CENTER OF NEUROLOGY
TÜBINGEN

Annual Report 2019

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DIRECTORS

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Prof. Dr. Holger Lerche
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EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Hertie-Institut für klinische Hirnforschung

Universitätsklinikum Tübingen

Content

The Center of Neurology

The Center of Neurology

The Center of Neurology at the University of Tübingen was founded in 2001. It unites the Hertie Institute for Clinical Brain Research (HIH) and the University Hospital's Clinical Neurology Department. In research, teaching and patient care the center is dedicated to excellence in the study of the human brain and its disorders.

The Center of Neurology presently consists of six departments: Department of Neurology with Neurovascular Medicine (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). At the end of 2019, a sixth Department with a focus on Interdisciplinary Neuro-Oncology (Prof. Dr. Dr. Ghazaleh Tabatabai) complemented the scope of the HIH. All departments provide patient care within the University Hospital, while their clinical and basic research groups are part of the Hertie Institute.

The fact that all departments of the center actively participate, albeit to a different degree, in the clinical care of patients with neurologic diseases is central to the concept of successful clinical brain research at the Hertie Institute.

This 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 of 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 sechs Abteilungen: Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen (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). Ende 2019 wurde das HIH um die sechste Abteilung Neurologie mit interdisziplinärem Schwerpunkt Neuroonkologie (Prof. Dr. Dr. Ghazaleh Tabatabai) erweitert. Die ersten drei Genannten sowie die neueste Abteilung sind bettenführende Abteilungen in der Neurologischen Klinik, die anderen beiden 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 rund 5.500 Patienten stationär und mehr als 15.000 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

* The "Indisciplinary Section of Neuro-Oncology" (Prof. Dr. Dr. Ghazaleh Tabatabai) became the HIH's sixth department on January 1, 2020

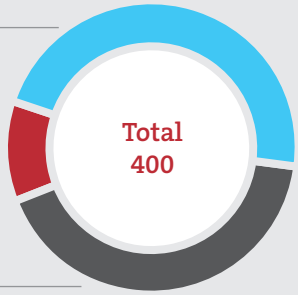
NUMBER OF STAFF IN 2019

Center of Neurology without nursing services (by headcount)

187
47% Third Party Funding

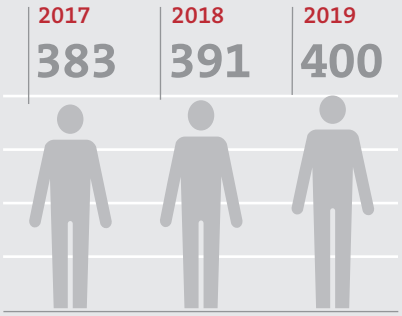
45
11% Hertie Foundation

168
42% Medical Faculty



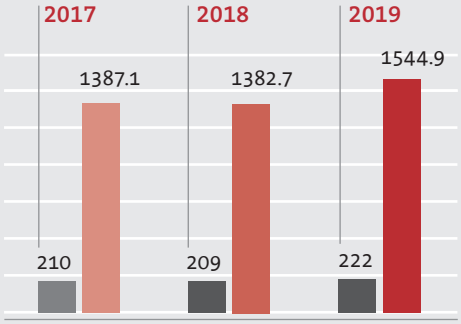
DEVELOPMENT OF STAFF

Center of Neurology (by headcount)



NUMBER OF PUBLICATIONS
IMPACT FACTORS

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



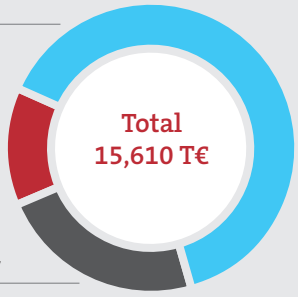
TOTAL FUNDINGS IN 2019

Center of Neurology

9,980 T€
64% Third party funding

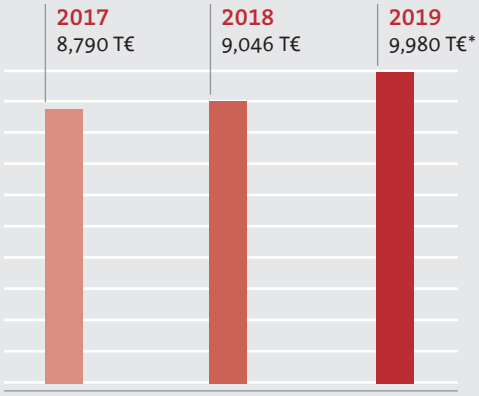
2,072 T€
13% Hertie Foundation

3,558 T€
23% University Hospital of Neurology & Medical Faculty



THIRD PARTY FUNDING

Center of Neurology



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

THIRD PARTY FUNDING IN 2019

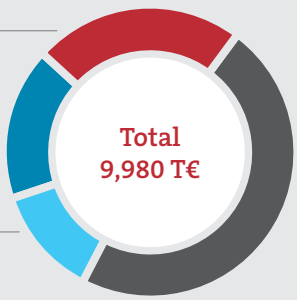
Center of Neurology

2,345 T€
DFG: 23.5%

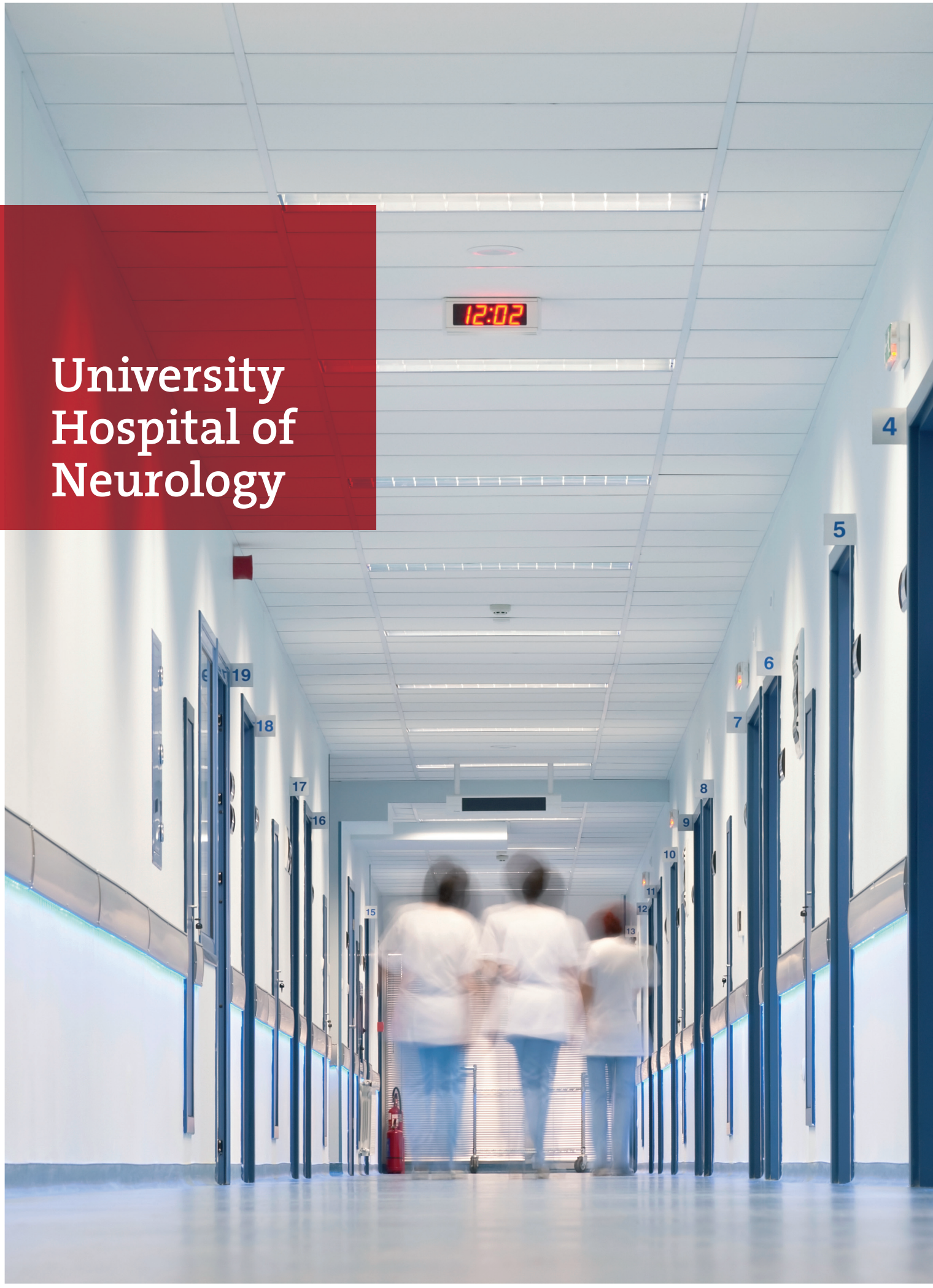
1,690 T€
BMBF: 16.9%

1,219 T€
EU: 12.2%

4,726 T€
Others: 47.4%



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 four 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 intensive care units of the University Hospital. A specialized video-EEG-monitoring unit allows continuous long-term recordings for patients with intractable epilepsies or those with an unclear diagnosis of a paroxysmal disorder.

In the outpatient unit of the clinic, more than 15,000 patients (including diagnostic procedures) 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 vier 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 auf Intensivstationen im Universitätsklinikum behandelt. Daneben gibt es eine spezielle Einheit zur kontinuierlichen Langzeit-Video-EEG-Ableitung (EEG-Monitoring) für Patienten mit schwer behandelbaren Epilepsien oder solchen mit unklarer Diagnose einer paroxysmalen Erkrankung.

In der neurologischen Poliklinik werden jährlich über 15.000 Patienten (inkl. diagnostischer Prozeduren) ambulant betreut, die meisten davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden.

Universitätsklinikum 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 5,400 patients in 2019.

NUMBER OF ADMISSIONS

5,448

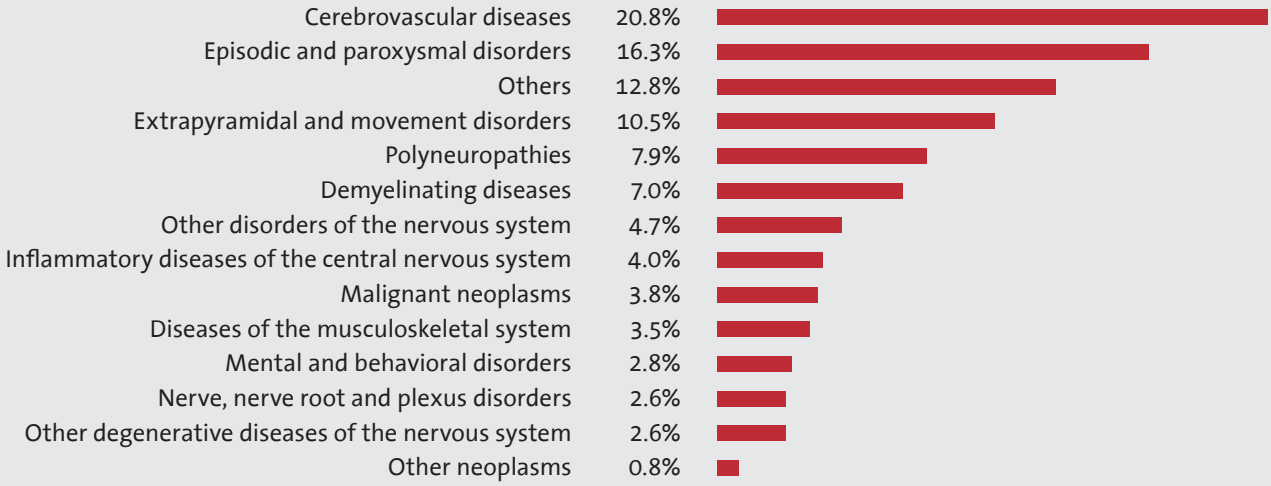
LENGTH OF STAY (IN DAYS)

4.7

CASE-MIX-INDEX 2019

1.47

INPATIENT DIAGNOSIS GROUPS



OUTPATIENT CARE

NUMBER OF CONSULTATIONS
(including diagnostic procedures)

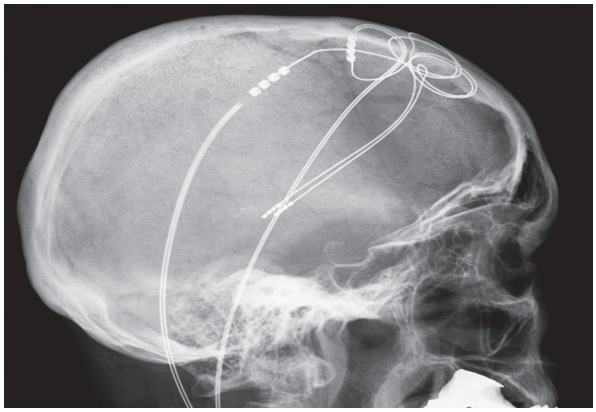
16,147

Outpatient Clinics

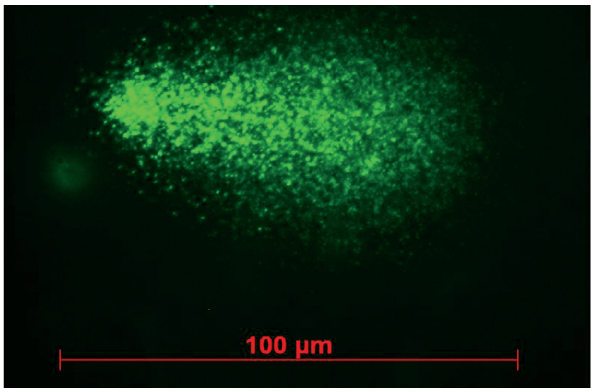
ATAXIA

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. TTo address the increasing number of genes causing ataxia we use latest next-generation techniques -such as whole exome-sequencing and whole genome sequencing for genetic diagnostics. On a research basis, this is complemented by transcriptomics to solve cases that remain without molecular diagnosis with routine procedures. Therapeutic options are tailored to the underlying cause of ataxia, the genetic defect, and concomitant symptoms.

Our outpatient clinics follows a stringent path towards trial-readiness. Together with Dr. W. Ilg and Prof. Dr. M. Giese from the Center for Integrative Neuroscience (CIN) we developed digital-motor outcome measures based on advanced movement recording and wearables technology, allowing to assess motor performance in ataxia patients' real-life. These measures allow to serve as treatment-response measures, as demonstrated by means of the novel neurorehabilitative treatment approaches developed by our team, e.g. ataxia-tailored physiotherapy protocols or special videogame-based exercise programs ("exergames") for ataxia. These digital-motor outcome measures are complemented by our omics research in molecular outcome measures, aiming to identify and validate fluid biomarkers ideally assessable even in peripheral blood. First candidate blood biomarkers (NfL, pNfH) have now been identified by our team for several degenerative ataxias.



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.

Within the European Ataxia Study Group (www.ataxia-study-group.net) we participate in natural history and biomarkers studies of sporadic late-onset ataxias (SPORTAX). Moreover, we are fundiong members 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 (RISCA). This initiative aims to develop interventions in stages where neuronal resources are not yet exhausted and subjects' way of living is not yet severely incapacitated. Further, our ataxia clinic is coordinating a global network on early onset ataxias (EOA). Prof. Synofzik leads the worldwide EOA registry and is scientific coordinator of the EU-funded consortia PREPARE –(Preparing therapies for autosomal-recessive ataxias) as well as PROSPAX (An integrated multimodal progression chart in spastic ataxias; together with Dr. Rebecca Schüle) which facilitate establishing trial-ready cohorts and future molecular treatments on a global scale. At the same time, these networks - together with innovative multi-omics trans-European project SOLVE-RD (Solving the Unsolved Rare Diseases) - provide rich resources 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 Prof. Dr. M. Synofzik and Prof. Dr. L. Schöls.

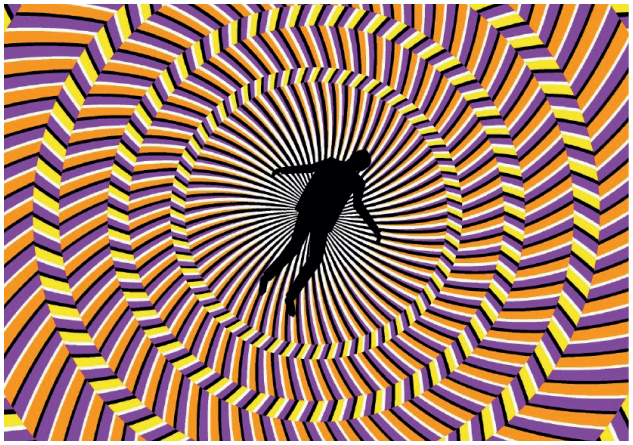
DEEP BRAIN STIMULATION

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.brain-stimnet.de) involves close interaction between neurologists, neurosurgeons, psychiatrists and therapists. Patients are referred from outside neurologists as well as from our own outpatient clinics for movement disorders.

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., 2013, NEJM,). In addition, it was demonstrated that DBS further improves hyperdopaminergic behaviours as compared to best medical treatment (L'Hommee et al., 2018; Lancet Neurol) and counteracts dopaminergic sensitization in motor, neuropsychiatric, sensory, and autonomous symptom domains. 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 suggested an effect on freezing of gait (Weiss et al., 2013, BRAIN). The work on nigral stimulation for resistant freezing of gait now translated into a large multicentre randomized controlled trial initiated and coordinated by the Tübingen Centre (ClinTrials.gov: NCT02588144). The trial recruitment was finished with results expected in summer 2020.

Patients who are likely to benefit from DBS undergo a detailed program of standardized neurological, neuropsychological, neuroradiological, and cardiological examinations on our inpatient 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. Additionally, video-based counseling are increasingly used in order to facilitate long-term care of DBS patients. Patients are seen by a specialized PD nurse (Mr Friedhelm Chmell), and expert neurologists, namely Idil Cebi, Mohammad Hormozi, Maria-Sophie Breu,and Prof. Dr. D. Weiß.

Outpatient Clinics



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 collaboration 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).

DYSTONIA AND BOTULINUM TOXIN TREATMENT

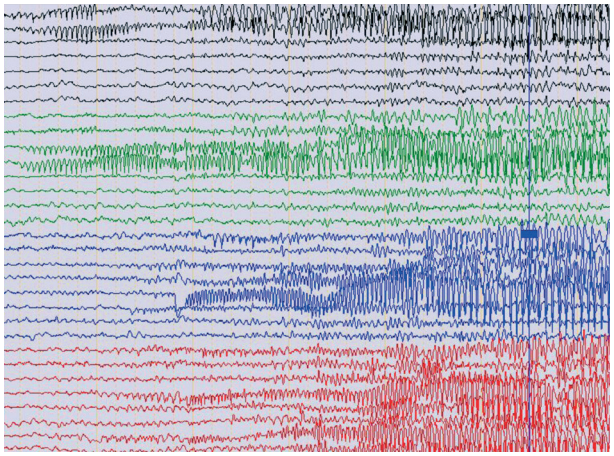
The outpatient clinic offers a comprehensive diagnostic work-up and the full range of treatment options for patients with different forms of dystonia, spasticity, and other movement disorders. In cooperation with the headache clinic (PD Dr. S. Schuh-Hofer) and the clinic for otolaryngology (Prof. Dr.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

Approximately 500 to 600 patients are treated regularly with botulinum toxin (BoNT) injections in intervals of 3 to 6 months. Of those nearly 50 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 20 % 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 ergo therapies are offered. Over the last years, an increasing number of outpatients with spasticity have been managed with a combined treatment of BoNT injections and physiotherapy at the local MTR (Medical Training and Rehabilitation Center, University of Tübingen).

Appointments are scheduled every week on Tuesday, Wednesday and Thursday in the Outpatient Clinic of the Center of Neurology (contact: bewegung@med.uni-tuebingen.de). The medical staff of this unit includes Dr. E. Lohmann (head), Dr. F. Thies (resident) and S. Killinger (technical assistant).



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

EPILEPSY

The Department of Neurology and Epileptology provides a large inpatient and outpatient clinic 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 psychogenic non-epileptic seizures, migraine, transient ischemia, and also rare disorders, such as episodic ataxias, narcolepsy and paroxysmal movement disorders.

The epilepsy outpatient clinic (Prof. Dr. H. Lerche, Dr. M. Schreiber) offers consulting and treatment in particular for new-onset patients and those that are difficult to diagnose or difficult to treat, and for specific questions including contraception and 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 22 beds (Ward 42/43L), running under the supervision of Prof. Dr. A. Grimm, Dr. P. Martin and Dr. M. Schreiber, 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 (current lead Prof. Dr. H. Lerche). Epilepsy surgery, an effective treatment for patients resistant to anti-epileptic 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. Gharabaghi, Dr. G. Naros). Altogether we treat about 2,000 adult epilepsy patients per year.

Outpatient Clinics

Neuro-geriatric patients receive physiotherapy for mobility training.

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 recruitment 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 multi-center 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. This will now be heralded by the trans-European consortium "GENFI-prox", which will establish a multimodal, multi-omics signature allowing to stratify genetic at-risk FTD subjects directly prior to clinical disease onset for these upcoming molecular treatment trials. The clinic is run by Dr. C. Wilke and Dr. D. Mengel and supervised by Prof Dr. M. Synofzik.

HEADACHE AND NEUROPATHIC PAIN

This outpatient unit is dedicated to provide state-of-the-art medical treatment to patients suffering from headache/facial pain or other neurological pain syndromes. The unit is specialized in the differential diagnosis and treatment of primary and secondary headache syndromes with a particular focus on chronic pain states like chronic migraine (CM), medication-overuse headache (MOH) or chronic tension-type headache (CTTH). Another particular focus is on the diagnosis and treatment of rare primary headache syndromes like e. g. cluster headache, episodic/chronic paroxysmal hemicrania, hemicrania continua or SUNCT syndrome. Inpatient treatment will be available in selected cases (e. g. exacerbation of migraine, cluster headache or trigeminal neuralgia).

Our outpatient unit is also specialized in the diagnosis and treatment of neuropathic pain, where we work in close collaboration with our in-house 'Neuromuscular Unit' and with the Departments of Anesthesiology and Neurosurgery. To address psychosomatic aspects and psychiatric comorbidities of our pain patients, our unit works in close collaboration with other local clinical partners (e.g. Dept. of Psychiatry, Dept. of Psychosomatic Medicine, Institute for General Medicine and Interprofessional Health Care). Multi-morbid patients who need concerted diagnostic and therapeutic measures of many different medical disciplines are discussed in a multi-professional team within our monthly held 'Interdisciplinary Pain Conferences', which is organized by the Department of Anesthesiology.

The Headache/Pain 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). To expand our knowledge on the pathophysiology of primary headache disorders like migraine, our unit is involved in experimental studies on the role of the neuropeptide CGRP for headache pathophysiology. A second focus is on the role of sleep for pain and headache, using psychophysical, electrophysiological and neuroendocrinological methods.

The outpatient clinic is run by PD Dr. Sigrid Schuh-Hofer, together with a team of three colleagues from the Neurological Department (Dr. med. Victoria Schubert, Dr med. Justus Marquetand and Dr. med. Sabine Thewes). Patients should be referred preferably by neurologists or pain specialists. Appointments can be arranged by telephone (07071-29-82051) and are available on Monday and Thursday (and in addition on an individual basis). Further practical information is provided by our Homepage (https://www.medizin.uni-tuebingen.de/de/das-klinikum/einrichtungen/kliniken/neurologie/ambulanzen/kopfschmerz-und-neuropathischer-schmerz).

Outpatient Clinics

LEUKODYSTROPHIES IN ADULTHOOD

Leukodystrophies are usually regarded as diseases of infancy and childhood. However, adult-onset forms are increasingly recognized in many leukodystrophies. In cooperation with the Institute of Medical Genetics and Applied Genomics in Tübingen we established whole exome sequencing for genetic diagnostics for our patients. On a research basis also whole genome sequencing and transcriptomics are used in cases that cannot be solved by standard procedures. In cooperation with the Department of Neuropediatrics in the Children's Hospital we assess the natural course of leukodystrophies and especially of adult-onset variants as an essential prerequisite for therapeutic trials. In collaboration with the Department of Neuroradiology we use high-end MRI techniques and MR spectroscopy to identify characteristic MRI patterns and 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. D. Mengel and supervised by Prof. Dr. M. Synofzik.

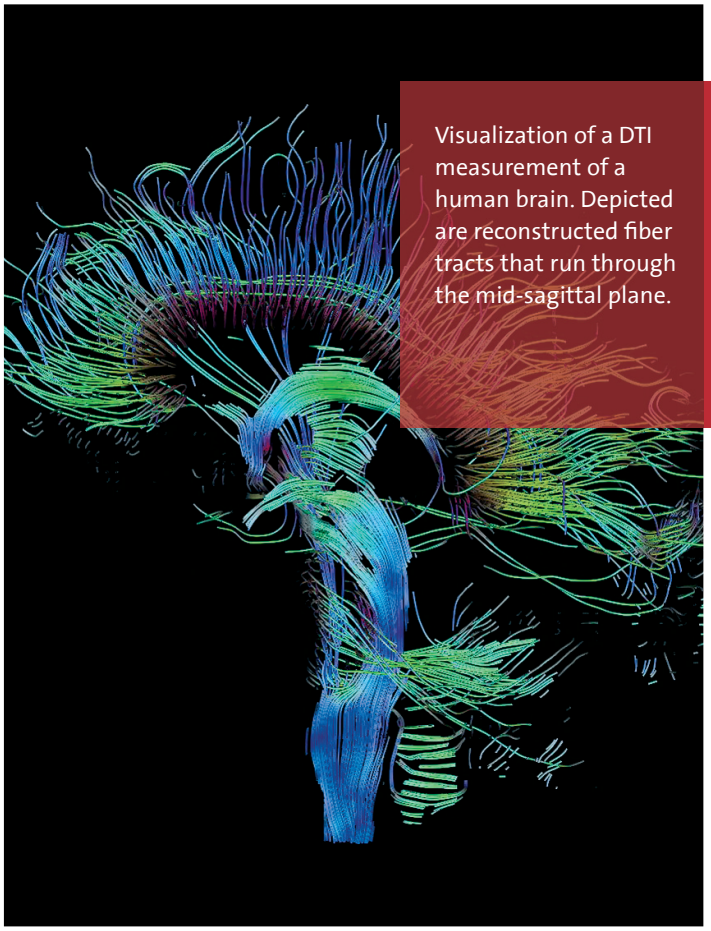
MYOPATHIES AND MYASTHENIA GRAVIS

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).

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 the rheumatology (INDIRA network), neuroophthalmology, neuroradiology, and neuropathology departments. 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 17 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 coordinators /nurses. In 2019, the outpatient clinic was run by Dr. J. Dünschede (resident) , Dr. C. Ruschil (resident), Dr. A. Abdelhak (resident) and supervised by PD Dr. M. Krumbholz and PD Dr. M. Kowarik (attending physicians) both with special expertise in MS and other immune-mediated neurological disorders), and Prof. Dr. U. Ziemann (director).



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

Outpatient Clinics

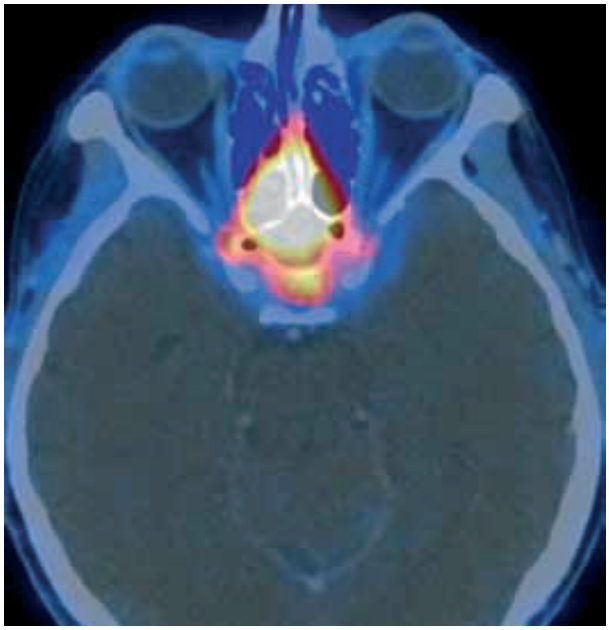
NEUROLOGIC MEMORY OUTPATIENT CLINIC

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, cognitive training, and social counseling are provided, in co-operation with the memory clinic of the Department of Psychiatry. The primary research aim is the early detection of cognitive worsening and dementia in movement disorders, especially to define prodromal markers for dementia in Parkinson's disease. As a substantial impact on the activities of daily living function is mandatory for diagnosis of dementia, varying scales and objective measurements are evaluated that might serve as diagnostic tools even in the pre-stage of dementia. 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.

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.



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

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).

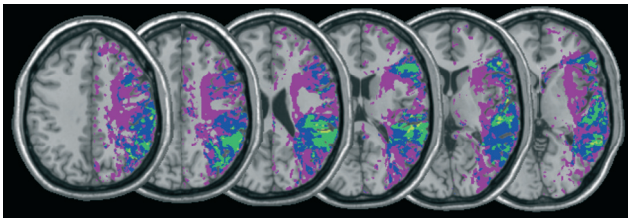
Patients who need surgical or postoperative treatments or procedures will be admitted to the wards in the Departments of Neurology or Neurosurgery depending on the treatment and will be supervised by the Neuro-Oncology team in both departments.

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

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. Sophie Hirsch (neurology resident), Dr. Mohamed Elnaggar (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), PD Dr. M. Renovanz (neurosurgery board-certified, interdisciplinary attending).

NEUROPSYCHOLOGY

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



In patients with stroke lesions, we use normalized Perfusion-Weighted Imaging (PWI) to identify the abnormally perfused brain area(s) that receive enough blood supply to remain structurally intact, but not enough to function normally. In order to recognize these common areas in groups of patients, we analyse the increase of time-to-peak (or TTP) lesion-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.

Outpatient Clinics

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, small vessel 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 Prof. Dr. S. Greulich (cardiologist and internist, shared appointment by the Department of Neurology & Stroke 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 PD Dr. S. Poli, and Prof. Dr. U. Ziemann.

PARKINSON'S DISEASE

Outpatient Clinic (Head Brockmann)
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 national and international 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. Importantly, we take part in the world-wide first clinical trials aiming at specific Parkinson-associated pathways: Epi589-15-002 by BioElectron, MitoPD, BP39528_ Pasadena by Roche, and ACT14820/MovesPD by Sanofi. Of note, our centre is the leading clinical site for Germany and PDGBA patients from our outpatient clinic are part of this first pathway-specific clinical trial in PD (ACT14820/MovesPD). Appointments are scheduled daily in the outpatient clinic of the Center of Neurology.

Focus of Research
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.

Outpatient clinic for deep brain stimulation and continous application (Head Weiß)
Another focus is the treatment of patients in later stages of the disease with severe non-motor symptoms or drug-related side effects. In some of these patients, treatment may be optimized in co-operation with the Ward for 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.

Outpatient Clinics

POLYNEUROPATHIES AND NERVE TRAUMA

Up to 1000 patients/year with polyneuropathy, including immune-mediated neuropathies, hereditary neuropathies or acquired neuropathies are diagnosed an treated by our team of Dr. Winter, Dr. Willikens, Dr. Stahl and Prof. Grimm. We perform several treating and observational studies concerning imaging and electrophysiology of the peripheral nerve system. Also rare polyneuropathies, such as the hereditary TTR-amyloidosis or the POEMS syndrome are diagnosed and treated. There is a broad cooperation with other University hospitals, i.e. Aachen, Jena and Basel as well as with internal partners, i.e. the department of human genetics and neuropediatrics.

Further, we installed the peripheral nerve lesion team, which gives us the possibility for interdisciplinary patient examinations twice a week together with the department of neurosurgery and reconstructive surgery of the BGU hospital. The Tübinger Nerve Team is an interdisciplinary staff, which is an innovative group, that handles therapeutic concepts and organizes observational studies concerning peripheral nerve traumata. Our department is involved with four colleagues (Prof. Grimm, Dr. Stahl, Dr. Kegele and Dr. Winter) and the team of the EMG.

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.

RARE NEUROLOGICAL DISEASES

The outpatient clinic for rare neurological diseases is part of the Rare Disease Center in Tübingen and is dedicated to patients with rare diseases of unknown cause. Doctors and patients are asked to submit a standardized questionnaire together with their medical records, family history and imaging data for interdisciplinary consideration by a board of neurologists, geneticists and neuroradiologists. If substantial indicators for a rare disease are evident, recommendations of additional investigations, an outpatient visit or admission to the ward are prepared including specific neurological procedures, genetic diagnostics or neuro-imaging. The clinic is run by Dr. L. Zeltner and Prof. Dr. L. Schöls.

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.

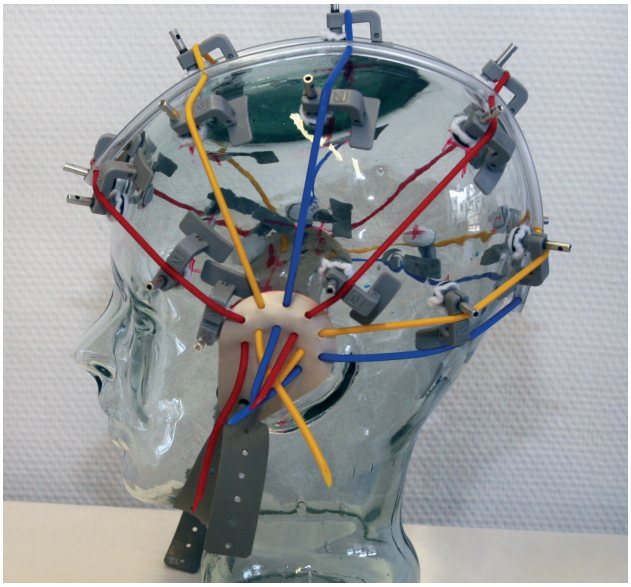
TMS

The transcranial magnetic stimulation (TMS) outpatient clinic was established at the Center of Neurology in 2019 and is one of the first such clinics in Europe providing state-of-the-art advanced therapeutic brain stimulation treatment options to support neurorehabilitation in patients with chronic stroke. The clinic closely collaborates with rehabilitation and physiotherapy centers and has a treatment capacity of more than 2.000 sessions annually. The treatment focuses on motor symptoms and aphasia. The scientific mission of this clinic is to advance the therapeutic efficacy of TMS and support a paradigm-shift toward innovative personalized closed-loop stimulation approaches. To this end, working closely with the center for clinical trials, it provides the expertise and infrastructure to design and perform large-scale multi-center scientifically-led clinical TMS trials conforming to a high GCP standard. The TMS outpatient clinic part of the department of vascular neurology (director: Prof. Ziemann) and is staffed with a dedicated team of medical doctors, scientists, study nurses and administrative personnel.

Clinical Laboratories

CLINICAL CHEMISTRY LABORATORY FOR NEUROLOGY

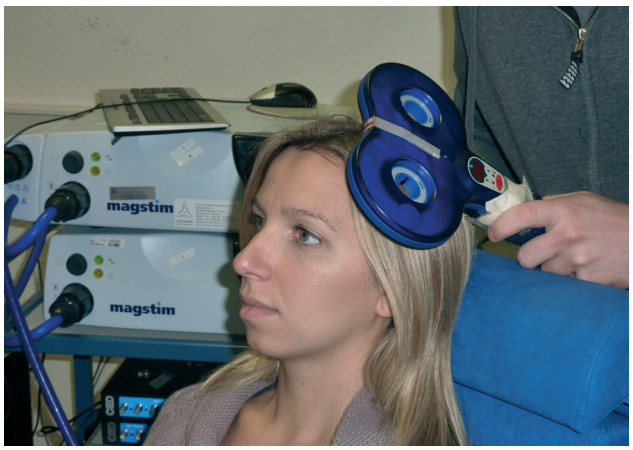
The Clinical Chemistry Laboratory collects more than 1,800 samples of cerebrospinal fluid (CSF) per year throughout the University Medical Center. Oligoclonal bands in CSF and serum are detected by isoelectric focusing and silver staining. Junior staff are routinely trained to perform basic CSF examination 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 disorders: autoantibodies to acetylcholine receptors, muscle specific tyrosine kinase (MuSK), titin (myasthenia gravis), aquaporin-4 (NMOSD), MOG ("MOGAD"), autoantibodies associated with neurological paraneoplastic syndromes and autoimmune encephalitis, myositis-associated antibodies, 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 PD 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 Dr. M. Schneider.



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.

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. Since this year we have a new high-resolution probe of up to 24 Mhz (Canon Medical Systems Aplio 800i). A further portable system with 1 up to 14Mhz broad band linear probe is also available. 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. In 2019 more than 2000 ultrasound examinations were performed. 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. 2018 the Tübinger nerve team was funded, consisting f medical staff of Neurosurgery (Prof. Schuhmann and Dr. Herlan) of the BG hospital (Prof. Daigeler, PD Dr. Koolbenschlag, Dr. Meier), Neuroradiology (Dr. Lindig) and our team (Dr. Stahl, Dr. Winter, Dr. Willikens, Dr. Kegele and Prof. Grimm). Prof. Dr. A. Grimm is the vice president of the german ultrasound society, department Neurology (DEGUM). Further DGKN/DEGUM certified colleagues are T. Rattay, C. Ruschil, N. Winter, N. Dammeier, V. Schubert 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 2019, more than 3100 patients were seen. 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, 2000 patients were examined by neuromuscular ultrasound ni 2019.

In 2019, the EMG Laboratory was run by a team of technical assistants (S. Berger, A. Deutsch, V. Servotka, J. Wittlinger) and residents (N. Winter, J. Tünnerhoff, H. Richter, J. Kegele, H. Hengel, B. Bender, L. Roncoroni, S. Hamzehian, J. Marquetand)under the supervision of Prof. Dr. A. Grimm and Dr. P. Martin. In 2019 further colleagues have been certified by the DGKN for EMG (V. Schubert) and by the DEGUM for nerve and muscle ultrasound (C. Ruschil, N. Winter, V. Schubert).

