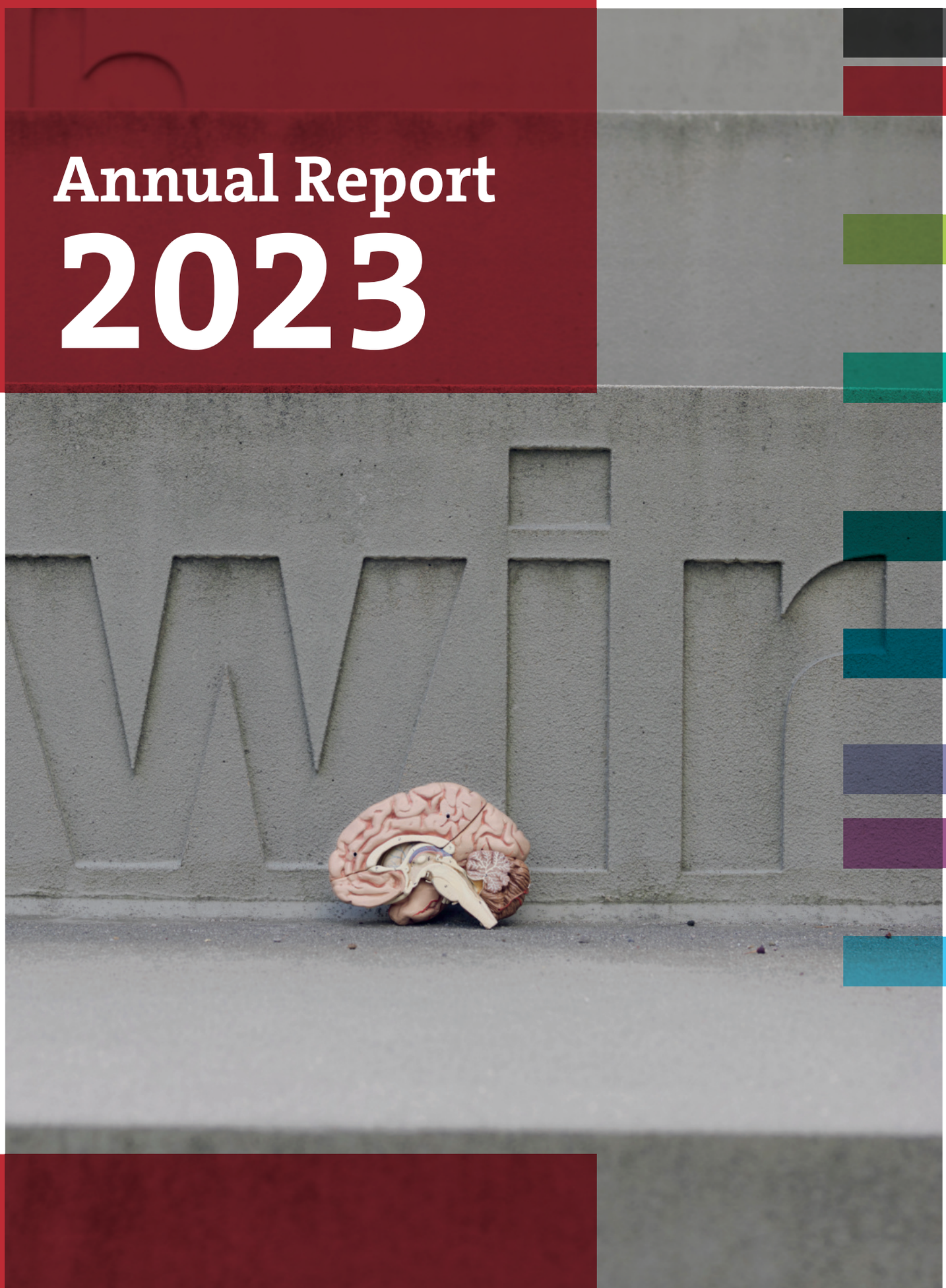
HERTIE CENTER OF NEUROLOGY
TÜBINGEN

Annual Report 2023



HERTIE CENTER OF NEUROLOGY TÜBINGEN

Annual Report 2023

DIRECTORS

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Markus Siegel
Prof. Dr. Dr. Ghazaleh Tabatabai
Prof. Dr. Ulf Ziemann

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Hertie-Institut für klinische Hirnforschung

Universitätsklinikum Tübingen

Content

The Hertie Center of Neurology

The Hertie 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. To emphasize the unity of research and patient care, the center has been renamed in 2023 as "Hertie Center of Neurology". In research, teaching and patient care, the center is dedicated to excellence in the study of the human brain and its disorders.

The Hertie Center of Neurology presently consists of six departments: the Department of Neurology with Neurovascular Medicine (Prof. Dr. Ulf Ziemann), the Department of Neurodegenerative Diseases (Prof. Dr. Thomas Gasser), the Department of Neurology and Epileptology (Prof. Dr. Holger Lerche), the Department of Neurology & Interdisciplinary Neuro-Oncology (Prof. Dr. Dr. Ghazaleh Tabatabai), the Department of Neural Dynamics and Magnetoencephalography (Prof. Dr. Markus Siegel), and the Department of Cellular Neurology (Prof. Dr. Mathias Jucker).

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 distinguishes the Hertie Center of Neurology from other neuroscience institutions. In particular, the close interaction between basic science and patient care 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. Um die Einheit von Forschung und Patientenversorgung zu betonen, wurde das Zentrum im Jahr 2023 in „Hertie-Zentrum für Neurologie" umbenannt.

Das Hertie-Zentrum für Neurologie setzt sich aus zwei eng verbundenen Institutionen zusammen, der Neurologischen Universitätsklinik und dem Hertie-Institut für klinische Hirnforschung (HIH). Die Aufgaben des Zentrums liegen sowohl in der Krankenversorgung durch die Neurologische Universitätsklinik als auch in der wissenschaftlichen Arbeit der im HIH zusammengeschlossenen Forscherinnen und 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 Professorinnen und Professoren mit Leitungsfunktion akademisch und korporationsrechtlich gleichgestellt.

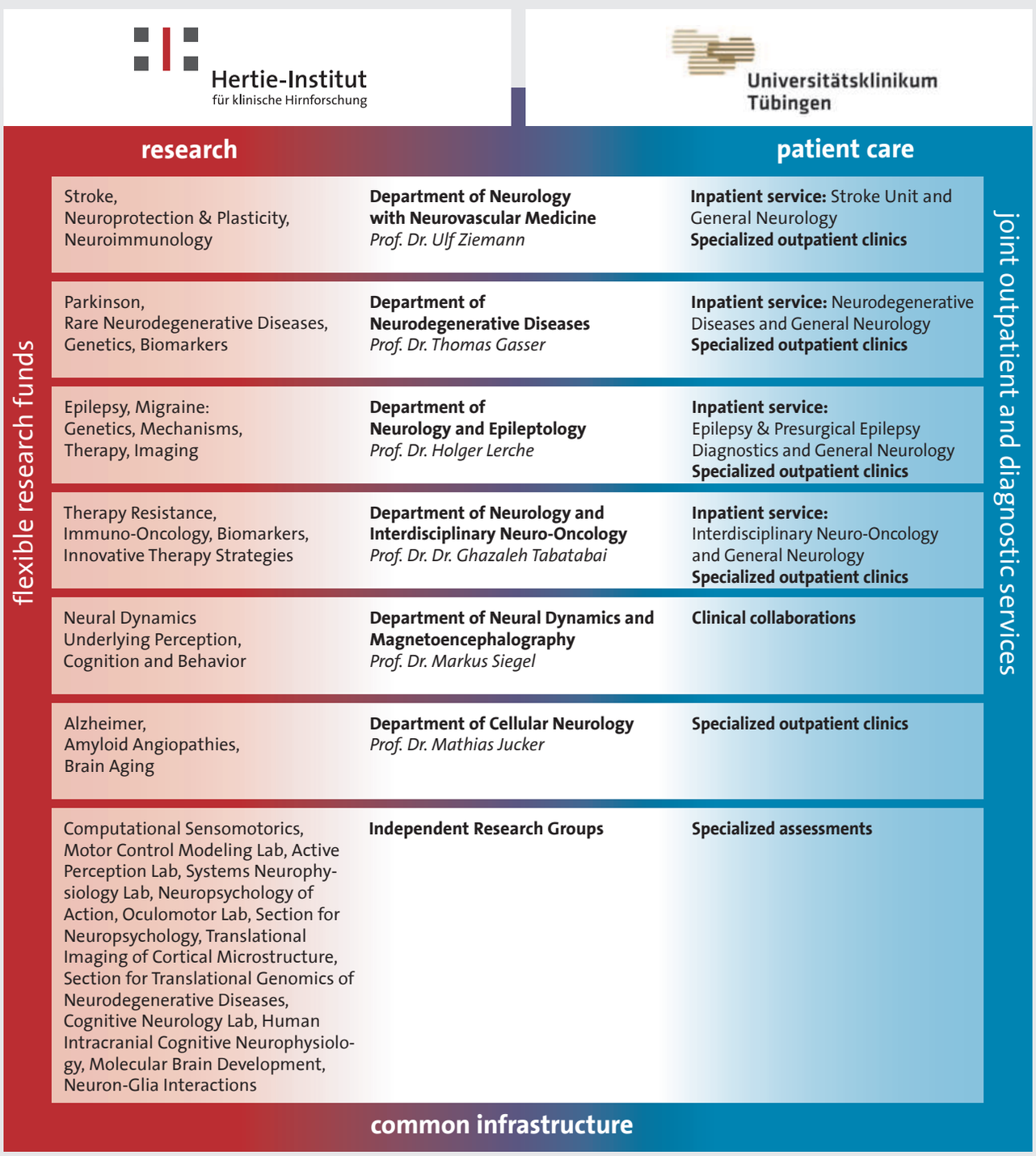
Das Hertie-Zentrum für Neurologie besteht aus sechs Abteilungen: der Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen (Prof. Dr. Ulf Ziemann), der Abteilung Neurologie mit Schwerpunkt neurodegenerative Erkrankungen (Prof. Dr. Thomas Gasser), der Abteilung Neurologie mit Schwerpunkt Epileptologie (Prof. Dr. Holger Lerche), der Abteilung Neurologie mit interdisziplinärem Schwerpunkt Neuroonkologie (Prof. Dr. Dr. Ghazaleh Tabatabai), der Abteilung Neuronale Dynamik und Magnetenzephalographie (Prof. Dr. Markus Siegel) und der Abteilung für Zellbiologie Neurologischer Erkrankungen (Prof. Dr. Mathias Jucker).

Die ersten vier Genannten sind bettenführende Abteilungen in der Neurologischen Universitätsklinik, die anderen beiden sind an der Patientenversorgung im Rahmen von Spezialambulanzen beteiligt. Die klinischen Abteilungen sind für die Versorgung von Patientinnen und Patienten mit der gesamten Breite neurologischer Erkrankungen gemeinsam verantwortlich. Die Einheit der Neurologischen Universitätsklinik in Lehre, Ausbildung und Krankenversorgung wird dabei durch eine gemeinsame Infrastruktur (Patientenaufnahme, Behandlungspfade, Poliklinik, diagnostische Labors, Bettenmanagement, Pflegedienst) gesichert. Die Neurologische Universitätsklinik besteht daher nach innen und außen weiterhin als einheitliche Struktur. In den klinischen Abteilungen werden pro Jahr rund 6.000 Patientinnen und Patienten stationär und mehr als 15.000 Patientinnen und 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.

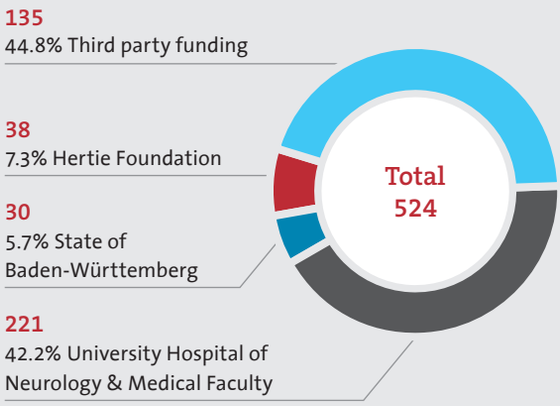
Facts & Figures

THE HERTIE CENTER OF NEUROLOGY



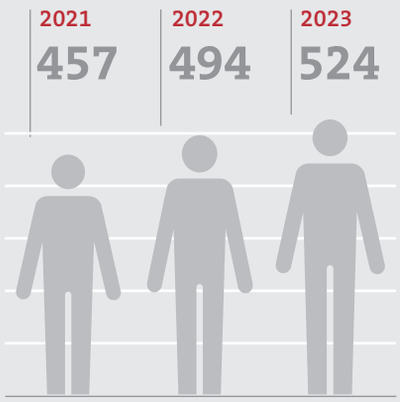
NUMBER OF STAFF IN 2023

Center of Neurology without nursing services (by headcount)



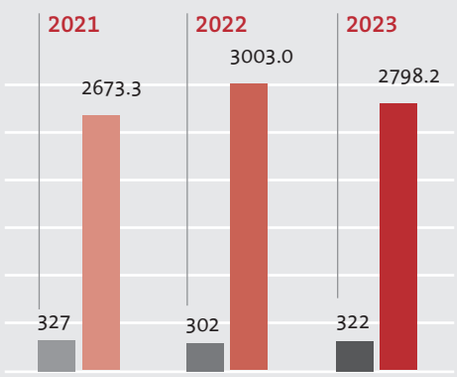
DEVELOPMENT OF STAFF

Center of Neurology (by headcount)



