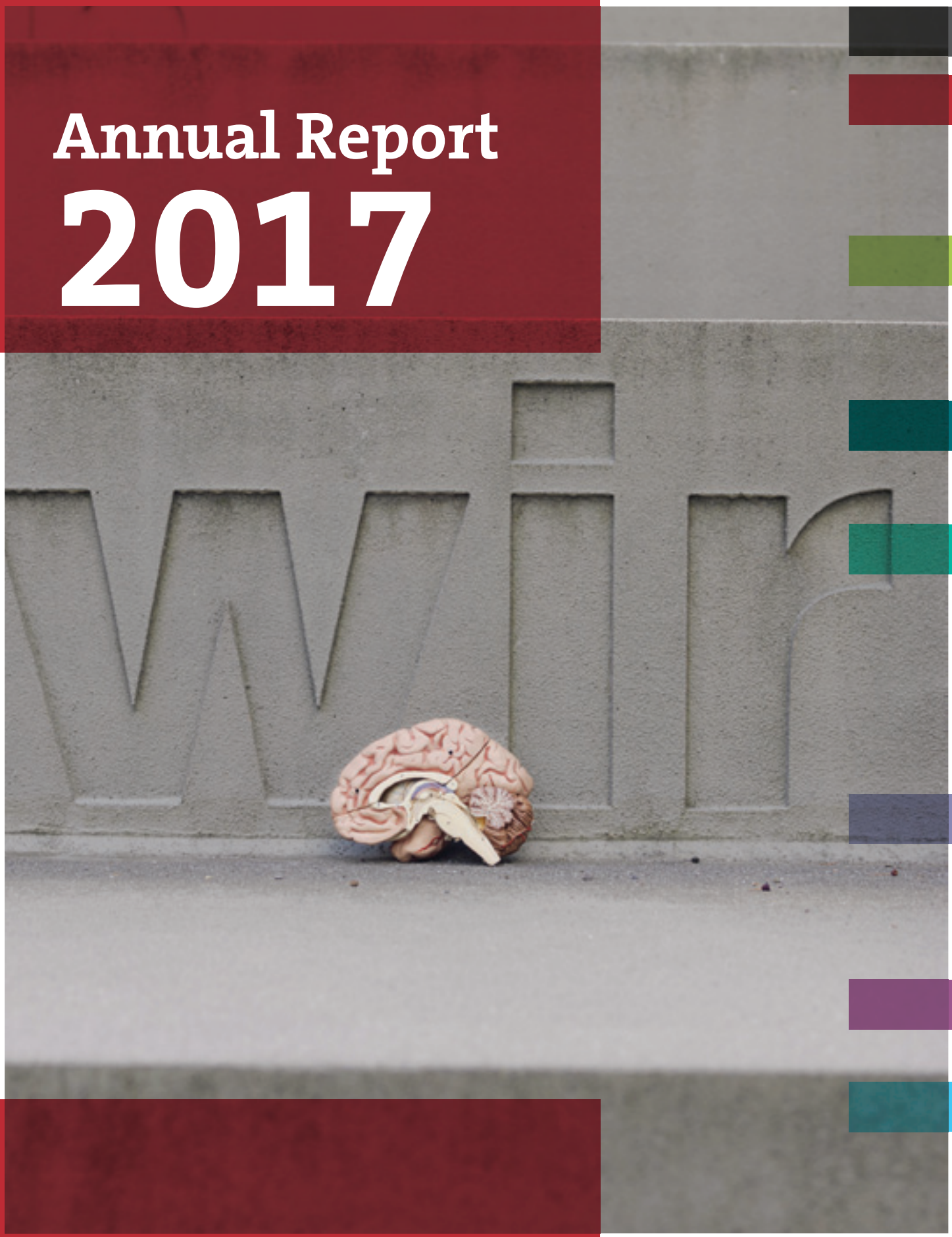
CENTER OF NEUROLOGY
TÜBINGEN

Annual Report 2017



CENTER OF NEUROLOGY TÜBINGEN

Annual Report 2017

DIRECTORS

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Peter Thier
Prof. Dr. Ulf Ziemann

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Hertie-Institut für klinische Hirnforschung

UNIVERSITÄTS KLINIKUM TÜBINGEN

Content

The Center of Neurology

The Center of Neurology

The Center for 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. In research, teaching and patient care the center is dedicated to excellence in the study of the human brain and its disorders.

The Center for Neurology presently consists of five departments: Department of Neurology with Neurovascular Medicine and Neuro-Oncology (Prof. Dr. med. Ulf Ziemann), Department of Neurodegenerative Diseases (Prof. Dr. med. Thomas Gasser), the Department of Neurology and Epileptology (Prof. Dr. med. Holger Lerche), the Department of Cognitive Neurology (Prof. Dr. med. Hans-Peter Thier) and the Department of Cellular Neurology (Prof. Dr. sc. nat. Mathias Jucker). All departments provide patient care within the University Hospital, while the 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 applies most obviously to clinical trials, which are conducted, for example, in the treatment of Parkinson's disease, multiple sclerosis, epilepsy and brain tumors. However, the intimate interconnection of science and patient care is of eminent importance to all areas of disease-related neuroscientific research. It forms the very center of the Hertie concept and distinguishes the Center for Neurology from other neuroscience institutions. In particular, the close interaction between basic science and patient care at the HIH and the University Hospital's Clinical Neurology Department was seen as a role model for clinical and translational research in Germany by the German Council of Science and Humanities (Wissenschaftsrat).

Mit dem im Jahre 2001 unterzeichneten Vertrag zwischen der Gemeinnützigen Hertie-Stiftung (GHS) und dem Land Baden-Württemberg, der Universität Tübingen und ihrer medizinischen Fakultät sowie dem Universitätsklinikum Tübingen wurde das „Zentrum für Neurologie" geschaffen. Damit entstand eines der größten Zentren für klinische und krankheitsorientierte Hirnforschung in Deutschland.

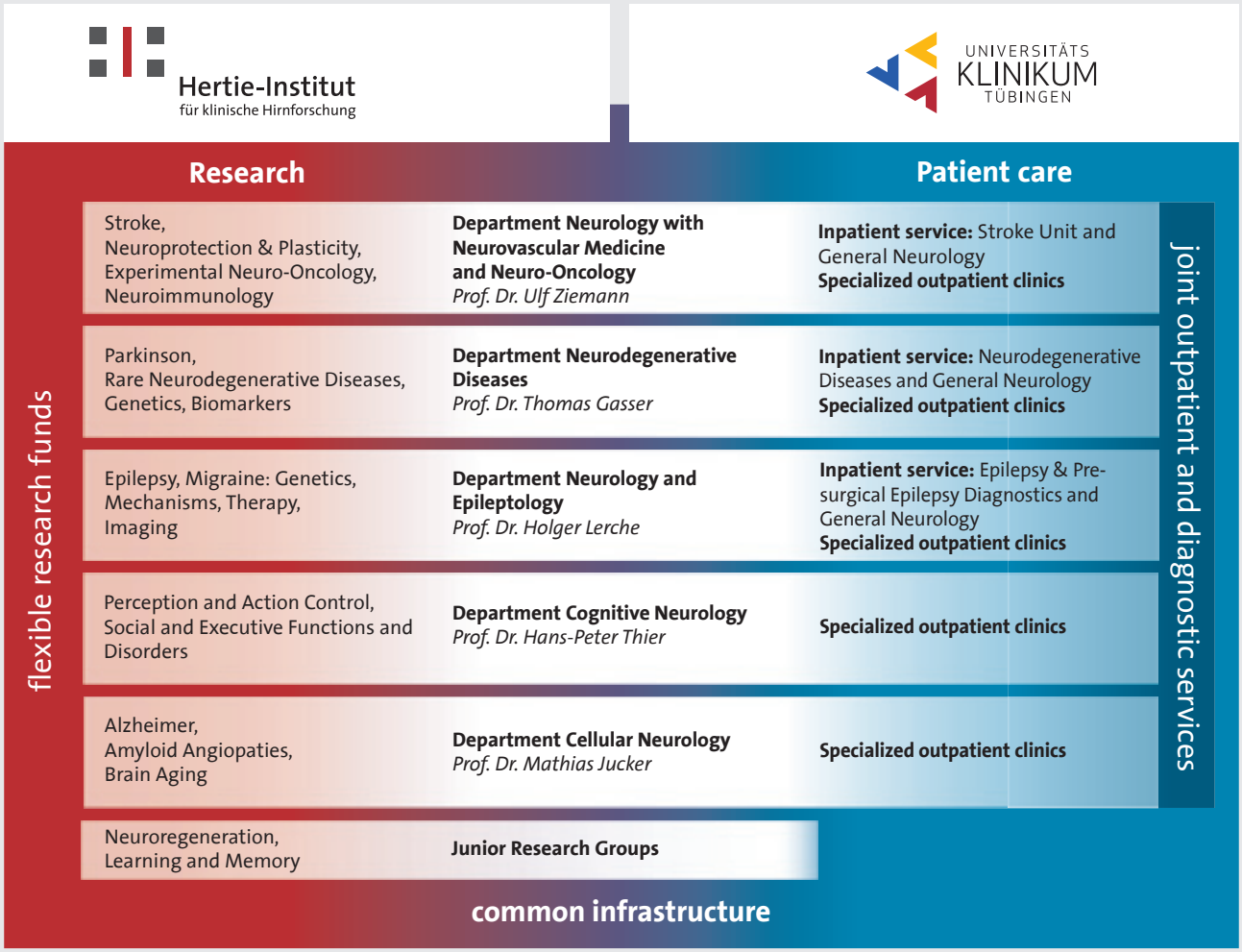
Das Zentrum besteht aus zwei eng verbundenen Institutionen, der Neurologischen Klinik und dem Hertie-Institut für klinische Hirnforschung (HIH). Die Aufgaben des Zentrums liegen sowohl in der Krankenversorgung durch die Neurologische Klinik als auch in der wissenschaftlichen Arbeit der im HIH zusammengeschlossenen Forscher. Die besonders enge Verknüpfung von Klinik und Grundlagenforschung innerhalb jeder einzelnen Abteilung und die Department-Struktur sind fundamentale Aspekte des Hertie-Konzeptes und ein Alleinstellungsmerkmal gegenüber anderen Institutionen der Hirnforschung in Deutschland. In der Department-Struktur sind die Professoren mit Leitungsfunktion akademisch und korporationsrechtlich gleichgestellt.

Das Zentrum besteht derzeit aus fünf Abteilungen: Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen und Neuroonkologie (Prof. Dr. med. Ulf Ziemann), der Abteilung Neurologie mit Schwerpunkt neurodegenerative Erkrankungen (Prof. Dr. med. Thomas Gasser), der Abteilung Neurologie mit Schwerpunkt Epileptologie (Prof. Dr. med. Holger Lerche), der Abteilung Kognitive Neurologie (Prof. Dr. med. Hans-Peter Thier) und der Abteilung für Zellbiologie Neurologischer Erkrankungen (Prof. Dr. sc. nat. Mathias Jucker). Die ersten drei Genannten sind bettenführende Abteilungen in der Neurologischen Klinik, die beiden Letztgenannten sind an der Patientenversorgung im Rahmen von Spezialambulanzen beteiligt. Die klinischen Abteilungen sind für die Versorgung von Patienten mit der gesamten Breite neurologischer Erkrankungen gemeinsam verantwortlich. Die Einheit der Neurologischen Klinik in Lehre, Ausbildung und Krankenversorgung wird dabei durch eine gemeinsame Infrastruktur (Patientenaufnahme, Behandlungspfade, Poliklinik, diagnostische Labors, Bettenmanagement, Pflegedienst gesichert. Die Neurologische Klinik besteht daher nach innen und außen weiterhin als einheitliche Struktur. In den klinischen Abteilungen werden pro Jahr mehr als 5.300 Patienten stationär und rund 14.500 Patienten ambulant behandelt.

Der Wissenschaftsrat hat das Zentrum als modellhaft für die Universitätsmedizin in Deutschland gewürdigt und insbesondere die praktizierte Verbindung von Grundlagenforschung und klinischer Praxis.

Facts & Figures

CENTER OF NEUROLOGY



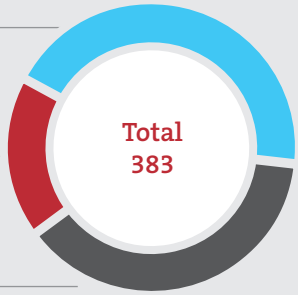
NUMBER OF STAFF IN 2017

Center of Neurology without nursing services (by headcount)

183
48% Third Party Funding

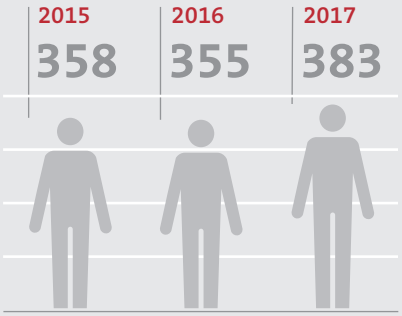
47
12 % Hertie Foundation

153
40% Medical Faculty



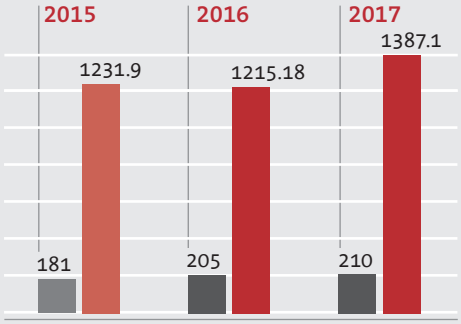
DEVELOPMENT OF STAFF

Center of Neurology (by headcount)



NUMBER OF PUBLICATIONS
IMPACT FACTORS

Center of Neurology (SCIE and SSCI / in 100 %)



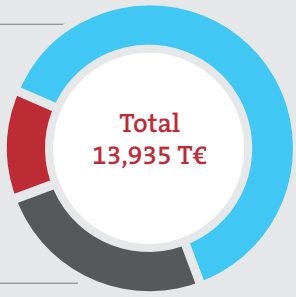
TOTAL FUNDINGS IN 2017

Center of Neurology

8,790 T€
63 % Third party funding

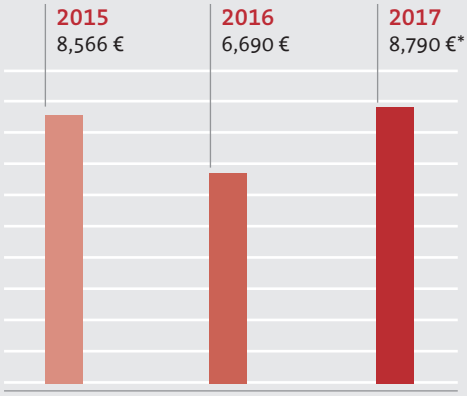
1,715 T€
12 % Hertie Foundation

3,430 T€
25 % University Hospital of Neurology & Medical Faculty



THIRD PARTY FUNDING

Center of Neurology (TE)



* includes 1 Mio € from the state of Baden-Württemberg

THIRD PARTY FUNDING IN 2017

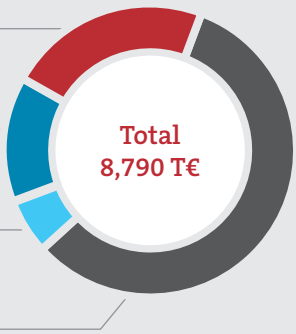
Center of Neurology

1,989 T€
DFG: 22,6 %

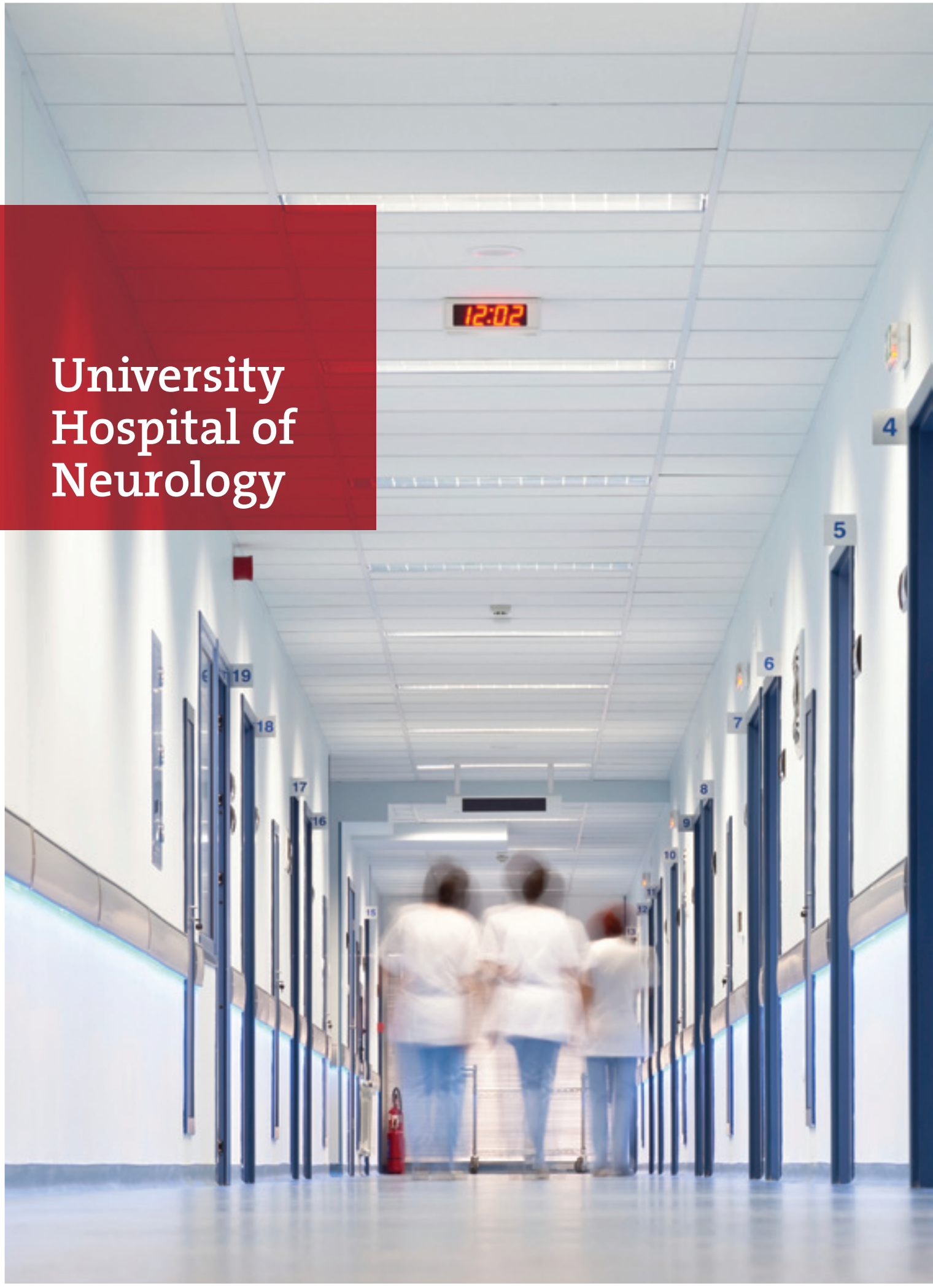
1,227 T€
BMBF: 14,0 %

530 T€
EU: 6,0 %

5,044 T€
Others: 57,4 %



University Hospital of Neurology



University Hospital of Neurology

CLINICAL CARE

The University Hospital's Clinic of Neurology treats inpatients with the complete spectrum of neurologic diseases on three general wards. Patients with acute strokes are treated on a specialized certified stroke-unit, which allows 24-hour surveillance and treatment. Neurointensive-care patients are treated in a cooperative model on the intensive care unit of the Clinic of Neurosurgery. A specialized video-EEG-monitoring unit allows continuous long-term recordings for patients with intractable epilepsies.

In the outpatient unit of the clinic about 14,500 (including diagnostic procedures) patients are examined and treated every year, most of them in specialty clinics which are directed by recognized specialists in their respective fields.

PATIENTENVERSORGUNG

Die Neurologische Klinik am Universitätsklinikum Tübingen behandelt Patienten mit dem gesamten Spektrum neurologischer Erkrankungen auf drei Allgemeinstationen. Patienten mit akuten Schlaganfällen werden auf einer zertifizierten Schlaganfall-Spezialstation („Stroke-Unit") behandelt, die rund um die Uhr die erforderlichen Überwachungs- und Therapiemaßnahmen erlaubt. Neurointensiv-Patienten werden in einem kooperativen Modell hauptsächlich auf der neurochirurgischen Intensivstation behandelt. Daneben gibt es eine spezielle Einheit zur kontinuierlichen Langzeit-Video-EEG-Ableitung (EEG-Monitoring) für Patienten mit schwer behandelbaren Epilepsien.

In der neurologischen Poliklinik werden jährlich rund 14.500 Patienten (inkl. diagnostischer Prozeduren) ambulant betreut, die meisten davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden.

UNIVERSITÄTS KLINIKUM TÜBINGEN

Clinical Performance Data

Close monitoring of patients at the intensive care unit.

INPATIENT CARE

The inpatient units of the University Hospital of Neurology treated more than 5,300 patients in 2017.

NUMBER OF ADMISSIONS

5,363

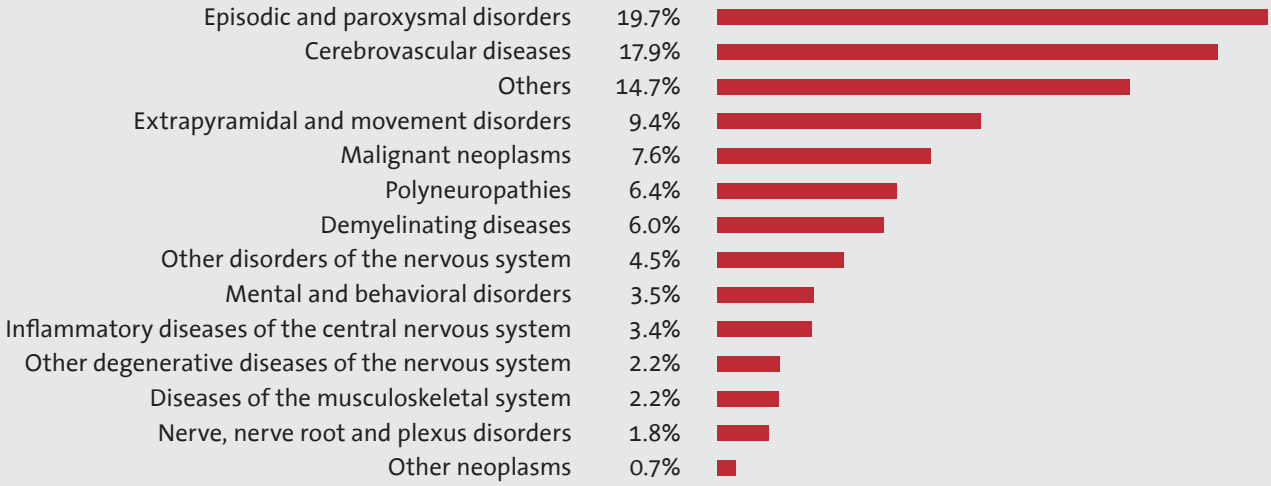
LENGTH OF STAY (IN DAYS)

4.8

CASE-MIX-INDEX 2017

1.48

INPATIENT DIAGNOSIS GROUPS

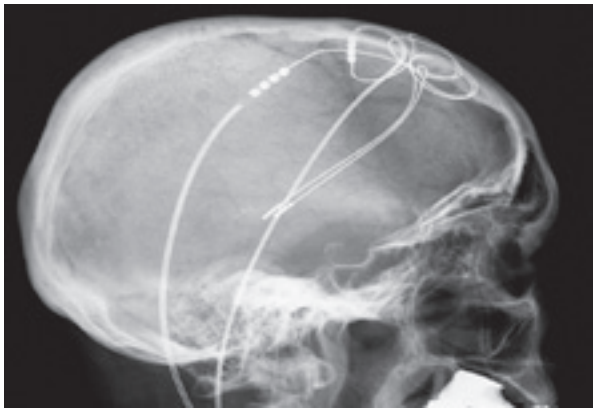


OUTPATIENT CARE

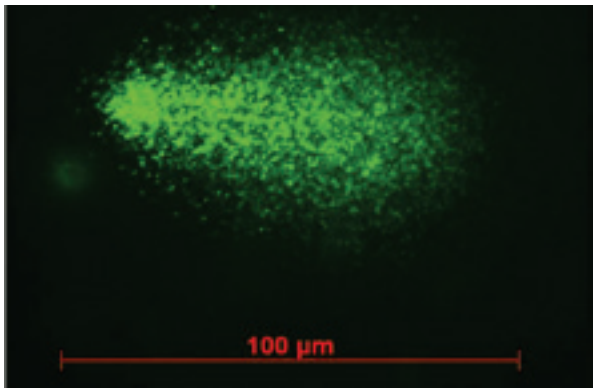
NUMBER OF CONSULTATIONS
(including diagnostic procedures)

14,500

Outpatient Clinics



Deep brain stimulation for Parkinson's disease: X-Ray image of an electrode inserted to the brain.



Comet assay indicating impaired DNA repair in lymphoblastoids of patients with recessive ataxias. Comet of DNA fragments in a lymphoblast with increased numbers of double strand brakes.

ATAXIA

The ataxia clinic provides state-of-the-art tools to discover the molecular causes of ataxia, thereby working 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 use not only most recent next generation-sequencing gene panels (allowing parallel sequencing of all known ataxia genes), but now also whole exome-sequencing (WES) and even whole genome sequencing (WGS). Therapeutic options depend largely on the underlying cause of ataxia, the genetic defect, and concomitant symptoms.

In cooperation with Dr. W. Ilg and Prof. M. Giese from the Center for Integretative Neuroscience (CIN), the experts developed special videogame-based exercise programs ("exergames") 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 and biomarkers study of sporadic late-onset ataxias (SPORTAX). Moreover, we are part of a worldwide consortium (EUROSCA) to aggregate and follow up patients with dominant spinocerebellar ataxias (SCA), which is an inevitable prerequisite for interventional trials in the future. This work now also focusses on presymptomatic SCA subjects, where the clinical disease has not yet started, aiming to detect motor, imaging and biosample biomarkers that allow to trace the disease trajectory even before its clinical beginning (RISCA). This might allow to develop interventions in stages where neuronal resources are not yet exhausted and subjects' way of living is not yet severely incapacitated. In addition, our ataxia clinic is one of the internationally leading clinics for aggregating and deep-phenotyping patients with early onset ataxias (EOA). PD Dr. Synofzik leads the worldwide EOA registry and is scientific coordinator of the EU-funded global consortium PREPARE- Preparing therapies for autosomal-recessive ataxias, which will pave the way for trial-ready cohorts and future molecular treatments. At the same time, this network is a rich resource for discovering new ataxia genes. The clinic is run by Dr. Dr. B. Bender, Dr. A. Traschütz and Dr. C. Wilke and is supervised by PD Dr. M. Synofzik and Prof. Dr. L. Schöls.

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 movement disorders and psychiatric diseases.

In 2013, the relevance of Tübingen as a specialized center for deep brain stimulation was underscored by its contribution to the European multicentre EARLYSTIM-study that proved for the first time an improved quality of life in patients undergoing DBS in early disease stages (Schuepbach et al., NEJM, 2013). Lateraly, it was demonstrated that DBS further improves hyperdopaminergic behaviours as compared to best medical treatment (L'Hommee et al., 2018; Lancet Neurol). Moreover, based on our 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 frequency stimulation of the substantia nigra pars reticulata (SNr) as an add-on to the conventional subthalamic nucleus stimulation was successfully accomplished and proved an effect on freezing of gait (Weiss et al., BRAIN, 2013). The work on nigral stimulation for resistant freezing of gait now translates into a large multicentre randomized controlled trial initiated and coordinated by the Tübingen Centre (ClinTrials.gov: NCT02588144). The trial is currently active and recruiting.

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 diseases. 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 counselling of patients eligible for DBS based on neurological examination and medical history. Moreover, the BrainStimNet Tübingen organizes regular conferences for patients and relatives in cooperation with the German Parkinson's Disease Association (dPV). Appointments are scheduled two days per week in the outpatient clinic for DBS. Patients are seen by a specialized PD nurse (Mr Friedhelm Chmell), and expert neurologists, namely Dr. A. Schöllmann, Dr. L. Roncoroni, I. Hanci, and PD Dr. D. Weiß.

DIZZINESS SERVICE

The dizziness outpatient service of the Department of Cognitive Neurology has merged into the "Tübinger Zentrum für Schwindel- und Gleichgewichtserkrankungen (TüSG)". This "dizziness center" is a colloboration between the Center for Neurology and the University of Tübingen´s ENT clinic. It reflects a logical extension of a symptom-oriented clinical service that goes beyond traditional boundaries

between medical disciplines. The focus is transdisciplinary. This means that we aim to think and act in a systematic way from the viewpoint of the patient's most prevalent complaint, which is dizziness here. Such a transdisciplinary approach – also on an academic level – is vital to complement the exponentially increasing specialization with regard to the diversity of pathomechanisms.

More specifically, given the background of Neurology on one hand and the background of ENT on the other we started to unify and harmonize the diagnostic evaluation, treatment and follow-up for patients suffering from acute or chronic dizziness in both clinics. Within the dizziness outpatient service each patient is seen by two physicians, one with a background in ENT, the other with a background in Neurology. 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 certain functional diagnostics. 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. The dizziness service is available for outpatients twice a week. It is led by Dr. J. Pomper (Neurology) and Dr. S. Wolpert (ENT).

Outpatient Clinics

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 other movement disorders. In cooperation with the headache clinic (PD Dr. T. Freilinger) and the clinic for otolaryngology (Prof. H. Löwenheim), treatment with botulinum toxin injections for patient with chronic migraine and spasmodic dysphonia/pharyngeal dystonia is provided.

Approximately 500 to 550 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 and tremor (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 difficult injection sites BoNT treatment is often optimized using EMG-, electro stimulation-, or ultrasound-guided injection techniques e.g. for the treatment of deep cervical muscles in cervical dystonia. Since last year preoperative component relaxation using BoNT enabling laparoscopic repair of complex ventral hernia in cooperation with our section of abdominal surgery is provided. The clinic also participates in several multicenter trials 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).

Besides pharmacologic and surgical treatment, a wide range of physical and ergotherapeutic therapies are offered. Over the last years, an increasing number of outpatients with spasticity have been managed with a combined treatment of BoNT injections and physiotherapy at the local MTR (Medical Training and Rehabiliation Center, University of Tübingen).

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 E. Feil (technical assistent), Dr. F. Thies and Dr. E. Lohmann.

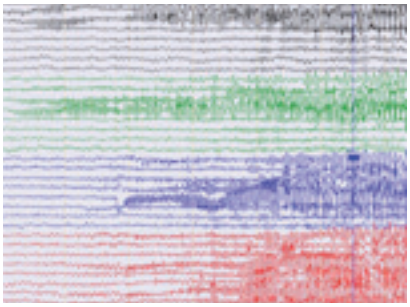
Over the last years, an increasing number of outpatients with spasticity have been managed with a combined treatment of BoNT injections and physiotherapy at the local Medical Training and Rehabiliation Center.

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, narcolepsy 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 41/46/27L), running under the supervision of Prof. Dr. Y. Weber, PD Dr. N. Focke (until May 2017), PD Dr. A. Grimm 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 (leader Prof. Dr. Y. Weber).

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 PD 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.



Start and spread of an epileptic seizure in the EEG over 10 seconds

FRONTOTEMPORAL DEMENTIA AND EARLY-ONSET DEMENTIAS

Frontotemporal Dementias (FTD) are a heterogeneous group of neurodegenerative diseases characterized by progressive changes in personality and behavior and/or progressive language disturbances. FTD often already starts between 50–60 years of age, yielding it one of the most common early-onset dementias (onset < 65 years).

The disease spectrum of FTD and possible differential diagnoses is complex, reaching from Progressive Supranuclear Gaze Palsy (PSP) to Alzheimer's disease (AD), and often extends to phenotypes complicated by additional Parkinsonian syndromes or Amyotrophic Lateral Sclerosis (ALS). Our experts in the FTD clinic are specialists on these differential diagnoses, including also rare neurometabolic dementias like Niemann Pick Type-C (NPC) or Cathepsin F (CTSF)-related dementia. A special focus is given on an extensive clinico-neuropsychological work-up complemented by latest cerebrospinal fluid biomarkers and next-generation genetics. Given the large share of genetic causes of FTD next-generation-sequencing procedures like panel sequencing, whole exome sequencing and whole genome sequencing offer a new window not only towards exact molecular diagnosis but also towards individualized counselling and therapy. We are the leading FTD center of the German Center for Neurodegenerative Diseases (DZNE), which is establishing a large nationwide cohort of patients with FTD-spectrum diseases, comprehensively characterized on a clinical, neuropsychological, imaging and biomarker level. Moreover, we participate in the international multicenter GENFI consortium, aggregating and characterizing symptomatic and asymptomatic carriers with mutations in FTD genes in a longitudinal fashion. This ambitious endeavor will allow to unravel the neuropsychological, imaging and molecular changes in FTD even before its clinical onset, thus offering a novel window for therapy in the future. In fact, we are currently preparing first targeted molecular therapies in our GENFI consortium. The clinic is run by Dr. C. Wilke and Dr. Dr. A. Traschütz and supervised by PD Dr. M. Synofzik.

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 PD Dr. M. Synofzik, PD Dr. D. Weiß and Dr. C. Wilke.

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. G. 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 headache and other neurological pain syndromes, offering state-of-the art medical care to patients with a wide range of mostly primary headache disorders. Patients should be referred preferably by neurologists or pain management specialists. Appointments are available from Monday through Thursday (and in addition on an individual basis), and patients will be provided with mailed headache/pain diaries and questionnaires well before their scheduled appointment.

One 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). Inpatient treatment will be available in selected cases (e. g. exacerbations of cluster headache, difficult cases of medication withdrawal). Finally, patients with neuropathic pain syndromes are diagnosed and treated in close collaboration with the Department of Anesthesiology, which organizes monthly interdisciplinary pain conferences.

The unit is in close collaboration also with other local clinical partners (e.g. psychiatry, psychosomatic medicine, neurosurgery) and serves as a teaching centre within the Deutsche Migräne – und Kopfschmerzgesellschaft (DMKG), for which PD Dr. Freilinger acts as as regional representative. Currently, we are initiating a certification process as a headache centre according to the DMKG guidelines.
The unit organizes teaching sessions for medical professionals as well as local patient education events and serves as a platform to provide access to ongoing clinical studies including both multi-center trials as well investigator-initiated pilot trials (e.g. HeMiLa). The outpatient clinic is run by PD Dr. T. Freilinger together with a team of colleagues (one board-certified neurologist, four neurology residents).

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. We use next-generation-sequencing techniques like targeted gene panels and whole exome analyses to explore the genetic cause of the diseases. In cooperation with the Department of Neuropediatrics in the Childrenís Hospital we analyze the natural course of the diseases and especially of adult-onset variants of leukodystrophies as an essential prerequisite for therapeutic trials. Neuroimaging and nerve conduction studies are currently investigated as potential progression markers. 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. H. Hengel and Prof. Dr. L. Schöls.

MOTONEURON DISEASE

Motoneuron diseases are caused by degeneration of motor neurons in the cerebral cortex (upper motor neuron) and/or the ventral horns of the spinal cord (lower motor neurons). The most common form of motoneuron disease – amyotrophic lateral sclerosis (ALS) – affects both upper and lower motor neurons.

