for movement analysis, motion capture, biomechanics and machine learning in order to quantify and study changes in complex whole-body movements. In cooperation with clinical partners we develop motor neurorehabilitation strategies based on scientific principles of motor learning.

In recent projects, we were able to show that physiotherapeutic training induces beneficial long-term effects in cerebellar ataxia patients, contrasting with the common opinion that cerebellar patients do not profit from motor training. Using computer games (Kinect and Wii system) we devised (in collaboration with L. Schöls, Dept. Neurodegeneration) novel training paradigms for children suffering from cerebellar ataxia at different levels of severity. Developing advanced mathematical methods for the analysis of coordination patterns, we were able to identify training-induced motor improvements in complex movement sequences that transfer to other motor tasks, indicating efficient generalization of the underlying control mechanisms. In collaboration with D. Timmann, (University Clinic Essen) we were able to examine the role of the cerebellum in the interaction of cognitive and motor tasks, as well as the influence of specific cerebellar lesion sites on such dual-task performance. In addition, we currently examine the influence of non-invasive stimulation on complex whole-body motor learning tasks (in cooperation with D. Timmann, and with U. Ziemann, Dept. Vascular Neurology) in order to explore...
the potential benefits for the support of motor rehabilitation.

**Neural mechanisms of action perception and representation**
A vast amount of evidence shows that neural representations for the perception and planning of actions are overlapping. However, the precise mechanisms of this interaction are largely unclear. Within a close collaboration that links theoretical modeling and electrophysiological experiments with non-human primates in the group of P. Thier (Dept. Cognitive Neurology), we investigate underlying detailed neural circuits in premotor cortex (area F5). For example, contrasting with established general ideas, we were able to show that mirror neurons in premotor cortex represent visual view parameters and do not show adaptation for repeated stimulus presentation. New results show also that mirror neurons represent the hierarchical temporal structure of actions while they can show extreme degrees of invariance against shape information. Based on such experimental results we develop physiologically-constrained neural models for the visual recognition of actions, and its relationship to motor representations, that recognize actions from real videos. These models demonstrate that action semantics and the perception of causality might be accounted for by relatively simple learning-based neural mechanisms.

A second central topic is the processing of social communication signals, such as bodily and facial movements, and underlying neural mechanisms. Exploiting techniques from machine learning and Virtual Reality, we study the processing of dynamic emotional body and facial expressions in the closed-loop interaction with virtual agents, investigating critical spatio-temporal features and underlying role of movement primitives. Stimuli generated by such methods are also useful for the study of the perception of emotions and social signals in psychiatric patients. In collaboration with S. Park (Vanderbilt University, Nashville) and A. Sekuler (McMasters University, Canada), we were able to show characteristic deficits in perception of emotional body expressions of schizophrenia patients. Collaborating with A. Fallgatter (Clinic of Psychiatry), we have investigated neural correlates of the processing of such stimuli using Near Infrared Spectroscopy (NIRS).

**Biologically-inspired technical applications and biomedical engineering**
Many technical systems require highly flexible and accurate representations of complex human movements. Exploiting machine learning approaches for the learning of hierarchical dynamical models combined with game engines, we were able to develop highly realistic models for the behavior of interacting humans that are used to study emotion perception, and which we plan to use also in monkey experiments for the study of the mirror neuron system. In several European projects, similar models are exploited in order to improve the control of humanoid robots. Most recent work in this domain has added a probabilistic semantic layer to such models. In collaboration with H.-O. Karnath (Division of Neuropsychology), we have successfully exploited such semantic models to detect automatically errors in the execution of complex manipulation actions that are characteristic for different sub-forms of apraxia.

In the domain of biomedical engineering we currently develop a mobile and low-cost (< 5000 EUR) motion analysis system (based on Kinect sensors), which will allow to quantify movement changes and rehabilitation outcomes, including also preclinical motor symptoms of movement disorders, e.g. in cerebellar ataxia and Parkinson’s disease.