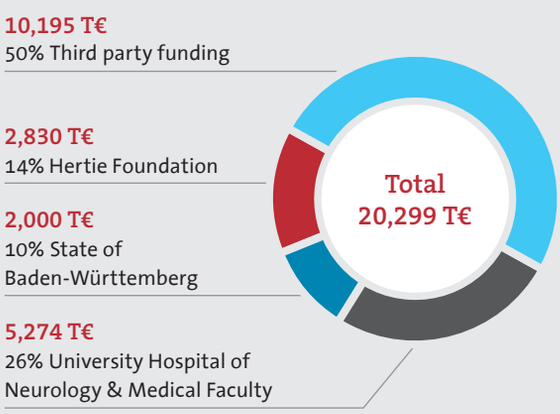
NUMBER OF PUBLICATIONS
IMPACT FACTORS

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



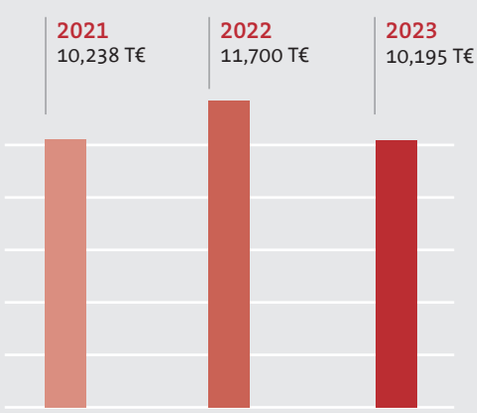
TOTAL FUNDINGS IN 2023

Center of Neurology



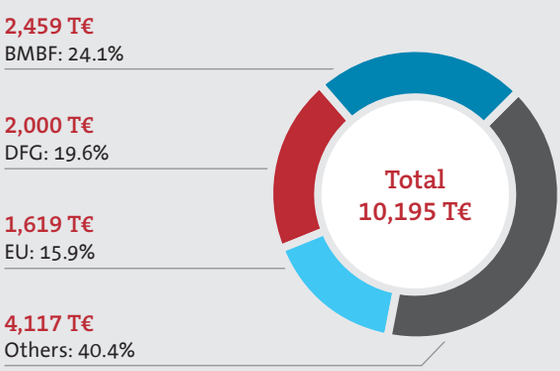
THIRD PARTY FUNDING

Center of Neurology

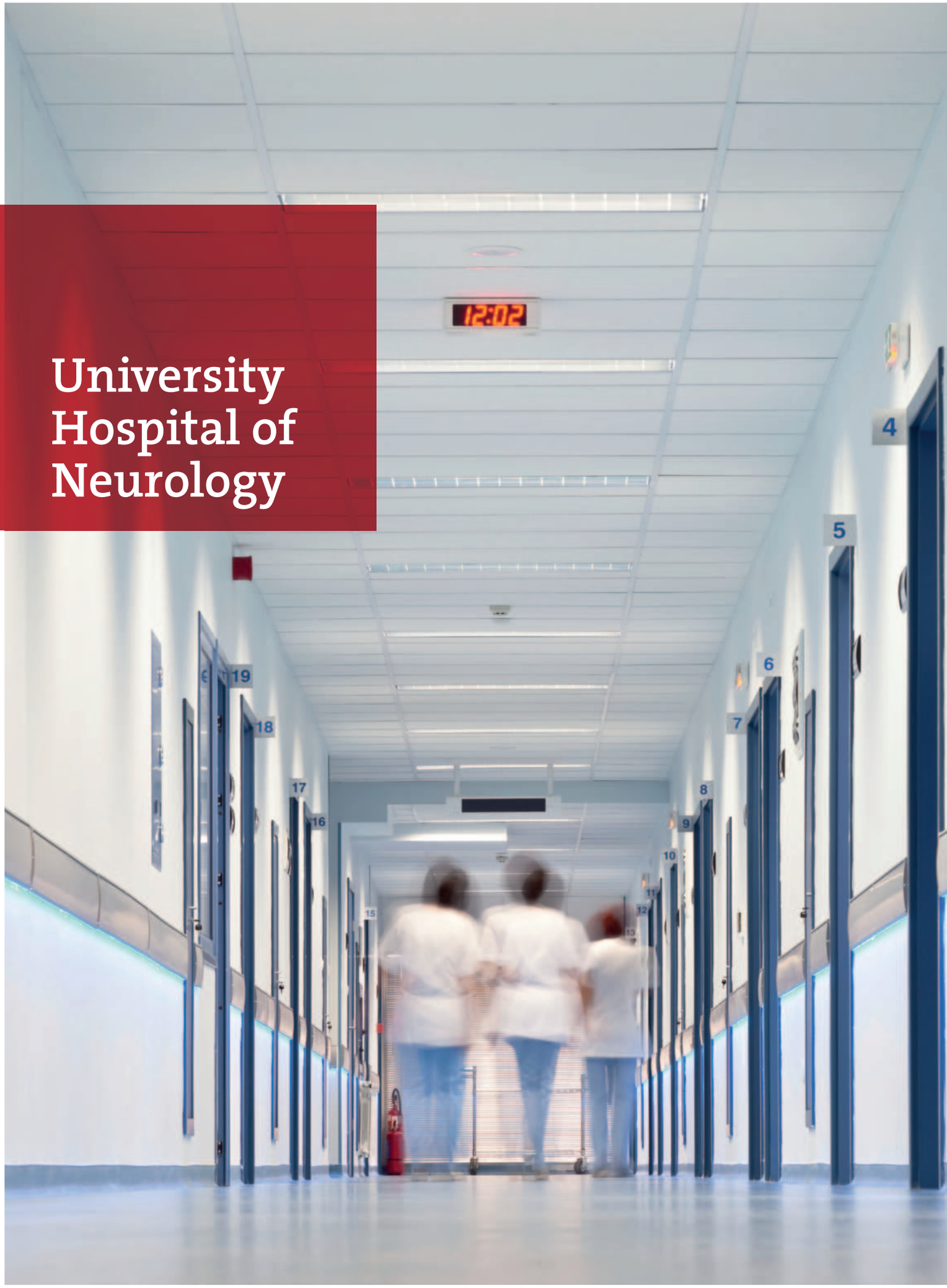


THIRD PARTY FUNDING IN 2023

Center of Neurology



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 on an interdisciplinary internal medicine-neurology intensive care unit 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.

Neurological emergencies are primarily handled in an interdisciplinary emergency unit with a 24/7 coverage by neurologists. In the outpatient unit of the clinic, more than 16,500 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. The day clinic provides care to patients needing complex diagnostic procedures and/or intravenous treatment subject to surveillance.

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 auf einer interdisziplinären internistisch-neurologischen Intensivstation 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.

Neurologische Notfälle werden primär in der interdisziplinären Notaufnahme behandelt, wofür rund um die Uhr neurologische Facharztexpertise zur Verfügung steht. In der neurologischen Poliklinik werden jährlich über 16.500 Patienten (inkl. diagnostischer Prozeduren) ambulant betreut, die meisten davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden. Die Tagesklinik behandelt Patienten mit komplexen diagnostischen Prozeduren und/oder überwachungspflichtigen Infusionstherapien.

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 5,500 patients in 2023.

NUMBER OF ADMISSIONS

5,517

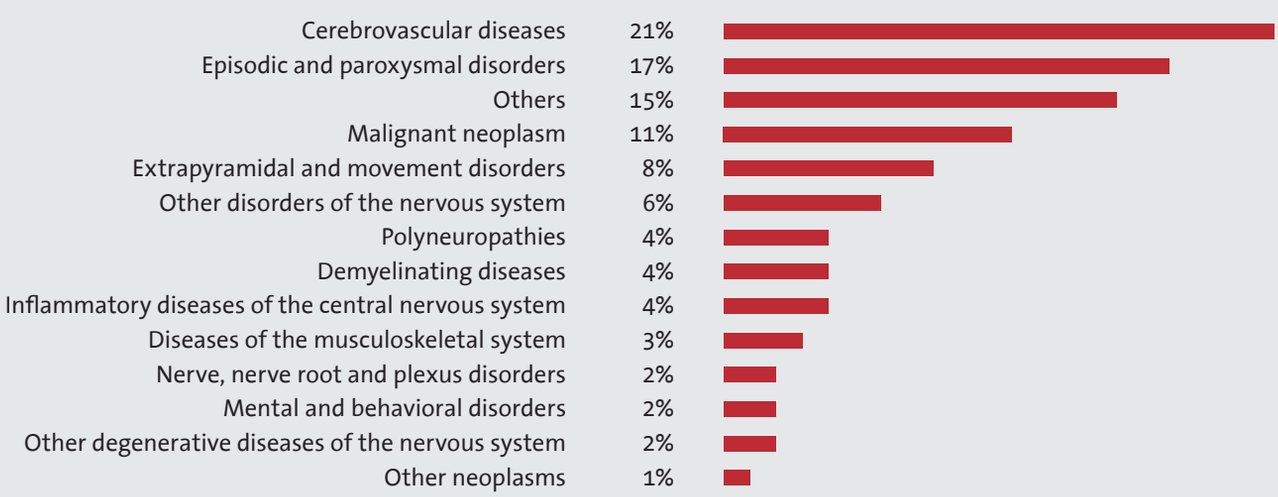
LENGTH OF STAY (IN DAYS)

4.9

CASE-MIX-INDEX 2023

1.069

INPATIENT DIAGNOSIS GROUPS



OUTPATIENT CARE

NUMBER OF CONSULTATIONS
(including diagnostic procedures)

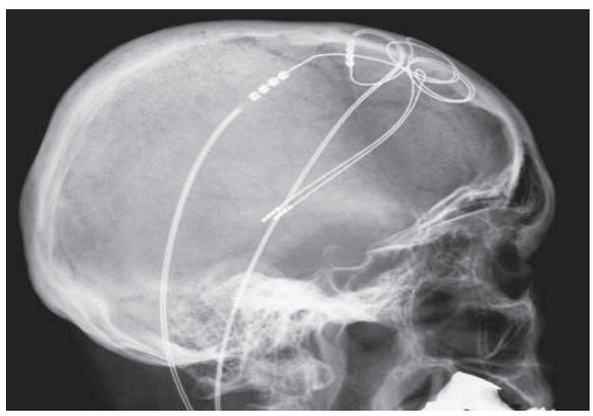
16,550

Outpatient Clinics

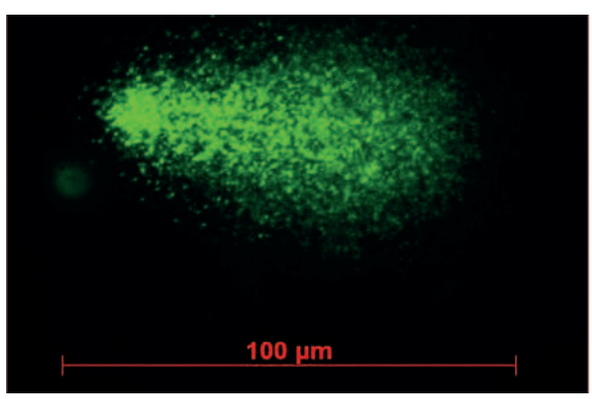
ATAXIA

Driven by the vision to make ataxias treatable, the ataxia clinic provides state-of-the-art tools to establish trial-readiness and run treatment trials across ataxias, both with promising targeted compounds as well as inspiring neurorehabilitative strategies. As targeted mechanistic therapies and outcome markers will be driven by the respective specific underlying molecular etiology, the first goal of our ataxia outpatient clinics is to discover the molecular causes of ataxia, hereby working in close cooperation with the Department of Neuroradiology (MRT, MR-Spectroscopy) and the Institute of Medical Genetics. To address the increasing number of genes causing ataxia we use latest next-generation techniques (e.g. whole exome-sequencing and whole genome sequencing) on a routine basis with the highest diagnostic standards. On a research basis, this is complemented by transcriptomics and even more advanced novel sequencing techniques (long-range WGS, optical genome mapping) 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 thus follow 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., complemented by innovative novel CSF-based assays, allowing e.g. to diagnostically distinguish Multiple Systems Atrophy of Cerebellar Type (MSA-C) from other degenerative ataxias based on an in vivo a-synuclein seeding assay. Both our digital-motor as well as fluid biomarkers are now adopted in the protocols of the first-in-human antisense oligonucleotide (ASO) trials, that we are running for spinocerebellar ataxias. In a highly innovative individualized precision medicine approach, we are even developing individualized ASOs specifically tailored to individual patients' mutations (n-of-1 ASO platform), making the Hertie-Institute for Clinical Brain Research the second institute worldwide (following Harvard Boston Children's Hospital) pioneering this disruptive therapy approach for rare, but severe brain diseases.



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.

Our local and national trial-readiness research lines are embedded in the worldwide Ataxia Global Initiative (AGI; https://ataxia-global-initiative.net), co-led by our center (Prof Synofzik), which is genuinely designed to facilitate all clinical, research and regulatory steps towards ataxia trial-readiness. As lead PI in multiple national and international consortia, we participate in natural history and biomarkers studies of (i) autosomal-dominant spinocerebellar ataxias (SCA) (e.g. world-wide EUROSCA and ESMI consortia), presymptomatic at-risk subjects (RISCA), (ii) sporadic late-onset ataxias (SPORTAX), and (iii) autosomal-recessive cerebellar ataxias (ARCAs) . As coordinating center for several ARCA networks, Synofzik leads the worldwide ARCA registry and is scientific coordinator of the EU-funded consortium PROSPAX (An integrated multimodal progression chart in spastic ataxias; together with Dr. Rebecca Schüle) and the RFC1 Natural history study, and now also for the SCA27B Natural History Study, with SCA27B representing the only very recently, but likely most frequent genetic ataxia world-wide. 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. A. Traschütz and Dr. Z. Fleszar and is supervised by Prof. Dr. M. Synofzik and Prof. Dr. L. Schöls.

CANCER THERAPY-ASSOCIATED NEUROLOGICAL SYNDROMES

The incidence of treatment-associated neurological symptoms in cancer patients is constantly increasing. This is mainly due to the fact that modern cancer therapies target specific molecular pathways that are also present in different compartments of the nervous system. Furthermore, immunotherapies including immune checkpoint inhibitors, cancer vaccines, immune cytokines, bispecific antibodies et c. might provoke neurological adverse events. Furthermore, chimeric antigen receptor (CAR) T-cell therapies have led to success in advanced leukemias and lymphomas and are now investigated in clinical trials in solid tumors. CAR T cell therapy is associated with common and severe neurological side effects as cytokine releasing syndrome (CRS) and the immune effector cell-associated neurotoxicity syndrome (ICANS) requiring neurooncological expertise.

Our outpatient clinic “Cancer therapy-associated neurological syndromes” is dedicated to this topic. We provide (i) fast and thorough neurological/neuro-oncological evaluation of complex neurological and oncological symptoms and (ii) treatment strategies as well as (iii) systematic follow up.