Though ALS mainly is a sporadic disease, in about 10 % of patients there is a familial background. Our specific focus is concentrated on the genetic work-up of both seemingly sporadic as well as familial cases, aiming to explore the frequencies of ALS genes, discovering new ALS genes and unravelling the molecular pathways underling genetic ALS as well as fluid biomarkers for ALS. We perform an in-depth phenotyping of both the motor and non-motor profile of the ALS patients, complemented by a comprehensive fluid and cell biobanking, which is the basis for our continuous research projects. Routine diagnostic tests include nerve conduction studies, electromyography, and evoked potentials. Additional diagnostic procedures (e. g. lumbar puncture, and imaging of the brain and spinal cord) are offered on our specialized neurodegenerative ward. Treatment of respiratory problems is provided in close cooperation with the pulmonological department.

Follow-up of patients as well as management of symptoms and complications are provided by the clinic. The clinic is run by Dr. C. Wilke, Dr. Dr. A. Traschütz and supervised by PD Dr. M. Synofzik.

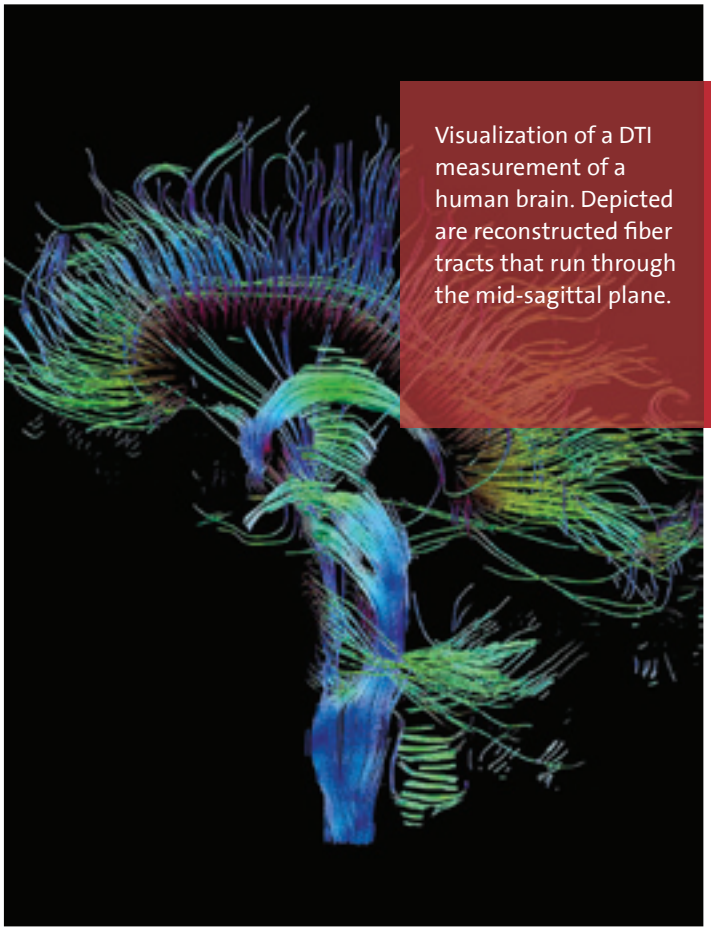
NEUROIMMUNOLOGICAL DISORDERS

Patients with multiple sclerosis (MS), neuromyelitis optica (NMO), and other neuroimmunological disorders are regularly seen in the outpatient-clinic for neuroimmunological diseases. Complex cases are discussed interdisciplinarily with colleagues from rheumatology, neuroophthalmology, neuroradiology, and neuropathology. The Center of Neurology is certified as an MS priority center by the German Multiple Sclerosis Society (DMSG) and is a member of the Clinical Competence Network for Multiple Sclerosis (KKNMS), the Neuromyelitis Optica Study Group (NEMOS) and European Susac Consortium (EUSAC).

Patients with MS 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). Nurses and study nurses organize appointments and offer training for subcutaneous injections and practical aspects of MS therapies. A large number of patients participate in currently approximately 15 different clinical trials, which explore safety and efficacy of new treatments in relapsing-remitting MS, progressive MS and NMOSD. Clinical trials are managed by a team of study nurses. In 2017, the outpatient clinic was run by Dr. M. Paech (Facharzt), C. Ruschil (resident) and supervised by Dr. M. Krumbholz and Dr. M. Kowarik, both with special expertise in MS and other immune-mediated neurological disorders), and Prof. U. Ziemann (director).

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 PD Dr. A. Grimm and Dr. N. Winter. We have an intensive cooperation with the clinic of neuropediatric disorders in Tuebingen, the neuromuscular center Stuttgart and the institute of neuropathology. Monthly meetings and interdisciplinary congresses are performed by our team. We are directly involved in the scientific board of the german muscle society (DGM) and the german society of clinical neurophysiology (DGKN).



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

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 PD Dr. I. Liepelt-Scarfone.

Outpatient Clinics

NEURO-ONCOLOGY

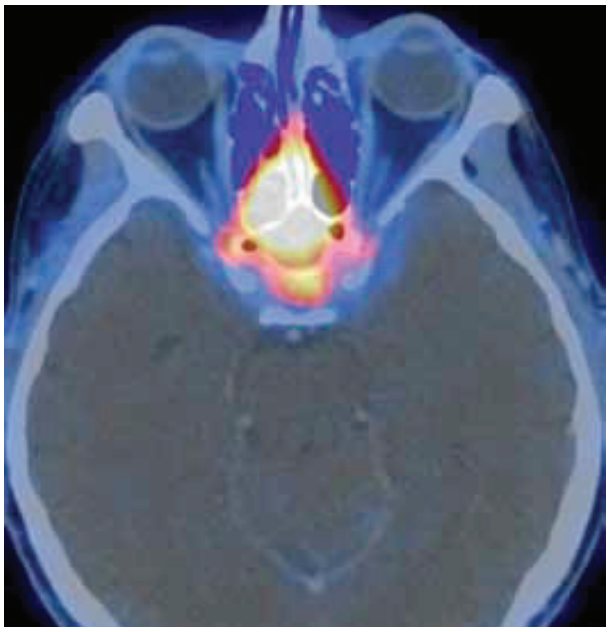
The management of neuro-oncological patients is coordinated in the Interdisciplinary Section of Neuro-Oncology. The defining feature of this section is (i) its affiliation to two departments, i.e. to the Department of Neurology (Prof. Dr. U. Ziemann) and to the Department of Neurosurgery (Prof. Dr. M. Tatagiba), and (ii) the appointment of the head of the section (Prof. Dr. G. Tabatabai) as a full (W3) professor of Neuro-Oncology on 18 July 2014.

As a consequence, the outpatient clinic is organized as an interdisciplinary outpatient clinic with neurological and neurosurgical appointments, and the reports use a header with both Departments reflecting a bridging between both Departments in the field of Neuro-Oncology.

In addition, the Interdisciplinary Section of Neuro-Oncology is part of the Center of CNS Tumors under the roof of the Comprehensive Cancer Center Tübingen-Stuttgart and very closely cooperates with the Departments of Radiation Oncology, Radiology & Neuroradiology & Nuclear Medicine, Pathology & Neuropathology. As Prof. G. Tabatabai is also the elected Chair of the Center of CNS Tumors, strategies of the CCC can be easily and readily implemented into the strategical plan of the Interdisciplinary Section of Neuro-Oncology. The center has recently received the certificate of the German Cancer Society (DKG).

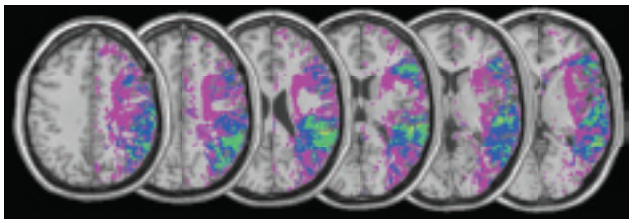
Patients who need surgical or postoperative treatments or procedures will be admitted to the wards in the Departments of Neurology or Neurosurgery depending on the treatment and will be supervised by the Neuro-Oncology team in both departments.

The main objectives of the Section of Neuro-Oncology are:
- To offer cutting-edge innovative treatments in clinical trials
- To participate in national and international consortia and trial groups (e.g. NOA, EORTC, RTOG)
- To diagnose, treat and monitor patients with neuro-oncology tumors at each stage of their disease
- To provide guidance for supportive care and palliative treatment
- To provide a second opinion for patients seeking for advice



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

The clinical team for patient treatment and/or clinical trials is composed of Prof. Dr. G. Tabatabai, Dr. F. Behling (neurosurgery resident), Dr. I. Gepfner-Tuma (neurology resident), Dr. M. Koch (neurology resident), PD Dr. S. Noell (neurosurgery board-certified), Dr. L. Füllbier (board-certified neurosurgeon, resident), PD Dr. C. Roder (neurosurgery resident and coordinator of the Center of CNS Tumors), PD Dr. J. Rieger (Neurology board-certified), PD Dr. M. Skardelly (neurosurgery attending).



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-inducted delays by using spatial normalization of PWI maps as well as symmetric voxel-wise inter-hemispheric comparisons. These new techniques allow comparison of the structurally intact but abnormally perfused areas of different individuals in the same stereotaxic space, and at the same time avoid problems due to regional perfusion differences and to possible observer-dependent biases.

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).

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).

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, contrast echocardiography, 24-hour Holter ECG and blood pressure monitoring, implantation of an event-recorder for long-term ECG monitoring in selected ischemic stroke patients with suspected atrial fibrillation, 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 experienced cardiologists under the guidance of PD Dr. S. Greulich (cardiologist and internist, shared appointment by the Department of Neurology with Focus on Neurovascular Diseases and Neurooncology and the Clinic of Cardiology). The neurovascular outpatient clinic is run by a team of neurovascular residents that are supervised by the consultant stroke physicians Dr. A. Mengel and Dr. S. Poli as well as Prof. Dr. U. Ziemann.

Outpatient Clinics

PARKINSON'S DISEASE

Outpatient Clinic

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 counselling 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 10-year follow-up of de novo Parkinson patients to better understand aetiology 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 cooperation with the Ward for Neurodegenereative Diseases by intermittent or continuous apomorphine or duodopa application, which is supervised by a specially trained nurse. Other patients are 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. Moreover, close cooperation with the outpatient rehabilitation center guarantee the involvement of additional therapeutic approaches.

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.

The outpatient unit cooperates with German Center for Neurodegenerative Diseases (DZNE) under a common roof, called the Integrated Care and Research Center (ICRU). Appointments are scheduled daily in the outpatient clinic of the Center of Neurology.

Since Parkinson's disease is a complex multifactorial disorder with a large variability in phenotypes and progression, our focus of research aims patient stratification according to genetic architecture and, importantly, the underlying pathologic processes, possibly reflected by distinct profiles in patient biomaterials such as blood and cerebrospinal fluid. This in turn is a most needed prerequisite to introduce patients to pathway-specific milestone-related therapies focusing e.g. on lysosomal, mitochondrial and inflammatory dysfunction.

In this context, special interest lies in genetically-associated forms of the disease such as patients carrying a mutation in the GBA or LRRK2 gene. Moreover, we focus on one of the most important milestone in the course of the disease, namely dementia. Next to pathophysiological aspects, we aim to evaluate risk factors and prodromal symptoms for the development of dementia as well as impact on quality of 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 cooperation with the Institute of Medical Genetics and the Department of Neuroradiology. Targeted HSP gene panels and whole exome sequencing are used for genetic diagnostics on a routine basis. Therapeutic options depend essentially on the underlying cause of the disease. Symptomatic treatment includes antispastic drugs, intrathecal application of Baclofen, local injections of Botulinum toxin and functional electrical stimulation. Tübingen is the disease coordinator for HSP in the DZNE network (German Center for Neurodegenerative Diseases) and 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 PD Dr. R. Schüle, Dr. S. Wiethoff, Dr. T. Rattay and Prof. Dr. L. Schöls.

TREMOR SYNDROMES

Essential tremor is with a prevalence of 1 to 5 % among 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. Beyond pharamcological treatment and ergotherapy, deep brain stimulation is considered in resistant tremor. The outpatient clinical for tremor is conducted by Dr. I. Wurster and PD Dr. D. Weiß.

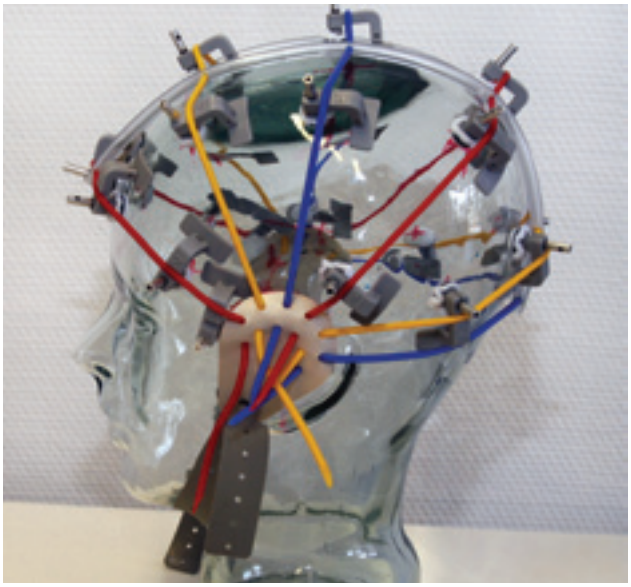
POLYNEUROPATHIES

The outpatient clinic for patients with polyneuropathies handles about 350 patients per year with several kinds of neuropathy, e.g. mononeuropathies (immune-mediated, traumatologic) as well as polyneuropathies (immune-mediated, e.g. CIDP, MMN, GBS, vasculitic or inherited as the Charcot-Marie-Tooth type 1,2, X) and orphan diseases, e.g. M. Refsum or amyloidosis. In cooperation with the department of Neurophysiology – including neurography, EMG or ultrasound – the diagnostic work out is well established. We have scientific cooperation with the University hospitals in Basel, Jena, Aachen, Göttingen and Bochum. Our main scientific topic is the peripheral nerve imaging and its role in the diagnosis of polyneuropathy. With the establishment of the ultrasound pattern sum score (UPSS) we could develop a first ultrasound screening tool for PNP: The clinic is run by PD Dr. A. Grimm and Ms. D. Vittore.

Clinical Laboratories

CLINICAL CHEMISTRY LABORATORY FOR NEUROLOGY

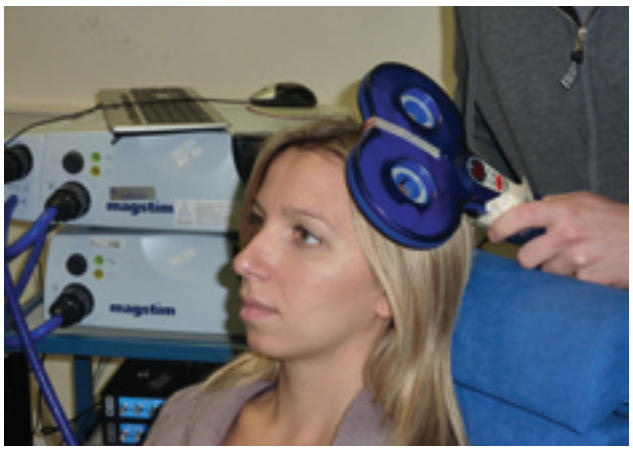
The Clinical Chemistry Laboratory collects more than 1,600 samples of cerebrospinal fluid (CSF) per year throughout the University Medical Center. Oligoclonal bands in CSF and serum are detected by isoelectric focusing and silver staining. Junior staff are routinely trained to perform basic CSF examination techniques and the interpretation of results as part of their speciality training. The laboratory takes part in quality management activities of CSF parameters. Immunopathology includes the determination of a set of autoantibodies for the diagnosis of certain neuroimmunological syndromes: autoantibodies to acetylcholine receptors, muscle specific tyrosine kinase (MuSK), titin (myasthenia gravis), aquaporin-4 (NMOSD), autoantibodies associated with neurological paraneoplastic syndromes and autoimmune encephalitis, and autoantibodies to gangliosides for immunoneuropathies. Cell populations in CSF and blood samples are examined by flow cytometry using a FACScalibur cytometer. These include determination of CD20+ cells in patients under B cell depleting therapies, CSF CD4/CD8 ratio in patients suspected to have neurosarcoidosis, assessment of CD4/CD62L cells in patients treated with natalizumab as well as detailed immunophenotyping in patients with complex inflammatory diseases of the nervous system. In addition, CSF-levels of amyloid beta42, tau, phospho-tau and NFL are measured to differentiate various forms of dementia/neurodegenerative diseases. In case samples that have to be sent to external reference laboratories (e.g. CSF JCV testing for natalizumab-associated PML in reference center), the neurochemical laboratory takes care of preparing and sending the samples, as well as organizing the reports. The laboratory is supervised by PD Dr. R. Schüle and Dr. M. Krumbholz.



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.

EEG LABORATORY

The electroencephalography (EEG) laboratory is equipped with four mobile digital and two stationary recording places (IT-Med). For analysis, six 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. At 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 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, R. Mahle, K. Vohrer (staff technicians), Prof. Dr. Y. Weber (head of the laboratory) and PD Dr. N. Focke (until May 2017).



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

ELECTROMYOGRAPHY, NEUROGRAPHY AND NEUROMUSCULAR ULTRASOUND

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. In addition, the new diagnostic tool of high resolution ultrasound (Phillips Epiq 7, 18 MHz Probe and Mindray T7, 14 MHz Probe) was introduced in 2015. With the ultrasound of the peripheral nervous system as well as of the muscles, several neuromuscular disorders, e.g. polyneuropathies, motoneuron diseases, myopathies, nerve tumours, entrapment syndromes and traumata can be visualized.

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This tool amplifies the interdisciplinary cooperation with the colleagues from the Nerve Surgery Department of the UKT as well as of the BG Hospital for Traumatology. PD Dr. A. Grimm is the vice president of the german ultrasound society, department Neurology (DEGUM). Further DGKN/ DEGUM certified colleagues are T. Rattay, N. Winter, N. Dammeier and M. Koch.

The laboratory is equipped with two digital systems (Dantec Keypoint G4). A portable system (Nicolet Viking Quest) is available for bedside examinations. In 2015, more than 2,500 patients were seen and more than 15,000 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 transcranial magnetic stimulation and recording of motor evoked potentials in approximately 800 patients per year. Further, 450 patients were examined by neuromuscular ultrasound since 05/2015.

In 2017, the EMG Laboratory was run by a team of technical assistants (S. Berger, A. Deutsch, V. Servotka) and residents (N. Winter, E. Auffenberg, B. Röben, C. Ruschil, S. Wiethof) under the supervision of PD Dr. A. Grimm and PD Dr. R. Schüle. Further colleagues have been certified by the DGKN for EMG (T. Rattay, S. Wolking, N. Dammeier, M. Koch) in 2017.

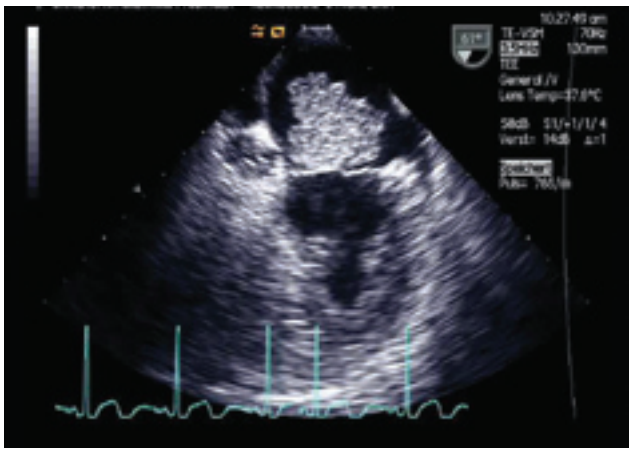
Clinical Laboratories

NVOM LABORATORY (FORMER ENG LABORATORY)

With the formation of the "Tübinger Zentrum für Schwindel- und Gleichgewichtserkrankungen (TüSG)" (also see Dizziness Service) the ENG laboratory is becoming part of the laboratory for Neuro-Vestibular and Oculo-Motor diagnostics (NVOM). This NVOM Laboratory will cover the whole spectrum of medical tests established to recognize functional deficits of the vestibular and oculomotor system. For example, caloric and rotatory stimuli with distinct accelerations will be used (chair rotation, head-impulse-test, head-shaking). Eye movements will be recorded by means of electrooculography or video-oculography dependent on the problem to clarify. The integrity of otolith organs and their central connections will be examined by applying acoustic or vibratory stimuli and the evaluation of evoked myogenic potentials of neck or facial muscles (cVEMP, oVEMP) complemented by the measurements of the Subjective Visual Vertical. For more complex questions, e.g., isolated testing of single canals, movements of the eyes and head, as a function of head rotation and visual stimulation, will be measured in three dimensions using magnetic search coils. The projected cutting-edge techniques comprise high-precision analysis of eye movements like microsaccades, standardized psychophysical measures related to motion perception, and dizziness, as a consequence of certain stimuli or specific pathologic eye movements, and the standardized combination of measurements by means of multivariate analyses. The NVOM laboratory is led by Dr. J. Pomper (Neurology) and Dr. S. Wolpert (ENT). The recordings are conducted by a team of technical assistants.

EVOKED POTENTIALS (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.



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

Around 2,500 examinations are performed every year on more than 1,600 patients. The recordings are conducted by A. Deutsch, K. Fuhrer and I. Köhnleinand are supervised by PD Dr. A. Grimm, PD DR. R. Schüle, and Prof. L. Schöls. The EP recordings are analyzed and interpreted during daily conferences according to the guidelines of the German Society for Clinical Neurophysiology (DGKN), and visited by up to six interns.

NEUROCARDIOLOGY LABORATORY

As diseases of the heart are responsible for up to 30 % of all strokes and usually cause territorial embolic ischemic infarcts, cardiac investigations are urgently required in stroke patients to find potential cardiac causes and in order to reduce the risk of stroke recurrence. Therefore, all stroke patients undergo a detailed cardiac investigation which is performed by the neurocardiology laboratory.

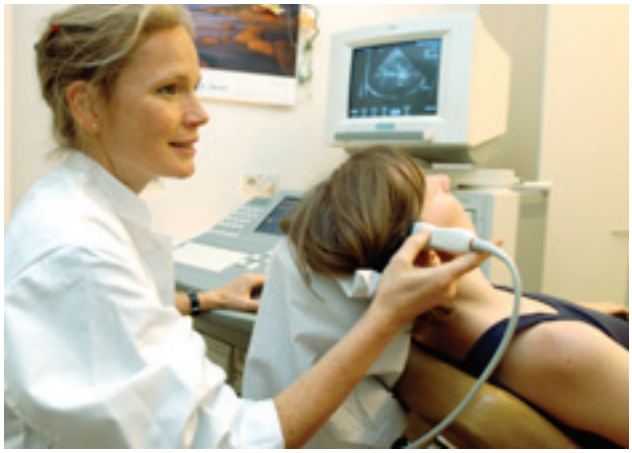
The neurocardiology laboratory, headed by the cardiologist and internist PD Dr. S. Greulich, provides the full spectrum of non-invasive cardiac work-up, such as transthoracic and transesophageal echocardiography including M-Mode, 2-D mode, pulse wave, continuous-wave and color Doppler investigations as well as contrast-enhanced echocardiography for the detection of intracardiac shunts or intracardiac thrombi. A close rhythm monitoring using 24-hour Holter ECG for the detection of atrial fibrillation is performed in selected stroke patients. Other diagnostic tools include 24-hour blood pressure monitoring, and selection of patients for cardiac MRI or CT in cooperation with the department of radiology. For invasive diagnostic and/or treatment, patients are referred to the department of cardiology.

Other patients of the neurology department, which are frequently examined in the neurocardiology laboratory, are patients with suspected heart failure, chest pain, Parkinson patients with planned deep brain stimulation and patients with unexplained syncope.

Yearly, we conduct approximately 1,800 echocardiographic examinations, over 1,200 Holter ECGs, and about 800 24-hour blood pressure measurements. All investigations are done according to the guidelines of the German and European Societies of Cardiology.

NEUROSONOLOGY LABORATORY

The neurosonological laboratory is equipped with two color-coded duplex sonography systems: a Toshiba Aplio and a Philips Epiq7. Additionally, two portable CW/PW Doppler systems – a DWL Multi-Dop pro and a DWL Multi-Dop T digital – are available. Neurosonological examinations are performed by the ultrasound assistants N. Vetter and a neurovascular resident under supervision of the consultant stroke neurologists, Dres. A. Mengel and S. Poli.



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.

The laboratory itself is situated within the outpatient clinic of the Department of Neurology and is mainly used for non-acute or elective ultrasound examinations of in- and outpatients. The mobile Doppler and duplex units are used for examinations of acutely ill patients on our Stroke Unit allowing for the full range of neurosonological assessment at the bedside immediately after admission.

Routine diagnostic tests include duplex imaging of extracranial carotid, vertebral, and subclavian arteries, as well as the transcranial Doppler and duplex sonography of the vertebrobasilar circulation and the Circle of Willis (with and without contrast). Functional testing for vertebral steal, bubble tests for assessment of 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 also routinely performed.

Each year, the total number of Doppler/duplex examinations conducted at our laboratory amounts to approximately 4,000 of extracranial arteries and approximately 3,000 of intracranial arteries.

Occupational, Physical and Speech Therapy

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 2017, 2,114 patients were treated.

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, and counselling of spouses and relatives. Currently eight occupational therapists are working within the "Therapie-Zentrum" responsible for the neurological wards under the supervision of Anke Nölck.

PHYSIOTHERAPY

All neurological inpatients with sensory or motor deficits, movement disorders, pain syndromes, and degenerative spinal column disease are allocated to individualized physiotherapy. Currently twelve physiotherapists under the supervision of MSc Marion Himmelbach are working within the "Therapie Zentrum" 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 2017, 2,842 patients were treated.

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 main focus within the team of eleven speech therapists under the supervision of BSc Lisa Stoll lies on the assessment and treatment of patients with dysphagia.

Every acute stroke patient receives a bedside and, if necessary, a video-endoscopic or video-fluoroscopic swallowing examination. This allows for early identification of dysphagia, prevention of aspiration pneumonia and efficient treatment planning. Every acute stroke patient also receives a bedside speech and language examination. The aim of speech therapy in these patients is to improve their communication ability. In 2017, 1,906 patients with dysphagia, aphasia and dysarthria received speech therapy.

The Hertie Institute for Clinical Brain Research

The Hertie Institute for Clinical Brain Research (HIH)

Hertie-Institut
für klinische Hirnforschung

Since its founding 16 years ago, the Hertie Institute has grown to more than 380 employees at all levels, from technicians to PhD students to full professors. The institute's achievements include discoveries related to the molecular, genetic and physiological basis of a number of major neurologic diseases.

The institute presently consists of five departments. They combine basic and clinical research with patient care, albeit to different degrees and with variable emphasis: three departments focusing on Stroke and Neuro-Oncology, Epileptology, and Neurodegenerative Disorders treat outpatients in specialty clinics, but also inpatients with the whole spectrum of neurological diseases, while the Departments of Cognitive Neurology and Cellular Neurology provide specialized diagnostic services and care in an outpatient setting only, focusing on neurocognitive impairments and Alzheimer's disease, respectively.

The institute is home to a total of 18 professors and 32 research groups. Thirty belong to the aforementioned departments, two are set up as independent research groups.

In 2017, scientists at the Center for Neurology obtained more than 8.7 million Euros in third party funding and published 205 papers in peer-reviewed journals.

For the first time, the Hertie Institute for Clinical Brain Research (HIH) was present with an information booth at the annual meeting of the Society of Neuroscience in Washington, DC, USA, from November, 11 to 15, 2017. At the joint booth "Neuroscience in Germany", the HIH presented its portfolio together with other neuroscientific institutions, networks and funding organizations.

Finally, the interaction with the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE) was strengthened since all activities of the DZNE have now moved to the new building in direct vicinity to the HIH. In the long term, this building will accommodate up to 150 scientists conducting research on nervous system diseases such as Alzheimer's or Parkinson's to develop new preventative, diagnostic and therapeutic strategies.

In autumn, Federal Minister of Health Hermann Gröhe and State Secretary Widmann-Mauz visited the Hertie Institute for Clinical Brain Research and took the opportunity to learn about current research projects.

To foster the interaction between the CIN (Werner Reichardt Centre for Integrative Neuroscience), DZNE and HIH, a Neuroscience Campus Get Together was jointly set up in the year 2015 and successfully repeated in 2016 and 2017.

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

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Peter Thier
Prof. Dr. Ulf Ziemann

Das Hertie-Institut für klinische Hirnforschung (HIH)

16 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.

Das HIH besteht derzeit aus fünf Abteilungen: der Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen und Neuroonkologie (Prof. Dr. med. Ulf Ziemann), der Abteilung Neurologie mit Schwerpunkt neurodegenerative Erkrankungen (Prof. Dr. med. Thomas Gasser), der Abteilung Neurologie mit Schwerpunkt Epileptologie (Prof. Dr. med. Holger Lerche, der Abteilung Kognitive Neurologie (Prof. Dr. med. Hans-Peter Thier) und der Abteilung für Zellbiologie Neurologischer Erkrankungen (Prof. Dr. sc. nat. Mathias Jucker). Die ersten drei Genannten sind bettenführende Abteilungen in der Neurologischen Klinik, die beiden Letztgenannten sind an der Patientenversorgung im Rahmen von Spezialambulanzen beteiligt. Die klinischen Abteilungen sind für die Versorgung von Patienten mit der gesamten Breite neurologischer Erkrankungen gemeinsam verantwortlich.

In den Abteilungen sind zurzeit 18 Professoren und etwa 380 Mitarbeiter in 32 Arbeitsgruppen tätig, wovon zwei unabhängige Forschungsgruppen darstellen.

Die Arbeitsschwerpunkte des HIH liegen im Bereich neurodegenerativer und entzündlicher Hirnerkrankungen, der Schlaganfallforschung, Epilepsien und der Erforschung der Grundlagen und Störungen von Wahrnehmung, Motorik und Lernen. Zu den bedeutenden Forschungserfolgen des HIH zählen die Entdeckung wichtiger genetischer und molekularer Grundlagen der Entstehung und Progression neurologischer Erkrankungen. Das HIH, ein Modellprojekt für Public Private Partnership, hat auch im Jahr 2017 rund 8,7 Millionen Euro an Drittmitteln eingeworben und 210 Veröffentlichungen in wissenschaftlichen Fachzeitschriften publiziert. Diese Zahlen belegen unter anderem die wissenschaftliche Leistungsfähigkeit des Zentrums. Die Gemeinnützige Hertie-Stiftung wendete bisher rund 50 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

In den Abteilungen sind zurzeit 18 Professoren und etwa 380 Mitarbeiter in 32 Arbeitsgruppen tätig. Die Gemeinnützige Hertie-Stiftung wendete bisher rund 50 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

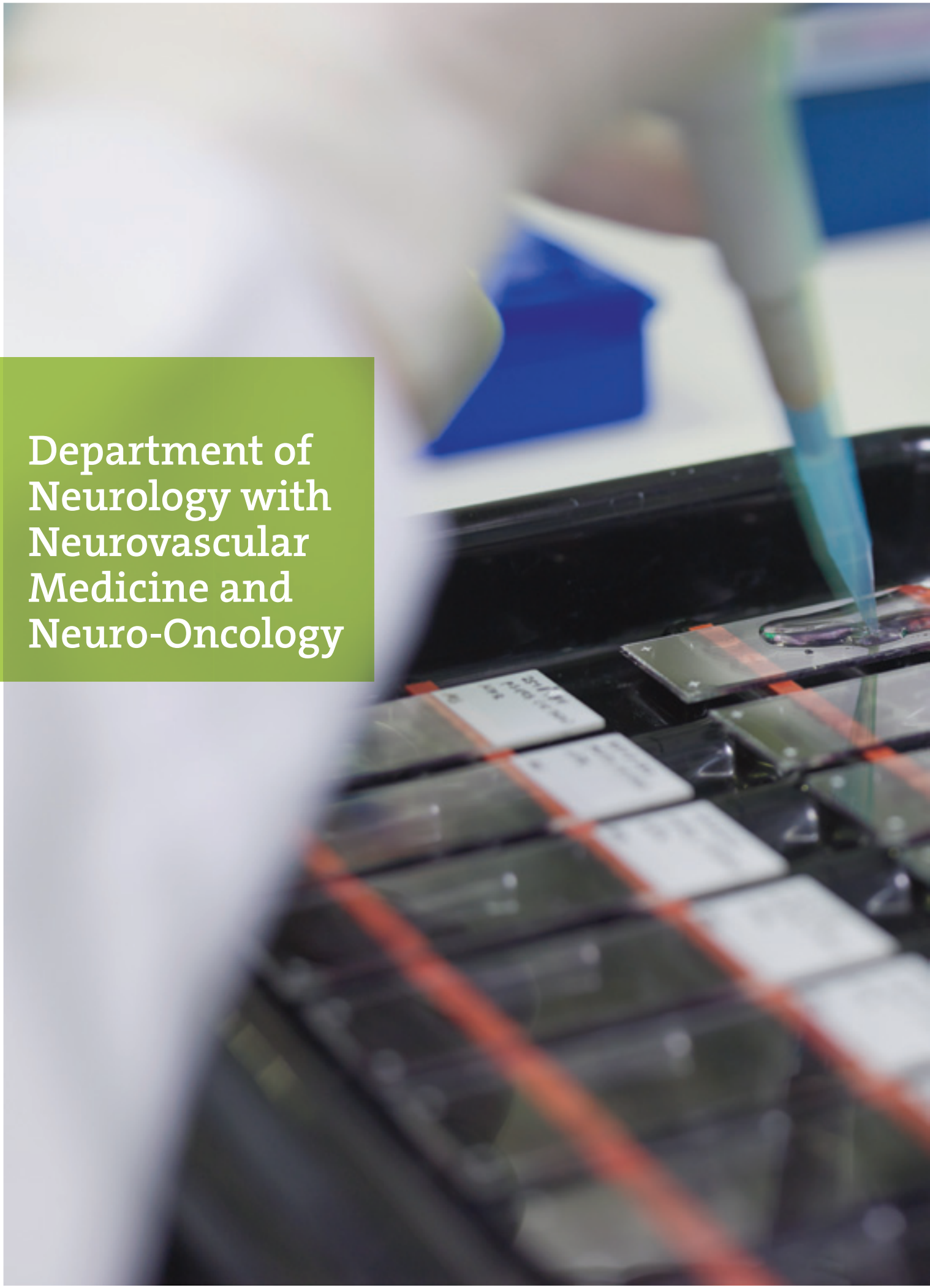
Das Hertie Institut für klinische Hirnforschung (HIH) war 2017 erstmalig mit einem Informationsstand auf der Jahrestagung der Society of Neuroscience vom 11. bis 15. November 2017 in Washington, DC, USA, vertreten. Unter dem Titel „Neuroscience in Germany" stellte das Institut gemeinsam mit anderen neurowissenschaftlichen Einrichtungen und Verbänden, sowie Förderorganisationen seine Inhalte und Angebote vor.

Im Herbst besuchten der Bundesminister für Gesundheit Hermann Gröhe und die Staatssekretärin Annette Widmann-Mauz, das Hertie-Institut für klinische Hirnforschung der Universität und des Universitätsklinikums Tübingen. Sie informierten sich dort gemeinsam über aktuelle Forschungsprojekte.