**SELECTED PUBLICATIONS**


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. In contradiction of established textbook knowledge, research in nonhuman primates through the last decade demonstrated that the superior colliculi play some role in the execution of arm movements. In our ongoing studies we found clear evidence for its role in the control of arm movements also in healthy humans. However, the precise functional contribution of the colliculi to the processes of planning and execution and the processing of a movement’s sensory feedback is still unknown. To explore this unknown territory we currently develop experimental designs that allow for event-related analyses and transfer our paradigms to the ultra-high field 9,4T scanner at the MPI for High-field Magnetic Resonance. Using tensor imaging and resting state fMRI we investigate the connectivity of the superior colliculi within the sensorimotor network. First studies in nonhuman primates have already demonstrated a connection between the functions of superior colliculi and the appearance of motor disorders like cervical dystonia. A precise functional mapping of the colliculi in living humans will not only be important for the understanding of neurological motor disorders but might also 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. Surprisingly, this is also true for experimental and clinical measures of proprioception. 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 established technically simple, but nevertheless sensitive and reliable procedures to elucidate proprioceptive impairments where these were previously overlooked. These procedures allow us to really determine the role of proprioceptive deficits in the occurrence of visuomotor disorders. In collaboration with the Department for Neurodegeneration we examine the proprioceptive status of patients suffering from hereditary ataxias to determine the impact of such a specific sensory disorder on the general status of these patients.

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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. We decided to examine possible effects of video game play (VGP) on human eye movements and the allocation of attention. However, we did not find differences in the correctness of eye movements and in the speed of changing the locus of attention. We are able to separate the effects of video game play from the regular effects of age.

We analyze the details of eye movements in various conditions as an ideal example of goal-directed behavior. We ask whether these details are different in people playing routinely video games compared to people who do not play. In several studies, we were able to show that video game players (VGP) have shorter latencies in general compared to non-players and a better control of the allocation of attention. However, we did not find differences in the correctness of eye movements and in the speed of changing the locus of attention. We are able to separate the effects of video game play from the regular effects of age.

As basis for our experiment we tested a total of 55 subjects aged 15 to 31 years. All subjects were classified as VGP and non-players in regard to their daily gaming time: VGP (n=35) played at least one hour per day video games.

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 VGP compared to non-players. 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 VGP reach higher peak velocities as gaze shifts executed by non-VGP.

To examine the cognitive control function, we examined the frequency of erroneous pro-saccades in the anti-saccade task. VGP as well as non-players showed an error rate of approximately 40%, there was no significant difference between players and non-players. 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.
In order to reveal the shifts of attention, we measure precisely the gaze movements of our subjects. A high-speed camera is connected to the laptop, whose software is able to determine the position of the pupil 220 times each second. Another computer generates the visual stimuli presented on the screen in front of our subject.

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.

Speed of shifting the spotlight of attention?
The decrease of reaction times in VGPs may be attributed to faster attentional processing. To test this hypothesis, we designed an experiment in which subjects had to report the identity of a specific visual target presented in the array of a total of 12 items (see Figure 2). We varied the cue leading times between 0 and 600 ms. We examined 116 subjects, 63 identified as VGPs and 53 as non-players, respectively.

We observed a better overall performance of VGPs in our experiments. We were especially interested in the speed of shifting the spotlight of attention. Therefore, we determined the cue leading time that resulted in peak performance of a given subject. Interestingly, we found no difference in the optimal cue leading time between VGPs and non-player. Therefore, our data do not support the hypothesis that VGPs are able to shift their spotlight of attention faster compared to non-players.

Suppression of an already planned movement
In certain conditions, it is important to suppress an already planned action triggered by a specific stimulus. Initially, we asked our subjects (n=80) to press the space bar as fast as possible upon the appearance of a green rectangle. As expected, VGPs showed shorter reaction times as non-players. In our second paradigm, in 50% of the trials, the green target changed to red at five different stimulus onset asynchronies (SOA 16 to 320 ms). The color red indicated that the space bar should not be pressed! Now, the latencies in the still present Go-trials (frequency of 50% of all trials) are significantly increased compared to the latencies obtained in the first paradigm. VGPs have significant shorter latencies.