CNS METASTASES AND MENINGEOSIS NEOPLASTICA

Deep According to current estimations, about 20-25% of all cancer patients will eventually suffer from invasion of their tumor into the central nervous system, either by parenchymal CNS metastases or by leptomeningeal disease. The neurological symptom profile of these patients is usually very complex including several differential diagnoses. In this outpatient clinic, we provide a comprehensive patient-centered care including a thorough neurological and oncological workup. All referred patients undergo a systematic process with intensive multidisciplinary collaboration including tumorboard discussion, therapy recommendation, follow up and referral to clinical trials. Prof. Dr. Tabatabai is the Principal Investigator of a national phase I trial in Meningeosis neoplastica evaluating intrathecal immunotherapy (IT-PD1/NOA26).m our own outpatient clinics for movement disorders.

Outpatient Clinics

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.brainstimnet.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 (Weiss et al., 2021; Ann Neurol). Moreover, based on our own basic research in the identification of novel targets for DBS in Parkinson's disease, two independent randomized controlled trials for unmet axial symptoms like "freezing of gait" and "imbalance and falls" in Parkinson's disease were initiated. Here, the first study on high frequency stimulation of the substantia nigra pars reticulata (SNr) as an add-on to the conventional subthalamic nucleus stimulation was successfully accomplished and 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). This study did not reach significance, but nevertheless showed that about half of the individual patients benefit from STN+SNr. This finding will be followed in future studies.

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 three days per week in the outpatient clinic for DBS. TelemedicineTelemedicine counseling is regularly and oftentimes used in order to facilitate long-term care of DBS patients. In particular, the Tübingen site was the first centre to apply the remote DBS programming platform (Neurosphere, Abbott) in 10/2021 in Europe. and included most patients worldwide in the first randomized controlled trial on remote DBS, demonstrating that televisits facilitate patient access to the expert Weiß. neurologist and thereby lead to earlier patient improvement compared to in clinic care alone (Gharabaghi, ..., Weiss*, Luca*; submitted, shared last authors).

In addition to DBS, continuous dopaminergic replacement therapy is increasingly applied, and this includes the established intestinal preparations with PEG-J tube (LCIG, LECIG). Since 12/2023 the first subcutaneous levodopa replacement therapy was released as foslevodopa/carbidopa and first patients have already been initiated on this novel therapy In 01/2024.

Patients with device-assisted therapies are seen by a specialized PD nurse (G. König, F. Chmell), and expert neurologists, namely Dr. I. Cebi, Dr. P. Klocke, Dr. M. Löffler, and Prof. Dr. D. Weiß.

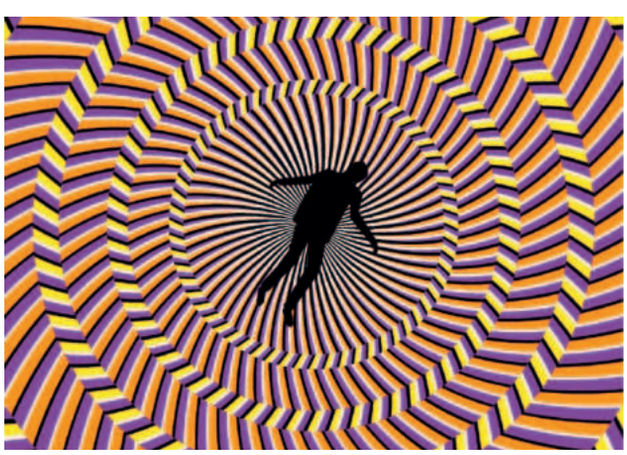
DIZZINESS SERVICE

The dizziness outpatient service (established in 2002 by the Department of Cognitive Neurology) is now operated by the "Tübinger Zentrum für Schwindel- und Gleichgewichtserkrankungen (TüSG)". This "dizziness center", founded in 2018, is a collaboration between the Center for Neurology and the University of Tübingen´s Department of Otolaryngology, Head and Neck Surgery . It reflects a logical extension of a symptom-oriented clinical specialization 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 or a disturbance of balance 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 one aim of the TüSG is to unify and harmonize the diagnostic evaluation, treatment and follow-up for patients suffering from acute or chronic dizziness, balance disorders or oculomotor disturbances in both clinics. The dizziness outpatient clinic focuses on patients with chronic dizziness or balance disorders. Most patients are 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, supplemented by a survey of possible psychopathological stress. 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 can be revealed that relate to the vestibular system and orientation and, in many cases, do not have a morphologic basis that can be detected with brain imaging techniques. In some cases with such functional alterations, additional diagnostics with regard to certain underlying diseases is necessary, which is partly performed in other outpatient clinics or as an inpatient at the Center for Neurology.

Revealing specific forms of dizziness leads to the application of specific therapeutic measures such as exercises customized to treat benign paroxysmal positional vertigo. Many 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. For this group of patients, who are often underserved in standard care, the emphasis is on detailed education about the possible mechanisms of disease and supportive psychotherapy.

The dizziness service is available for outpatients twice a week. It is conducted by a physician in residency in Neurology and a physician in residency in ENT. It is supervised by Dr. J. Pomper (Neurology) and Dr. S. Wolpert (ENT). Physicians in residency rotate every 6-12 months, so performing the dizziness outpatient clinic is a rotation in residency for many physicians in both ENT and Neurology.



Outpatient Clinics

DYSTONIA AND BOTULINUM TOXIN TREATMENT

The outpatient clinic offers a comprehensive diagnostic work-up and the full range of treatment options for patients with different forms of dystonia, spasticity, and other movement disorders. In cooperation with the headache clinic (Prof. 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.

In cooperation with the dentist (Dr v.d.Gracht), the headache clinic (Prof. Dr. S. Schuh-Hofer) and the clinic for otolaryngology (Prof. Dr. H. Löwenheim), treatment with botulinum toxin injections for patient with craniomandibular dysfunction, chronic migraine and spasmodic dysphonia/pharyngeal dystonia is provided.

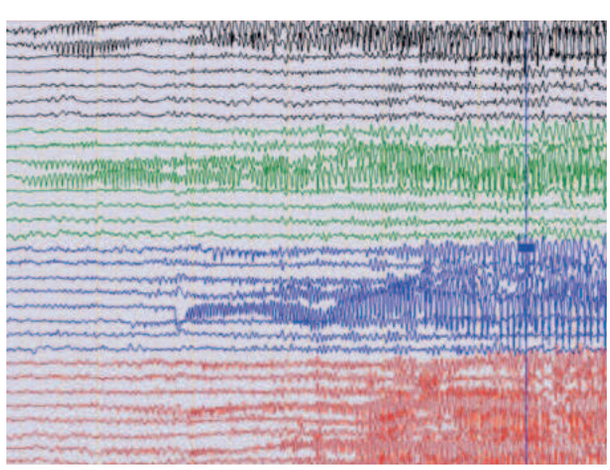
Approximately 550 to 600 patients are treated regularly with botulinum toxin (BoNT) injections in intervals of 3 to 6 months. Of those nearly 50 percent are treated for dystonia and tremor (including craniomandibular dysfunction, blepharospasm and Meige-Syndrom as well as cervical, segmental, multifocal, 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 or physical conditions 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 or also realized with short time anesthesia. Since two years 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).

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 ion channel disorders, narcolepsy and paroxysmal movement disorders.



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

The epilepsy outpatient clinic (supervised by Prof. Dr. H. Lerche, Dr. S. Lauxmann, Dr. M. Schreiber) is run by our team composed of Dr. F. Rosa, Dr. R. Helfrich, Dr. J. Kegele, Dr. P. Müller, Dr. R. Lauerer-Braun, Dr. S. Liebe and 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 Dr. P. Martin, Dr. N. Winter, Dr. S. Lauxmann and Dr. J. Kegele, 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 anti-epileptic medication, deep brain stimulation of the thalamus, thermocoagulations and vagal nerve stimulation are provided in close cooperation with the Department of Neurosurgery (Dr. S. Ethofer, Dr. M. Alber, Prof. Dr. J. Honegger, Dr. G. Naros). Altogether we treat about 2,000 adult epilepsy patients per year.

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).

While considered to be out of reach for long, targeted molecular treatment trials are now on the horizon or even starting for literally all major genetic FTDs. Our FTD outpatient clinic is one of the national and European forerunners on this stringent path towards trial-readiness. Our experts in the FTD clinic are specialists on the manifold differential diagnoses and overlap diseases of FTD. These include common neurodegenerative diseases like Progressive Supranuclear Gaze Palsy (PSP) or Alzheimer's disease (AD), phenotypic spectra complicated by additional Parkinsonian syndromes or Amyotrophic Lateral Sclerosis (ALS), and 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 and blood fluid biomarkers, including discovery of novel FTD fluid biomarkers on a research level. Moreover, all our FTD patients are offered latest next-generation genomics diagnostics (whole exome, whole genome sequencing) to unravel the underlying molecular cause of the disease, which is key for stratification into molecular precision medicine treatment trials.

We are the leading FTD recruitment center of the German Center for Neurodegenerative Diseases (DZNE), which has allowed toestablish a large nationwide cohort of patients with FTD-spectrum diseases, comprehensively characterized on a clinical, neuropsychological, imaging and biomarker level. Moreover, we are the German lead center in the international multi-center GENFI consortium, aggregating and characterizing symptomatic and asymptomatic carriers with mutations in FTD genes in a longitudinal fashion, on a stringent path towards trial-readiness. This ambitious endeavor has already allowed to unravel the neuropsychological, imaging and molecular changes in FTD even before its clinical onset, thus offering a novel window for therapy These efforts are now heralded by the EU-funded consortium "GENFI-prox", which establishes 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. In fact, we are now already offering several first-in-human targeted molecular therapy trials for genetic FTD, targeting the earliest stages of this disease. The clinic is run by Dr. D. Mengel and Dr. L. Beichert and supervised by Prof Dr. M. Synofzik.

Outpatient Clinics

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. 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 Prof. Dr. S. Schuh-Hofer, together with a team of three colleagues from the Neurological Department (Dr. V. Ruschil, Dr. S. Straub and Dr. S. Thewes). Patients should be referred preferably by neurologists or pain specialists.

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.

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 genome sequencing as first line diagnostics for our patients. This helps us to fix the cause of disease in more than 2/3 of adult patients in our adult leukodystrophy cohort. A molecular genetic diagnosis becomes more and more important not only for the counselling of families but also in respect of therapy as for an increasing number of leukodystrophies treatment by enzyme replacement, substrate inhibition, stem cell transplantation or gene therapy becomes available. In cooperation with the department of haematology in Tübingen we offer haematopoietic stem cell transplantation in MLD, ALD and CSF1R-related leukodystrophy. The indication for stem cell transplantation is discussed in international expert panels of the European Reference Network for Rare Neurological Diseases (ERN-RND) in the MLD initiative. In Tübingen we coordinate the national guideline group for adult leukodystrophies and are also involved in the international guideline development in cooperation with the European Academy of Neurology (EAN).

In cooperation with the Department of Neuropediatrics in the Children's Hospital we assess the natural course of disease and develop biomarkers indicating disease activity and target engagement e.g. in metachromatic leukodystrophy, cerebrotendinosis xanthomatosa and CSF1R-related leukodystrophy as essential prerequisites for therapeutic trials. In CSF1R-related leukodystrophy we are part of an international natural history and biomarker study that serves as control arm and run-in study for an interventional trial that aims to compensate the defective CSF1R signalling by stimulating the TREM2 pathway. collaborate. In collaboration with the Department of Neuroradiology we use high-end MRI techniques and MR spectroscopy to disclose characteristic MRI patters and progression markers. To support radiologists and neurologists in every day practice in the identification of patients with hereditary leukodystrophies, we develop machine learning algorithms that will be trained to differentiate genetic white matter diseases from leukoencephalopathies of other causes in the LeukoExpert network funded by the German Ministry of Health (BMG). Patients in the leukodystrophy outpatient clinic are seen by Dr. H. Hengel, Dr. N. Weissert and Prof. Dr. L. Schöls.

MENINGIOMA

Meningiomas comprise of 37% of all CNS tumors. Even though they are predominantly categorized as CNS WHO grade 1, they can also cause neurological symptoms and/or recur depending on their CNS WHO grade and extent of resection. One of the main challenges is the localization in the skull base, where intracranial nerves, brain stem and medulla oblongata are at risk to be compressed by the tumor causing severe neurological deficits. The main corner stones of therapeutic strategies are surgery and radiotherapy. In recent years, several molecular features of meningiomas have been investigated that could also be exploited for targeted therapeutic strategies. In this outpatient clinic, we realize an interdisciplinary patient-centered care, new approaches including systemic therapy and biomarker-based therapy. Together with our colleagues from the Departments of Radiation-Oncology, Neurosurgery and Nuclear Medicine, we provide comprehensive clinical consulting in every stage of the disease.

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. This is complemented by highly innovative, novel mechanistic first-in-man treatment trials and compassionate use applications of latest antisense oligonucleotide (ASO) therapies, e.g. for C9orf72-associated ALS and SOD1-associated ALS.

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 Dr. L. Beichert and supervised by Prof. Dr. M. Synofzik.

Outpatient Clinics

MYOPATHIES AND MYASTHENIA GRAVIS

For the diagnosis of neuromuscular diseases, the correct collection of medical history, including family history, is important. In addition, the patients are examined neurologically and electrophysiologically. Further we added muscle imaging by ultrasound to the diagnostic algorithm, which is an extraordinary specialty in our department. Many patients from all over Germany and even Europe come to our unit to receive this diagnostic tool. In the clinic the indication to further necessary investigations such as MRI, nerve or muscle biopsy as well as genetics 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 Prof. Dr. A. Grimm, Dr. P. Martin, and Dr. N. Winter. We have an intensive cooperation with the clinic of neuropediatric disorders in Tübingen, 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). We take part In several IITs concerning new therapies concerning myasthenia gravis.

MZEB

The MZEB (Center for multiple handicapped adults) in Tübingen has recently been established to build a continuum into adulthood for patients from the Social Pediatric Center (SPZ). It cares for patients with multiple severe handicaps including cognitive dysfunction and neurological deficits or combinations of deafness and blindness. To this end the MZEB provides a multi-disciplinary team of neurologists, ophthalmologists and otologists, physiotherapists, speech therapists, gastrostomy and wound specialists and social workers. The MZEB offers coordination of disease management as well as advanced therapies like intrathecal pumps of antispastic drugs and botulinum toxin injections. The MZEB is coordinated by K. Dillmann-Jehn and headed by Dr. L. Zeltner and Prof. Dr. L. Schöls.