Eine besondere Bedeutung für die Zukunft des Zentrums kommt auch seiner Beteiligung an der erfolgreichen Bewerbung von Tübingen als Partnerstandort des „Deutschen Zentrums für Neurodegenerative Erkrankungen, DZNE" zu. Die Etablierung dieses Partnerstandortes führt zu einer erheblichen Stärkung des neurowissenschaftlichen Standorts. Mit dem Bezug des Neubaus des DZNE in direkter Nachbarschaft konnte die enge Zusammenarbeit weiter ausgebaut werden. Um die Interaktion zwischen den neurowissenschaftlichen Instituten am Standort Tübingen zu stärken, wurde 2015 ein Neuroscience Campus Get Together gemeinsam mit unseren Nachbarn, dem Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE) und dem Werner Reichardt Centre for Integrated Neuroscience (CIN), initiiert und im Jahr 2016 und 2017 erfolgreich fortgeführt.

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Peter Thier
Prof. Dr. Ulf Ziemann

Department of Neurology with Neurovascular Medicine and Neuro-Oncology



Departmental Structure

Prof. Dr. Ulf Ziemann is head of the Department of Neurology with Neurovascular Medicine and Neuro-Oncology

The Department of Neurology with Neurovascular Medicine and Neuro-Oncology 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.

The clinical and scientific expertise of the Department of Neurology with Neurovascular Medicine and Neuro-Oncology (Director: Prof. Ulf Ziemann) covers complex neurovascular diseases (ischemic stroke, intracranial hemorrhage, cerebral vasculitis, vascular malformations, rare neurovascular diseases such as endovascular lymphoma, paraneoplastic coagulopathy, or reversible cerebral vasoconstriction syndrome), neuroimmunology (multiple sclerosis, neuromyelitis optica, myasthenia gravis, autoimmune neuropathies and others), and brain tumors and brain metasteses. Specialized teams in stroke medicine (intensive care and stroke unit, rehabilitation), neuroimmunology and neurooncology provide expert multidisciplinary care for patient 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. The newly established Interdisciplinary Section of Neuro-Oncology (Head: Prof. Ghazaleh Tabatabai) is a unique section associated with this Department and the Clinic of Neurosurgery to coordinate clinical service and research in Neurooncology. 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 with Neurovascular Medicine and Neuro-Oncology 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 & plasticity (Prof. Dr. Ulf Ziemann), stroke and neuroprotection (Dr. Sven Poli), clinical and experimental neuro-oncology (Prof. Dr. Dr. Ghazaleh Tabatabai), molecular neuro-oncology (Prof. Dr. Ulrike Naumann) and speech disorders (Prof. Dr. Hermann Ackermann). The Research Groups are located in immediate proximity of the clinical services 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 has a focus on physiotherapy for stroke rehabilitation.

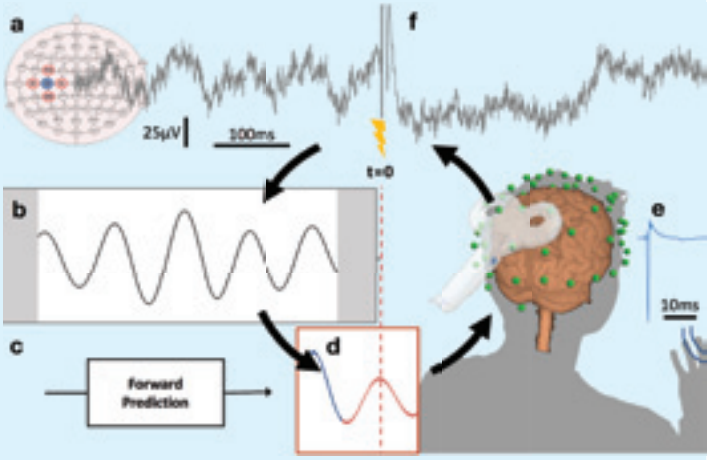
The Department of Neurology with Neurovascular Medicine and Neuro-Oncology offers lectures for medical students, physicians in training, nursing staff, physiotherapists and speech therapists. The grand round series welcomes internationally renowned clinical scientists giving state of the art lectures. The neurology therapy seminar gives up-to-date overviews on recent advances in neurology, internal medicine, neurosurgery, neuro-ophthalmology, 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 Department offers lectures for medical students, physicians in training, nursing staff, physiotherapists and speech therapists.

Neuroplasticity

Brain Networks & Plasticity (BNP) Laboratory

Head: Prof. Dr. Ulf Ziemann
Team: 18 members
Key words: human motor cortex / motor learning / plasticity / cortical connectivity / stroke rehabilitation / non-invasive brain stimulation / real-time closed-loop stimulation / EEG / MEG / MRI / fMRI / TMS-EEG / EEG-TMS / neuropharmacology



µ-oscillation phase-triggered stimulation of human motor cortex: the EEG-TMS approach

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. Our group focuses on understanding principles of neural plasticity in the human cortex, and on applying novel techniques of non-invasive brain stimulation, in particular personalized stimulation using information of instantaneous brain states based on real-time EEG analysis to highly efficiently modify neuronal networks. Our goal is to further the understanding of mesoscopic principles of brain network dynamics in the awake human and to develop new rehabilitative strategies of patients with brain network disorders.

Das menschliche Gehirn besitzt eine erstaunliche Fähigkeit zur Reorganisation, die Voraussetzung für die Anpassung an sich ständig ändernde Umweltbedingungen ist. Diese Fähigkeit zur Plastizität ist von herausragender Bedeutung für Erholungsprozesse nach Schädigungen des Gehirns, wie einem Schlaganfall. Unsere Arbeitsgruppe setzt ihren Fokus auf die Untersuchung von Plastizität der motorischen Hirnrinde auf systemneurowissenschaftlicher Ebene und der Entwicklung innovativer Methoden der nicht-invasiven Hirnstimulation, insbesondere die personalisierte hirnzustandsabhängige Stimulation unter Nutzung der EEG-Echtzeitanalyse von instantanen elektrophysiologischen Zuständen des Gehirns, um neuronale Netzwerke zielgerichtet und hoch-effizient zu modifizieren. Unser Ziel ist, die mesoskopischen Prinzipen der Hirnnetzwerkdynamik im wachen Menschen besser zu verstehen und innovative und effektive neurorehabilitative Strategien bei Patienten mit Hirnnetzwerkerkrankungen zu entwickeln.

Bi-Directional Real-time Interaction with Brain Networks

Our group has pioneered the development of real-time digital biosignal processing methods to esti-mate instantaneous brain states as the EEG signal is acquired. We are capable of triggering TMS based on the current amplitude and phases of specific endogenous oscillations at millisecond preci-sion and to design individually optimized spatial filters to isolate target brain oscillations at multiple sites including interhemispherics network states. This major advancement towards closed-loop stimulation allows us to trigger TMS at pre-specified brain states as they naturally occur. While our focus is on the sensorimotor mu-alpha oscillation and its role in modulating motor cortical excitabil-ity and connectivity and gating TMS-induced plasticity in the motor cortex, we have also started tar-geting beta oscillations in the motor cortex, alpha and theta oscillations in prefrontal brain regions, and are currently extending our research also to slow oscilllations and spindles during sleep.

We have demonstrated for the first time in the human that EEG-triggred TMS can (i) reveal phase-dependent excitability shifts during the sensorimotor mu-alpha oscillation and (ii) that repetitive targeting of the more excitable mu-alpha trough (but not the peak) by TMS bursts can induce LTP-like plasticity in the motor cortex. Using dual-coil paired-pulse protocols triggered by the phase of left and right motor cortex we demonstrated phase synchronization-dependent inter-hemispheric functional connectivity; and we found only mu-alpha not beta phase to reflect motor-cortical excita-bility shifts. We are currently working on further advancing this technique by reading out the rele-vant oscillatory states using more sophisticated spatial fitlers and eventually source space based real-time signal analyses. The approach of EEG-triggered TMS has the potential to significantly im-prove therapeutic brain stimulation in the near future by taking the current brain state into account. This will enable individualized modulation of neuronal networks of the human brain with the neces-sary precision in space and time.

Translational Clinical Research Toward Personalized Therapeutic Brain Stimulation

A major goal in the BNP lab is to translate the insights gained from innovative fundamental research using transcranial brain stimulation, in particular in combination with EEG in closed-loop-EEG-TMS approaches, into clinical research and eventually therapeutic applications. The BNP lab is conducting two investigator initiated trials with patients, one in collaboration with the department for Psychia-try with patients with depression (BOSSFRONT) and one in collaboration with the University Hospital in Cologne (STROKE-TEP). We were successful in acquiring a federal funding grant (EXIST) to develop a therapeutic personalized brain-stimulation device (NEUROSYNC). Finally, we are preparing to set-up a TMS outpatient clinic to offer currently established TMS treatment protocols in patients with chronic stroke and as a center to run further clinical trials with neuropsychiatric patients using brain oscillation synchronized brain-stimulation.

Pharmaco-TMS-EEG

Several projects are aiming at improving our understanding of the physiological underpinnings of TMS-evoked EEG potentials: Combining transcranial magnetic stimulation (TMS) and electroenceph-alography (EEG) constitutes a powerful tool to directly assess human cortical excitability and connec-tivity. TMS of the primary motor cortex elicits a sequence of TMS-evoked EEG potentials (TEPs) and TMS-induced oscillations (TIOs). We had previously studied the impact of GABA-Aergic (alprazolam, diazepam, zolpidem) and GABA-Bergic drugs (baclofen) on certain TEPs components, and have now shown how these drugs also alter TIOs, independently of the evoked components. Recently, we also extended our work to evaluating the novel alpha5-GABAAR antagonist S44819, as well as specific antiepileptic drugs (such as carbamacepine, brivaracetam, and tiagabine), and we will also investi-gate the effects of neuromodulators like Acetylcholine (rivastigmine, biperiden) in the future. The Pharmaco-TMS-EEG approach opens a novel window of opportunity to study both (i) the effects of specific drugs, which are relevant for disorders such as epilepsy, schizophrenia, or ischemic stroke, on excitability and functional connectivity in the brain, and (ii) the underlying neurophysiology of TEPs and TIOs.

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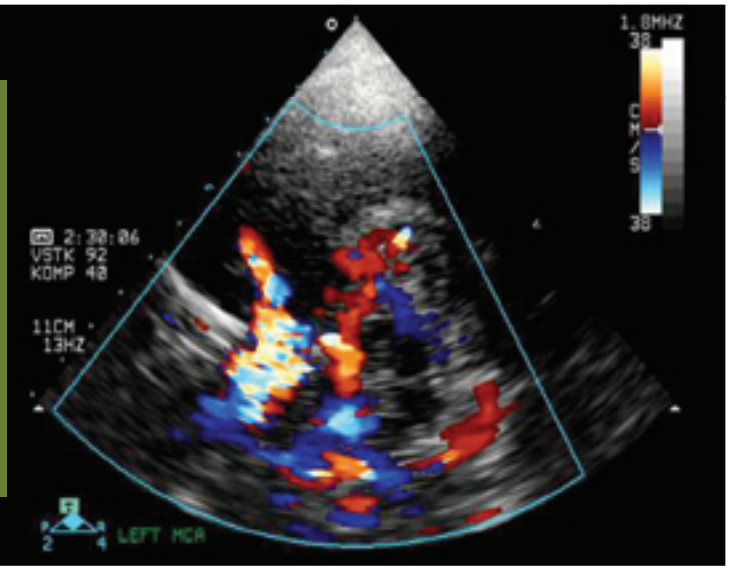
Stroke and Neuroprotection Laboratory

Head: Dr. Sven Poli
Team: 12 members
Key words: stroke / neuroprotection / temperature management / hypothermia / oxygen therapy / neuromonitoring / ESUS / DOAC / central retinal artery occlusion / prehospital triage



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 goal is to provide translational research with a close link to clinical application. Current experimental focus are intra-arterial cold infusions for selective brain hypothermia in combination with hyperoxygenation and other neuroprotectants. Further research activities comprise normobaric hyperoxygenation in acute ischemic stroke, multimodal neuromonitoring and neuroimaging including neurosonology, and interdisciplinary treatment of stroke including detection of atrial fibrillation and secondary prevention in patients after cryptogenic stroke / embolic stroke of undetermined source (ESUS), rapid coagulation assessment in patients treated with direct oral anticoagulants (DOAC), thrombolysis in acute central retinal artery occlusion, as well as prehospital stroke triage.

Forschungsschwerpunkt unseres Stroke & Neuroprotection Labors ist die Entwicklung neuer und die Optimierung existierender neuroprotektiver Strategien um den Hirnschaden nach einem Schlaganfall zu reduzieren. Darüber hinaus ist es unser Ziel die molekularen Mechanismen zu charakterisieren, welche der ischämisch-hypoxischen aber auch der reperfusions-reoxygenierungs-induzierten neuronalen Schädigung zugrunde liegen. Unsere Forschung ist translational mit einem engen Bezug zur klinischen Anwendung. Aktueller experimenteller Fokus ist die selektive Hirnkühlung durch intra-arterielle kalte Infusionen in Kombination mit Hyperoxygenierung und anderen Neuroprotektiva. Weitere Forschungsaktivitäten umfassen die normobare Hyperoxygenierung beim akuten ischämischen Schlaganfall, multimodales Neuromonitoring und Neuroimaging einschließlich Neurosonologie, und die interdisziplinäre Schlaganfallbehandlung einschließlich Detektion von Vorhofflimmern und Sekundärprophylaxe bei Patienten nach embolischem Schlaganfall ungeklärter Quelle (ESUS), Gerinnungsschnelltestung für direkte orale Antikoagulanzien, Thrombolyse beim akuten Zentralarterienverschluss, prähospitale Schlaganfallversorgung und Triage.

Neuroprotective effects of selective brain cooling with intra-arterial cold infusions (IACI) in acute ischemic stroke

Due to a significantly smaller target volume, selective brain cooling allows for higher brain cooling rates with only minor body core temperature reductions. “Hijacking” the brain-supplying blood flow, intra-arterial cold infusions (IACI) could be a promising strategy for rapid induction of brain hypothermia and may easily be performed during endovascular intervention.

We applied IACI (0°C) in a filament middle cerebral artery occlusion rat model through the internal carotid artery via a specifically designed infusion port allowing for continuous pre- and post-reperfusion brain cooling. So far, we have systemically studied the brain temperature change under different infusion rates and infusate temperatures. We are investigating the dose- and time-effect of IACI induced neuroprotection in MCAO stroke model, as well as associated mechanisms and potential complications.

Hypothermia & hyperoxygenation: Co-stars in neuroprotection after acute ischemic stroke

To study the synergistic neuroprotective effects of hypothermia and hyperoxygenation is another research interest of ours. As even selective and more so whole-body cooling may cause shivering and therefore increased oxygen consumption, hypothermia without additional oxygen supply might worsen hypoxic conditions in penumbral tissue. Besides, hypothermia causes a left-shift in the hemoglobin (Hb)-O2 binding curve which leads to an increased affinity of O2 towards hemoglobin and thus to a decreased release of O2 from the blood into the surrounding tissue.

By combining hyperoxygenation and hypothermia, the potential hypoxic condition brought by hyperthermia can be minimized. Since hypothermia not only increases the concentration of Hb-bound O_2 in the blood, but also that of physically dissolved O_2 in the plasma which diffuses out of capillaries along a concentration gradient and independent of the Hb- O_2 binding curve. Similarly, hypothermia may also attenuate potentially neurotoxic reactive oxygen species (ROS) produced during hyperoxygenation. In our previous work, the neuroprotective capacity of whole body hypothermia (HT) combined with / without normal baric oxygenation (NBO) was preliminarily evaluated. Significantly lower infarct volume was observed in HT + NBO compared to HT. Currently, the synergistic neuroprotective effects of intra-arterial cold infusions (IACI) + NBO are under investigation.

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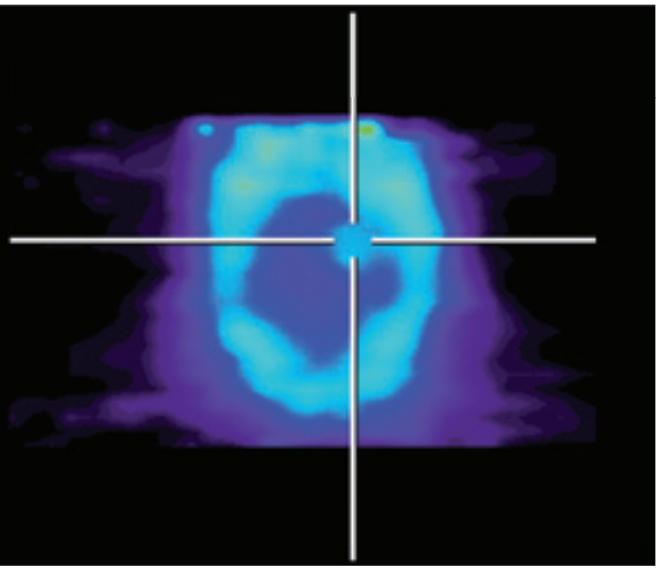
Interdisciplinary Section of Neuro-Oncology

Head: Prof. Dr. Dr. Ghazaleh Tabatabai
Team: 18 members
Key words: neuro-oncology / primary brain tumor / brain metastasis / acquired therapy resistance / cellular therapy / innovative clinical trials



The central nervous system (CNS) can be affected by primary or by metastatic tumors. The majority of meningiomas, vestibular schwannomas and pituitary gland adenomas can be efficiently treated with neurosurgical intervention alone. Yet, recurrent or progressive disease occurs in these diseases, too. For most other histological entities, including astrocytoma, oligodendroglioma or ependymoma, even multimodality treatments only lead to a transient window of stable disease, depending on the additional molecular features that are present in the tumor, for example: presence or absence of mutations in the isocytrate dehydrogensase (IDH), presence or absence of methylation of the O6-methylguaninmethyltransferase (MGMT), presence or absence of deletions of chromosomal regions 1p and/or 19q, presence or loss of alpha-thalassemia/mental retardation X-linked (ATRX), presence or absence and location of mutations in the human telomerase reverse transcriptase (TERT). Moreover, clinical evidence-based standards for metastatic CNS tumors are rare, because these patients have been mainly excluded from clinical trial enrollment until recently. Taken together, basic and translational research is a necessity to better understand molecular mechanisms of tumor initiation and acquired therapy resistance.

The scientific objectives of our group (students, technicians, postdoctoral researchers and physicians) are

(i) To understand molecular principles of tumor initiation and recurrence, particularly by studying cancer stem cell biology and mechanisms of acquired therapy resistance.
(ii) To generate novel and precise treatment strategies, particularly by using cell-based vehicles, oncolytic viruses, immunotherapeutic strategies
(iii) To understand and overcome acquired therapy resistance
(iv) To conduct innovative clinical trials

Im Zentralen Nervensystem (ZNS) entstehen verschiedene primäre oder metastatische Tumoren. Zwar führt bei den meisten Patienten mit Meningeomen, Schwannomen und Hypophysenadenomen bereits die alleinige neurochirurgische Resektion zu einer Heilung. Jedoch gibt es auch hier wiederkehrende Tumoren. Bei den meisten anderen histologischen Entitäten, z.B. die Gruppe der Astrozytome, Oligodendrogliome or Ependymome, führen hingegen sogar kombinierte multimodale Therapiestrategien nur zu einer vorübergehenden Stabilisierung, deren Dauer von weiteren molekularen Charakteristika in diesen Tumoren abhängt. Für Patienten mit ZNS-Metastasen, also Absiedlungen von Tumoren außerhalb des ZNS, sind klinische evidenzgesicherte Therapiestrategien selten, weil diese Patienten bis vor kurzem von einer Teilnahmen in klinischen Studien ausgeschlossen wurden.

Folglich sind grundlagenwissenschaftliche und translationale Forschungsprojekte darauf ausgerichtet, eine conditio sine qua non, um die molekularen Grundlagen der Tumorbiologie besser zu verstehen und darauf basierend neue therapeutische Zielstrukturen zu definieren.

Die wissenschaftlichen Ziele unserer Forschung sind

(i) Analyse molekularer Grundlagen der Tumorinitiierung und –progression (Tumorstammzellen, Therapieresistenz)
(ii) Entwicklung neuer Behandlungsstrategien und ihrer Kombination (Zellbasierte Therapie, onkolytische Viren, Immuntherapie)
(iii) Analyse, Verständnis und Überwinden der erworbenen Therapie-Resistenz
(iv) Konzeption und Durchführung innovativer klinischer Studien

Combining oncolytic measles virus with conventional therapeutic modalities

Collaboration partner: Michael Mühlebach, PhD (Paul Ehrlich Institut), Ulrich Lauer, MD (Medizinische Klinik, Universitätsklinikum Tübingen)

Glioblastoma is an aggressive primary tumor of the central nervous system with a median overall survival in the range of 1.5 years despite multimodal treatment regimens. Novel therapeutic strategies are urgently needed. Oncolytic measles virus (MeV) provides an exciting opportunity in this regard. We investigated here the combination of MeV with conventional therapies and identified that chemotherapy, virotherapy, and radiotherapy (CT-VT-RT) as a treatment sequence exhibits synergistic anti-glioma effects. Using RNA sequencing and immunopeptidome analysis with subsequent validations, we characterized the underlying molecular mechanisms. CT-VT-RT initiated a type 1 interferon-response along with canonical Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling and interferon-stimulated genes expression resulting in the activation of apoptotic cascades. Moreover, we identified novel immunogenic peptides presented in the HLA ligandome of MeV-infected glioma cells. Our data could be exploited for the generation of novel tailored immunovirotherapeutic strategies combining MeV and personalized peptide vaccinations. Based on these results we have filed a patent (Non-published European patent application no. 18 161 259.9) and are currently in the process of manuscript submssion.

Targeting the transciptional bHLH network

Collaboration partner: Olivier Raineteau, PhD (Stem Cell and Brain Research Institute Lyon, France); Peter Heutink, PhD (Deutsches Zentrum für Neurodegenerative Erkrankungen); Quantitative Biology Center Tübingen

Helix-loop-helix (HLH, ID proteins) and basic HLH (bHLH, e.g., Olig2) proteins are transcription factors and are well-characterized in the context of neural stem cell proliferation and maintenance. Glioblastoma express (b)HLH, too, and their overexpression correlates with poor clinical outcome. HLH/bHLH proteins need dimerization partners form either homo- or heterodimers with E proteins in the cytoplasm and translocate only then from the cytoplasm to the nuclear for DNA binding and transcriptional initiation. We overexpressed a dominant negative form of E47 (dnE47) that lacks its nuclear localization signal in long-term glioma cells and in glioma stem-like cells and thereby prevented nuclear translocation of bHLH proteins (Fig. 1). Our current experiments focus on dissecting the molecular network upon dnE47 overexpression for identifying potential therapeutic targets that can be applied in the clinical seeting. To this end we performed CAGE (in collaboration with Peter Heutink, DZNE) and RNA sequencing and identified key pathways that are involved. Interestingly, these pathways are druggable, and thus our current studies focus on identifying therapeutic regimens with these compounds in glioma mouse models *in vivo*.

Prologation of Temozolomide maintenance therapy

Radiation therapy with concomitant and adjuvant temozolomide (TMZ) maintenance therapy is still the standard of care in patients below the age of 65 years in newly diagnosed glioblastoma. However, in clinical practice, many centers continue TMZ maintenance therapy beyond six cycles. The impact of this continuation is controversial and has not yet been addressed in prospective randomized clinical trials. We compared the effect of more than six cycles of TMZ in comparison with exactly six cycles on overall survival (OS) and progression-free survival (PFS) by multivariate analysis and found a benefit in PFS but not OS. Our data do not support a general extension of TMZ maintenance therapy beyond six cycles. Thus, our data do not suggest prolonging TMZ maintenance therapy beyond six cycles, which should be considered in neurooncological practice. Of note, two retrospective studies from the German Glioma Network (Gramatzki et al., Neurology 2017) and from an international network (Blumenthal et al., Neuro Oncol 2017) were published on the same topic in 2017 and draw the same conclusion.

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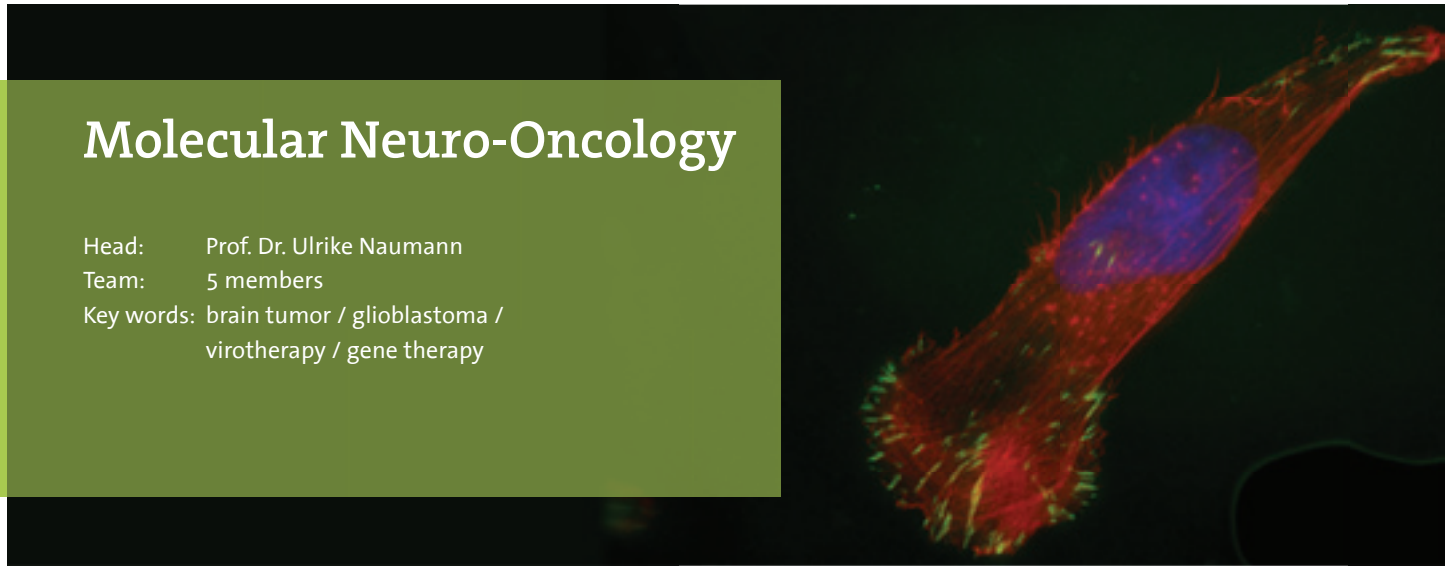
Molecular Neuro-Oncology

Head: Prof. Dr. Ulrike Naumann
Team: 5 members
Key words: brain tumor / glioblastoma / virotherapy / gene therapy



Migrating glioblastoma cell

The Research Group Molecular Neuro-Oncology is interested in various aspects of the biology of glioblastomas (GBM), the most frequent and letal human brain tumor. Characteristics of this tumor are its rapid and invasive growth into the healthy brain, its capability to suppress immune cells to attack the tumor as well as its resistance to chemotherapeutic drugs and radiation therapy. To know the biology of GBM in detail is important for the development of novel therapeutic strategies. In one of our research projects we focus to combine immunotherapy and oncovirotherapy and to optimize the shuttle of oncolytic viruses towards invaded glioma cells. Besides, we examine the impact of pericytes on glioma neoangiogenesis. In a third project we evaluate the therapeutic impact of viscumins, natural plant lectins, in the treatment of glioblastoma.

Die Arbeitsgruppe für Molekulare Neuro-Onkologie befasst sich mit Fragestellungen zur Tumorbiologie des Glioblastoms (GBM), dem häufigsten und bösartigsten Hirntumor mit einer, selbst bei optimaler Therapie, medianen Überlebenszeit von nur 12 bis 15 Monaten. Die Bösartigkeit dieses Tumors basiert darauf, dass Glioblstome schnell und invasiv in gesundes Hirngewebe einwachsen. Gliomzellen hindern zudem Immunzellen daran, sie zu attackieren und sind größtenteils resistent gegenüber Standardtherapien wie Bestrahlung oder Chemotherapie. Die Biologie des GBM zu kennen ist deshalb eine Grundvoraussetzung für die Entwicklung neuer Therapieansätze. Wir arbeiten unter Verwendung verschiedener Strategien daran, das invasive Wachstum von GBM-Zellen zu vermindern und versuchen Tumorzellen wieder für Standard-Therapieansätze zu sensibilisieren. Zudem beschäftigen wir uns mit der Wirkung „onkolytischer" Adenoviren, die für die GBM-Therapie eingesetzt werden können. Um die Onkovirotherapie zu optimieren, wird diese mit immuntherapeutischen Ansätzen kombiniert sowie Virus-beladene Zellen als „Trojanische Pferde" verwendet, im Viren auch zu invadierten GBM-Zellen zu transportieren. In einem weiteren Pojekt untersuchen wir, wie Perizyten das Einwachsen von Gefässen in das GBM modulieren und wie GBM-Zellen Perizyten hinsichtlich dieser Funktion beinflussen.

Glioblastoma (GBM) is the most common and lethal brain neoplasm with a median patient survival after standard therapy of 12 to 15 month. Only few therapeutic regimens provide a short increase in survival. The failure of effective therapy regimens is based on its malignant characteristics: glioma cells are mainly resistant to chemotherapeutic drugs and irradiation, they are highly motile, this way invading the healthy brain, and actively suppress the function of tumor-specific immune cells. In our research projects we are interested to receive information concerning the tumor immunology, to identify factors that regulate the capability of a glioma cells to move, and to analyze how glioma cells manipulate their surrounding micromilieu to optimize survival and growth.

A glioma cell either migrates or proliferates, but never does both at the same time. This is known as the GO OR GROW hypothesis of glioma. Drivers of GBM motility are bad growth conditions like starvation or hypoxia. The induction of migration and invasion needs cytokines, protein modifiers altering the extracellular matrix, cytoskeleton members and regulators of adhesion. Contrarily, drivers of growth, which means proliferation, are optimal living conditions. Induction of proliferation in glioma cells is caused by dysregulated signaling pathways as well by overexpression of growth factors. Until today, less is known about the cellular factors that regulate the switch from GROW to GO or from GO to GROW. In collaboration with Prof. Mittelbronn (Neuropathology, Frankfurt and LCNP, Luxembourg) we identified the neuropeptide processor carboxypeptidase E (CPE) as a switch factor involved in

the decision of a cell to stay and grow or to move away if conditions are suboptimal. Reduced 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. In glioma cells a secreted version of CPE (sCPE) is a regulator of the expression of motility-associated genes and pathways. Especially the EMT transcriptional regulator SLUG that boosts cell motility and invasion is downregulated by sCPE. sCPE does not exclusiverly provide its anti-migratory function by downregulation of SLUG. Additionally, sCPE diminished glioma cell migration is linked to a negative regulation of Rac1 signaling via RPS6, this way influencing cytoskeleton-organissation. Apart from this, sCPE enhances glucose flux into the tricarboxylic acid cycle at the expense of lactate production, thereby decreasing aerobic glycolysis, which might as well contribute to a less invasive behavior of tumor cells. Our data contributes to a better understanding of the complexity of GBM cell migration and sheds new light on how tumor cell invasion and metabolic plasticity are interconnected.

In Europe Viscumins, lectins from the semiparasitic plant Viscum album L., are often used by patients to adjuvantly treat cancer. In a project sponsored by the ISUS and Software AG Foundation we have shown that viscumins reduce glioma cell proliferation, induce cell death and enforce immune cells to attack and to kill GBM cells. Additionally, viscumins mitigate GBM cell motility, paralleled by a reduced expression of genes known to push and by an enhanced expression of genes known to delimitate cancer progression. Besides, viscumins strengthen the effects of the glioma standard therapy both in cell culture and in glioma bearing mice.

Oncolytic adenoviruses (OAV) that replicate selectively in tumor, but not in normal cells are used as potent and safe 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 YB-1 dependent OAV, named XVir-N31. We have demonstrated that in vitro XVir-N31 works synergistically with the chemotherapeutic drug temozolomide (TMZ) which is commonly used to treat GBM. In a mouse model using highly TMZ-resistant GBM stem cells, intratumoral injection of XVir-N31 induced tumor lysis and prolonged the survival of tumor bearing mice. In ongoing experiments, funded by the German Research Foundation, we will develope next generation OAVs and will combine oncovirotherapy and cancer immunotherapy. To further optimize the impact of OAVs we will use virus-loaded cells as “Trojan Horses” to shuttle the oncolytic viruses towards invaded glioma cells.

One pathological hallmark that distinguishes GBM from lower grade glioma is its abundant and aberrant vasculature resulting in bizarre vascular formations. The malformed GBM vasculature is accompanied by vessel permeability and the breakdown of the blood-brain barrier (BBB). Since we have observed that gene expression in pericytes is modulated by glioma-secreted cytokines and that pericytes with these altered gene expression are exculively found on glioma-associated vessels, we were interested whether “glioma-pericytes” are involved in formation of novel tumor-associated vessels, will influence the structure of these vessels and the integrity of the BBB.

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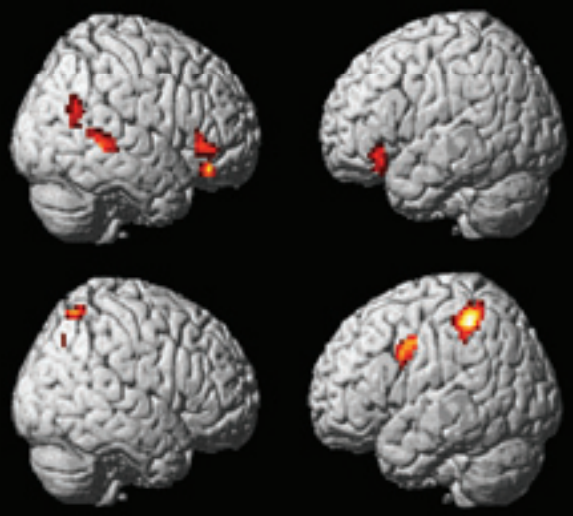
Neurophonetics and Translational Neurorehabilitation



Head: Prof. Dr. Hermann Ackermann
Team: 3 members
Key words: speech production and perception / neurobiology of language / acoustic communication / brain connectivity

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

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

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

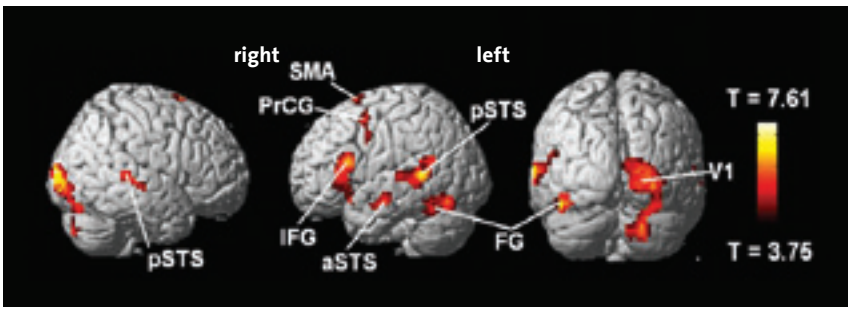
Blind individuals may learn to comprehend ultra-fast speech at a rate of up to about 22 syllables per second (syl/s), exceeding by far the maximum performance level of normal-sighted listeners (8-10 syl/s). Based on the results of two subsequent projects over the last years (a group study and a training experiment), the hypothesis of a "visual" strategy could be supported, comprising the engagement of right primary visual cortex in blind subjects for early perceptual processing. Evidence could be provided in terms of hemodynamic activity in visual cortex, structural changes in optical radiation pathways (Dietrich et al., 2015b), functional connectivity (Dietrich et al., 2015a), and phase locking between the speech signal and magnetic activity in visual cortex (Hertrich et al., under review).