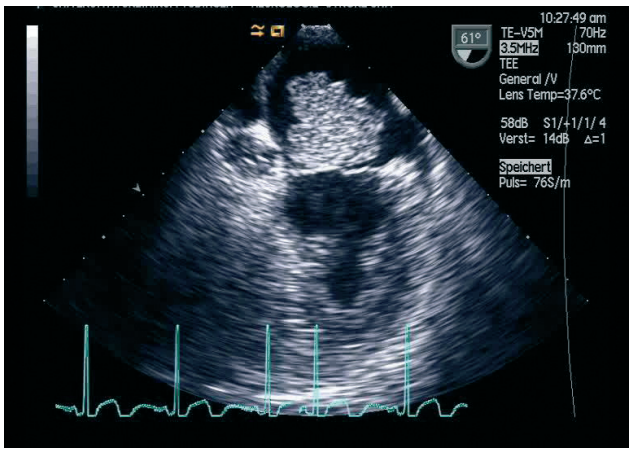
Clinical Laboratories

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 covers 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 are used (chair rotation, head-impulse-test, head-shaking). Eye movements are usually studied by deploying video-oculography. The integrity of otolith organs and their central connections are examined by applying acoustic 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 are 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 specific visual experiences or distinct disturbances of 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. Prof. Z. Hafed and Prof. U. Ilg (both HIH) contribute their expertise in the study of eye movements and eye movement-related vision to clinical research projects.

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 Prof. Dr. A. Grimm, Dr. P. Martin 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 four 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.

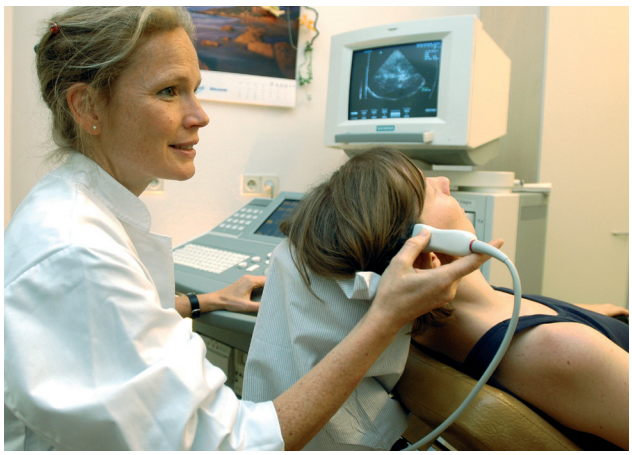
The neurocardiology laboratory, headed by the cardiologist and internist PD Dr. S. Greulich, provides the full spectrum of non-invasive cardiac work-up, such as transthoracic and transesophageal echocardiography including M-Mode, 2-D mode, pulse wave, continuous-wave and color Doppler investigations 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. Ruckwied, M. Früchel, J. Wittlinger 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 2019, 2,103 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 Lena Rempfer.

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 2019, 2,549 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 14 speech therapists under the supervision of M.Sc. Natalie Rommel 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 2019, 1,961 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 18 years ago, the Hertie Institute has grown to more than 400 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 six departments. They combine basic and clinical research with patient care, albeit to different degrees and with variable emphasis: four departments focusing on Stroke, Epileptology, Neurodegenerative Disorders, and Neuro-Oncology 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 24 professors and 32 research groups. Twenty-nine belong to the aforementioned departments, three are set up as independent research groups. The independent research group of Prof. Dr. Markus Siegel has joined the HIH in 2019, investigating neural dynamics and magnetoencephalography.

In 2019, scientists at the Center of Neurology obtained more than 9 million Euros in third party funding and published more than 220 papers in peer-reviewed journals.

In February 2019, Theresia Bauer, Baden-Württemberg's Minister of Science, visited the HIH to learn more about the research at the institute. She emphasized the importance of the HIH as the only center in Germany that combines basic neuroscientific and research with patient care under one roof.

The Neuroscience Campus Get Together, which was jointly organized and funded by the HIH and its neighbors, the German Center for Neurodegenerative Diseases (DZNE) and the Werner Reichardt Center for Integrative Neuroscience (CIN) in the year 2015 and has continued since then on a yearly basis, met again with great success among scientists and staff members in July 2019.

Tübingen is one of six top research locations in Germany that have been granted funding in December 2019 as part of the newly initiated "Hertie Network of Excellence in Clinical Neuroscience". The Hertie Foundation's network and junior researcher support programme, which is funded with five million euros, aims to facilitate the transfer of scientific findings into clinical practice in the field of clinical neurosciences.

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)

18 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 sechs 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). Ende 2019 wurde das HIH um die sechste Abteilung Neurologie mit interdisziplinärem Schwerpunkt Neuroonkologie (Prof. Dr. Dr. Ghazaleh Tabatabai) erweitert. Die ersten drei Genannten sowie die neueste Abteilung sind bettenführende Abteilungen in der Neurologischen Klinik, die anderen beiden 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 24 Professorinnen und Professoren und 400 Mitarbeitende in 32 Arbeitsgruppen tätig, wovon drei unabhängige Forschungsgruppen darstellen. Die unabhängige Forschungsgruppe von Prof. Dr. Markus Siegel verstärkt seit 2019 das HIH. Sie beschäftigt sich mit neuronaler Dynamik und Magnetenzephalographie.

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

Theresia Bauer, Ministerin für Wissenschaft, Forschung und Kunst Baden-Württemberg, zu Besuch am HIH.

In den Abteilungen sind zurzeit 24 Professoren und etwa 400 Mitarbeiter in 32 Arbeitsgruppen tätig. Die Gemeinnützige Hertie-Stiftung wendete bisher rund 60 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

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 2019 rund 9 Millionen Euro an Drittmitteln eingeworben und mehr als 220 Veröffentlichungen in wissenschaftlichen Fachzeitschriften publiziert. Diese Zahlen belegen unter anderem die wissenschaftliche Leistungsfähigkeit des Zentrums. Die Gemeinnützige Hertie-Stiftung wendete bisher 60 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

Theresia Bauer, Ministerin für Wissenschaft, Forschung und Kunst Baden-Württembergs besuchte im Februar das HIH, um sich über dessen Forschungsaktivitäten zu informieren. Dabei hob sie die Bedeutung des HIH als bislang einziges Zentrum in Deutschland hervor, das neurowissenschaftliche Grundlagenwissenschaft und Forschung mit der Patientenversorgung unter einem Dach verbinde.

Das Neuroscience Campus Get Together, das gemeinsam mit seinen Nachbarn, dem Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE) und dem Werner Reichardt Centrum für Integrative Neurowissenschaften (CIN), im Jahr 2015 initiiert und seitdem jährlich fortgeführt wurde, stieß auch im Juli 2019 auf großen Erfolg bei Wissenschaftlerinnen und Wissenschaftlern und allen Mitarbeitenden.

Tübingen ist einer von deutschlandweit sechs Spitzenstandorten, die seit Dezember 2019 im Rahmen des neu initiierten „Hertie Network of Excellence in Clinical Neuroscience“ gefördert werden. Das mit fünf Millionen Euro geförderte Netzwerk und Nachwuchsförderprogramm der Gemeinnützigen Hertie-Stiftung zielt darauf ab, im Bereich der klinischen Neurowissenschaften die Umsetzung von wissenschaftlichen Erkenntnissen in die klinische Praxis zu erleichtern.

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

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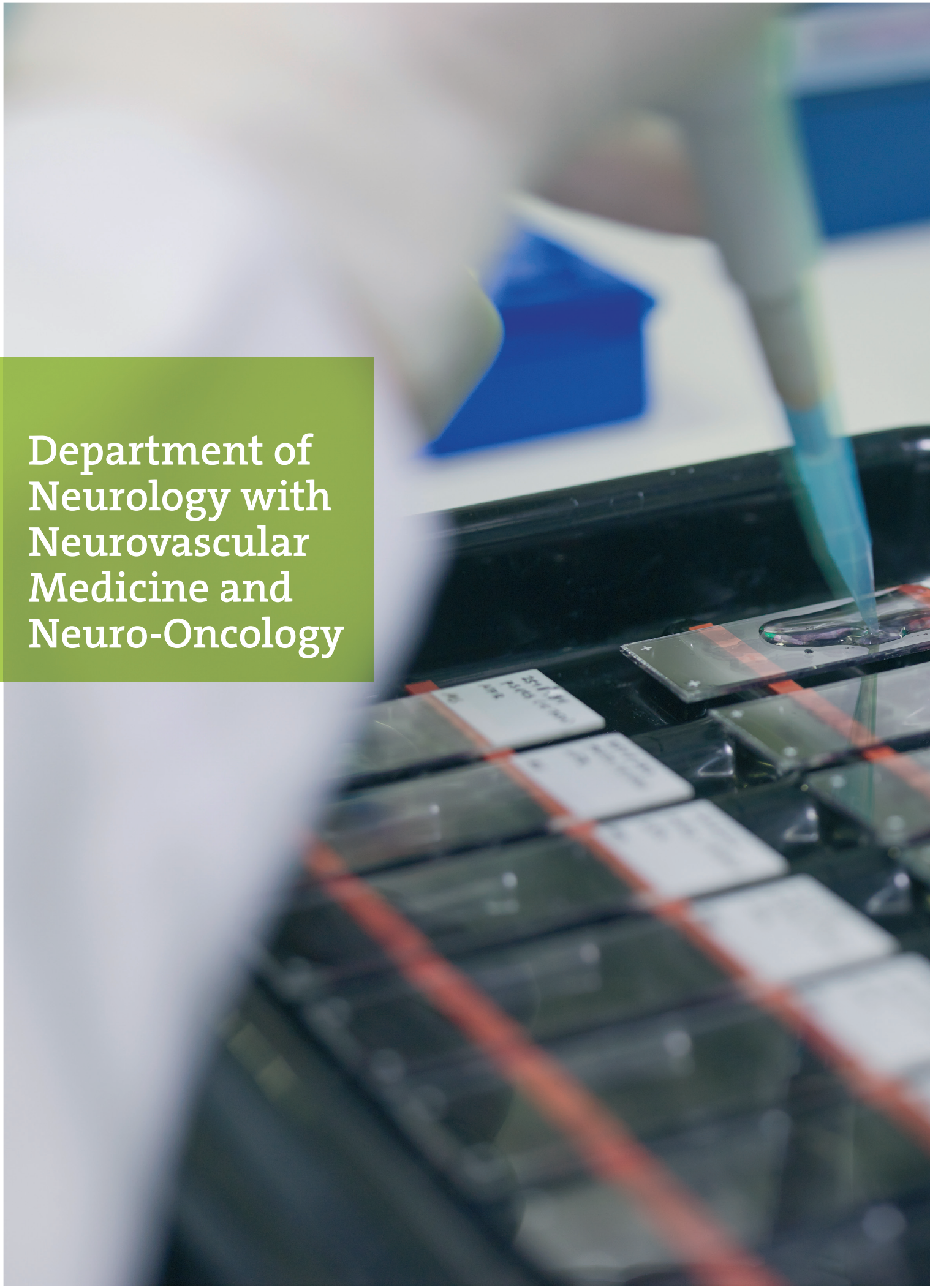
Department of Neurology with Neurovascular Medicine and Neuro-Oncology



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 metastases. Specialized teams in stroke medicine (intensive care and stroke unit, acute stroke rehabilitation), neuroimmunology and neurooncology provide expert multidisciplinary care for patient with these disorders. Stroke medicine is also represented in the Center of Neurovascular Disease Tübingen (ZNET) that coordinates patient care and

research at the interdisciplinary interface of Neurology, Neurosurgery and Neuroradiology. The ZNET has also formed a network with surrounding hospitals (Reutlingen, Albstadt, Calw, Rottenmünster, Kirchheim) to provide emergency care for acute stroke patients. 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 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 expert counseling of patients, the best available therapy, and provide the infrastructure for clinical trials and investigator-initiated research. By the end of 2019, the department was renamed "Department of Neurology & Stroke" to account for the advancement of the Section of Neuro-Oncology into a new department within the Center of Neurology: "Department Neurology with Interdisciplinary Focus Neuro-Oncology" (director: Prof. Ghazaleh Tabatabai).

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, six Research Groups exist with focus on brain networks & plasticity (Prof. Dr. Ulf Ziemann), stroke and neuroprotection (PD Dr. Sven Poli), clinical and experimental neuro-oncology (Prof. Dr. Dr. Ghazaleh Tabatabai), molecular neuro-oncology (Prof. Dr. Ulrike Naumann), speech disorders (Prof. Dr. Hermann Ackermann) and the newly formed group on neurological B-cell immunology (PD Dr. Markus Kowarik). The research laboratories are located in immediate proximity of the clinical services in the CRONA hospital building, in the Hertie Institute for Clinical Brain Research, and in the Center of Integrative Neuroscience building.

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 offers lectures for medical students, physicians in training, nursing staff, physiotherapists and speech therapists.

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 neurology scientific colloquium features guest researchers who present their current work that typically covers translational aspects of brain research, and is of broad interest for clinicians, clinician scientists and medical scientists alike. 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.

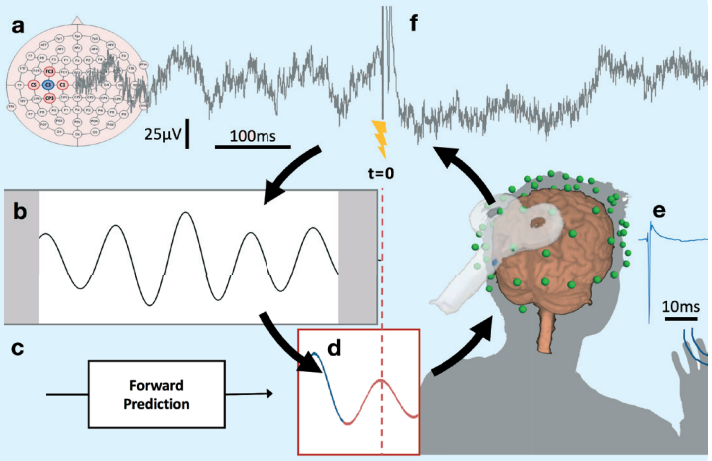
Neuroplasticity

Brain Networks & Plasticity (BNP) Laboratory

Head: Prof. Dr. Ulf Ziemann

Team: 29 members

Key words: human motor cortex / motor learning / plasticity / connectivity / stroke rehabilitation / non-invasive brain stimulation / brain-state-dependent stimulation / closed-loop stimulation / EEG / MEG / MRI / fMRI / TMS-EEG / EEG-TMS / neuropharmacology / working-memory network / motor network



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 estimate instantaneous brain states from the ongoing electroencephalography (EEG) signal. We are capable of triggering transcranial magnetic stimulation (TMS), based on the amplitude and phases of specific endogenous oscillations at millisecond precision. We design individually optimized spatial filters to isolate target brain oscillations at multiple sites including inter- and intrahemispheric 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 excitability and connectivity and gating TMS-induced plasticity in the motor cortex, we also tar-get beta oscillations in the motor cortex, and alpha and theta oscillations in prefrontal cortex, which are important for regulating working memory and emotion.

We have demonstrated, for the first time in the human, that EEG-triggered 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 long-term potentiation (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 effective connectivity. We are currently working on further advancing this technique by reading out the relevant oscillatory states using more sophisticated spatial filters and developing source space-based real-time signal analyses. The approach of EEG-triggered TMS has the potential to significantly improve 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 necessary 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 research using TMS in healthy subjects, 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 Psychiatry with patients with depression (BOSSFRONT) and one in subacute stroke patients (STROKEBOSS). We were successful in acquiring a federal funding grant (EXIST) to develop a therapeutic personalized brain-stimulation device (NEUROSYNC) and a Synergy grant from the European Research Council (ConnectToBrain) that will develop highly innovative therapeutic whole-brain closed-loop stimulation in collaboration with partners at Aalto University (Finland) and Chieti University (Italy). Finally, we have established a TMS outpatient clinic to offer established and novel brain-state-dependent TMS treatment protocols in patients with chronic stroke. This clinic is unique in Germany at the level of university hospitals.

Pharmaco-TMS-EEG

Several projects aim at improving our understanding of the physiological underpinnings of TMS-evoked EEG potentials: Combining TMS and EEG constitutes a powerful tool to directly assess human cortical excitability and connectivity. TMS of the primary motor cortex elicits a sequence of TMS-evoked EEG potentials (TEPs) and TMS-induced oscillations. Building on our earlier work in the GABAergic system, we have now studied the effects of specific antiepileptic drugs (such as carbamazepine, brivaracetam, and tiagabine), and drugs with action in the glutamatergic system (perampanel, dextromethorphan). The pharmaco-TMS-EEG approach opens a novel window of opportunity to study the effects of specific drugs, which are relevant for neurological disorders such as epilepsy or ischemic stroke, on brain excitability and effective connectivity. We currently also experimentally address the problem that TEPs are contaminated by peripherally evoked potentials due to somatosensory stimulation of the scalp and auditory stimulation by the TMS pulse. We do this by developing a realistic sham condition and repeating pharmaco-TMS-EEG experiments. The aim is to provide TEPs that represent a "clean" brain response to TMS.

SELECTED PUBLICATIONS (2018 - 2020)

Bergmann TO, Lieb A, Zrenner C, Ziemann U (2019) Pulsed facilitation of corticospinal excitability by the sensorimotor mu-alpha rhythm. *J Neurosci* 39:10034-43

Darmani G, Bergmann TO, Zipser C, Baur D, Müller-Dahlhaus F, Ziemann U (2019) Effects of antiepileptic drugs on cortical excitability in humans: A TMS-EMG and TMS-EEG study. *Hum Brain Mapp* 40:1276-89

Desideri D, Zrenner C, Ziemann U, Belardinelli P (2019) Phase of sensorimotor mu-oscillation modulates cortical responses to TMS of the human motor cortex. *J Physiol* 597:5671-86

Gordon PC, Desideri D, Belardinelli P, Zrenner C, Ziemann U (2018) Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. *Brain Stimul* 11:1322-1330

Gordon PC, Zrenner C, Desideri D, Belardinelli P, Zrenner B, Brunoni AR, **Ziemann U** (2018) Modulation of cortical responses by transcranial direct current stimulation of dorsolateral prefrontal cortex: A resting-state EEG and TMS-EEG study. *Brain Stimul* 11:1024-32

Rogasch NC, **Zipser C, Darmani G**, Mutanen TP, Biabani M, **Zrenner C, Desideri D, Belardinelli P, Müller-Dahlhaus F, Ziemann U** (2020) The effects of NMDA receptor blockade on TMS-evoked EEG potentials from prefrontal and parietal cortex. *Sci Rep* 10:3168

Schaworonkow N, Gordon PC, Belardinelli P, Ziemann U, Bergmann TO, Zrenner C (2018) mu-Rhythm Extracted With Personalized EEG Filters Correlates With Corticospinal Excitability in Real-Time Phase-Triggered EEG-TMS. *Front Neurosci* 12:954

Schaworonkow N, Triesch J, **Ziemann U, Zrenner C** (2019) EEG-triggered TMS reveals stronger brain state-dependent modulation of motor evoked potentials at weaker stimulation intensities. *Brain Stimul* 12:110-8

Stefanou MI, Baur D, Belardinelli P, Bergmann TO, Blum C, Gordon PC, Nieminen JO, **Zrenner B, Ziemann U, Zrenner C** (2019) Brain State-dependent Brain Stimulation with Real-time Electroencephalography-Triggered Transcranial Magnetic Stimulation. *J Vis Exp* (150). doi: 10.3791/59711

Stefanou MI, Desideri D, Belardinelli P, Zrenner C, Ziemann U (2018) Phase synchronicity of mu-rhythm determines efficacy of interhemispheric communication between human motor cortices. *J Neurosci* 38: 10525-34

Thies M, Zrenner C, Ziemann U, Bergmann TO (2018) Sensorimotor mu-alpha power is positively related to corticospinal excitability. *Brain Stimul* 11:1119-22

Ziemann U, Romani GL, Ilmoniemi RJ (2019) "ConnectToBrain" : Synergy project for therapeutic closed-loop stimulation of brain network disorders. *Nervenarzt* 90:804-8

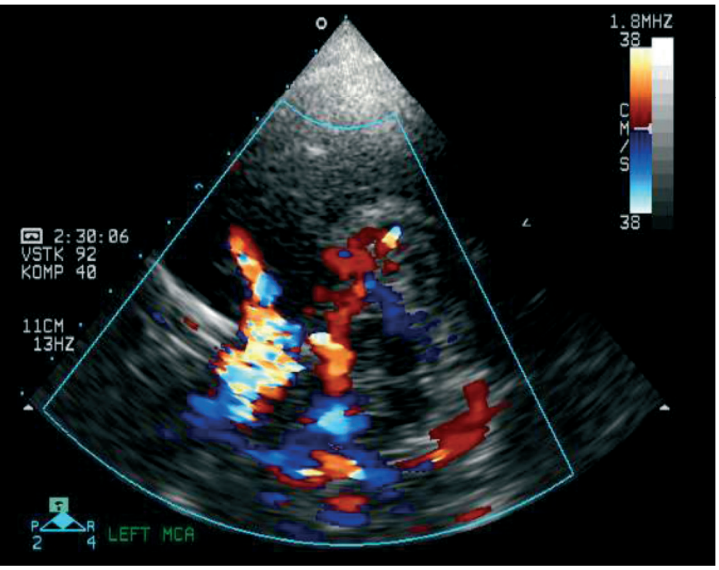
Zrenner B, Zrenner C, Gordon PC, Belardinelli P, McDermott EJ, Soekadar SR, Fallgatter AJ, **Ziemann U, Müller-Dahlhaus F** (2020) Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS. *Brain Stimul* 13:197-205

Zrenner C, Desideri D, Belardinelli P, Ziemann U (2018) Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimul* 11:374-89

Zrenner C, Galevska D, Nieminen JO, **Baur D, Stefanou MI, Ziemann U** (2020) The shaky ground truth of real-time phase estimation. *Neuroimage*:116761

Stroke and Neuro-protection Laboratory

Head: PD Dr. Sven Poli
Team: 13 members
Key words: stroke / neuroprotection / temperature management / hypothermia / oxygen therapy / cryptogenic stroke / hemostasis / central retinal artery occlusion / prehospital stroke care



Our research projects comprise preclinical translational studies on neuroprotection and clinical trials on a broad spectrum of acute stroke care and diagnostics.

Unsere Forschungsprojekte reichen von translationalen präklinischen Studien zur Neuroprotektion bis hin zu klinischen multizentrischen Studien zu einem breiten Spektrum der akuten Schlaganfalltherapie und -diagnostik.

The focus of our preclinical stroke research is on identification, evaluation and optimization of neuroprotective strategies that might help to minimize brain damage after experimental ischemic and haemorrhagic stroke. In this context, we aim to study and characterize the underlying molecular mechanisms involved in brain tissue protection from ischemic-hypoxic and reperfusion-reoxygenation-induced brain damage. Our goal is to provide translational research with a close link to clinical application. Currently we test novel technologies for selective brain hypothermia and ischemic tissue (hyper)oxygenation.

Furthermore, we run an interdisciplinary study center for clinical stroke research. We have initiated and run a broad spectrum of clinical trials on cooling technologies, hyperoxygenation in thrombectomy candidates, neurosonology, detection of atrial fibrillation, secondary prevention after cryptogenic stroke, thrombolysis in acute central retinal artery occlusion, hemostasis in intracerebral hemorrhage, point-of-care coagulation testing in DOAC-treated patients, and others. We cooperate at an international level.

SELECTED PUBLICATIONS

Mengel A, Stefanou MI, Hadaschik KA, Wolf M, Stadler V, Poli K, Lindig T, Ernemann U, Grimm F, Tatagiba M, **Ziemann U, Poli S**. Early Administration of Desmopressin and Platelet Transfusion for Reducing Hematoma Expansion in Patients With Acute Antiplatelet Therapy Associated Intracerebral Hemorrhage. *Crit Care Med.* 2020 Apr 16. doi: 10.1097/CCM.0000000000004348.

Sykora M, Kellert L, Michel P, Eskandari A, Feil K, Rémi J, Ferrari J, Krebs S, Lang W, Serles W, Siarnik P, Turcani P, Kovacik M, Bender B, **Mengel A, Poli K, Poli S**. Thrombolysis in Stroke With Unknown Onset Based on Non-Contrast Computerized Tomography (TRUST CT). *J Am Heart Assoc.* 2020 Feb 18;9(4):e014265.

Ochakovski GA, Wenzel DA, Spitzer MS, **Poli S, Härtig F**, Fischer MD, Dimopoulos S, Schultheiss M. Retinal oedema in central retinal artery occlusion develops as a function of time. *Acta Ophthalmol.* 2020 Feb 10. doi: 10.1111/aos.14375.

Almekhlafi MA, **Poli S**, Goyal M, Demchuk AM. Therapeutic hypothermia in stroke: Quo Vadis? *Brain Circ.* 2019 Dec 27;5(4):157-159.

Härtig F, Poli S, Ebner M, Birschmann I, Kuhn J, **Ziemann U**, Häring HU, Lehmann R, Peter A, Hörber S. Monitoring of low dabigatran concentrations: diagnostic performance at clinically relevant decision thresholds. *J Thromb Thrombolysis.* 2020 Apr;49(3):457-467.

Poli S, Bombach P, Geisler T. Atrial fibrosis and its implications on a revised ESUS concept. *Neurology.* 2019 Jul 23;93(4): 141-142.

Ringleb P, Bendszus M, Bluhmki E, Donnan G, Eschenfelder C, Fatar M, Kessler C, Molina C, Leys D, Muddegowda G, **Poli S**, Schellinger P, Schwab S, Serena J, Toni D, Wahlgren N, Hacke W; ECASS-4 study group. Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. *Int J Stroke.* 2019 Jul;14(5):483-490.

Neugebauer H, Schneider H, Bösel J, Hobohm C, **Poli S**, Kollmar R, Sobesky J, Wolf S, Bauer M, Tittel S, Beyersmann J, Woitzik J, Heuschmann PU, Jüttler E. Outcomes of Hypothermia in Addition to Decompressive Hemicraniectomy in Treatment of Malignant Middle Cerebral Artery Stroke: A Randomized Clinical Trial. *JAMA Neurol.* 2019 May 1;76(5):571-579.

Stefanou MI, Richter H, Härtig F, Wang Y, Örgel A, Bender B, **Mengel A, Ziemann U, Poli S**. Recurrent ischaemic cerebrovascular events as presenting manifestations of myeloproliferative neoplasms. *Eur J Neurol.* 2019 Jun;26(6):903-e64.

Ebner M, Birschmann I, Peter A, **Härtig F, Spencer C**, Kuhn J, Rupp A, Blumenstock G, Zuern CS, **Ziemann U, Poli S**. Limitations of Specific Coagulation Tests for Direct Oral Anticoagulants: A Critical Analysis. *J Am Heart Assoc.* 2018 Oct 2;7(19):e009807.

Schultheiss M, **Härtig F,** Spitzer MS, Feltgen N, Spitzer B, Hüsing J, Rupp A, **Ziemann U**, Bartz-Schmidt KU, **Poli S**. Intravenous thrombolysis in acute central retinal artery occlusion - A prospective interventional case series. *PLoS One.* 2018 May 29;13(5):e0198114.

Geisler T, **Mengel A, Ziemann U, Poli S**. Management of Embolic Stroke of Undetermined Source (ESUS). *Drugs.* 2018 Jun;78(8):823-831.

Poli S, Härtig F, Spencer C, Ebner M, Birschmann I, Kuhn J, Faix S, **Ziemann U**, Häring HU, Lehmann R, Peter A, Hörber S. Diagnostic Accuracy of a Novel Chromogenic Direct Thrombin Inhibitor Assay: Clinical Experiences for Dabigatran Monitoring. *Thromb Haemost.* 2017 Dec;117(12):2369-2375.

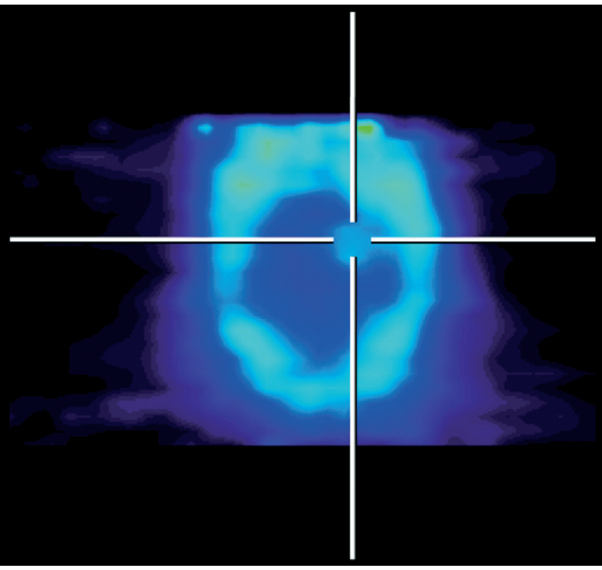
Poli S, Baron JC, Singhal AB, **Härtig F**. Normobaric hyperoxygenation: a potential neuroprotective therapy for acute ischemic stroke? *Expert Rev Neurother.* 2017 Dec;17(12):1131-1134.

Purrucker JC, **Härtig F, Richter H**, Engelbrecht A, Hartmann J, Auer J, Hametner C, Popp E, Ringleb PA, Nagel S, Poli S. Design and validation of a clinical scale for prehospital stroke recognition, severity grading and prediction of large vessel occlusion: the shortened NIH Stroke Scale for emergency medical services. *BMJ Open.* 2017 Sep 1;7(9):e016893.

Ebner M, Birschmann I, Peter A, **Härtig F, Spencer C**, Kuhn J, Blumenstock G, Zuern CS, **Ziemann U, Poli S**. Emergency Coagulation Assessment During Treatment With Direct Oral Anticoagulants: Limitations and Solutions. *Stroke.* 2017 Sep;48(9):2457-2463.

Steiner T, **Poli S**, Griebe M, Hüsing J, Hajda J, Freiberger A, Bendszus M, Bösel J, Christensen H, Dohmen C, Hennerici M, Kollmer J, Stetefeld H, Wartenberg KE, Weimar C, Hacke W, Veltkamp R. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol.* 2016 May;15(6):566-73.

Interdisciplinary Section of Neuro-Oncology



Head: Prof. Dr. Dr. Ghazaleh Tabatabai
Team: 15 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.

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.

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

Combining immune checkpoint inhibitors and CSF1R antibodies in experimental glioma

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. Targeting the immunosuppressive glioblastoma-associated microenvironment is an interesting approach in this regard. Yet, clinical experience with anti-PD1 antibodies in glioblastoma so far does not suggest the same efficacy compared with other tumor entities, e.g. melanoma. Rational combination therapies to enhance the efficacy are therefore warranted. Tumor-associated macrophages represent a highly abundant population of tumor-infiltrating host cells and have tumor-promoting features. The colony stimulating factor-1/ colony stimulating factor-1 receptor (CSF-1/CSF1R) axis plays an important role for macrophage differentiation and survival. We thus aimed at investigating the anti-glioma activity of co-targeting of CSF1R and PD1. We investigated CSF1R staining in human primary and matching progressive glioblastoma samples. We performed different combination treatments

with anti-CSF1R and anti-PD1 antibodies and respective controls in the orthotopic syngeneic SMA-560/VMDk experimental glioma mouse model. We evaluated post-treatment effects by histology and immunochemistry.

The monotherapy with CSF1R antibody increased the latency until the onset of neurological symptoms in SMA-560-bearing VMDk mice. Combinations of anti-CSF1R and anti-PD1 antibodies prolonged survival in vivo particularly if applied sequentially with PD1 blockade following CSF1R blockade. Post-treatment samples indicated reduced cluster of differentiation (CD)204 and CD11b positive cells after CSF1R antibody, an increased CD8+/ CD4+ and CD8+/FoxP3+ ratio in vivo after combinations of anti-CSF1R and anti-PD1 antibodies. Our results identify CSF1R as a promising therapeutic target for glioblastoma, particularly in combination with PD1 inhibition.

Molecular diagnostics for the detection FGFR3 overexpression in glioblastoma

Fibroblast growth factor receptor (FGFR) inhibitors are currently in advanced clinical development. A subset of glioblastomas carries gene fusion of FGFR3 and transforming acidic coiled-coil protein 3 (TACC3). The prevalence of other FGFR3 alterations in glioma is currently unclear. We performed a screening by reverse transcriptase polymerase chain reaction (RT-PCR) in 101 glioblastoma samples to detect FGFR3–TACC3 fusions ("RT-PCR cohort"). Then, we performed FGFR3 immunohistochemistry (IHC) and correlated all RT PCR results with FGFR3 stainings. Further, we applied FGFR3 IHC in 548 tissue microarray (TMA) glioma samples ("TMA cohort") and validated these results in two external cohorts with 319 patients. Gene panel sequencing was carried out in 88 samples ("NGS cohort") to identify other possible FGFR3 alterations. Molecular modelling was performed on newly detected mutations. In the "RT-PCR cohort", we identified FGFR3-TACC3 fusions in 2/101 glioblastomas, both cases strongly expressing FGFR3 in IHC. Positive IHC staining was observed in 74/1020 TMA samples which 11 being strongly positive. In the "NGS cohort" we identified FGFR3-fusions in 9/88 cases, FGFR3 amplification in 2/88 cases and FGFR3 gene mutations in 7/88 cases in targeted sequencing. All FGFR3 fusions and amplifications and a novel FGFR3 K649R missense mutation were associated with strong FGFR3 protein expression (sensitivity and specificity of 93 and 95% respectively, at cutoff IHC score 8). Modelling of these data indicated that Tyr647, a residue phosphorylated as a part of FGFR3 activation is affected by the K649R mutation. FGFR3 immunohistochemistry is a useful screening tool for the detection of FGFR3 alterations. Given the clinical relevance of FGFR3 as a therapeutic target, FGFR3 IHC could be included in the immunohistological workflow for IDH wildtype glioma diagnostics. Samples with positive FGFR3 staining could then be selected for NGS-based diagnostic tools.

Early phase clinical trials for the use of personalized multipeptide vaccination for glioblastoma patients

We participated in the phase I trial of the GAPVAC-101 of the Glioma Actively Personalized Vaccine Consortium (GAPVAC), coordinated by Immatics Tübingen. In this phase I trial, we integrated highly individualized vaccinations with both types of tumour antigens into standard care for glioblastoma patients positive for human leukocyte antigen (HLA)-A*02:01 or HLA-A*24:02. The multipeptide vaccines were used with poly-ICLC (polyriboinosinic-polyribocytidylic acid-poly-L-lysine carboxymethylcellulose) and granulocyte-macrophage colony-stimulating factor as adjuvants. This GAPVAC approach displayed favourable safety and strong immunogenicity. In an **on**going collaboration with the Department of Immunology, we are working on the next phase I clinical trial using a new adjuvans for further augment immune responses. We estimate a start of our trial in 2021.

SELECTED PUBLICATIONS

Hilf N, Kuttruff-Coqui S, Frenzel K, Bukur V, Stevanovic S, Gouttefangeas C, Platten M, **Tabatabai G**, Dutoit V, van der Burg SH, (...) Rammensee HG, Singh-Jasuja H, Sahin U, Dietrich PY, Wick W (2019) Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature* 565:240-45

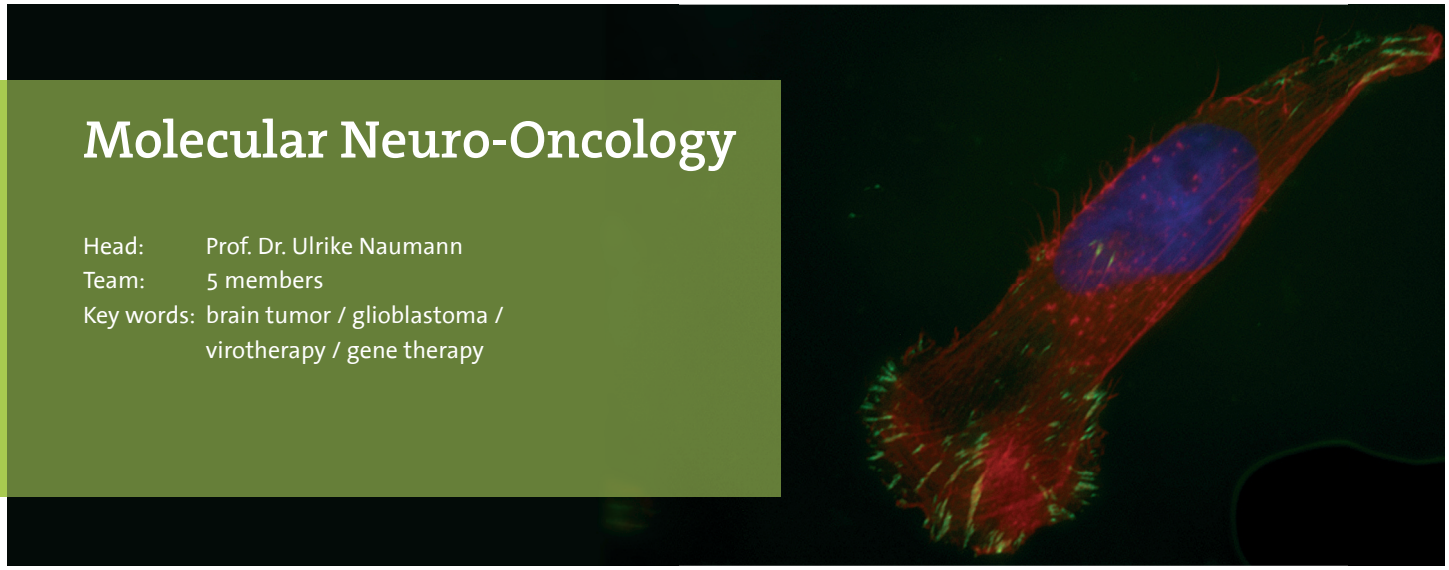
Weller J, Tzaridis T, Mack F, Steinbach JP, Schlegel U, Hau P, Krex D, Grauer O, Goldbrunner R, Bahr O, Uhl M, Seidel C, **Tabatabai G**, Brehmer S, Bullinger L, Galldiks N, Schaub C, Kebir S, Stummer W, Simon M, Fimmers R, Coch C, Glas M, Herrlinger U, Schafer N (2019) Health-related quality of life and neurocognitive functioning with lomustine-temozolomide versus temozolomide in patients with newly diagnosed, MGMT-methylated glioblastoma (CeTeG/NOA-09): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 20:1444-53

Herrlinger U, Tzaridis T, Mack F, Steinbach JP, Schlegel U, Sabel M, Hau P, Kortmann RD, Krex D, Grauer O, Goldbrunner R, Schnell O, Bahr O, Uhl M, Seidel C, **Tabatabai G**, Kowalski T, Ringel F, (...), Coenen M, Wick W, Weller M, Fimmers R, Schmid M, Hattingen E, Pietsch T, Coch C, Glas M, Neurooncology Working Group of the German Cancer S (2019) Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet* 393:678-88

Schittenhelm J, Krischker N, Gepfner-Tuma I, Behling F, Noell S, Eckert F, Biskup S, **Tabatabai G** (2019) Oncogenic KRAS hotspot mutations are rare in IDH-mutant gliomas. *Brain Pathol* 29:321-24

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 lethal 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 further project we evaluated 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 GBM 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. In einem zentralen Projekt 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, um Viren auch zu invadierten GBM-Zellen zu transportieren. In einem zweiten Projekt untersuchen wir, wie Gliome Perizyten hinsichtlich dieser Funktion beeinflussen und sie zu Gliom-adaptierten, tumor-fördernden Zellen umwandeln, somit das Einwachsen von Gefäßen in den Tumor, die Gefäßstruktur und die Integrität der Blut-Hirn-Schranke modulieren. In einem weiteren Projekt, gesponsert durch die Innovationsstiftung Sauer (ISUS) und die Software AG Stiftung, welches wir 2019 erfolgreich beenden konnten, untersuchten wir die Effekte von Viscuminen, pflanzlichen Lektinen, in der adjuvanten GBM-Therapie. Wir konnten sowohl in vitro als auch in vivo zeigen, dass Visumine anti-tumorale Eigenschaften besitzen und, wenn adjuvant appliziert, in Synergie mit der GBM-Standardtherapie wirken.