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 2023, the outpatient clinic was run by Dr. J. Dünschede (resident), Dr. C. Ruschil (resident), M. Tieck (resident), Dr. P. Schwarz (resident), and supervised by PD Dr. M. Kowarik and PD Dr. A. Giede-Jeppe (attending physicians, with special expertise in MS and other immune-mediated neurological disorders), and Prof. Dr. U. Ziemann (director).

NEURO-ONCOLOGY

The clinical management of neuro-oncological patients requires an interdisciplinary approach for offering guideline-based therapies and clinical trials. This task is organized and coordinated in the Department of Neurology & Neuro-Oncology with clinical partners.

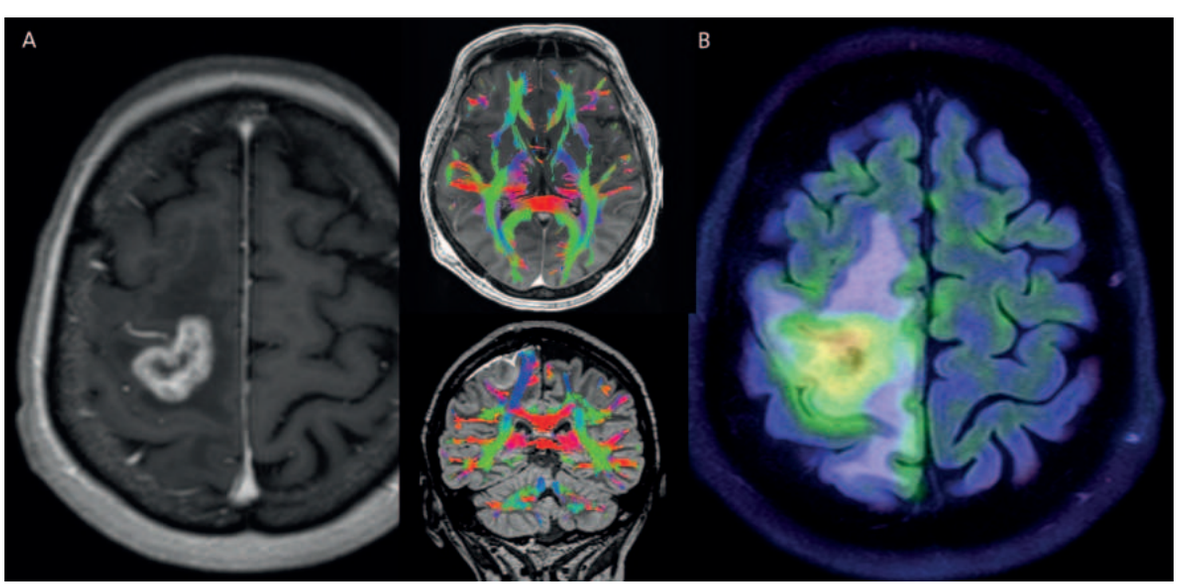
The Department is part of the Center of Neuro-Oncology under the roof of the Comprehensive Cancer Center Tübingen-Stuttgart and very closely cooperates with the Departments of Neurosurgery, Radiation Oncology, Radiology & Neuroradiology & Nuclear Medicine, Pathology & Neuropathology. As Prof. Dr. Dr. G. Tabatabai is also the elected Chair of the Center of Neuro-Oncology, strategies of the CCC can be easily and readily implemented into the strategical plan of the Department of Neurology & Neuro-Oncology. The center has the certificate of the German Cancer Society (DKG) and is the largest Neuro-Oncology center among the DKG-certified centers.

Tumors of the nervous system include primary and metastatic tumors. Therefore, the Neuro Oncology Outpatient clinic provides several specialized consultations. Furthermore, oncologic tumor-specific therapy especially immunotherapy and biomarker-based therapies can provoke side effects with neurological symptoms and are diagnosed and treated in our center.

The main objectives of the Neuro-Oncology outpatient clinics are:

- To offer an innovative landscape of clinical trials
- To design and conduct investigator-initiating trials
- To act as a strong partner in in national and international cooperative trial groups (e.g. NOA, EORTC, RTOG)
- To provide patient-centered clinical care for patients with neurooncology tumors at each stage of their disease
- To provide patient-centered 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. Dr. G. Tabatabai, PD Dr. M. Renovanz (deputy director), P. Bombach (board-certified neurologist), PD Dr. J. Rieger (board-certified neurologist), PD Dr. M. Skardelly (board-certified neurosurgeon), L. Grosse, and D. Rieger (neurology residents).

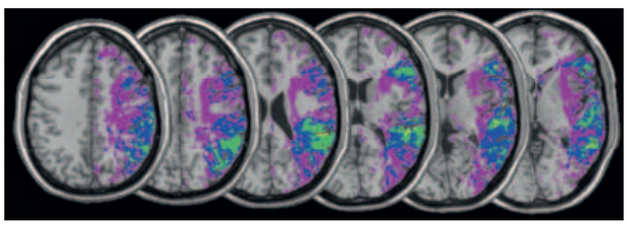


Multimodal imaging for glioma patients: A| contrast enhanced MRI with preoperative tractography for planning the surgical approach in an eloquently located glioma (right precentral gyrus), B| positron-emission-tomography (PET) with the amino-acid tracer 18F-Fluoro-Ethyl-Tyrosine (18F-FET) allows for optimal therapy monitoring.

Outpatient Clinics

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 is capable of planning appropriate actions to perform given tasks, whether speech is impaired, which kinds of attention-related functions may have been damaged and need to be treated, or whether a patient exhibits an abnormal degree of forgetfulness. These and other examinations are carried out in the Neuropsychology Outpatient Clinic of the Neuropsychology Section (head: Prof. Dr. Dr. H.-O. Karnath).



Inpatients 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.

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 PD Dr. A. Mengel, Prof. Dr. S. Poli and PD Dr. K. Feil.

PARKINSON'S DISEASE

Outpatient Clinic (Head Brockmann)
The Center of Neurology at the University of Tübingen runs one of the largest outpatient clinics for patients with Parkinson syndromes in Southern Germany. More than 100 patients are seen every month. A major focus is the early differential diagnosis of different Parkinson syndromes as well as individual treatment adaption based on longitudinal symptom development. Genetic testing is offered broadly to predict clinical progression. The outpatient clinic is directly linked to the research group of Prof. Dr. K. Brockmann lab to foster translational research and patient care.

The clinicopathological heterogeneity in Parkinson's disease (PD) and the limitation of current clinical diagnostic criteria, especially at disease onset, highlights the need for pathology-specific biomarkers. Misfolded alpha-synuclein (alpha-Syn) as pathological hallmark is a lead candidate based on its crucial role in disease pathophysiology. With disease-modifying compounds such as monoclonal antibodies or active vaccination targeting alpha-Syn currently tested in clinical trials, patient stratification according to alpha-Syn-specific enrichment strategies is a much-needed prerequisite. As there are (until now) no reliable imaging markers to assess the cerebral load of alpha-Syn, research has focused on biofluids. Recently, highly sensitive seed amplification assays (SAA) have been developed and also successfully implemented in our lab. These assays exploit the seeding capacities of prion and prion-like proteins using an amplification strategy to reveal minute amounts of disease-specific protein aggregates in CSF. SAAs show a high sensitivity (88-96%) and specificity (83-98%) for sporadic PD and dementia with Lewy bodies (DLB) compared to healthy individuals.

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 milestones 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.

Specifically, we are one of three German centers that participate in the international Parkinson Progression Marker Initiative (PPMI), a 15-year follow-up of de novo Parkinson patients to better understand aetiology and disease progression which is 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. In this context, we focus on patient stratification according to genetic architecture and the underlying pathologic processes, reflected by profiles in patient biomaterials. This allows to directly translate research findings into the clinics and to introduce patients to pathway-specific therapies. Importantly, we recently initiated a European-wide multi center, randomized, double-blind, placebo-controlled proof-of-concept clinical trial to investigate the alpha-synuclein antibody Prasinezumab (provided pro-bono by F. Hoffmann-La Roche Ltd) for its ability to prevent cognitive decline in patients carrying a GBA mutation. We further take part in world-wide first clinical trials aiming at specific Parkinson-associated pathways and disease modification: MitoPD, BP39528_Pasadena by Roche,

Outpatient Clinics

Outpatient clinic for deep brain stimulation and continuous 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 Neurodegenerative 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 guarantees 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.

Neuro-geriatric patients receive physiotherapy for mobility training.

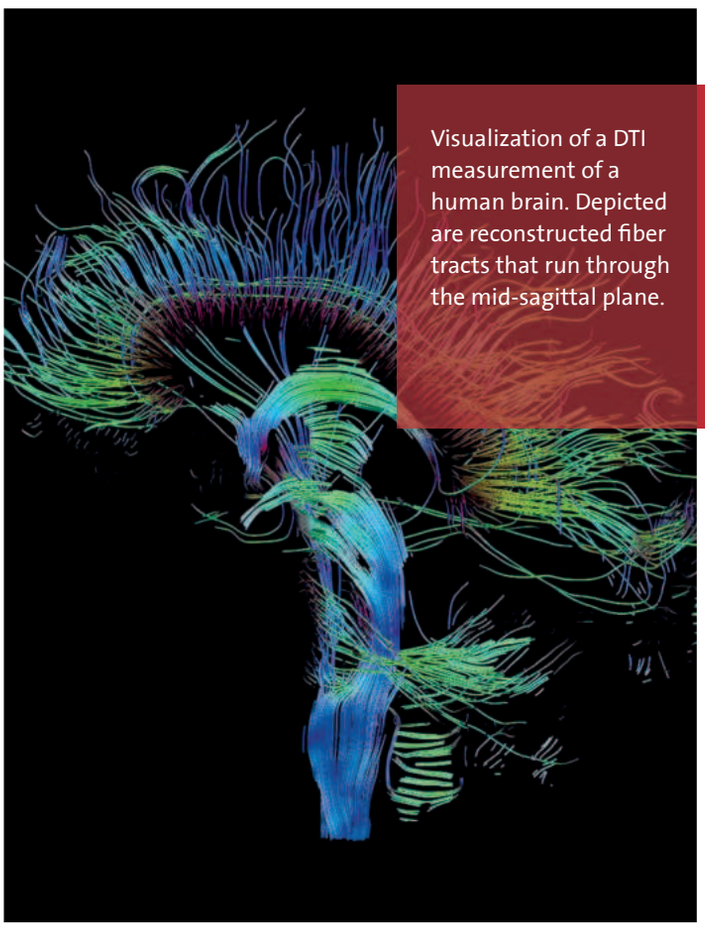
The outpatient unit cooperates with the German Center for Neurodegenerative Diseases (DZNE) under a common roof, called the Integrated Care and Research Center (ICRU). Appointments are scheduled daily in the outpatient clinic of the Center of Neurology.

PERSONALIZED NEURO-ONCOLOGY

Many tumors of the nervous system remain a therapeutic challenge with a limited availability of established therapies and clinical trial options. Biomarker-based targeted therapies may offer additional therapeutic options and are currently applied in innovative clinical trials. Still, a substantial proporion of patients cannot be enrolled in these clinical trials due to restrictive inclusion and exclusion criteria. Within the Center for Personalized Medicine, we have established a "real-world" precision medicine workflow from comprehensive molecularprofiling to biomarker-based treatments in adult neurooncology patients. This approach expands therapeutic options and results in clinical benefits for a subset of patients (Renovanz et al., Neurooncol Adv 2023). We provide this comprehensive diagnostic and treatment strategy for patients in later disease stages and with very rare neurooncological tumor types lacking guideline-based recommendations or clinical trials options. Patients referred to our outpatient for evaluation of biomarked-based therapies undergo a standardized, quality-controlled process including an extended molecular diagnostic and subsequently evaluation in the Molecular Tumor Board (MTB) regarding biomarker-based therapy options. The indication regarding extended molecular testing and therapy options are systematically evaluated and considered in the neuro oncological tumor board. Furthermore, we follow the clinical course and outcome in an observational study MTB@ZPM (NCT03503149) and intensively cooperate within the ZPM and the Comprehensive Cancer Center.

PRIMARY BRAIN TUMORS

The current WHO classification defines morphological and molecular diagnostic crtieria for primary tumors of the CNS. Currently, > 120 different entities have been defined. We treat the full spectrum of these diagnoses by our patient-centered and interdisciplinary approach.
After preoperative evaluation patients will be admitted to the wards in the Departments of Neurology or Neurosurgery depending on the treatment and will be supervised by specific members of the Neuro-Oncology team in both departments. The clinical examination of the patients includes systematic neurological and neuropsychological examination, psychosocial screening and clinical evaluation according to the Karnofsky Performance Scale, Eastern Cooperative Oncology Group (ECOG) score and Neurologic Assessment in Neuro-Oncology (NANO) score. Our treatment strategies include all guideline-based treatments and innovative clinical trials with a particular focus on early phase clinical trials (phase 1 and 2) investigating immunotherapy strategies and molecular therapies. All treatment recommendations are discussed in our interdisciplinary tumor board of the Center of Neuro-Oncology and (if applicable) also in the Molecular Tumor Board. Members of our team are active in national (DGN) and international (e.g. EANO) Guideline Committees



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

POLYNEUROPATHIES AND NERVE TRAUMA

Up to 1000 patients/year with polyneuropathy, including immune-mediated neuropathies, hereditary neuropathies or acquired neuropathies are diagnosed and treated by our team of Dr. N. Winter, Dr. J. Stahl, Dr. C. Kronlage, Dr. K. Kneer, Dr. S. Willikens, Dr. M. Kramer, Dr. MS Breu,. Dr. S. Straub and Prof. Dr. A. Grimm. Further we use nerve imaging by ultrasound to the diagnostic algorithm, which is an extraordinary specialty in our department. Many patients from all over Germany and even Europe come to our unit to receive this diagnostic tool. 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. We take part in several IITs concerning new treatment options for hereditary and immune-mediated neuropathies as CMT1 and CIDP. Together with our study team (Ana Onyschenko, Christian Hengsbach, Prof. S. Schuh-Hofer and Dr. MS Breu) we are taking part in more than five multicentric studies concerning FcRn-modulation, complement inhibition and others.

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 several colleagues (Prof. Dr. A. Grimm, Dr. J. Stahl, Dr. K. Kneer, Dr. S. Straub, PA J. Wittlinger and Dr. N. Winter) and the team of the EMG.