The role of supplementary motor area (SMA) and pre-SMA in speech perception

SMA and pre-SMA are linked to the anterior parts of the language network by subcortical loops and via the frontal "Aslant tract". As outlined in a review paper, these structures have a cognitive control function with predominantly inhibitory characteristics (Hertrich et al., 2016). As, among other things, indicated by our investigations of ultra-fast speech perception, pre-SMA seems to be involved in top-down mechanisms of speech perception under the condition of increased task demands comprising both "phonological" and "semantic" aspects of speech perception. A Transcranial Magnetic Stimulation (TMS) experiment was performed to further determine in how far SMA and pre-SMA are engaged in time-critical aspects of speech processing (Dietrich et al., under review, in cooperation with the Brain Networks & Plasticity Lab).

Studies in neurophonetics and psycholinguistics

Our research group was affiliated with Project B2 of the DFG-Sonderforschungsbereich 833, University of Tübingen, which addressed the semantic processing of so-called presuppositions. The behavioral, electroencephalographoc (EEG), and magnetoencephalographic (MEG) studies conducted showed, among other things, that presuppositions - depending on linguistic context - may give rise to (i) increased reaction times (Tiemann et al., 2015), (ii) evoked EEG responses such as the N400 and P600, and (iii) altered auditory MEG responses to syllable onsets as well as widespread suppression of MEG alpha activity (Hertrich et al., 2015). Currently, in cooperation with the Institute of Evolutionary Cognition of the University or Tübingen, an fMRI study is performed in order to localize brain activity involved in the processing of presuppositions.



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".

Investigation of brain connectivity for translational neurorehabilitation
Currently, a project is in preparation addressing the investigation of brain connectivity in patients who are unable to communicate, in order to obtain physiological data for predicting their further development and rehabilitation potential. To these ends, a protocol will be developed for performing EEG recordings in response to magnetic stimulation of pre-defined brain regions that are relevant for the communication network in the brain. In particular, these regions comprise parts of inferior frontal gyrus and premotor cortex (language and speech generation network), upper and medial temporal lobe (phonological and semantic interfaces to the mental lexicon), and the (pre-) supplementary motor area (cognitive control). The most relevant cortico-cortical white matter pathways in this network are branches of the arcuate fasciculus (dorsal language pathway), the capsula extrema and the uncinate facsiculus (ventral language pathways), and the frontal Aslant tract (cognitive control).

An evolutionary perspective on spoken language: vocal continuity between non-human and human primates
Vocal learning is an exclusively human trait among primates. However, songbirds demonstrate behavioral features resembling human speech learning. Two circuits have a preeminent role in this human behavior; namely, the corticostriatal and the cerebrocerebellar motor loops. While the striatal contribution can be traced back to the avian anterior forebrain pathway (AFP), the sensorimotor adaptation functions of the cerebellum appear to be human specific in acoustic communication. The ongoing discussion on how birdsong translates into human speech was addressed in a review paper (Ziegler & Ackermann, 2017). The review focusses on motor aspects of speaking, bringing together genetic data with clinical and developmental evidence to outline the role of cerebrocerebellar and corticostriatal interactions in human speech.

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Department of Neurology and Epileptology

Departmental Structure

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

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 department's activities have been focusing on effective structures 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 45 and 42), running under the supervision of Prof. Dr. Y. Weber, PD Dr. T. Freilinger, and PD Dr. A. Grimm, 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

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).

with the Department of Neurosurgery (Dr. S. Rona, Prof. Dr. J. Honegger, Prof. Dr. A. Garabaghi). The epilepsy outpatient clinic (Prof. Dr. Y. Weber and Prof. Dr. H. Lerche) offers consulting and treatment in particular for difficult cases and specific questions including pregnancy under antiepileptic treatment and genetic aspects.

Other outpatient clinics are focused on headache and facial pain as well as other neurological pain syndromes (PD Dr. T. Freilinger), on neuromuscular diseases (PD Dr. A. Grimm), and genetically determined paroxysmal neurological and ion channel disorders (Prof. Dr. H. Lerche and Prof. Dr. Y. Weber). Specific genetic diagnostic testing using parallel next generation sequencing of all known epilepsy genes in one step (also available for other neurological disorders) is established together with the Institute of Medical Genetics and Applieed Genomics (Medical Faculty/UKT, Prof. O. Riess and Dr. T. Haack) and with PD Dr. S. Biskup at CeGaT GmbH, Tübingen. The department's study center has been involved in diverse medical trials to explore novel treatment options. The department supports the medical and neuroscientific education at the University of Tübingen by providing a comprehensive offer of lectures, seminars and courses.

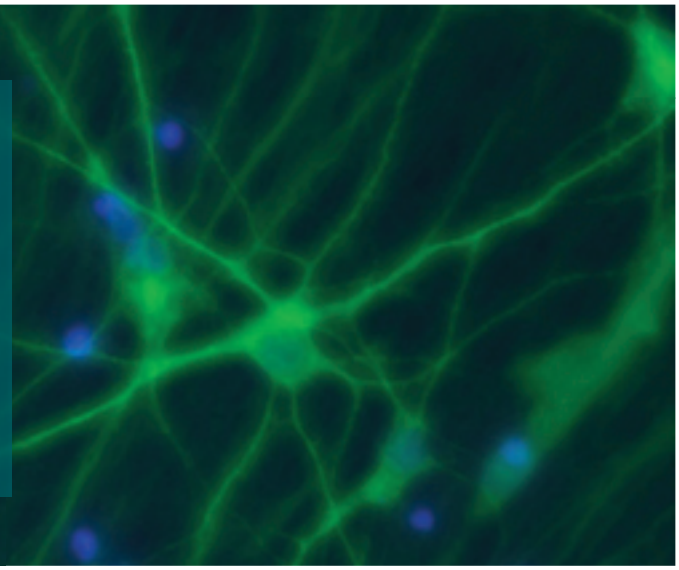
The department stimulates synergies between physicians in the Neurological Clinic and basic research groups in the Hertie Institute with the aim to work on clinically driven basic research questions and rapidly transfer scientific progress into clinical practice.

Our main research topics are

(i) the genetics and pathophysiology, and increasingly personalized treatment options of hereditary epilepsy syndromes and related neurological disorders
(ii) the closely related biophysics and physiology of ion channels and transporters, as well as the mechanisms of the excitability of nerve cells and neuronal networks
(iii) the genetics and molecular pathophysiology of rare monogenic (e. g. hemiplegic migraine) as well as common types of migraine and other primary headache disorders
(iv) clinical characterization, ultrasound and genetics of neuromuscular diseases
(v) structural and functional brain imaging to detect epileptogenic lesions and foci, as well as epileptogenic networks in the brain in acquired and genetically determined epilepsies (in cooperation with the MEG Center and the Departments of Neuroradiology and Neuroimaging)

Experimental Epileptology

Head: Prof. Dr. Holger Lerche
Team: 22 members
Key words: channelopathies / genetics / seizures / imaging / neuronal networks



Mouse primary hippocampal neurons expressing a GFP-tagged voltage gated potassium channel.

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. A particular focus is on finding and exploring new personalized therapies for genetic disorders. 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.

Das Ziel unserer Forschung ist es, die molekularen Mechanismen vor allem genetischer, neurologischer Krankheiten mit einer gestörten neuronalen Erregbarkeit mit ihren klinischen Symptomen zu verknüpfen. Wir rekrutieren gut definierte Kohorten von Patienten mit Epilepsien und verwandten Krankheiten, suchen nach den genetischen Defekten mit modernen Sequenziermethoden, insbesondere in Ionenkanälen oder -transportern, und untersuchen deren funktionelle Auswirkungen, um die Pathomechanismen zu verstehen. Ein besonderer Schwerpunkt liegt auf der Identifikation und Testung neuer personalisierter Therapien für genetische Syndrome. Wir untersuchen die Mechanismen neuronaler Übererregbarkeit auf molekularer, zellulärer und Netzwerkebene mit Screening-Methoden, wie automatisierter Elektrophysiologie in Oozyten oder Säugerzellen, in neuronalen Expressionssystemen einschließlich induzierter pluripotenter Stammzellen, und in genetisch veränderten Mausmodellen.

Epilepsy affects up to 3 % of people during their life time, 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, NGFNplus and German Network of Neurological and Ophthalmological Ion Channel Disorders, IonNeurONet), European (FP6: Epicure, ESF: EuroEPINOMICS, FP7: EpiPGX) and international (ILAE consortium on the genetics of complex epilepsies, collaboration with Epi4k, Epi25) research networks confined to the recruitment of large cohorts of affected individuals and/or families and their genetic analyses. A major achievement in 2017, emerging as a consequence of our continued work on this topic, was the establishment of a Research Unit funded by the DFG (FOR 2715) under our guidance, entitled 'Epileptogenesis of Genetic Epilepsies'. Important examples from recent studies are the identification of mutations in KCNA2 causing three distinct forms of epileptic encephalopathies correlating with gain- or loss-of-function mutations (Syrbe et al. Nat Genet 2015; Masnada et al., 2017), or in genes encoding different GABAA receptor subunits (e.g. describing GABRA3 as an epilepsy gene, Niturad et al., 2017).

Beside gene discovery and pathophysiology, we are increasingly focusing on specific therapies for genetic disorders which can partially 'correct' the genetic defect. Two recent examples are (i) the treatment of patients with KCNA2 gain-of-function mutations with 4-amonipyridine (a K+ channel blocker) which we performed with first preliminary success in n-of-1 trials particularly in young children and for which we obtained the Eva-Luise

Köhler prize for rare diseases to improve studies on the exact mechanism of action and to prepare a clinical trial, and (ii) a systematic retrospective clinical study combined with functional work on the Na+ channel gene SCN2A, in which we showed that early onset disease within the first three months of life is caused by gain-of-function mutations responding well to Na+ channel blockers, whereas a later onset after three months of age is caused by loss-of-function mutations and those patients do not respond well or even deteriorate on Na+ channel blockers (Wolff et al. 2017).

Functional implications of selected mutations are further examined in neuronal expression systems, such as transfected murine primary neurons and genetically-altered animal models carrying a human mutation (so-called "humanized mouse models"). The advantage of such mouse models is that altered channels can be studied in their natural environment and additionally, the consequences on intrinsic neuronal properties and network activity can be studied. Electrophysiological methods, including single cell patch clamp, extracellular recording or multielectrode array (MEA) techniques to analyze neuronal network activity are employed. With these techniques we characterized a knock-in mouse carrying a SCN1A mutation associated with generalized epilepsy with febrile seizures plus (GEFS+) showing an inhibitory interneuron firing deficit (Hedrich et al. J Neurosci 2014), and have been studying a SCN2A knock-in Maus together with Dirk Isbrandt from the Universty of Cologne showing an increase of neuronal firing in excitatory pyramidal neurons (Schattling et al., 2016, and unpublished data). To take this further, we now use our mouse models to study network dysfunction in vivo together with O. Garaschuk (Inst. Neurophysiology) using Ca2+ imaging in the frame of the newly established DFG Research Unit.

Sudden unexplained death in epilepsy (SUDEP) is the main reason for a more than tenfold increased mortality of epilepsy patients before the age of 50, and the SUDEP rate is particularly high in severe genetic epilepsies. In an ongoing project, we test the hypothesis if a dysfunction of the central regulation of breathing in the main underlying neuronal network (the PreBötzinger Complex) may be an important factor contributing to SUDEP. Therefore, we have been studying the consequences of known epilepsy-causing mutations in our genetic mouse models (SCN1A and SCN2A) on the function of the PreBötC (Koch et al., unpublished).

Finally, we have been establishing work on human neuronal tissue using fresh samples derived from epilepsy surgery and reprogramming fibroblasts and keratinocytes obtained from patients carrying different epilepsy-causing mutations in ion channel genes to generate human induced pluripotent cells (hiPSC). We found out that human slice cultures can be maintained for up to four weeks with good neurophysiological properties when human cerebrospinal fluid (CSF) is used as culture medium, whereas these cultures die within a week in commonly used arteficial CSF (Schwarz et al. 2017).

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(*equally contributing authors; #corresponding authors)

Clinical Genetics of Paroxysmal Neurological Diseases

Head: Prof. Dr. Yvonne Weber
Team: 10 members
Key words: paroxysmal neurological diseases / epilepsies / developmental and epileptic encephalopathies

Expression of the glucose transporter type 1 (Glut1) in Xenopus laevis oocytes.

Paroxysmal neurological disorders include a broad spectrum of clinical entities. The research group is focused on the clinical genetics of epilepsies and paroxysmal dyskinesias, paroxysmal neurological disorders with overlapping clinical and pathophysiological features. In the last years, the main topics were the analysis of a special type of epilepsies the "Developmental and Epileptic encephalopathies" (formerly epileptic encephalopathie, EE), the standardization of genetic biomarkers for a precision medicine in epilepsy and the analysis of the sodium channel gene SCN8A as a gene in which mutations are leading to EE as well as to a paroxysmal dyskinesia and isolated mental retardation. Additionally, a completely novel research field was started namely the development of a seizure detection system together with a start-up company.

Der Überbegriff der paroxysmalen neurologschen Erkrankungen beinhaltet ein breites Spektrum an klinischen Entitäten. Der wissenschaftliche Schwerpunkt der Arbeitsgruppe ist die klinisch genetische-genetische Untersuchung von Epilepsien und paroxysmalen Dyskinesien, die häufig pathophysiologische Uüberlappenungen zeigen und ebenfalls zum Krankheitsspektrum der paroxyxmalen neurologischen Erkrankungen zählen. In den letzten Jahren lag der Fokus auf speziellen Epilepsieformen, nämlich den Entwicklungsbedigten und epileptischen Epilepsien (früher epileptische Enzephalopathien, EE), der Standardisierung von genetischen Biomarkern für eine individualiserte Therapie sowie der Analyse des SCN8A-Gens, das neben den EE mit einer paroxysmalen Dyskinesie und mentaler Retardierung assoziiert sein kann. Darüber hinaus wurde ein komplett neues Forschungsfeld mit der Entwicklung eines Anfallsdetektors zusammen mit einem Start-up-Unternehmen begonnen.

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 structural (induced by e. g. scars, dysplasias or strokes), infectious, autoimmune, metabolic and genetic forms looking from a pathophysiological point of view. Up to 30 % of epilepsies are genetically determined. Epileptic encephalopathies (EE, development and epileptic encephalopathies) are defined as early onset and pharmaco-resistant epilepsies associated to developmetal delay or regression. Several subtypes are known such as West syndrome or Lennox-Gastaut syndrome encompassing syndrome with defined age of onset, seizures types and EEG characteristics.

Epilepsies are commonly related to other diseases such as mental retardation, ataxia or paroxysmal dyskinesias since thoses 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) induced by stress or alcohol
(ii) kinesigenic dysinesia (PKD), attacks induced by sudden voluntary movements
(iii) exertion-induced dyskinesia (PED) induced by prolonged periods of exercise

Activities in 2017

We detected a novel gene for the PKD/BFIS complex, SCN8A coding for sodium channel subtype which is known to be associated to pure mental retardation (Gardella et al. 2016). Together with others we described several novel genes such as DNM1 and OTU6B (EuroEpinomics Consortium et al. 2017, Epi4k Consortium et al. 2017, Santiago-Sim et al. 2017) in patients with epileptic encephalopathies. Additionally, during the actually running DFG funded project we detected several novel genes in cohort of unclassified EEs such as AIFM1, AIFM3 and OGDHL important for the mitochondrial cycle and AP2M1 which is component of the AP2 complex securing the endocytosis of GABA receptor (functional analysis under way, several manuscripts in preparation). In order to standardize genetic biomarker triggered precision medicine and the genetic diagnostic in epilepsy in general the Commission for Epilepsy and Genetics under the head of the German Society of Epilepsy (DGfE, leader: Prof. Y. Weber and PD S. Spiczak, Univesity of Kiel, Germany) established standards which are available at the homepage of the DGfE (see also Weber et al. 2017).

Furthermore, the seizure detection system was further developed especially concerning the self-learning algorithm which could detect now more 70% of dyscognitive seizure which a high rate compared to all other system on the marked. The seizure system was developed together with start-up company which recently received a funding of 1.77 Mio Euro by the Life Science Incubator of Bonn over 3 years. The budget is supplied by the German Ministry for Research (BMBF, Bundesministerum für Bildung und Forschung) and Prof. Y. Weber is the mentor of the project.

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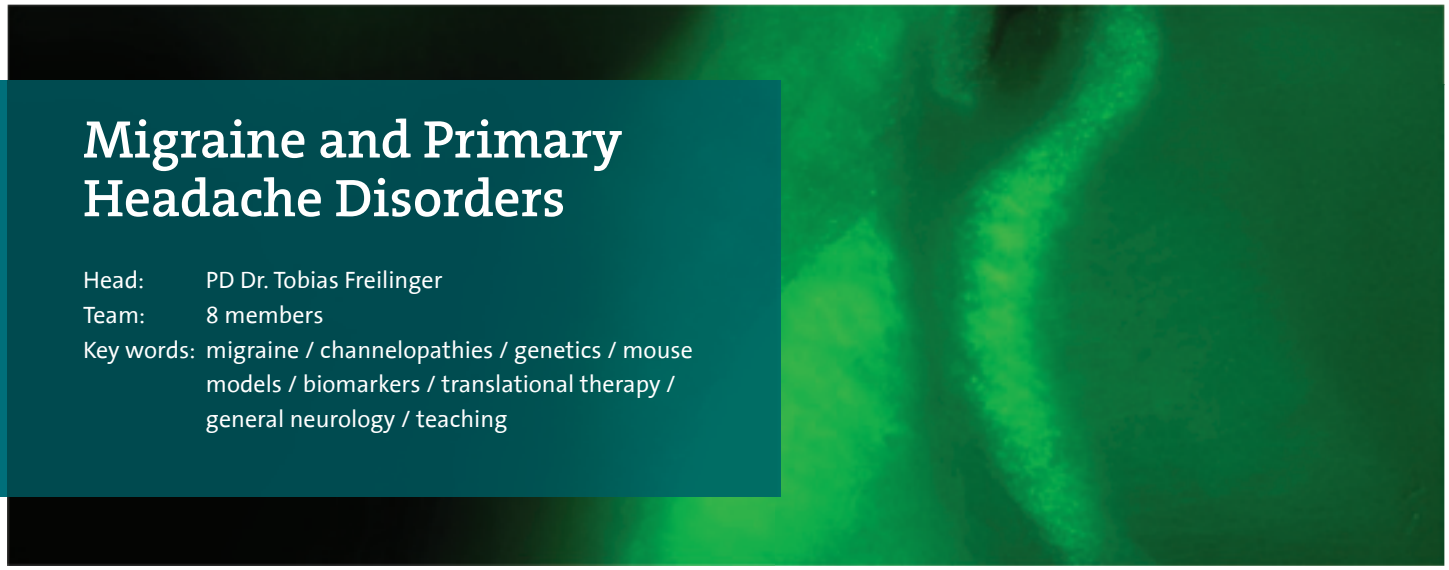
Migraine and Primary Headache Disorders

Head: PD Dr. Tobias Freilinger
Team: 8 members
Key words: migraine / channelopathies / genetics / mouse models / biomarkers / translational therapy / general neurology / teaching



Thalamocortical brain slice of a mouse strain expressing GFP in GAD67-positive inhibitory neurons

Our group is interested in clinical and genetic aspects of migraine and other (primary) headache disorders, aiming at a better understanding of pathophysiology and establishing novel (translational) treatment options. Our portfolio in migraine genetics covers the entire spectrum from rare monogenic forms to the common, genetically complex types. We further study epidemiological aspects, (vascular) comorbidities of migraine and symptomatic entities (e.g. reversible cerebral vasoconstriction syndrome). Finally, our interests include general clinical neurology, the role of placebo effects in neurology and medical teaching in neurology.

Unsere Gruppe interessiert sich für klinische und genetische Aspekte der Migräne und anderer (primärer) Kopfschmerzerkrankungen, mit dem Ziel eines besseren pathophysiologischen Verständnisses und der Etablierung neuer (translationaler) Therapiestrategien. Unser Portfolio umfasst das gesamte Spektrum der Migräne-Genetik von seltenen monogenen bis hin zu den häufigen genetisch komplexen Formen. Wir untersuchen weiterhin epidemiologische Aspekte, (vaskuläre) Komorbiditäten der Migräne und sekundäre Kopfschmerz-Entitäten (z.B. reversibles cerebrales Vasokonstriktionssyndrom). Zuletzt gilt unser Interesse allgemeinen neurologischen Fragestellungen, der Rolle von Placebo-Effekten in der Neurologie und Aspekten der neurologischen Lehre.

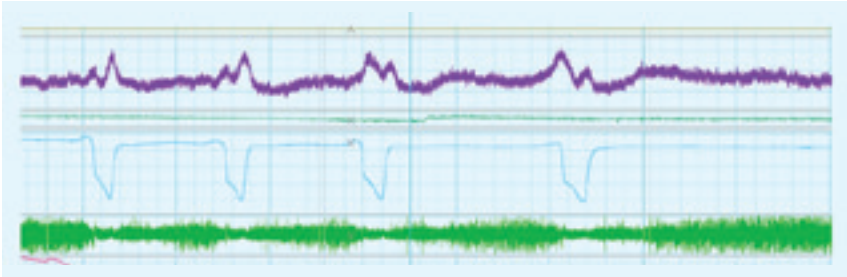
One major focus of our research is hemiplegic migraine (HM), a monogenic subtype of migraine with some degree of unilateral motor weakness during the aura. Building on previous work at LMU Munich, we have access to one of the worldwide largest HM cohorts, which is actively expanded through ongoing recruitment as well as clinical and genetic work-up, with new insights into the mutational spectrum and genotype-phenotype correlations (e.g. Fan et al. 2016; Schubert et al. 2017). In a sporadic HM patient, we had previously for the first time identified a novel missense mutation (T387P) in SCL1A3, the gene encoding the astrocytic glutamate transporter hEAAT2. In collaboration with C. Fahlke (Jülich) we have comprehensively characterized this novel variant to find a loss-of-function effect, highlighting impaired K+ binding to hEAAT1 as a novel mechanism (Kovermann et al. 2017).
To comprehensively study mechanisms underlying cortical hyperexcitabilitiy in HM, we are performing multimodal analysis of a transgenic Scn1a knock-in HM mouse model generated by our group, focusing specifically on cortical spreading depolarisation (CSD), the likely correlate of migraine aura (Auffenberg et al., in preparation). This model is also used to look into the differential pathophysiology of migraine vs. epilepsy and to study stroke susceptibility in migraine.

In parallel to these functional analyses, we are interested in improving clinical care of HM patients. Building on research support from the Centre of Rare Diseases (ZSE) as well as the intramural AKF program, we have established an explorative single center, prospective, open pilot trial (HeMiLa, Prophylactic treatment of hemiplegic migraine with Lamotrigine; EudraCT-Nr. 2016-003223-30), which started recruiting in 2017; further approaches directed at acute aura treatment are in the planning stage (grant from ZSE).

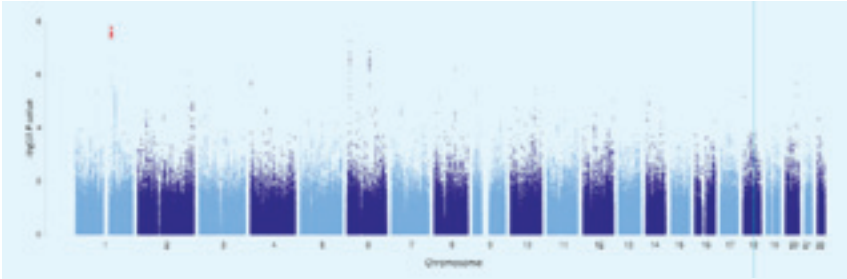
As a second focus we are interested in the common genetically complex types of migraine. We are a founding member of the International Headache Genetics Consortium (IHGC) and prominently involved in the identification of all currently established risk variants. Especially in the last few recent years, the knowledge of the genetic architecture of common migraine has been subtantially advanced, with more than 30 genome-wide significant risk

loci (Gormley et al. 2016). Many of these variants are located in or near genes implicated in vascular biology, suggesting a major role of a vascular component in migraine susceptibility, as highlighted e.g. by comorbidity of migraine with (cerebro)vascular phenotypes such as cervical artery dissection. Our group has a special interest in this migraine – vascular diease connection, and we are looking further into this (e.g. Malik et al. 2015 and 2016; Winsvold et al. 2017), aiming at identification of novel genetic as well as other types of biomarkers.

Finally, our portfolio covers aspects of general clinical neurology (e.g. Freilinger C et al. 2016; Auffenberg et al. 2017). In collaboration with the Department of Psychosomatic Medicine we have completed a prospective clinical study (ADAM) of patients with persistent sensory disturbances, in which routine clinical work-up is not conclusive. We are interested in both the clinical profile and the pathophysiology of the autonomous nervous system in this clinically prevalent cohort, implementing also placebo paradigms (Schubert et al., in preparation). Finally, we are establishing a novel problem-oriented neurological teaching module (Neuro-CliPS Tübigen) with support from intramural funding.



Representative traces from multiparametric in vivo monitoring of transgenic HM animals



Graphical representation ('Manhattan plot') of several risk loci for the common types of migraine (adopted from Freilinger et al. 2012)

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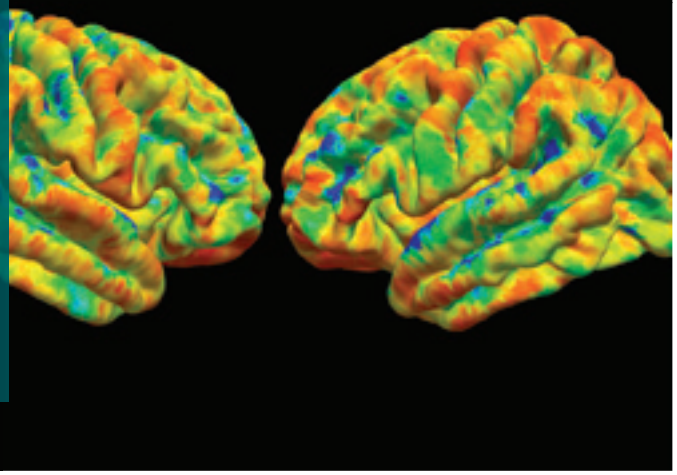
Translational Neuroimaging

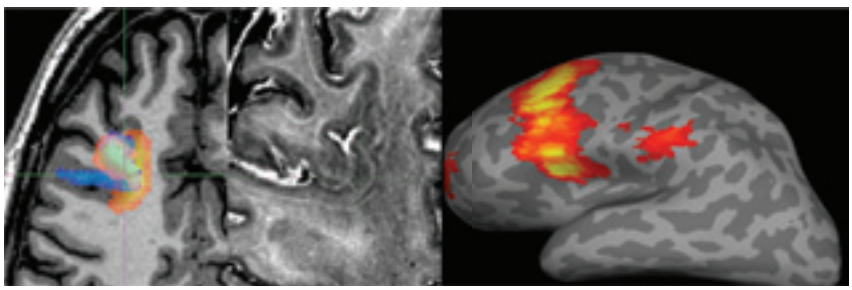
Head: Prof. Dr. Niels Focke
Team: 9 members
Key words: multi-modal imaging / epilepsy / post-processing / classification methods



Cortical structual connectivity derived from whole brain fibre tracking

The focus of our group is structural and functional imaging in neurological diseases with a particular focus on epilepsy. We are interested in better understanding the biology of pathological, neurological processes and translating these results to improved patient care and earlier diagnosis. We apply several computational, post-processing methods including voxel-based morphometry, machine learning and network analysis based on MRI, MEG, HD-EEG and PET.

Der Schwerpunkt unserer Forschungsgruppe ist die strukturelle und funktionelle Bildgebung neurologischer Erkrankungen mit besonderem Fokus auf die Epileptologie. Wir nutzen die technischen Methoden multi-modaler Bildgebung, um das Verständnis der Erkrankungsentstehung zu verbessern und in klinisch nutzbare Anwendungen zu überführen („Translation"). Ziele sind frühere Diagnosestellungen, automatisierte Läsion-Detektionen und Entwicklung bildgebungs-basierte Biomarker für die Klinik. Hierfür verwenden wir zahlreiche, Computer-basierte Techniken wie Voxel-basierte Morphometrie, Maschinen-Lernen und Netzwerk-Analysen basierend auf MRT, MEG, HD-EEG und PET.



Focal cortical dysplasia at 3T (including voxel-based morphometry) and at 9.4T, as well as regionally increased functional connectivity based on resting-state MEG (left to right).

In epilepsy, we are interested in better defining the structural and functional abnormalities associated with seizure generation ("epileptogenic zone") by means of imaging including high-field MRI (3T and 9.4T) and post-processing. Moreover, we apply diffusion-tensor imaging to analyze how epilepsy and seizures affect the structural networks of the brain. On the functional side, we use functional MRI together with high-density EEG (256 channels) and MEG to assess functional networks characteristics and spread of ictal discharges i.e. epileptic activity. We also apply PET to study metabolic disease effects. This broad range of non-invasive methods provides us with comprehensive access to brain networks in humans and in-vivo.

Imaging Modalities

- MRI (structural and functional incl. simultaneous EEG-fMRI)
- HD-EEG (256 channels)
- MEG (275 channels, whole brain)
- PET-MRI (hybrid system, incl. simultaneous PET-MRI-EEG)

Recent results

IIn patients with idiopathic/genetic generalized epilepsy (IGE/GGE) we could demonstrate microstructural network alterations based on diffusion tensor imaging although routine MR imaging was completely normal (Focke et al., 2014). Moreover, based on functional imaging (MEG) we could show increased network connectivity in IGE/GGE in the resting state (Elshahabi et al., 2015). In focal epilepsy, we have successfully applied our multi-modal imaging approach in a case with musicogenic epilepsy to non-invasively predict the propagation of epileptic activity using dynamic causal modelling. These predictions were later confirmed by invasive EEG and surgical resection (Klamer et al., 2015b). Also, we have worked on integrating and systematically comparing different functional imaging modalities (Klamer et al., 2015a) and improving structural VBM for lesion detection in epilepsy (Lindig et al., 2017) as well as systematically assessing VBM as a tool for presurgical epilepsy diagnstics (Martin et el., 2017). Furthermore, we have worked on assessing and improving the reliability of structural network analysis based on DTI (Bonilha et al., 2015) and enabling ultra-fast fMRI (Sahib et al., 2016 and Sahib et al., 2018).

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Department of Neuro-degenerative Diseases

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

Departmental Structure

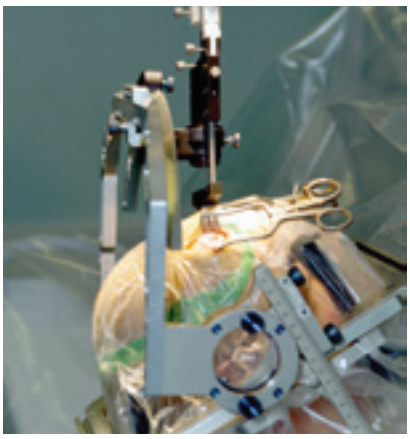
The Department of Neurodegenerative Diseases was founded with the support of the Charitable Hertie Foundation and started operations on September 1, 2002. Since 2009, it is also a part of the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE). Prof. Peter Heutink, speaker of the DZNE Tübingen and head of the Research Group on Genome Biology of Neurodegenerative Diseases, holds an affiliation with the Hertie Institute and is a member of the Department for Neurodegenerative diseases. 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) 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. Recently, a structured training curriculum for medical residents in training for board certification has been implemented, that covers a wide variety of movement disorders and rare neurogenetic diseases.

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

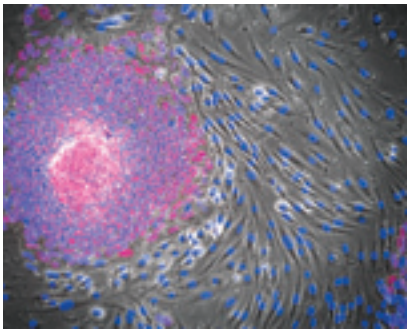
treatment in Parkinson's patients with severe fluctuations, or botulinum toxin treatment in patients with dystonias and spastic gait disorders. The close collaboration of the specialized inpatient unit with the outpatient clinics for PD, dementia, dystonia, motor neuron diseases, ataxias, spastic paraplegias, and other rare neurogenetic disorders allows highly individualized patient management. The equally close interaction of clinicians with basic scientists within the Hertie Institute for Clinical Brain Research and the DZNE, on the other hand, allows truly translational research. This innovative concept includes active education and training of scientific and clinical junior staff. In 2015, the clinical department was named for the third time in a row as one of Germany's Top Ten hospital departments in Parkinson's Disease by the Magazine Focus.

Research is currently organized within 10 research groups. The group of Prof. T. Gasser investigates the genetic basis of Parkinson's disease and other movement disorders with high throughput array and next generation sequencing techniques. The group works closely with the Clinical Parkinson's Research group with its focus on clinical cohort studies, phenotyping and neuroimaging. This group is now lead by Dr. Kathrin Brockmann and PD Dr. Inga Liepelt, after its former head, Prof. Daniela Berg, has moved to become Chair of Neurology at the University of Kiel in 2016. The research section for Clinical Neurogenetics, headed by Prof. L. Schöls focuses on clinical and fundamental aspects of inherited ataxias, spastic paraplegias, motor neuron diseases, leukodystrophies and other rare neurogenetic conditions. PD Dr. D. Weiß took over the lead of the deep brain stimulation (DBS) group from Prof. R. Krüger, who accepted a chair at the University of Luxembourg in June 2014 and develops novel DBS stimulation paradigms, while Prof. Krüger still works with HIH basic research scientists on fundamental pathogenetic mechanisms of neurodegeneration in PD, with a particular focus on mitochondrial function and dysfunction. Prof. P. Kahle's group (Section of Functional Neurogenetics) investigates also fundamental aspects of neurodegeneration mainly related to tau and alpha-synuclein aggregation. The group of PD Dr. M. Synofzik applies systems neurobiologic and genetic approaches to elucidate the basis and develop novel treatments of complex movement disorders including ataxias, but also dementias and motor neuron diseases, while PD Dr. R. Schüle focuses on the genetic basis of spastic paraplegias, also spanning the entire translational spectrum from gene identification to individualized treatments. In 2016, Dr. Ebba Lohmann has joined the department to run the outpatient unit for botulinum toxin treatment of dystonias and spasticity, linking this clinical approach with the search for the genetic basis of these hyperkinetic movement disorders. Dr. Dr. S. Biskup leads a research group on LRRK2-biology, but also a highly successful company that offers innovative methods of genetic diagnosis. Finally, Dr. J. Simon-Sanchez, "Genetics and Epigenetics of Neurodegeneration" has recently established a group jointly supported by the Department and the German Center for Neurodegenerative Diseases (DZNE) with a primary interest in the genetics and genomics of neurodegenerative disorders.