From our behavioral data at different SOAs we were able to calculate the stop signal reaction time (SSRT) for each subject, i.e. the minimal lead for a successful suppression of the key press. We found mean SSRT of approx. 250 ms with no difference between VGPs and non-player.

Differences in latencies between subjects
In the course of our experiments, we observed the natural scatter of saccadic latencies. We asked whether the individual value of saccadic latency of a given subject is determined by the processing time of the early visual system. We compared saccadic latencies obtained in two different saccade paradigms (regular and gap) with the latencies of visual-evoked potentials (VEP). We emphasized the latency of the p100 component. Our data revealed a highly significant correlation of the saccade latencies obtained in both paradigms. However, there was no correlation between saccadic latencies and p100 latencies suggesting that differences in eye movements are not determined by the processing time of the early visual system.

Effect of age
In the course of our studies, we had the possibility to compare the anti-saccade parameters in subjects with very different age (total of 334 subjects ranging from 15 to 80 years). We found that the saccadic peak velocities are not affected by age. The latencies of pro- and anti-saccades drop from young to adults and slowly increase again towards elderly subjects. The frequency of pro-saccades showed a similar dependency of age.

SELECTED PUBLICATIONS


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 arbeitet im Themengebiet Kognitive Neurowissenschaften. Arbeitsschwerpunkte der Sektion sind die Untersuchung der Raumorientierung und des Objekterkennens des Menschen, der Wahrnehmung der eigenen Körperorientierung, Prozesse der Aufmerksamkeit und Raumexploration, die visuomotorischen Koordinationsprozesse beim Zeigen und Greifen sowie die akustische Raumorientierung.

The Division of Neuropsychology’s main areas of research are the study of spatial orientation and object perception in humans. By using 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, 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.

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 are derived from constantly changing coordination systems. How the human brain accomplishes this task is a main focus of the Cognitive Neurosciences. The findings to our research questions not only allow us to have a better basic scientific understanding of these processes but will also aid us to develop new strategies for the treatment of patients with brain damage who show deficits in these areas.
We employed a multivariate pattern analysis (MVPA) procedure for using brain injury maps to predict the presence or absence of cognitive functions (Smith et al., PNAS 2013: 1518-1523).

MVPA involves both training and testing a predictive model. The training procedure employed machine-learning algorithms (support vector machines; SVMs) to construct a model of how distributed patterns of lesion data are consistent in indicating the presence or absence of spatial neglect. The constructed model is then tested on new data (i.e., not used to train the model).

This procedure was repeated for each individual in our dataset (N = 140), meaning each individual was tested on a model that was built independently of that individual’s data. The average of those predictions is the predictive power of the model.

**SELECTED PUBLICATIONS**


Capturing the complexity of the human brain requires gathering diverse information at multiple scales. Imaging the brain is evidently the most proximate approach to reveal these details. Functional neuroimaging includes all imaging techniques that help us to understand the functioning of the nervous system, either via detecting activity related signals (e.g. fMRI) related to neuronal activity in defined brain regions or by linking anatomy to function via comparative, quantitative or computational approaches. In this lab-unit, we use different imaging methods that allow us to visualize the complex molecular and cellular architecture of the brain at the microscopic level and also widely-distributed brain networks (electrical stimulation with fMRI) at the meso-macroscopic level. We image (with laser confocal microscopy) the neuropil of subcortical regions in the cerebellum in rodents and primates and relate these to specializations in network architecture of the human brain. We also use imaging techniques in order to address functional aspects of subcortical networks in targeting and influencing cortical network activity.