Outpatient Clinics

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 neuroradiologists, geneticists and specialists in psychosomatic medicine. If substantial indicators for a rare disease are evident, recommendations of complementary investigations, an outpatient visit or admission to the ward are prepared including specific neurological assessment, genetic diagnostics or neuroimaging. The clinic is run by Dr. V. Wilke and Prof. Dr. L. Schöls.

SPASTIC PARAPLEGIAS

To achieve optimum diagnostics and treatment of Hereditary Spastic Paraplegias (HSP) we established a comprehensive differential diagnostic workup, counselling and management for patients and families with HSP. We employed whole genome sequencing as first line diagnostic tool to meet the challenges presented by the extreme genetic heterogeneity of HSP. To provide families still unsolved by this with a diagnosis and increase our understanding of the underlying genetic etiology and biology of HSPs we partner with the European Horizon2020 project Solve-RD. Here we apply multi-omics approaches combined with advanced bioinformatics to ‘solve the unsolved’. Understanding the underlying genetic and molecular mechanisms and biology of HSPs is a prerequisite for the development of causal therapies slowing down the course of disease. To foster research into the pathogenesis of HSP and the development of biomarkers that Indicate disease activity or can serve to monitor target engagement of new therapies we perform highly standardized, longitudinal biobanking of biofluids and patients’ cells.

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.

Therapeutically, we offer a wide range of symptomatic treatments including intrathecal application of Baclofen, local injections of Botulinum toxin and functional electrical stimulation. To harmonize standards of care for HSP across European member states, we are actively involved in the European Reference Network for Rare Neurological Diseases (disease group coordination for HSPs and ataxia).

With recent advances in genetics, gene therapy and pathway-based precision therapies, translational research is becoming increasingly important. The BMBF-funded TreatHSP network (treathsp.net), coordinated by Prof. Dr. Schüle, together with the German Center for Neurodegenerative Diseases (DZNE) coordinates and advances translational research in HSPs, performs natural history studies, develops trial outcome parameters, identifies novel therapeutic targets and implements precision therapies in HSP. In this respect, the central infrastructure maintained by TreatHSP – consisting of an international clinical registry für HSPs (hsp-registry.net), a central biobank as well as a shared OMICS repository – plays an important role in enabling sustainable research into this rare disease. To enable disease modifying interventions as early as possible we established the preSPG4 study with a worldwide unique cohort of pre-symptomatic carriers of a SPG4 mutation. Deep phenotyping including digital gait recording, sophisticated neuroimaging and biomarker analyses helped to identify early markers of disease activity that may be used to monitor effects of interventions before the manifestation of gait impairment. The HSP clinic is run by Dr. M. Wayand, Dr. C. Kessler and Dr. M. Schlotterbek and is supervised by 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 pharmacological treatment and ergotherapy, deep brain stimulation is considered in resistant tremor. Further, we support sensor-based solutions for tremor. As such, we collaborate in the development of instrumented tremor assessments with Dr. Daniel Häufle, with the longstanding aim to obtain i) objective readouts on tremor severity in daily life, ii) objective readouts for clinical trials, and iii) sensor data to facilitate the development of “intelligent” neuroprosthesis in cooperation with Max Planck Institute Stuttgart. The outpatient clinical for tremor is conducted by Dr. Isabel Wurster and Prof. Dr. D. Weiß.

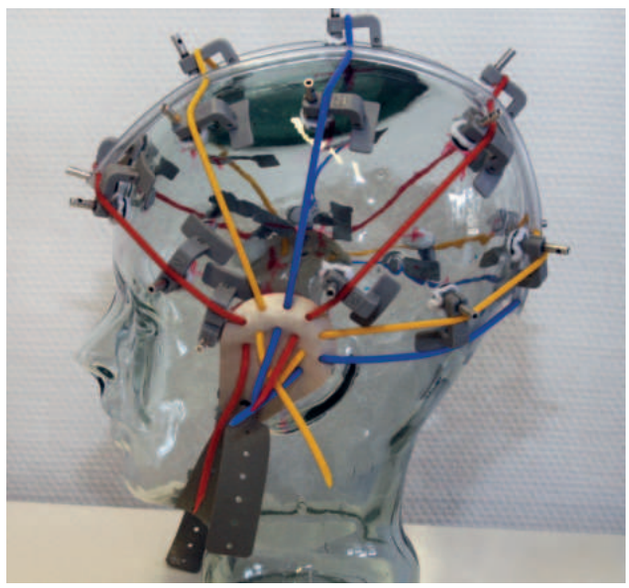
TMS

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 stroke. The clinic closely collaborates with rehabilitation and physiotherapy centers and has a treatment capacity of more than 1.000 sessions annually. The treatment focuses on motor symptoms and aphasia. The scientific mission of this clinic together with the translational research done in the Brain Networks & Plasticity Group (head: Prof. Dr. U. Ziemann) is to advance the therapeutic efficacy of TMS and support a paradigm-shift toward innovative personalized closed-loop stimulation approaches. Since the ISO certification of the outpatient clinic as TMS study centre in 2022, 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. The TMS outpatient clinic is part of the department of vascular neurology (director: Prof. Dr. U. Ziemann) and is staffed with a dedicated team of medical doctors (lead: Dr. A. Lieb), scientists, study nurses and administrative personnel.

Clinical Laboratories

CLINICAL CHEMISTRY LABORATORY FOR NEUROLOGY

The Clinical Chemistry Laboratory collects more than 1800 samples of cerebrospinal fluid (CSF) and serum 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 specialty 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, amyloid beta40, total-tau, phospho-tau and NFL are measured to differentiate various forms of dementia/neurodegenerative diseases. Recently, a new serum assay for NFL was successfully established. 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 Prof. Dr. K. Brockmann and PD Dr. M. Kowarik.



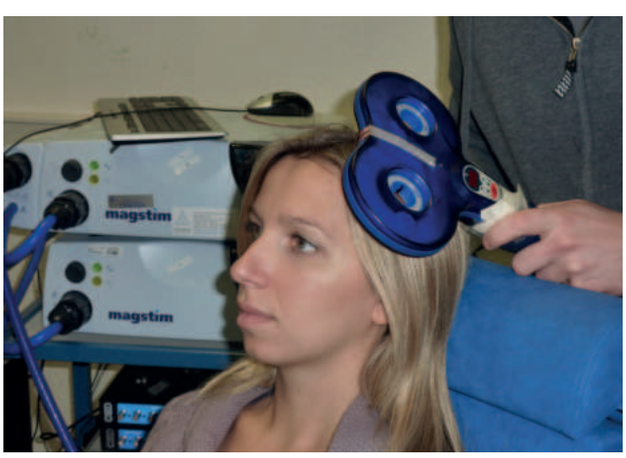
Electroencephalography (EEG) is used to record the spontaneous electrical activity of the brain by multiple electrodes placed on the scalp in a standardized manner. Abnormalities in EEG due to epileptiform brain activity represent the major diagnostic feature of epilepsy.

EEG LABORATORY

The electroencephalography (EEG) laboratory is equipped with three 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 six months and is provided for four neurological residents at a time. Laboratory staff: B. Wörner, Vohrer (staff technicians), Dr. M. Schneider and Dr. S. Lauxmann (heads of the laboratory).

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 tumors, entrapment syndromes and traumata can be visualized.



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

Since 2020 we have a new high-resolution probe of up to 24 MHz (Canon Medical Systems Aplio 800i). In 2023 more than 4,000 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 of medical staff of Neurosurgery (Prof. Dr. M. Schuhmann and Dr. H. Hurth) of the BG hospital (Prof. Dr. A. Daigeler, Prof. Dr. J. Kolbenschlag and Dr. J. Heinzel), Neuroradiology (Dr. T. Lindig) and our team (Dr. J. Stahl, Dr. N. Winter, Dr. K. Kneer, Dr. S. Straub and Prof. Dr. A. Grimm). Dr. N. Winter is the vice president of the German ultrasound society, department Neurology (DEGUM). Further DGKN/DEGUM certified colleagues are Dr. C. Ruschil, Dr. V. Ruschil, Dr. N. Winter, Dr. J. Marquetand and Dr. C. Kronlage. With J. Wittlinger we have the new position of a Physician assistant PA, who runs the EMG laboratory and is responsible for continuous education of our fellows and residents.

The laboratory is equipped with three digital systems (Cadwell Summit 3.1). In 2023, more than 3,100 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, 2,000 patients were examined by neuromuscular ultrasound in 2023.

In 2023, the EMG Laboratory was run by a team of technical assistants (A. Deutsch, V. Carver, I. Köhnlein), residents under the supervision of Prof. Dr. A. Grimm, Dr. N. Winter and Dr. P. Martin. In 2023 further colleagues have been certified by the DGKN for EMG (Dr. J. Stahl) and by the DEGUM for nerve and muscle ultrasound (Dr. J. Marquetand).

Clinical Laboratories

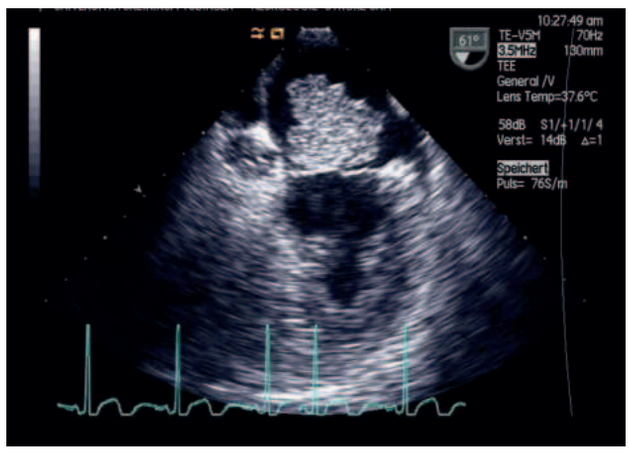
EVOKED POTENTIALS (EP) LABORATORY

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.

Around 2,500 examinations are performed every year on more than 1,600 patients. The recordings are conducted by A. Deutsch, K. Vohrer and I. Köhnlein and are supervised by Prof. Dr. A. Grimm, Dr. P. Martin and Dr. N. Winter. 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.

NVOM LABORATORY (FORMER ENG LABORATORY)

The laboratory for Neuro-Vestibular and Oculo-Motor diagnostics (NVOM) is part of the "Tübinger Zentrum für Schwindel- und Gleichgewichtserkrankungen (TüSG)". It 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, headshaking). Eye movements are usually studied by deploying video-oculography, although it has been ensured that in certain cases it is still possible to determine eye movements electrooculographically. 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. 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)



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

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.

NEUROCARDIOLOGY LABORATORY

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

The neurocardiology laboratory is headed by the cardiologist and internist Prof Dr. S. Greulich and the stroke neurologist Prof. Dr. S. Poli. It is equipped with a modern mobile ultrasound system (Philips CX50) to perform bedside transthoracic and transesophageal echocardiography in patients on the Stroke Unit the earliest possible after stroke diagnosis. To assess the overall vascular burden and to identify cardio-embolic sources (e.g., atrial fibrillation or a patent foramen ovale with atrial septum aneurysm), the full spectrum of echocardiography including M-Mode, 2-D mode, pulse wave, continuous-wave and color Doppler

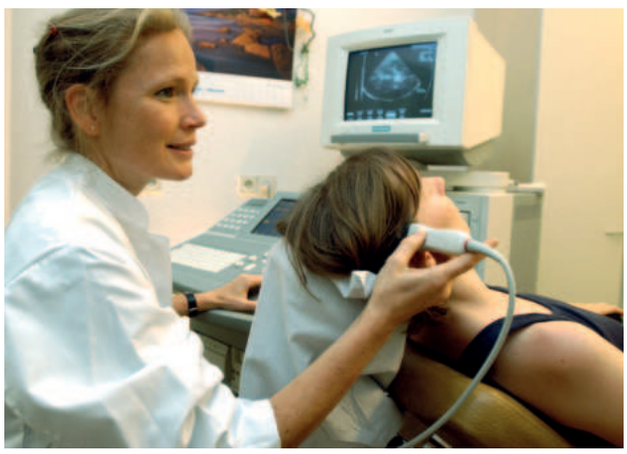
investigations as well as contrast-enhanced echocardiography for the detection of intracardiac shunts or intracardiac thrombi is provided. All patients on our Stroke Unit undergo automated analysis of continuous digital ECG monitoring for detection of atrial fibrillation. Selected stroke patients receive additional conventional 24-hour Holter ECG or are equipped with 7-day event recorders during hospital stay. Implantable cardiac event recorders offer advanced long-term cardiac rhythm monitoring. Since 2015, we have implanted over 500 such devices mainly in patients with embolic stroke of undetermined source and suspected atrial fibrillation. Close follow-up is guaranteed using daily home monitoring. Due to a risk factor-based selection algorithm, we were able to achieve a one-year AF-detection rate exceeding 30%. Other diagnostic tools include 24-hour blood pressure monitoring, and selection of patients for cardiac MRI or CT in collaboration 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 1,500 echocardiographic examinations are performed, and more than 1,000 Holter ECGs and 800 24-hour blood pressure measurements are recorded. All investigations are done according to the guidelines of the German and European Societies of Cardiology.

NEUROSONOLOGY LABORATORY

Our Neurovascular Ultrasound Laboratories A and B are equipped with three color-coded duplex sonography systems, the Cannon Aplio i800, the Philips Epiq7, and the GE Healthcare LOGIQ P9. Additionally, two portable CW/PW Doppler systems – a DWL Doppler-BoxX and an Atys WAKIe 2TC – are available. Neurovascular ultrasound examinations are performed by the ultrasound assistant N. Ruckwied as well as two neurovascular residents under supervision of the consultant stroke neurologists, PD Dr. A. Mengel and Prof. Dr. S. Poli who are DEGUM-certified level 2 and 3 ultrasound trainers.



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.

Acutely ill patients on our Stroke Unit are either examined at the bedside using our mobile Doppler and duplex units that allow the full range of neurosonological assessment immediately after admission, or in our Neurovascular Ultrasound Laboratory A, which is located close to the Stroke Unit. The Neurovascular Ultrasound Laboratory B is situated within the outpatient unit of the Department of Neurology and is mainly used for non-acute or elective ultrasound examinations of in- and outpatients.

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., patent foramen ovale), and continuous Doppler monitoring of the cerebral blood flow and for testing vasoreactivity (e.g., before, during and after neuroradiological interventions or extracranial-intracranial bypass neurosurgery)) 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 more than 5,000 of extracranial arteries and more than 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 2023, 2,265 patients were treated.