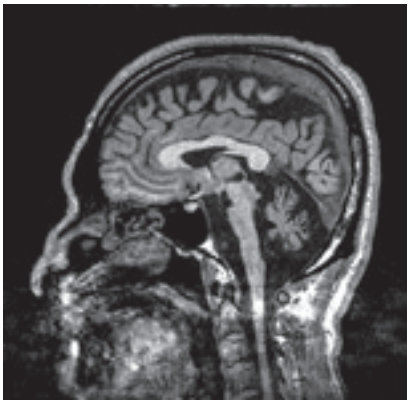
Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with Parkinson's disease and other neurodegenerative diseases.



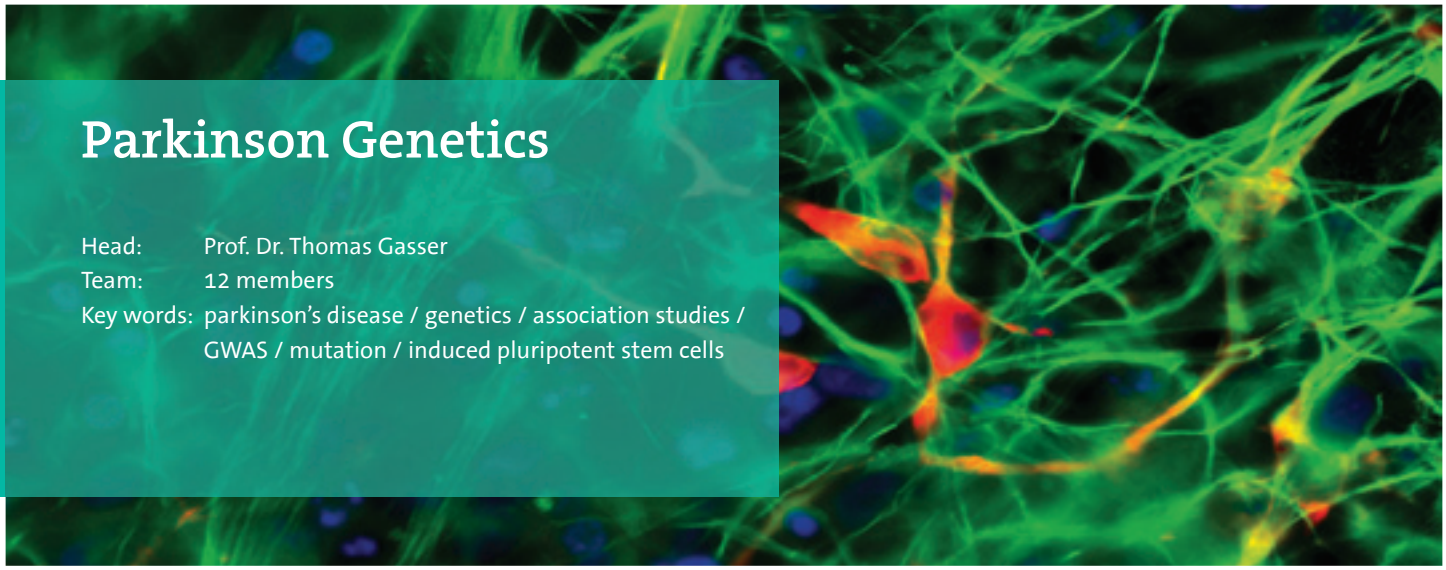
Insertion of an electrode during deep brain stimulation for Parkinson's disease.



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).



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

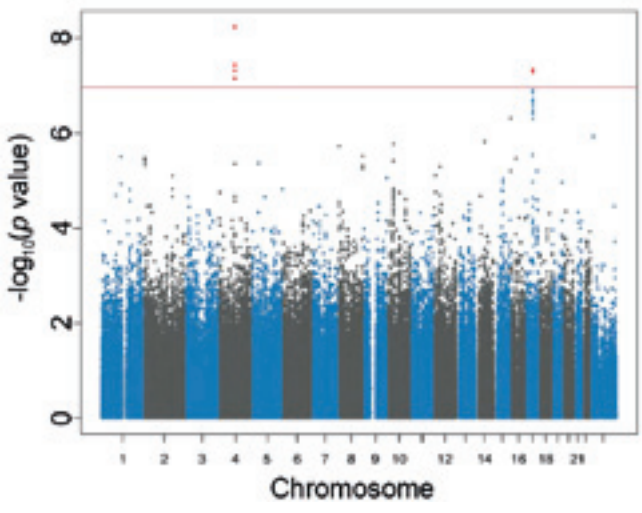


Parkinson Genetics

Head: Prof. Dr. Thomas Gasser
Team: 12 members
Key words: parkinson's disease / genetics / association studies / GWAS / mutation / induced pluripotent stem cells

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 several international consortia, we are striving to identify these genetic variants by state-of-the-art high throughput techniques in conjunction with in depth clinical analyses.

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

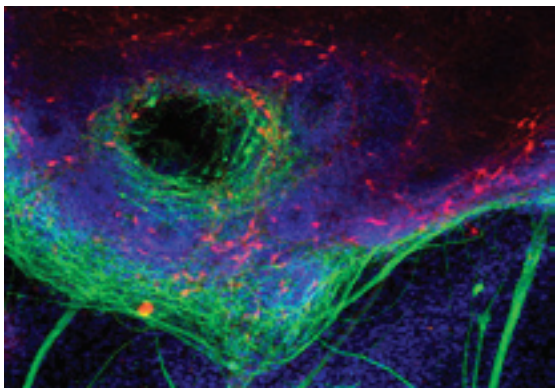


A large genome-wide study identified two genetic risk loci for sporadic PD. One is MAPT, containing the gene for the microtubule associated protein tau.

Specific mutations in some genes can cause rare inherited forms of Parkinson's disease (PD). Mutations in the LRRK2-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) form 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 Research Network, NGFN2, in a collaboration with the laboratory for neurogenetics of the National Institutes of Health (NIH). (Simon-Sanchez et al., Nat Genet 2009). Since this initial study, we have worked with numerous collaborators in the International Parkinson's disease Genomics Consortium (IPDGC), so that current analyses are now based on a sample size of more than 25,000 cases and 400,000 controls. The latest meta-analysis resulted in the confirmation of a total of over 40 risk loci with genome wide significance (Chang et al., Nat Genet 2017).

A network of neurons (i.e. nerve cells) with long neuronal extensions (in green). They were generated from reprogrammed fibroblasts (skin cells) of a Parkinson's patient. Dopaminergic neurons (in red) are also generated according to a special protocol for the maturation of stem cells into neurons. These are the cells that are most sensitive in Parkinson's patients and therefore die off more quickly. This allows us to work on dopaminergic neurons of Parkinson's patients in the "test tube". Cell nuclei are shown in blue.



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. Based in part on these studies, we have contributed to the development of a genotyping array, a novel tool to capture a large proportion of common and rare genetic variability contributing to neurodegenerative diseases (Nalls et al., 2015). Using this array, we have lead an international consortium, funded by the Joint Programming in Neurodegenerative Diseases (JPND) program, to genotype a large independent cohort of more than 20,000 patients (CouragePD-project).

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 lead to disease. Until recently, studies on gene function have only been possible in animal and cellular models, which often fail to the specific features of human diseases. The revolutionary technology of "reprogramming cells" into so-called "induced pluripotent stem cells" (iPSC) has opened up a whole new research area. 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 used this technology to analyze the consequences of disruption of mitochondrial pathways as seen in autosomal-recessive early-onset PD (Fitzgerald et al., 2017) and also to study the effect of common variability in the LRRK2 gene associated with PD (Marrone et al, 2017).

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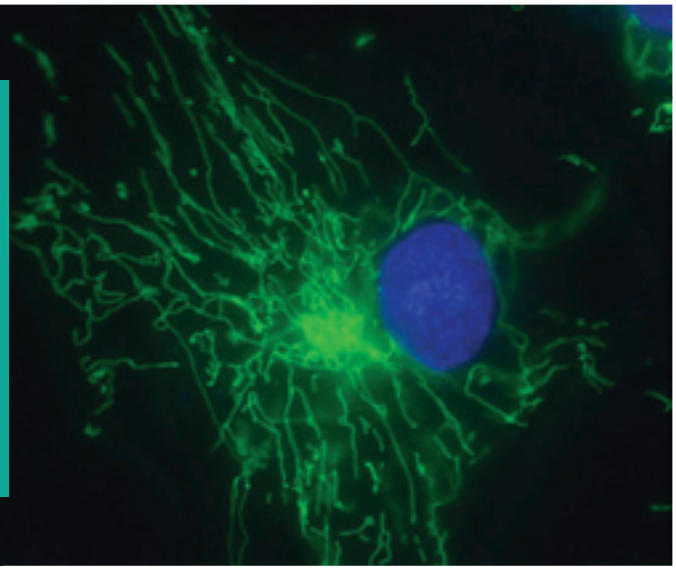
Functional Neurogenomics



Head: Prof. Dr. Rejko Krüger
Team: 4 members
Key words: mitochondrial dysfunction / mitophagy / patient-based cellular models

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 newly 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; Seidel et al. 2010) and the 'E64D' mutation in the DJ-1 gene (Hering et al. 2004; Krebiehl et al. 2010). Using patient fibroblasts to study mitochondrial function and dynamics the group identified mitochondrial pathologies in Parkinson's disease and defined robust mitochondrial phenotypes related to mutations in the DJ-1 and the mortalin gene (Krebiehl et al. 2010; Fitzgerald, Burbulla et al. 2014). More recently in collaboration with the group of Dimitri Krainc (Northwestern University Chicago, USA), we found that dopamine oxidation is mediating mitochondrial and lysosomal phenotypes in neurons derived from DJ-1 mutation carriers, which is a shared mechanism with sporadic PD (Burbulla et al. 2017).

Our studies aim at the identification of shared pathways of different PD-associated proteins linked to mitochondrial quality control. . Here we first described an functional link between Omi/HtrA2 and the mitochondrial chaperone TRAP1 and characterized a patient-based cellular model of loss of TRAP1 (Fitzgerald et al. 2017). In a mouse model of PD, we are also investigating mitochondrial function and neuronal survival in vivo focusing on mutations in the mitochondrial serine protease Omi/HtrA2 (Casadei et al. 2016).

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 (Boussaad, Obermaier et al. 2017; Abstract).

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

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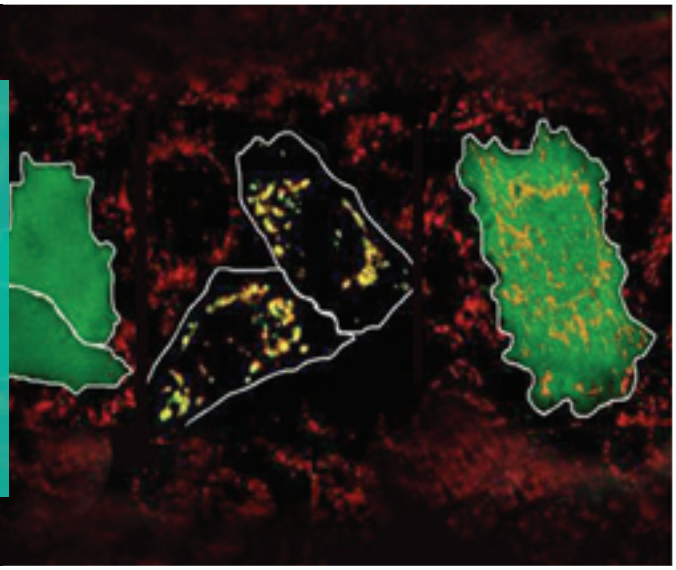
Functional Neurogenetics



Head: Prof. Dr. Philipp Kahle
Team: 8 members
Key words: parkinson's disease / amyotrophic lateral sclerosis / frontotemporal dementia / synuclein / ubiquitin / mitochondria / signal transduction / innate immunity

We are elucidating the molecular mechanisms of neurodegeneration and physiological roles of genes linked to Parkinson's disease (PD) with emphasis on the major genetic and neuropathological hallmark α-synuclein 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 as well as histological techniques, applying to cell culture, fly and mouse models, and patient-derived biomaterials.

Wir erforschen molekulare Mechanismen von neurodegenerativen Genprodukten, sowohl deren normale physiologische Funktionen als auch pathologische Aberrationen. Die untersuchten Gene verursachen Morbus Parkinson, hier vor allem das genetisch und neuropathologisch zentrale α-Synuklein, sowie im Falle der RNA-bindenden Genprodukte TDP-43 und FUS frontotemporale Demenzen und amyotrophe Lateralsklerose. Unsere Grundlagenforschergruppe verwendet biochemische, molekularbiologische und histologische Techniken. Wir untersuchen Zellkultur- und Tiermodelle (Fliegen und Mäuse) sowie Patienten-Biomaterialen.

A major focus of our research is the autophagic removal of damaged mitochondria (mitophagy) controlled by the recessive Parkinson's disease (PD) genes PINK1 and parkin. In collaboration with Thorsten Stafforst at the Interfaculty Institute of Biochemistry we could demonstrate the applicability of a novel RNA editing technology to correct gene deficits. Specifically, we created a model cell line expressing the PD-linked W437X PINK1 mutant, also employing CRISPR/Cas methodology. We confirmed that these PINK1 mutant cells were deficient in mitophagy, which could be corrected by targeting the RNA editing enzyme ADAR2 to the PINK1 mutation via specific guide RNAs. This study provides proof of principle that such guide RNAs are useful to correct nonsense mutations thereby rescuing cellular defects caused by recessive mutations (Wettengel et al. NAR). Moreover, we continue investigate novel regulators of parkin-mediated mitophagy. Research is partially supported by ONO Pharmaceuticals, and very recently a DFG Research Training Group MOMbrane was established in the Institute of Biochemistry, for which we contribute a project about post-translational modifications at the mitochondrial outer membrane mediated by the kinase PINK1 and the ubiquitin ligase parkin.

We extended our long-standing investigation of the dominant Parkinson's disease (PD) gene α-synuclein to alcoholism. While SNCA is a well-established contributor to PD, reports linking α-synuclein with addictive behavior are more scattered. In the attempt to test whether α-synuclein indeed contributes to alcoholism we collaborated with Ainhoa Bilbao at the Central Institute for Mental Health in Mannheim. Our study indicated that α-synuclein overexpression in mice enhanced the motivation for ethyl alcohol. Consistently, α-synuclein transgenic mice showed stronger neuronal activity in the nucleus accumbens and amygdala in response to alcohol, as evidenced by phospho-CREB immunostaining (Rotermund et al. JNC). Moreover, we contribute to the ongoing efforts of the Department of Cellular Neurology (Mathias Jucker) to elucidate the seeding of proteinopathies, specifically PD α-synucleinopathy. We published an overview of such studies in transgenic mice (Recasens et al. CTR). Our continued collaboration with Uppsala University, Sweden, yielded a report mapping surface exposed epitopes of aggregated α-synuclein species (Almandoz-Gil et al. CMN), which could help to refine the development of immune-therapeutics against α-synucleinopathies. Finally, our research on epigenomic effects of α-synuclein with the German-Canadian-French research consortium decipherPD resulted in a submitted manuscript (with Julia Schulze-Hentrich, Institute for Medical Genetics) and novel further insights into transcriptomic changes in α-synuclein transgenic mice exposed to nutricional stress (high fat diet).

Our studies on post-translational modifications of the frontotemporal dementia and amyotrophic lateral sclerosis causing gene product TDP-43 the mass spectrometric analyses in collaboration with the DZNE Proteomics facility (Johannes Glöckner) are completed. Cellular and functional validations for the ubiquitinylation sites are done and submitted, for acetylations the studies are ongoing. This research is supported by the German Center for Neurodegenerative Diseases.

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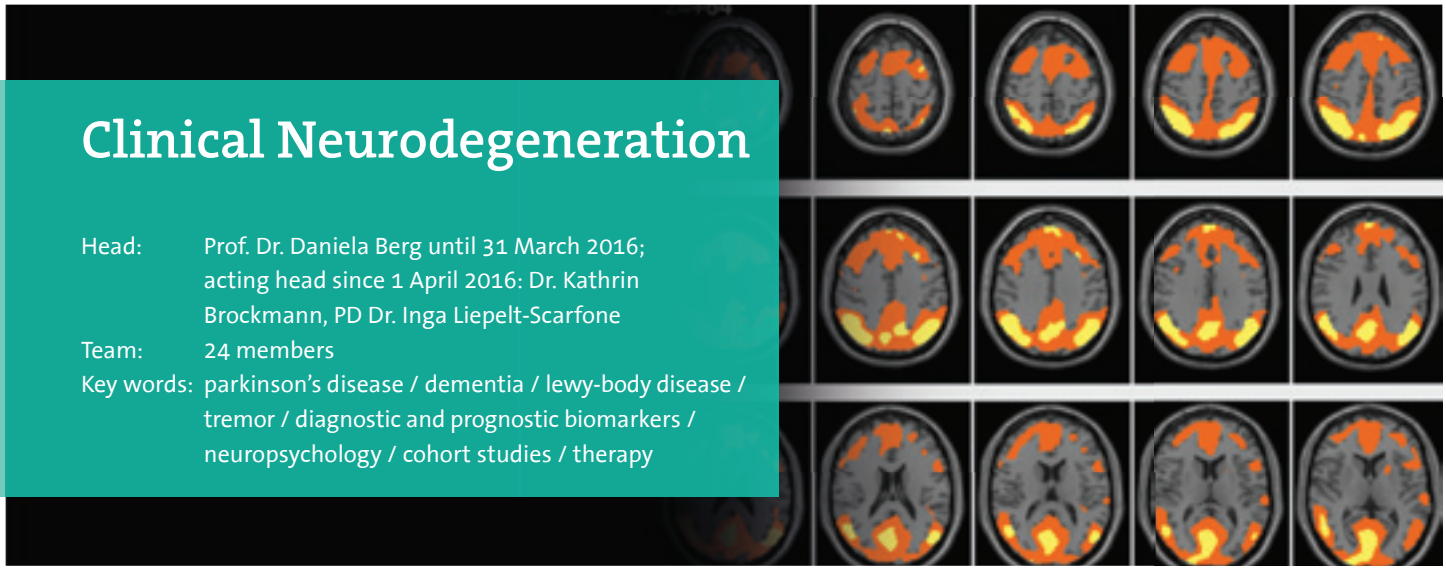

Clinical Neurodegeneration

Head: Prof. Dr. Daniela Berg until 31 March 2016; acting head since 1 April 2016: Dr. Kathrin Brockmann, PD Dr. Inga Liepelt-Scarfone
Team: 24 members
Key words: parkinson's disease / dementia / lewy-body disease / tremor / diagnostic and prognostic biomarkers / neuropsychology / cohort studies / therapy

Since Parkinson's disease (PD) is a complex multifactorial disorder with a large variability in phenotypes and progression, our focus of research aims patient stratification according to clinical markers, imaging patterns, genetic architecture (GBA or LRRK2) and, importantly, the underlying pathologic processes. Moreover, we focus on risk factors and prodromal symptoms on dementia. Therefore, the group Clinical Neurodegeneration follows large cohorts of PD 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. Novel medication and conservative therapeutic strategies are offered in numerous studies with a specific focus on individualized therapy.

In der immer älter werdenden Bevölkerung nimmt die Zahl an Patienten, die von Parkinson oder neurodegenerativen Demenzen betroffen sind, stetig zu. Neben den typischen Bewegungsauffälligkeiten zeigen sich bei vielen Patienten eine Reihe von weiteren Begleitsymptomen z.B. Verstopfung, Riechverlust oder Depression. Es besteht jedoch eine hohe Variabilität hinsichtlich Ausprägung und Verlauf einzelner Symptome. Die Demenz stellt dabei einen der wichtigsten Meilensteine und Prädiktor für reduzierte Lebensqualität und Mortalität der Patienten dar. Die AG Klinische Neurodegeneration untersucht in großen Kohortenstudien charakteristische Veränderungensowie mögliche genetische Ursachen der Parkinson Erkrankung. Auffälligkeiten des Gehirns in bildgebenden Verfahren wie Ultraschall und MRT, klinische Veränderungen (z. B. bei bestimmten Bewegungsmustern oder beim Denken) sowie Marker im Nervenwasser wurden bereits als Diagnose- und Verlaufsmarker identifiziert. Zudem werden neue medikamentöse und konservative Therapiestrategien im Rahmen von Studien angeboten.

Parkinson's disease

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 collaboration with the Integrated Care and Research Unit of the German Center for Neurodegenerative Diseases (DZNE) 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.

Selected examples of recent findings are:

(i) Research criteria for Prodromal PD could be validated in prospective cohorts for the first time.
(ii) Aiming for Study Comparability in Parkinson's Disease a Proposal for a Modular Set of Biomarker Assessments to be Used in Longitudinal Studies has been suggested by an European consortium (JPND).
(iii) Inflammation plays a decicive role in PD phenotypes as shown by inflammatory profiles discriminating clinical subtypes in LRRK2-associated Parkinson's disease.
(iv) An influence of Aß -pathology on the development of dementia in PD was demonstrated by lower CSF Ab1-42 levels and earlier onset of dementia in PD.

A further focus of the group is standardization of assessments in collaboration with other experts. In cooperation with Prof. Walter Maetzler, unobtrusive 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 deficits related to motor performance and cognition.

Since September 2016 Dr. Kathrin Brockmann is head of the Neurobiobank funded by the Hertie Institute and the DZNE. Therefore, the group has been crucially involved in the development and maintenance of the Neurobiobank, 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 is involved in a number of mono- and multicenter clinical phase II to IV studies, including also the allied health services, for all stages of PD with a focus on individualized interventions.

Milestones in Parkinson's disease
In the era where motor symptoms can be increasingly well controlled, dementia represents a key milestone in the course of PD, dramatically lowering patient's quality of life. This calls for the identification of modifying factors which in turn might help to predict the course of the disease and possibly opens new therapeutic windows. Besides the quantification of clinical markers (neuropsychological scores, activity of daily living function), genetic variants and CSF profiles may help to define a high-risk group for Parkinson's disease dementia at an early stage.

Atypical Parkinsonian syndromes
In the last years, huge effort of many groups has been put into a better characterization of the different endophenotypes of atypical Parkinsonian syndromes. The group Clinical Neurodegeneration is currently extending this effort by a comprehensive analysis of extensive clinical assessments and genetic data in individuals with atypical Parkinsonian syndromes.

Alzheimer's disease and tremor
So far, diagnosis of Alzheimer's disease is based on neuropsychological, CSF, MRI and (in specific centers) PET-findings. As MRI and PETis not possible in all individuals and not suitable as a screening instrument, the group Clinical Neurodegeneration set out to establish transcranial sonography (TCS) markers of the medial temporal lobe as a diagnostic and progression marker. Understanding of the etiology of essential tremor is limited, which is at least in part due to a great phenotypic variance of this most frequent disorder. 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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Dystonia

Acting Head:	Dr. Ebba Lohmann
Team:	5 members
Key words:	dystonia / torticollis / genetics / botulinum toxin

An artists depiction of a dystonic syndrom (above and below).

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, which is now run by Dr. E. Lohmann, who also brought a large number of patient samples from her previous position at the University of Istanbul in Turkey, where she was supported by a Margarete von Wrangell-stipend. Dr. Lohmann now continues her work with funding from the German Research Foundation (DFG). Detailed phenotyping and a thorough work-up of the families provide the basis for genetic analysis. Interestingly, phenotypes such as parkinsonism, spasticity and motor neuron diseases are often overlapping with genetic forms of dystonia.

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Clinical Neurogenetics

Head: Prof. Dr. Ludger Schöls
Team: 14 members
Key words: ataxias / spastic paraplegias / rare neurogenetic diseases / induced pluripotent stem cells / biomarker development / translational medicine / clinical trials

Immunocytochemical staining of iPSC-derived cortical neurons (in green: neuronal marker ß-III-tubulin; in red: cortical marker CTIP2; in blue: nucleus)

The Section of Clinical Neurogenetics is dedicated to translational research in neurogenetic diseases like cerebellar ataxias, hereditary spastic paraplegias, choeratic disorders and leukodystrophies. We aim to discover the genetic cause of the diseases using whole exome and genome sequencing to provide a definite diagnosis for our patients and open a window into pathogenesis and potential interventions in early stages of the disease process.
We see many patients with these rare diseases in our specialized outpatient clinics and include them into studies establishing measures for progression in the natural course of disease. Biosamples like DNA, RNA, serum, CSF and fibroblasts are used for the development of biomarkers indicating disease activity.
Clinical studies are matched by basic research generating induced pluripotent stem cells (iPSC) from skin biopsies of our patients. iPS cells are re-differentiated into neurons that constitute cell culture models that are genetically identical with our patients and represent the cell type that is affected most by the disease. This helps us studying very early consequences of the respective mutations and identifying new targets for therapeutic approaches. Finally, new compounds can be screened in these disease-specific neuronal cell models before they are tested in animal models and finally come to the clinic in interventional trials.

Die Sektion Klinische Neurogenetik widmet sich der translationalen Forschung bei neurogenetischen Erkrankungen wie zerebellären Ataxien, Hereditären Spastischen Spinalparalysen (HSP), Chorea-Erkrankungen und Leukodsytrophien. Mittels Exom- und Genomsequenzierung suchen wir die genetischen Ursachen dieser Erkrankungen, da so für unsere Patienten die molekulare Diagnose zu sichern und ein Fenster zur Erforschung der Pathophysiologie und Entwicklung kausaler Therapien zu öffnen ist.
Die Patienten werden in unseren Spezialambulanzen in Studien eingeschlossen, die Maße für die Progression dieser seltenen Erkrankungen entwickeln. Außerdem bitten wir unsere Patienten um Blut- und Gewebeproben wie DNA, RNA, Serum, Liquor und Hautbiopsien, die wir für die Entwicklung von Biomarkern nutzen, die die Erkrankungsaktivität anzeigen.
Die klinischen Studien werden im Labor durch Zellkulturmodelle der Erkrankungen komplementiert. Aus Hautbiopsien werden induzierte pluripotente Stammzellen (iPSC) reprogrammiert, die dann zu Neuronen differenziert werden, die genetisch identisch mit den Patienten sind und genau die Zellen repräsentieren, die von der Erkrankung betroffen sind. So können wir sehr frühe Schritte in der Krankheitsentstehung untersuchen und Ansatzpunkte für neue Therapien identifizieren. Substanzen mit positiven Effekten in neuronalen Zellkulturen, können dann in Therapiestudien für Patienten untersucht werden.

Ataxia

In preparation for interventional trials in spinocerebellar ataxias (SCA) we are part of the EU funded ESMI concsortium that is setting up a trial ready cohort for the most frequent genotype, SCA3. Here we coordinate the movement recording project that is supposed to provide an objective outcome measure for trials. In addition, we proved the high sensitivity of this motion capture system in individuals at risk to develop SCA, i. e. first degree relatives of a patient, and found signigicant alterations in movements in presymptomatic mutation carriers in tests with increasing motor complexity (Ilg et al. Mov Disord 2016). Early onset ataxias are a major challenge to physicians as they divide into numerous genetic subtypes, almost all of them being extremely rare.

The complex genetics of early onset ataxias leave most patients without a molecular diagnosis. To overcome this problem we established diagnostic whole exome sequencing to analyse all known ataxia genes in one single approach. Combining next-generation sequencing techniques and deep-phenotyping (clinics, magnetic resonance imaging, positron emission tomography, muscle histology), we established the frequency, phenotypic spectrum and genetic spectrum of SYNE1 in a screening of 434 index patients from seven centres across Europe. We identified 23 unrelated families with recessive truncating SYNE1 mutations (23/434 = 5.3%) and demonstratet that the majority of patients present exhibited complicating features like motor neuron affection in addition to ataxia (Synofzik et al. Brain 2016, Mademan et al. Brain 2016).

In families negative for mutations in all known ataxia genes we identified de novo mutations in the KCNA2 gene, encoding the voltage gated K1-channel, KV1.2, in two unrelated families with ataxia in combination with spasticity and intellectual disability (Syrbe et al. Nature Genet 2015; Helbig et al. 2016). This finding is of major relevance as this type of ataxia may be treatable by modifiers of the potassium channel. For the most frequent subtype of early onset ataxia, Friedreich's ataxia, we participate in the European EFACTS consortium and established the natural progression rate in a longitudinal prespective study that allows now to calculate the number of patients required for sufficiently powered interventional trials in the future (Reetz et al. Lancet Neurol 2016).

Hereditary spastic paraplegia (HSP)
HSP is characterized by mostly selective degeneration of the corticospinal tract leading to progressive spastic gait disorder. Although HSP is a rare disease with a prevalence of about 4-5 : 100,000, it splits up into more than 80 genetic subtypes. In Tübingen we gathered one of the world largest cohorts including more than 600 patients with HSP. In a recent cross-sectional study of this unique cohort we defined essential basic clinical and genetic characteristics of HSP. Quite unexpected, analyses of disease progression proved earlier age at onset to be associated with a more benign course of disease, e.g. early onset cases became walking aid or wheelchair dependent after significantly longer disease durations than late onset cases (Schüle et al. Ann Neurol 2016). Extensive genetic characterisation by targeted gene panel and whole exome sequencing approaches defined for the first time the frequency distribution of genotypes in an unselected and representative cohort (Schüle et al. Ann Neurol 2016).

In SPG5, we found oxysterols like 27-hydroxy-cholesterol (27-OHC) to be increased in plasma and CSF due to a metabolic block caused by mutations in the cytochrome P450 enzyme CYP7B1 (Theofilopoulos et al. JCI 2014). In iPSC-derived neurons we could show that 27-hydroxy-cholesterol at levels found in CSF of SPG5 patients hinders axonal outgrowth (Schöls et al. Brain 2017). Recently, we completed an investigator initiated, randomized controlled trial that aimed to establish a therapeutic approach that reduces 27-OHC. We proved that the lowering of cholesterol by atorvastatin also leads to a reduction in 27-OHC by about 30% in plasma of every single patient in the verum groups but in none of the placebo group (Schöls et al. Brain 2017).

Trilateral project in Arab societies
IThe DFG funds a collaboration of Israeli and Palestinian are working together and German groups coordinated by the HIH that aims to discoer new genetic diseases in consanguineous families of the Arab population. More than 100 families have been identified in Israel and the West Jordan land and underwent homozygosity mapping and whole exome sequencing that allowed for the identification of the molecular cause of the disease in an increasing number of families including the identification of new genes (Hengel et al. Neurol Genet 2017; Mallaret et al. Brain 2015; Minnerop et al. Brain 2017).

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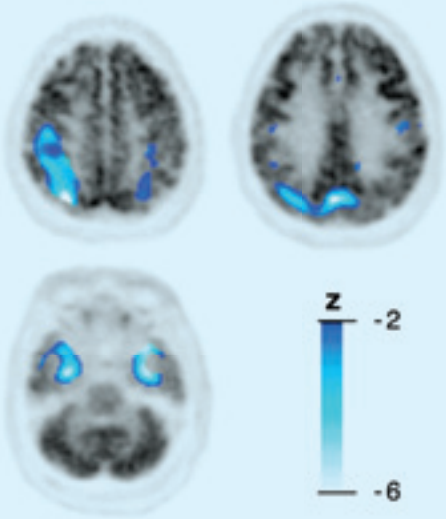
Systems Neurodegeneration

Head: PD Dr. Matthis Synofzik
Team: 7 members
Key words: rare neurogenetic diseases / ataxias/ frontotemporal dementias / early-onset dementias / Amyotrophic Lateral Sclerosis / next-generation sequencing / neurorehabilitation



FDG-PET bei einem Patienten mit frontotemporaler Demenz bei C9orf72-Repeatexpansion.

Our research focuses on the investigation of the genetic basis, systems neuroscience and paradigmatic therapy approaches in

- **movement disorders (e.g. degenerative ataxias, in particular early-onset ataxias, neurometabolic diseases, and rare complex movement disorders)**
- **frontotemporal dementias and other complex dementias (e.g. early-onset dementias, rare variants of Alzheimer's disease, genetic dementias)**
- **motor neuron diseases (Amyotrophic Lateral Sclerosis, in particular genetic variants; ALS-FTD spectrum diseases, lysosomal motor neuron diseases)**

We use a broad spectrum of very different methods, reaching from recent molecular genetics techniques (e.g. whole exome and target sequencing panel analyses) and protein biomarker profiling to deep clinical phenotyping, neuropsychology and pioneering neurorehabilitative approaches.

Unsere Forschungsgruppe ist spezialisiert auf die Erforschung genetischer Grundlagen, system-neurologischer Charakteristika und paradigmatischer Therapieansätze bei

- *Bewegungsstörungen (v.a. degenerative Ataxien, insbesondere frühbeginnende Ataxien; neurometabolische Erkrankungen; komplexe seltene Bewegungsstörungen)*
- *frontotemporale Demenzen und andere komplexe Demenzen (u.a. frühbeginnende Demenzen, seltene Varianten der Alzheimer-Demenz, genetische Demenz-Formen)*
- *Motorneuronerkrankungen (Amyotrophe Lateralsklerose, v.a. hereditäre Formen; ALS-FTD-Spektrum-Erkrankungen; lysosomale Motorneuronerkrankungen).*

Wir verwenden dabei ein breites Spektrum unterschiedlicher methodischer Ansätze. Diese reichen von neuen molekulargenetischen Techniken (z.B. whole exome oder Panel-Analysen) und Protein-Biomarker Profilen bis zu tiefer klinischer Phänotypisierung, Neuropsychologie und Pionier-Ansätzen für neurorehabilitative Therapien.

Early-onset ataxias and other rare movement disorders

Elaborating on the prospective longitudinal international multicenter Early-Onset Ataxia registry (EOA) established by us in 2012, we were able to establish a large national and international network on early-onset ataxias. Our registry and our work in next-generation genetics was the basis for a successful EU Erare JTC grant application „PREPARE" in 2015. This novel EU consortium, coordinated and led by Dr. Synofzik, prepares targeted treatment trials for rare autosomal-recessive ataxias. A substantial part of our early-onset ataxia research in 2017 focussed on investigating the clinical, genetic and biochemical properties of novel or still underdiagnosed recessive ataxia genes. Often jointly with the HIH groups of Prof. Ludger Schöls and Dr. Rebecca Schüle, we helped to expand and delineate the phenotypic spectrum of STUB1 [1], SERAC1 [2}, POLR3A [3], PLA2G6 [4],ATP13A2 [5], and KCNA2 .Our large web-based cohort of ataxia exome data-sets, which has been continously increased throughout 2017, allowed us to identify SERAC1 mutations as a novel cause of complicated hereditary spastic paraplegia [6]. A novel diagnostic algorithm will help clinicians and neurogeneticists worldwide to identify the underlying genetic cause in so far unexplained autosomal-recessive ataxias [7] .

Frontotemporal dementias and other complex dementias

In cooperation with Prof. Peter Heutink (HIH/DZNE Tübingen) we established a cohort of >180 whole exome data-sets from subjects with FTD or with other early-onset dementias. This comprehensive cohort allowed us to run an in-depth analysis on the genes that underlie frontotemporal dementia (FTD) and their respective frequencies, demonstrating that FTD is a converging downstream result of multiple different molecular pathways [8]. Moreover, it allowed us to delineate the phenotypic and mutational spectrum of FTD genes like TBK1 [9, 10]. Our contributions to the global GENFI consortium" will help to

Hypothetisches Modell zum Erkrankungsverlauf spinocerebellärer Ataxien vor dem klinischen Beginn.
Auf dem Weg zur Früherkennung und für frühstmögliche Interventionsoptionen untersucht unsere Forschungsgruppe die Veränderungen in motorischen Parametern und Gehirnstrukturen bei spinocerebellären Ataxien noch vor ihrem klinischen Beginn.

systematically aggregate longitudinal clinical, imaging and biomaterial data c from presymptomatic and symptomatic subjects from families with hereditary FTD to prepare future trials for genetic FTD. Such trials will be facilitated by the identification of possible fluid biomarkers for FTD, like neurofilament light chain (NfL) or progranulin, as described by us [11-13].