1. Imaging quantitative traits typical for the human cerebellar dentate

Compared to most mammals the cerebellar hemispheres are expanded in size in primates and even more so in apes and humans. A long-standing division of the primate dentate into an evolutionary older dorsal thin-folded (microgyric) and a newer ventral thick-folded (macrogyric) half based on dentate morphology has recently been linked to the emergence of a major projection from the cerebellum to the prefrontal cortex, and hence also to the development of related prefrontal specific human abilities (e.g. executive functions). In this study, we re-examined the human dentate morphology using detailed 3D surface models. Our reconstructions showed that the major part of the nucleus is similar to the phylogenetically older microgyric dorsal motor part of the dentate. Therefore, the characteristic of the human dentate is its folding and surface increase and not the emergence of a ventral macrogyric region. From these observations, we propose that the crucial enlargement of the human cerebellum was along the medio-lateral dimension and that the folding of the dentate has the function to ensure less convergence from neighboring parasagittal stripes. In future studies we want to relate the remarkable folding of the dentate to underlying cellular and molecular processes in order to better understand the mechanisms that underlie the emergence of folds in the ape and human dentate.

2. Cellular and molecular architecture of the mammalian cerebellar nuclei: searching for the human-typical traits in the dentate nucleus

A common view of the architecture of different brain regions is that despite their heterogeneity they optimized their wiring schemes to make maximal use of space. Based on experimental findings, computational models have delineated how about 2/3 of the neuropil is filled out with dendrites and axons optimizing cable costs and conduction time whilst keeping the connectivity at the highest level. However, whether this assumption can be generalized to all brain regions has not yet been tested. In this project, we have used semi-automated 3D reconstructions of immune-stained rat brains to quantify and chart the components of the neuropil in the four deep cerebellar nuclei (DCN). Our approach allowed us to be sufficiently fast to systematically sample all DCN regions and reconstruct the neuropil with detail. We observe differences in dendritic and axonal fiber length density, average fiber diameters and volume fraction within the four different nuclei that comprise the DCN. We observe a relative increase in the length density of dendrites and Purkinje cell axons in two of the DCN, namely the posterior interposed nucleus and the lateral nucleus (also called dentate in primates). Furthermore, the DCN have a surprisingly low volume fraction of their dendritic length density, which we propose is related to their special circuitry.

3. In-vivo imaging of the monkey brain’s connectivity

Electrical stimulation, combined with functional magnetic resonance imaging (es-fMRI), has become an important tool to study the functional properties of spatially distributed neuronal networks of the brain (Logothetis et al., 2010; Sultan et al., 2012). 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 bolus 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 (≥ 400Hz), suggesting a projection system optimized to mediate fast and temporally 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.

SELECTED PUBLICATIONS


Hamodeh S, Sugihara I, Baizer J, Sultan F (In press) Systematic analysis of neuronal wiring of the rodent deep cerebellar nuclei reveals differences reflecting adaptations at the neuronal circuit and internuclear level. Journal of Comparative Neurology.


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.

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).


**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.

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Our model for studying these questions is the sensorimotor 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 decision 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 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.

SELECTED PUBLICATIONS


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.

Our department hosts scientists from more than 10 nations ranging from short-term fellows, master students, PhD/MD students to postdocs and group leaders. To bridge our basic and preclinical research towards clinical applications we run the Section of Dementia Research, that includes the memory clinic, in collaboration with the University Clinic of Psychiatry. 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 co-workers.
In the past few years we have managed to generate transgenic mouse models that either mirror Alzheimer’s pathology by developing Aβ plaques or serve as a model for cerebral amyloid angiopathy by depositing Aβ protein in blood vessels. With the help of these models we have been able to show that β-amyloid aggregation can be induced exogenously by inoculations of mice with brain extracts from deceased Alzheimer patients or from aged transgenic mice with Aβ deposition. The amyloid-inducing agent in the extract is probably the misfolded Aβ protein itself. Thereby, soluble proteinase K (PK)-sensitive Aβ species have been found to reveal the highest β-amyloid-inducing activity.

These observations are mechanistically reminiscent of prion diseases and are now used to develop new therapeutic approaches for Alzheimer’s disease and other amyloidoses. First immunotherapy trials in transgenic mice are promising and show that β-amyloid aggregation can be reduced by targeting the initial proteopathic Aβ seeds. Microglia appear to play a crucial role in Aβ immunotherapy.