Occupational therapy provides the following training programs: training in motor function to improve the 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 disk herniation, stroke, ataxia, Parkinson's disease. In the course of the year 2023, 2,623 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 focus within the team of 14 speech therapists under the supervision of BSc Laura Broßette 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 2023, 2,020 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 more than 20 years ago, the Hertie Institute has grown to more than 500 employees at all levels, from technicians and 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 as well as relevant advances in their treatment.

The institute presently consists of six departments. They combine basic and clinical research with patient care, albeit to different degrees and with variable emphasis: the four departments focusing on Stroke, Epileptology, Neurodegenerative Disorders, and Neuro-Oncology treat outpatients in specialized clinics, but also inpatients with the whole spectrum of neurological diseases, while the Department of Neural Dynamics and Magnetoencephalography and the Department of 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 27 professors and 33 research groups. Twenty groups belong to the aforementioned departments, thirteen are led as independent research groups. The main focus of the HIH is on neurodegenerative and inflammatory brain diseases as well as on stroke, brain tumors, epilepsy, and the fundamentals and disorders of perception and motor function.

Some examples of the HIH's most significant research successes in 2023 include a gene-based therapy that was – for the first time in Europe - specifically tailored to the individual genetic defect of a 5-year-old child, led by Prof. Dr. Matthis Synofzik, research group leader at the HIH. Other research highlights were the development of a three-dimensional brain tissue model to study environmental influences on embryonal brain development *in vitro*, which was invented by a team led by independent research group leader Prof. Dr. Simone Mayer. A research team under the supervision of Prof. Dr. Markus Siegel, head of the Department of Neural Dynamics and Magnetoencephalography, found out that the content and form of a speech sound can be read out from brain signals several seconds before the sound is uttered. Moreover, Dr. Dr. Randolph Helfrich, independent research group leader at the HIH, was able to recognize a connection between neurological diseases and brain activity during sleep, which could lead to a new approach to treating diseases such as Parkinson's or epilepsy.

An extraordinary highlight in 2023 was the awarding of the "Breakthrough Prize in Life Sciences" to Prof. Dr. Thomas Gasser, chairman of the Board of the HIH and head of the Department for Neurodegenerative Diseases, for the discovery of genetic risk factors for Parkinson's disease. He shares the world's most highly endowed science prize, worth three million dollars, with two researchers from the USA.

In June 2023, independent research group leader Prof. Dr. Simone Mayer, was awarded the "15. Eva Luise Köhler Forschungspreis", worth 50.000 €, from Eva Luise Köhler in the presence of Federal Minister of Health Prof. Dr. Karl Lauterbach in the Berlin-Brandenburg Academy of Sciences. She received the prestigious Rare Diseases Research Award for her research on Pontocerebellar Hypoplasia Type 2 (PCH2), a very serious neurodevelopmental disorder in children.

Promoting young researchers is a main focus of the HIH, and so Dr. Deborah Kronenberg-Versteeg has started her research group "Glial Cell Biology" in the fall of 2023 in the Department of Cellular Neurology headed by Prof. Dr. Mathias Jucker. She devotes her research to the function of glial cells and their role in the development of diseases. Moreover, Prof. Dr. Alexander Grimm from the Department of Neurology and Epileptology headed by Prof. Dr. Holger Lerche, and PD Dr. Markus Kowarik from the Department of Neurology with Neurovascular Medicine headed by Prof. Dr. Ulf Ziemann, were promoted to research group leaders. Prof. Dr. Grimm is the head of the "Neuromuscular Imaging Group", PD Dr. Kowarik the head of the "Neurological B-Cell Immunology" lab.

In 2023, scientists at the Hertie Center of Neurology have obtained more than 10 million Euros in third party funding and published more than 320 papers in peer-reviewed journals. These figures attest to the excellent scientific performance of the Center. Over the last 20-plus years, the Hertie Foundation has spent about 65 million euros on the HIH and plans to continue its support.

In line with its mission to provide cutting-edge research and optimal patient care for the benefit of patients and society, the HIH will continue to develop its research structures. In the future, it will devote itself even more to developing strategies for the early detection, prevention and rehabilitation of neurological diseases. While expanding its research spectrum the institute will focus on two promising research fields: systems-based neurology and personalized and genetically stratified medicine.

Tübingen is one of six top research locations in Germany that form the "Hertie Network of Excellence in Clinical Neuroscience". The Hertie Foundation's network and junior researcher support program, which is funded with five million euros over a period of three years, aims to facilitate the transfer of scientific findings into clinical practice in the field of clinical neurosciences. A second funding period was approved, based on outstanding reviews by a panel of international neuroscientists and clinicians. In the fall of 2023, the Tübingen fellows organized a Symposium with keynote lectures, scientific talks, a panel discussion, and lots of time for exchange and discussion.

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Markus Siegel
Prof. Dr. Dr. Ghazaleh Tabatabai
Prof. Dr. Ulf Ziemann

Das Hertie-Institut für klinische Hirnforschung (HIH)

Mehr als 20 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 aus sechs Abteilungen: Der Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen (Prof. Dr. Ulf Ziemann), der Abteilung Neurologie mit Schwerpunkt neurodegenerative Erkrankungen (Prof. Dr. Thomas Gasser), der Abteilung Neurologie mit Schwerpunkt Epileptologie (Prof. Dr. Holger Lerche), der Abteilung Neurologie mit interdisziplinärem Schwerpunkt Neuroonkologie (Prof. Dr. Dr. Ghazaleh Tabatabai), die Abteilung Neuronale Dynamik und Magnetenzephalographie (Prof. Dr. Markus Siegel) und der Abteilung für Zellbiologie Neurologischer Erkrankungen (Prof. Dr. Mathias Jucker).

Die ersten vier Genannten sind bettenführende Abteilungen in der Neurologischen Klinik, die anderen beiden sind an der Patientenversorgung im Rahmen von Spezialambulanzen und speziellen diagnostischen Verfahren beteiligt. Die klinischen Abteilungen sind für die Versorgung von Patientinnen und Patienten mit der gesamten Breite neurologischer Erkrankungen gemeinsam verantwortlich.

In den Abteilungen sind zurzeit 27 Professorinnen und Professoren und über 500 Mitarbeitende in 33 Arbeitsgruppen tätig, wovon 13 unabhängige Forschungsgruppen darstellen. Die Arbeitsschwerpunkte des HIH liegen im Bereich neurodegenerativer und entzündlicher Hirnerkrankungen, der Schlaganfallforschung, Epilepsien und der Erforschung der Grundlagen und Störungen von Wahrnehmung und Motorik. Zu den bedeutendsten Forschungserfolgen des HIH im Jahr 2023 gehört eine genbasierte Therapie, die, unter der Leitung von Forschungsgruppenleiter Prof. Dr. Matthis Synofzik, erstmals in Europa speziell auf den individuellen Gendefekt eines 5-jährigen Kindes zugeschnitten wurde. Weitere Forschungshöhepunkte waren die Entwicklung eines dreidimensionalen Hirngewebemodells zur Untersuchung von Umwelteinflüssen auf die embryonale Hirnentwicklung in der Petrischale, geleitet von einem Team um die unabhängige Forschungsgruppenleiterin Prof. Dr. Simone Mayer. Ein Forschungsteam um Prof. Dr. Markus Siegel, Leiter der Abteilung für Neuronale Dynamik und Magnetoenzephalographie, fand heraus, dass Inhalt und Form eines Sprachlauts mehrere Sekunden vor der Lautäußerung aus Gehirnsignalen herausgelesen werden können. Darüber hinaus konnte Dr. Dr. Randolph Helfrich, unabhängiger Forschungsgruppenleiter am HIH, einen Zusammenhang zwischen neurologischen Erkrankungen und der Hirnaktivität im Schlaf erkennen, was zu einem neuen Ansatz zur Behandlung von Krankheiten wie Parkinson oder Epilepsie führen könnte.

Ein besonderes Highlight 2023 war die Vergabe des „Breakthrough Prize in Life Sciences“ an Prof. Dr. Thomas Gasser, Vorstandsvorsitzender des HIH und Leiter der Abteilung „Neurologie mit Schwerpunkt Neurodegenerative Erkrankungen“ für die Entdeckung genetischer Risikofaktoren der Parkinson-Erkrankung. Er teilt sich den mit drei Millionen Dollar höchstdotierten Wissenschaftspreis der Welt mit zwei Forschenden aus den USA.

In den Abteilungen sind zurzeit 27 Professorinnen und Professoren und mehr als 500 Mitarbeitende in 33 Arbeitsgruppen tätig. Die Gemeinnützige Hertie-Stiftung wendete bisher etwa 65 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

Im Juni 2023 wurde Prof. Dr. Simone Mayer, unabhängige Forschungsgruppenleiterin am HIH, der mit 50.000 Euro dotierte „15. Eva Luise Köhler Forschungspreis“ von Eva Luise Köhler im Beisein von Bundesgesundheitsminister Prof. Dr. Karl Lauterbach in der Berlin-Brandenburgischen Akademie der Wissenschaften verliehen. Sie erhielt den renommierten Forschungspreis für Seltene Erkrankungen für ihr Forschung zur Pontocerebellären Hypoplasie Typ 2 (PCH2), einer sehr schweren neurologischen Entwicklungsstörung bei Kindern.

Die Förderung junger Wissenschaftler und Wissenschaftlerinnen ist dem HIH ein wichtiges Anliegen: Seit Herbst 2023 verstärkt Dr. Deborah Kronenberg-Versteeg mit ihrer Forschungsgruppe „Glia-Zellbiologie“ das HIH in der Abteilung „Zellbiologie Neurologischer Erkrankungen“ von Prof. Dr. Mathias Jucker. Sie widmet sich in ihrer Forschung der Funktion von Gliazellen und deren Rolle bei der Entstehung von Krankheiten. Darüber hinaus wurden Prof. Dr. Alexander Grimm aus der Abteilung für „Neurologie mit Schwerpunkt Epileptologie“ unter Leitung von Prof. Dr. Holger Lerche sowie PD Dr. Markus Kowarik aus der Abteilung „Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen“ geleitet von Prof. Dr. Ulf Ziemann zu Forschungsgruppenleitern ernannt. Prof. Dr. Grimm leitet die Forschungsgruppe „Neuromuskuläre Bildgebung“, PD Dr. Kowarik die Forschungsgruppe „Neurologische B-Zell Immunologie“.

Das HIH, ein Modellprojekt für Public Private Partnership, hat auch im Jahr 2023 über 10 Millionen Euro an Drittmitteln eingeworben und mehr als 320 Veröffentlichungen in wissenschaftlichen Fachzeitschriften publiziert. Diese Zahlen belegen die exzellente wissenschaftliche Leistungsfähigkeit des Zentrums. In den letzten mehr als zwanzig Jahren hat die Gemeinnützige Hertie-Stiftung annähernd 65 Millionen Euro für das HIH aufgewendet und sie plant ihre Förderung fortzusetzen.

Gemäß seiner Mission, Spitzenforschung und optimale Krankenversorgung zum Wohle der Erkrankten und Gesellschaft zu leisten, wird das HIH seine Forschungsstrukturen weiterentwickeln. Künftig wird es sich noch mehr der Entwicklung von Strategien zur Früherkennung, Prävention und Rehabilitation neurologischer Erkrankungen widmen und sich bei dem Ausbau seines Forschungsspektrums auf zwei Zukunftsfelder konzentrieren: der systembasierten Neuromedizin sowie der personalisierten Medizin.

Tübingen ist einer von deutschlandweit sechs Spitzenstandorten des „Hertie Network of Excellence in Clinical Neuroscience“. 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. Auf der Grundlage hervorragender Beurteilungen durch ein Gremium internationaler Neurowissenschaftler und Kliniker wurde eine zweite Förderperiode bewilligt. Im Herbst 2023 organisierten die Fellows des Tübinger Standorts ein Symposium mit Keynote-Vorträgen, wissenschaftlichen Inputs, einer Podiumsdiskussion und viel Zeit für Austausch und Diskussion.

Prof. Dr. Thomas Gasser
Prof. Dr. Mathias Jucker
Prof. Dr. Holger Lerche
Prof. Dr. Markus Siegel
Prof. Dr. Dr. Ghazaleh Tabatabai
Prof. Dr. Ulf Ziemann

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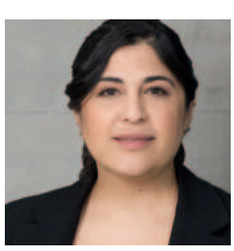
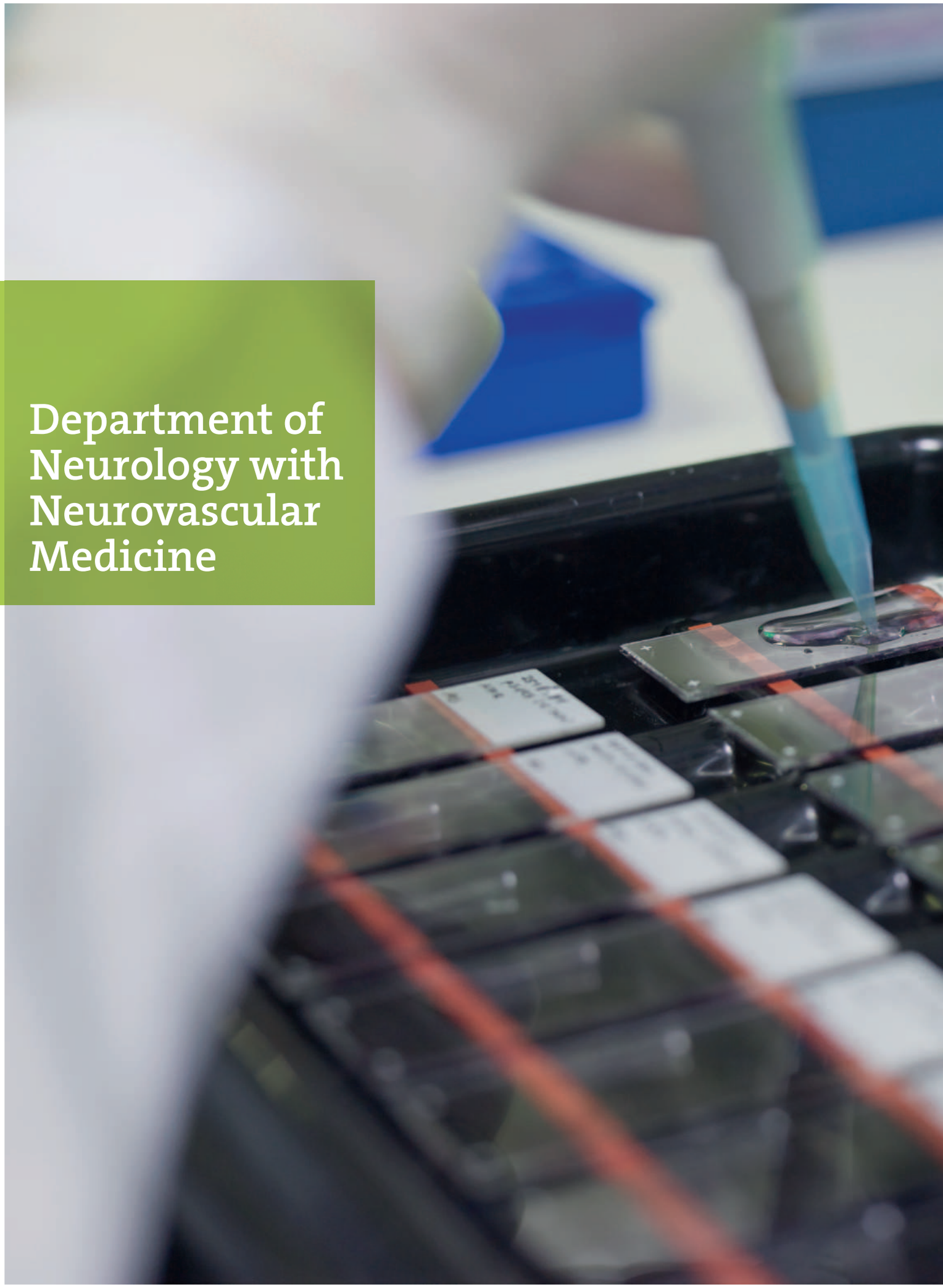