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 micro-milieu to optimize survival and growth. 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 irradiation, 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. This effect can be improved by irradiation of the tumor before oncovirotherapy due to the fact, that irradiation has been shown to potentiate XVir-N31 replication. In ongoing experiments, funded by the German Research and the German Cancer Foundation, we developed next generation OAVs that express the immune checkpoint inhibitor alpha-PD-L1and 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 exclusively 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. In a strong collaboration with Prof. Michel Mittelbronn (LNC Luxembourg) we have identified TGF-ß as a central GBM-secreted cytokine that influences the function of pericytes regarding their metabolic activity, proliferation and motility.

In a project we finalized in 2019 we examined the effects of viscumins as adjuvant drugs to treat GBM. Viscumins, lectins from the semiparasitic plant Viscum album L., are often used by patients to adjuvantly treat cancer. In this 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.

SELECTED PUBLICATIONS

Schotterl S, Miemietz JT, Ilina EI, Wirsik NM, Ehrlich I, Gall A, Huber SM, Lentzen H, Mittelbronn M, **Naumann U** (2019) Mistletoe-Based Drugs Work in Synergy with Radio-Chemotherapy in the Treatment of Glioma In Vitro and In Vivo in Glioblastoma Bearing Mice. *Evid Based Complement Alternat Med* 2019:1376140

Czolk R, Schwarz N, Koch H, Schotterl S, Wuttke TV, Holm PS, Huber SM, **Naumann U** (2019) Irradiation enhances the therapeutic effect of the oncolytic adenovirus XVir-N-31 in brain tumor initiating cells. *Int J Mol Med* 44:1484-94

Schotterl S, Hubner M, Armento A, Veninga V, Wirsik NM, Bernatz S, Lentzen H, Mittelbronn M., **Naumann U** (2019) Mistletoe lectin I reduces glioma cell motility by changing mainly the expression of genes assoiated to TGF-ß signaling. *Phytomedicine* 61:3-4

Schotterl S, Huber SM, Lentzen H, Mittelbronn M, **Naumann U** (2018) Adjuvant Therapy Using Mistletoe Containing Drugs Boosts the T-Cell-Mediated Killing of Glioma Cells and Prolongs the Survival of Glioma Bearing Mice. *Evid Based Complement Alternat Med* 2018:3928572

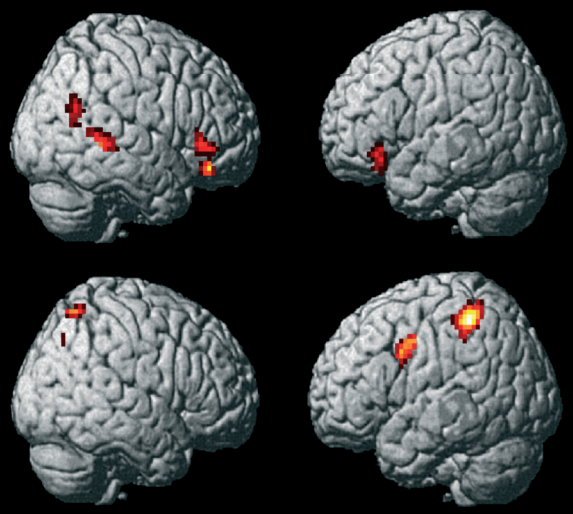
Mader L, Blank AE, Capper D, Jansong J, Baumgarten P, Wirsik NM, Zachskorn C, Ehlers J, Seifert M, Klink B, Liebner S, Niclou S, **Naumann U**, Harter PN, Mittelbronn M (2018) Pericytes/vessel-associated mural cells (VAMCs) are the major source of key epithelial-mesenchymal transition (EMT) factors SLUG and TWIST in human glioma. *Oncotarget* 9:24041-53

Schotterl S, Hubner M, Armento A, Veninga V, Wirsik NM, Bernatz S, Lentzen H, Mittelbronn M, **Naumann U** (2017) Viscumins functionally modulate cell motility-associated gene expression. *Int J Oncol* 50:684-96

Armento A, Ehlers J, Schötterl S, Naumann U (2017) Molecular mechanisms of glioma cell motility. In: *Glioblastoma*. Steven De Vleeschouwer (Editor), Codon Publications, Brisbane, Australia. ISBN: 978-0-9944381-2-6

Neurophonetics and Translational Neurorehabilitation

Head: Prof. Dr. Hermann Ackermann
Team: 2 members
Key words: speech production and perception / neurobiology of language / acoustic communication / brain connectivity



The Neurophonetics Group investigates the neural bases of speech communication – a 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

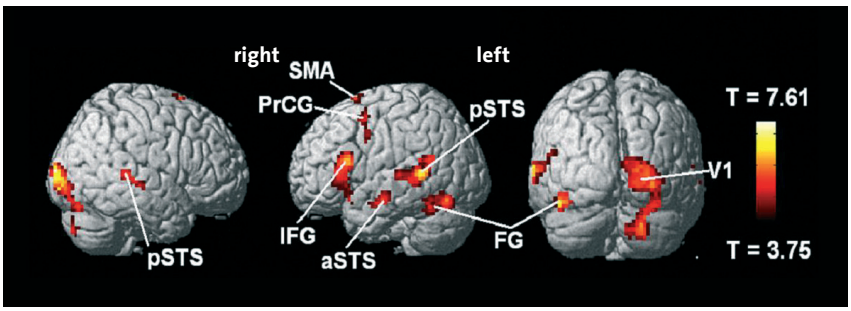
Blind individuals may learn to comprehend ultra-fast speech at a rate of up to about 22 syllables per second (syl/s), exceeding by far the maximum performance level of normal-sighted listeners (8-10 syl/s). Based on the results of two subsequent projects over the last years (a group study and a training experiment), the hypothesis of a "visual" strategy could be further 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 and, as the most recent finding, phase locking between the speech signal and magnetic activity in visual cortex (Hertrich et al., 2018).

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 showed that transient impairment of pre-SMA affects its inhibitory function that normally eliminates erroneous speech material prior to speaking or, in case of perception, prior to its integration into a semantically/pragmatically meaningful message (Dietrich et al., 2018, 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. Previous behavioral, electroencephalographic (EEG), and magnetoencephalographic (MEG) studies had shown that presuppositions - depending on linguistic context - may give rise to (i) increased reaction times, (ii) evoked EEG responses such as the N400 and P600, and (iii) altered auditory processing as reflected in MEG responses. In cooperation with the Institute of Evolutionary Cognition of the University or Tübingen, an fMRI study was performed in order to better localize the brain activity associated with the processing of presuppositions. Presupposition-related pragmatic discourse violations yielded three different activation patterns, corresponding to (i) a reference process including working memory functions (inferior frontal



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".

gyrus), (ii) retrieval and integration of semantic/pragmatic information (inferior parietal lobe and angular gyrus), and (iii) cognitive control of inconsistency management in terms of accomodation processes (pre-supplementary motor area and basal ganglia (Dietrich et al., 2019).

Modeling the language network in the brain

Currently, two review papers are in preparation considering language in the brain from a theoretical point of view. The first one is entitled "The margins of the language network in the brain" (submitted). Starting with historical views such as the Broca-Wernicke-Lichtheim-Geschwind model, a more refined "core" language model has been outlined which is surrounded by additional modules, i.e., the "margins". These margins serve various functions that are required to integrate linguistic processing into ecologically meaningful behavior and thinking. In particular, they comprise (1) the embodiment of language in sensory and motor systems, motivational and affective processing, context integration linking verbal working memory to nonverbal memory structures, and theory of mind functions. The second review paper considers the particular role of the dorsolateral prefrontal cortex for language processing. This region seems to be particularly involved in cognitive control functions enabling us to use language in an "intelligent" way, for example, by releasing the attachment to literal word meanings in case of irony or metaphors.

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.

SELECTED PUBLICATIONS

Hertrich I, Ackermann H. Motor speech disorders. In: Damico J, Ball M eds, *The SAGE Encyclopedia of Human Communication Sciences and Disorders*. Thousand Oaks, CA: SAGE Publications, Inc.; 2019: 1193-1197

Dietrich S, **Hertrich I**, Seibold VC, Rolke B. Discourse management during speech perception: A functional magnetic resonance imaging (fMRI) study. *Neuroimage* 2019; 202: 116047

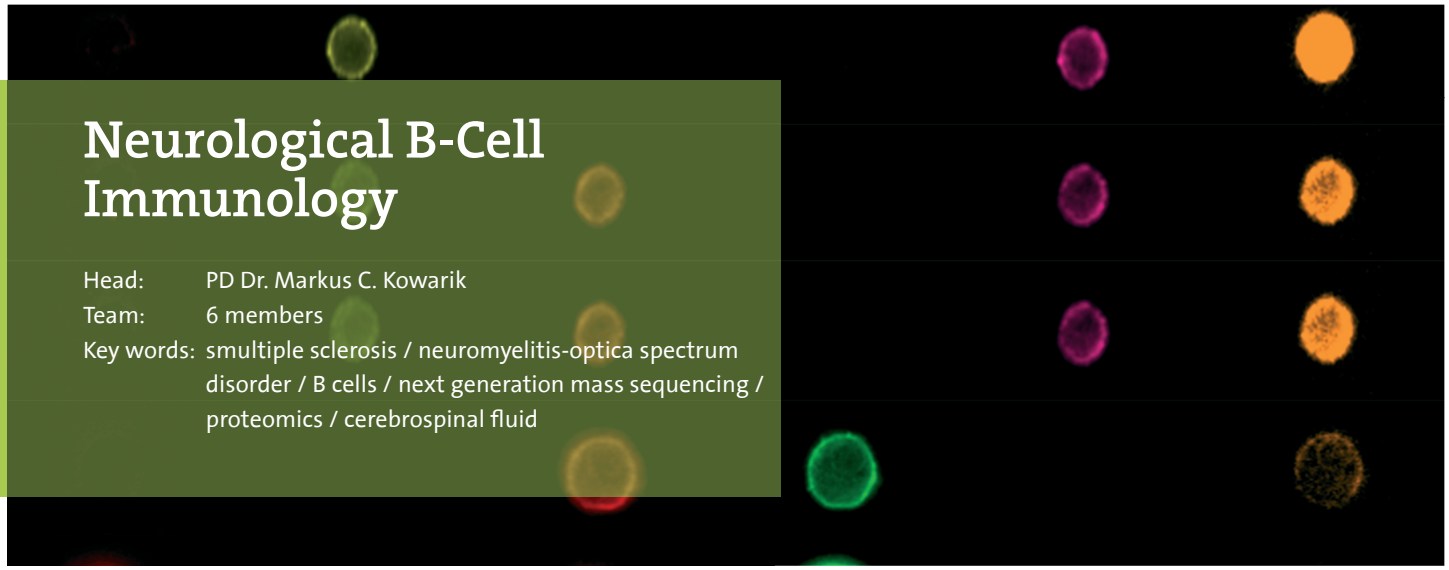
Dietrich S, **Hertrich I**, Müller-Dahlhaus F, **Ackermann H**, Belardinelli P, Desideri D, Seibold VC, Ziemann U. Reduced Performance During a Sentence Repetition Task by Continuous Theta-Burst Magnetic Stimulation of the Pre-supplementary Motor Area. *Front Neurosci* 2018; 12: 361

Hertrich I, Dietrich S, **Ackermann H.** Cortical phase locking to accelerated speech in blind and sighted listeners prior to and after training. *Brain Lang* 2018; 185: 19-29

Ziegler W, **Ackermann H**. Subcortical Contributions to Motor Speech: Phylogenetic, Developmental, Clinical. *Trends Neurosci* 2017; 40: 458-468

Hertrich I, Ackermann H. Dysarthrie des Parkinson-Syndroms - klinische Befunde, instrumentelle Daten, in *Dysarthrie und Dysphagie bei Morbus Parkinson*, A. Nebel and G. Deuschl, Editors. 2016, Thieme: Stuttgart. p. 56-75

Hertrich I, Dietrich S, Ackermann H. The role of the supplementary motor area for speech and language processing. *Neuroscience & Biobehavioral Reviews* 2016;68:602-610



Neurological B-Cell Immunology

Head: PD Dr. Markus C. Kowarik
Team: 6 members
Key words: smultiple sclerosis / neuromyelitis-optica spectrum disorder / B cells / next generation mass sequencing / proteomics / cerebrospinal fluid

The research group "Neurological B-Cell Immunology" is focused on the role of B cells in neuro-inflammatory diseases including multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). Whereas aquaporin (AQP4) autoantibodies could be clearly linked to NMOSD pathophysiology, the exact role of B cells in multiple sclerosis still remains unknown. However, B cell depleting therapies have been shown to be highly effective in multiple sclerosis, indicating that B cells play an important role in MS pathogenesis. Our primary aim is to further understand the specific functions of B cells in multiple sclerosis and other autoimmune diseases. By using a multiomics approach including next generation mass sequencing and proteomics, we are able to gain a deeper understanding of immunoglobulin repertoire changes under conditions of autoimmunity and immunomodulation.

Die Forschungsgruppe „Neurologische B-Zell Immunologie" beschäftigt sich mit der Rolle von B-Zellen bei neuro-inflammatorischen Erkrankungen des Zentralnervensystems (ZNS) wie der Multiplen Sklerose und Neuromyelitis-optica-Spektrum-Erkrankung (NMOSD). Während bei der NMOSD die Produktion von pathologisch relevanten Antikörpern gegen Aquaporin-4 Wasserkanäle eindeutig nachgewiesen werden konnte, ist die Rolle von B Zellen bei der Multiplen Sklerose aktuell noch nicht hinreichend verstanden. Durch den erfolgreichen Einsatz von B-Zell depletierenden Therapien in der Multiplen Sklerose konnte ein relevanter Einfluss von B-Zellen in der Pathogenese jedoch klar belegt werden. Ziel der Arbeitsgruppe ist es, die Rolle von B Zellen bei der Multiplen Sklerose als auch bei anderen Autoimmunerkrankungen im Detail zu verstehen. Mittels eines Multiomics Ansatzes („Next Generation" Massensequenzierung, Proteomics) untersuchen wir im Detail die Veränderungen des B Zell Kompartments auf Ebene des Immunglobulin Repertoires.

B cells in multiple sclerosis

Multiple lines of evidence indicate that B cells play an important role in the pathogenesis of multiple sclerosis (MS). Beside the persistence of intrathecal oligoclonal IgG bands, elevated B cell numbers within the cerebrospinal fluid (CSF) and detection of B cells in MS lesions, B cell depleting therapies have been shown to be highly effective in MS. Moreover, various MS treatments exert differential effects on B cell subsets but the exact mechanisms during immunomodulation often remain inconclusive. Our aim is to study treatment specific effects on B cells during various immunomodulating MS therapies in order to gain insights in the different drugs' mode of action and the role of B cells during MS pathogenesis itself.

Differential effects of disease modifying drugs on B cell subsets in multiple sclerosis patients

In order to get a basic understanding of treatment associated effects on B cells, we perform systematic FACS analyses of specific subsets of peripheral blood B cells of MS patients under various therapies. In a current study, we found differential effects on B cell subsets including naïve B cells, non-class switched and class-switched memory B cells, double negative B cells and plasmablasts following treatment with interferon-β, glatiramer acetate, dimethyl fumarate, fingolimod, or natalizumab (Figure 1). Across the examined treatments, decreased percentages of memory B cells were found in dimethyl fumarate, interferon-β and fingolimod treated patients, which highlights a potential role of memory B cells during immunomodulation in MS. The exact role of the double negative B cell population – a so far less characterized B cell population developing in a germinal center independent way – in MS is currently unclear and needs further examination.

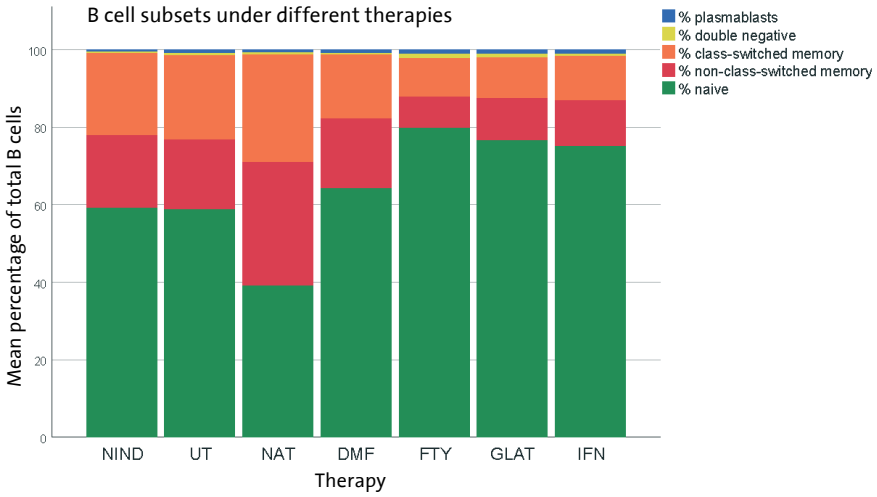


Figure 1: Displayed are the percentages of the B cell subsets among the total CD19+ B cell pool (NIND=non-inflammatory neurological disease, UT= untreated MS patients, NAT= natalizumab, DMF= dimethyl fumarate, FTY= fingolimod, GLAT= glatiramer acetate and IFN= interferon-β treated MS patients).

Immunoglobulin repertoire analyses on a transcriptome and proteome level

Cooperations: quantitative biology center (Sven Nahnsen, QBIC), sequencing core facility (Nicolas Casadei) and proteome core facility (Karsten Boldt) Tübingen

Beside the analysis of B cell subset-specific changes, we are also interested in functional effects of different immunomodulating treatments on the B cell compound. We perform next generation mass sequencing of immunoglobulin (Ig) transcripts in order to get deeper insights in Ig transcriptome changes. We additionally perform Ig proteome analysis by mass spectrometry and overlap the recovered Ig peptides with Ig transcriptome libraries. This multiomics approach offers the unique opportunity to examine immunoglobulin repertoire alterations and B cell maturation in great detail under conditions of immunomodulation and auto-immunity itself. We recently established an advanced data and downstream processing pipeline in cooperation with the QBIC to study treatment effects of dimethyl fumarate, teriflunomide, cladribine, and other therapies. Preliminary results suggest that certain therapies (e.g. dimethyl fumarate) not only diminish absolute B cell numbers but also alter Ig repertoires in terms of reduced numbers of Ig sequences and altered B cell clonality in specific B cell subsets. In contrast, other treatment such as teriflunomide did not change the Ig repertoire significantly on an overall level. A deeper understanding of the different drugs' mode of action will help to further define treatment algorithms for MS patients in the future.

Future directions

The CSF is metabolically active liquid that maintains homeostatic functions and serves as an important surrogate to monitor microenvironmental CNS changes in MS. Distinct changes in the number and composition of immune cells and cytokine profiles can be observed in the CSF during MS. Whereas previous work on CSF was mainly restricted to FACS analyses of immune cell subtypes and the detection of a limited number of e.g. cytokines, new techniques offer the opportunity to get deeper insights into cellular changes within the CSF. Our aim is to further extend our experimental approach to the CSF compartment. We will apply a multiomics approach and study MS specific CSF changes by massively correlating transcriptome data of immune cell subsets with cytokine assays and proteome data in the CSF. We thereby aim to identity disease driving CSF immune cell sub-populations and cell associated disease markers.

SELECTED PUBLICATIONS

Lepennetier G, Hracsko Z, Unger M, Van Griensven M, Grummel V, Krumbholz M, Berthele A, Hemmer B, **Kowarik MC** (2019) Cytokine and immune cell profiling in the cerebrospinal fluid of patients with neuro-inflammatory diseases. *J Neuroinflammation.* 14;16(1):219.

Kowarik MC, Astling D, Gasperi C, Wemlinger S, Schumann H, Dzieciatkowska Monika, Ritchie AM, Hemmer B, Owens GP, Bennett JL (2017) CNS Aquaporin-4 specific B cells connect with multiple B cell compartments in neuromyelitis optica spectrum disorder. *Ann Clin Transl Neurol.* 4(6):369-380.

Kowarik MC, Dzieciatkowska M, Wemlinger S, Ritchie AM, Hemmer B, Owens GP, Bennett JL (2015) The cerebrospinal fluid immunoglobulin transcriptome and proteome in neuromyelitis optica reveals central nervous system-specific B cell populations. *Journal of Neuroinflammation.* 12:19.

Kowarik MC, V Grummel, S Wemlinger, D Buck, M S Weber, A Berthele, B Hemmer (2013) Immune cell subtyping in the cerebrospinal fluid of patients with neurological diseases. *Journal of Neurology.* 261(1):130-43.

Kowarik MC, Cepok S, Sellner J, Grummel V, Weber MS, Korn T, Berthele A, Hemmer B (2012) CXCL13 is the major chemokine for B cell recruitment and B cell response in the CSF during neuroinflammation. *Journal of Neuroinflammation.* 9:93.

Kowarik MC, Pellkofer HL, Cepok S, Korn T, Kümpfel T, Buck D, Hohlfeld R, Berthele A, Hemmer B (2011) Differential effects of fingolimod (FTY720) therapy on immune cells in the cerebrospinal fluid and blood of multiple sclerosis patients. *Neurology.* 76(14):1214-21.

Department of Neurology and Epileptology

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

Departmental Structure

As part of the Center of Neurology and together with the other Neurological Departments, the Department of Neurology and 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 headache and neuropathic pain disorders, and neuromuscular diseases. The clinic offers the whole spectrum of modern diagnostic and therapeutic procedures. The inpatient unit with 22 beds (Wards 42/43L), running under the supervision of Prof. Dr. A. Grimm, Dr. M. Schreiber, and Dr. P. Martin, 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,

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).

vagal nerve and other brain stimulation paradigms are provided in close cooperation with the Department of Neurosurgery (Dr. S. Rona, Prof. Dr. J. Honegger, Prof. Dr. A. Garabaghi, Dr. G. Naros). The epilepsy outpatient clinic (Prof. Dr. H. Lerche and Dr. M. Schreiber) offers consulting and treatment in particular for difficult cases and specific questions including pregnancy under antiepileptic treatment and genetic aspects.

The other outpatient clinics are focused on headache and neuropathic pain syndromes (PD Dr. S. Schuh-Hofer), on neuromuscular diseases (Prof. Dr. A. Grimm, Dr. P. Martin), and rare, genetically determined paroxysmal neurological and ion channel disorders (Prof. Dr. H. Lerche). Specific genetic diagnostic testing using next generation (whole exome) sequencing 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.

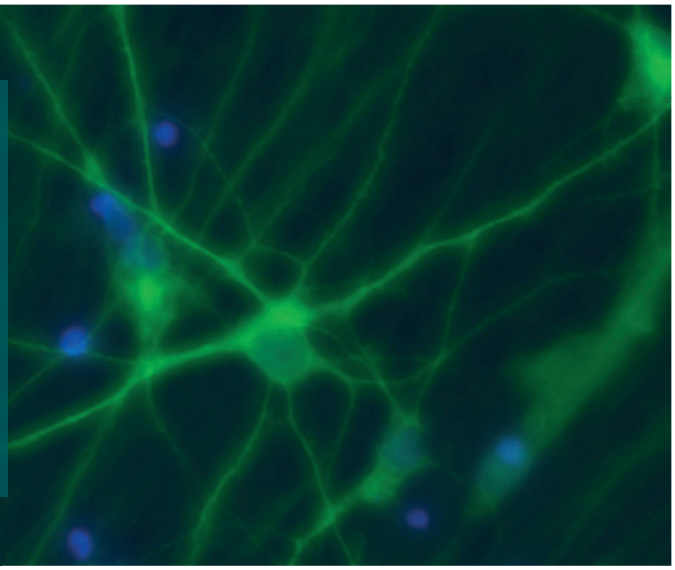
The department stimulates synergies between physicians in the Neurological Clinic and basic research groups in the Hertie Institute with the aim to work on clinically driven basic research questions and rapidly transfer scientific progress into clinical practice.

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: 25 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 and a personalized treatment. We are recruiting well-defined cohorts of patients with epilepsies and related disorders, searching for disease-causing genetic defects with modern sequencing techniques, particularly in ion channels or transporters, and analyzing their functional consequences to understand the pathomechanisms. 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 human brain slices, 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 und personalisierte Therapien zu ermöglichen. 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 humanen Hirnschnitten, 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, IonNeurONet/Treat-ION, DFG FOR-2715), European (FP6: Epicure, ESF: EuroEPINOMICS, FP7: EpiPGX, ERANet Neuron: SNAREopathies) 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., Brain 2017), or in genes encoding different Ca2+, Na+ channels (e.g. CACNA1E and SCN8A Helbig, Lauerer et al., 2018; Liu et al., 2019) or GABAA receptor subunits (May et al., 2018) found in rare or common forms of epilepsy.

Beside gene discovery and pathophysiology, we are increasingly focusing on specific therapies for genetic disorders which can partially 'correct' the genetic defect. Three recent examples are (i) the treatment of patients with KCNA2 gain-of-function mutations with 4-aminopyridine (a K+ channel blocker) which we performed with first success in n-of-1 trials particularly in young children (Hedrich, Lauxmann et al., in revision) and for which we obtained the Eva-Luise Köhler prize 2018 for rare diseases, (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) and (iii) functional analysis of variants in the SCN8A gene encoding the Na+ channel NaV1.6 revealing distinct neuropsychiatric diseases ranging from severe epilepsy to intellectual disability which were correlated with specific gain- or loss-of-function features (Liu et al., 2019) and with specific pharmacological effects of sodium channel blockers.
With the BMBF-funded Treat-ION consortium on Neurological Ion Channel and Transporter Disorders we focus on therapeutic studies in cellular, animal and human models, which are complemented by in silico searches for new treatments, better predictions for the functional consequences of mutations for therapeutic purposes and cellular drug screens. The use of approved and available 'repurposed' drugs such as 4-aminopyridine is an additional goal to enable personalized treatment. Our findings will be directly delivered to patients through a structured molecular therapeutic board attached to the German academy of rare neurological diseases (DASNE). Functional implications of selected mutations are examined in neuronal expression systems, such as transfected murine primary neurons, in utero electroporated neurons and genetically-altered animal models carrying a human mutation (so-called "humanized mouse models"). The advantage of both in utero electroporated neurons and gene-targeted 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 using single cell patch clamp, extracellular recording or multielectrode array (MEA) techniques. We perform 256 electrode MEA recordings and high-resolution electrical imaging (CMOS with 4000 electrodes) to analyze single cell compartments and neuronal network activity in brain slices of transgenic animals and study network dysfunction of our mouse models in vivo together with O. Garaschuk (Inst. Neurophysiology) using Ca2+ imaging in the frame of the newly established DFG Research Unit. To gain insight into the exact mechanisms as to how epilepsy develops as a consequence of a genetic defect, we investigate brain region- and time-specific RNA expression using single cell RNA sequencing in distinct neuronal subpopulations in mouse models.

Finally, we have been establishing to reprogram fibroblasts and keratinocytes obtained from patients carrying different epilepsy-causing mutations in ion channel genes to generate human induced pluripotent cells (hiPSC). Like embryonic stem cells iPSCs can be differentiated into cortical neurons and glial cells by addition of different growth factors, defined culture conditions or by over-expression of transcription factors. Thus, it is possible to investigate cortical cells, which were previously inaccessible, from patients carrying genetic diversity or specific mutations of epileptic syndroms.

Furthermore , we generated a new model system using human slice cultures which 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. The use of ex vivo brain slices derived from adult human neurosurgical-resected tissue allows to probe electrophysiological properties at single cell and at small network level. We now demonstrate robust preservation of the complex neuronal cytoarchitecture and electrophysiological properties of human pyramidal neurons in long-term brain slice cultures. Further experiments delineate the optimal conditions for efficient viral transduction of cultures, enabling 'high throughput' fluorescence-mediated 3D reconstruction of genetically targeted neurons, and demonstrate feasibility of long term live cell imaging of human cells in vitro (Schwarz et al., 2019).

SELECTED PUBLICATIONS

Helbig KL*, **Lauerer RJ*, Bahr JC**, Souza IA, Myers CT, **Uysal B, Schwarz N**, (...,) **Hedrich UBS**, (...), **Lerche H#**, Mefford HC#. De Novo Pathogenic Variants in CACNA1E Cause Developmental and Epileptic Encephalopathy with Contractures, Macrocephaly, and Dyskinesias. *Am J Hum Genet* 2018; 103:666-678.

Liu Y, Schubert J, Sonnenberg L, Helbig KL, Hoei-Hansen CE, **Koko M, Rannap M, Lauxmann S**, (...) , **Becker F, Weber YG**, Benda J, Møller RS, **Lerche H**. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain 2019; 142:376-390.

May P*, Girard S*, **Harrer M***, Bobbili DR*, **Schubert J***, **Wolking S***, (...), Epicure Consortium; EuroEPINOMICS CoGIE Consortium; EpiPGX Consortium, (...), **Maljevic S**, Zara F, Cossette P, Krause R, **Lerche H**. Rare coding variants in genes encoding GABAA receptors in genetic generalised epilepsies: an exome-based case-control study. *Lancet Neurol* 2018;17:699-708.

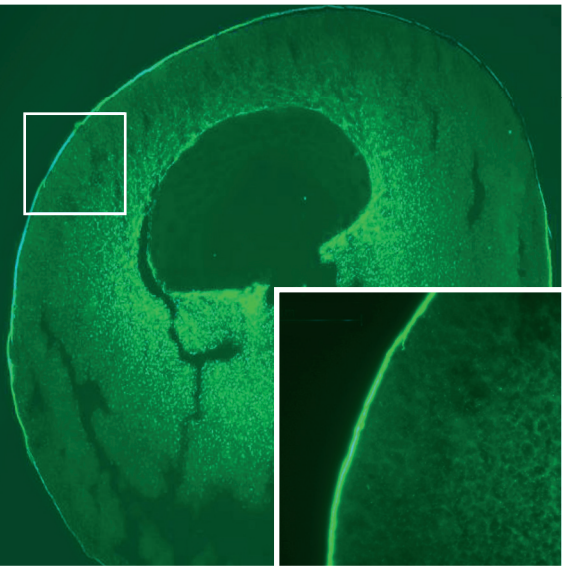
Schwarz N, Uysal B, Welzer M, **Bahr J, Layer N, Löffler H, Stanaitis K, PA H, Weber YG, Hedrich UBS**, Honegger JB, Skodras A, Becker AJ, **Wuttke TV, Koch H**. Long-term adult human brain slice cultures as a model system to study human CNS circuitry and disease. *Elife*. 2019 Sep 9;8. pii: e48417. doi: 10.7554/eLife.48417.

Wolff M*, Johannesen KM*, **Hedrich UBS***, (...), **Schwarz N**, (...), Kluger G, **Lerche H#**, Møller RS#. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain* 2017;140:1316-36.

(*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 novel epilepsy genes with a focus on the synaptic metabolism. Additionally, completely novel research fields were started namely the development of a seizure detection system together with a start-up company and a so-called Clinical Decision Support System (CDSS) which provides the practioners all necessary research informations to find an individual therapy for the patient.

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 entwicklungsbedingten und epileptischen Epilepsien (früher epileptische Enzephalopathien, EE), der Standardisierung von genetischen Biomarkern für eine individualiserte Therapie sowie der Analyse von neuen Epilepsiegenen mit Fokus auf dem synaptischen Metabolismus. Darüber hinaus wurde ein komplett neues Forschungsfeld mit der Entwicklung eines Anfallsdetektors zusammen mit einem Start-up-Unternehmen begonnen sowie die Entwicklung eines sog. Clinical Decision Support Systems, das dem Kliniker alle Informationen zur Verfügung stellt, um eine individualisierte Therapie festzulegen.

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.

Activities in 2019

We detected a novel gene for a developmental and epileptic encephalopathy AP2M1 which is relevant in the vesicle metabolism of the synapse (Helbig et al. 2019). Together with others we described several novel genes such as KMT2E (O'Donnell-Luria et al. 2019) and were part of an international initiative sequencing the biggest epilepsy cohort ever (Epi25 collaborative 2019). We were interested in the analysis of somatic mutions in epilepsy surgery tissue (Niestroj et al. 2019) and published one of the biggest cohorts of gene exome panel analysis for epilepsy patients demonstrating that the analysis of 30-50 genes in DEE patients is sufficient to find pathological genetic changes in up to 4% of patients (Heyne et al. 2019). Furthermore, the seizure detection system was further developed together with a start-up company especially concerning the self-learning algorithm.

SELECTED PUBLICATIONS

Helbig I, Lopez-Hernandez T, Shor O, Galer P, Ganesan S, Pendziwiat M, Rademacher A, Ellis CA, Humpfer N, Schwarz N, Seiffert S, Peeden J, Shen J, Sterbova K, Hammer TB, Moller RS, Shinde DN, Tang S, Smith L, Poduri A, Krause R, Benninger F, Helbig KL, Haucke V, **Weber YG**, EuroEPINOMICS-RES Consortium; GRIN Consortium (2019) A Recurrent Missense Variant in AP2M1 Impairs Clathrin-Mediated Endocytosis and Causes Developmental and Epileptic Encephalopathy. American *Journal of Human Genetics* 104:1060-72

Heyne HO, Artomov M, Battke F, Bianchini C, Smith DR, Liebmann N, Tadigotla V, Stanley CM, Lal D, Rehm H, Lerche H, Daly MJ, Helbig I, Biskup S, **Weber YG**, Lemke JR (2019) Targeted gene sequencing in 6994 individuals with neurodevelopmental disorder with epilepsy. *Genetics in Medicine* 21:2496-503

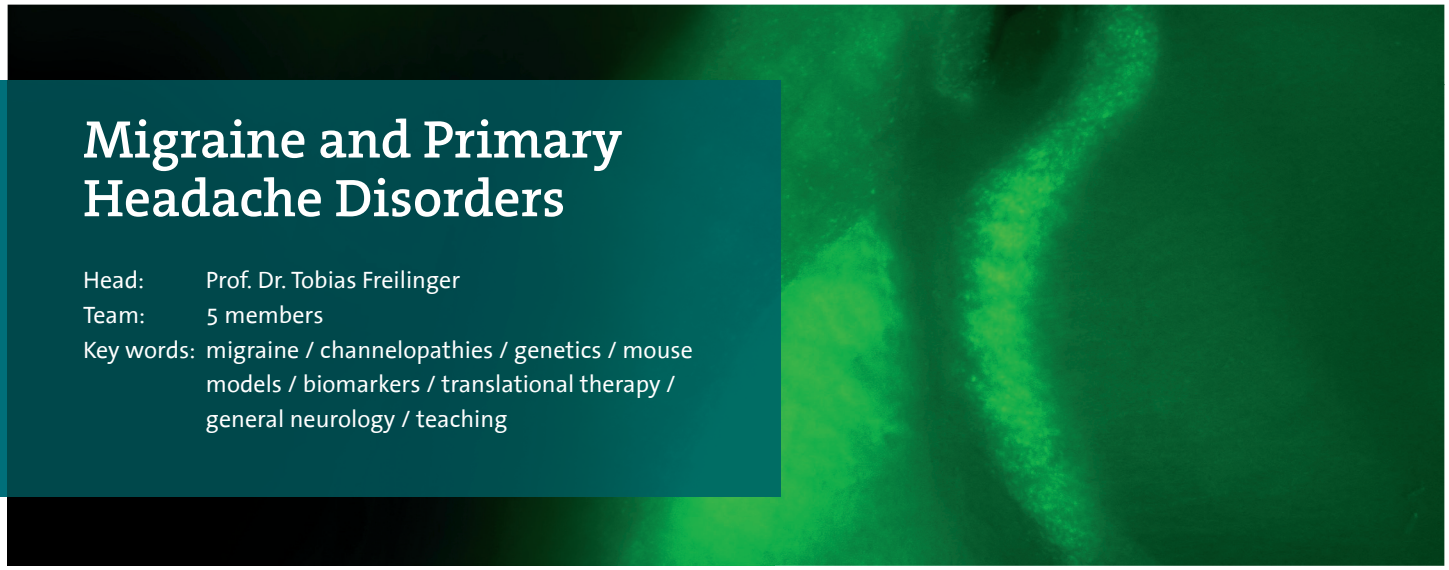
Niestroj LM, May P, Artomov M, Kobow K, Coras R, Perez-Palma E, Altmuller J, Thiele H, Nurnberg P, Leu C, Palotie A, Daly MJ, Klein KM, Beschorner R, **Weber YG**, Blumcke I, Lal D (2019) Assessment of genetic variant burden in epilepsy-associated brain lesions. *European Journal of Human Genetics* 27:1738-44

O'Donnell-Luria AH, (...), Vogt J, **Weber YG**, Wentzensen IM, Widjaja E, Zak J, Baxter S, Banka S, Rodan LH (2019) Heterozygous Variants in KMT2E Cause a Spectrum of Neurodevelopmental Disorders and Epilepsy. *American Journal of Human Genetics* 104:1210-22

Feng YCA, Howrigan DP, Abbott LE, Tashman K, Cerrato F, Singh T, Heyne H, Byrnes A, Churchhouse C, Watts N, (...), Muhle H, Rademacher A, van Baalen A, von Spiczak S, Stephani U, Afawi Z, Korczyn AD, Kanaan M, Canavati C, Kurlemann G, Muller-Schluter K, Kluger G, Hausler M, Blatt I, Lemke JR, Krey I, **Weber YG,** Wolking S, Becker F, Hengsbach C, Rau S, Maisch AF, Steinhoff BJ, Schulze-Bonhage A, Schubert-Bast S, Schreiber H, Borggrafe I, Schankin CJ, Mayer T, Korinthenberg R, Brockmann K, Dennig D, Madeleyn R, Kalviainen R , (...), Goldstein DB, Lerche H, Berkovic SF, Neale BM, Epi C, Genomic Psychiat Cohort GPCC (2019) Ultra-Rare Genetic Variation in the Epilepsies: A Whole-Exome Sequencing Study of 17,606 Individuals. *American Journal of Human Genetics* 105**:**267-82

Migraine and Primary Headache Disorders

Head: Prof. Dr. Tobias Freilinger
Team: 5 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 severe monogenic subtype of migraine with some degree of unilateral motor weakness during the aura. 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, genotype-phenotype correlations (e.g. Schubert et al. 2018) and imaging findings (Roth et al. 2018). In a sporadic HM patient, we had previously identified a novel missense mutation 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).