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 β-amyloid (Aβ) protein is deposited extracellularly in so-called amyloid plaques. Aggregated Aβ leads to a miscommunication between the cells and in a second stage to neuron death. The same Aβ protein can also build up in blood vessels which will cause amyloid angiopathy with potential vessel wall rupture and fatal cerebral bleedings.

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.
**SELECTED PUBLICATIONS**


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

(i) Processing and cellular function of the amyloid precursor protein (APP)
(ii) Identification of essential factors causing protein aggregation and amyloid formation
(iii) Uptake, accumulation 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 β- and β-secretase leads to generation of amyloid-beta (Aβ) 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 Aβ peptides as a therapeutic strategy for AD. Profound insights into the mechanism of Gleevec, a known tyrosine kinase inhibitor, were gained.

Recently another protein Bri2 came into focus. APP and Bri2 are both genetically linked to specific forms of dementia. Mutations in the Bri2 gene cause Familial British Dementia (FBD) and Familial Danish Dementia (FDD). One similarity is that both APP and Bri2 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 Bri2 with APP which lead to altered APP processing and decreased Aβ secretion. Our further indepth analysis revealed a new mechanism of interaction.

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-Erkranckung. Dabei nutzen wir Methoden der Molekular- und Zellbiologie, um Schlüsselschritte und Interventionspunkte zu finden.

In agreement with previous results we found that overexpression of Bri2 leads to a significant decrease in total secreted Aβ 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 Bri2 and also worked in a truncated version of the protein. We suggest now that Bri2 might act as a receptor that regulates IDE levels which in turn affects Aβ levels by influencing APP metabolism. Therefore the regulation of IDE activity may be a new promising therapeutic approach.

Aβ 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 Aβ though never forming plaquelike aggregates.

Electron micrograph of recombinant Aβ fibrillized after seeding.
To understand this discrepancy we started to investigate uptake and spreading of Aβ 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 Aβ may result in the accumulation of Aβ also within cells and organelles. Previous reports have drawn attention to the accumulation of Aβ within mitochondria. With a novel in vivo targeting approach based on previous studies we established the exclusive sorting of Aβ to mitochondria and are currently investigating metabolic consequences.

Transgenic mouse brain tissue has been previously shown to stimulate β-amyloid deposition in young transgenic mice. This process was termed seeding but little is known about the nature of the seed. We established a high throughput assay that can identify the presence of seeds in tissue homogenates. With this powerful tool we are now able to analyze defined fractions of brain tissue for the qualitative and quantitative presence of amyloid seeds. The assay is further explored to detect minute amounts of such seeds also in body fluids for diagnostic purpose.

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

SELECTED PUBLICATIONS


The Section for Dementia Research is run by the Department of Cellular Neurology and the University Clinic for Psychiatry and Psychotherapy. The section consists of an outpatient Memory Clinic and a Research Unit.

Memory Clinic
Memory disorders can be a consequence of a variety of diseases. The Memory Clinic provides early and differential diagnoses and the treatment of these disorders. Counselling of affected patients and their families is also provided. An initial visit at the Memory Clinic includes a physical, neurological and psychiatric examination. In most cases a blood sample will be taken. If indicated, a lumbar puncture to obtain cerebrospinal fluid as well as neuro-imaging (CCT or MRI), a electrocardiogram (ECG) and/or a electroencephalogram (EEG) will be performed. At a second appointment a thorough neuropsychological test of your memory will be performed by a physician and the results as well as treatment options will be discussed with you. A social worker will advice you on how to handle memory disorders in daily life. If you are interested and suitable you will be offered to participate in one of our clinical trials.

Research Unit
a) DIAN study
DIAN stands for "Dominantly Inherited Alzheimer Network", the international network for dominantly inherited Alzheimer’s disease. The study was founded in the US in 2008 in order to further investigate genetic forms of Alzheimer’s disease. Individuals from families with inherited forms of Alzheimer’s disease (the autosomal dominant form or the related Abeta amyloid angiopathy) are welcome to participate in this study. These rare forms of Alzheimer’s disease are caused by mutations in one of three genes (APP, PSEN1 or PSEN2).