Prof. Dr. Markus Siegel
Prof. Dr. Dr. Ghazaleh Tabatabai
Prof. Dr. Ulf Ziemann

Dr. Astrid Proksch

Department of Neurology with Neurovascular Medicine



Prof. Dr. Ulf Ziemann is head of the Department of Neurology with Neurovascular Medicine.

Departmental Structure

The Department of Neurology with Neurovascular Medicine (Director: Prof. Ulf Ziemann) covers a broad spectrum of neurological disorders, in particular neurovascular diseases (ischemic stroke, intracranial hemorrhage, cerebral vasculitis, vascular malformations, rare neurovascular diseases such as endovascular lymphoma, paraneoplastic coagulopathy, or reversible cerebral vasoconstriction syndrome), neuroimmunological disorders (multiple sclerosis, neuromyelitis optica, MOG antibody-associated autoimmune disease, myasthenia gravis, autoimmune neuropathies and others), complex neurovestibular disorders, neurological emergencies, and neurointensive care patients.

Specialized teams in stroke medicine (intensive care and stroke unit, acute stroke rehabilitation), neuroimmunology and vertigo/dizziness 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, Freudenstadt, Sigmaringen) to provide emergency care for acute stroke patients. This structure

has been certified by the German Stroke Society as a Neurovascular Network. In addition, tele-stroke counseling is offered to the hospital in Freudenstadt. Neurocritical care is provided by our experts on an interdisciplinary internal medicine-neurology intensive care unit. Specialized outpatient clinics in Neurovascular Diseases, Neuroimmunology and Transcranial Magnetic Stimulation treatment of stroke patients offer expert counseling of patients, the best available therapy, and provide the infrastructure for clinical trials and investigator-initiated research.

The Department of Neurology with Neurovascular Medicine 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, four Research Groups exist with focus on brain networks & plasticity (Prof. Dr. Ulf Ziemann), stroke and neuroprotection (Prof. Dr. Sven Poli), molecular neuro-oncology (Prof. Dr. Ulrike Naumann), and 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 tightly with the physiotherapy department at the University Medical Center (Zentrum für ambulante Rehabilitation), which has a focus on physiotherapy for stroke rehabilitation.

The Department of Neurology with Neurovascular Medicine offers teaching 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 regularly honored by the evaluation of the students.

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

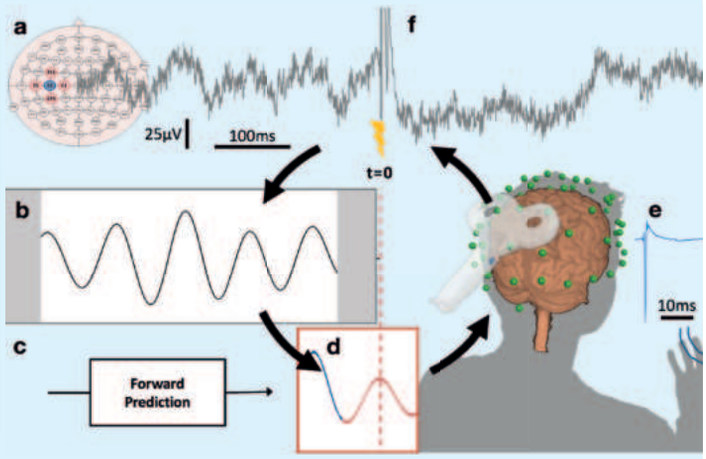
Neuroplasticity

Brain Networks & Plasticity (BNP) Laboratory

Head: Prof. Dr. Ulf Ziemann

Team: 37 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. This enables 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 modify neuronal networks highly efficiently. 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 dorsolateral and dorsomedial 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. Similar advancements have been made when stimulating prefrontal cortex. Moreover, first successful attempts have been made to implement a closed-loop approach by

using reinforced machine learning to identify in a fully automated manner the optimal phase of the ongoing mu-rhythm for enhancing effective connectivity between supplementary motor area and primary motor cortex, a connection important for stroke rehabilitation.

Translational Clinical Research Toward Personalized Therapeutic Brain Stimulation

A major goal in the BNP lab is to translate the insights gained from innovative fundamental research using EEG-TMS in healthy subjects 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 (BOSSFRONT2), and one multi-center trial in subacute stroke patients (BOSS-STROKE) funded by the Federal Ministry of Education and Research (BMBF). 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 structure 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 (TEPs): 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 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, on brain excitability and effective connectivity. We have also experimentally addressed the problem that TEPs are contaminated by peripherally evoked potentials due to somatosensory stimulation of the scalp and auditory stimulation by the TMS pulse by development of a realistic sham condition.

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Bai Y, Belardinelli P, Thoennes C, Blum C, Baur D, Laichinger K, Lindig T, **Ziemann U, Mengel A** (2023) Cortical reactivity to transcranial magnetic stimulation predicts risk of post-stroke delirium. *Clin Neurophysiol* 148:97–108

Bai Y, Belardinelli P, Ziemann U (2022) Bihemispheric sensorimotor oscillatory network states determine cortical responses to transcranial magnetic stimulation. *Brain Stimul* 15(1):167-178

Baur D, Ermolova M, Souza VH, **Zrenner C, Ziemann U** (2022) Phase-amplitude coupling in high-gamma frequency range induces LTP-like plasticity in human motor cortex: EEG-TMS evidence. *Brain Stimul* 15(6):1508-1510

Bai Y, He J, Xia X, Wang Y, Yang Y, Di H, Li X, **Ziemann U** (2021) Spontaneous transient brain states in EEG source space in disorders of consciousness. *Neuroimage*:118407

Bai Y, Xuan J, Jia S, **Ziemann U** (2023) TMS of parietal and occipital cortex locked to spontaneous transient large-scale brain states enhances natural oscillations in EEG. *Brain Stimul* 16(6):1588-1597

Gassmann L, Gordon PC, Ziemann U (2022) Assessing effective connectivity of the cerebellum with cerebral cortex using TMS-EEG. *Brain Stimul* 15(6):1354-1369

Gordon PC, Belardinelli P, Stenroos M, **Ziemann U, Zrenner C** (2022) Prefrontal theta phase-dependent rTMS-induced plasticity of cortical and behavioral responses in human cortex. Brain Stimul 15:391-402

Gordon PC, Jovellar DB, Song Y, Zrenner C, Belardinelli P, Siebner HR, **Ziemann U** (2021) Recording brain responses to TMS of primary motor cortex by EEG - utility of an optimized sham procedure. *Neuroimage*:118708

Gordon PC, Song YF, Jovellar DB, Rostami M, Belardinelli P, Ziemann U (2023) Untangling TMS-EEG responses caused by TMS versus sensory input using optimized sham control and GABAergic challenge. *J Physiol* 601:1981-1998

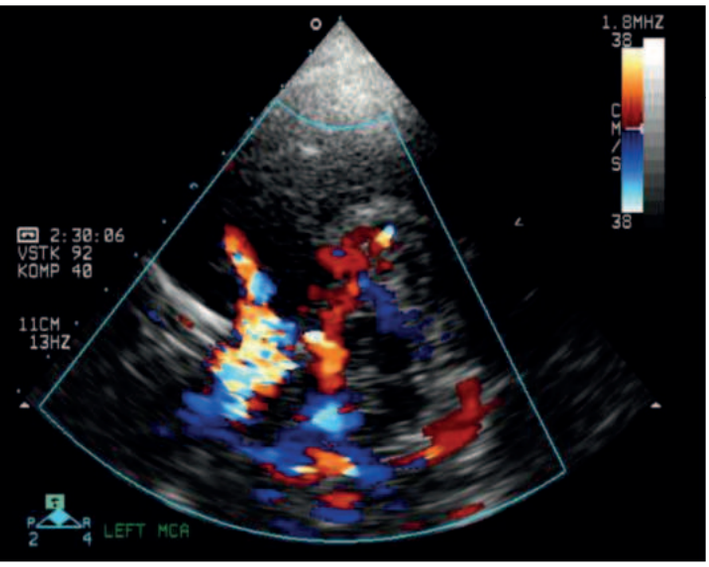
Metsomaa J, Belardinelli P, Ermolova M, Ziemann U, Zrenner C (2021) Causal decoding of individual cortical excitability states. *Neuroimage* 245:118652

Vetter DE, Zrenner C, Belardinelli P, Mutanen TP, **Kozák G**, Marzetti L, **Ziemann U** (2023) Targeting motor cortex high-excitability states defined by functional connectivity with real-time EEG-TMS. *Neuroimage* 120427.

Zrenner C, Kozák G, Schaworonkow N, Metsomaa J, **Baur D, Vetter D**, Blumberger DM, **Ziemann U, Belardinelli P** (2023) Corticospinal excitability is highest at the early rising phase of sensorimotor μ-rhythm. *Neuroimage* 266:119805

Stroke and Neuroprotection Laboratory

Head: Prof. Dr. Sven Poli
Team: 11 members + 7 MD students
Key words: stroke / neuroprotection / hypothermia / oxygen therapy / cryptogenic stroke / hemostasis / central retinal artery occlusion / prehospital stroke care / direct oral anticoagulants / deep learning



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

Unsere Forschungsprojekte reichen von translationalen präklinischen Studien zur Neuroprotektion bis hin zu klinischen multizentrischen Studien zu einem breiten Spektrum der akuten Schlaganfalltherapie, Schlaganfallsekundärprophylaxe 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 hemorrhagic 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.

For clinical stroke research, we run a neurovascular trial unit, which is a globally leading recruitment center in several international multi-center trials with the indications ischemic stroke, intracranial hemorrhage, and cerebral venous thrombosis. More than 2.600 patients were recruited into neurovascular trials since 2014. The neurovascular trial unit is part of the interdisciplinary Neuro-Cardio-Vascular Emergency and Intensive Care Medicine Trials Unit (NVKNI, directed by Prof. Dr. Sven Poli) and is certified according to DIN EN ISO 9001:2015. 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 have been (co-)coordinating several (inter-)national projects such as APICES (www.apices-trial.de), ATTICUS (DOI: 10.1056/EVIDoa2300235), INCH (DOI: 10.1016/S1474-4422(16)00110-1), PROOF (www.proof-trial.eu) and REVISION (www.revision-trial.de).

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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.

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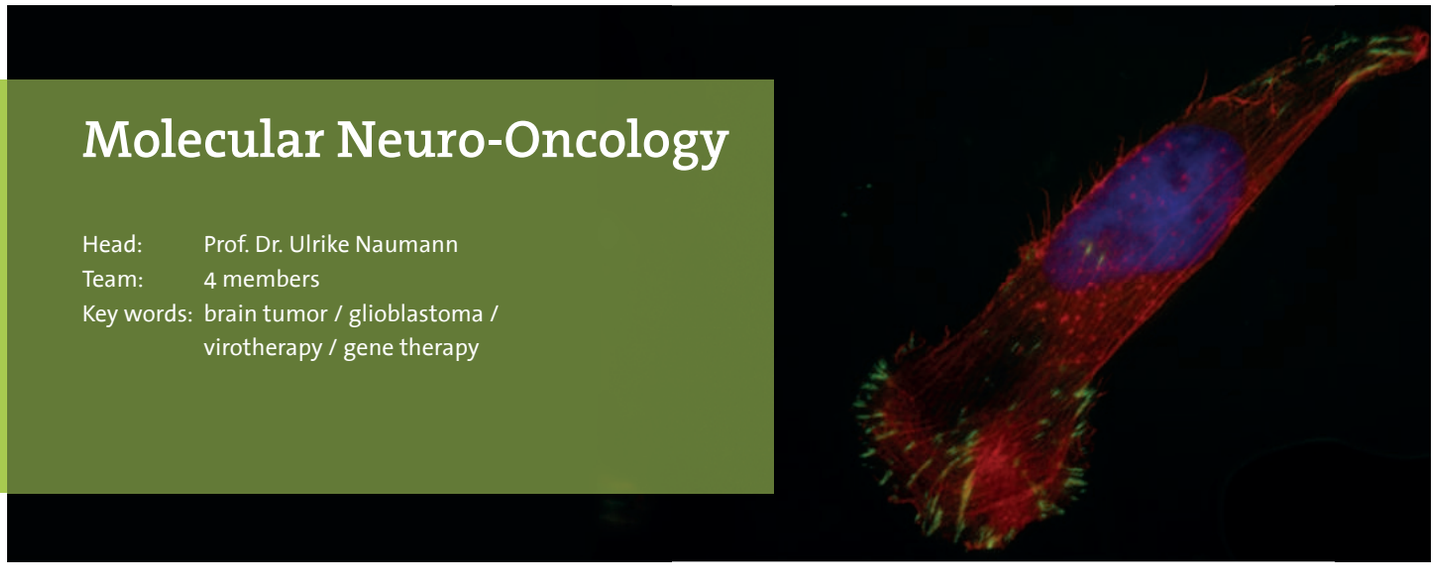
Molecular Neuro-Oncology

Head: Prof. Dr. Ulrike Naumann
Team: 4 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.