Preparing treatments for neurodegenerative disease and first neurorehabiltative trials

In close collaboration with Dr. Adam Vogel (Hertie-Institute for Clinical Brain Research and University of Melbourne, Australia), we functionally characterized dysarthria and dysphagia deficits in hereditary ataxias, which will allow to prepare trials for drug and neurorehabilitative treatment interventions targeting these dysfunctions highly detrimental in daily living. In parallel, we demonstrated that gait analysis might serve as an outcome marker even at the presymptomatic stage of hereditary ataxia [14], opening up a window for treatment even before the clinical manifestation of the disease has started. As a first use case for a treatment intervention in degenerative ataxias, we utilized videogame-based coordination traing (exergame training). Our intra-individually controlled, rater-blinded trial demonstrated that such exergame training is effective even in subjects in an advanced, multisystemic disease state [15].

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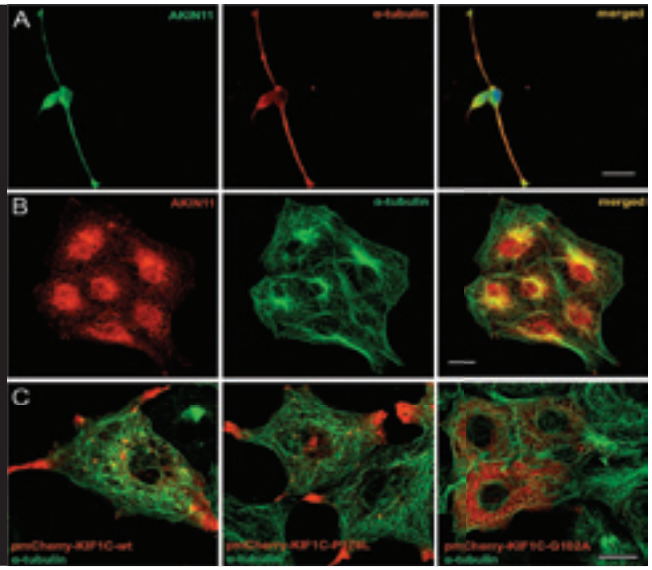
Genomics of Rare Movement Disorders

Head: PD Dr. Rebecca Schüle
Team: 13 members
Key words: whole exome sequencing / whole genome sequencing / rare diseases / spastic paraplegia / ataxia / induced pluripotent stem cells / CRISPR / CAs9 / translational medicine / clinical trials



Rare disease by definition affect not more than 5 in 10.000 people and yet, about 6–8 % of the population are affected by on of ~6.000 rare disease recognized by the European Union. Our team systematically adresses challenges specific to rare diseases, including definition of standard of care, validation of trial outcome parameters, performance of natural history studies, identification of novel disease genes and new therapeutic targets, disease modeling in cell culture and iPS-derived human model systems, preclinical and clinical trials. Supported by the European Union, the National Institutes of Health (NIH), the Spastic Paraplegia Foundation Inc. and others we team up with collaborators all over the world to promote trial readiness in rare diseases.

Seltene Erkrankungen betreffen definitionsgemäß nicht mehr als 5 in 10.000 Personen und doch sind ca. 6–8 % der Bevölkerung in der Europäischen Union von einer der rund 6.000 seltenen Erkrankungen betroffen. Unsere Forschungsgruppe stellt sich systematisch den Herausvorderungen, die einer Therapieentwicklung für seltene Erkrankungen im Wege stehen: Definition von Therapiestandards, Validierung von Zielparametern für klinische Studien, Studien des natürlichen Verlaufes, Identifizierung neuer Erkrankungsgene und Ansatzpunkte für Therapien, Erkrankungsmodellierung in Zellkultur und humanen Stammzellmodellen, sowie die Durchführung präklinischer und klinischer Studien. Gefördert durch die Europäische Union, die amerikanischen 'National Institutes of Health' (NIH), die Spastic Paraplegia Foundation Inc. und andere kooperieren wir hierbei mit Forschungsgruppen aus der ganzen Welt, um 'Trial Readiness' für seltene Erkrankungen zu fördern.

Hereditary spastic paraplegias (HSP) and ataxias are rare neurodegenerative disorders primarily affecting the corticospinal tract motoneurons and/or cerebellar Purkinje cells. Initially defined as independent disease groups the clinical and genetic overlap between HSPs and ataxias is increasingly recognized. With over 150 known disease genes causing the conditions known, they are one of the genetically most heterogeneous groups of Mendelian diseases.

Mutations in known genes still explain only about half of the cases. To identify novel disease genes and ultimately novel therapeutic targets we have performed whole exome and whole genome sequencing in > 400 families with HSP, spastic ataxia and ataxia and led and participated in the identification of > 15 novel genes for these conditions. Among the hiighlights of the work were the identification of deep-intronic mutations in POLR3A which are a frequent cause of spastic ataxia. This genomic work is funded by the NIH in an RO1 grant awarded to Rebecca Schüle and her collaborator Stephan Zuchner from the University of Miami, Florida.

HSP type SPG5 is caused by mutations in the 7α-hydroxylase CYP7B1, an enzyme involved in degradation of cholesterol to primary bile acids. We have demonstrated that CYP7B1

Subcellular localization of endogeneous and overexpressed KIF1C.

A. Endogenous KIF1C: In the mouse motor-neuron like spinal chord cell line NSC-34, endogenous KIF1C is found throughout the cell body with an accumulation in the pericentrosome, along the neurites, and strong accumulation at the neurite tips. In fibroblast-like COS-7 cells, endogenous KIF1C is sparsely distributed throughout the cell and accumulates perinuclear in a reticular pattern. In COS-7 cells displaying cellular processes, accumulation at the tips of these processes can be seen (not shown).

B. Overexpressed, mCherry-tagged KIF1C accumulates at the tips of cellular processes in the COS-7 monkey fibroblast cell line (left). The same localization pattern can be observed for mCherry-tagged KIF1CPro176Leu (middle). In contrast, mCherry-tagged KIF1CGly102Ala (right) fails to reach cellular processes and instead is observed in a reticular pattern around the nucleus.

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deficiency leads to marked accumulation of oxysterols in serum and CSF of SPG5 patients. Levels of oxysterols found in patients impair metabolic activity and are toxic towards human cortical neurons derived from induced pluripotent stem cells. This led us to the hypothesis that oxysterol elevation may not only be an epiphenomenon but the driver of pathology in SPG5. In a randomized controlled clinical trial (STOP-SPG5), the first of it's kind ever performed in HSPs, we were able to demonstrate a reduction of of oxysterols in serum of patients by >30% after just 9 weeks of atorvastatin treatment.

To promote trial readiness in HSP we have initiated and coordinate a global network of major national HSP initiatives, the Alliance for Treatment in HSP and PLS. The network that is funded by the Spastic Paraplegia Foundation Inc. includes national HSP networks from Canada, the US, France, Belgium and other countries. The Alliance will institute a global HSP registry and perform systematic studies to identify new biomarkers and other potential trial outcome parameters in HSP. The first studies systematically evaluating biomarkers of axonal degeneration in HSP have started in late 2017.

The Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium is an NIH funded network led by Michael Benatar at the University of Miami, Florida. The goals of CReATe are to promote therapeutic development for neurodegenerative disorders through study of genotype-phenotype correlation and discovery and development of biomarkers. Diseases in the focus of CReATe include amyostrophic lateral sclerosis, frontotemporal dementia, primary lateral sclerosis, hereditary spastic paraplegia and progressive muscular atrophy. With the PI Dr. R. Schüle the University of Tübingen is the only European partner in this otherwise U.S. American consortium.

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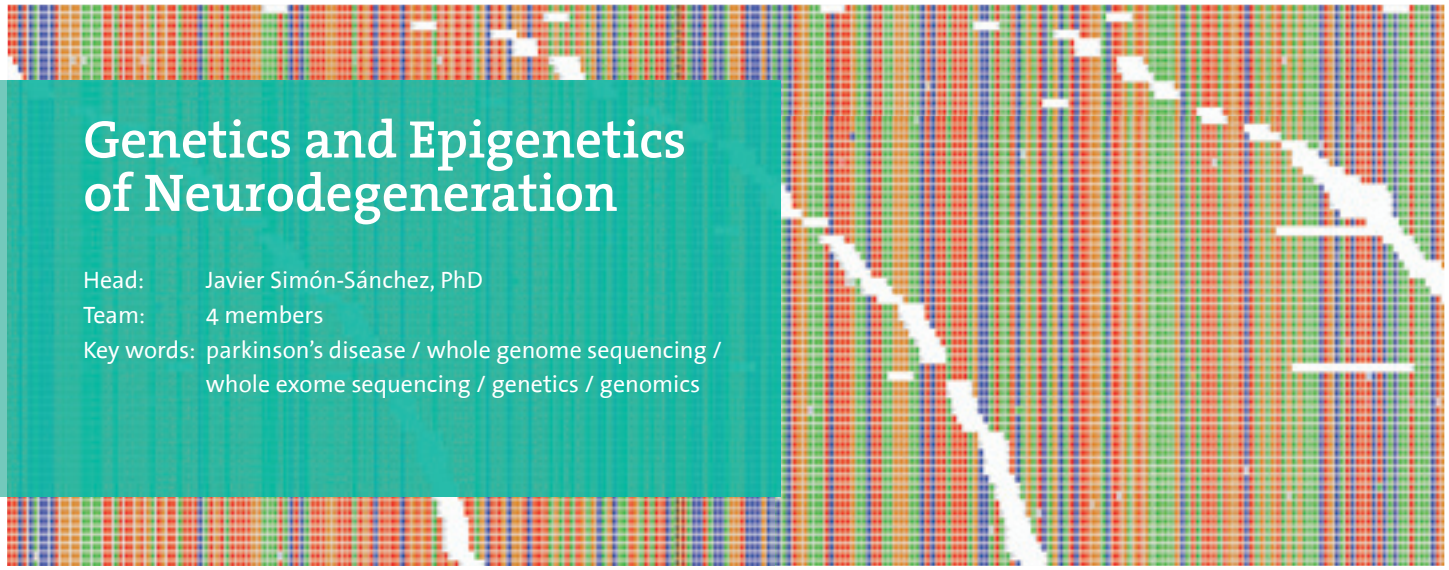
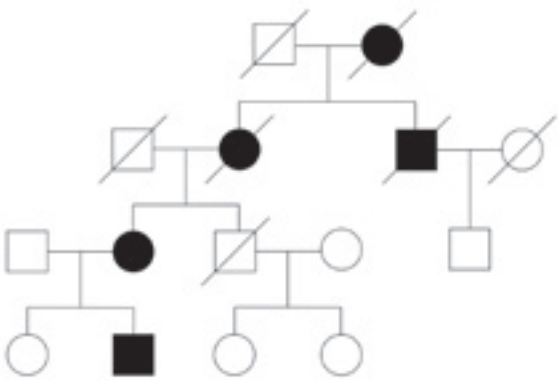


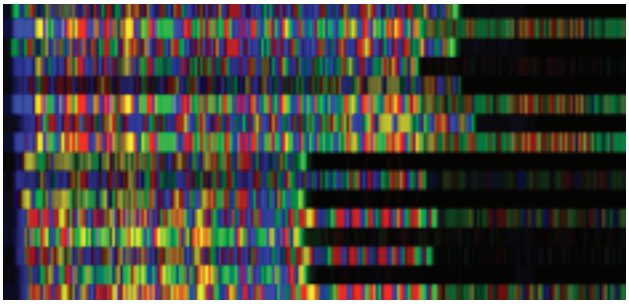
Genetics and Epigenetics of Neurodegeneration

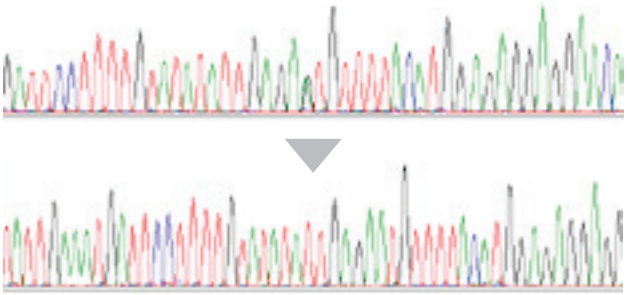
Head: Javier Simón-Sánchez, PhD
Team: 4 members
Key words: parkinson's disease / whole genome sequencing / whole exome sequencing / genetics / genomics

The group of "Genetics and Epigenetics of Neurodegeneration" has been jointly established at the Department of Neurodegenerative Diseases within the Hertie Institute for Clinical Brain Research (HIH) and the German Center for Neurodegenerative Diseases (DZNE). The research focus of our group is to further understand the genomic and transcriptomic basis of neurodegeneration, with special focus on Parkinson's disease (PD) and Frontotemporal dementias (FTD). Thus, one of our main lines of research aims to dissect the complex genetic architecture of PD in ethnically diverse populations. For this purpose, we have used a comprehensive unbiased method based on different next generation sequencing (NGS) strategies, to generate a list of rare genetic variants potentially associated to the risk of PD. Hence, whole genome sequencing (WGS) was used to identify rare variants co-segregating with PD in multiplex families from different populations, while resequencing of candidate risk loci in a large cohort of sporadic PD cases and controls was used to identify potential risk variants within these loci. These variants are currently being replicated in a vast cohort of 12,000 PD cases and 10,000 controls from different European, Asian, and African population. For this purpose, we are using NeuroChip array, which we have developed in collaboration with Illumina Inc., and contains all the variants derived from the mentioned experiments, as well as variants resulting from NGS experiments on different neurodegenerative disorders from the research community. Results derived from these experiments will be available on October 2017 and will help us understanding the genetic etiology of PD in different populations.

As mentioned above, our group is also interested in the patho-mechanisms underlying FTD. In this regard, we want to understand why mutations in MAPT, GRN and c9orf72, all lead to a very similar clinical phenotype but quite distinct neuropathology. To reach this goal, genome-wide RNA expression of coding and non-coding transcripts (CAGE-seq and RNAseq) complemented by methylation profiling with Infinium MethylationEPIC technology, has been performed on post-mortem brain material from patients with mutations in the mentioned genes, as well as neuropathologically confirmed controls. As human post-mortem tissue presents only an endpoint of disease, we have also performed profiling of matching samples from a longitudinal series of induced pluripotent stem cells (iPS) using different time points in their differentiation to cortical neurons. Integrated bioinformatics analysis of these data has allowed us to construct gene expression networks based on genetic subtypes of FTD. The biological significance of these networks will be validated in cellular and animal models in a targeted fashion and will pinpoint potential patho-mechanisms that are specific to a single FTD-subtype or common to all forms. The results will be utilized to improve theoretical disease models and improve the quality of our predictions needed to design targeted intervention strategies.







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Functional Characterization of LRRK2

Head: Dr. Dr. Saskia Biskup
Team: 2 members
Key words: parkinson's syndrome / next generation sequencing

LRRK2 is described as a risk factor for the development of Parkinson's syndrome if genetically modified. Knowledge of the cause of a disease can be the first step towards understanding the disease but also a goal-oriented therapy approach. It is often a long way from diagnosis to therapy. With the use of new methods, we try to better understand the cause of the disease as well as to identify new therapeutic approaches.

LRRK2 ist als Risikofaktor für die Entstehung von Parkinson Syndrom beschrieben wenn es genetisch verändert ist. Das Wissen um die Ursache einer Erkrankung kann der erste Schritt in Richtung Verständnis der Erkrankung aber auch zielgerichtete Therapieansätze sein. Es ist oft ein weiter Weg von Diagnosesicherung zur Therapie. Mit dem Einsatz neuer Methoden versuchen wir sowohl die Ursache der Erkrankung besser zu verstehen als auch neue therapeutische Ansätze aufzuzeigen.

Several different loci in the genome are described for being associated with familial forms of Parkinson syndrome. Finding the underlying cause of the disease has been a tremendous step forward towards understanding the pathomechanism of the disease. There is hope that at some point this understanding will guide us to novel therapeutic approaches in a so far incurable neurodegenerative disease.

The PARK8 locus was initially described in a large Japanese kindred in 2002. Soon after, the locus on chromosome 12 was confirmed in 2 large and 8 smaller additional kindreds by Zimprich, Gasser et al. In a common world spanning effort that was initiated many years ago it was possible to identify the causative gene in 2004 (Biskup, Gasser et al.). The protein LRRK2 consists of 2527 amino acids translated from 51 exons and is expressed in all regions of the brain relevant to Parkinson syndrome. The function of wildtype and mutated LRRK2 in human cells is far from being understood but there is increasing evidence that LRRK2 protein which is highly expressed in immune cells might have a disease relevant function in these cells in addition to its relevance in neuronal cells.

Inhibition of LRRK2 kinase activity is discussed and tested as novel treatment approach. This treatment may lead to "loss-of" LRRK2 function. Our group focusses to investigate possible consequences of LRRK2 inhibition. Our preliminary data indicates that "loss-of" LRRK2 function may lead to an increased risk for cancer development. We aim to improve the understanding of the biological role of LRRK2 with respect to tumorigenesis. Furthermore we have evidence that LRRK2 is involved in the regulation of the insulin signaling pathway. This might have implications for treatment of a subsets of patients with Parkinson syndrome. The Michael J Fox Foundation has been crucial in founding our research.

In 2009 CeGaT GmbH in Tübingen was co-founded by Saskia Biskup with the aim to implement next generation sequencing in a diagnostic setting. LRRK2 was one of the reasons to drive the interest in such a company. With 51 exons it could not be efficiently sequenced in large cohorts of patients and controls by Sanger sequencing. Today CeGaT and subsidiaries have more than 150 employees. There is still a great interest in research leading to discovery and publications of genes associated with diseases.

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Deep Brain Stimulation

Head: PD Dr. Daniel Weiß
Team: 9 members
Key words: deep brain stimulation / gait / freezing

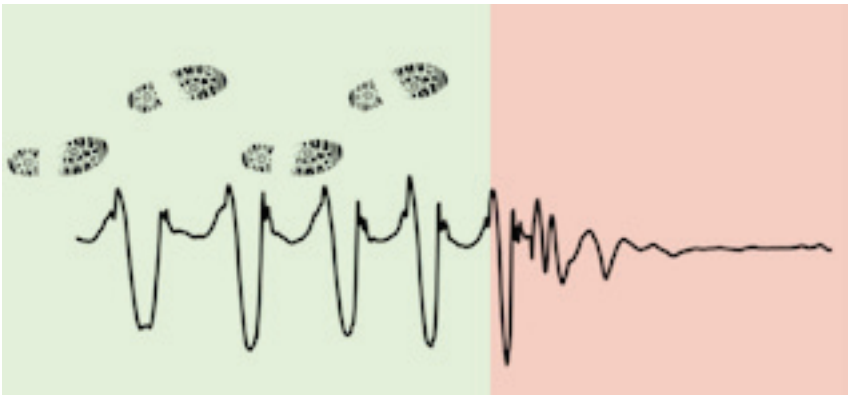
The research group for deep brain stimulation (DBS) strives for refining and expanding neurostimulation therapy for movement disorders therapy by interfering with functional large-scale neuro-circuitries. We give particular emphasis to modulate otherwise resistant axial symptoms of Parkinson's disease (PD) – namely gait, freezing of gait, falls, and dysphagia. Moreover, we perform electrophysiological and kinematic studies to characterize the network correlates of gait impairment in Parkinson's disease.

Die Forschungsgruppe für Tiefe Hirnstimulation setzt es sich zum Ziel die Tiefe Hirnstimulation zu verbessern und für schwer behandelbare Symptome bei der Parkinson-Krankheit verfügbar zu machen. Besonderes Augenmerk liegt hier auf der Therapie axialer Symptome: Gangstörungen incl. Gang-Freezing, Stürze und Schluckstörungen. Zudem werden elektrophysiologische und kinematische Studien an mobilen Parkinsonpatienten durchgeführt, um die pathophysiologischen neuromuskulären Netzwerkkorrelate von Gangstörungen bei der Parkinsonkrankheit zu charakterisieren.

Clinical studies: making DBS available for resistant axial symptoms

Axial symptoms like freezing of gait, falls, and dysphagia characterize the late stage of PD. These symptoms heavily interfere with quality of life, and cause substantial caregiver dependence, morbidity and mortality. Standard DBS regimens and dopaminergic therapy often fall short to control these symptoms, underscoring the need for improved stimulation strategies. The main concept in recent years was to modulate the nigro-pontine circuitry that is deregulated as a consequence of both dopaminergic depletion and brainstem neurodegeneration.

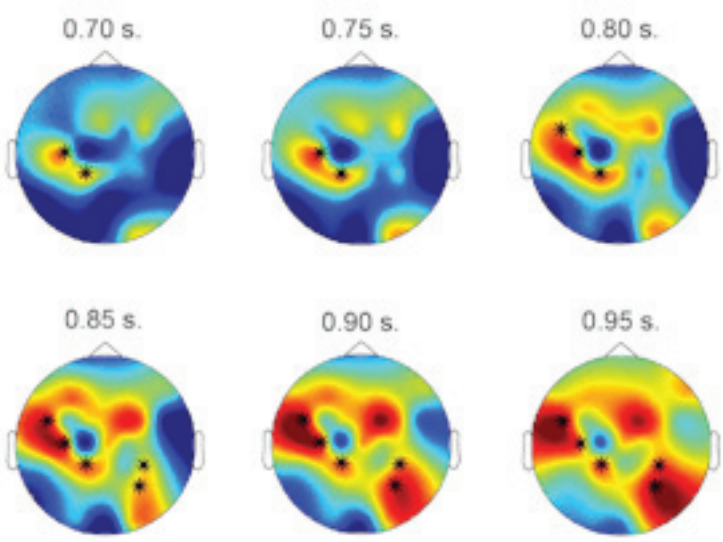
In this framework, we take advantage to co-stimulate the substantia nigra pars reticulata in addition to the subthalamic nucleus as distal electrode tip of a subthalamic lead. First clinical observations were made between 2009 – 2011 [1], and further substantiated by a monocenter randomized controlled trial. This trial pointed to an additional effect of nigral co-stimulation to attenuate otherwise resistant freezing of gait [2]. The Tübingen working group for 'deep brain stimulation' is coordinating a randomized controlled multicentre trial across Germany and Luxembourg (ClinTrials.gov: NCT02588144). Moreover, a monocenter trial was recently approved and supported by the Michael J Fox Foundation in order to study the effect of nigral stimulation with respect to resistant dysphagia in PD. This approach is plausible from pathophysiological reasoning, i.e. nigral overactivity may lead to defective neuronal integration of PD swallowing and oral transport in the substantia nigra pars reticulata –superior colliculus circuit. The ongoing clinical trials have potential to inform future personalized both DBS implantation and re-programming strategies in PD patients.



De-mystifying the pathophysiology of freezing phenomena

Freezing phenomena in Parkinson's disease were paraphrased as 'enigmatic phenomena'. Most obviously, this reflects the profound lack of pathophysiological understanding about the underlying brain and circuit mechanisms.

Technological advancement enabled only in recent years to obtain mobile recordings from PD patients during real gait experiments and characterization of defective neuromuscular gait integration on high both temporal and spatial resolution. We conduct fully synchronized and mobile recordings with motion kinematics, EEG, EMG, and videotaping in freely moving PD patients (supported by the German Research Foundation). With combined electrophysiological and kinematic data, we are able to decipher both brain activation and neuromuscular coupling with respect to single steps and to capture the pathophysiological processes in freezing phenomena in comparison to healthy subjects [3-5]. Even more important, we are increasingly able to characterize the transition periods between regular gait and freezing in PD patients. This is of utmost importance to develop freezing forecasts, i.e. to predict the disruption of locomotion several seconds before the network disturbance becomes clinically apparent in terms of freezing of gait.



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Department of Cognitive Neurology

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

Departmental Structure

The Department of Cognitive Neurology 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 and Prof. Hans-Peter Thier was appointed head of the department. In the year 2002, in which the Neurology Clinic was reorganized, the Department of Cognitive Neurology 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 for Neuropsychology associated with a professorship for neuropsychology both taken over by Prof. Hans-Otto Karnath.

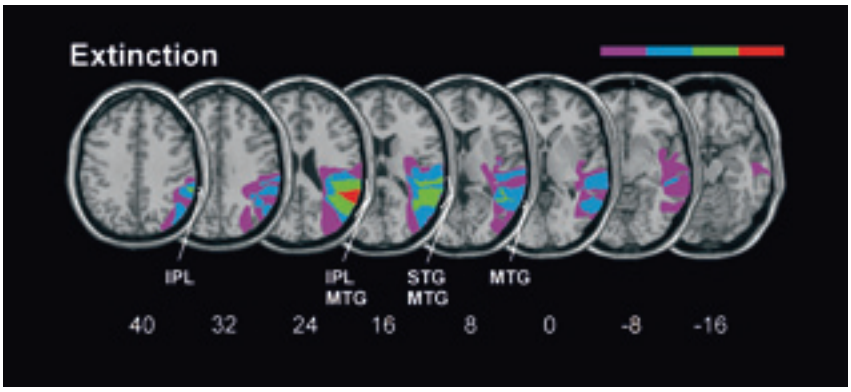
In summer 2008 the Section for Computational Sensomotorics, headed by the newly appointed Prof. Martin Giese and funded conjointly by the Hertie Foundation and the German Research Council within the framework of the Excellence Cluster "Centre for Integrative Neuroscience" (CIN), was installed at the department. In 2009 Cornelius Schwarz was appointed professor and head of the research group on Systems Neurophysiology within the CIN. This group was integrated into the Department of Cognitive Neurology. In autumn 2016 Dr. Daniel Häufle joined the department and established a research lab on 'Multi-Level Modeling in Motor Control and Rehabilitation Robotics', funded by the State of Baden-Wuerttemberg within the framework of the Regional Research Alliance, System Human Being'. In 2017 the Active Perception Lab of Dr. Ziad Hafed, who accepted one of the CIN's tenure track professorships (appointment pending), reinforced the research teams of the department.

The department currently comprises seven independent labs, namely, the Sections for Neuropsychology (Hans-Otto Karnath) and Computational Sensomotorics (Martin Giese) respectively, the Systems Neurophysiology Lab (Cornelius Schwarz), the Neuropsychology of Action Control Lab (Marc Himmelbach), originally set up with funds from a 2007 ERC starting grant, the Sensorimotor Lab, headed by Hans-Peter Thier, who also serves as the chairman of the department, the Motor Control Modeling Lab of Daniel Häufle and the Oculomotor Lab of Uwe Ilg. The latter is also head of the Neuroscience Lab for High School Students at the Werner Reichardt Centre for Integrative Neuroscience (CIN). Two independent young investigator groups, namely the Neurobiology of Decision Making Lab headed by Axel Lindner and the Neuropsychology of Attention group headed by Bianca de Haan form also part of the department. The Lindner group as well as the Hafed lab operate under the roof of the Sensorimotor Lab, while the de Haan group forms part of the Section of Neuropsychology.

The Department of Cognitive Neurology is devoted to research on the underpinnings of higher brain functions and their disturbances due to disease of the nervous system. The spectrum of research topics is wide – which is a consequence of the existence of quite a few independent research groups with individual interests. The topics addressed comprise among others the basis and disturbances of spatial processing and orientation including the mechanisms of perceptual stability with respect to ego-motion, of attention, of motor learning and motor rehabilitation, as well as of social interactions. To this end, the Department of Cognitive Neurology 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, 'motion capturing' and virtual reality. Transcranial magnetic stimulation is used to simulate virtual lesions in the healthy brain. 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 recordings 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. Recently, with the help of the CIN, 2P-imaging of cortical circuits has been added. Experiments using genetically modified non-human primates as a model system for autism are currently being established. 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. The tools for theoretical approaches and modeling offered by the Giese group are used to integrate the obtained data and to generate experimentally testable predictions. The variety of methods responds to the need to examine complex brain functions and their disturbances due to disease at various levels and from various perspectives. Starting point is always a clinical problem as for example a better understanding of the pathophysiology of cerebellar ataxia, an indispensable gateway for any attempt to alleviate or mitigate this condition. These questions can be answered only if the normal operation of the structure, compromised by brain disease is understood. We believe that any promising attempt to understand complex cognitive or motor disturbances like neglect, ataxia or autism will require a better understanding of the normal functional architecture of the underlying healthy systems.

In past and present, the Department of Cognitive Neurology has played a central role in the development and coordination of various research networks. For instance, the DFG-funded Collaborative Research Center (SFB) 550, that ended in 2009, as well as a preceding research unit have been coordinated by Hans-Peter Thier. Many members of the department are also part of the excellence cluster 'Werner Reichardt Centre for Integrative Neuroscience (CIN)', currently involving more than 80 principle investigators associated with three faculties of the University of Tübingen and several non-university research institutions in Tübingen and its vicinity, which is likewise coordinated by Hans-Peter Thier. The DFG-funded trans-regional research unit FOR 1847 'Primate Systems Neuroscience', which brings together research groups from Göttingen, Marburg, Frankfurt and Tübingen working with non-human primates, is conjointly coordinated by Hans-Peter Thier and Prof. Stefan Treue, German Primate Centre Göttingen, the latter actually a former member of the department. The research unit took up work in March 2014 and is currently in its second funding period.



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

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

Martin Giese, Axel Lindner, Cornelius Schwarz, and Hans-Peter Thier are members of the Tübingen Bernstein Centre for Computational Neuroscience that was supported with funding from the BMBF from 2010 to 2015. Daniel Häufle is member of the Research Alliance 'System Human Being', funded by the State of Baden-Wuerttemberg and representing research groups from different faculties of the Universities of Tübingen and Stuttgart respectively. It is also worth mentioning that Martin Giese has been one of only three neuroscientists from Tübingen who was a member of the EC funded Human Brain Project.

Sensorimotor Laboratory

Groups P. Thier, Z. Hafed, A. Lindner, J. Pomper

Head: Prof. Dr. Peter Thier
Team: 32 members
Key words: mirror neurons / attention / autism / social cognition / motor learning / fatigue / ataxia / (control of) eye movements / visual perception

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

The lab works on the underpinnings of social interactions and the mechanisms underlying motor learning and their disturbances due to disease. Furthermore, we are interested in the investigation of the neural mechanisms through which visual perception interacts with motor control.

Das Labor befasst sich mit den neuronalen Grundlagen sozialer Interaktionen und denen motorischen Lernens sowie deren krankheitsbedingter Störungen. Ein weiterer Schwerpunkt ist die Untersuchung der neuralen Mechanismen, die der Interaktion zwischen visueller Wahrnehmung und Bewegungskontrolle zugrundeliegen.

One of the key interests of the sensorimotor laboratory are 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, 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. It hypothesizes that malfunction of the brain structures involved 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 and response selection. 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. In an attempt to better understand the complex features of mirror neurons, to put the so-called simulation theory to a critical test and to assess alternative concepts such as a role of the mirror neuron system in response selection, the lab is carrying out experiments on premotor cortical area F5. In a nutshell, our past work has shown that this particular area has access to streams of information which are obviously very important for the evaluation of the 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 or that observation-related responses of mirror neurons are to some extent viewpoint invariant.

A second major interest of the sensorimotor laboratory pertains to the role of the cerebellum in motor control. Using short-term saccadic adaptation, but also smooth pursuit eye movements and goal-directed hand movements as models of motor learning, the sensorimotor lab has been able to develop a detailed concept of the neuronal underpinnings of cerebellum-based learning. 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,

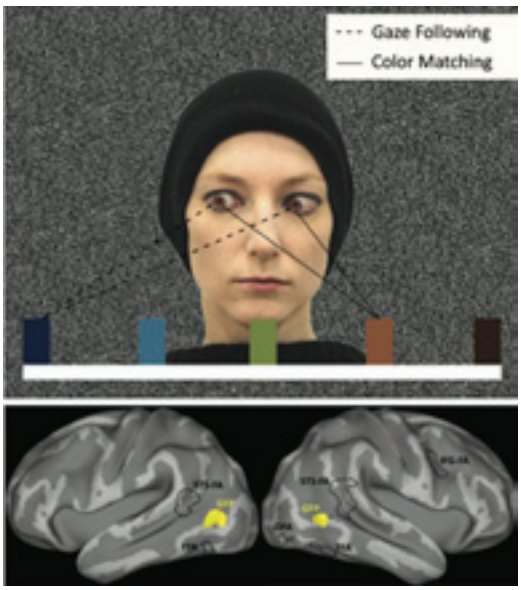


Illustration of the paradigm needed to activate brain structures underlying gaze following as compared to spatial shifts of attention guided by non-gaze cues (here: iris color). The eyes of the person are directed to the dark-blue target (gaze cue), but the person's iris color corresponds to the light-brown target (color cue). According to the introduced condition at the beginning of the block, the subject would have to make a saccade toward the dark-blue target (gaze-following condition) or toward the light-brown target (color-matching condition). The demonstrator has agreed for her portrait to be published. Lower part: Spatial organization of face-selective areas and the gaze-following patch. Note that the gaze-following patch does not overlap with any of the face patches.

reduced velocity and increased variance is an inevitable consequence of the motor system's inability to compensate fatigue. We have 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.

Yet another focus lies on the investigation of the neural mechanisms through which visual perception interacts with motor control (Hafed group). High-resolution vision in humans is only limited to a small area of the visual field. Despite this fact, humans have the perception of a vivid, clear scene *throughout* the visual field, and this is due to the fact that humans are active observers. The visual brain is perpetually faced with first, a need to move the eyes in order to align the high-resolution portion of the retina with objects of interest, and second, a need for spurious visual signals caused by eye movements to escape perception in order for us to experience a stable and clear vision of our environment. Our research addresses both of these challenges to visual perception using a multi-disciplinary approach involving human perceptual experiments, invasive neurophysiology in non-human primates, and theoretical modeling. Finally, our work investigates action and perception taking into account ecological constraints on brain function. Ultimately, our brain operates in a natural environment, and therefore is expected to be optimized to the statistics of this environment. Such intuition implies both anatomical and functional specializations in the eye movement system in order to best serve perception in the natural environment, which we are systematically uncovering.