An autosomal dominant form of the disease is suspected if several family members are or were affected with an onset at the age of 60 years or younger. In the first phase of the DIAN study affected individuals are identified and examined via multimodal diagnostics (e.g. PET-PIB; MRI; biofluids) in regard to preclinical changes. In the second and future phase treatment trials are planned. The goal is to treat the disease preventively already at a preclinical stage, i.e. before any symptoms appear.
b) DELCODE study
DELCODE (DZNE – Longitudinal Cognitive Impairment and Dementia Study) is a multicenter longitudinal observational study of the German Center for Neurodegenerative Diseases (DZNE) specifically focusing on the preclinical stage of Alzheimer’s disease. The aim of the study is to characterize the neuronal network mechanisms of cognitive adaption and decompensation. The recruitment will be via memory clinics of the DZNE sites. All DZNE sites with memory clinics will participate in DELCODE. The inclusion period is three years. Baseline and annual follow-ups are planned to cover 5 years per subject. It is planned to extend the observational follow-up per patient beyond 5 years. All subjects will undergo extensive structural and functional neuroimaging, including cognitive fMRI tasks and resting state fMRI at baseline and at follow-ups.

c) Identification and validation of new biomarkers for Alzheimer’s disease
We aim to identify and validate new biomarkers for Alzheimer’s disease using various technology platforms (ELISAs, flow cytometry, multiplex assays, mass spectrometry) and by examining a number of bioliquids (blood, cerebrospinal fluid, urine, tear fluid). For example we have found that by means of three biomarkers measured in the blood (Cortisol, von Willebrand factor [vWF] and oxidized LDL-antibodies [OLAB]) Alzheimer patients can be distinguished from healthy controls with a test accuracy of more than 80% (Laske C et al., Int J Neuropsychopharmacol 2011). This little invasive and low-cost method may be suitable for the screening of Alzheimer patients.
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Axonal regenerative failure being a major cause of neurological impairment occurs following central nervous system (CNS), but not peripheral nervous system (PNS) injury. Importantly, PNS injury triggers a coordinated regenerative gene expression program not found after CNS injury such as spinal cord lesions, whose core molecular substrate remains elusive. Here we show that epigenetic pathways mediated by PCAF-dependent acetylation of H3K9 at the promoters of key regeneration associated genes are triggered by a conditioning peripheral sciatic nerve lesion but not by a spinal dorsal column injury. Next, we found that NGF-MEK-ERK retrograde axonal signaling trigger PCAF-dependent regenerative gene reprogramming. Finally, PCAF is required for conditioning mediated axonal regeneration and PCAF overexpression promotes axonal regeneration across the inhibitory environment of the injured spinal cord. This work provides evidence that a specific epigenetic code regulates the capacity for axonal regeneration of CNS neurons providing a novel epigenetic-based target for regenerative therapies for clinical spinal injury.

PCAF-dependent epigenetic changes promote axonal regeneration in the central nervous system (Puttagunta et al., Nature comm, in press)