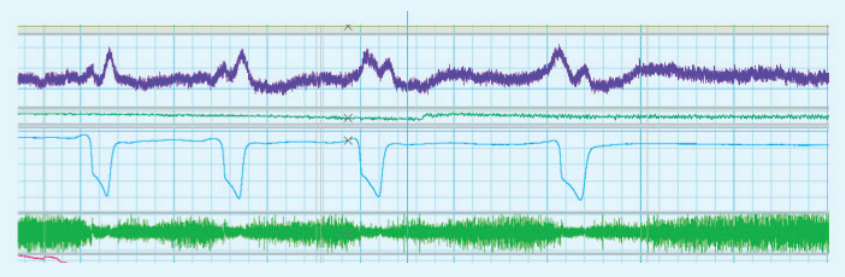
To comprehensively study mechanisms underlying cortical hyperexcitabilitiy in HM, we are performing multimodal analysis of a transgenic Scn1a knock-in HM mouse model. By in vivo analyses we could show increased susceptibility to cortical spreading depolarisation (CSD), the likely correlate of migraine aura. Further, this model allowed us to establish increased activity of interneurons as a potential novel mechanism of CSD generation (Auffenberg et al., in preparation). Ongoing analyses focus e.g. on the the differential pathophysiology of migraine vs. epilepsy and stroke susceptibility in migraine (cooperation with N. Plesnila, ISD, Munich).

We are also 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 were able to launch the first mechanism-based translational prospective treatment trial in HM evaluating the role of the sodium channel blocker lamotrigine in preventing HM attacks (HeMiLA, HeMiLa, Prophylactic treatment of hemiplegic migraine with Lamotrigine; EudraCT-Nr. 2016-003223-30). In addition, we are in in the final process of setting up another translational

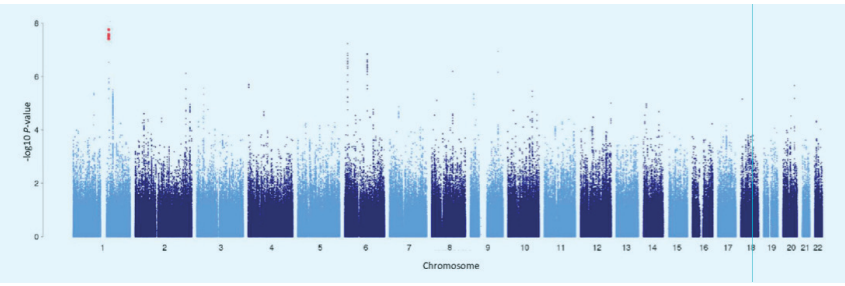
trial, which will focus on acute treatment of attacks by means of non-invasive vagal nerve stimulation (grant from ZSE).

As a second focus we are interested in the common genetically complex types of migraine. As a founding member of the International Headache Genetics Consortium (IHGC), we were prominently involved in the identification of all currently established risk variants as well as more recent downstream analyses (e.g. Gormley et al. 2018, Yang et al. 2018, Brainstorm Consortium et al. 2018). Our group has a special interest in the migraine – vascular diease connection, and we are looking further into this (e.g. 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. Auffenberg et al. 2018; Hoffmann et al. 2019; Niller et al. 2020; Schubert et al., in preparation) as well as medical teaching in neurology; a recent pilot project was dedicated to developing a novel interactive learning and teaching toolbox for medical students comprising more than 20 case vignettes on classical neurological disease entities (Neuro-CliPS Tübigen; 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)

SELECTED PUBLICATIONS

Niller HH, Angstwurm K, ..., **Freilinger T**, Gartner L, Wenzel JJ, Reischl U, Jilg W, Gessner A, Jantsch J, Beer M, Schmidt B (2020) Zoonotic spillover infections with Borna disease virus 1 leading to fatal human encephalitis, 1999-2019: an epidemiological investigation. *Lancet Infect Dis* 7:S1473-3099(19)30546-8

Hoffmann E, Boßelmann C, Forchhammer S, Lerche H, **Freilinger** T (2019) Neuro-Sweet syndrome - a rare differential diagnosis in aseptic meningoencephalitis. *Neurological Research and Practice* 1:36

Gormley P, Kurki MI, ..., 23andMe Research Team; International Headache Genetics Consortium (IHGC), Runz H, Daly MJ, Neale BM, Ripatti S, Kallela M, Wessman M, Palotie A (2018) Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families. *Neuron* 99:1098

Yang Y, Zhao H, Boomsma DI, Ligthart L, Belin AC, Smith GD, Esko T, **Freilinger TM**, Hansen TF, ... International Headache Genetics Consortium, van den Maagdenberg AMJM, Terwindt GM, Nyholt DR (2018) Molecular genetic overlap between migraine and major depressive disorder. *Eur J Hum Genet* 26:1202-6

Brainstorm Consortium et al. Analysis of shared heritability in common disorders of the brain (2018) *Science* 360:eaap8757

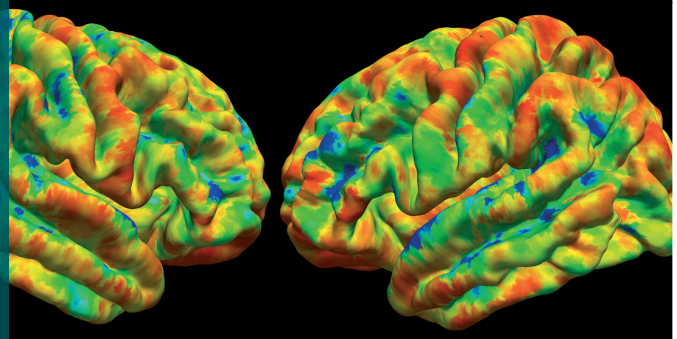
Roth C, Ferbert A, Huegens-Penzel M, Siekmann R, **Freilinger T** (2018) Multimodal imaging findings during severe attacks of familial hemiplegic migraine type 2. *J Neurol Sci* 392:22-7

Schubert V, Bender B, Kinzel M, Peters N, **Freilinger T** (2018) A novel frameshift variant in the CADASIL gene NOTCH3: pathogenic or not? *J Neurol* 265:1338-42

Schubert V, Auffenberg E, Biskup S, Jurkat-Rott K, **Freilinger T** (2018) Two novel families with hemiplegic migraine caused by recurrent SCN1A mutation p.F1499L. *Cephalalgia* 38:1503-8

Translational Neuroimaging

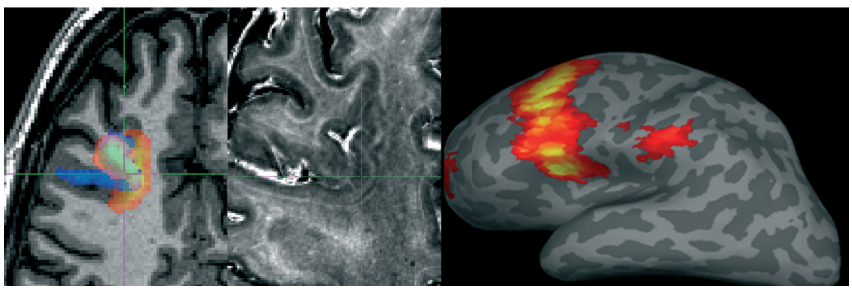
Head: Prof. Dr. Niels Focke
Team: 4 members
Key words: multi-modal imaging / epilepsy / post-processing / classification methods



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

In 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). 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, Kotikalapudi et al., 2019) as well as systematically assessing VBM as a tool for presurgical epilepsy diagnostics (Martin et el., 2017). Furthermore, we have worked on assessing and improving the reliability of network analysis based on DTI (Bonilha et al., 2015), MEG/EEG (Marquetand et al. 2019) and enabling ultra-fast fMRI (Sahib et al., 2016 and Sahib et al., 2018).

SELECTED PUBLICATIONS

Kotikalapudi R, Martin P, Erb M, Scheffler K, **Marquetand J**, Bender B, **Focke NK** (2019) MP2RAGE multispectral voxel-based morphometry in focal epilepsy. *Human Brain Mapping* 40:5042-55

Marquetand J, Vannoni S, Carboni M, **Hegner YL, Stier C**, Braun C, **Focke NK** (2019) Reliability of Magnetoencephalography and High-Density Electroencephalography Resting-State Functional Connectivity Metrics. *Brain Connectivity* 9:539-53

Sahib AK, Erb M, **Marquetand J, Martin P, Elshahabi A, Klamer S,** Vulliemoz S, Scheffler K, Ethofer T, **Focke NK.** Evaluating the impact of fast-fMRI on dynamic functional connectivity in an event-based paradigm. *PLoS One* 2018; 13(1):e0190480

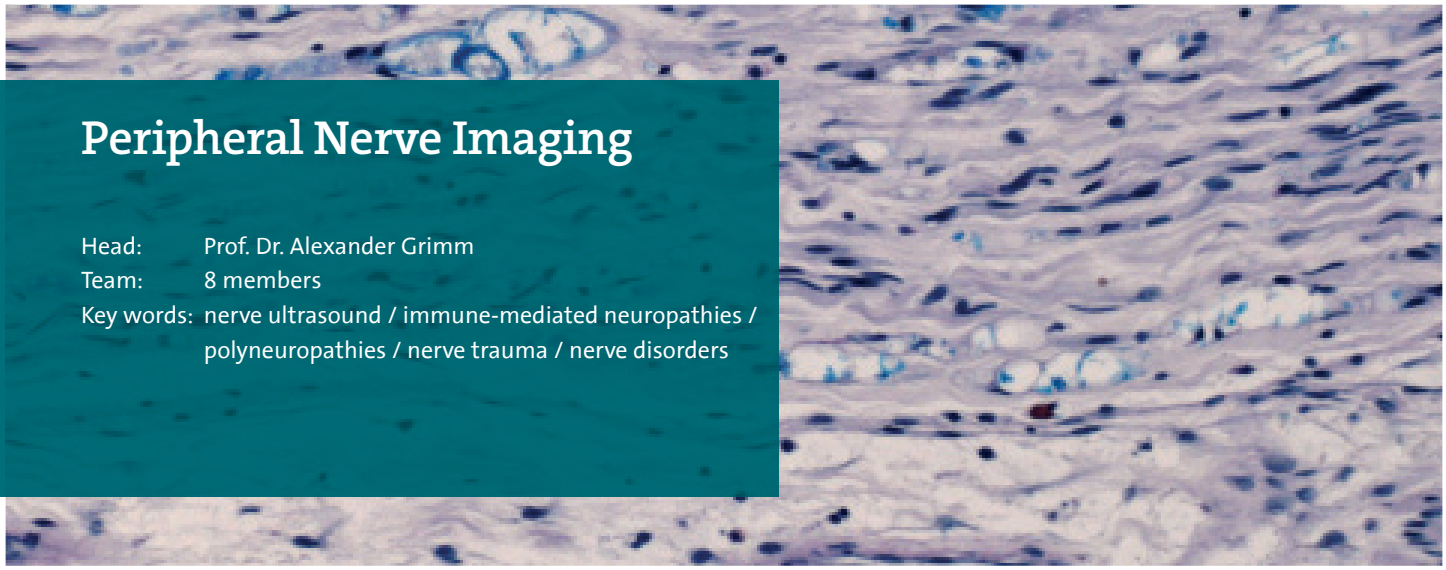
Martin P, Winston GP, Bartlett P, de Tisi J, Duncan JS, **Focke NK**. Voxel-based magnetic resonance image postprocessing in epilepsy. *Epilepsia* 2017; 58(9):1653-64

Lindig T, Kotikalapudi R, Schweikardt D, **Martin P**, Bender F, Klose U, Ernemann U, **Focke NK***, Bender B. Evaluation of multimodal segmentation based on 3D T1-, T2- and FLAIR-weighted images - the difficulty of choosing. *NeuroImage* 2017, S1053-8119(17):30120-9 * corresponding author

Elshahabi A, Klamer S, Sahib AK, Lerche H, Braun C, **Focke NK**. Magnetoencephalography Reveals a Widespread Increase in Network Connectivity in Idiopathic/Genetic Generalized Epilepsy. *PLoS One* 2015; 10(9): e0138119.

Bonilha L, Gleichgerrcht E, Fridriksson J, Rorden C, Breedlove JL, Nesland T, Paulus W, Helms G, **Focke NK**. Reproducibility of the Structural Brain Connectome Derived from Diffusion Tensor Imaging. *PLoS One* 2015; 10(9):e0135247

Focke NK, Diederich C, Helms G, Nitsche MA, **Lerche H**, Paulus W. Idiopathic-generalized epilepsy shows profound white matter diffusion-tensor imaging alterations. *Human Brain Mapping* 2014; 35(7): 3332-42



Peripheral Nerve Imaging

Head: Prof. Dr. Alexander Grimm
Team: 8 members
Key words: nerve ultrasound / immune-mediated neuropathies / polyneuropathies / nerve trauma / nerve disorders

The goal of our research is to visualize the peripheral nerves and the muscles by high-resolution ultrasound. Next to the development of normative nerve size data, we examine nerve pathology, i.e. nerve enlargement, atrophy, changed echointensity and perineural tissue in neuropathies, nerve traumata, nerve tumours and systemic nerve disorders, such as motoneuron diseases, lysosomal storage diseases or automimmune disorders. Moreover we want to know, what happens during therapy or after surgery. How do nerves regenerate in humans and can we visualize this process by ultrasound? We further look after muscle morphology changes in ALS, myopathies and radiculopathies as well as in nerve trauma. We try to find out the way of muscle changes during disease course. As peripheral nerve disorders are a common problem, we can reach well defined cohorts and thus establish our method in sufficient sample sizes.

Das Ziel unserer Forschung ist es, die Struktur peripherer Nerven und Muskeln im Ultraschall darzustellen, und das sowohl bei gesunden Probanden als auch Patienten mit Polyneuropathien, Nervenverletzungen, -tumoren und Patienten mit Systemerkrankungen, z.B. ALS oder lysosomalen speichererkrankungen. Dabei achten wir auf Veränderungen der Nervengröße, der Nervenechogenität und des umliegenden Gewebes. Uns interessieren außerdem Veränderungen, die die Regeneration von Nerven nach Operationen oder nach medikamantösen Therapien erklären könnten. Zuletzt sehen wir uns den Muskel an, sei es bei Motoneuronerkrankungen, Myopathien oder auch Wurzel- und Nervenschädigungen.

Different types of polyneuropathy may show different sonomorphological abnormalities. In general, nerve enlargement is most often seen in demyelinating neuropathies, both inherited and acquired. Massive nerve enlargement is particularly characteristic of Charcot-Marie-Tooth (CMT) disease type 1A, but can also be seen in chronic inflammatory demyelinating polyneuropathy (CIDP) and leprosy. Nerve enlargement to a lesser degree has been described in several other demyelinating or inflammatory neuropathies. Other axonal neuropathies typically have either no or very mild nerve enlargement, with rare exceptions including some patients with diabetic neuropathy. By establishing the ultrasound pattern sum score (UPSS), we could define a tool for operationalizing these sonomporphological findings and thus simplify an examiner-independent scanning process (Grimm A et al., 2018).

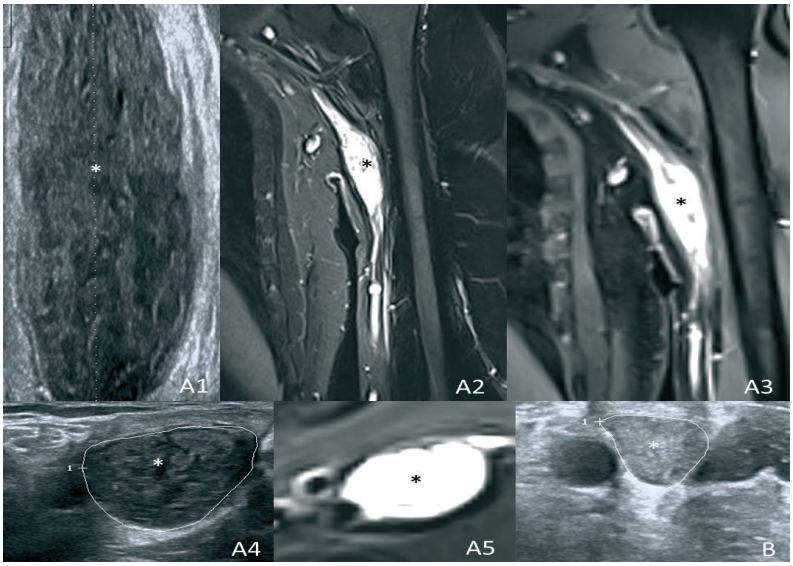
In another study, we could show that this UPSS together with electrodiagnostics can be handled as follow-up tool in immune-mediated neuropathies under treatment. Generally spoken, hypoechoic nerve sweeling is a more therapy-susceptible inflammation type than hyperechoic nerve swelling. Compared to histology, increased echosignal seems to reflect axonal damage and scare tissue, which might be a consequence of a more harmful and chronic damage. Those patients without nerve swelling at all seem to be the less reactive to treatment (Haertig et al., 2018).

Further, the UPSS seems to be a suitable method to follow-up and differentiate acute from chronic inflammatory neuropathies, which is not always possible by electrophysiology and clinical course alone (Grimm et al., 2019). This work also received the Felix-Jerusalem Prize of the German muscle society.

Ultrasound has been further proven, to detect the inflammatory base of several mononeuropathies of unknown origin (Winter et al. , 2019). So far, the cause of those sporadic mononeuropathies remained often unclear as it only showed axonal damage in electrophysiology without clarifying the underlying pathology. By ultrasound however, our group could find tremendeous nerve swelling and edema, which decreased with treatment and correlated to the clinical improvement (Figure). This finding is emerging for many patients as it might facilitate early therapeutic steps. Ongoing studies handle the huge field of hereditary neuropathies, lysosomal storage diseases and their nerve ultrasound presentation.

Next to polyneuropathies, our group established normative data in children, which is significant for the diagnosis of pediatric nerve disorders (Schubert C et al., 2020). Nerve growth correlates with age just until the late adolescence and then reaches adult values. During adulthood nerve sizes remain stable in healthy individuals. Only in the extreme of age, nerve area decreases a little.

We also have cooperations with the colleagues of pediatric neurology concerning nerve dusorders in children. Some work has already been finished (Küpper et al., 2020), other studies are still ongoing. Moreover, we have projects with our department of Neurosurgery as well as the BG hospital concerning nerve traumata, their treatment as well as nerve morphology in those patients, which is granted by the German Ultrasound Society.



Median nerve (marked with a star) image with tumefactive nerve enlargement before therapy in ultrasonography in long-axis (A1, 90° skipped). In MRI, the nerve is hyperintense in T2 with almost homogeneous gadolinium enhancement in T1, length>6cm in MRI (A2 and A3, only partially shown in ultrasonography). A4: ultrasonography (and corresponding T2-MRI, A5) before treatment, cross-sectional area CSA 177mm², hyperechoic and B: after treatment with steroids (CSA 40mm², length 4.5cm [not shown]).

SELECTED PUBLICATIONS

Schubert C, Grimm AS, Stahl JH, Kupper H, Kegele J, Wittlinger J, Serna-Higuita L, Winter N, Groeschel S, **Grimm A** (2020) Nerve ultrasound reference data in children from two to seven years. *Clin Neurophysiol* 131:859-65

Kupper H, Kaiser N, Winter N, Kehrer C, Groeschel S, Bevot A, Nagele T, Krageloh-Mann I, **Grimm A** (2020) Enlargement of peripheral nerves in Krabbe disease: The diagnostic value of nerve ultrasound. *Muscle Nerve* 61:E24-E27

Winter N, Dammeier N, Schaffer E, Bornemann A, Stahl JH, Herlan S, Schuhmann MU, **Grimm A** (2019) Nerve Ultrasonography as an Additive Tool to Clinical Examination and Electrodiagnostics in Sporadic Mononeuritis - Imaging is the Key. *Ultraschall Med* 40:465-72

Grimm A, Oertl H, Auffenberg E, Schubert V, Ruschil C, Axer H, Winter N (2019) Differentiation Between Guillain-Barre Syndrome and Acute-Onset Chronic Inflammatory Demyelinating Polyradiculoneuritis-a Prospective Follow-up Study Using Ultrasound and Neurophysiological Measurements. *Neurotherapeutics* 16:838-47

Grimm A, Axer H, Heiling B, Winter N (2018) Nerve ultrasound normal values - Readjustment of the ultrasound pattern sum score UPSS. *Clin Neurophysiol* 129:1403-09

Hartig F, Ross M, Dammeier NM, Fedtke N, Heiling B, Axer H, Decard BF, Auffenberg E, Koch M, Rattay TW, Krumbholz M, Bornemann A, Lerche H, Winter N, **Grimm A** (2018) Nerve Ultrasound Predicts Treatment Response in Chronic Inflammatory Demyelinating Polyradiculoneuropathy-a Prospective Follow-Up. *Neurotherapeutics* 15:439-51

Department of Neuro-degenerative Diseases

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

Departmental Structure

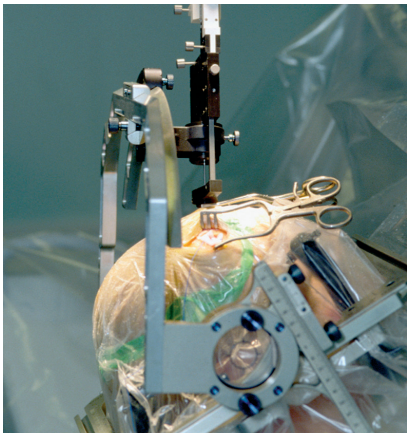
The Department of Neurodegenerative Diseases was founded with the support of the Charitable Hertie Foundation and started operations on September 1, 2002. Since 2009, it is also a part of the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE). Prof. Peter Heutink, speaker of the 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 45) 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. A structured training, the Movement Disorders Curriculum for medical residents in training for board certification has been implemented, that covers a wide variety of movement disorders and rare neurogenetic diseases and includes clinic rotations, talks and journal clubs.

The clinical branch of 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

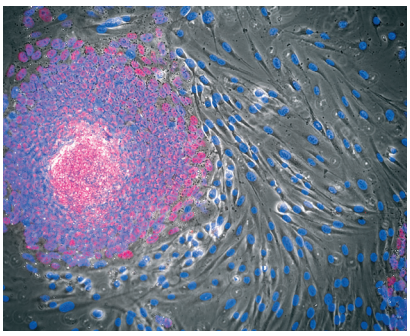
deep brain stimulation (in close collaboration with the Department of Neurosurgery), but also continuous apomorphine or levodopa infusion treatment in Parkinson's patients with severe fluctuations, or botulinum toxin treatment in patients with dystonias and spastic gait disorders. The close collaboration 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 2020, the clinical department was named for the sixth 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 9 research groups and four associated 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 lead by Dr. Kathrin Brockmann. 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 and pursues innovative approaches of gene therapy. Prof Dr. D. Weiß heads the deep brain stimulation (DBS) group with a special focus on difficult to treat symptoms of PD like gait disorders and freezing. Prof. P. Kahle's group (Section of Functional Neurogenetics) investigates fundamental aspects of neurodegeneration mainly related to tau and alpha-synuclein aggregation. The group of Prof. 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. Julia Fitzgerald has become junior group leader, studying the mitochondrial biology of PD. Two research groups with a primary affiliation with the DZNE, Jun-Prof. Dr. Dr. Michela Deleidi, and PD Dr. Johannes Gloeckner are also members of the Department. Two previous members, Prof. Daniela Berg and Prof. Rejko Krüger, have both accepted chairs for Neurology at the University of Kiel and Luxembourg, respectively. They both still hold affiliations at the Department and provide their expertise in research and teaching and closely collaborate in a number of externally funded projects.

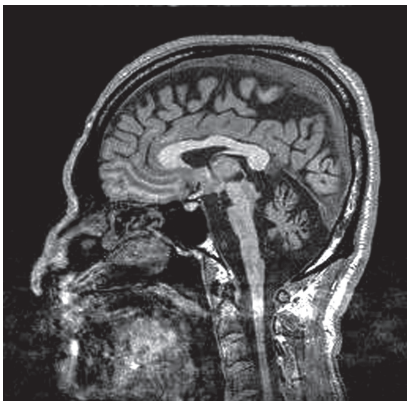
Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with Parkinson's disease and other neurodegenerative diseases.



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).



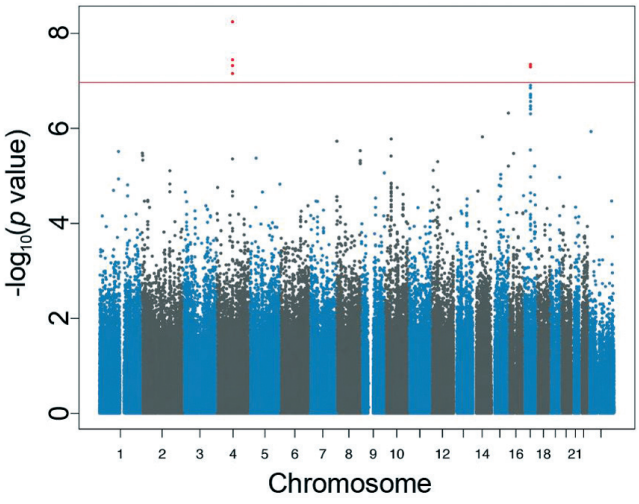
Both, fundamental mechanisms of neurodegeneration in Parkinson's disease and the effects of deep brain stimulation are investgated in Professor Krüger's group.

Parkinson Genetics

Head: Prof. Dr. Thomas Gasser
Team: 7 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 and fluid biomarker analyses.

Obwohl bei den meisten Parkinson-Patienten keine weiteren Familienmitglieder von dieser Erkrankung betroffenen sind, wird immer klarer, dass genetische Faktoren dennoch auch in diesen Fällen das Erkrankungsrisiko und den Verlauf wesentlich beeinflussen. Innerhalb großer internationaler Konsortien arbeiten wir daher mit modernen Hochdurchsatzmethoden verbunden mit genauen klinischen Analysen daran, die hierfür verantwortlichen genetischen Varianten zu identifizieren und die Mechanismen ihrer Auswirkungen zu verstehen.

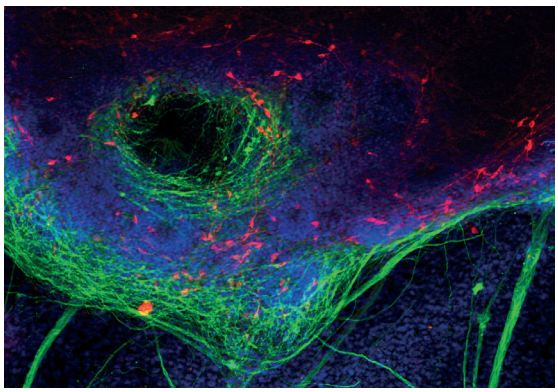


A large genome-wide study identified two genetic risk loci for sporadic PD. One is MAPT, containing the gene for the microtubule associated protein tau.

As in most complex neurodegenerative disorders, specific mutations in some genes can cause rare inherited forms of Parkinson's disease (PD). Mutations in the LRRK2-gene, for example cause the most prevalent autosomal-dominant form of PD, which 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 35,000 cases and 1.500,000 controls. The latest meta-analysis resulted in the confirmation of a total of over 80 risk loci with genome wide significance (Nalls et al., Lancet Neurology 2019).

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. 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). Novel strategies of statistical analysis including machine learning approaches allow us to analyze these large multimodal datasets in order to better understand the development of the disease.

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. Therefore, more recently, we have also started to pursue research into biomarkers by targeting brain-derived exosomes and to use single-cell sequencing strategies on post-mortem brain to understand the pathogenic pathways that constitute the chain of events that lead from genetic mutation to a diseased brain.

SELECTED PUBLICATIONS

Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol.* 2019;18(12):1091-102.

Marrone L., ... **Gasser T.**, Sterneckert J. Generation of iPSCs carrying a common LRRK2 risk allele for in vitro modeling of idiopathic Parkinson's disease. *PLoS One.* 2018;13(3):e0192497.

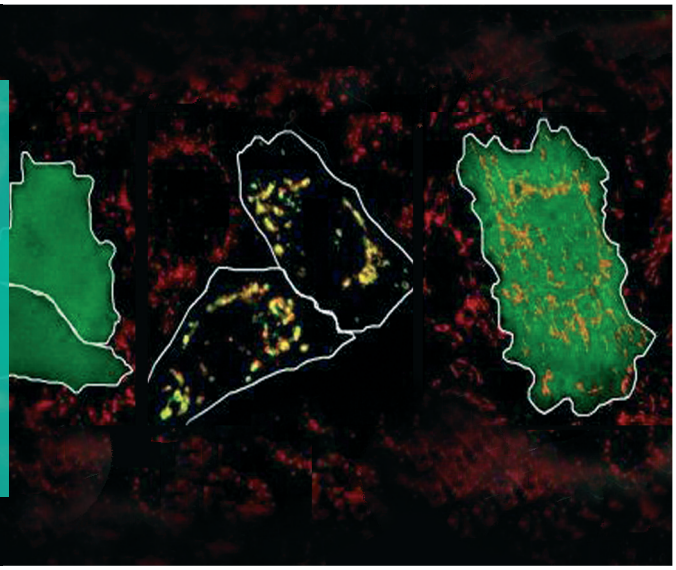
Chang D., Nalls M. A., Hallgrimsdottir I. B., Hunkapiller J., van der Brug M., Cai F., International Parkinson's Disease Genomics C., 23andMe Research Team et al., A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet.* 2017;49(10):1511-6.

Nalls, M. A., ... **T. Gasser**, et al. Parkinson's Disease meta-analysis. NeuroX, a fast and efficient genotyping platform for investigation of neurodegenerative diseases. *Neurobiol Aging.* 2015;36(3): 1605 e1607-1612.

Simon-Sanchez J, ..., **Gasser T**. Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet.* 2009;41(12): 1308-12.

Zimprich A, Biskup S, ... **Gasser T**. Mutations in LRRK2 Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology. *Neuron.* 2004;18; 44(4): 601-7.

Functional Neurogenetics



Head: Prof. Dr. Philipp Kahle
Team: 6 members
Key words: parkinson's disease / amyotrophic lateral sclerosis / frontotemporal dementia / synuclein / ubiquitin / mitochondria / parkin / TDP-43 / post-translational modifications

Parkinson's disease and Lewy body dementia as well as frontotemporal dementia and amyotrophic lateral sclerosis are neuropathologically characterized by intracellular protein inclusions of α-synuclein and TDP-43, respectively. We investigate the molecular, cellular, and histopathological mechanisms underlying aggregation of these proteins and their impact on neural dysfunction. Pathological pathways are modeled in cell culture and animal models. Investigated mechanisms include protein aggregation and post-translational modifications, mitophagy, and nucleocytoplasmic protein transport. We wish to understand the molecular basis how intracellular protein aggregation affects particular neuronal functions, which cause the characteristic syndromes of neurodegenerative movement disorders and dementias.

Die Parkinson'sche Krankheit und Lewy-Körper-Demenz sowie frontotemporale Demenz und amyotrophe Lateralsklerose sind neuropathologisch gekennzeichnet durch Ablagerungen der Proteine α-Synuklein und TDP-43. Wir untersuchen molekulare, zelluläre und histopathologische Mechanismen, welche diesen Proteinablagerungen zugrunde liegen, und wie sie neuronale Fehlfunktionen bewirken. Pathologische Vorgänge werden in Zellkulturen und Tiermodellen dargestellt. Wir untersuchen Mechanismen der Proteinaggregation und post-translationaler Modifikationen, Mitophagie und nucleocytoplasmatischen Transport. Wir versuchen die molekularen Grundlagen intrazellulärer Proteinaggregation zu verstehen und wie diese Vorgänge die spezifischen neuronalen Funktionen stören, die für die charakteristischen Symptome dieser neurodegenerativen Bewegungsstörungen und Demenzen verantwortlich sind.

A major, longstanding focus of our research is the autophagic removal of damaged mitochondria (mitophagy) controlled by the recessive Parkinson's disease (PD) gene products PINK1 and parkin. It is known that depolarization of the inner mitochondrial membrane potential prevents the import of nuclear encoded proteins. As a result, the mitochondrial protein kinase PINK1 accumulates at the mitochondrial outer membrane (MOM), where it phosphorylates ubiquitin as well as the mitochondria recruited ubiquitin ligase parkin. By this mechanism, PINK1 activates parkin to ubiquitinylate several MOM proteins in a coordinated process mediating mitophagy. Screening for **parkin-mitophagy** ubiquitinylation regulating enzymes, we could confirm the previously reported ubiquitin-specific protease USP15 as a direct deubiquitinylating (DUB) enzyme antagonizing the action of the ubiquitin ligase parkin when inducing mitophagy with the mitochondrial uncoupling agent CCCP. Importantly, we discovered a novel DUB, USP36 as a very strong regulator of parkin-dependent mitophagy. Surprisingly, USP36 is localized exclusively within the nucleus and does not move to mitochondria even under mitophagy-promoting conditions. Thus, USP36 cannot be a direct mitophagy DUB but affects this process by a novel mechanism.

We discovered that USP36 modulated histone H2B mono-ubiquitinylation during parkin-mediated mitophagy, pointing to epigenetic control. We found that USP36 knockdown promoted the expression of an isoform of the phosphatase PTEN that antagonizes PINK1-mediated ubiquitin phosphorylation and repressed the expression of the key autophagy regulators Beclin-1 and ATG14L. Indeed, restoration of ATG14L levels could rescue the mitophagy phenotype after USP36 knockdown. In summary, the study by Geisler et al. identified USP36 as a major regulator of parkin-mediated mitophagy affecting several components of the PINK1 pathway and autophagy machinery in a complex manner. Currently we are continuing our research on the regulation of parkin-mediated mitophagy in the framework of a DFG Research Training Group "MOMbrane". We are performing systematic mass spectrometry analyses of phospho-proteomes and ubiquitinylomes at distinct time points of CCCP treatments in cells expressing wild-type and mutant parkin. We wish to get a comprehensive view on the sequential post-translational modifications during parkin-mediated mitophagy for full understanding of this important cellular process, hopefully leading to the discovery of novel PD targets.

For **α-synuclein** we contributed our well-established transgenic mouse model to the study of Keane et al. assessing the PD-relevant nigral dopamine neurodegeneration by the toxins trichloroethylene and TaClo. We also provided tools for the generation of an in vivo (Drosophila melanogaster) system to monitor α-synuclein oligomerization (Prasad et al.)

For **TDP-43** we continued our studies on post-translational modifications. We examined cellular pathways that promote the pathological TDP-43 ubiquitinylation we found in our previous research. As might have been expected, stress granule (SG) forming conditions were most powerful inducers of TDP-43 ubiquitinylation and insoluble protein aggregation. Surprisingly, pharmacological inhibition of SG formation per se did not prevent pathological TDP-43 ubiquitinylation. Thus, our results do not support the original hypothesis that SGs act as seeds for TDP-43 aggregation.

Instead, we confirmed that arsenite confers its effects via oxidative stress on TDP-43 directly. Our investigation of sorbitol-treated cells points to a novel pathway leading to pathological TDP-43 ubiquitinylation. This study is completed and accepted for publication. Moreover, the study of TDP-43 acetylation indicates regulation of nucleocytoplasmic shuttling at the nuclear localization sequence and excitingly liquid-liquid phase separation and TDP-43 aggregation after acetylation within RNA-binding domain, For this purpose we have adapted a novel method to incorporate acetyl-lysine at defined sites in TDP-43 transfected cells. The manuscript is in preparation. This research is supported by the German Center for Neurodegenerative Diseases and the NOMIS foundation.