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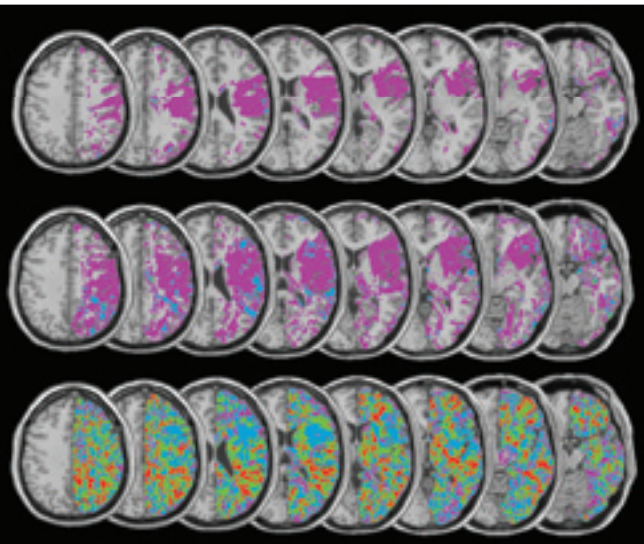
Neuropsychology

Head: Prof. Dr. Dr. Hans-Otto Karnath
Team: 23 members (including Neuropsychology of Action group)
Key words: cognitive neuroscience / neuropsychology



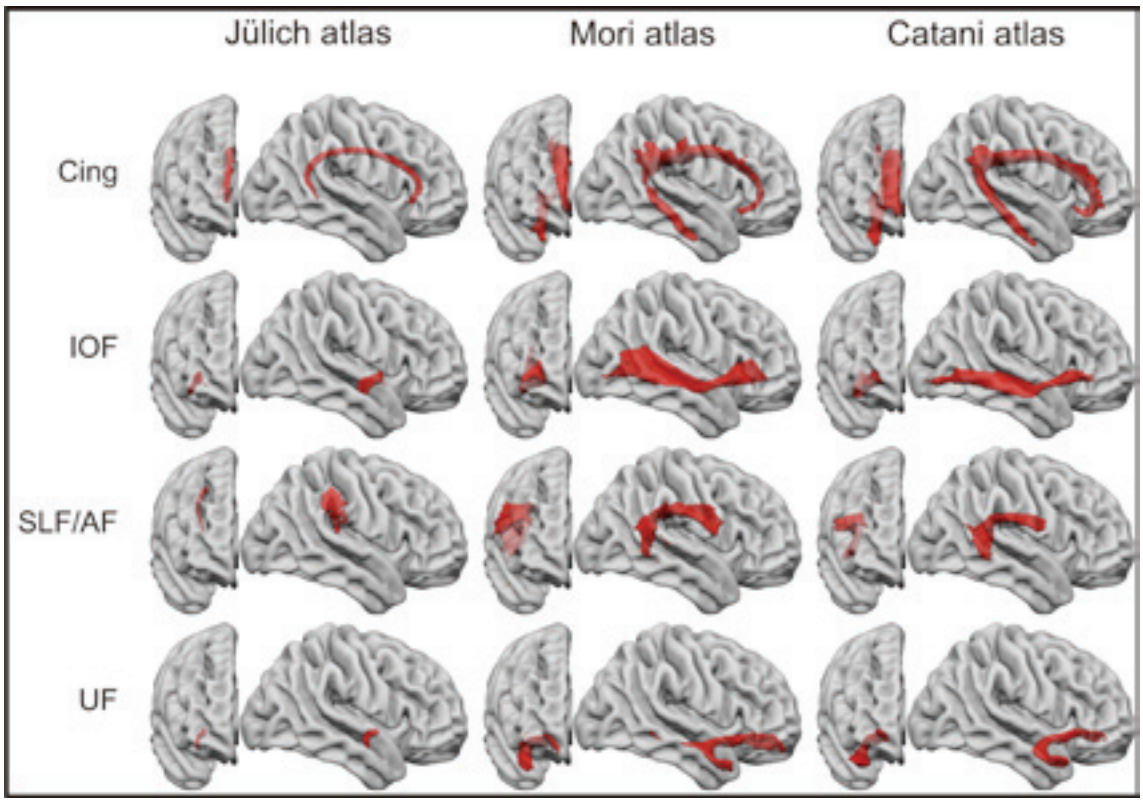
Evaluation of methods for detecting perfusion abnormalities after stroke in dysfunctional brain regions.

The Section 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 Section 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 Section of Neuropsychology's research is "how do organisms perform sensorimotor coordination processes?" For example, in order to generate successful motor actions (e. g. pointing or grasping movements) we must actively deal with the problem of spatial exploration and orientation. In order to do this it is necessary to process a multitude of sensorimotor information that is derived from constantly changing coordination systems. 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.



Nowadays, different anatomical atlases exist for the anatomical interpretation of the results from neuroimaging and lesion analysis studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys) function. A major problem with the use of different atlases in different studies, however, is that the anatomical interpretation of neuroimaging and lesion analysis results might vary as a function of the atlas used. We used a single large-sample dataset of right brain damaged stroke patients with and without cognitive deficit to systematically compare the influence of three different, widely-used white matter fiber tract atlases. Results suggest that studies that use tractography-based atlases are more likely to conclude that white matter integrity is critical for a cognitive (dys)function than studies that use a histology-based atlas. (de Haan B, Karnath H-O [2017]. 'Whose atlas I use, his song I sing?' – The impact of anatomical atlases on fiber tract contributions to cognitive deficits. NeuroImage 163: 301–309.)

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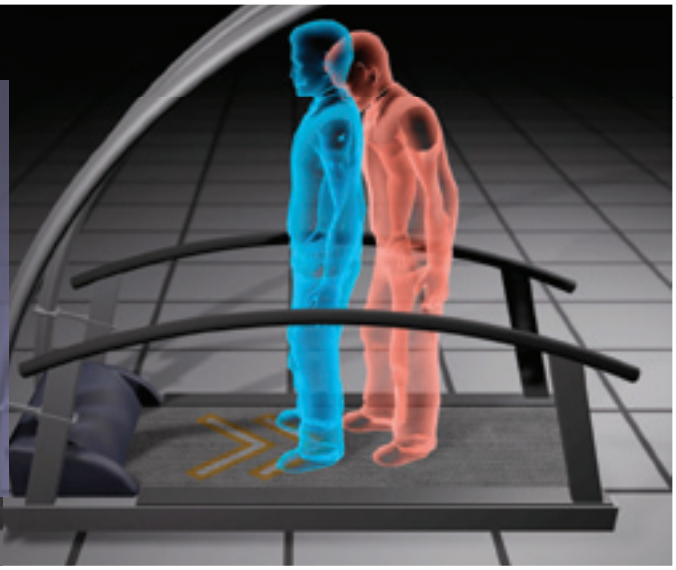
Computational Sensomotorics



Head: Prof. Dr. Martin Giese
Team: 16 members
Key words: sensorimotor control / neural modeling / movement quantification / motor learning and rehabilitation / biologically-motivated technical applications

The Section Computational Sensomotorics investigates theoretical principles in the perception and control of motor actions, and associated technical applications. Research in 2017 focused on three topic areas:

Die Sektion Theoretische Sensomotorik erforscht die theoretischen Prinzipien der Erkennung und Steuerung motorischer Handlungen und assoziierte technische Anwendungen. Unsere Forschung war 2017 auf drei Themengebiete fokussiert:

Clinical movement control and rehabilitation

Neurodegenerative disorders, such as cerebellar ataxia or Parkinson's disease, are associated with characteristic movement deficits. Motor training often helps to improve everyday symptoms of these patients, even for diseases without causal treatment options. The accurate quantification of changes in movement patterns supports the preclinical and differential diagnosis of movement disorders, and it helps to optimize personalized optimal intervention strategies. A particularly important, but technically very challenging problem is the modeling and quantification of complex body movements with relevance for everyday life. To solve this problem, we combine motion capture and other measurements, biomechanics, and advanced machine learning approaches in order to model and quantify complex movements. In cooperation with clinical partners, we develop motor neurorehabilitation strategies, exploiting modern technologies such as Virtual Reality (VR) and robot devices. Collaborating with electrophysiologists, we also contributed to the development of novel electrophysiological approaches for the study of the electrophysiological basis of the influence of non-invasive brain stimulation on motor plasticity and learning.

Specifically, after having demonstrated substantial long-term benefits induced by motor training in cerebellar ataxia patients (in collaboration with M. Synofzik and L. Schöls, Dept. Neurodegeneration), we have successfully exploited computer games (exergames) and VR setups for the rehabilitation training of cerebellar ataxia patients, and especially in ataxic children. In addition, we tested the influence of such motor training at preclinical stages of ataxia. In patients with focal cerebellar lesions (collaborating with D. Timmann-Braun, University of Essen) we tested the relevance of cerebellar structures for different forms of motor learning and perception–action coupling. Also exploiting VR technology (collaborating with O. Karnath, Dept. Cognitive Neurology) we investigate the use of optical information in apraxia patients. In addition, collaborating with the groups of C. Schwarz (Dept. Cognitive Neurology) and U. Ziemann (Dept. Vascular Neurology & Stroke), we have developed a novel electrophysiological platform for rats that allows to measure single-cell spiking activity already one millisecond after single-pulse TMS, adequately blocking induced electromagnetic artifacts.

Neural and computational mechanisms of social perception and action processing

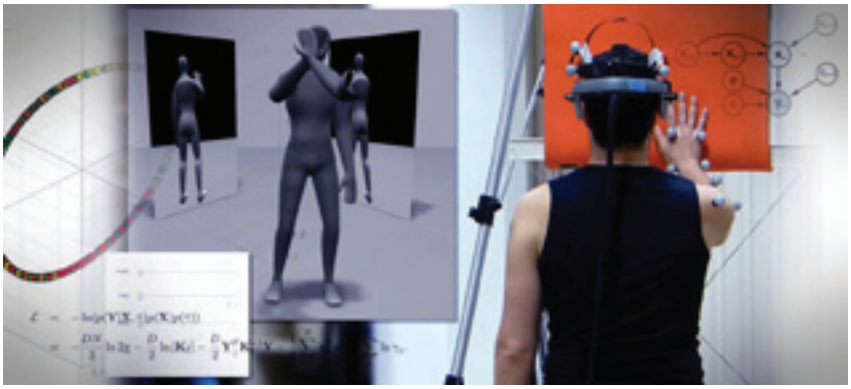
Action perception can show bistability, e.g. showing the same walker locomoting in two alternating directions. We have studied the neural dynamics of such representations and have investigated how perceptual switching in the perception of body movements can be accounted for by recurrent neural circuits in the visual pathway by an interplay between adaptation and noise. Also, we have studied how the illumination direction affects the perceptual organization of such body motion stimuli, discovering a new visual illusion that demonstrates that body motion perception is influenced by a 'lighting-from-above prior'. In collaboration with P. Thier (Dept. Cognitive Neurology) we have investigated the representation of reward signals in mirror neurons in premotor cortex (area F5). As part of a project in the Human Frontiers Science Program (HFSP) (also collaborating with P. Thier) we have developed a highly realistic computer-graphics model for dynamic macaque facial expressions.

The model is driven by motion capture data from monkeys and is used for comparing the neural processing of facial expressions in neurons in the Superior Temporal Sulcus. A second project in this grant (in collaboration with D. Tsao (CALTECH) and A. Martinez (OSU)) is the development of a physiologically-inspired neural model that accounts for the perception of animacy and social interaction from movies showing abstract interacting shapes, similar to the stimuli in a famous classical experiment from Heider and Simmel.

Biomedical and biologically-motivated technical applications

Optical methods provide the most accurate way for the measurement of body movements. However, previously existing technical systems for optical motion capture were quite expensive (far above 10.000 EUR). Recent developments, like the Microsoft Kinect sensor, make it possible to develop much cheaper systems for clinical applications. Based on the Kinect sensor, we have developed a system for body motion tracking for less than 5.000 EUR that is suitable for large measurement volumes. We applied it successfully for the analysis of gait patterns in cerebellar ataxia patients. The system, meanwhile, has been deployed to multiple other clinical facilities as part of a multi-center study on the natural history of cerebellar ataxia, where the acquisition of high-end optical motion capture systems for all partner institutions would have been way too expensive.

In the context of the EC H2020 project COGIMON we have also started to explore the use of a humanoid robot for the training of neurological patients using a catching–throwing game. As intermediate step for the efficient development of appropriate robot control systems in clinical scenarios, we have integrated a physics simulator of the COMAN robot (developed by the Italian Institute of Technology, Genova) into a virtual reality simulation for patients, and we have used this system for coordination training in healthy participants.



Using video games and virtual-reality (VR) setups developed in our own laboratory we have established (in collaboration with clinical partners) novel training paradigms for patients suffering from cerebellar ataxia. The figure shows a VR system for the simulation of highly-realistic reactive body movements with controlled motion style. The system has been used to study the perception of emotions from body movements in interactive situations.

Computer graphics models for monkey and human faces. The macaque face model was derived from an anatomical MRI scan. The mesh shown in the left panel is augmented by layers modeling skin and fur, resulting in an animation with the same level of realism as the human avatar shown in the right panel. Both avatars are animated using motion-capture data from monkeys and humans, by deformation of muscle-like elastic ribbons, which are derived from the monkey and human muscle anatomy (shown in violet in the left panel). Both avatars have moving eye balls in order to simulate social attention cues.

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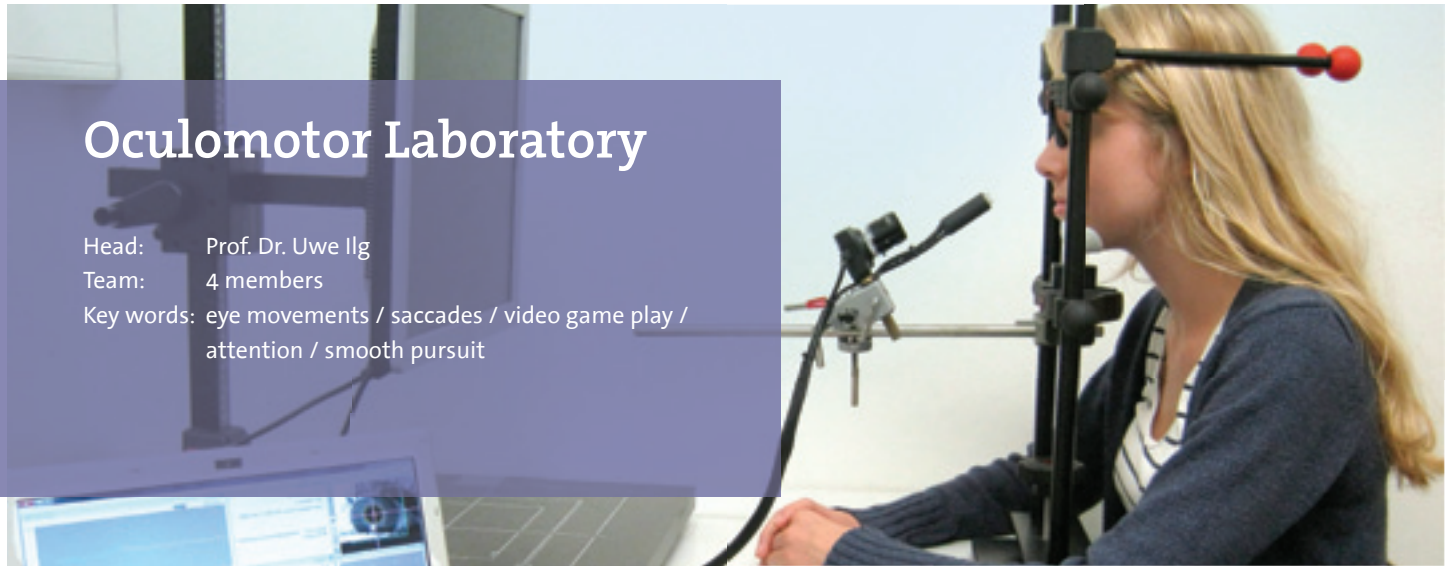


Oculomotor Laboratory

Head: Prof. Dr. Uwe Ilg
Team: 4 members
Key words: eye movements / saccades / video game play / attention / smooth pursuit

Video-game play is a very widely distributed leisure activity in our society. Especially younger individuals do play video games every day. Actually, there is a vivid debate about possible consequences, either positive or negative, of these activities. We decided to examine the differences in oculomotor control and perceptual performance in video-game players (VGP) and non-players (NVGP). VGPs are much better in performing anticipatory smooth pursuit compared to NVGPs. In addition, we find shorter saccadic latencies and higher saccade velocities in VGPs compared to NVGPs. However, there is no difference in the error rates in the anti-saccade paradigm.

Videospiele sind eine sehr weit verbreitete Freizeitaktivität in unserer Gesellschaft, vor allem jüngere Menschen vergnügen sich täglich damit. Die möglichen Konsequenzen werden gegenwärtig sehr kontrovers diskutiert. Wir untersuchen die Unterschiede in den Blickbewegungen und den Wahrnehmungsleistungen von Computerspielern und Nicht-Spielern. Video-Spieler können wesentlich höhere Augengeschwindigkeiten in der Erwartung eines bewegten Ziels erzeugen als Nicht-Spieler. Außerdem konnten wir kürzere Latenzen und höhere Geschwindigkeiten der Sakakden bei Computerspielern zeigen. Wohingegen bei den Anti-Sakkaden kein Unterschied in der Fehlerrate der Augenbewegungen in beiden Gruppen zu erkennen ist.

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 in a wide battery of tests addressing eye movements and the allocation of attention.

Smooth pursuit eye movements

We developed a new paradigm in which human observers are able to initialize smooth pursuit eye movements (SPEM) in total darkness during the expectation of an upcoming moving target. The eye velocity of the anticipatory pursuit is scaled to the expected target velocity. We compared this predictive ability in VGPs and NVGPs. Interestingly, we did not find any significant differences between both groups with respect of visually-guided pursuit (i.e. steady-state gain, initial acceleration, pursuit onset latency, or saccade timing). In contrast, VGPs produce significant higher eye velocities in the expectation of an upcoming target compared to NVGPs. Obviously, playing video-games enhances the ability to anticipate future events.

Please do not look at the target! – Anti-Saccades

We applied a very simple oculomotor task in our first study. We asked our subject to perform a saccade to the mirror position of a visual target. In some cases, the subject is unable to suppress the gaze shift towards the target, triggered by a reflexive shift of attention towards the target. These saccades are directional errors quite similar to the visually-guided saccades called pro-saccades. There is compelling evidence that the fast visual orienting responses (directional errors) are generated by the superior colliculus in the midbrain. In contrast, the cognitively driven anti-saccades are mediated by the frontal eye field (area 8) in the frontal cortex. So the frequency of directional errors can be used as a direct measure for the strength of the executive control function of the frontal cortex upon the midbrain circuit. We tested a total of 55 subjects aged 15 to 31 years in our experiment. All subjects were either classified as VGPs or as non-players depending on their daily gaming time: VGPs (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 directional errors had about 100 ms shorter reaction times than the correctly executed anti-saccades. More strikingly, the reaction times of both types of saccades were decreased for approximately 10 ms in VGPs compared to non-players. The eye speed during gaze shifts reaches very high values. In our data, the maximal velocity of the eye during a 10-degree saccade is between 350

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.

and 400 degrees/second. In other words, if the eyes could rotate without limitations, a complete rotation of the eyeball would occur within one second. As reported by others, direction errors reach higher peak velocities than anti-saccades. Surprisingly, both types of saccades of VGPs reach higher peak velocities gaze shifts executed by non-VGPs.

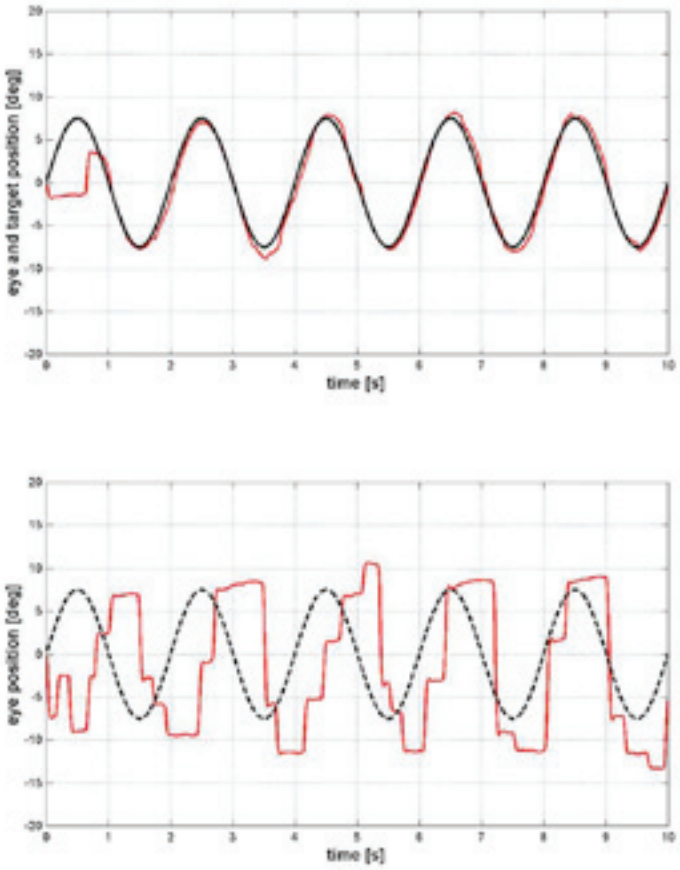
To address the cognitive control function, which might be reduced in VGPs as supposed by others, we examined the frequency of direction errors in the anti-saccade task. VGPs as well as non-players showed an error rate of approximately 40%, there was no significant difference between players and non-players. 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 rates than subjects with longer latencies. Despite this general relationship, we failed to find an increased amount of errors in VGPs compared to non-players. Since the frequency of directional errors is a direct measure for the amount of executive control function, our results show that this function is not impaired in VGPs compared to non-VGPs. Therefore, we conclude that playing video games does not produce negative effects on the control function of the frontal lobe. We used a modification of this paradigm to disentangle visual processing from motor preparation in the human superior colliculus. Here, the subjects had to reach out to the mirror position of a visual target. Brain activity revealed by functional MRI could be associated to either processing of visual information to one side and preparation of reaching movement to the opposite side.

Speed of shifting the spotlight of attention?

The above described decrease of reaction times in VGPs compared to non-VGPs may be attributed to the ability of VGPs to shift their spotlight of attention faster. To test this hypothesis, we designed an experiment in which subjects had to report the identity of a specific visual target presented at a cued location. By varying the cue leading times between 0 and 600 ms, we were able to measure the benefit of changing the focus of attention towards the cued location. In this study, we examined 116 subjects, 63 identified as VGPs and 53 as non-VGPs, 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. Although peak performance was higher in VGPs compared to non-VGPs, we found no difference in the optimal cue leading time between VGPs and non-players. Therefore, our data do not support the hypothesis that VGPs are able to shift their spotlight of attention faster compared to non-players. Alternatively, VGPs might have a larger spotlight of attention or the ability to process visual information more efficiently.

Horizontal target and eye position of a human observer tracking a sinusoidal moving target (upper) and imagining a moving target (lower). Note that smooth pursuit can only be executed in the presence of a moving target.



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Systems Neurophysiology Laboratory

Head: Prof. Dr. Cornelius Schwarz
Team: 9 members
Key words: neocortex / tactile coding and perception / active scanning / motor coding and movements / associative learning

Rodents deploy their whiskers to explore their environment.

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 and learning in rodents that let us study neocortical function during highly defined and precisely monitored behavior. The similarity of neocortex in animals and humans suggests that the results can be transferred easily to research on human disease (Alzheimer's, Parkinson's, schizophrenia, and depression).

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

Problem, model system, and methods

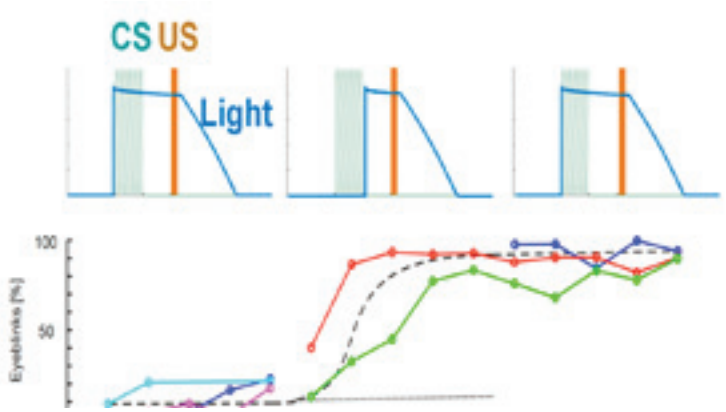
The generality of cortical neuronal architecture related to vastly diverse functions renders it likely that, beyond specific signal processing, there must be a generic function common to all cortical areas. Our over-arching hypothesis is that the neocortex is a giant associative storage device, which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

Research into cortex function 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/stimulation and combine it with behavioral observation at highest precision. Our major model for studying these questions is the sensorimotor vibrissal system (vibrissae = whiskers) of rodents. We further study the tactile human fingertip system. Rodents and humans use an 'active' strategy of sampling tactile information about their immediate environment by actively moving their fingertips or vibrissae across objects in their vicinity.

Learning

We hypothesize that cortex-based associative learning can involve mechanistically separate learning processes that are hierarchically linked. The first is the generation of declarative memory – 'knowing the rule of the game'. The second is procedural knowledge – 'learning to generate movement' in a new context. To test this hypothesis we use a cortex-dependent Pavlovian learning paradigm in rodents, the so-called 'tactile trace eye blink conditioning' (TTEBC). In this paradigm the conditioned tactile stimulus (CS, a whisker twitch) is related to the unconditioned stimulus (US, an aversive corneal air puff) only across a stimulus-free time interval, through which the subject has to keep a memory 'trace' (hence the name), to be able to associate the two stimuli. We employ 2-Photon imaging, optogentic blockade, and multielectode electrophysiology to study the role of the primary somatosensory cortex (S1) for this learning process. On the behavioral and functional cortical level, we have successfully demonstrated the involvement of S1 in TTEBC learning. We found a steep generalization gradient and a matching spatial specificity of cortical neuronal

Active tactile exploration of the environment using vibriss.



Top: Optogenetic experiment blocking the primary somatosensory cortex using blue light during conditioned stimulus (CS, repetitive whisker deflection), Trace (between CS and US), and unconditioned stimulus presentations (US, airpuff against the cornea).

Bottom: Resulting learning curves of TTEBC training (see text). Before learning (left), CS and Trace inhibition blocked the generation of CRs (eyeblinks), while inhibition during trace period alone did not (center). After learning, inhibition of CS/Trace does not prevent the generation of eyeblinks (right), arguing against the interpretation that effects of S1 blockade are simply due to blocking entry of sensory signals to the cortical level.

rewiring. Neuronal activity in S1 during CS presentation and memory period tightly tracks the learning progress. Causal interference using optogenetic blockade of S1, shows that S1 activity during CS presentation is responsible for acquisition of the conditioned response but does not block behavior once the task is learned. As the activity of neurons is changed in the trace period during learning, we have begun to set up novel behavioral paradigms to investigate the hypothesis that S1 trace activity is related to the generation of declarative knowledge, rather than to the generation of CRs.

Active perception

We hypothesize that S1 is involved in two forms of predictive coding. The first is related to predictions based on ego-movement, and/or contingencies in the sensory signals. These are generated by subcortical loops involving the cerebellum and affect perception in a bottom-up fashion. The second form of predictive coding is of a more vaguely specified cognitive origin. It is based on the idea that cognitive centers on the cortical level control the inflow of sensory signals in a top-down fashion at peripheral sensory stations. Using multi-electrode electrophysiology and lesion-based analsyis in rodents operantly conditioned to a movement task, we have found that top-down, cortex-dependent sensory gating in brainstem tactile nuclei exists. We are now in the process to elucidate in how far these predictive signals may be related to the assumed bottom-up predictive signals in the tactile system.

We further study the possibility that the tactile system uses a local code, i.e. short-lived features in the vibrotactile signal (Figure), rather than so-called global variables that can be obtained by signal averaging. We find on the perceptual and neuronal level strong evidence for local codes. We have started to relate this novel hypothesis also to processing of tactile signals in the human fingertip system. Ongoing research, therefore, tests perception of stimuli containing distinct local stimulus features. In cooperation with applied mathematicians we explore if and how such local features are generated and amplified by biomechanical properties of skin and hair.

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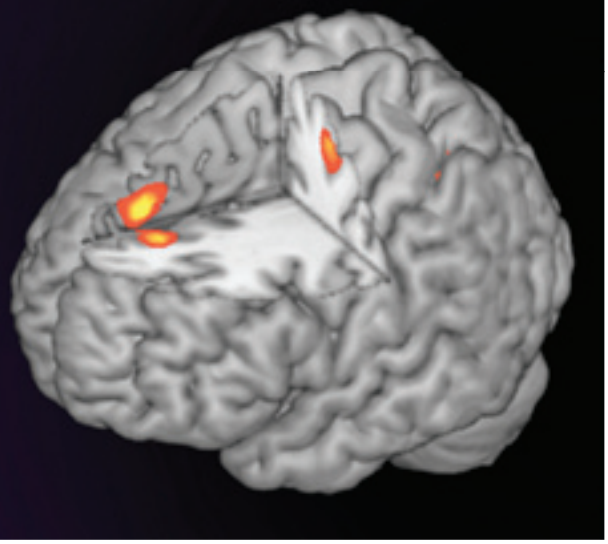
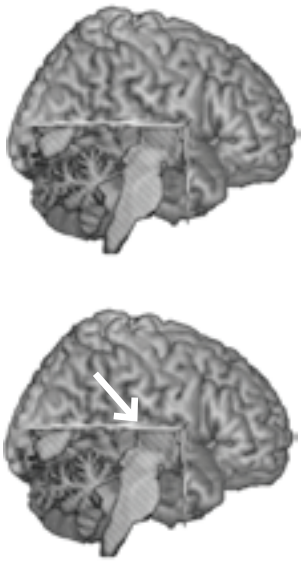
Neuropsychology of Action



Head: Dr. Marc Himmelbach
Team: 9 members
Key words: reaching / grasping / optic ataxia / apraxia / visual agnosia

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

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



The superior colliculi are part of the tectum which additionally comprises the inferior colliculi right below. Traditionally the superior colliculi have been associated with visual and oculomotor functions.

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.

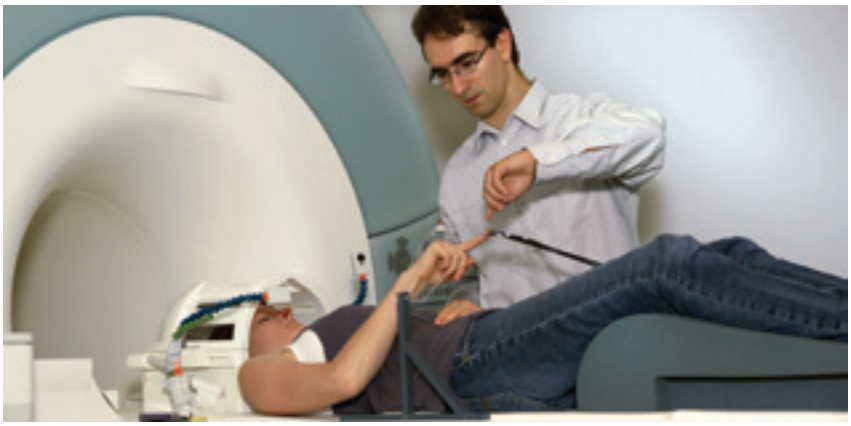
Evaluation of object functionality and mechanical reasoning in humans

Human action control is characterized by its impressive complexity and flexible adjustment in tool use and object manipulation. We investigate the cognitive control mechanisms involved in the evaluation of action affordances and potential applications associated with an object and their neuronal correlates. How do we recognize a usable tool for a particular technical problem? How do memory and acquired knowledge about tools on the one hand and visual analysis and deductive reasoning on the other hand contribute to our respective decision? A small group of brain damaged patients are especially impaired in using novel, unfamiliar tools while they are less impaired in using familiar tools. The examination of such patients and further behavioral and neuroimaging studies based on observations in these patients can help us to understand the way different cognitive sources are combined to come up with a motor behavior that no other living species can match.

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. In our current 3T experiments we explore its actual functional contribution to the processes of planning, execution, or sensory feedback of hand and arm movements. Using tensor imaging and resting state fMRI we investigate the short- and long-distance connectivity of the superior colliculi. Working at ultra-high field 9.4T in collaboration with colleagues from the MPI Tübingen we go for highest anatomical resolutions up to 132 mm in-plane resolution and strive for < 1 mm isotropic resolutions of brainstem fMRI in event-related experiments. Our research on the SC and its connectivity currently moves into the field of clinical neurosciences: we conducted first analyses of local connectivity in the upper brainstem between colliculus, basal ganglia, and thalamus addressing current topics in research on Parkinson's disease and dystonia.



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

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.

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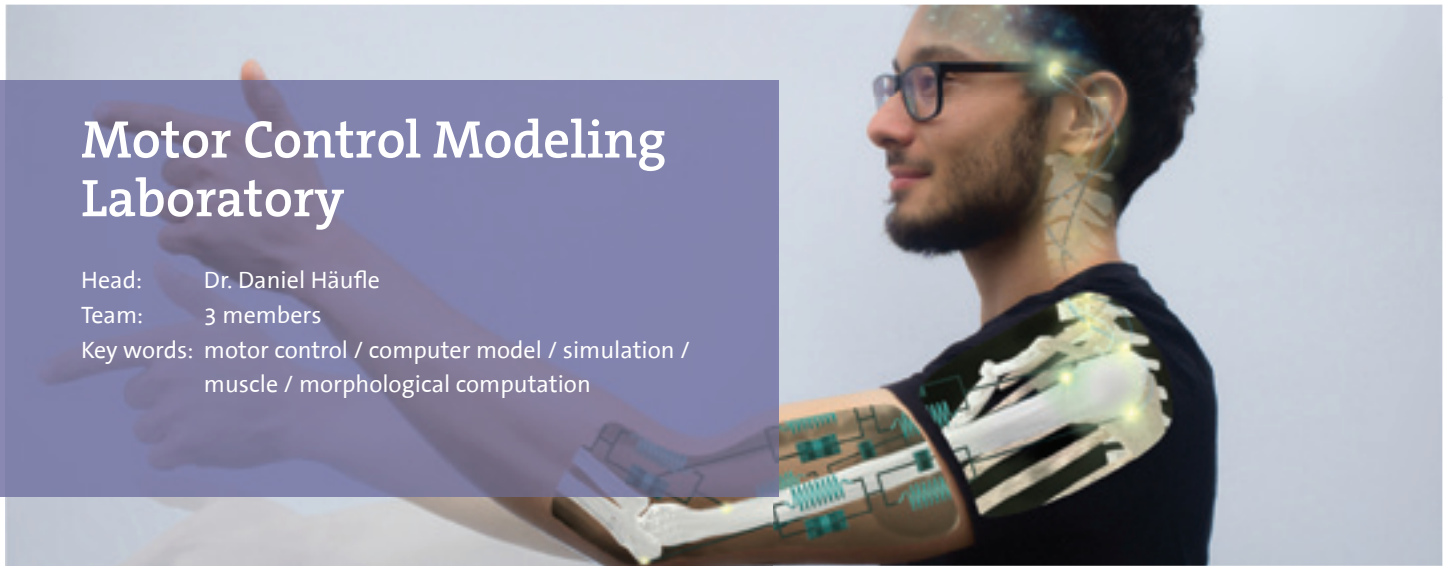
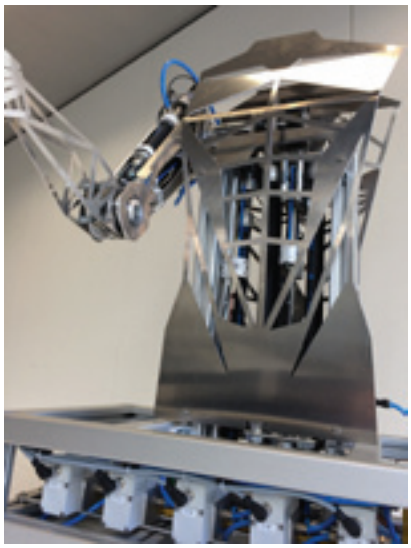


Motor Control Modeling Laboratory

Head: Dr. Daniel Häufle
Team: 3 members
Key words: motor control / computer model / simulation / muscle / morphological computation

The research group "Multi-Level Modeling in Motor Control and Rehabilitation Robotics" investigates the generation and control of active biological movements. We develop computer models and simulations of the neuro-musculo-skeletal system. In a multi-level approach we consider the different hierarchical levels contributing to movement generation. This interdisciplinary approach is mainly based on biophysics, biomechanics, and computational motor control.