Initially after a peripheral nerve injury rapid ion fluxes increase, followed by a rise in cAMP levels, axonal translation occurs, phosphorylation retrograde cascades activate transcription factors, gene expression is induced and finally regeneration occurs. However, the final link between axonal injury-induced retrograde signaling and the regulation of essential regenerative gene expression remains elusive. As epigenetic changes are a rapid and dynamic way to translate external stimuli into targeted, we believed that a positive retrograde signal initiated by PNS injury could relax the chromatin environment surrounding specific promoters and allow for gene expression; however, a negative signal following CNS injury may restrict promoter accessibility and inhibit gene expression. Given that DNA methylation did not show a clear pattern associated with axotomy, we investigated whether key histone modifications would be specifically enriched on established critical genes for the regenerative program in DRG neurons. Of all histone modifications that correlate with active gene transcription (H3K9ac, H3K-18ac, H3K4me2) or gene repression (H3K9me2 and H3K27me3) that were screened, H3K9ac and H3K9me2 and H3K27me3 were enriched compared to IgG on most promoters, but only H3K9ac and H3K9me2 were found differentially enriched at GAP-43, Galanin and BDNF promoters, consistently correlating with early and sustained increased expression following SNA (1-7 days). In contrast, SCG-10, whose gene expression is unaltered after 24h and only modestly increased following 3 and 7 days SNA, did not show an enhancement of H3K9ac or PCAF at its promoter. Given that a preconditioning lesion (SNA preceding DCA) activates the regenerative capacity of the CNS, we questioned if a PNS epigenetic signal overrides a CNS signal. We observed an increase in the gene expression of these genes following preconditioned DCA versus DCA alone, which correlated with an increase in PCAF at these promoters. Furthermore, a broader picture of post-axotomy H3K9ac promoter enrichment provides evidence that a specific epigenetic code regulates the capacity for axonal regeneration of CNS neurons providing a novel epigenetic-based target for regenerative therapies for clinical spinal injury.
is depicted by regeneration-associated (Chl1, Lgals, L1cam, CAP-23 and SPRR1a), axonal growth (ATF3 and Bcl-xL), housekeeping (ribosomal unit 18S) genes or axonal structure (NF-L) genes. Importantly, these experiments show that H3K9ac, a marker of actively transcribing genes linked to the enhancement of gene expression, is selectively enriched on the promoters of GAP-43, Galanin and BDNF, but not on the promoters of other SNA induced genes such as SPRR1a, ATF3 and HSP27, suggesting that their common regulation maybe linked to their importance in regeneration.

We then turned our attention to understanding whether retrograde signaling following SNA plays a role in this positive chromatin remodeling. Immediately following peripheral injury, pERK levels rise in the injured axon and ERK signaling modules are retrogradely transported to the DRG cell body, where we show that global PCAF and H3K9ac levels rise. In adult primary DRG cultures, nerve growth factor (NGF), an activator of ERK signaling and neurite outgrowth, increased expression of PCAF and H3K9ac, while the ERK kinase (MEK) inhibitor, PD98059 (PD), prevented PCAF and H3K9ac induction. NGF induces PCAF expression, nuclear localization and activation of acetyltransferase activity specifically by threonine phosphorylation at its histone acetyltransferase domain. In L4-L6 DRGs, SNA induced the expression of nuclear PCAF and PCAF threonine but not serine phosphorylation. This correlated with an increase of pERK in DRGs, as well as nuclear PCAF translocation and acetylation of H3K9, all of which are dependent on ERK activation following SNA. As suspected, inhibition of ERK activation following SNA decreased gene expression as well as PCAF and H3K9ac at the promoters of GAP-43, Galanin and BDNF. These data present the first link between retrogradely transported PNS-injury related signals and epigenetic modifications at the promoters of specific established regenerative genes.

As a preconditioning lesion is able to induce neurite outgrowth in primary adult DRG neurons cultured on permissive (laminin) or non-permissive (myelin) substrates, we tested whether increased PCAF expression by adenovirus infection of myelin-associated virus could also drive neurite outgrowth. Indeed, neurite outgrowth increased on laminin and myelin by PCAF overexpression in DRGs as well as another CNS primary culture, cerebellar granule neurons. In ex vivo experiments, the inhibition of PCAF activity by Garcinol was able to significantly limit neurite outgrowth on both laminin and myelin as well as repress H3K9ac induced by SNA. Correspondingly, PCAF -/- mice provided full abolishment of neurite outgrowth induced by SNA in ex vivo cultured DRG neurons. Additionally, SNA-dependent neurite outgrowth in ex vivo cultured DRG neurons was blocked by ERK inhibition via delivery of PD at the nerve stump phenocopying PCAF loss of function experiments.