SELECTED PUBLICATIONS

Geisler S, Jäger L, Golombek S, Nakanishi E, Hans F, Casadei N, **Terradas AL, Linnemann C, Kahle PJ** (2019) Ubiquitin-specific protease USP36 knockdown impairs Parkin-dependent mitophagy via downregulation of Beclin-1-associated autophagy-related ATG14L. *Exp Cell Res* 384:111641.

Keane PC, Hanson PS, Patterson L, Blain PG, Hepplewhite P, Khundakar AA, Judge SJ, **Kahle PJ**, LeBeau FEN, Morris CM (2019) Trichloroethylene and its metabolite TaClo lead to degeneration of substantia nigra dopaminergic neurones: Effects in wild type and human A30P mutant α-synuclein mice. *Neurosci Lett* 711:134437.

Prasad V, Wasser Y, **Hans F**, Goswami A, Katona I, Outeiro TF, **Kahle PJ**, Schulz JB, Voigt A (2019) Monitoring α-synuclein multimerization in vivo. *FASEB J* 33:2116-2131.

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.

Die Dystonie-Erkrankungen stehen an dritter Stelle der häufig vorkommenden Bewegungsstörungen, und Varianten in einer zunehmenden Anzahl von Genen konnten in vielen Fällen als Ursache einer genetisch bedingten Dystonie-Erkrankung nachgewiesen werden. Ziel unserer Arbeitsgruppe, welche sich durch die Zusammensetzung von Dystonie-erfahrenen Klinikern und molekulargenetisch ausgebildeten Experten auszeichnet, ist es zum einen, die Rolle der bereits bekannten Dystonie-Gene besser zu definieren, und zum anderen, neue Gene zu finden, um die molekularen Mechanismen der Dystonie besser zu verstehen.

Patient recruitment is based on the departmental outpatient clinic for botulinum toxin treatment, which is run by Dr. E. Lohmann since end of 2015. She brought a large number of patient samples from her previous position at the University of Istanbul in Turkey, where she founded a neurogenetic research group and was supported by a Margarete von Wrangell-stipend. Dr. E. Lohmann continued 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.

SELECTED PUBLICATIONS

Pogoda M, Hilke FJ, **Lohmann E**, Sturm M, Lenz F, Matthes J, Muyas F, Ossowski S, Hoischen A, Faust U, Sepahi I, Casadei N, Poths S, Riess O, Schroeder C, Grundmann K (2019) Single Molecule Molecular Inversion Probes for High Throughput Germline Screenings in Dystonia. *Front Neurol* 10:1332

Guven G, Bilgic B, Tufekcioglu Z, Erginel Unaltuna N, Hanagasi H, Gurvit H, Singleton A, Hardy J, Emre M, Gulec C, Bras J, Guerreiro R, **Lohmann E** (2019) Peripheral GRN mRNA and Serum Progranulin Levels as a Potential Indicator for Both the Presence of Splice Site Mutations and Individuals at Risk for Frontotemporal Dementia. *J Alzheimers Dis* 67:159-67

Atasu B, Hanagasi H, Bilgic B, Pak M, Erginel-Unaltuna N, Hauser AK, Guven G, Simón-Sánchez J, Heutink P, Gasser T**, Lohmann E** (2018) HPCA confirmed as a genetic cause of DYT2-like dystonia phenotype. *Mov Disord* 33:1354-8

Kessler C, Atasu B, Hanagasi H, Simón-Sánchez J, Hauser AK, Pak M, Bilgic B, Erginel-Unaltuna N, Gurvit H, Gasser T, **Lohmann E** (2018) Role of LRRK2 and SNCA in autosomal dominant Parkinson's disease in Turkey. *Parkinsonism Relat Disord* 48:34-9

Darwent L, Carmona S, **Lohmann E**, Guven G, Kun-Rodrigues C, Bilgic B, Hanagasi H, Gurvit H, Erginel-Unaltuna N, Pak M, Hardy J, Singleton A, Brás J, Guerreiro R (2017) Mutations in TYROBP are not a common cause of dementia in a Turkish cohort. *Neurobiol Aging* 58:240.e1-240.e3

Clinical Neurogenetics

Head: Prof. Dr. Ludger Schöls
Team: 15 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 ataxia, hereditary spastic paraplegia, choreatic disorders and leukodystrophies. To discover the genetic cause of the diseases we use transciptomics and proteomics beside 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. In our specialized outpatient clinics we see many patients with these rare diseases and include them into clinical studies to establish measures of disease progression that can be used to monitor therapeutic effects. We establish biorepositories of DNA, RNA, serum, CSF and fibroblasts 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 which constitute cell culture models that are genetically identical with our patients and represent the cell type that is primarily affected by the disease. This helps us to study very early consequences of the disease causing mutations and to identify new targets for therapeutic approaches. These neuronal cell culture models also help to screen new compounds before they are tested in animal models and finally come to the clinic in interventional trials.

Die Sektion Klinische Neurogenetik ist auf translationale Forschung bei neurogenetischen Erkrankungen wie zerebellären Ataxien, Hereditären Spastischen Spinalparalysen (HSP), Chorea-Erkrankungen und Leukodsytrophien fokussiert. Wir nutzen Transkriptom- und Proteomanalysen als Ergänzung zur Exom- und Genomsequenzierung um die genetischen Ursachen dieser Erkrankungen aufzudecken und so für unsere Patienten die molekulare Diagnose zu sichern und ein Fenster zur Erforschung der Pathophysiologie und Entwicklung kausaler Therapien zu öffnen. In unseren Spezialambulanzen wirden Patienten 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 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. Vielversprechende Substanzen mit positiven Effekten in neuronalen Zellkulturen, können dann in Therapiestudien für Patienten weiter untersucht werden.

Ataxia

In preparation for interventional trials in spinocerebellar ataxias (SCA) we are part of the EU funded ESMI problem we established diagnostic consortium 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. We proved the superiority of this motion capture system over clinical measures in the assessment of disease progression in a multi-center setting and in individuals at risk to develop SCA, i. e. first degree relatives of patients (Ilg et al., in preparation). Further, we performed the first multicentric assessment on the influence of lifestyle factors on the course of ataxia. In the European SCA consortium (EUROSCA) we provided first data

on long-term survival of SCA patients in a longitudinal prospective cohort study (Diallo et al. Lancet Neurol 2018). The increasing complexity of autosomal recessive ataxias has been reviewed by our group in Neuron (Synofzik et al. 2019) with a focus on genetics and trial readiness. We clearly show that genetic stratification of cohorts and quantitative markers of disease activity are key for the development of new therapeutic options in hereditary ataxias.

Hereditary spastic paraplegia (HSP)
HSP is a group of neurodegenerative diseases of the spinal cord with the clinical hallmark of progressive spastic gait disorder. Although rare, HSP is highly heterogeneous with more than 80 genetically defined subtypes. We took advantage of a large cohort of >1000 HSP patients seen in Tübingen and collaborative centers to analyse the phenotypic spectrum and course of disease in SPG35 as an ultra-rare subtype of HSP caused by mutations in the fatty acid 2-hydroxylase (FA2H). In 19 SPG35 patients we identified a broad spectrum of disease manifestation including cognitive deficits, ataxia, dystonia, rigidity and bristly hair in most cases. Further characteristics include manifestation in early childhood, a rapid progression to wheelchair within an average of 7 years and characteristic changes on MRI (WHAT sign: white matter changes, hypointensity of globus pallidus on T2 images, atrophy of the cerebellum and thin corpus callosum) (Rattay et al. Brain 2019).

Many autosomal recessive types of HSP are caused by loss of function mutations in the respective genes. This makes supplementation of DNA (by gene transfer), RNA or protein promising approaches. We set-out to explore the therapeutic potential of a RNA-based therapy in SPG5 that is caused by loss of function mutations in CYP7B1 coding for a cytochrome important for oxysterol degradation in the liver (Schöls et al. Brain 2017). In cooperation with the CureVac Company in Tübingen, we tested the application of human CYP7B1 RNA to mice that lack the endogenous Cyp7b1 gene. We found a single-dose injection of CYP7B1 RNA to decrease the amounts of oxysterols drastically in liver as well as in blood within 2 days. Pharmacokinetic studies indicated the effect to last for about 5 days. Repetitive applications of RNA were safe for at least 4 injections and resulted in a significant reduction of neurotoxic oxysterols not only in liver and serum but also to some extend in the brain after 17 days (Hauser et al. Mol Ther Methods Clin Dev 2019).

Leukodystrophies
Leukodystrophies and hereditary leukoencephalopathies are frequently regarded as disorders of childhood. In Tübingen we see more than 300 patients with adult forms of these rare diseases. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is an autosomal dominantly inherited and rapidly progressive disease due to mutations in the CSF1R gene. In preparation of gene therapeutic trials we established neurofilament light chain (NfL) as a biomarker that is highly increased in CSF as well as in serum of all HDLS patients. Compared to healthy controls we found NfL to be slightly increased already in presymptomatic mutation carriers indicating some minor disease activities several years prior to clinical manifestation. Monitoring of NfL may help to identify the optimal time point for hematopoetic stem cell transplantation (Hayer et al. Neurology 2018).

Trilateral project in Arab societies
In a DFG funded project that brings together Israeli, Palestinian and German groups we aim to disclose the genetic cause of disease in consanguineous families of the Arab population. More than 100 families have been identified in Israel and the Westbank and underwent cutting edge genetics that allowed for the identification of the molecular cause of the disease in more than 50% of families (Hengel et al Eur J Hum Genet 2020). In addition four new disease genes have been identified in this cohort including UGDH that has been shown to be a rather frequent cause of developmental epileptic encephalopathy (Hengel et al. Nature Comm 2020).

SELECTED PUBLICATIONS

Hengel H*, Bosso-Lefevre C*, ..., **Schöls L**#, Reversade B#. Loss-of-function mutations in UDP-Glucose 6-Dehydrogenase cause recessive developmental epileptic encephalopathy. *Nat Commun* 2020;11:595

Hauser S, Poenisch M, Schelling Y, Hoflinger P, Schuster S, Teegler A, Betten R, Gustafsson JA, Hubener-Schmid J, Schlake T, Chevessier-Tunnesen F, Horscroft N, Bjorkhem I, **Schöls L**. mRNA as a Novel Treatment Strategy for Hereditary Spastic Paraplegia Type 5. *Mol Ther Methods Clin Dev* 2019;15:359-70

Rattay TW, Lindig T, ..., Bauer P, **Schöls L**, Schüle R. FAHN/SPG35: a narrow phenotypic spectrum across disease classifications. *Brain* 2019;142:1561-72

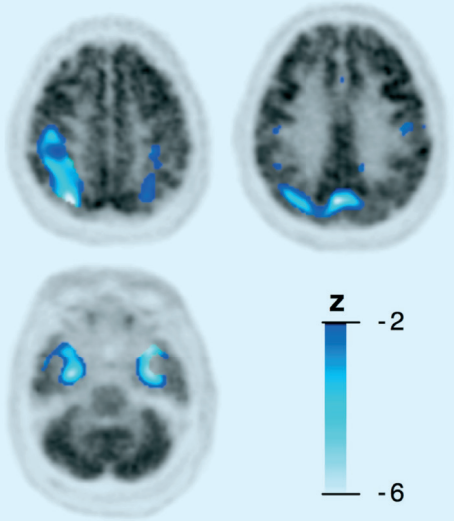
Synofzik M, Puccio H, Mochel F, **Schöls L**. Autosomal Recessive Cerebellar Ataxias: Paving the Way toward Targeted Molecular Therapies. *Neuron* 2019;101:560-83

Diallo A, Jacobi H, Cook A, ..., **Schöls L**, ..., Klockgether T, du Montcel ST. Survival in patients with spinocerebellar ataxia types 1, 2, 3, and 6 (EUROSCA): a longitudinal cohort study. *Lancet Neurology* 2018;17:327-34

Hayer SN, Krey I, Barro C, Rossler F, Kortvelyessy P, Lemke JR, Kuhle J, **Schöls L**. NfL is a biomarker for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. *Neurology* 2018;91:755-57

Systems Neurodegeneration

Head: Prof. Dr. Matthis Synofzik
Team: 14 members (including MD students)
Key words: rare neurogenetic diseases / ataxias/ frontotemporal dementias / early-onset dementias / Amyotrophic Lateral Sclerosis / next-generation sequencing / fluid biomarkers/ digital-motor outcome measures/ trial-readiness



FDG-PET in a patient with frontotemporal dementia due to a C9orf72 repeat expansion

Our translational 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)**

Unsere Forschungsgruppe ist spezialisiert auf die translationale Erforschung genetischer Grundlagen, systemneurologischer 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).*

The concept

For these diseases, we have implemented a comprehensive methodological spectrum which allowed us to establish a translational pipeline for rare neurodegenerative diseases;

- proceeding from genetic stratification of patients with so far molecularly unsolved diseases, leveraging latest whole exome, whole genome and transcriptome sequencing;
- via deciphering underlying molecular pathways and associated fluid biomarkers, using both targeted and unbiased omics approaches;
- identification and validation of digital-motor outcome measures, exploiting sensor wearables both in the lab as well as in the real-life home setting;
- conducting deep clinical, neuropsychological and imaging profiling;
- to implement first-in-man drug and neurorehabilitative proof-of-principle treatment studies.

Early-onset ataxias and other rare movement disorders

Building on the prospective longitudinal international multicenter Early-Onset Ataxia registry (EOA) established by us already back in 2012, we were since then able to establish a large national and international network on autosomal-recessive and other early-onset ataxias. Our registry and our work in next-generation genomics was the basis for: (i) the translational EU E-Rare JTC consortium „PREPARE" which prepares targeted treatment trials for rare autosomal-recessive ataxias (launched in 2015); (ii) the trial-readiness EU EJP RD consortium "PROSPAX" which charts the natural progression of spastic ataxias by rigorous multi-center trial-readiness studies (launched in 2020, together with Dr. Schüle, HIH); (iii) the translational global network "ARCA GLOBAL", which coordinates and harmonizes trial-readiness research on autosomal-recessive ataxias across the leading centers around all continents (launched in 2019).

Often jointly with the HIH groups of Prof. Ludger Schöls and Dr. Rebecca Schüle, we helped to expand and delineate the phenotypic spectrum of >20 ataxia genes, including SYNE1, PNPLA6, STUB1 [1], SERAC1 [2}, POLR3A [3], PLA2G6 [4], and ATP13A2 [5].Our large web-based cohort of >1700 ataxia exome data-sets, allowed us to identify > 7 novel ataxia/hereditary spastic paraplegia genes, like DNAJC3 or KCNA2.

Frontotemporal dementias and other complex dementias

In cooperation with Prof. Peter Heutink (HIH/DZNE Tübingen) we established a cohort of >2500 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 (Blauwendraat et al, 2018). Moreover, it allowed us to delineate the phenotypic and mutational spectrum of FTD genes like TBK1 . Our contributions to the global GENFI consortium" have helped to systematically aggregate longitudinal clinical, imaging and biomaterial data from presymptomatic and symptomatic subjects from families with hereditary FTD allowing to already start first targeted molecular treatment trials in genetic FTD. Such trials will be facilitated by the identification of possible fluid biomarkers for FTD, like neurofilament light chain (NfL), progranulin, or glial fibrillary acid protein as described by us, and as already validated in first stringent longitudinal biomarker studies in genetic FTD by our GENFI consortium, including biomarker mapping of the "conversion phase" from the presymptomatic to the symptomatic stage in FTD (van der Ende et al, 2019) as well as other neurodegenerative diseases like Parkinson's Disease (Wilke et al, in press). This very early-stage disease phase which might be uniquely amendable for molecular treatments will now be characterized molecularly in-depth by our novel EU JPND "GENFI-prox" consortium (launched in 2020).

Trial-readiness: preparing treatments for neurodegenerative disease

To achieve trial-readiness, we have developed digital-motor outcome measures capturing ataxia-specific gait changes even already at the preataxic stage in at-risk subjects (Ilg et al, 2016), and also in symptomatic subjects' real-life by body-worn sensor wearables (Ilg et al, in press, Neurology), thus demonstrating ecological validity as required for regulatory approval as trial outcome measures.

Also our digital-motor parameters of speech allowed us to detect speech changes in at-risk subjects already at the preataxic stage (Vogel et al, in press, Neurology), thus complementing our molecular biomarkers (see above) in stratifying a window for treatment before the clinical manifestation of the disease has started. As first use cases for treatment interventions in degenerative ataxias, we utilized different types of computer-based intensive neurorehabilitative training which allows training by subjects themselves in their home-settings. Our two intra-individually controlled, rater-blinded trials of videogame-based coordinative training demonstrated that such exergame training is effective in improving gait and trunk ataxia even in subjects in an advanced, multisystemic disease state (Schatton et al, 2017). Likewise, computer-based speech training might improve dysarthric speech also in subjects with multisystemic ataxia (Vogel et al, 2019).

SELECTED PUBLICATIONS

Ilg W, Fleszar Z, Schatton C, Ö, **Synofzik M** (2016) Individual changes in preclinical spinocerebellar ataxia identified via increased motor complexity. *Mov Disord* 31:1891-1900

Synofzik M, Smets K, Mallaret M, Di Bella D, Gallenmuller C, Baets J, (...), Bauer P (2016) SYNE1 ataxia is a common recessive ataxia with major non-cerebellar features: a large multi-centre study. *Brain* 139:1378-93

Schatton C*, **Synofzik M***, Fleszar Z, Giese MA, Schols L, Ilg W (2017) Individualized exergame training improves postural control in advanced degenerative spinocerebellar ataxia: A rater-blinded, intra-individually controlled trial. *Parkinsonism Related Disord* 39:80-4 (*equally contributed)

Blauwendraat C, Wilke C, Simon-Sanchez J, Ö, **Synofzik M** (2018) The wide genetic landscape of clinical frontotemporal dementia: systematic combined sequencing of 121 consecutive subjects. *Genet Med* 20:240-9

Synofzik M, Puccio H, Mochel F, Schols L (2019) Autosomal Recessive Cerebellar Ataxias: Paving the Way toward Targeted Molecular Therapies. *Neuron* 101:560-83

van der Ende EL., Meeter LH, (...), **Synofzik M**.,(...), Swieten J **(**2019) Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. *Lancet Neurol* 18:1103-11

Vogel AP, Stoll LH, Oettinger A, Rommel N, Kraus EM, Timmann D, (...), **Synofzik M** (2019) Speech treatment improves dysarthria in multisystemic ataxia: a rater-blinded, controlled pilot-study in ARSACS. *J Neurol* 266:1260-6

Ilg W, Seemann J, Giese MA, Traschutz A, Schöls L, Timmann D, **Synofzik M** (2020) Towards ecologically valid biomarkers:real-life gait assessment in cerebellar ataxia. *Neurology*, in press

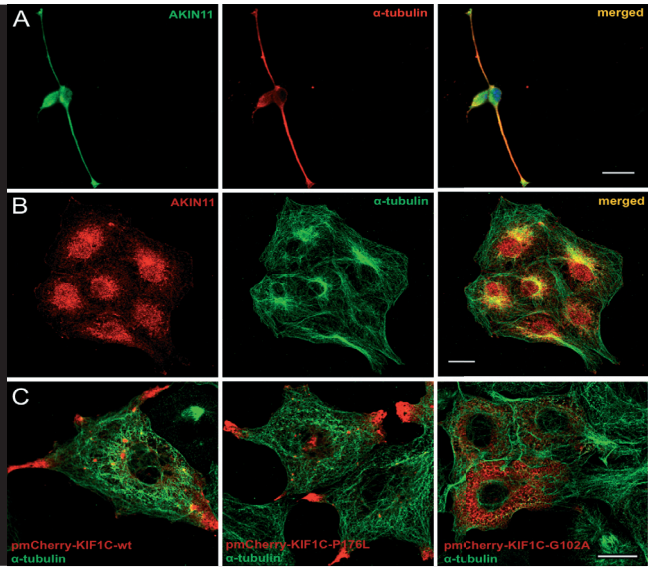
Traschutz A, Schirinzi T, Laugwitz L, Murray NHM, Bingman C, Reich S, (...), **Synofzik M** (2020) Clinico-genetic, imaging and molecular delineation of COQ8A-ataxia: a multicenter study of 59 patients. *Annals of Neurology*, in press

Vogel AP, Magee M, Torres-Vega R, Medrano-Montero J, Cyngler MP, Kruse M (...), **Synofzik M** (2020) Features of speech and swallowing dysfunction in pre-ataxic Spinocerebellar Ataxia Type 2. *Neurology*, in press

Wilke C, Teixeira dos Santos M, Schulte C, Deuschle C, (....), **Synofzik M**, Berg D (2020) Intraindividual neurofilament dynamics in serum mark the conversion to sporadic Parkinson's disease. *Movement Disorders*, in press

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 Federal Ministry for Education and Research (BMBF), 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 das Bundesministerium für Bildung und Forschung (BMBF), 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 mutation types, novel disease genes and ultimately novel therapeutic targets we combine whole exome / genome sequencing with other omics technologies including transcriptomics, metabolomics and proteomics. This work has led to the identification of > 20 novel genes for Hereditary Spastic Paraplegias, Spastic Ataxias and Hereditary Ataxias. Among the recent highlights of the work were the identification of UBAP1 mutations as a frequent cause of autosomal dominant HSPs, the recognition of IP3 receptor signaling as a mutational hotspot for motoneuron diseases and ataxias and the identification of deep-intronic mutations in POLR3A which are a frequent cause of spastic ataxia. This genomic work is funded by the European Union through funding for the Horizon2020 programme Solve-RD, the BMBF and the NIH in an RO1 grant awarded to Rebecca Schüle and her collaborator Stephan Zuchner from the University of Miami, Florida.

To promote trial readiness in HSP we have initiated and coordinate the TreatHSP translational network for HSPs and related disorders. TreatHSP is funded by the Bundesministerium für Bildung und Forschung (BMBF). TreatHSP.net concentrates its translation-oriented research approach on pathophysiological key pathways of HSP (mitochondrial – ER/microtubule-related – endo-lyso-autophagosomal related) that unify multiple and frequent forms of HSP. To make substantial progress towards implementation of novel therapies TreatHSP.net (i) is generating a

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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shared infrastructure that provides federated access to clinical data, biological samples and OMICS data for TreatHSP.net and beyond, (ii) is systematically developing and validating outcome parameters for clinical trials including sensor-based, patient- and caregiver-reported as well as molecular outcomes, (iii) is using unbiased high-throughput approaches in murine as well as stem cell-derived human models of HSP to identify shared pathways and novel therapeutic targets, and (iv) prioritizes drug-repurposing strategies to evaluate novel therapeutic approaches in preclinical trials that promise rapid translatability to human trials.

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.

SELECTED PUBLICATIONS

Wagner M*, Osborn DPS*, Gehweiler I, Nagel M, Ulmer U, Bakhtiari S, Amouri R, Boostani R, Hentati F, Hockley MM, Holbling B, Schwarzmayr T, Karimiani EG, Kernstock C, Maroofian R, Muller-Felber W, Ozkan E, Padilla-Lopez S, Reich S, Reichbauer J, Darvish H, Shahmohammadibeni N, Tafakhori A, Vill K, Zuchner S, Kruer MC, Winkelmann J, Jamshidi Y*, **Schule R.*** Bi-allelic variants in RNF170 are associated with hereditary spastic paraplegia. *Nat Commun* 2019;10(1):4790. * equal contribution

Farazi Fard MA, Rebelo AP, Buglo E, Nemati H, Dastsooz H, Gehweiler I, Reich S, Reichbauer J, Quintans B, Ordonez-Ugalde A, Cortese A, Courel S, Abreu L, Powell E, Danzi MC, Martuscelli NB, Bis-Brewer DM, Tao F, Zarei F, Habibzadeh P, Yavarian M, Modarresi F, Silawi M, Tabatabaei Z, Yousefi M, Farpour HR, Kessler C, Mangold E, Kobeleva X, Tournev I, Chamova T, Mueller AJ, Haack TB, Tarnopolsky M, Gan-Or Z, Rouleau GA, Synofzik M, Sobrido MJ, Jordanova A, **Schule R***, Zuchner S*, Faghihi MA*. Truncating Mutations in UBAP1 Cause Hereditary Spastic Paraplegia. *Am J Hum Genet* 2019;104(6):1251. * equal contribution

Minnerop M, Kurzwelly D, Rattay TW, Timmann D, Hengel H, Synofzik M, Stendel C, Horvath R, **Schule R**, Ramirez A. Reply: POLR3A variants in hereditary spastic paraplegia and ataxia. *Brain* 2018; 141(1): e2.

Schule R. Reply: Complicated hereditary spastic paraplegia due to ATP13A2 mutations: what's in a name? *Brain* 2017; 140(12): e74.

Synofzik M, **Schule R**. Overcoming the divide between ataxias and spastic paraplegias: Shared phenotypes, genes, and pathways. *Mov Disord* 2017; 32(3): 332-45.

Schols L, Rattay TW, Martus P, Meisner C, Baets J, Fischer I, Jagle C, Fraidakis MJ, Martinuzzi A, Saute JA, Scarlato M, Antenora A, Stendel C, Hoflinger P, Lourenco CM, Abreu L, Smets K, Paucar M, Deconinck T, Bis DM, Wiethoff S, Bauer P, Arnoldi A, Marques W, Jardim LB, Hauser S, Criscuolo C, Filla A, Zuchner S, Bassi MT, Klopstock T, De Jonghe P, Bjorkhem I, **Schule R**. Hereditary spastic paraplegia type 5: natural history, biomarkers and a randomized controlled trial. *Brain* 2017; 140(12): 3112-27.

Estrada-Cuzcano A, Martin S, Chamova T, Synofzik M, Timmann D, Holemans T, Andreeva A, Reichbauer J, De Rycke R, Chang DI, van Veen S, Samuel J, Schols L, Poppel T, Mollerup Sorensen D, Asselbergh B, Klein C, Zuchner S, Jordanova A, Vangheluwe P, Tournev I, **Schule R**. Loss-of-function mutations in the ATP13A2/PARK9 gene cause complicated hereditary spastic paraplegia (SPG78). *Brain* 2017; 140(2): 287-305.

Minnerop M, Kurzwelly D, Wagner H, Soehn AS, Reichbauer J, Tao F, Rattay TW, Peitz M, Rehbach K, Giorgetti A, Pyle A, Thiele H, Altmuller J, Timmann D, Karaca I, Lennarz M, Baets J, Hengel H, Synofzik M, Atasu B, Feely S, Kennerson M, Stendel C, Lindig T, Gonzalez MA, Stirnberg R, Sturm M, Roeske S, Jung J, Bauer P, Lohmann E, Herms S, Heilmann-Heimbach S, Nicholson G, Mahanjah M, Sharkia R, Carloni P, Brustle O, Klopstock T, Mathews KD, Shy ME, de Jonghe P, Chinnery PF, Horvath R, Kohlhase J, Schmitt I, Wolf M, Greschus S, Amunts K, Maier W, Schols L, Nurnberg P, Zuchner S, Klockgether T, Ramirez A, **Schule R**. Hypomorphic mutations in POLR3A are a frequent cause of sporadic and recessive spastic ataxia. *Brain* 2017; 140(6): 1561-78.

Deep Brain Stimulation

Head: Prof. Dr. Daniel Weiß
Team: 11 members
Key words: deep brain stimulation / gait / freezing

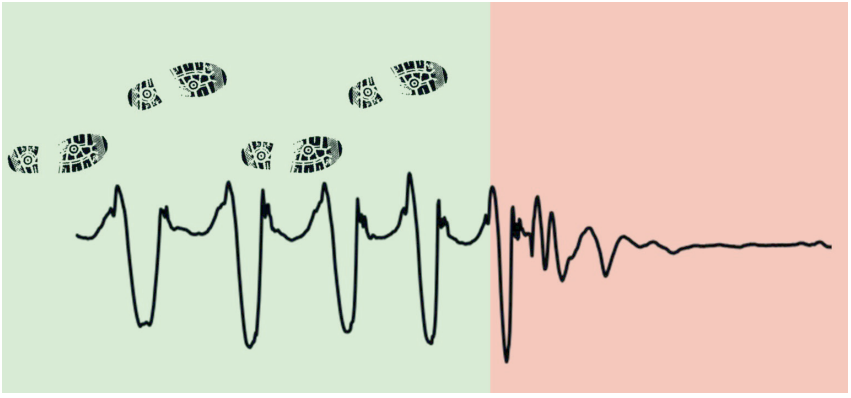
The research group for deep brain stimulation (DBS) strives for refining and expanding neurostimulation therapy for movement disorders therapy by interfering with functional large-scale functional circuits. We give particular emphasis to modulate otherwise resistant axial symptoms of Parkinson's disease (PD) – namely gait, freezing of gait, falls, and dysphagia. Moreover, we combine neurophysiological and kinematic methods in order 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.

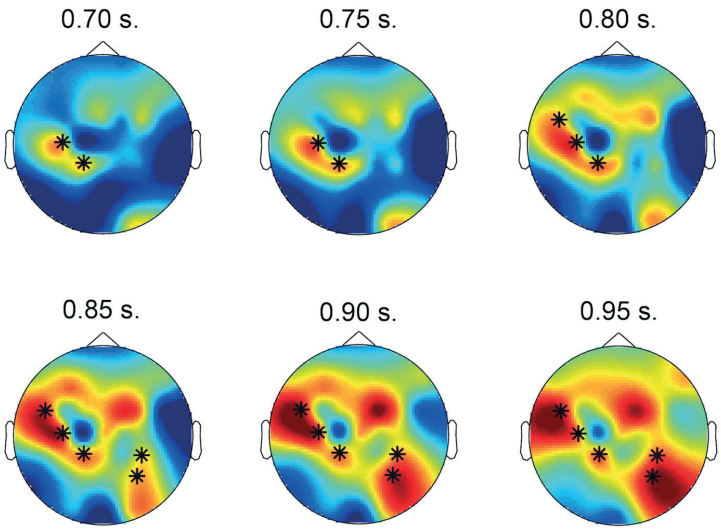
In this framework, we take advantage to co-stimulate the substantia nigra pars reticulata in addition to the subthalamic nucleus as distal electrode tip of a subthalamic lead. First clinical observations were made between 2009 – 2011 [1], and further substantiated by a monocenter randomized controlled 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' coordinated and finished a randomized controlled multicentre trial with 12 DBS expert centres (ClinTrials.gov: NCT02588144). Moreover, a monocenter trial is close to its end 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 (Weiss et al., 2019).

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.



SELECTED PUBLICATIONS

Weiss D, Schöllmann A, Fox MD, Bohnen NI, Factor SA, Nieuwboer A, Hallett M, Lewis SJG (2019) Freezing of gait: understanding the complexity of an enigmatic phenomenon, *Brain* 143:14-30

Weiss D, Breit S, Wachter T, Plewnia C, Gharabaghi A, Kruger R (2011) Combined stimulation of the substantia nigra pars reticulata and the subthalamic nucleus is effective in hypokinetic gait disturbance in Parkinson's disease, *J Neurol* 258:1183-5 [1]

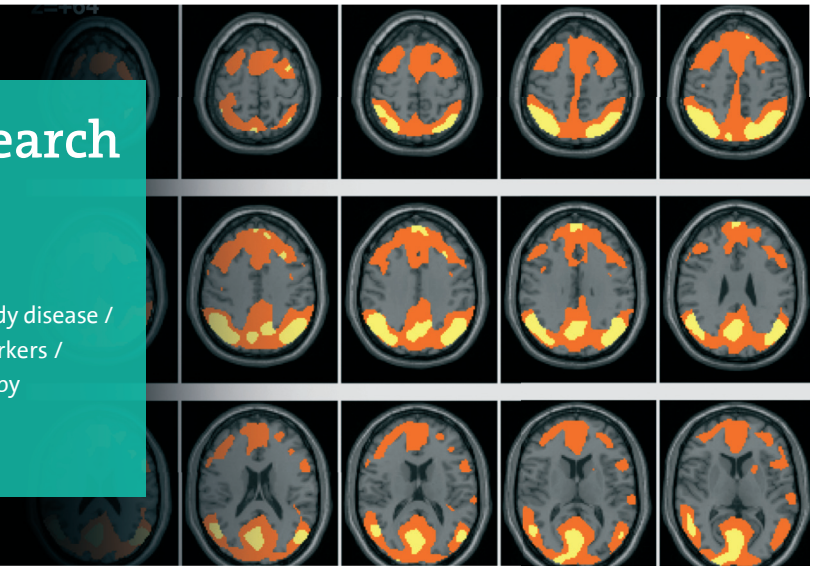
Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, Plewnia C, Bender B, Gharabaghi A, Wachter T, Kruger R (2013) Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain* 136:2098-108 [2]

Scholten M, Klemt J, Heilbronn M, Plewnia C, Bloem BR, Bunjes F, Kruger R, Gharabaghi A, **Weiss D** (2017) Effects of Subthalamic and Nigral Stimulation on Gait Kinematics in Parkinson's Disease. *Front Neurol* 8:543 [3]

Scholten M, Govindan RB, Braun C, Bloem BR, Plewnia C, Kruger R, Gharabaghi A, **Weiss D** (2016) Cortical correlates of susceptibility to upper limb freezing in Parkinson's disease. *Clin Neurophysiol* 127:2386-93 [4]

Scholten M, Klotz R, Plewnia C, Wachter T, Mielke C, Bloem BR, Braun C, Ziemann U, Govindan RB, Gharabaghi A, Kruger R, **Weiss D** (2016) Neuromuscular correlates of subthalamic stimulation and upper limb freezing in Parkinson's disease. *Clin Neurophysiol* 127:610-20 [5]

Clinical Parkinson Research



Head: Dr. Kathrin Brockmann
Team: 14 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 at patient stratification according to genetic architecture and, importantly, the underlying pathologic processes, possibly reflected by distinct profiles in patient biomaterials such as blood and CSF. This in turn is a most needed prerequisite to introduce patients to pathway-specific milestone-related therapies.

Die Parkinson-Erkrankung ist eine komplexe Erkrankung mit multifaktoriellen Ursachen und einer großen Variabilität von klinischer Ausprägung und Verlauf. Schwerpunkt unserer Forschung ist die Stratifizierung von Patientengruppen anhand klinischer, genetischer und molekularer Marker aus Blut und Nervenwasser. Dies ist die Basis für die Identifizierung möglicher modifizierender Faktoren, deren zugrundeliegender Mechanismen und Vorhersagewert. So ist zukünftig auch das Definieren von Progressionsmarkern und Endpunkten für Verlaufs-modifizierende Therapien möglich.

Parkinson's disease

To overcome the gap iin knowledge on PD progression and improve our understanding of disease biology, our group is conducting a number of large prospective longitudinal studies in national and international collaborations in patients with PD and individuals at risk. A particular focus is the identification and the better understanding of subgroups of PD, i.e. genetic forms or forms in which specific pathophysiological aspects play a major role (lysosomal dysfunction, mitochondrial impairment, inflammation). In this context, we focus on patient stratification according to genetic architecture and the underlying pathologic processes, reflected by profiles in patient biomaterials such as CSF to introduce patients to translational pathway-specific therapies. Such a scenario with recent research findings from our group is exemplified for GBA-associated PD (PD_{GBA}).

Clinical Profile

Based on our previous cross-sectional finding that PDGBA patients present with an earlier age at onset and prominent non-motor symptoms (dementia, depression, anxiety, sleep disturbances, autonomic dysfunction) when compared to $PD_{GBA\_wildtype}$ [1], we evaluated disease progression longitudinally. We could show that PD_{GBA} compared to $PD_{GBA\_wildtype}$, although younger in age, demonstrate a more rapid disease progression regarding motor impairment and cognitive decline. Thereby, GBA mutations represent an important predictor for reaching prominent disease milestones relatively early in the disease course [2]. All of these characteristics seem dependent on GBA mutation severity and were pronounced the most in PD_{GBA} with severe mutations (PD_{GBA_severe}) [3].

Given the findings from the manifest disease phase, we focused on patient's perception of the prodromal phase. PDGBA demonstrate a shorter prodromal interval with almost parallel beginning of non-motor and early motor signs before the diagnosis of PD as opposed to PDGBA_wildtype who presented with a long prodromal phase starting with non-motor symptoms followed by early motor signs only shortly before the diagnosis of PD. Again, patients carrying severe GBA mutations show the most prominent prodromal phase. These findings implicate that clinical and possibly also histopathological characteristics known from the manifest disease might be also translated into the prodromal phase [4].

Biochemical Profile

The underlying pathological process follows a bidirectional pathogenic loop. GBA mutations resulting in lower lysosomal GCase activity cause a build-up of lysosomal sphingolipids which also impairs the lysosomal degradation of alpha-synuclein and promote its aggregation. Additionally, increasing amounts of alpha-synuclein itself lead to a decrease of lysosomal GCase enzyme activity. Using magnetic resonance spectroscopic imaging, we showed that PD_{GBA} patients display a disturbed phospholipid metabolism in the putamen and midbrain, accompanied by neuronal loss in these brain regions [5].

With pathway-related clinical trials under way, we specifically face the need for biochemical markers that allow patient stratification and serve as biochemical read-out for target engagement. We conducted a comprehensive biomarker study and could show: (1) GCase activity was significantly lower in PD_{GBA} compared to $PD_{GBA\_wildtype}$. (2) CSF levels of upstream substrates as well as CSF levels of downstream products of GCase were higher in PD_{GBA} compared to $PD_{GBA\_wildtype}$. (3) CSF levels of total alpha-synuclein were lower in PD_{GBA} compared to $PD_{GBA\_wildtype}$ [3]. Of note, all clinical and biochemical findings were most prominent in PD_{GBA} patients with severe mutations suggesting a relevant biological effect depending on mutation severity.

As opposed to $PD_{GBA\_wildtype}$, the prominent cognitive decline in PD_{GBA} seems not primarily associated with concomitant Abeta and Tau pathology as represented by CSF $Abeta_{1\_42}$ and Tau profiles [6] but seems rather caused by neocortical alpha-synuclein/Lewy body pathology represented by decreased CSF levels of alpha-synuclein [7]. Of note, these findings could be confirmed also in patients with dementia with Lewy bodies which represent a clinico-histhopathological continuum to PD. Again, decreased CSF levels of alpha-synuclein were most pronounced in DLB_{GBA} patients with severe mutations [8].