Die Forschungsgruppe „Multi-Level Modeling in Motor Control and Rehabilitation Robotics" untersucht die Erzeugung und Kontrolle aktiver biologischer Bewegungen. Wir entwickeln Modelle und Computersimulationen des neuro-muskulo-skelettalen Systems. In einem Mehrskalen-Ansatz können wir die unterschiedlichen hierarchischen Ebenen berücksichtigen, die zur Bewegungserzeugung beitragen. Unser interdisziplinärer Ansatz integriert Konzepte der Biophysik, Biomechanik und Motorik.

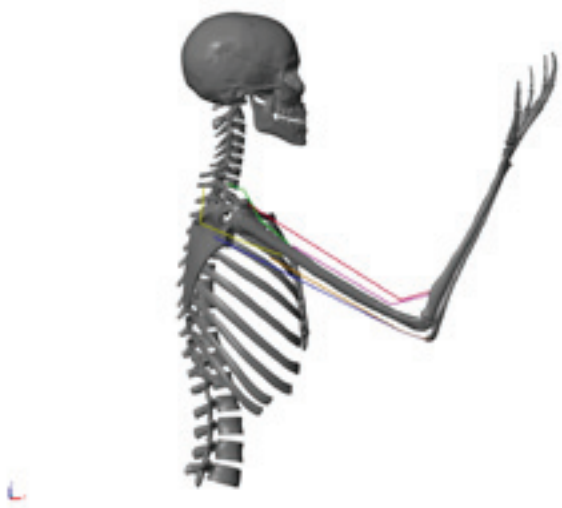


Biorobotic model of the human arm with two joints actuated by five mono- and biarticular pneumatic muscles of different lengths and thicknesses. The robot considers non-linear lever arms and actuators with a nonlinear force-length and force-velocity relation. Built in collaboration with Syn Schmitt, Biomechanics and Bio-robotics, University of Stuttgart.

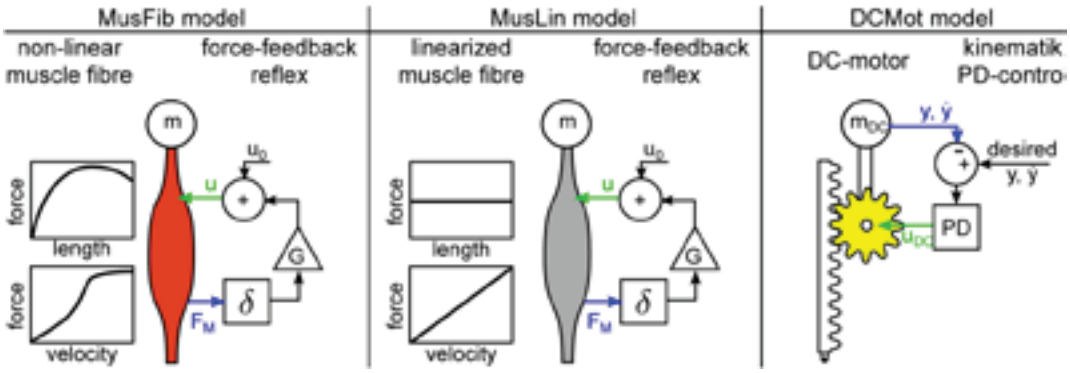
To successfully generate a goal-directed movement in the interaction with their environment, humans and animals perform control. They acquire information about their environment by sensors and generate actions by sending signals to their actuators. However, the resulting movement is not only governed by the control signals but also by physical characteristics and interactions of the materials in the system. In our work we focus on the interaction between neuronal system, biomechanical structures and biochemical processes. The following examples demonstrate the approach:

Motor control dysfunction

In the context of the Hertie Institute for Clinical Brain Research we investigate fundamental sensorimotor control mechanisms and their dysfunction in neurological disease. We develop computer models, e.g., of the human arm. These models consider the structure of the skeleton with its rather rigid bones and the joints, which allow movement. Muscle models predict forces, which act on the bones via tendons. Other soft tissue models consider passive viso-elastic forces. Finally, a model of sensor signals and spinal neuronal processing allows to estimate a stimulation signal, which controls muscle force and, hence, the movement. All these structures are described by mathematical equations (ordinary differential equations). The benefit of such models is, that we can investigate the contribution of individual structures and neuronal signals to the movement. The goal is to identify the mechanisms of motor control dysfunction and to gain a deeper understanding of the dynamics of impaired control. This research may be the starting point for the development of functional assistive devices. In this field we work together with the Sections for Computational Sensomotorics (Giese) and Clinical Neurogenetics (Schöls).



Computer model of the human arm with six mono- and biarticular muscles actuating shoulder and elbow joint. The model was developed in collaboration with Syn Schmitt, Biomechanics and Biorobotics, University of Stuttgart.



Simplified hopping model. To understand the contribution of biomechanical non-linearities to the control of movement, we exchanged the muscle by a linearized muscle and a DC motor. The model shows that hopping requires much less information to be processed by the nervous system if we include the muscle characteristics.

Biorobotics
We develop robotic platforms as tools to study concepts on biological motor control. These tools support the computer simulations and transfer the concepts into the real world, where biological experiments are not possible.

Morphological computation
The concept of morphological computation captures the observation that the physical structures contribute to the control in biological systems. We develop methods to quantify the contribution of the morphology and compare biological systems to robotic systems in computer simulations.

The group is part of the regional research alliance "System Human Being" between the University of Tübingen and the University of Stuttgart. Our goal is to link the neuroscientific expertise in Tübingen with the expertise in computer simulation at the Stuttgart Research Center for Simulation Science (SC SimTech).

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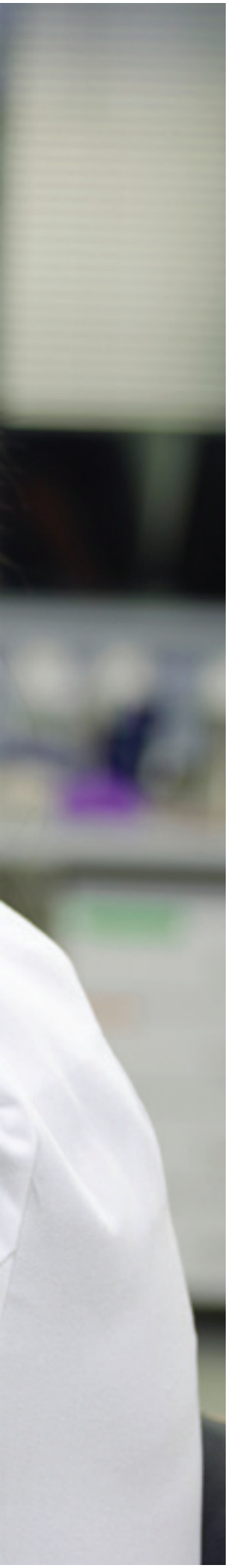
Department of Cellular Neurology



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

Departmental Structure

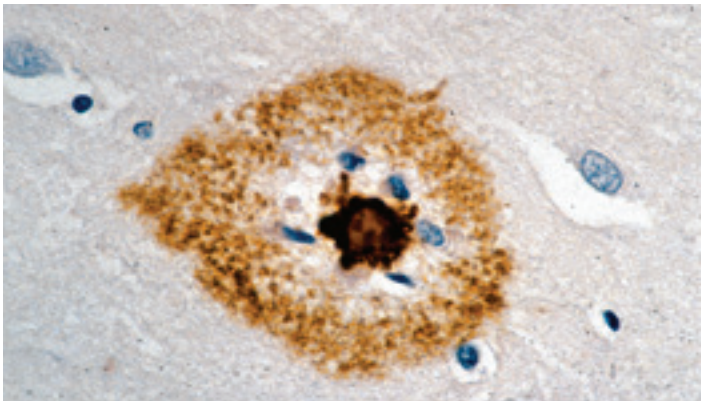
The Department is headed by Professor Mathias Jucker and was founded in 2003. The research focus is on the cellular and molecular mechanisms of brain aging and age-related neurodegenerative diseases, with a special emphasis on the pathogenesis of Alzheimer's disease and other cerebral amyloidoses. Alzheimer's 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 first described the disease to his colleagues in 1906. To mark this occasion, the Department of Cellular Neurology hosted a centennial symposium in 2006 (Alzheimer: 100 Years and Beyond). As of 2010 our department is also part of the German Center for Neurodegenerative Diseases (DZNE).

Currently our department is composed of five research groups and one core unit: The Amyloid Biology group studies the molecular mechanisms of amyloid formation using in vitro and biochemical methods. The Experimental Neuropathology group uses transgenic mouse models to analyze the pathomechanisms of Alzheimer´s disease and cerebral amyloidoses.

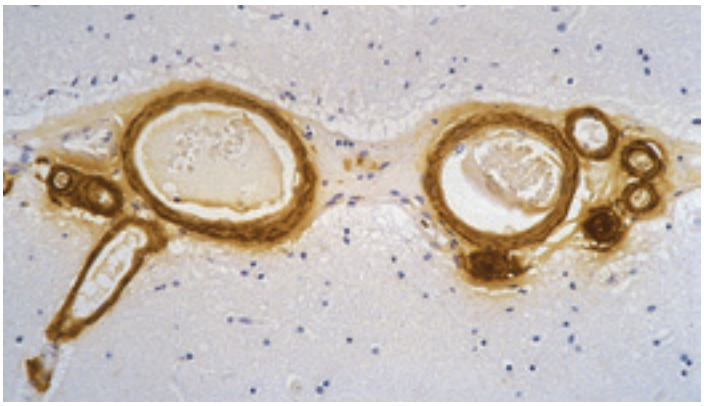
The Molecular Imaging group studies how Alzheimer´s disease lesions and neurodegeneration develop over time in the transgenic mouse models using in vivo multiphoton microscopy. The Molecular Biomarkers group uses immunoassays to identify early biomarkers in the cerebrospinal fluid and blood of mouse models and human subjects with Alzheimer´s disease and related disorders. The Experimental Neuroimmunology group works on aspects of innate immunity in the aging brain and in neurodegenerative diseases. Finally, the core unit supports the department with mouse genotyping, ELISA measurements, and other technical and administrative activities.

We are primarily a department of basic research with a focus on preclinical investigations of disease mechanisms. To foster the translation of our research to clinical applications, we partnered with the University Clinic of Psychiatry and Psychotherapy to establish the Section for Dementia Research with its Memory Clinic. Moreover, we are coordinating the international Dominantly Inherited Alzheimer Network (DIAN) study in Germany, which aims to understand the rare genetic forms of Alzheimer's disease by longitudinal analysis of gene mutation carriers and non-mutation carrier siblings. Understanding this type of Alzheimer's disease is expected to provide important clues to the development of the more common sporadic form of Alzheimer's disease.

Our department hosts scientists from more than 10 nations, ranging from short-term fellows, master students, PhD and MD students to postdoctoral fellows and group leaders. This diversity, along with our extensive expertise in brain aging and neurodegenerative disease, creates a socially and intellectually stimulating intramural environment that is also highly competitive extramurally.



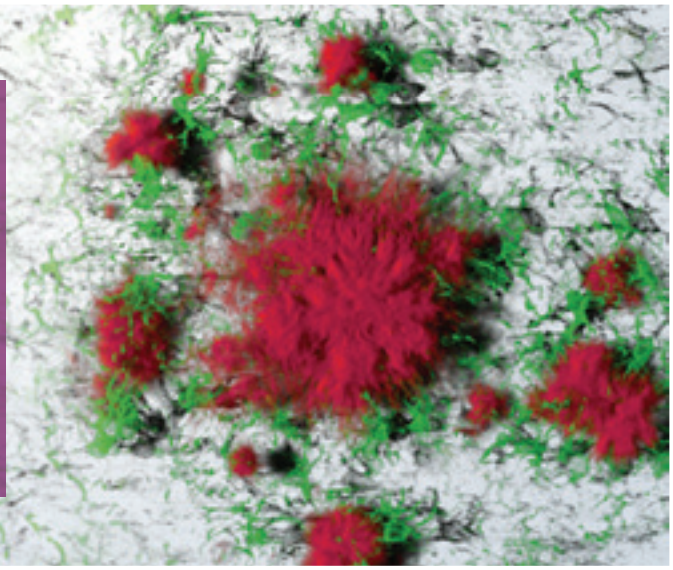
Amyloid plaque (Aβ immunochemistry) in an Alzheimer brain.



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

Experimental Neuropathology

Head: Prof. Dr. Mathias Jucker
Team: 18 members
Key words: cellular neurology / alzheimer's disease / cerebral amyloid angiopathy



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

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.

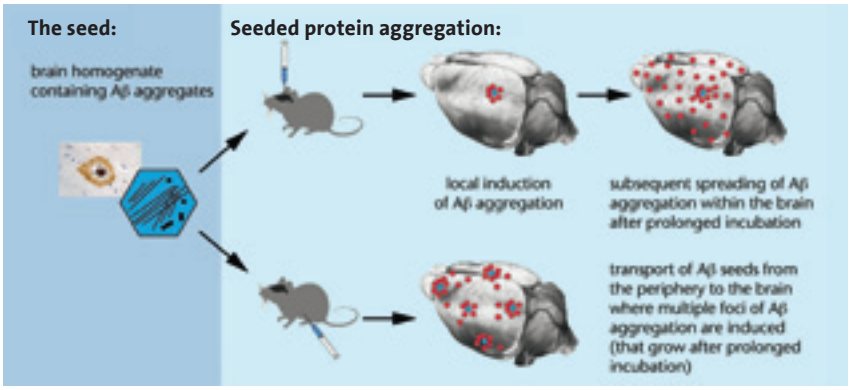
Misfolded proteins are the cause of many neurodegenerative diseases. How these proteins misfold and what the initial trigger is for the misfolding and their subsequent aggregation is, however, largely unknown. Furthermore, it remains unclear why the aging brain is a risk factor for neurodegenerative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

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 reminescent 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.

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



β-amyloid containing brain extracts which are intracerebrally or intraperitoneally injected in young APP transgenic mice induce Aβ-aggregation and deposition in the animals.

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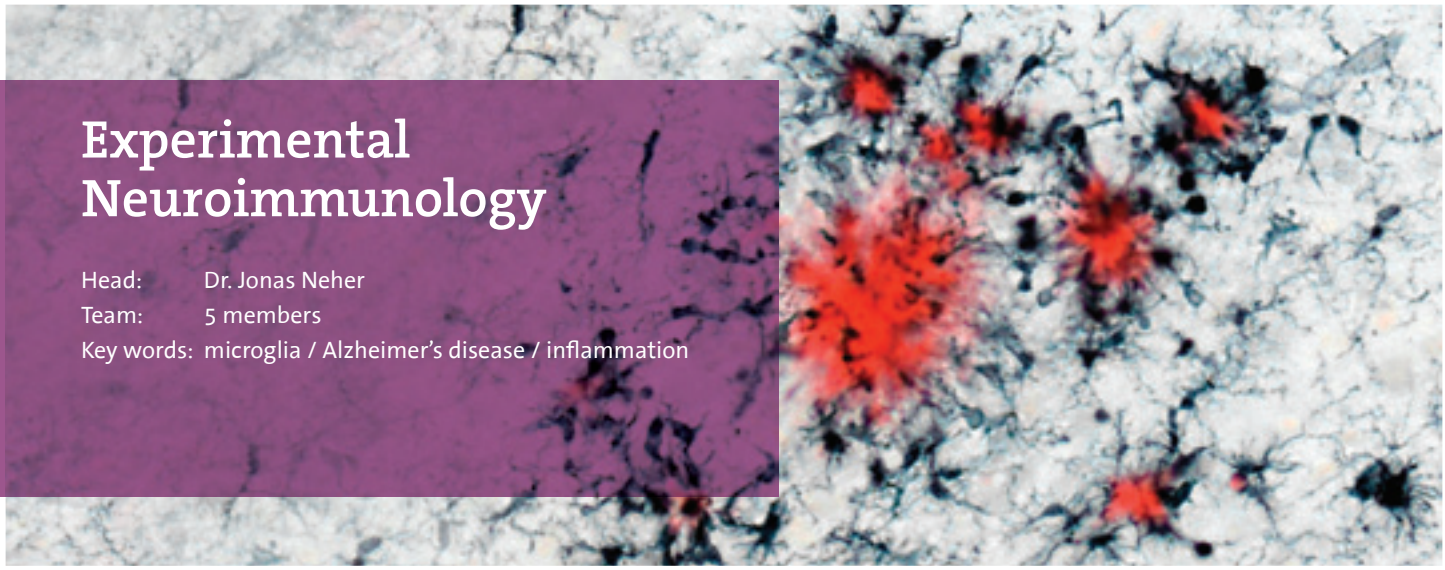


Experimental Neuroimmunology

Head: Dr. Jonas Neher
Team: 5 members
Key words: microglia / Alzheimer's disease / inflammation

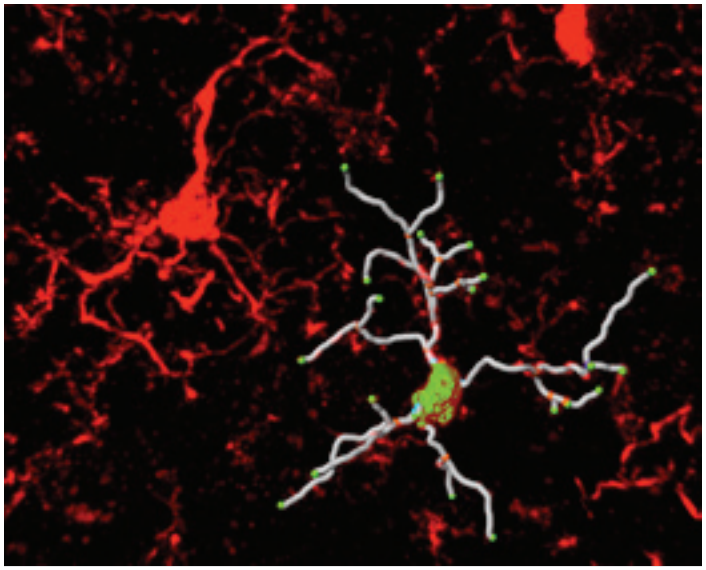
Amyloid-β plaques (red) surrounded by microglia (black).

Our objective is to understand how the brain's immune system contributes to the pathogenic mechanism of Alzheimer's disease and to develop therapeutic interventions that target the immune system.

Unser Ziel ist es zu verstehen, wie das Immunsystem des Gehirns zu dem Pathomechanismus der Alzheimer-Erkrankung beiträgt, um aus diesen Erkenntnissen therapeutische Interventionen zu entwickeln.

It is now well established that most (if not all) neurological diseases present with an inflammatory component. These include acute conditions such as stroke as well as chronic neurodegenerative diseases such as Alzheimer's disease (AD). However, it has proven difficult to determine when the activation of the brain's immune system is beneficial or detrimental in these diseases and considerable controversy still exists in the literature. This controversy may partially be due to the fact that tissue resident macrophages (including microglia) are highly plastic cells that can adapt to their particular microenvironment. Therefore, one of our aims is to understand how the microglial activation state changes in Alzheimer's disease. To this end we are analyzing the gene expression and epigenetic profile of microglia in mouse models and investigate how these cells adapt in response to inflammatory stimuli. In particular, we are interested how peripheral inflammation changes the microglial activation state. In this regard, we were able to demonstrate recently that microglia are capable of immune memory. This means that these cells undergo long-term epigenetic reprogramming, which modulates their immune responses to later developing neurological disease. Importantly, we found that microglial immune memory is sufficient to modulate hallmarks of neurological disease, indicating that this mechanism may be a novel risk factor for neurodegenerative conditions.

Further, it has been suggested that microglial dysfunction, i.e. the inability of these cells to perform their normal surveillance function in the brain, may contribute to the onset or progression of Alzheimer's disease. We have recently tested this hypothesis by replacing brain-resident microglia with circulating monocytes from the blood. This was possible because we initially observed that in a genetic mouse model, which allows the selective destruction of microglia, peripheral monocytes rapidly invaded the brain and completely repopulated the tissue. We used this model to replace microglia in models of Alzheimer's disease to test whether the new, invading immune cells could prevent or alleviate pathology. To our surprise, the new immune cells were unable to improve pathological hallmarks of Alzheimer's disease.



Three-dimensional reconstruction of microglia in a tissue section (cell body green, processes grey).

Rather, they adopted features of microglia indicating that the tissue environment dominated the function of the immune cells. We will investigate in future studies whether monocytes can indeed become microglia-like following long-term brain engraftment.

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Section of Dementia Research

Head: Prof. Dr. Christoph Laske
Team: 6 members
Key words: memory clinic / alzheimer's disease / mild cognitive impairment / subjective memory complaints

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 a Research Unit and collaborates with an outpatient Memory Clinic in the Department of Psychiatry and Psychotherapy.

Die Sektion für Demenzforschung wird zusammen mit der Universitätsklinik für Psychiatrie und Psychotherapie Tübingen betrieben. Die Sektion besteht aus einer Forschungsgruppe und arbeitet mit der Gedächtnisambulanz in der Klinik für Psychiatrie und Psychotherapie zusammen.

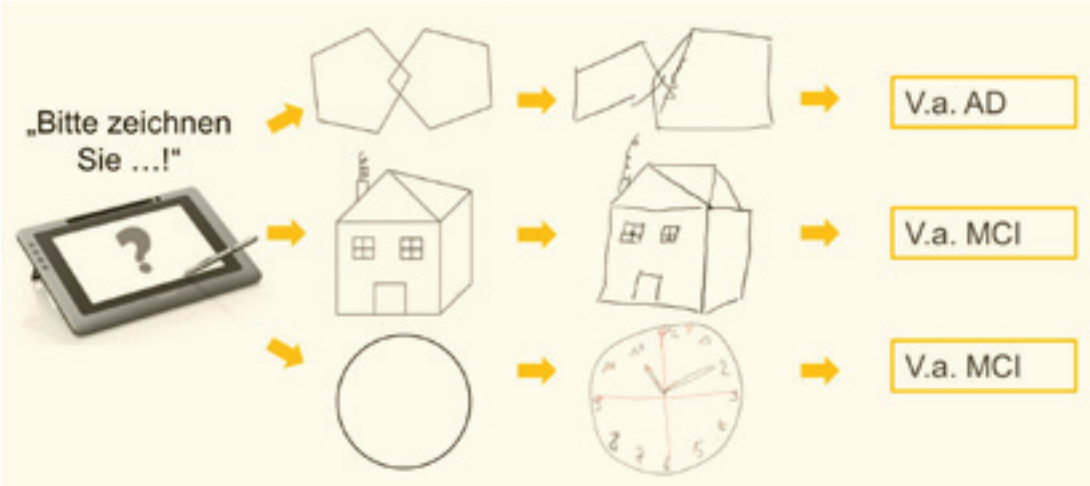
The Section of Dementia Research has its focus on the following three research topics:

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). We currently examine the intestinal microbiome in patients with Alzheimer`s disease (AD), mild cognitive impairment (MCI) and in healthy controls (AlzBiom Study).
In addition, we are developing an innovative tablet-based drawing test to screen for cognitive impairment in patients with Alzheimer's disease.



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Independent Research Groups

Laboratory for Neuro-regeneration and Repair

Head: Dr. Simone Di Giovanni
Team: 7 members
Key words: axonal signalling / spinal cord injury / axonal regeneration / neurogenesis / transcription

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

The MDM4/MDM2-p53-IGF1 axis controls axonal regeneration, sprouting and functional recovery after CNS injury *(Joshi and Soria et al. Brain, 2015)*

Regeneration of injured central nervous system (CNS) axons is highly restricted, causing neurological impairment. To date, although the lack of intrinsic regenerative potential is well described, a key regulatory molecular mechanism for the enhancement of both axonal regrowth and functional recovery after CNS injury remains elusive. While ubiquitin ligases coordinate neuronal morphogenesis and connectivity during development as well as after axonal injury, their role specifically in axonal regeneration is unknown. Following a bioinformatics network analysis combining ubiquitin ligases with previously defined axonal regenerative proteins, we found a triad composed of the ubiquitin ligases MDM4-MDM2 and the transcription factor p53 as a putative central signalling complex restricting the regeneration program. Indeed, conditional deletion of MDM4 or pharmacological inhibition of MDM2/p53 interaction in the eye and spinal cord promote axonal regeneration and sprouting of the optic nerve after crush and of supraspinal tracts after spinal cord injury. The double conditional deletion of MDM4-p53 as well as MDM2 inhibition in p53 deficient mice blocks this regenerative phenotype, showing its dependence upon p53. Genome-wide gene expression analysis from ex vivo fluorescence-activated cell sorting (FACS) in MDM4 deficient retinal ganglion cells identifies the downstream target IGF1R, whose activity and expression was found to be required for the regeneration elicited by MDM4 deletion. Importantly, we demonstrate that pharmacological enhancement of the MDM2/p53-IGF1R axis enhances axonal sprouting as well as functional recovery after spinal cord injury. Thus, our results show MDM4-MDM2/p53-IGF1R as an original regulatory mechanism for CNS regeneration and offer novel targets to enhance neurological recovery.

The adult mammalian central nervous system (CNS) is unable to regenerate following axonal injury due to the presence of glial inhibitory environment as well as the lack of a neuronal intrinsic regenerative potential. Research over the past two decades has elucidated several key molecular mechanisms and pathways that limit axonal sprouting and regeneration following CNS axonal injury, including myelin or proteoglycan-dependent inhibitory signaling. More recently, accumulating evidence suggests that the modulation of the neuronal intrinsic potential via the manipulation of selected genes in specific neuronal populations may enhance axonal regeneration in the injured CNS. More often, these are developmentally regulated pathways that contribute to locking the adult CNS neurons in a non-regenerative mode. Remarkably, deletion of phosphatase and tensin homolog (PTEN) in retinal ganglion cells (RGCs) or in corticospinal tract (CST) axons enhances mTOR activity and leads to robust axonal regeneration after optic nerve or CST injury respectively, which is further enhanced with conditional co-deletion of SOCS3. Furthermore, modifications of the developmentally regulated neuronal transcriptional program can lead to increased axonal regeneration after optic nerve crush (ONC) or spinal cord injury (SCI) as demonstrated by the deletion of kruppel-like factor 4 (KLF4), the overexpression of p300 in RGCs as well as the overexpression of KLF7 or retinoic acid receptor ß (RARß) in corticospinal neurons.

Ubiquitin ligases and ubiquitin ligase-like proteins, including neuronal precursor cell-expressed developmentally downregulated protein (Nedd), Smad ubiquitin regulatory factor (Smurf) and murine double minute 2 and 4 (MDM2 and 4), coordinate neuronal morphogenesis and connectivity both during development and after axonal injury. Moreover, they regulate the turnover, localization and activity of a number of proteins and transcription factors involved in the axonal regeneration program, including PTEN, p300, KLFs, Smads, p21 and p53. Ubiquitin ligases and ubiquitin ligase-like proteins may therefore represent a regulatory hub controlling the regenerative neuronal response following injury. However, their role in axonal regeneration remains unaddressed. Therefore, to functionally rank ubiquitin ligase dependent control of the regeneration programme, we systematically analysed protein networks using STRING bioinformatic tool including of proteins previously described to be involved in axonal regeneration and sprouting in the CNS and the corresponding ubiquitin ligases. This had the goal to identify central protein networks that control the regeneration program that may have positive implications for functional recovery.

This analysis showed that MDM4, in association with MDM2, and p53 constitutes a central regulatory complex, potentially involved in repressing axonal regeneration. The ubiquitin ligase-like MDM4 and MDM2 can form inhibitory protein complexes with at least four key proteins involved in axonal outgrowth: Smad1/2, p300, p53. Strikingly, MDM4 and MDM2 expression is developmentally regulated in the retina reaching its maximal levels in adulthood, potentially keeping the post-injury RGC growth program in check. Therefore, MDM4 and MDM2 appear to be strong candidates for limiting axonal regeneration in the CNS, particularly in the injured optic nerve.

We investigated whether disruption of MDM4 and MDM2-dependent regulation would affect the axonal regeneration program. Indeed, we found that MDM4 and MDM2 restrict axonal regeneration after optic nerve crush. In fact, conditional MDM4 deletion in RGCs leads to axonal regeneration and sprouting of RGC axons following ONC. Additionally, conditional co-deletion of MDM4 and its target protein p53 in RGCs after ONC blocks nerve regeneration elicited by MDM4 deletion alone. Similarly, pharmacological inhibition of the interaction between the MDM4 co-factor MDM2 and p53 via the MDM2/p53 antagonist Nutlin-3a also enables regeneration after ONC, which is abolished in p53 deficient mice. Further, genome-wide gene expression analysis from a pure RGC population after conditional deletion of MDM4 showed enhancement of IGF1R expression suggesting IGF1 signaling as a downstream effector of the MDM4 deletion. Indeed, co-inhibition of MDM4 and IGF1 signalling after ONC via a specific IGF1R antagonist impairs axonal regeneration, while viral overexpression of IGF-1 in the eye enhances it. Finally, we demonstrate that MDM4/2-p53-IGF1 regulation is critical for axonal sprouting and neurological recovery after spinal cord injury. Both conditional deletion of MDM4 and Nutlin-3 delivery after spinal cord dorsal hemisection in mice enhance axonal sprouting of supraspinal descending fibers and functional recovery, which is blocked when IGF-1R signaling is inhibited.

Together, this work portrays the MDM4-MDM2/p53-IGF1R axis as a novel molecular target for axonal regeneration and neurological recovery after spinal injury.

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Physiology of Learning and Memory

Head: Dr. Ingrid Ehrlich
Team: 5 members
Key words: synaptic plasticity / amygdala / fear learning / extinction / anxiety disorders

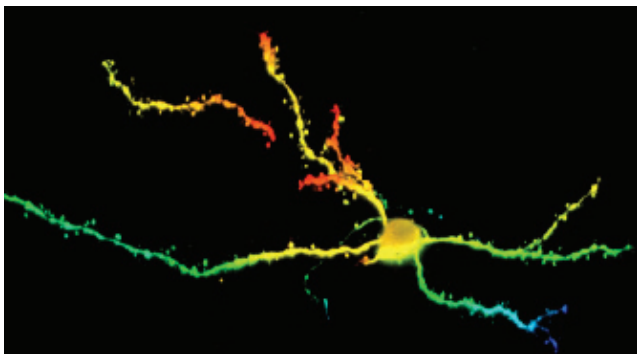
We investigate learning and memory processes using associative fear conditioning and extinction in rodents. We apply mainly physiological techniques to decipher cellular and synaptic processes and neural circuits of the amygdala and fear-related areas. This allows us to understand how learning modifies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

Wir untersuchen Lern- und Gedächtnisprozesse anhand von klassischer Furchtkonditionierung und Extinktionslernen. Dabei verwenden wir vor allem physiologische Methoden, um zelluläre und synaptischn Prozesse sowie neurale Schaltkreise der Amygdala und verknüpfter Hirngebiete zu ergründen. Dies gibt Aufschluss darüber, wie Lernprozesse im Gehirn umgesetzt werden, aber auch wie eine Fehlsteuerung dieser Prozesse zu Angststörungen führen kann.

Organisms have to continuously adapt their behavior to survive, which is highly relevant when threats are encountered. Experience-driven adaptations in behavior are mediated by modifications in brain function. We use classical Pavlovian paradigms, i.e. fear learning and extinction of fear in mice, as our model to study the mechanisms that underlie behavioral adaptation during learning and memory processes. Our goal is to elucidate the molecular, synaptic and cellular changes and the neural circuits that process fear-related information. We combine several techniques, including slice electrophysiology, optogenetics, imaging, histology, virally-mediate gene transfer, and behavioral analysis.

The amygdala, a highly conserved region in the temporal lobe of the brain, is a key structure for storing emotional and fear memories. Acquired fear memories can be modified by extinction learning. Here, an individual learns that certain stimuli are not fearful anymore in a specific setting. Extinction depends on a brain network comprising the amygdala, the hippocampus (a structure important for memory and processing of spatial information) and the medial prefrontal cortex (a structure associated with the control of actions), and interactions between them. Understanding extinction is highly relevant for improving cognitive behavioral therapies used as treatment for anxiety- and other emotional disorders, because they are based on extinction learning. Emerging themes in the last years have been that fear and extinction memories are encoded by specialized, parallel neural networks in the engaged brain areas. Our goal is to identify and investigate these networks and their learning-dependent changes.

One line of our research aims to understand the function and plasticity of a specific inhibitory network in the amygdala, the so-called intercalated cells. These cells likely play a critical role in extinction behavior, possibly by inhibiting the output of the amygdala and providing a break on the fear response. However, how they receive information and transfer is still incompletely understood. In a recent project, we identified a new plastic brain circuit integrating intercalated cells that becomes engaged in fear learning and memory (Asede et al., 2015). We demonstrated that intercalated cells directly receive sensory thalamic information about external stimuli, that these pathways undergo plasticity upon fear and extinction learning, and that they are dynamically modulate to enable extinction in disease conditions (Zussy et al, 2018). In turn, intercalated cells relay information to input and output stations of the amygdala, thereby controlling in coming and outgoing activity. We currently combine optogenetic and anatomical techniques to delineate the mechanism of synaptic plasticity in intercalated cells and obtain a more complete picture of their connectivity. Additional collaborative projects are addressing the effects of neuromodulatory systems engaged in learning, as well as how specific and reversibly manipulation of these cells in behaving animals impacts fear and extinction behavior.



Example of an amygdala intercalated cell filled during an electrophysiological recording. Neurons are revealed using histological methods, subjected to confocal imaging, and subsequently reconstructed in three dimensions to identify their anatomical properties.

A second line of research investigates extinction mechanisms and extinction networks, i.e. interactions of amygdala, hippocampus, and prefrontal cortex, which is critical for understanding extinction mechanisms and return of fear. By delineating the connectivity of subpopulations of excitatory and inhibitory neuron in the basolateral amygdala using optogenetic, targeted stimulation of prefrontal and hippocampal inputs to the amygdala we discovered microcircuits in the basolateral amygdala with distinct input properties (Hübner et al, 2014). Furthermore, we unraveled a specific role for a set of inhibitory synapses in fear extinction (Saha et al, 2017). In a parallel systemic approach, we asked which behavioral modulations impact extinction memories and found that sleep plays a critical role in the consolidation of fear extinction memories, a finding directly relevant for cognitive behavioral therapies (Melo and Ehrlich, 2016). Our future goal is to understand mechanisms that support extinction learning and that may be perturbed by interventions that compromise extinction, such as sleep perturbations.

A third line of research addressed 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 and extinction learning in juveniles also differes from adults. We investigated changes in amygdala networks. We have identified a number of changes in amygdala inhibitory control of excitatory neurons that occur between infancy and adulthood. Furthermore, we have shown that this changing inhibition can modulate excitatory sensory inputs differentially during development (Bosch and Ehrlich, 2015). Our data suggest that different aspects of increased inhibitory control may contribute to control fear specificity later in development. Our future goal is to further investigate development of specific inhibitory synapses and their affect plasticity to ultimately to address if and how this is linked to changes in learning behavior.

Overall, studying the circuits and mechanisms of fear and extinction memory provides basic insight into principles of memory formation. On the other hand, it allows to pinpoint mechanism that may be dysfunctional during inappropriate control of fear in conditions such as human anxiety and other neurophsychiatric or emotional disorders.

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