To validate these observations in vivo, we studied regeneration of ascending sensory fibers following a preconditioning lesion (SNA 7 days prior to DCA) in the absence of PCAF and found that PCAF is required for regeneration induced by a conditioning lesion and for the expression of GAP-43, Galanin and BDNF in DRGs. Importantly, axonal tracing in SCI experiments in a cohort of PCAF -/- mice and strain matched controls showed that PCAF -/- mice did not display any abnormalities or overt phenotype in axonal tracing or regarding the lesion site (data not shown). Finally overexpression of PCAF promotes regeneration across the injured spinal cord.

We have shown the first systematic study of various epigenetic modifications revealing specifically that increased H3K9ac and PCAF as well as decreased H3K9me2 at the promoters of GAP-43, Galanin and BDNF are due to retrogradely induced pERK activation of PCAF leading to essential gene activation, which is sufficient to mimic the regenerative response assembled by a conditioning lesion, thus driving regeneration in the CNS.

SELECTED PUBLICATIONS


Quadrato G, Benevento M, Alber S, Jacob C, Floriddia EM, Nguyen T, Elnaggar MV, Pedroarena CM, Molkentin JD, Di Giovanni S. Nuclear factor of activated T cells (NFATc4) is required for BDNF-dependent survival of adult-born neurons and spatial memory formation in the hippocampus. Proc Natl Acad Sci U S A. 2012 Jun 5; 109(23)


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


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, optogenetics, 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 extinction, where an 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. While plastic changes of sensory inputs (from thalamus and cortex) to excitatory cells in the amygdala are well understood, plasticity may also occur at other inputs and amygdala inhibitory elements, thus, encoding memories in parallel and distributed networks. Our goal is to identify and investigate these networks and their learning-dependent changes.

One line of research aims to understand properties and function of a specific inhibitory network in the amygdala, the intercalated cells. These cells have recently received much attention, as they are active during fear behavior and are critical for extinction, possibly providing a break for the fear response. However, their function and connectivity is poorly understood. We have discovered novel wiring principles of intercalated cells that suggest that they process information...
about external sensory stimuli during learning and are part of a novel network that inhibits input and output nuclei of the amygdala. Our future goals are to decipher the mechanisms of intercalated cell plasticity and to develop molecular tools to specifically manipulate these cells to understand their function in vivo.

A second line of research investigates interactions of amygdala, hippocampus, and prefrontal cortex at the level of individual cells, which is critical for understanding extinction mechanisms and why fear memories can come back after extinction. Toward this end, we employ optogenetic, targeted stimulation of prefrontal and hippocampal inputs to the amygdala. We discovered that prefrontal cortex and hippocampus innervate distinct subpopulations of neurons in the basolateral amygdala with distinct input properties. Our next goals are to address the physiological impact of these inputs, whether they converge or diverge onto individual cells, and if the synaptic communication between these brain areas changes in animals after fear and extinction learning.

A third line of research addresses the development of amygdala circuits and its relationship to developmental differences in learning behavior. The ability to learn fear first emerges in juvenile animals and changes into adulthood. Extinction learning in juveniles is also different from adults. We have identified a number of changes in amygdala inhibitory networks that occur between infancy and adulthood. Our future goal is to elucidate the underlying mechanisms, how these changes affect plasticity in the amygdala, and ultimately to see if they are linked to differences in learning behavior.

Studying circuits and mechanisms of fear and extinction memory not only provides us with insights into general principles of memory formation, but also into neural dysfunction during inappropriate control of fear in conditions such as human anxiety and other neuropsychiatric disorders.

**SELECTED PUBLICATIONS**


Recently we described a microscopy technique that enables the analysis of synapse assembly in intact Drosophila larvae. The assay is useful for studying the dynamics of 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 with 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. dendra2). 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
We have a 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. Using this software, 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 the possibility of testing and characterizing drugs that can take effect 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 cargos 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 cargos that are inadequately transported in neurodegenerative and neurodevelopmental disorder include: mitochondria, RNA, proteins important for stability and dynamics of the cytoskeleton and structural proteins important for the formation of new active zones.

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