Pathway-specific treatment options

Based on these results, a coherent picture of the pathway involved in GBA-associated PD along with personalized modifying treatment options is beginning to emerge:

i. GCase-enhancing strategies via chaperones and small molecules.
ii. Substrate reduction therapies. Our centre is the leading clinical site for Germany and PD_{GBA} patients from our cohort are part of the first pathway-specific clinical trial in PD (third-party funded by Sanofi: MovesPD, ACT 14820).
iii. Monoclonal antibody-based therapies targeting alpha-synuclein. With primarily alpha-synuclein-driven widespread Lewy body pathology in the brain and corresponding CSF profiles, PD_{GBA} represent a role model for alpha-synuclein-lowering compounds.
iv. Adeno-associated Virus (AAV)-based gene therapies that provide neurons with a fully-working copy of the GBA gene.

SELECTED PUBLICATIONS

Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, Berg D (2011) GBA-associated PD presents with nonmotor characteristics. *Neurology* 77:276-80 [1]

Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, Gasser T, Berg D (2015) GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. *Mov Disord* 30:407-11 [2]

Lerche S, Wurster I, Roeben B, Zimmermann M, Riebenbauer B, Deuschle C, Hauser AK, Schulte C, Berg D, Maetzler W, Waniek K, Lachmann I, Liepelt-Scarfone I, Gasser T, **Brockmann K** (2020) Parkinson's Disease: Glucocerebrosidase 1 Mutation Severity Is Associated with CSF Alpha-Synuclein Profiles. *Mov Disord* 35:495-99 [3]

Zimmermann M, Gaenslen A, Prahl K, Srulijes K, Hauser AK, Schulte C, Csoti I, Berg D, **Brockmann K** (2019) Patient's perception: shorter and more severe prodromal phase in GBA-associated PD. *Eur J Neurol* 26:694-98 [4]

Brockmann K, Hilker R, Pilatus U, Baudrexel S, Srulijes K, Magerkurth J, Hauser AK, Schulte C, Csoti I, Merten CD, Gasser T, Berg D, Hattingen E (2012) GBA-associated PD. Neurodegeneration, altered membrane metabolism, and lack of energy failure. *Neurology* 79:213-20 [5]

Lerche S, Wurster I, Roben B, Machetanz G, Zimmermann M, Bernhard F, Stransky E, Deuschle C, Schulte C, Hansson O, Zetterberg H, Gasser T, Berg D, Maetzler W, **Brockmann K** (2019) Parkinson's disease: evolution of cognitive impairment and CSF Abeta1-42 profiles in a prospective longitudinal study. *J Neurol Neurosurg Psychiatry* 90:165-70 [6]

Lerche S, Schulte C, Srulijes K, Pilotto A, Rattay TW, Hauser AK, Stransky E, Deuschle C, Csoti I, Lachmann I, Zetterberg H, Liepelt-Scarfone I, Gasser T, Maetzler W, Berg D, **Brockmann K** (2017) Cognitive impairment in Glucocerebrosidase (GBA)-associated PD: Not primarily associated with cerebrospinal fluid Abeta and Tau profiles. *Mov Disord* 32:1780-83 [7]

Lerche S, Machetanz G, Wurster I, Roeben B, Zimmermann M, Pilotto A, Preische O, Stransky E, Deuschle C, Hauser AK, Schulte C, Lachmann I, Waniek K, Gasser T, Berg D, Maetzler W, **Brockmann K** (2019) Dementia with lewy bodies: GBA1 mutations are associated with cerebrospinal fluid alpha-synuclein profile. *Mov Disord* 34:1069-73 [8]

Mitochondrial Biology of Parkinson's Disease

Head: Dr. Julia Fitzgerald
Team: 5 members
Key words: Parkinson's disease / atypical parkinsonism / mitochondria / PINK1 / MIRO1 / TRAP1 metabolism / neurochemistry / synaptic membranes

We study the molecular mechanisms of neurodegeneration and the roles of proteins associated with Parkinson's disease. Our focus is on mitochondrial proteins and mitochondrial metabolism and how this links to the function of dopaminergic neurons. We are also working to identify mitochondrial biomarkers for Parkinson's disease. We are doing basic research using biochemical, molecular biology and imaging methods. We have expertise in inducible miRNA systems and gene editing. We are working in cell models and patient-derived cell models such as fibroblasts and induced pluripotent stem cells (IPSCs). From iPSCs we derive neuronal precursor cells that can be differentiated into mature mid-brain specific neurons. We also work with tissue, blood cells and other patient-derived biomaterials including exosomes.

Wir untersuchen die molekularen Mechanismen der Neurodegeneration und die Rolle der mit der Parkinson-Krankheit assoziierten Proteine. Unser Schwerpunkt liegt auf mitochondrialen Proteinen und dem mitochondrialen Stoffwechsel und wie dieser mit der Funktion dopaminerger Neuronen zusammenhängt. Wir arbeiten auch an der Identifizierung mitochondrialer Biomarker für die Parkinson-Krankheit. Wir betreiben Grundlagenforschung mit biochemischen, molekularbiologischen und bildgebenden Methoden. Wir haben Erfahrung mit induzierbaren miRNA-Systemen und mit der Bearbeitung von Genen. Wir arbeiten an Zellmodellen und von Patienten abgeleiteten Zellmodellen wie Fibroblasten und induzierten pluripotenten Stammzellen (IPSCs). Aus iPSCs leiten wir neuronale Vorläuferzellen ab, die in reife, mittelhirnspezifische Neuronen differenziert werden können. Wir arbeiten auch mit Gewebe, Blutzellen und anderen von Patienten gewonnenen Biomaterialien einschließlich Exosomen.

Involvement of Mitochondrial Proteins in Parkinson's Disease: Miro1/TRAP1

We are researching mitochondrial proteins that function in known Parkinson's disease pathways. Miro1 is a protein attached to the outer mitochondrial membrane that binds calcium, is important for the movement of mitochondria and may have additional roles for example at mitochondrial ER-contact sites. Miro1 gene variants have been described in Parkinson's disease patients, but these mutations are rare and complete loss of function is lethal. We are interested in the roles of Miro1 in human dopaminergic neurons and how Miro1 interacts with other proteins associated with Parkinson's disease. TRAP1 is a protein residing in the matrix of mitochondria which is important for respiration and metabolic control. TRAP1 has previously been described as an interactor of the Parkinson protein PINK1 and in cancer. We described rare TRAP1 gene variants in Parkinson's disease and are interested in the role of TRAP1 in mitochondrial pathways in Parkinson's disease. Particularly metabolic control of neurons and protective metabolic adaption by mitochondria.

Mitochondrial Biomarkers in Parkinson's Disease

We are investigating markers of mitochondrial health and function in the blood cells of healthy people versus Parkinson's disease patients to try to identify readouts that could help us stratify groups of patients that may benefit from targeted therapies. We have collected blood cells, blood and blood spots from a large Parkinson's disease cohort including those that have mutations in mitochondria-associated genes such as Parkin, PINK1 and DJ-1. We create a picture of the mitochondrial DNA health by assessing copy number, the transcription rate and look for common deletions. We do this in blood cells so that we can overlay the data with functional readouts such as mitochondrial membrane potential. In addition, we are comparing the mitochondrial DNA profiles from blood cells, to DNA from whole blood and extracellular vesicles derived from serum and CSF (known as exosomes). Here the aim is to explore potential biomarkers for Parkinson's disease in living patients and to identify those that are retained in the blood as well as in the brain.

Mitochondrial Parkinson's Disease: Human Dopaminergic Neuronal Models

We work on the mitochondrial Parkinson's disease protein PINK1 as an archetypal model for investigating the mitochondrial biology of the disease in the cell types affected. We are currently working in 2D human midbrain specific dopaminergic neurons derived from neuronal progenitors and induced pluripotent stem cells (iPSCs). We work in isogenic models so that we can compare the effect of a patient gene mutation or gene knockout with the same genetic background. We are investigating the contribution of mitochondrial defects to developing neurons and looking for specific biochemical and metabolic changes that are relevant to the demise of dopaminergic neurons in Parkinson's disease. We are also interested in how PINK1 interacts with and influences other Parkinson's disease pathways outside of the mitochondria.

Atypical Parkinsonism

We are working on understanding the biology of a rare, currently untreatable form of atypical parkinsonism, called Corticobasal syndrome. Although it is a distinct disease entity, the underlying pathologies overlap with Corticobasal degeneration and tauopathy. The genetics of Corticobasal syndrome is substantially heterogeneous but a recent study pointed towards genes encoding endosomal trafficking and the endosomal-lysosomal system. We are studying dysfunction of the endosomal system in Corticobasal syndrome and interested in the role of the endosomal cation exchanger NHE6. We are studying the effect of acidification on the endosomal lumen and how this impacts autophagy and the build-up of toxic forms of tau.

SELECTED PUBLICATIONS

Bus C, Geisler S, Feldkaemper M, Flores-Romero H, Schaedler A, Zittlau K, Zarani M, Uysal B, Casadei N, Fallier-Becker P, Schwarz L, Brouwers JF, Koch H, Ugun-Klusek A, Maruszczak K, Vogt-Weisenhor DM, Wurst W, Schmidt B Martens G, Brügger B, Rapaport D, Krüger R, Garcia A, Macek B, Gasser T, Kahle P, **Fitzgerald JC** (2019) PINK1 Regulates Dopamine and Lipids at Mitochondria to Maintain Synapses and Neuronal Function *bioRxiv* MS: 814343

Hertlein V, Flores-Romero H, Das KK, Fischer S, Heunemann M, Calleja-Felipe M, Knafo S, Hipp K, Harter K, **Fitzgerald JC**, Garcia-Saez AJ (2020) MERLIN: a novel BRET-based proximity biosensor for studying mitochondria-ER contact sites. *Life Sci Alliance* 3:e201900600

Grossmann D, Berenguer-Escuder C, Bellet ME, Scheibner D, Bohler J, Massart F, Rapaport D, Skupin A, Fouquier d'Herouel A, Sharma M, Ghelfi J, Rakovic A, Lichtner P, Antony P, Glaab E, May P, Dimmer KS, **Fitzgerald JC**, Grunewald A, Kruger R (2019) Mutations in RHOT1 Disrupt Endoplasmic Reticulum-Mitochondria Contact Sites Interfering with Calcium Homeostasis and Mitochondrial Dynamics in Parkinson's Disease. *Antioxid Redox Signal* 31:1213-34

Ugun-Klusek A, Theodosi TS, **Fitzgerald JC**, Burte F, Ufer C, Boocock DJ, Yu-Wai-Man P, Bedford L, Billett EE (2019) Monoamine oxidase-A promotes protective autophagy in human SH-SY5Y neuroblastoma cells through Bcl-2 phosphorylation. *Redox Biol* 20:167-81

Rotermund C, Machetanz G, **Fitzgerald JC** (2018) The Therapeutic Potential of Metformin in Neurodegenerative Diseases. *Front Endocrinol* (Lausanne) 9:400

Jores T, Lawatscheck J, Beke V, Franz-Wachtel M, Yunoki K, **Fitzgerald JC**, Macek B, Endo T, Kalbacher H, Buchner J, Rapaport D (2018) Cytosolic Hsp70 and Hsp40 chaperones enable the biogenesis of mitochondrial beta-barrel proteins. *J Cell Biol* 217:3091-108

Fitzgerald JC, Zimprich A, Reddy Bobbili D, Sharma M, May P, Kruger R (2018) Reply: No evidence for rare TRAP1 mutations influencing the risk of idiopathic Parkinson's disease. *Brain* 141:e17

Sofi S, **Fitzgerald JC**, Jahn D, Dumoulin B, Stehling S, Kuhn H, Ufer C (2018) Functional characterization of naturally occurring genetic variations of the human guanine-rich RNA sequence binding factor 1 (GRSF1). *Biochim Biophys Acta Gen Subj* 1862:866-76

Marrone L, Bus C, Schondorf D, **Fitzgerald JC**, Kubler M, Schmid B, Reinhardt P, Reinhardt L, Deleidi M, Levin T, Meixner A, Klink B, Glatza M, Gloeckner CJ, Gasser T, Sterneckert J (2018) Generation of iPSCs carrying a common LRRK2 risk allele for in vitro modeling of idiopathic Parkinson's disease. *PLoS One* 13:e0192497

Fitzgerald JC, Zimprich A, Carvajal Berrio DA, Schindler KM, Maurer B, Schulte C, Bus C, Hauser AK, Kubler M, Lewin R, Bobbili DR, Schwarz LM, Vartholomaiou E, Brockmann K, Wust R, Madlung J, Nordheim A, Riess O, Martins LM, Glaab E, May P, Schenke-Layland K, Picard D, Sharma M, Gasser T, Kruger R (2017) Metformin reverses TRAP1 mutation-associated alterations in mitochondrial function in Parkinson's disease. *Brain* 140:2444-59

Casadei N, Sood P, Ulrich T, Fallier-Becker P, Kieper N, Helling S, May C, Glaab E, Chen J, Nuber S, Wolburg H, Marcus K, Rapaport D, Ott T, Riess O, Kruger R, **Fitzgerald JC** (2016) Mitochondrial defects and neurodegeneration in mice overexpressing wild-type or G399S mutant HtrA2. *Hum Mol Genet* 25:459-71

Fitzgerald JC, Burbulla, L, Stegen, K, Westermeier, J, Kato H, Mokranjac D, Sauerwald J, Martins LM, Woitalla D, Proikas-Cezanne T, Rapaport D, Riess O, Rasse T, Krüger R. (2014) Mitochondrial proteolytic stress induced by loss of Mortalin function is rescued by Parkin and PINK1. *Cell Death and Disease* 19:257-66

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.

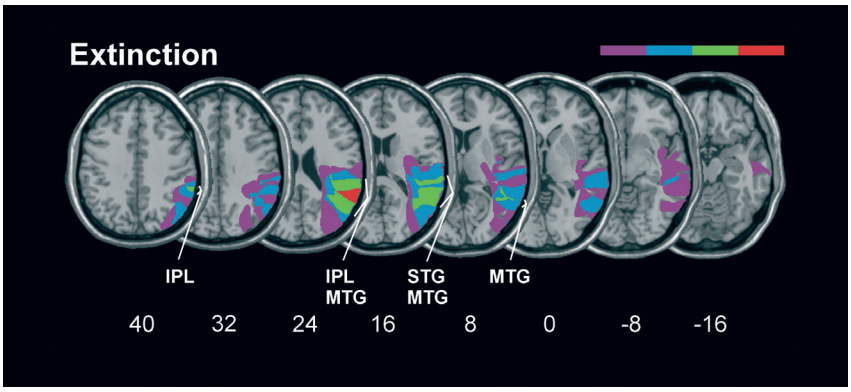
In summer 2008 the Section for Computational Sensomotorics, headed by the newly appointed Prof. Martin Giese and funded conjointly by the Hertie Foundation and the German Research Council within the framework of the Excellence Cluster "Centre for Integrative Neuroscience" (CIN), was installed at the 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 Mensch'. In 2017 the Active Perception Lab of Prof. Ziad Hafed, who accepted one of the CIN's tenure track professorships, reinforced the research teams of the department.

The department currently comprises eight 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 , the Active Perception Lab of Ziad Hafed, 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 formed also part of the department. Both young investigator groups have been dissolved in 2018 as the group leaders took a position at other institutions, whereas the Neuropsychology of Action Control Lab is still maintained although Marc Himmelbach was appointed Dean of Studies at the Graduate Training Center of Neuroscience in spring 2019.

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 produce 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 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 have also been part of the excellence cluster 'Werner Reichardt Centre for Integrative Neuroscience (CIN)', involving more than 80 principle investigators associated with three faculties of the University of Tübingen and several non-university research institutions



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.

in Tübingen and its vicinity, likewise coordinated by Hans-Peter Thier. At the end of the year the CIN was converted into a permanent interfaculty Institute of systems neuroscience with four members of the Department of Cognitive Neurology (Giese, Hafed, Schwarz, Thier) having a second affiliation with the CIN. The DFG-funded transregional 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.

Martin Giese, Axel Lindner, Cornelius Schwarz, and Hans-Peter Thier were members of the Tübingen Bernstein Centre for Computational Neuroscience that was supported with funding from the BMBF from 2010 to 2015. Martin Giese remains an active member of the Tübingen computational neuroscience framework that emerged from the Bernstein Centre. Ziad Hafed is a principal investigator within the DFG-funded Collaborative Research Center (SFB) 1233 ("Robust Vision"). Daniel Häufle is member of the Research Alliance 'System Mensch', funded by the State of Baden-Wuerttemberg and representing research groups from different faculties of the Universities of Tübingen and Stuttgart respectively. Martin Giese is a recipient of a 2020 ERC Synergy Grant awarded to a consortium working on "How body relevance drives brain organization" involving Rufin Vogels (Leuven) and Beatrice De Gelder (Maastricht) as further group members.

Sensorimotor Laboratory

Groups P. Thier, J. Pomper

Head: Prof. Dr. Peter Thier
Team: 22 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 focuses on the underpinnings of social interactions and the mechanisms underlying motor learning and their disturbances due to disease.

Das Labor bearbeitet die neuronalen Grundlagen sozialer Interaktionen und die motorischen Lernens sowie deren krankheitsbedingte Störungen.

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.

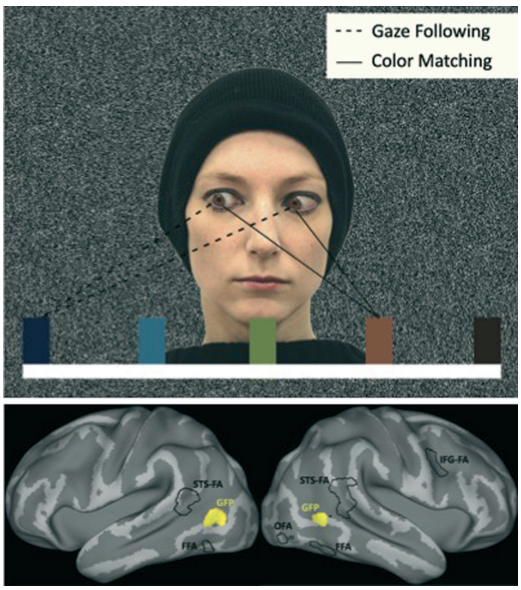


Illustration of the paradigm needed to activate brain structures underlying gaze following as compared to spatial shifts of attention guided by non-gaze cues (here: iris color). The eyes of the person are directed to the dark-blue target (gaze cue), but the person's iris color corresponds to the light-brown 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.

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, 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.

SELECTED PUBLICATIONS

Flierman NA, Ignashchenkova A, Negrello M, T**hier P**, De Zeeuw CI, Badura A. Glissades are altered by lesions to the oculomotor vermis but not by saccadic adaptation. *Frontiers in Behavioral Neuroscience* 2019; 13: 194. doi: 10.3389/fnbeh.2019.00194. eCollection 2019.

Markanday A*, Bellet J*, Bellet ME*, **Hafed ZM**, Thier P****. Using deep neural networks to detect complex spikes of cerebellar Purkinje cells. *BioRxiv* 2019; doi: 10.1101/600536. (* Contributed equally; ** Co-corresponding authors)

Pilacinski A, Lindner A. Distinct contributions of human posterior parietal and dorsal premotor cortex to reach trajectory planning. *Scientific Reports* 2019; 9(1): 1962. doi: 10.1038/s41598-019-39188-0.

Spadacenta S, Dicke PW, Thier P. Reflexive gaze following in common marmoset monkeys. *Scientific Reports* 2019; 9(1): 15292; doi: 10.1038/s41598-019-51783-9.

Spivak O, Thier P, Barash S. Individual variation of the dark-background-contingent upshift of gaze: effect of past habituation. *BioRxiv* 2019; doi: https://doi.org/10.1101/628610

Thier P, Markanday A. Role of the vermal cerebellum in visually guided eye movements and visual motion perception. *Annual Reviews in Visual Science* 2019; 5: 247-268. doi: 10.1146/annurev-vision-091718-015000. Epub 2019 Jul 12.

Reutskaja E, **Lindner A**, Nagel R, Andersen RA, Camerer CF. Choice overload reduces neural signatures of choice set value in dorsal striatum and anterior cingulate cortex. *Nature Human Behaviour* 2018; 2(12):925-935. doi: 10.1038/s41562-018-0440-2.

Neuropsychology

Head: Prof. Dr. Dr. Hans-Otto Karnath
Team: 18 members
Key words: cognitive neuroscience / neuropsychology

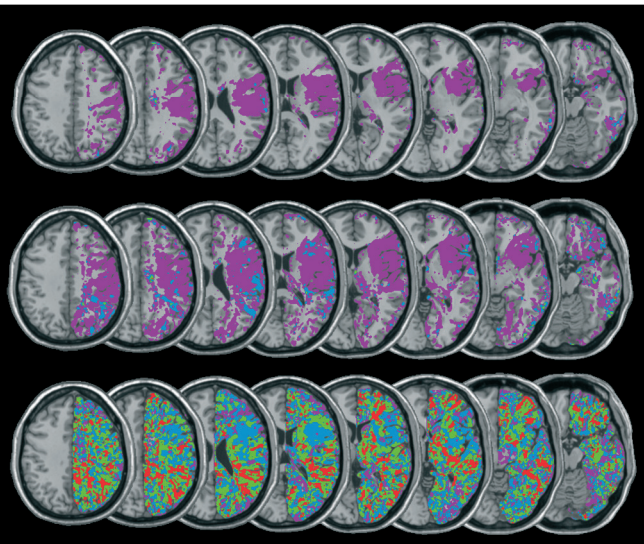


Figure 1: Nowadays, different anatomical atlases exist for the anatomical interpretation of the results from neuroimaging and lesion analysis studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function. A major problem with the use of different atlases in 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.)

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.

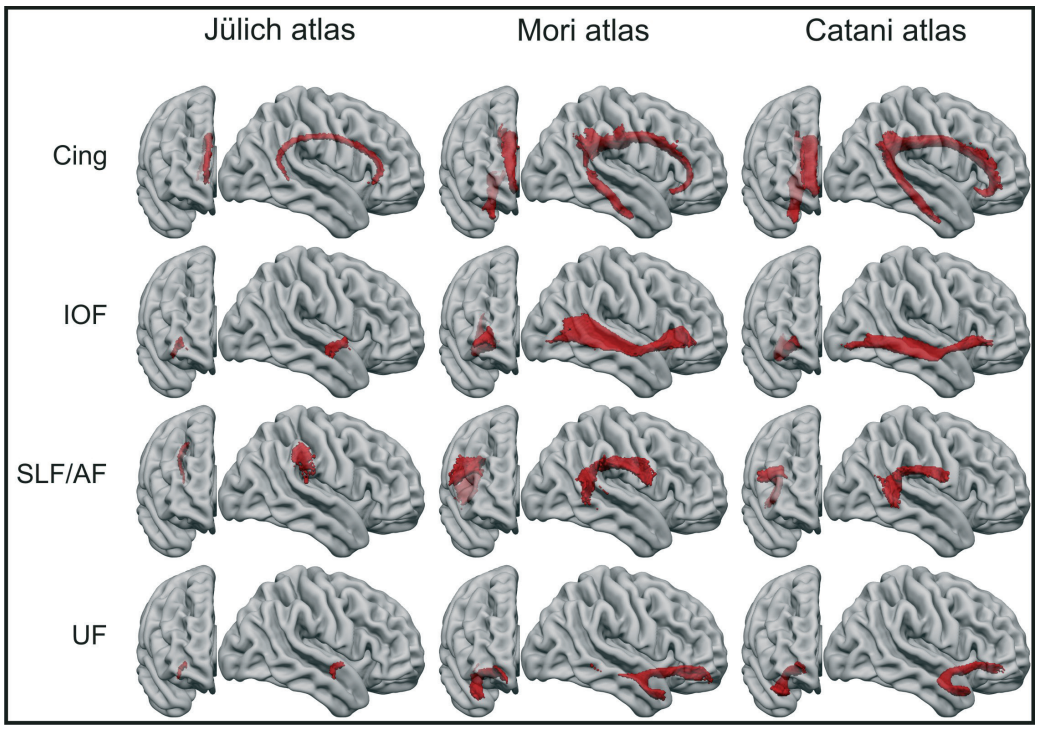


Figure 1

PUBLICATIONS 2019

Balslev D, Odoj B. Distorted gaze direction input to attentional priority map in spatial neglect. *Neuropsychologia* 2019; 131: 119-128.

Feierabend M, Karnath H-O, Lewald J. Auditory space perception in the blind: horizontal sound localization in acoustically simple and complex situations. *Perception* 2019; 48: 1039-1057.

Karnath H-O, Kriechel I, Tesch J, Mohler BJ, **Mölbert SC**. Caloric vestibular stimulation has no effect on perceived body size. *Scientific Reports* 2019; 9: 11411.

Karnath H-O, Mölbert SC, Klaner AK, Tesch J, Giel KE, Wong HY, Mohler BJ. Visual perception of one's own body under vestibular stimulation using biometric self-avatars in virtual reality. *PLoS One* 2019; 14: e0213944.

Karnath H-O, Sperber C, Rorden C. Reprint of: Mapping human brain lesions and their functional consequences. *Neuroimage* 2019; 190: 4-13.

Karnath H-O, Sperber C, Wiesen D, de Haan B. Lesion-behaviour mapping in cognitive neuroscience – A practical guide to univariate and multivariate approaches. In: S Pollmann (ed.) *Spatial Learning and Attention Guidance*. Neuromethods. New York, Humana Press, 2019; DOI: https://doi.org/10.1007/7657_2019_18

McDermott EJ, Himmelbach M. Effects of arm weight and target height on hand selection: a low-cost virtual reality paradigm. *PLoS One* 2019; 14: e0207326.

Mock J, Huber S, **Bloechle J**, Bahnmueller J, Moeller K, Klein E. Processing symbolic and non-symbolic proportions: domain-specific numerical and domain-general processes in intraparietal cortex. *Brain Research* 2019; 1714: 133-146.

Ninaus M, Greipl S, Kiili K, Lindstedt A, Huber S, Klein E, **Karnath H-O**, Moeller K. Increased emotional engagement in game-based learning – a machine learning approach on facial emotion detection data. *Computers & Education* 2019; 142: 103641.

Praß M, de Haan B. Multi-target attention and visual short-term memory capacity are closely linked in the intraparietal sulcus. *Human Brain Mapping* 2019; 40: 3589-3605.

Sperber C, Wiesen D, Goldenberg G, **Karnath H-O**. A network underlying human higher-order motor control: insights from machine learning-based lesion-behaviour mapping in apraxia of pantomime. *Cortex* 2019; 121: 308-321.

Sperber C, Wiesen D, Karnath H-O. An empirical evaluation of multivariate lesion behaviour mapping using support vector regression. *Human Brain Mapping* 2019; 40: 1381-1390.

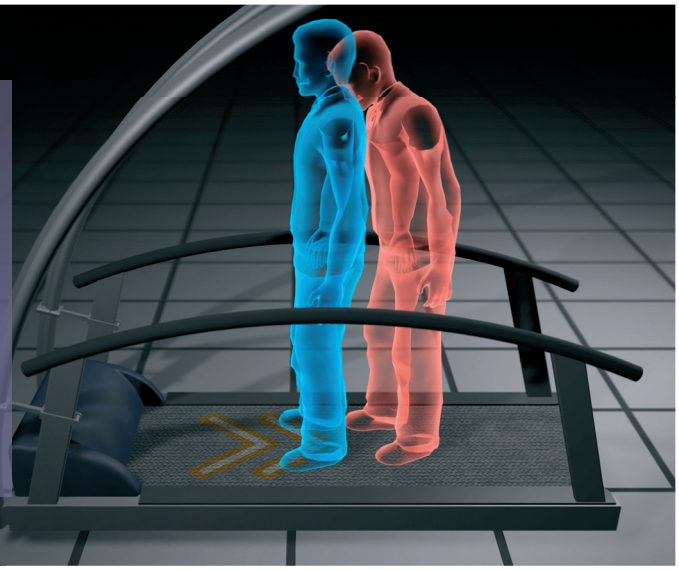
Umarova RM, **Sperber C**, Kaller CP, Schmidt CSM, Urbach H, Klöppel S, Weiller C, **Karnath H-O**. Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *Journal of Neurology* 2019; 266: 2495-2504.

von Bernstorff M, Rapp J, Bausenhart F, **Feierabend M**, Ipach I, Hofmann UK. Estimating braking performance in osteoarthritis of the knee or hip with a reaction timer. *Orthopaedic Surgery* 2019; 11: 248-254.

Wiesen D, Sperber C, Yourganov G, Rorden C, **Karnath H-O**. Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: spatial neglect and attention. *Neuroimage* 2019; 201: 116000.

Computational Sensomotorics

Head: Prof. Dr. Martin Giese
Team: 17 members
Key words: sensorimotor control / motor learning and rehabilitation / social perception / neural modeling / technical applications in neurology and psychiatry



The Section Computational Sensomotorics investigates theoretical principles in the perception and control of motor actions, and associated technical applications. Research in 2019 focused on three topic areas:

Die Sektion Theoretische Sensomotorik erforscht die theoretischen Prinzipien der Erkennung und Steuerung motorischer Handlungen und assoziierter technischer Anwendungen. Unsere Forschung war 2019 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. The accurate quantification of specific changes in movement patterns supports the understanding of underlying neural control mechanisms as well as their degeneration. This is particularly important to identify pre-clinical phases of neurodegenerative diseases, when movement changes are subtle or only present in complex motor behavior. This phase attracts increasing research interest as it could provide a promising window for early therapeutic intervention—both pharmaceutical and rehabilitative—before substantial irreversible neurodegeneration has occurred. A particularly important, but technically challenging problem is the modeling and quantification of complex body movements with relevance for everyday life. To solve this problem, we combine motion capture, biomechanics, and advanced machine learning approaches in order to model complex everyday movements of patients with wearable sensors. In collaboration with Profes. M. Synofzik and L. Schöls (Dept. Neurodegeneration), these new methods result in ecologically valid biomarkers that characterize the motor behavior of cerebellar ataxia patients in natural situations, enabling novel types of intervention studies. Together with Prof. Renner (Dept. Psychiatry) we are presently extending such methods for the analysis of the motor behavior of autistic children.

Despite greatly improved understanding of the genetic underpinnings of neurodegenerative diseases, usually no curative treatments are yet available. However, motor training often helps to improve everyday symptoms of these patients. In cooperation with Profes. Synofzik and Schöls and physiotherapists we develop motor neurorehabilitation strategies based on theories of motor learning, integrating modern technologies such as Virtual Reality (VR), exergames and robot devices. Collaborating with Prof. Timmann-Braun (University Clinic Essen), we investigate the relevance of different cerebellar structures for different forms of motor learning. In addition, together with Prof. Schwarz (Dept. Cognitive Neurology) and Prof. Ziemann (Dept. Neurovascular Diseases) we investigate the neural mechanisms of Transcranial Magnetic Stimulation (TMS) at the single-cell level in rodents as basis for protocols that can improve motor plasticity.

Neural and computational mechanisms of social perception

Facial movements belong to the most prominent social signals in primates including humans. In spite of this importance, the mechanisms of the processing of dynamic faces at the single-cell level remain largely unknown. Collaborating closely with the laboratory of P. Thier (Dept. Cognitive Neurology) we have developed a highly realistic monkey and human avatar head model that we are using to investigate the perception of dynamic facial expressions in humans and monkeys, and of corresponding mechanisms at the single-cell level. Behavioral experiments show that monkeys perceive this avatar model

as almost as realistic as movies from real monkeys. Previous avatar models in research resulted in perceptions in an 'uncanny valley', where the animals strongly preferred the real movies over the avatars. Present work aims at making this avatar model real-time capable so that it can be controlled by the actual behavior of the observer, enabling experiments on the interaction between monkeys and reactive avatars. In addition, we develop neural models that reproduce the properties of dynamic face-selective cortical neurons. Another important class of social signals are scenes that include multiple social interacting agents. In a project of the Human Frontiers Science Program (HFSP), together with D. Tsao (CALTECH) and A. Martinez (OSU), we developed a novel class of stimuli showing multiple socially interacting agents, which can be either simple geometrical figures (as in classical psychological experiments by Heider and Simmel) or fully articulating avatar models of animals that fight, follow each other, etc. These stimuli are used to find neural correlates at the single-cell level for the visual processing of social interaction and to develop physiologically-inspired neural network models for the recognition of social interactions. In collaboration with the Max Planck Institute for Biological Cybernetics we have exploited a psychophysical adaptation paradigm to show that scenes with multiple interacting human agents are jointly encoded, as opposed to separate encoding of the individual interacting agents.

Biomedical and biologically-motivated technical applications

Optical motion capture provides the most accurate way for the measurement of body movements, but is relatively expensive and requires complex calibrated camera setups. Novel movement sensors, like the Microsoft Kinect system, make it possible to develop much cheaper motion registration systems for clinical applications. A system of this type (cost below 5000 EUR) has been developed for full-body movement analysis in measurement volumes and deployed to multiple other clinical facilities in Europe as part of a longitudinal multi-center study on cerebellar ataxia. In the context of the EC H2020 project COGIMON we have also explored the usability of a compliant humanoid robot (COMAN+, IIT) for the training of neurological patients, implementing a catching–throwing game. As part of this project, we have a VR version of this task with feedback from patients in a physiotherapy facility outside the clinic. Since the real robot was not robust enough for studies with patients we integrated a physics simulation of the robot in the VR environment and showed that patients in principle can successfully interact with the robot, including its mechanical limitations.

Cerebellar ataxia patient training in Virtual Reality environment that allows to integrate simulation of humanoid robot for development of robot controllers. Bildrechte: Thomas Müller, FRG / Universitätsklinikum Tübingen

SELECTED PUBLICATIONS

Ludolph N, Ernst TM, Mueller OM, Goericke SL, **Giese MA**, Timmann D, et al. Cerebellar involvement in learning to balance a cart-pole system. *BioRxiv* 2019; 10.1101/586990.

Fleszar Z, Mellone S, **Giese MA**, Tacconi C, Becker C, Schöls L et al. Real-time use of audio-biofeedback can improve postural sway in patients with degenerative ataxia. *Ann Clin Transl Neurol* 2019; 6(2): 285-294.

Ilg W, Branscheidt M, Butala A, Celnik P, de Paola L, Horak FB et al. Consensus paper: Neurophysiological assessments of ataxias in daily practice. *Cerebellum* 2018; 17(5): 628-653.

Fedorov L, Chang D, **Giese MA,** Bülthoff H & de la Rosa S. Adaptation aftereffects reveal representations for encoding of contingent social actions. *PNAS* 2018; 115(29): 7515-7520.

Mohammadi P, Malekzadeh MS, **Kodl J, Mukovskiy A**, Wigand D, **Giese MA** et al. Real-time control of whole-body robot motion and trajectory generation for physiotherapeutic juggling in VR 2018; *IROS2018*, 270-277.

Oculomotor Laboratory

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

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 NVGPs.

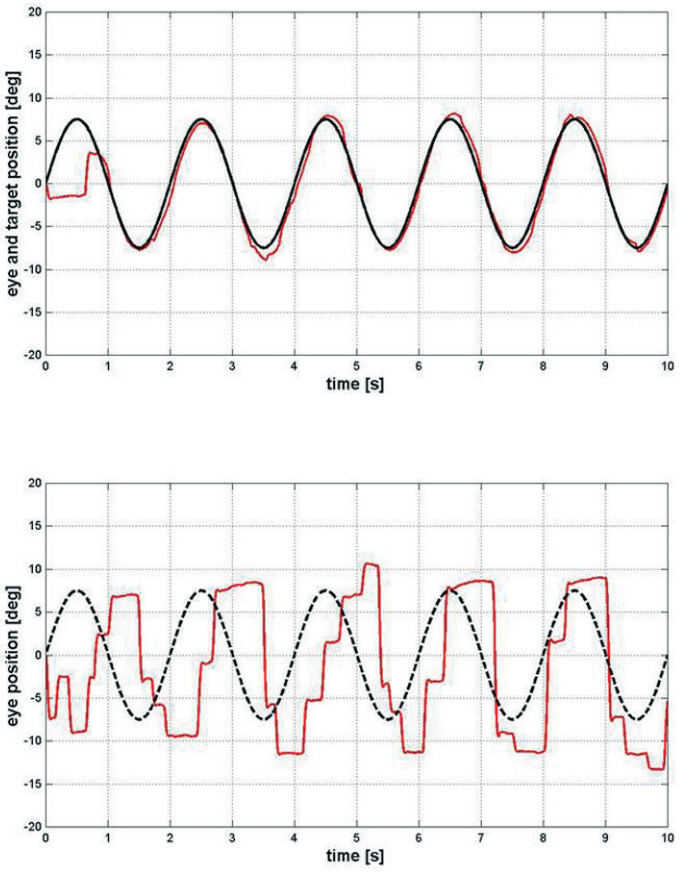
To address the cognitive control function, which might be reduced in VGPs as supposed by others, we examined the frequency of direction errors in the anti-saccade task. VGPs as well as non-players showed an error rate of approximately 40%, there was no significant difference between players and non-players. 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.

The superior colliculus in the midbrain is an essential structure to perform saccades. Amazingly, this structure receives no direct retinal input form the s-cones. Therefore, we examined the ability to perform pro- and anti-saccades directed towards isoluminant targets stimulating either exclusively the s-cones (violet) or the remaining cone types (red) in 28 subjects. Interestingly, the error rates in the anti-saccade task were lower for the stimulus at short wave length compared to long wave length or black and white stimuli.

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.

Number Sense

We performed psychophysical experiments addressing the ability to compare the numerosity of two simultaneously presented visual samples. The samples were presented for 200 ms only and cover the number space from five to ten. Based on the results of 67 subjects, we are able to show the predictions of the analog number system: numerical distance effect as well as the numerical size effect. In addition, our data related to the just noticeable difference (JND) proof that VGPs (32 subjects) have superior ability to judge numbers correctly compared to NVGPs (35 subjects). We are looking forward to training studies in the future to proof the causal relationship between video-game play and superior sensory and attentional processing.



SELECTED PUBLICATIONS

Ilg UJ. Neuroscience for the next generation: Was Schülerlabore für die Neurowissenschaft leisten. Neuroforum 2019; 25(2): 139-142.

Mack DJ, Wiesmann H, **Ilg UJ**. Video game players show higher performance but no difference in speed of attention shifts. *Acta Psychol* (Amst) 2016; 169: 11-19.

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 and its extensive interaction with sub-cortical circuits during highly defined and precisely monitored behavior. The similarity of neocortex in animals and humans suggests that the results will be highly appropriate to inform research on human disease (Alzheimer's, Parkinson's, schizophrenia, and depression).

Wir erforschen die Funktion des Großhirns (Neokortex) und angeschlossener sub-kortikaler Kreisläufe 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).

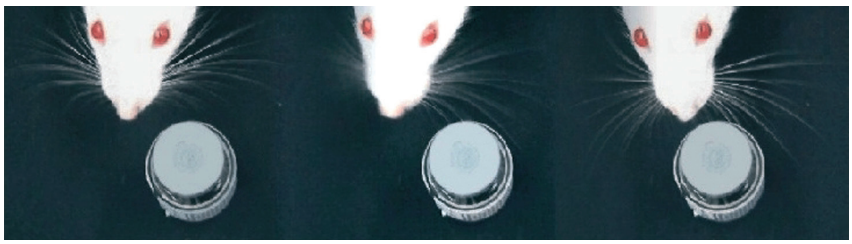
Problem, model system, and methods

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 gained access to evolutionary more ancient sub-cortical systems to handle 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

The mammalian brain uses several learning systems that cooperatively adapt behavior to the needs of the individual and to the constraints of the world. Explicit learning is a neocortex-based form of either unsupervised learning, driven by coincidences or correlations, or supervised learning based on reward-prediction errors. Rule learning or exploration behavior fall in this category. Reward-prediction errors are also used by implicit, unconscious, procedural learning systems, located in the basal ganglia: Habit learning is an example. Finally, procedural learning of another type is located in the cerebellum: Driven by sensory-prediction errors it functions to optimize movement parameters and to improve perception. We study the interaction of these learning systems in thalamocortical systems using models of Pavlovian conditioning as well as motor adaptation.



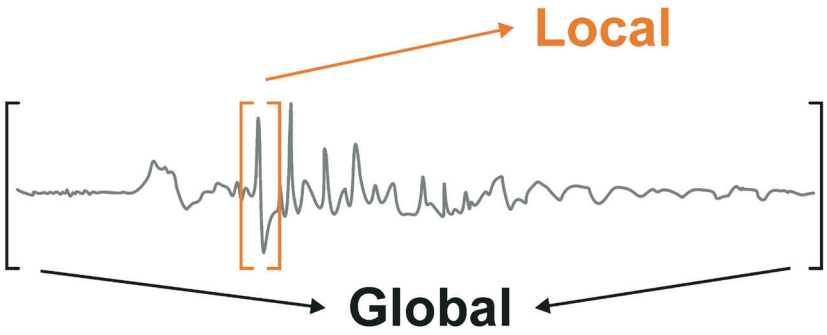
Active tactile exploration of the environment using vibrissae.

Active perception

We hypothesize that primary somatosensory cortex is involved in two forms of predictive coding. The first is called state estimation and combines tactile predictions calculated from internal sources, like contextual information intrinsic to the brain (e.g. movement plans and motor commands), and external sources, i.e. sensory signals. These are generated with the help of subcortical loops involving the cerebellum and affect perception in a bottom-up fashion. The second, called sensory gating, is of a more vaguely specified cognitive origin. It consists in cortical top-down control of inflow of sensory signals. Using multi-electrode electrophysiology and lesion-based analysis in rodents operantly conditioned to a movement task, we have found that top-down, cortex -dependent sensory gating in brainstem tactile nuclei exists. We have developed an experimental model that allows us to simultaneously demonstrate the two predictive systems, state estimation and sensory gating, in the sensorimotor cortex to further disentangle their neuronal bases.

Tactile coding

We test the notion that the tactile system uses a local code, i.e. short-lived features in the vibrotactile signal, rather than so-called global variables that can be obtained by signal averaging. We use insights gained from work in the rodent whisker system using biomechanical, neurophysiological and behavioral measurements, to investigate the biomechanical, neurophysiological and behavioral correlates of active touch in humans. In both, rodents and humans, psychophysical experiments yielded strong evidence for local codes.



Local coding is based on extraction of short-lasting instantaneous features from the vibrotactile signal. An example is the analysis of frictional stick-slip movements (gold). Global coding analyzes the whole or large stretches of the signal, e.g. using spectral decomposition or averaging (black).

SELECTED PUBLICATIONS

Bhattacharjee A, Kajal DS, Patrono A, Hegner YL, Zampini M, **Schwarz C,** Braun C. (2020) A tactile virtual reality for the study of active somatosensation. *Frontiers in Integrative Neuroscience* 2020; 14: 1-15.

Bhattacharjee A, Braun C, **Schwarz C**. Humans use a local code for tactile perception. *BioRxiv* 2019; DOI: 10.1101/2019.12.12.874206.

Hofmann JI, Schwarz C, Rudolph U, Antkowiak B. Effects of diazepam on low-frequency and high-frequency electrocortical γ-power mediated by α1- and α2-$GABA_A$ receptors. I*nternational Journal of Molecular Science* 2019; 20: 3486.

Chakrabarti S, Schwarz C. Cortical modulation of sensory flow during active touch in the rat whisker system. *Nature Communications* 2018; 9: 3907.

Gerdjikov TV, Bergner CG, **Schwarz C**. Global coding in rat barrel cortex in the absence of local cues. *Cerebral Cortex* 2018; 28: 2015-2027.

Li B, Virtanen JP, Oeltermann A, **Schwarz C, Giese MA**, Ziemann U, **Benali A**. Lifting the veil on the dynamics of neuronal activities evoked by transcranial magnetic stimulation. *eLife* 2018; pii: e30552.

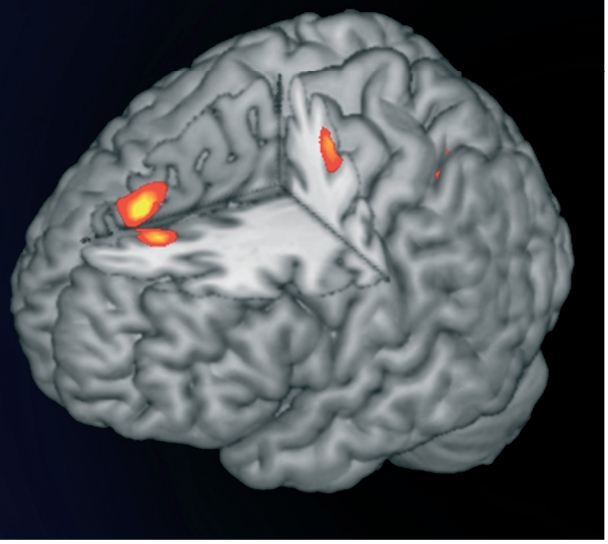
Oladazimi M, Brendel W, **Schwarz C**. Biomechanical texture coding in rat whiskers. *Scientific Reports* 2018; 8: 11139.

Stüttgen MC, Schwarz C. Barrel cortex: What is it good for? *Neuroscience* 2018; 368: 3-16.

Waiblinger C, Whitmire CJ, Sederberg A, Stanley GB, **Schwarz C**. Primary tactile thalamus spiking reflects cognitive signals. *Journal of Neuroscience* 2018; 38: 4870-4885.

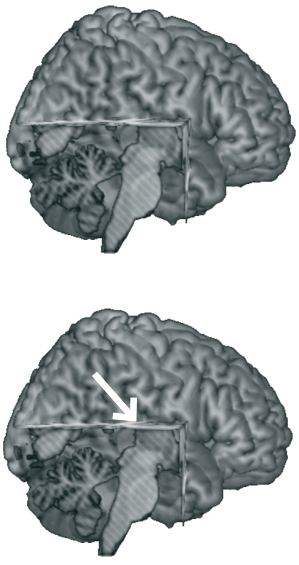
Neuropsychology of Action

Head: PD Dr. Marc Himmelbach
Team: 4 members
Key words: reaching / grasping / optic ataxia / apraxia / visual agnosia / UHF fMRI



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.

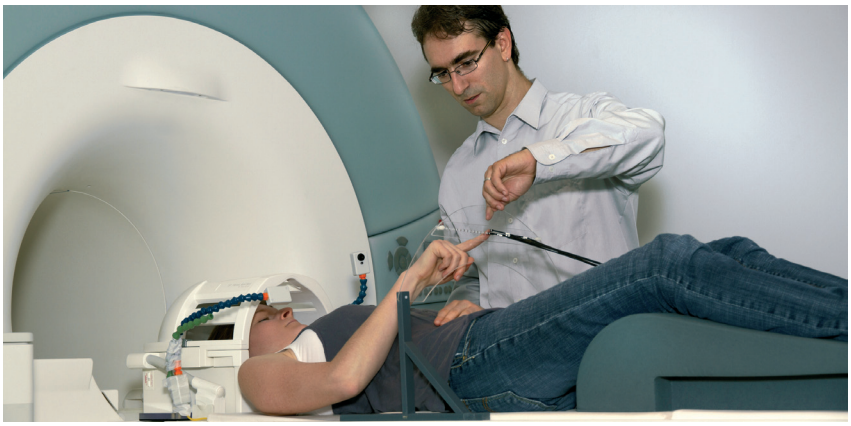
Evaluation of object functionality and mechanical reasoning in humans

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, built 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.

SELECTED PUBLICATIONS

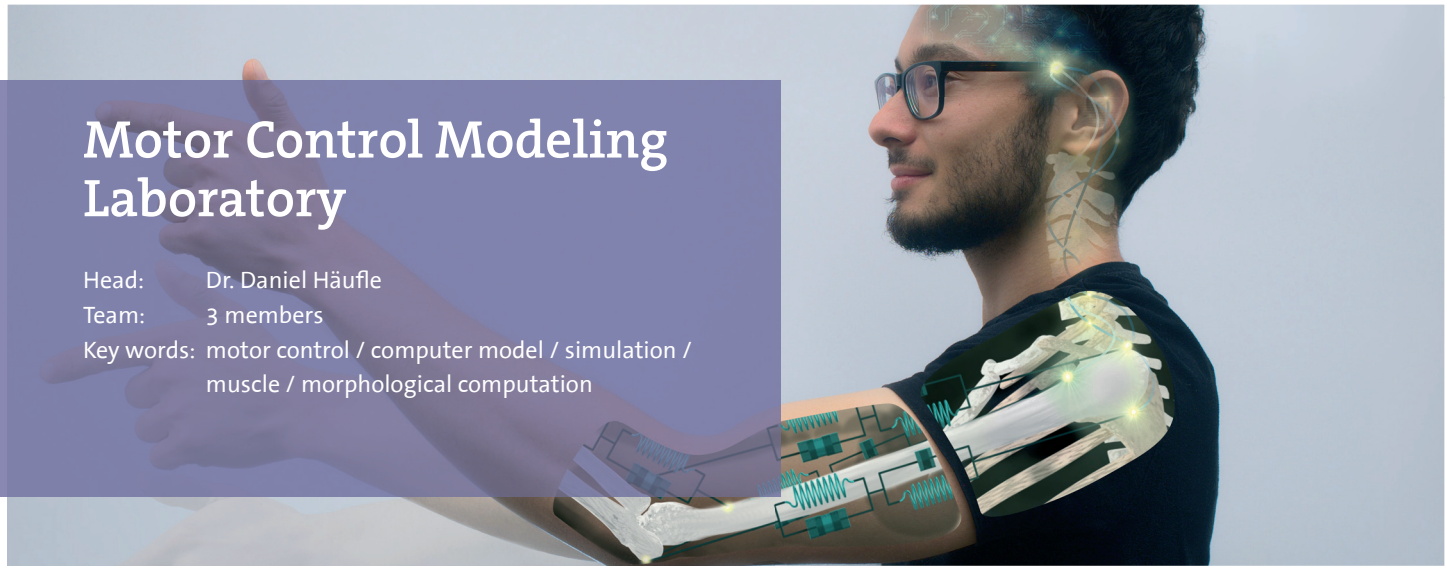
McDermott EJ, Himmelbach M. Effects of arm weight and target height on hand selection: A low-cost virtual reality paradigm. *PLoS One* 2019; 14(6): e0207326.

Loureiro JR, Himmelbach M, Ethofer T, Pohmann R, Martin P, Bause J, Grodd W, Scheffler K, Hagberg GE. In-vivo quantitative structural imaging of the human midbrain and the superior colliculus at 9.4T. *Neuroimage* 2018; 177: 117-128.

Loureiro JR, Hagberg GE, Ethofer T, Erb M, Bause J, Ehses P, Scheffler K, **Himmelbach M**. Depth-dependence of visual signals in the human superior colliculus at 9.4 T. *Human Brain Mapping* 2017; 38: 574-587.

Rennig J, Karnath H-O, Cornelsen S, Wilhelm H, **Himmelbach M.** Hemifield coding in ventral object-sensitive areas – evidence from visual hemiagnosia. *Cortex* 2018 ; 98:149-162.

Vogel AP, Rommel N, Sauer C, Horger M, Krumm P, **Himmelbach M**, Synofzik M. Clinical assessment of dysphagia in neurodegeneration (CADN): development, validity and reliability of a bedside tool for dysphagia assessment. *Journal of Neurology* 2017; 264: 1107-1117.

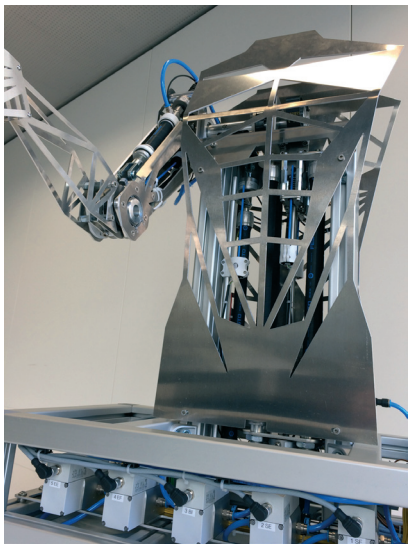


Motor Control Modeling Laboratory

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.

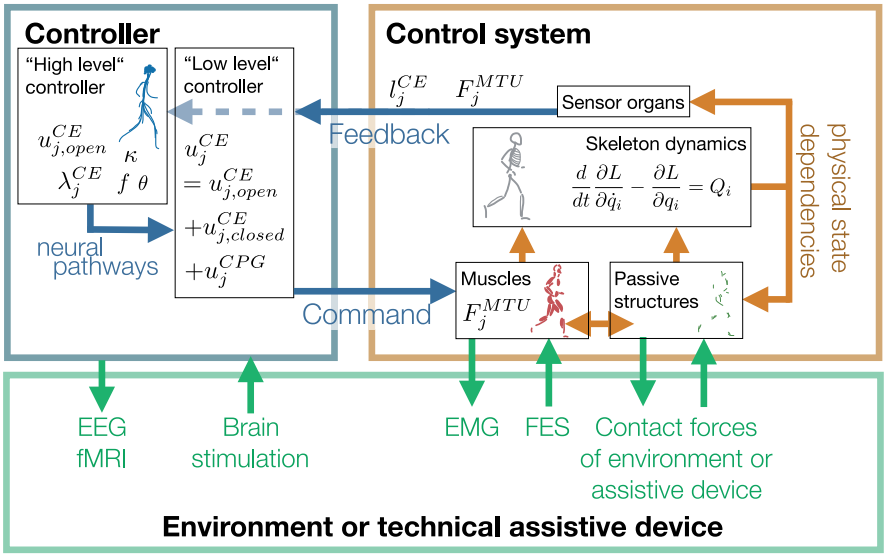


Biorobotic model of the human arm with two joints actuated by five mono- and biarticular pneumatic muscles of different lengths and thicknesses. The robot considers non-linear lever arms and actuators with a nonlinear force-length and force-velocity relation. Built in collaboration with Syn Schmitt,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

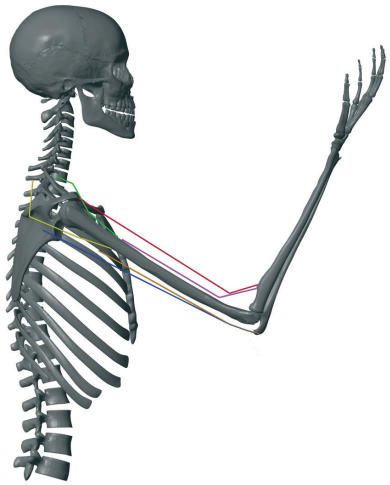
To successfully generate a goal-directed movement in the interaction with their environment, humans and animals perform control. They acquire information about their environment by sensors and generate actions by sending signals to their actuators. However, the resulting movement is not only governed 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. In this field we work together with the Sections for Computational Sensomotorics (Giese) and Clinical Neurogenetics (Schöls).



Schematics of the interaction of the human system with assistive devices for motor control rehabilitation. Adapted from Schmitt et al. 2019.



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

Wearable assistive devices for rehabilitation

The research on motor control dysfunction may be the starting point for the development of functional assistive devices. With the neuro-musculo-skeletal models we are able to predict required assistive forces. We can further predict the patients' reaction to such assistive forces, at least to some extent, and estimate from this which type of controller may be suitable to improve motor coordination. This is especially relevant in the context of neuronal disorders, as the muscle stimulation signals cannot be used to drive assistive devices.

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.

Ergonomics of exoskeletons

Occupational medicine and ergonomics need to assess the risk of musculo-skeletal disorders for specific work places. For this, it would often be desirable to know, or at least to estimate, internal forces and loads e.g., in the intervertebral discs or the carpal tunnel. Biomechanical computer simulations are a tool to estimate such internal forces and even predict them. This is especially interesting for the evaluation of novel exoskeletons which are intended to support a worker e.g., by reducing the load on the intervertebral discs or the muscles in the lower back. We started to investigate this in a joint research project with the Institute for Occupational Medicine in Tübingen and the Institute for Modelling and Simulation of Biomechanical Systems at the University of Stuttgart.

The group is part of the regional research alliance "System Mensch" 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).

PUBLICATIONS 2019

Schmitt S, Günther M, **Häufle DFB**. The dynamics of the skeletal muscle: A systems biophysics perspective on muscle modeling with the focus on Hill-type muscle models. *GAMM-Mitteilungen* 2019; 42(3): e201900013, doi: 10.1002/gamm.201900013.

Active Perception Laboratory

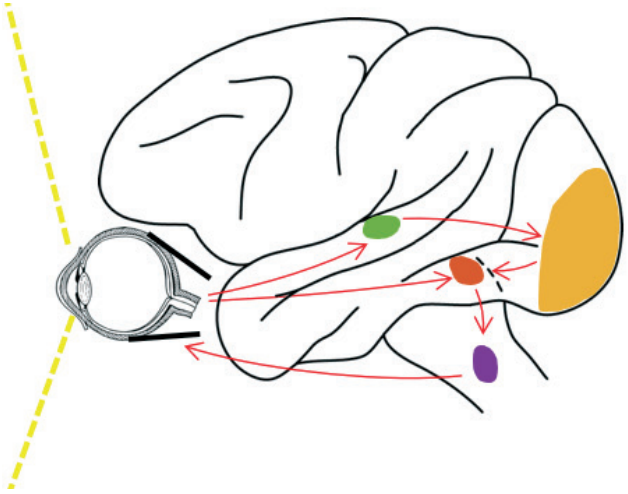
Head: Prof. Dr. Ziad Hafed
Team: 7 members
Key words: visual perception / eye movements / brainstem control of eye movements / perceptual stability / visual field representations

Our research aims to investigate the neural mechanisms through which visual perception interacts with motor control. We employ techniques for monitoring and focally perturbing neural activity to understand the functional contribution of individual brain circuits in coordinating perception and action. Besides clarifying our understanding of the sense of vision, our research also sheds light on how neural activity that is distributed across multiple brain areas is organized to support behavior.

Ziel unserer wissenschaftlichen Arbeit ist die Untersuchung der neuralen Mechanismen, die der Interaktion zwischen visueller Wahrnehmung und Bewegungskontrolle zugrundeliegen. Wir nutzen verschiedene Techniken, mit denen wir neurale Aktivität beobachten und fokal reizen, um so den funktionellen Beitrag individueller Hirnströme zur Koordination von Wahrnehmung und Handlung zu verstehen. Außer zu einem besseren Verständnis des Sehens beizutragen, beleuchten unsere Untersuchungen auch die Frage, wie neurale Aktivität, die über mehrere Hirnareale verteilt ist, zusammenspielt, um bestimmte Verhaltenweisen zu unterstützen.

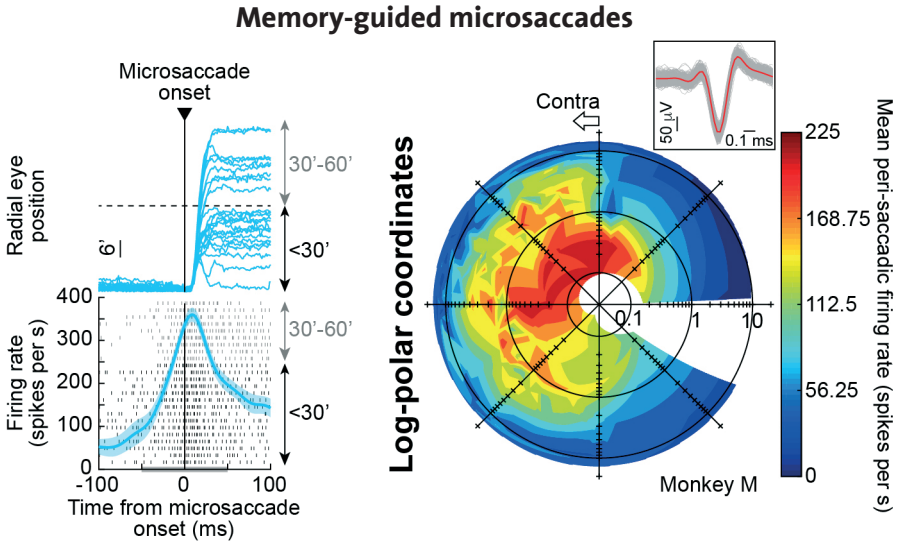
High-resolution vision in humans is only limited to a small area of the visual field. Despite this fact, humans have the perception of a vivid, clear scene throughout the visual field, and this is due to the fact that humans are active observers. By moving their eyes around, humans effectively compensate for the resolution limitations that are inherent in the retina. However, the mere act of moving the eyes creates retinal image shifts and motions that are not present in the real world. The visual brain is therefore perpetually faced with both: 1) a need to move the eyes in order to align the high-resolution portion of the retina with objects of interest, and 2) 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. The insights that we gain have strong relevance for understanding clinical orders of stability, balance, and bodily reference frames (e.g. dizziness, vertigo, and so on).

There are two main classes of eye movements that are employed by humans in everyday life: saccades, which are rapid changes in eye position that align gaze on peripheral objects, and smooth pursuit eye movements, which are smooth movements that stabilize the image of a moving object on the retina. Associated with every eye movement are various sensory and motor processes that not only ensure that the eye lands on its intended target, but that also serve higher-level perceptual and cognitive processes. We are interested in learning about these processes in more detail. An additional hallmark of our work is to explore a much-less understood class of eye movements that occur during maintained gaze fixation. These tiny subliminal eye movements were traditionally considered to be completely irrelevant for action and perception, but it turns out that they are highly systematic, and with substantial impacts on vision. Our research is uncovering interesting analogies between these subliminal eye movements and their larger counterparts, resulting in unifying theories on the entire gamut of oculomotor behavior that the brain is capable of exhibiting. The transformative aspects of this research relate to how changes in perception caused by these tiny eye movements can amplify changes often attributed to cognitive state, like attention, independently of oculomotor behavior.



Finally, our work investigates action and perception taking into account ecological constraints on brain function. Ultimately, our brain operates in a natural environment and is therefore 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.

Microsaccades are the smallest possible rapid eye movements that the brain is capable of generating. Recent work in the laboratory suggests that these eye movements not only can be generated voluntarily and at will from unseen memory representations (memory-guided microsaccades), but that their driving circuitry in the midbrain also precisely dictates their tiny amplitudes, directions, and timings.



PUBLICATIONS 2019

Bellet ME*, Bellet J*, Nienborg H, **Hafed ZM****, Berens P**. Human-level saccade detection performance using deep neural networks. *Journal of Neurophysiology* 2019; 121: 646-661; doi: 10.1152/jn.00601.2018. (* Contributed equally; ** Co-corresponding authors)

Buonocore A, Skinner J, Hafed ZM. Eye-position error influence over "open-loop" smooth pursuit initiation. *Journal of Neuroscience* 2019; 39: 2709-2721; doi: 10.1523/Journal of Neuroscience.2178-18.2019.

Chen C-Y, Hoffmann KP, Distler C, **Hafed ZM**. The foveal visual representation of the primate superior colliculus. *Current Biology* 2019; 29: 2109-2119; doi: 10.1016/j.cub.2019.05.040.

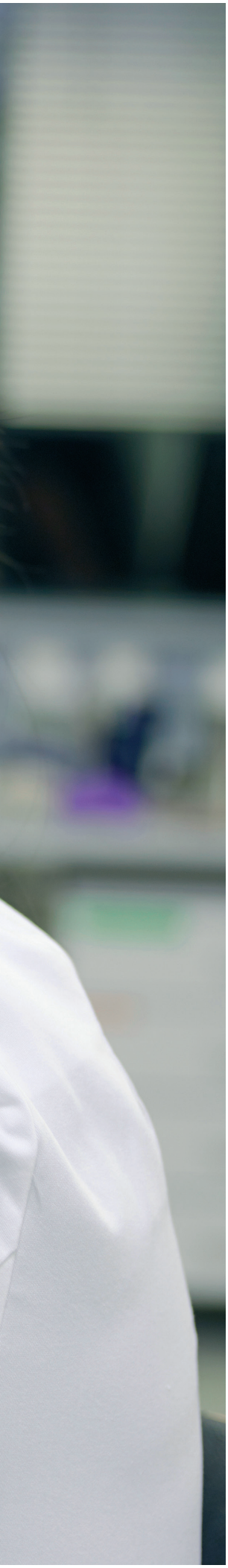
Idrees S*, Baumann MP*, Franke F, Münch TA**, **Hafed ZM****. Perceptual saccadic suppression starts in the retina. *BioRxiv* 2019; doi: 10.1101/562595. (* Contributed equally; ** Co-corresponding authors)

Markanday A*, **Bellet J*, Bellet ME, Hafed ZM****, Thier P**. Using deep neural networks to detect complex spikes of cerebellar Purkinje cells. *BioRxiv* 2019; doi: 10.1101/600536. (* Contributed equally; ** Co-corresponding authors)

Skinner J, Buonocore A, Hafed ZM. Transfer function of the rhesus macaque oculomotor system for small-amplitude slow motion trajectories. *Journal of Neurophysiology* (Special Issue on the Role of Eye Movements in Perception, Cognition, and Action) 2019; 121: 513-529; doi: 10.1152/jn.00437.2018.

Willeke KF*, Tian X*, Buonocore A*, Bellet J, Ramirez-Cardenas A, Hafed ZM. Memory-guided microsaccades. *Nature Communications* 2019; 10: 3710; doi: 10.1038/s41467-019-11711-x. (* Contributed equally).

Department of Cellular Neurology



Departmental Structure

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

Our 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 proteopathies. Alzheimer's disease is the most frequently occurring age-related dementia, with more than one million people affected in Germany. As of 2010 our department is also part of the German Center for Neurodegenerative Diseases (DZNE).

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 department of Psychiatry and established a clinical Research unit that closely collaborates with the outpatient Memory Clinic. We also maintain a biobank for biofluids and brain tissue of mouse models and this is done in close collaboration with the corresponding local human biobanks at the HIH and DZNE.

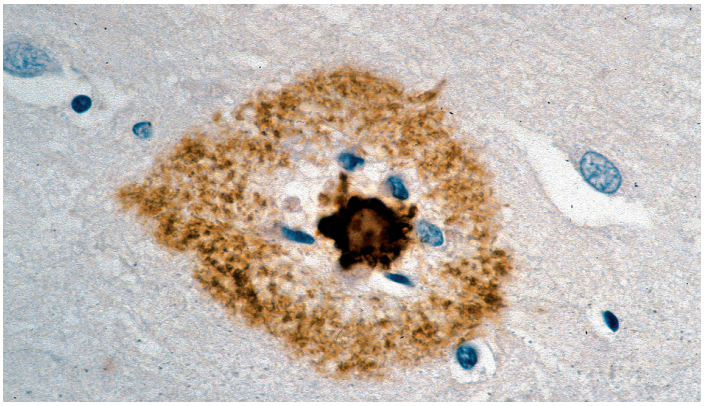
We also coordinate the international Dominantly Inherited Alzheimer Network (DIAN) study in Germany, which aims to understand the rare genetic forms of Alzheimer's disease by longitudinal analysis of gene mutation carriers and non-mutation carrier siblings. Understanding this type of Alzheimer's disease is expected to provide important clues to the development of the more common sporadic form of Alzheimer's disease.

Currently our department is composed of three research groups and three research units:

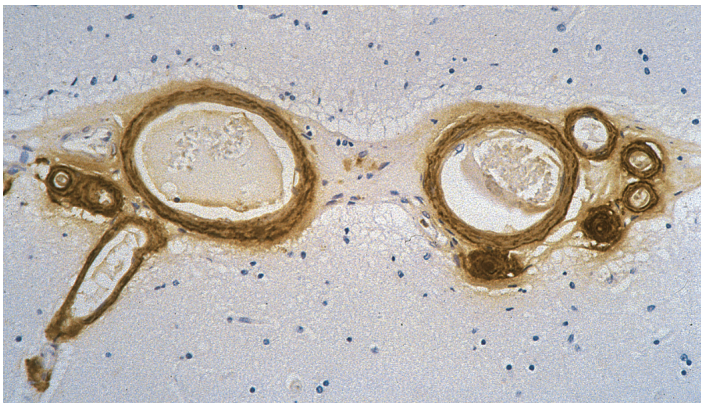
- Experimental Neuropathology
- Experimental Neuroimmunoloy
- Molecular Imaging unit
- Molecular Biomarker unit
- Dementia research unit (clinical)

We also maintain a Core Unit and a mini-department for our little ones, i.e. a playroom.

Our department hosts scientists from more than ten nations, ranging from short-term fellows, master students, PhD and MD students to postdoctoral fellows, clinicians, group leaders, and guest professors. This variety is also reflected in our funding that includes support for DIAN families as well as support to study protein structures. The department's goal is to create an intellectually and socially stimulating intramural environment that is also highly competitive extramurally.



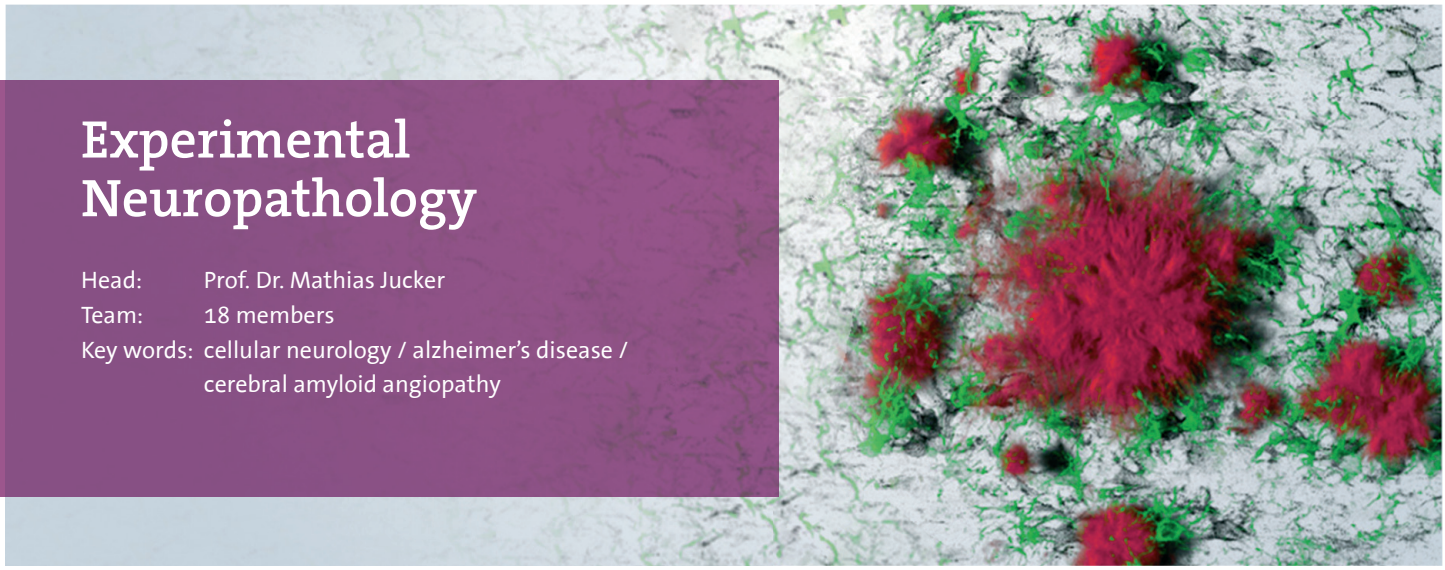
Amyloid plaque (Aβ immunochemistry) in an Alzheimer brain.



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.

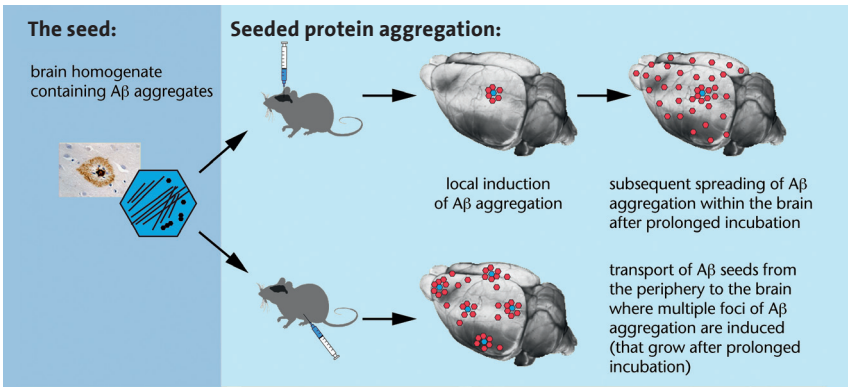
Misfolded proteins are the cause of many neurodegenerative diseases. How these proteins misfold and what the initial trigger is for the misfolding and their subsequent aggregation is, however, largely unknown. Furthermore, it remains unclear why the aging brain is a risk factor for neurodegenerative 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 reminiscent of prion diseases and are now used to develop new therapeutic approaches for Alzheimer's disease and other amyloidoses. First immunotherapy trials in transgenic mice are promising and show that β-amyloid aggregation can be reduced by targeting the initial proteopathic Aβ seeds. Microglia appear to play a crucial role in Aβ immunotherapy and also play an important role in early pathogenesis. To this end, we now use in vivo 2-photon microscopy to track initial Aβ aggregation and the response of microglia cells.

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. Using ultrasensitive immunoassays we study disease-associated biomarkers in murine cerebrospinal fluid and blood. In turn, we then use the results to develop fluid disease-biomarker for the early stages of Alzheimer's disease.



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

SELECTED PUBLICATIONS

Schelle J, **Wegenast-Braun BM**, Fritschi SK, **Kaeser SA**, Jährling N, Eicke D, **Skodras A, Beschorner N, Obermueller U, Häsler M,** Wolfer DP, Mueggler T, Shimshek DR, Neumann U, Dodt H-U, **Staufenbiel M, Jucker M** (2019) Early Aβ reduction prevents progression of cerebral amyloid angiopathy. *Ann Neurology* 86:561-571

Preische O, Schultz S, **Apel A**, Kuhle J, **Kaeser SA**, Barro C, **Gräber S, Kuder-Buletta E**, LaFougere C, **Laske C**, Vöglein J, Levin J, Masters CL, Martins R, Schofield PR, Rossor MN, Graff-Radford NR, Salloway S, Ghetti B, Ringman JM, Noble JM, Chhatwal J, Goate AM, Benzinger TLS, Morris JC, Bateman RJ, Wang G, Fagan AM, McDade EM, Gordon BA, **Jucker M**, Dominantly Inherited Alzheimer Network (2019) Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer´s disease. *Nature Medicine* 25: 277-283

Jucker M, Walker LC (2018) Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. *Nature Neuroscience* 21:1341-1349

Rasmussen J, Mahler J, Beschorner N, Kaeser SA, Häsler LM, Baumann F, Nyström S, Portelius E, Blennow K, Lashley T, Fox NC, Sepulveda-Falla D, Glatzel M, Oblak AL, Ghetti B, Nilsson KPR, Hammarström P, **Staufenbiel M,** Walker LC, **Jucker M** (2017) Amyloid polymorphisms constitute distinct clouds of conformational variants in different etiological subtypes of Alzheimer's disease. *Proc Natl Acad Sci USA*, 114: 13018-23

Ye L, Rasmussen J, Kaeser SA, Marzesco A-M, Obermüller U, Mahler J, Schelle J, Odenthal J, Krüger C, Fritschi SK , Walker LC, **Staufenbiel M, Baumann F, Jucker M** (2017) Aß seeding potency peaks in the early stages of cerebral β-amyloidosis. *EMBO Reports*, 18: 1536-44

Fuger P, Hefendehl JK, Veeraraghavalu K, **Wendeln AC**, Schlosser C, **Obermuller U, Wegenast-Braun BM, Neher JJ,** Martus P, Kohsaka S, Thunemann M, Feil R, Sisodia SS, **Skodras A, Jucker M (**2017) Microglia turnover with aging and in an Alzheimer's model via long-term in vivo single-cell imaging. *Nature Neuroscience* 20: 1371-6

Bacioglu M, Maia LF, Preische O, Schelle J, Apel A, Kaeser SA, Schweighauser M, Eninger T, Lambert M, Pilotto A, Shimshek DR, Neumann U, Kahle PJ, **Staufenbiel M**, Neumann M, Maetzler W, Kuhle J, **Jucker M** (2016) Neurofilament Light Chain in Blood and CSF as Marker of Disease Progression in Mouse Models and in Neurodegenerative Diseases. *Neuron* 91: 56-66

Novotny R, Langer F, Mahler J, Skodras A, Vlachos A, **Wegenast-Braun BM, Kaeser SA, Neher JJ, Eisele YS**, Pietrowski MJ, Nilsson KPR, Deller T, **Staufenbiel M**, Heimrich B, **Jucker M** (2016) Conversion of synthetic Aß to in vivo active seeds and amyloid plaque formation in a hippocampal slice culture model. *Journal of Neuroscience* 36: 5084-93

Schweighauser M, Bacioglu M, Fritschi SK, Shimshek DR, Kahle PJ, **Eisele YS, Jucker M** (2015) Formaldehyde-fixed brain tissue from spontaneously ill α-synuclein transgenic mice induces fatal α-synucleinopathy in transgenic hosts. *Acta Neuropathologica* 129: 157-9

Jucker M, Walker LC (2015) Neurodegeneration: Amyloid-β pathology induced in humans. *Nature* 525: 193-4

Maia LF, Kaeser SA, Reichwald J, **Lambert M, Obermüller U, Schelle J, Odenthal J**, Martus P, **Staufenbiel M, Jucker M** (2015) Increased CSF Aβ during the very early phase of cerebral Aβ deposition in mouse models. *EMBO Molecular Medicine* 7: 895-903

Ye L, Fritschi SK, Schelle J, Obermüller U, Degenhardt K, Kaeser SA, Eisele YS, Walker LC, **Baumann F, Staufenbiel M, Jucker M** (2015) Persistence of Aβ seeds in APP null mouse brain. *Nature Neuroscience* 18: 1559-61

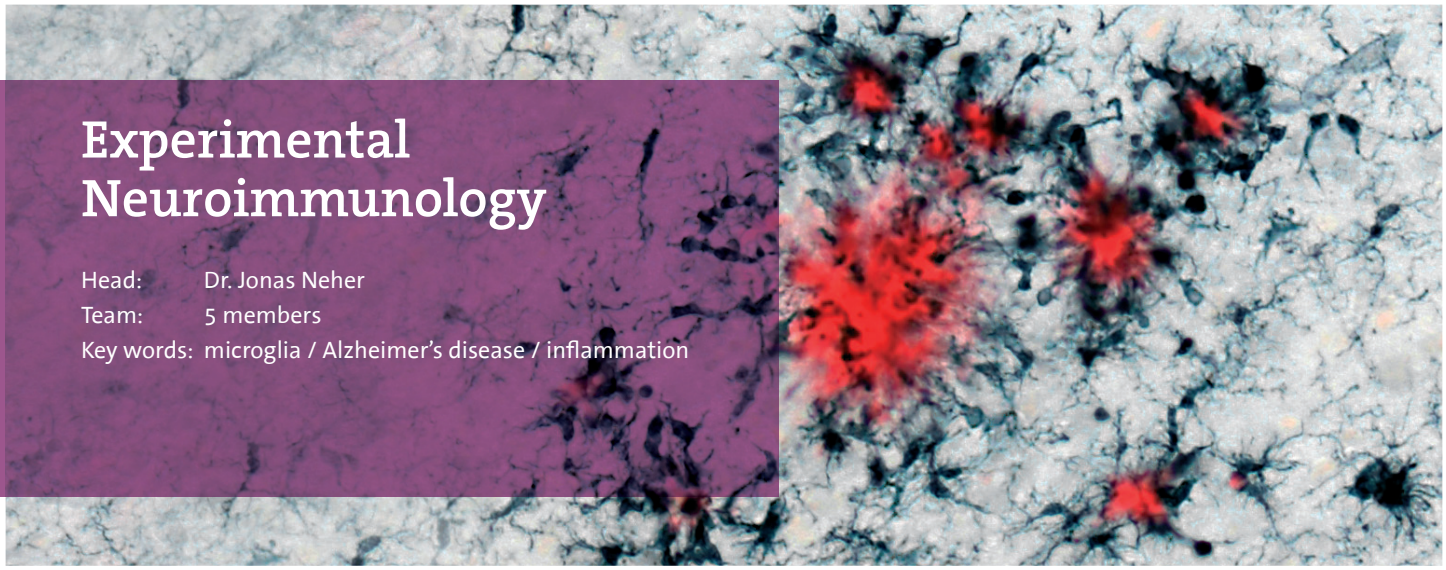
Walker LC, **Jucker M** (2015) Neurodegenerative diseases: Expanding the prion concept. *Annual Review of Neuroscience* 38: 87-103

Fritschi SK, Langer F, Kaeser S, Maia LF, Portelius E, Pinotsi D, Kaminski CF, Winkler DT, Maetzler W, Keyvani K, Spitzer P, Wiltfang J, Kaminski Schierle GS, Zetterberg H, **Staufenbiel M, Jucker M** (2014) Highly potent soluble amyloid-β seeds in human Alzheimer brain but not cerebrospinal fluid. *Brain* 137: 2909-15

Heilbronner G, Eisele YS, Langer F, Kaeser SA, Novotny R, Nagarathinam A, Aslund A, Hammarstrom P, Nilsson KPR, **Jucker M** (2013) Seeded strain-like transmission of β-amyloid morpho-types in APP transgenic mice. *EMBO reports* 14: 1017-22

Jucker M, Walker LC (2013) Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature* 501: 45-51

Maia LF, Kaeser SA, Reichwald J, **Hruscha M**, Martus P, **Staufenbiel M, Jucker M** (2013) Changes in amyloid-β and Tau in the cerebrospinal fluid of transgenic mice overexpressing amyloid precursor protein. *Science Translational Medicine* 5, 194re2



Experimental Neuroimmunology

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

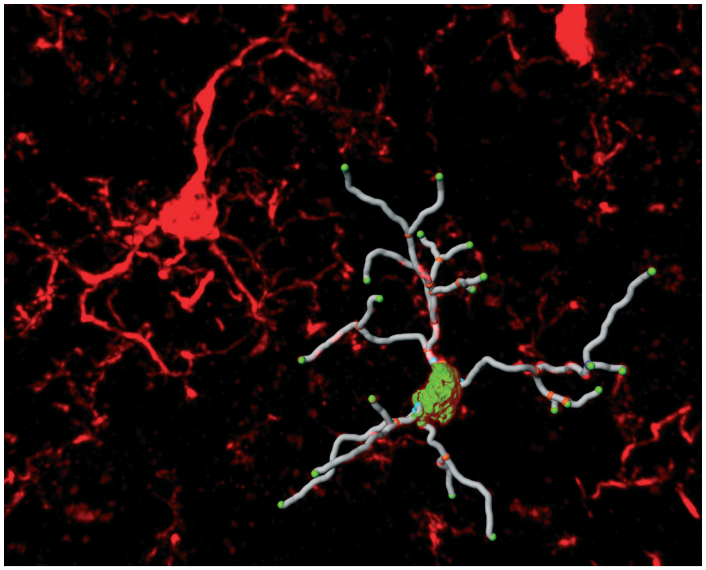
Amyloid-β plaques (red) surrounded by microglia (black).

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

Unser Ziel ist es zu verstehen, wie das Immunsystem des Gehirns zu dem Pathomechanismus neurodegenerativer Erkrankungen 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 profiles 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.

In current projects, we are analyzing the molecular mechanisms of innate immune memory in microglia. In addition, we study whether epigenetic microglial reprogramming occurs across neurodegenerative diseases and whether innate immune memory impacts on other neurodegenerative conditions, such as Parkinson's and Huntington's disease.



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

SELECTED PUBLICATIONS

Neher JJ, Cunningham C (2019) Priming Microglia for Innate Immune Memory in the Brain. *Trends in immunology* 40:358-374

Parhizkar S, Arzberger T, Brendel M, Kleinberger G, Deussing M, Focke C, Nuscher B, Xiong M, Ghasemigharagoz A, Katzmarski N, Krasemann S, Lichtenthaler SF, Müller SA, Colombo A, Nonasor LS, Tahirovic S, Herms J, Willem M, Pettkus N, Butovsky O, Bartenstein P, Edbauer D, Rominger A, Ertürk A, **Grathwohl SA, Neher JJ**, Holtzman DM, Meyer-Luehmann M, Haass C (2019) Loss of TREM2 fuction increases amyloid seeding but reduces plaque-associated ApoE. *Nature Neuroscience* 22:191-204

Wendeln AC, Degenhardt K, Kaurani L, Gertig M, Ulas T, Jain G, **Wagner J, Häsler LM, Wild K, Skodras A,** Blank T, Staszewski O, Datta M, Centeno TP, Capece V, Islam MR, Kerimoglu C, **Staufenbiel M**, Schultze JL, Beyer M, Prinz M, **Jucker M,** Fischer A, **Neher JJ**. (2018) Innate immune memory in the brain shapes neurological disease hallmarks. *Nature*, 556:332-338

Varvel NH, Grathwohl SA, Degenhardt K, Resch C, Bosch A, Jucker M, Neher JJ (2015) Replacement of brain-resident myeloid cells does not alter cerebral amyloid-β deposition in mouse models of Alzheimer's disease. *Journal of Experimental Medicine* 212:1803–9

Brown GC, **Neher JJ** (2014) Microglial phagocytosis of live neurons. *Nature Reviews Neuroscience* 15:209–6

Dementia Research Unit

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

The Dementia Research Unit is a clinical research unit of the Department of Cellular Neurology and the University Clinic of Psychiatry and Psychotherapy. It closely collaborates with the outpatient Memory Clinic.

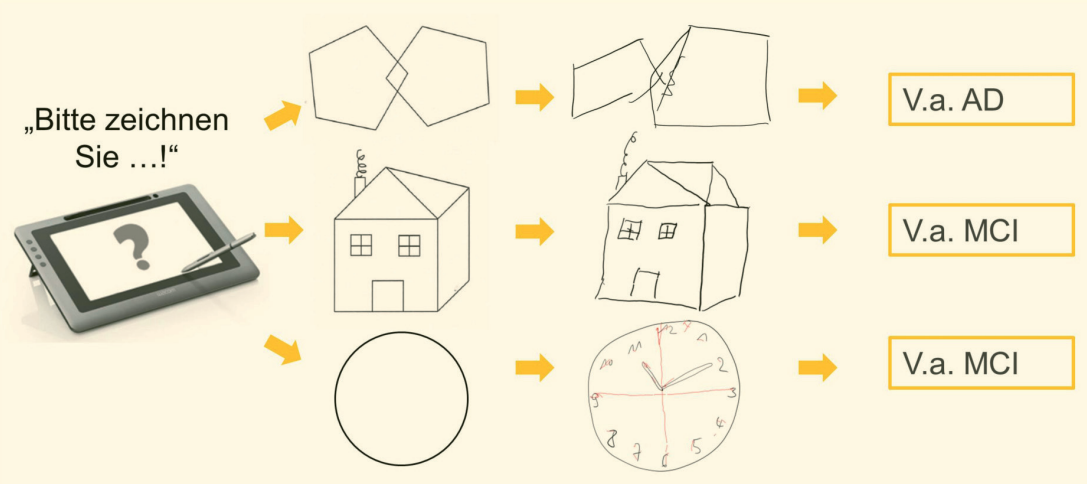
Die Unit Demenzforschung ist eine gemeinsame klinische Forschungsgruppe der Abteilung für Zellbiologie neurologischer Erkrankungen und der Universitätsklinik für Psychiatrie und Psychotherapie. Die Unit arbeitet eng mit der Gedächtnisambulanz der Universitätsklinik zusammen.

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 longitudinally follow Individuals from families with inherited forms of Alzheimer's disease. These rare forms of autosomal-dominant Alzheimer's disease are caused by mutations in one of three genes (APP, PSEN1 or PSEN2). In the DIAN observational study, individuals with such mutations and their non-affected siblings are examined via multimodal diagnostics (e.g. PET-PIB; MRI; biofluids; neuropsychology) in regard to preclinical changes. We have now recruited 40 subjects at each German site in Tübingen and Munich. A major finding of the DIAN-Observational study is that AD pathology begins in the brain 1-2 decades before clinical symptoms appear. In DIAN-TU (the therapy platform of the DIAN study) the BACE inhibitor atabecestat was discontinued while two antibodys against Aβ (gantenerumab and solanezumab) are still under investigation. The goal is to treat the disease preventively already at preclinical stages, i.e. before any symptoms appear.

Within the DIAN research framework, we performed several data analyses. For example, we found that body mass index starts to decline about one decade before clinical onset. Moreover, mutation carriers with high exercise levels showed significantly better global cognition for the time period from 3 years before until 11 years after disease onset compared to low exercisers.

We have also identified Neurofilament light chain (NfL) as a promising fluid biomarker of disease progression for AD. In short, we found that the rate of change of serum NfL increases more than a decade before onset of clinical symptoms and peaks when participants are converting from the presymptomatic to the symptomatic stage. Moreover, NfL levels are associated with cortical thinning assessed by MRI, and are predictive for both the rate of cortical thinning and cognitive changes assessed by mini-mental state examination and logical memory testing.

To identify new imaging biomarkers for Alzheimer's disease, we are using high resolution structural magnetic resonance imaging (9.4T MRI in Alzheimer patients with different disease stages and in healthy controls.



SELECTED PUBLICATIONS

Laske C, Sohrabi H, Jasielec M, **Müller S**, Köhler N, Gräber S, Foerster S, Drzezga A, Mueller-Sarnowski F, Danek A, Jucker M, Bateman R, Buckles V, Saykin AJ, Martins R, Morris JC, Dominantly Inherited Alzheimer Network Dian (2015) Diagnostic value of subjective memory complaints assessed with a single item in dominantly inherited Alzheimer's disease: results of the DIAN study. *BioMed Res* 2015: 828120.

Laske C, Sohrabi HR, Frost SM, López-de-Ipiña K, Garrard P, Buscema M, Dauwels J, Soekadar SR, Mueller S, Linnemann C, Bridenbaugh SA, Kanagasingam Y, Martins RN, O'Bryant SE (2015) Innovative diagnostic tools for early detection of Alzheimer's disease. *Alzheimer's & Dementia* 11:561-578.

Müller S, Preische O, Sohrabi HR, **Gräber S, Jucker M**, Dietzsch J, Ringman JM, Martins RN, McDade E, Schofield PR, Ghetti B, Rossor M, Graff-Radford NR, Levin J, Galasko D, Quaid KA, Salloway S, Xiong C, Benzinger T, Buckles V, Masters CL, Sperling R, Bateman RJ, Morris JC, **Laske C** (2017) Decreased body mass index in the preclinical stage of autosomal dominant Alzheimer's disease. *Sci Rep* 7:1225.

Müller S, Preische O, Sohrabi HR, **Gräber S, Jucker M**, Ringman JM, Martins RN, McDade E, Schofield PR, Ghetti B, Rossor M, Fox NN, Graff-Radford NR, Levin J, Danek A, Vöglein J, Salloway S, Xiong C, Benzinger T, Buckles V, Masters CL, Sperling R, Bateman RJ, Morris JC, **Laske C**; Dominantly Inherited Alzheimer Network DIAN (2018) Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. *Alzheimers Dement* 14:1427-1437.

Müller S, Herde L, **Preische O**, Zeller A, Heymann P, Robens S, Elbing U, **Laske C** (2019) Diagnostic value of digital clock drawing test in comparison with CERAD neuropsychological battery total score for discrimination of patients in the early course of Alzheimer's disease from healthy individuals. *Sci Rep* 9:3543.

Preische O, Schultz SA, **Apel A**, Kuhle J, **Kaeser SA**, Barro C, **Gräber S, Kuder-Buletta E**, LaFougere C, **Laske C**, Vöglein J, Levin J, Masters CL, Martins R, Schofield PR, Rossor MN, Graff-Radford NR, Salloway S Ghetti B, Ringman JM, Noble JM, Chhatwal J, Goate AM, Benzinger TLS, Morris JC, Bateman RJ, Wang G, Fagan AM, McDade EM, Gordon BA**, Jucker M**, Dominantly Inherited Alzheimer Network (2019) Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nature Medicine* 25:277-283.

Independent Research Groups

INDEPENDENT RESEARCH GROUPS 126

Physiology of Learning and Memory

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

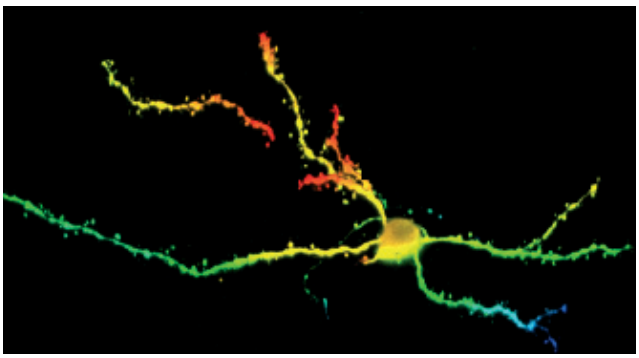
Our main interest is to investigate learning and memory processes using associative fear conditioning and extinction in rodents. We apply mainly physiological techniques to decipher cellular and synaptic processes and neural circuits in amygdala and fear-related brain areas. This allows us to understand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

Unser Hauptinteresse gilt der Untersuchung von Lern- und Gedächtnisprozessen anhand von klassischer Furchtkonditionierung und Extinktionslernen. Dabei verwenden wir vor allem physiologische Methoden, um zelluläre und synaptische Prozesse in neuralen Schaltkreise der Amygdala und verknüpfter Hirngebiete zu ergründen. Dies gibt Aufschluss darüber, wie sich Lernprozesse im Gehirn manifestieren, aber auch wie eine Fehlsteuerung dieser Prozesse zu Angststörungen führen kann.

Organisms 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 mainly use classical Pavlovian learning paradigms, i.e. fear learning and extinction of fear in mice, 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 approaches that include 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. The main goal of our research is to identify and investigate these networks and their learning-dependent changes.

One line of projects aims to understand the function and plasticity of a specific inhibitory network in the amygdala, the so-called intercalated cells. These cells play a critical role in extinction behavior, possibly by inhibiting the output of the amygdala and providing a break on the fear response. We have identified a new plastic brain circuit integrating intercalated cells that becomes engaged in fear learning and memory. 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 (Asede et al., 2015) (Zussy et al, 2018). We currently combine optogenetic and anatomical techniques to (1) delineate mechanisms of synaptic plasticity in intercalated cells, (2) investigate novel principles of reciprocal interconnectivity between different intercalated cell clusters, and (3) investigate different aspects of signaling from dopaminergic midbrain to intercalated cells on physiology and plasticity. Furthermore, in an international collaboration we aim at elucidating differential roles of ITC clusters in behavior using specific and reversibly manipulation of these cells.



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 investigated 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. 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). Within the SFB "Plasticity and Sleep" we collaborated on a project investigating cell-physiological underpinnings of the hallmarks of slow wave sleep, i.e. sleep spindles and slow oscillations (Niethard et al, 2018). Based on our own data, we are currently analyzing which sleep-stages and hallmarks of sleep-related brain activity may support extinction learning and memory.

Thirdly, apart from our core interests, we maintain a number of local and international collaborations to which we bring our core expertise in synaptic physiology and amygdala circuitry related to disease states. One recently completed project shows a critical role of the ionotropic glutamate receptor subunit GluA2 at neuron-glia synapses in regulating oligodendrocyte precursor cells, critical for establishing and maintaining myelination in the brain (Chen et al, 2018). Another recently started project investigates the role of the metabotropic glutamate receptor mGlu4 in amygdala circuits and mouse models on autism spectrum disorders.

SELECTED PUBLICATIONS

Chen T-J, Kula B, Nagy B, Barzan R, Gall A, **Ehrlich I,** Kukley M (2018) In vivo regulation of oligodendrocyte precursor cell proliferation and differentiation by the AMPA-receptor subunit GluA2. *Cell Reports* 25(4):852-861.

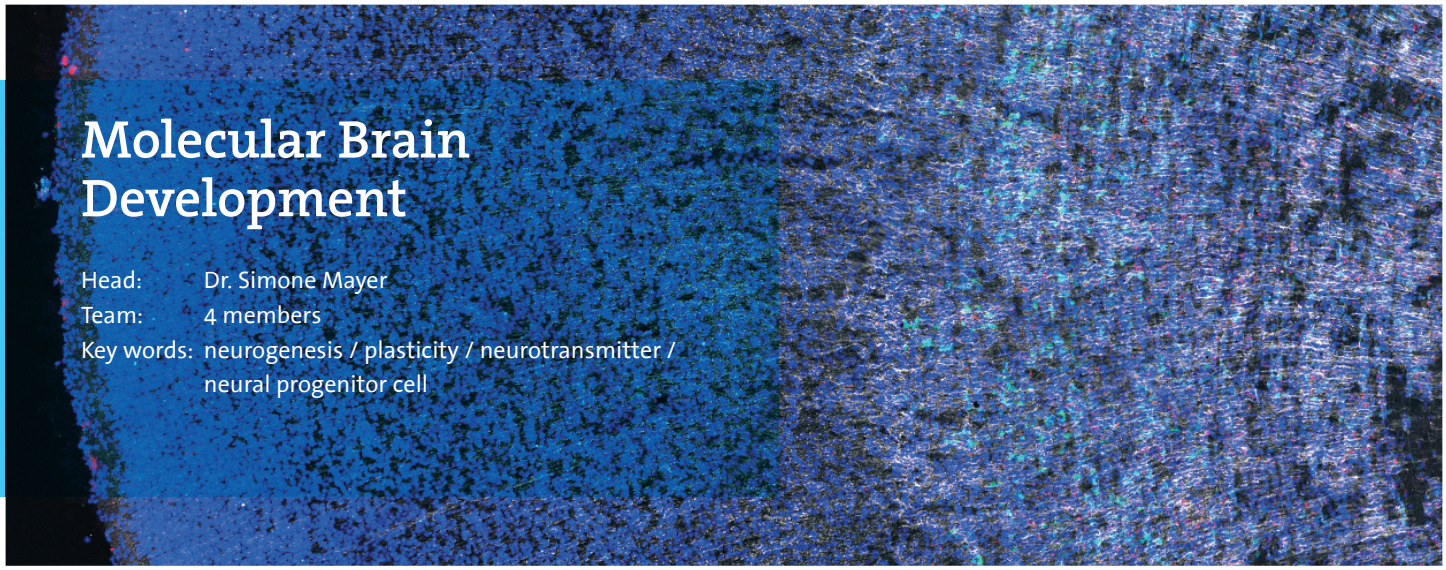
Niethard N, Ngo H-V, **Ehrlich I**, Born J. (2018) Cortical circuit activity underlying sleep slow oscillations and spindles. *Proc Natl Acad Sci USA* 115(39): E9220-E9229.

Zussy C, Gómez-Santacana X, Rovira X, De Bundel D, Ferrazzo S, **Bosch D, Asede D,** Malhaire F, Acher F, Giraldo J, Valjent E, **Ehrlich I** et al (2018) Dynamic modulation of inflammatory pain-related behaviors by optical control of amygdala metabotropic glutamate receptor 4. *Mol Psychiatry* 23: 509-520.

Saha R, **Knapp S**, Chakraborty D, Horovitz O, Albrecht A, Kriebel M, Kaphzan H, **Ehrlich I** et al (2017) GABAergic synapses at the axon initial segment of basolateral amygdala projection neurons modulate fear extinction. *Neuropsychopharmacology* 42: 473-484.

Melo I, Ehrlich I (2016) Sleep supports cued fear extinction memor consolidation independent of circadian phase. *Neurobiol Learn Mem* 132: 9-17.

Asede D, Bosch D, Lüthi A, Ferraguti F, **Ehrlich I** (2015) Sensory inputs to intercalated cells provide fear-learning modulated inhibition to the basolateral amygdala. *Neuron* 86: 541-554.



Molecular Brain Development

Head: Dr. Simone Mayer
Team: 4 members
Key words: neurogenesis / plasticity / neurotransmitter / neural progenitor cell

The mammalian neocortex is a highly complex and spatially heterogeneous structure, which has expanded significantly in mammalian evolution. Neocortical networks are at the heart of cognitive function. While the increased complexity of the human neocortex may have contributed to the higher cognitive abilities, it may have also caused the emergence of a plethora of psychiatric and neurological disorders. Since major differences in brain anatomy and hence function between species arise during development, it is crucial to understand the cellular and molecular mechanisms governing cortical development. Although we have recently gained significant insights into the contribution of genetically "hard-wired" mechanisms of proliferation, differentiation, and maturation, less is known about the degree to which environmental influences affect neocortical development, especially in humans. We aim to understand how plasticity contributes to human brain development in health and disease. Our long-term research goal is to identify factors that boost the resilience of neocortical development and thus help to prevent neurodevelopmental disorders.

Der menschliche Neocortex ist ein komplexer und heterogener Teil des Gehirns, der sich während der Evolution von Säugern stark vergrößert hat. Neokortikale Netzwerke sind das Kernstück der menschlichen Kognition, aber ihre hohe Komplexität kann auch zur Entstehung zahlreicher psychiatrischer und neurologischer Erkrankungen beigetragen haben. Da sich die großen Unterschiede in Anatomie und Funktion zwischen verschiedenen Spezies während der Entwicklung manifestieren, ist es unabdingbar, die zugrundeliegenden molekularen und zellulären Mechanismen zu verstehen. In den vergangenen Jahren haben wir viel über den Einfluss von genetischen Faktoren auf die Teilung, Differenzierung und Reifung von Zellen im Neocortex gelernt. Inwieweit Umwelteinflüsse insbesondere beim Menschen die neokortikale Entwicklung beeinflussen ist jedoch wenig untersucht. Wir wollen verstehen, wie Plastizität zur Entwicklung des menschlichen Gehirns beiträgt. Unser langfristiges Forschungsziel ist es, Faktoren zu identifizieren, die die Widerstandsfähigkeit der neokortikalen Entwicklung erhöhen und somit dazu beitragen, neurologische Entwicklungsstörungen zu verhindern.

Model: In vitro reconstitution of fetal neocortical development including cerebral organoids

In order to study human brain development, an in vitro model that allows diverse experimental manipulations is needed. We use two-dimensional neural cultures derived from primary neocortical tissue or human induced pluripotent stem cells (hiPSCs), which have been available for more than 10 years. In 2013, the first three-dimensional cerebral models - called organoids - derived from hiPSCs were generated. They have clear advantages over two-dimensional cultures in modelling cellular diversity, cell-cell interactions, and anatomical features (as reviewed by our group, Khakipoor et al., Brain Research, in press). Since then, cerebral organoid protocols have been improved by increasing reproducibility, incorporating long-distance cellular interactions and adding glial cells. We use both two-dimensional culture systems and cerebral organoids as human model systems of brain development in our lab. The use of hiPSC models contributes to the goal of reducing the number of animal experiments (3R).

Methodology: Multimodal single-cell readouts determine cell state-specific responses

Recent developments in single-cell RNA-Sequencing (scRNA-seq) have emphasized the importance of investigating phenotypes on a single-cell level in order to reveal cell-type-specific signalling pathways (see for example our recent review, Khakipoor et al., Neuroforum, 2019). I have recently developed a multimodal single-cell analysis method and contributed to studying neurological disorders at the single-cell level (e.g. Mayer et al., Neuron, 2019; Velmeshev

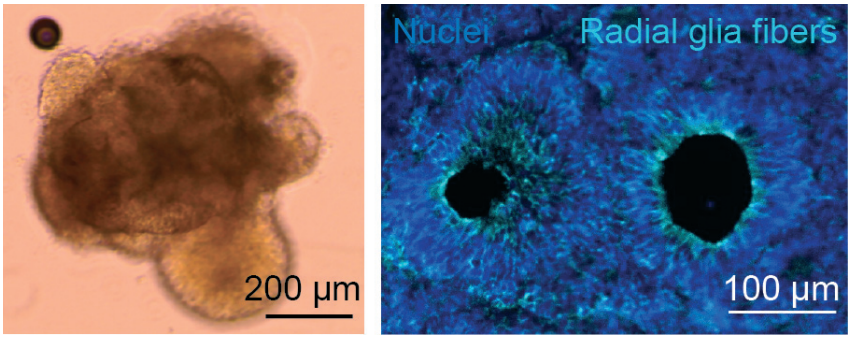
et al., Science, 2019). Therefore, we aim to employ multimodal single-cell approaches to quantitatively characterize cell type-specific responses to different experimental perturbations with a focus on the transcriptome and epigenome. Additionally, we perform signaling pathway analysis using classical methods such as immunofluorescence, western blotting, and live imaging.

Plasticity in neocortical development in health and disease

Using diverse in vitro models of human neocortical development as well as multimodal single-cell readouts, we aim to determine how environmental and genetic factors can affect neocortical development. Several projects in the lab approach this topic from diverse angles.

As an example for environmental factors, we study the effects of neurotransmitters on neocortical development. For instance, a body of literature has indicated that serotonin plays important roles in the developing neocortex including controlling proliferation, migration, and neuronal maturation. We have recently shown that early in development, serotonin activates human but not mouse neural progenitor cells, and this may be important to maintain the radial fiber morphology of human neural progenitor cells (Mayer et al., Neuron, 2019). In one on-going project, we are therefore further exploring the roles of serotonin and other neurotransmitters in human brain development. Serotonin is also interesting from a clinical point of view as its metabolism is altered in mood disorders, such as depression. Anti-depressants, such as serotonin reuptake inhibitors taken during pregnancy, could thus affect fetal serotonin levels.

Genetic perturbations may also affect human brain development. As a disease model, in cooperation with the Pediatrics department at Universitätklinikum Tübingen and a parents' initiative, we are investigating cellular mechanisms of pathology in pontocerebellar hypoplasias (PCH). PCH are a group of rare neurogenetic disorders that mostly affect the cerebellum and pons resulting in a severely disturbed development of patients during childhood. Additionally, patients develop severe microcephaly, indicating that neocortical development is also affected by the genetic abnormalities. Understanding the cellular and molecular mechanisms that drive disease progression may pave the way for personalized medicine or prevention of pathogenesis through in utero interventions.



Cerebral organoids grown in our lab. The protocol developed by Lancaster et al., Nature, 2013 was used. Left: Neuroectodermal tissue embedded in Matrigel droplet at day 11. Right: Radial organization of neural progenitor cells in selected regions of the organoid ressembling the anatomy in the human neocortex at day 31. Images were taken by Kseniia Sarieva.

SELECTED PUBLICATIONS

Khakipoor S, Crouch EE, **Mayer S**. Human organoids to model the developing human neocortex in health and disease. *Brain Research*, accepted

Khakipoor S, Drömer MA, Cozetto DA, Mayer S (2019) Single-cell RNA-Sequencing in Neuroscience. *Neuroforum* 25:251-8

Velmeshev D, Schirmer L, Jung D, Haeussler M, Perez Y, **Mayer S**, Bhaduri A, Goyal N, Rowitch DH, Kriegstein AR (2019) Single-cell genomics identifies cell type-specific molecular changes in autism. *Science* 364:685-9

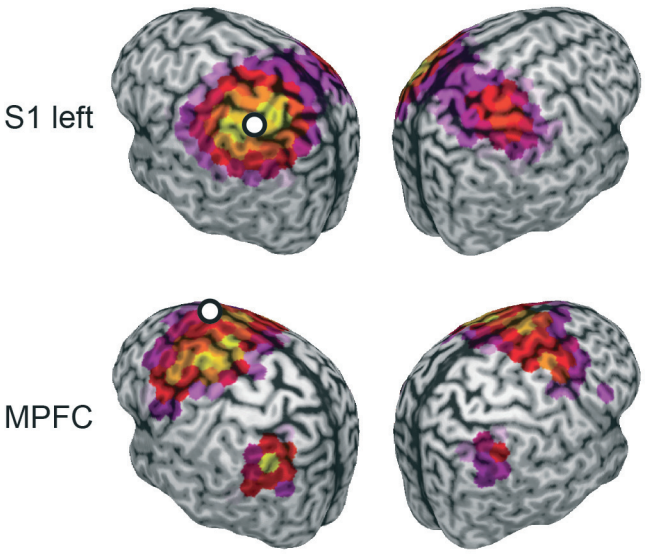
Mayer S, Chen J, Velmeshev D, Mayer A, Eze UC, Bhaduri A, Cunha CE, Jung D, Arjun A, Li E, Alvarado B, Wang S, Lovegren N, Gonzales ML, Szpankowski L, Leyrat A, West JAA, Panagiotakos G, Alvarez-Buylla A, Paredes MF, Nowakowski TJ, Pollen AA, Kriegstein AR (2019) Multimodal Single-Cell Analysis Reveals Physiological Maturation in the Developing Human Neocortex. *Neuron* 102:143-58 e7

Neural Dynamics and Magnetoencephalography

Head: Prof. Dr. Markus Siegel
Team: 21 members
Key words: large-scale neuronal interactions / cognition / behavior / neuronal oscillations

Our goal is to investigate how cognition and behavior emerges from dynamic interactions across widely distributed neuronal ensembles. We apply a multiscale approach to identify these interactions and to investigate how they are disturbed in the diseased brain.

Unser Ziel ist es zu erforschen wie dynamische Interkationen weitverteilter Nervenzellpopulationen Kognition und Verhalten hervorbringen. Wir verwenden einen Mehrskalen-Ansatz, um diese Interaktionen zu identifizieren und um zu untersuchen, wie diese bei Erkrankungen des Gehirns gestört sind.



Coupled brain networks imaged with MEG.
Left primary somatosensory cortex (S1) is coupled with the homologue region in the right hemisphere. Medial prefrontal cortex (MPFC) is coupled to a bilateral frontoparietal network.

The brain is a highly dynamic and distributed system. How do sophisticated cognitive processes such as perception, decision-making, and motor behavior emerge from dynamic interactions across the brain? Which neural mechanisms coordinate these interactions and how are they disturbed in neuropsychiatric diseases?

To address these questions, we link large-scale population measures of neuronal activity to circuit and cellular-level mechanisms. We combine human MEG and EEG, animal electrophysiology, psychophysics and sophisticated analytical techniques.

Spectral Fingerprints of Normal and Diseased Brain Function

One focus of the lab are oscillatory dynamics of neuronal activity. Brain activity exhibits oscillations, i.e. periodicity, at various different frequencies and spatial scales. These oscillations may not only serve as highly informative markers, or 'spectral fingerprints' of the circuit interactions involved in different cognitive functions but may also dynamically mediate these interactions.

In one line of research, we investigate these spectral fingerprints with MEG in the resting human brain. We investigate how networks of brain regions spontaneously coordinate their oscillations at different frequencies and how these large-scale oscillatory interactions are altered in the diseased brain. Our recent results show that, based on their amplitude and phase, brain rhythms are coupled in two distinct modes that are expressed in different brain networks. Together with our clinical collaborators, we investigate these rhythmic networks as novel biomarkers of different neurological pathologies, such as e.g. Multiple sclerosis and Epilepsy. Furthermore, we characterize the temporal microstructure of different brain rhythms and how they are linked to neuronal spiking at the cellular level.

Neuronal Dynamics During Cognition and Behavior

In another line of research, we investigate neural dynamics underlying specific cognitive functions. We characterize the flow of information and neuronal interactions across distributed cortical and sub-cortical networks during complex behavioral tasks, involving e.g. visual and auditory decision-making, working memory, and proprioception. Our recent results show how sensory, cognitive, and motor neuronal information can be non-invasively decoded from the human brain, how this information flows across the brain and how such information relates to cortical spiking activity. Together with our clinical collaborators, we investigate alterations of neuronal dynamics during pathological conditions, such as e.g. dyslexia in children and spatial hearing in cochlear implant users.

Magnetoencephalography – Imaging Human Brain Dynamics

Magnetoencephalography (MEG) allows for non-invasively and directly measuring human brain activity with unparalleled temporal resolution and signal quality. Our lab operates the Tübingen MEG Center, which provides state-of-the-art MEG techniques and services to the Tübingen neuroscience community and beyond. The MEG Center hosts a 275-channels whole-head MEG system, synchronized high-density EEG, transcranial electrical stimulation, precise visual, auditory and somatosensory stimulation, various response systems and high-speed binocular eye-tracking. The MEG Center is involved in a broad spectrum of collaborative research projects with partners at the Center for Neurology, the Centre for Integrative Neuroscience, the Institute of Medical Psychology, the Department of Otolaryngology, the Centre for Ophthalmology, the Department of Psychiatry and Psychotherapy and the Department of Psychosomatic Medicine.

MEG system installed at the Tübingen MEG Center. The MEG system consists of 275 SQUID magnetometers (superconducting quantum unit interference devices) that allow for measuring the magnetic fields generated by the electrical brain activity.

SELECTED PUBLICATIONS

Trainito C, von Nicolai C, Miller EK, **Siegel M (2019)** Extracellular spike waveform dissociates four functionally distinct cell classes in primate cortex. *Current Biology* 29

Sandhaeger F, von Nicolai C, Miller EK, **Siegel M** (2019) Monkey EEG links neuronal color and motion information across species and scales. *eLife* 8:e45645

Siems M, Siegel M (2020) Dissociated neuronal phase- and amplitude-coupling patterns in the human brain. *Neuroimage* 209:116538

Supp GG, Higgen FL, **Hipp JF**, Engel AK, **Siegel M** (2018) Mid-latency auditory evoked potentials differentially predict sedation and drug level under opioid and hypnotic agents. *Frontiers in Pharmacology* 9:1427

Fioravanti C, Kajal SD, Carboni M, Mazzetti C, **Ziemann U, Braun C** (2019) Inhibition in the somatosensory system: An integrative neuropharmacological and neuroimaging approach. *Neuroimage* 202:116139

Marquetand J, Vannoni S, Carboni M, **Li Hegner Y, Stier C, Braun C, Focke NK** (2019) Reliability of Magnetoencephalography and High-Density Electroencephalography Resting-State Functional Connectivity Metrics. *Brain Connectivity* 9:539-553

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