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 ihrer 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.

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 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 and University Innsbruck, Austria) we have analyzed the antitumoral effects of an oncolytic adenovirus (XVir-N31). We have demonstrated that in vitro XVir-N31 works synergistically with 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 recent experiments, funded by the German Research Foundation and the German Cancer Aid Society, we developed an offspring of XVir-N-31 that is armed to expresses, as an immune checkpoint inhibitor (ICI), a PD-L1 blocking antibody (XVir-N-31-anti-PD-L1).). In human immune

cell engrafted mice harboring HLA A/B matched immune cells and orthotopically growing gliomas in both brain hemispheres, we combined oncovirotherapy and immune checkpoint inhibition using either Nivolumab, a PD-1 neutralizing antibody, or by our modified OAV XVir-N-31-anti-PD-L1. We demonstrated that, in contrast to wildtype adenovirus that has a higher capacity to kill glioma cells than our OAVs, both XVir-N-31 and XVir-N-31-anti-PD-L1 induce a very efficient immunogenic cell death, push the immune response against the tumor, lead to an elevated number of tumor infiltrating lymphocytes and reduce tumor growth. In this regard, in the groups of mice where we combined OAVs and ICIs (either systemic application of Nivolumab or intratumoral injection of XVir-N-31-anti-PD-L1) not only virus-injected tumors were smaller than those of control groups, but also those gliomas that grew in the contralateral hemisphere and that have never been treated with OAVs. The manuscript containing data from this project has been published in 2022 (Klawitter et al, IJMS).

To further optimize the impact of OAVs we used OAV-loaded cells as "Trojan Horses" to shuttle XVir-N-31, via intranasal application, towards infiltratively growing glioma cells that cannot be directly targeted by the intratumoral injection of OAVs. We developed an optimized shuttle cell line with high migratory capacity that additionally contains HSV-TK as a safety gene. Intranasal delivery of XVir-N-31-loaded shuttle cells led to the transport of OAV-loaded shuttle cells towards the tumor, the production of new infectious oncolytic virus particles in the tumor area which then further infect and replicate in the tumor cells, also in infiltratively growing GBM cells. Finally, the intranasal delivery of OAV-loaded shuttle cells, especially in combination with a single intratumoral Injection of XVir-N-31, led to a significant survival prolongation of GBM bearing mice (El Ayoubi et al, Cancers 2023; Al Ayoubi et al, Mol. Oncol. 2023).

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). We observed that gene expression in pericytes is modulated by glioma-secreted cytokines and that pericytes with this altered gene expression are exclusively found on glioma-associated vessels. We have identified TGF-β as a central GBM-secreted cytokine that influences the function of pericytes by Inducing an EMT-like program in these cells, associated with changes in the cell´s metabolic activity, proliferation and motility as well as In their function as a guardian of the integrity of vessel structure and BBB (Wirsik et al, Neuropathol Appl Neurobiol 2021; Schumacher et al., Biomedicines, 2023). Further In vivo experiments in GFP-pericyte-reporter mice using TGF-β-knockout GBM cells for Implantation, or by prohibiting the induction of the EMT-program in GBM associated pericytes, we demonstrated that both approaches reduced the amount of vascular proliferates in the tumor area and resulted in a more normal vessel structure. This indicates that not only endothelial cells, but also pericytes, activated by GBM released TGF-β, are important for the chaotic vessel structure observed in GBMs. Results of the latter study have been send to "Free Neuropathology" and are recently in the status of second revision.

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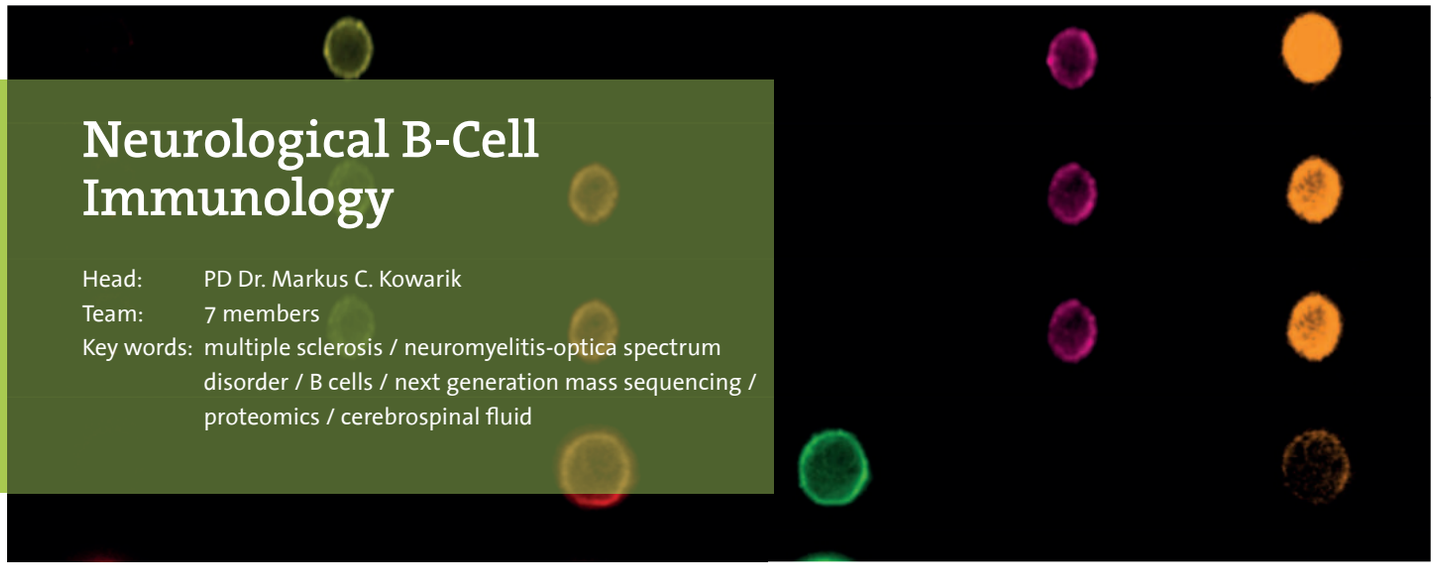

Neurological B-Cell Immunology

Head: PD Dr. Markus C. Kowarik
Team: 7 members
Key words: multiple 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 multi-omics approach including next generation mass sequencing and proteomics, we are able to get a deeper understanding of immunoglobulin repertoire changes under conditions of autoimmunity and immunomodulation. Besides the role of B cells during neuro-inflammation, we also extend our approach to the inflammatory milieu of primarily non-inflammatory neurological diseases such as CNS tumors.

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. Neben der Rolle von B-Zellen bei entzündlichen Erkrankungen weiten wir unseren Ansatz auch auf die inflammatorische Komponente bei primär nicht entzündlichen ZNS-Erkrankungen wie z.B. ZNS-Tumoren aus.

B cells in multiple sclerosis

Multiple lines of evidence indicate that B cells play an important role in the pathogenesis of multiple sclerosis (MS). Besides the persistence of intrathecal oligoclonal bands, elevated B cell numbers within the cerebrospinal fluid 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 MS therapies in order to gain insights in the different drugs' mode of action and the role of B cells during MS pathogenesis itself.

In addition to B cell subset specific quantitative changes, we are also interested in functional effects of different treatments on B cell subsets. We perform next generation mass sequencing of immunoglobulin (Ig) transcripts in order to get deeper insights in Ig transcriptome changes. We additionally assess Ig proteome analysis by mass spectrometry and overlap the recovered Ig peptides with Ig transcriptome libraries. This multi-omics 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

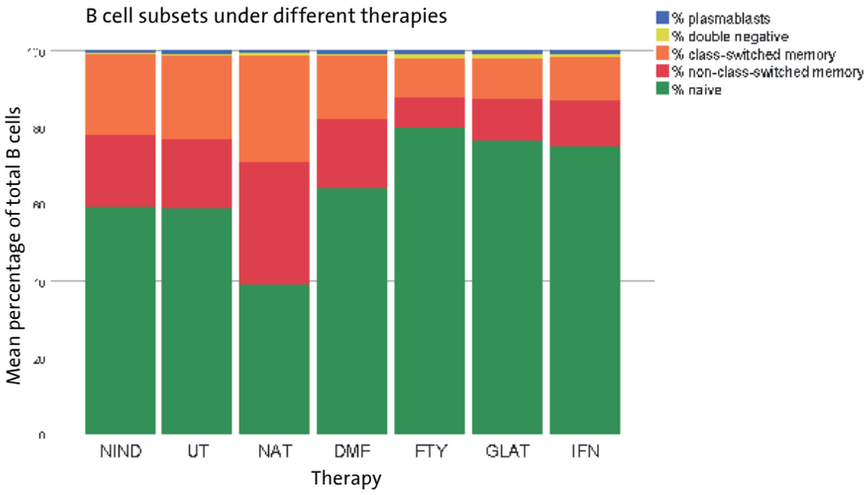

Figure 1: Displayed are the percentages of the B cell subsets among the total CD19+ B cell pool (NIND=non-inflammatory neurological disease, UT= untreated MS patients, NAT= natalizumab, DMF= dimethyl fumarate, FTY= fingolimod, GLAT= glatiramer acetate and IFN= interferon-ß treated MS patients).

treatment effects and are currently analyzing the effects of multiple therapies. A deeper understanding of the different drugs' mode of action will help to further define treatment algorithms for MS patients in the future. Cooperations: quantitative biology center (Sven Nahnsen, QBIC), sequencing core facility (Nicolas Casadei) and proteome core facility (Mohamed Ali Jarboui) Tübingen

Future directions

The cerebrospinal fluid (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 flow-cytometric 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 multi-omics approach and study specific CSF changes by 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. For this approach, we will not only concentrate on multiple sclerosis but also study the role of B cells in various neurological diseases including e.g. CNS metastasis. Cooperations: quantitative biology center (Sven Nahnsen, QBIC), Ulrike Naumann

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Department of Neuro-degenerative Diseases

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

Departmental Structure

The Department of Neurodegenerative Diseases was founded with the support of the Charitable Hertie Foundation and started operations on September 1, 2002. Since 2009, it is also a part of the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE) with several affiliated research groups. 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 treatments and patient care. Through its clinical division, the department cares for patients with neurodegenerative diseases and movement disorders on an inpatient unit of 22 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.

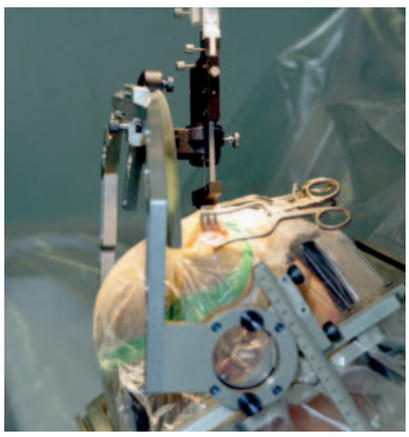
The clinical branch of the department offers specialized and up-to-date diagnostic procedures for neurodegenerative diseases, including genetic testing. Innovative treatment for patients with Parkinson's disease (PD) and other movement disorders include deep brain stimulation (in close collaboration 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. Over the last year, the first innovative molecular treatments, for example using antibodies that target alpha-synuclein aggregates in Parkinson's disease or antisense oligonucleotides aimed at the Tau-mRNA in Progressive Supranuclear Palsy have been initiated in the framework of clinical trials. The close collaboration of the specialized inpatient unit with the outpatient clinics for PD, dementia, dystonia, motor neuron diseases, ataxias, spastic paraplegias, and rare neurogenetic disorders allows highly individualized patient management. The equally close interaction of clinicians with basic scientists of the Hertie Institute for Clinical Brain Research and the DZNE, on the other hand, promotes truly translational research. This innovative concept includes active education and training of scientific and clinical junior staff. In 2023, the clinical department was named for the ninth time in a row as one of Germany's Top hospital departments in Parkinson's Disease by the Magazine Focus.

Research is currently organized within 7 research groups and 3 associated groups. The group of Prof. Dr. Thomas 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 led by Prof Dr. Kathrin Brockmann. The research section for Clinical Neurogenetics, headed by Prof. Dr. Ludger 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. Daniel 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. Dr. Philipp Kahle's group (Section of Functional Neurogenetics) investigates fundamental aspects of neurodegeneration mainly related to tau and alpha-synuclein aggregation. Dr. Julia Fitzgerald is a junior group leader, studying the mitochondrial biology of PD. Since 2016, Dr. Ebba Lohmann runs 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.

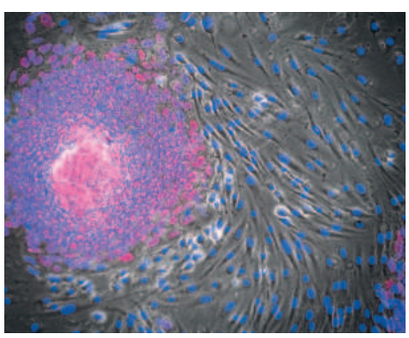
Former group leader Prof. Dr. Rebecca Schüle has accepted a W3-professorship for Neurodegenerative Diseases at the University of Heidelberg, but has kept an affiliation with the department to coninue her work focussing on the genetic basis of spastic paraplegias. Jun-Prof. Dr. Dr. Michela Deleidi, who had held a joint group leader position with the DZNE Tübingen, has accepted a faculty position at the Institute Imagine in Paris, a research institution affiliated to Paris University and dedicated to translational research in genetic disorders. She also continues to do research as an affiliated group within the Department PD Dr. Johannes Gloeckner, a biochemst and research group leader at the DZNE Tübingen, is also member of the Department.

Finally, Prof. Dr. M. Synofzik, who now heads an independent research section on translational genomics of neurodegenerative diseases at the HIH, continues to pursue all patient work, including outpatient clinics, the characterization of patient cohorts and innovative clinical trials, within the Department of Neurodegenerative Diseases.

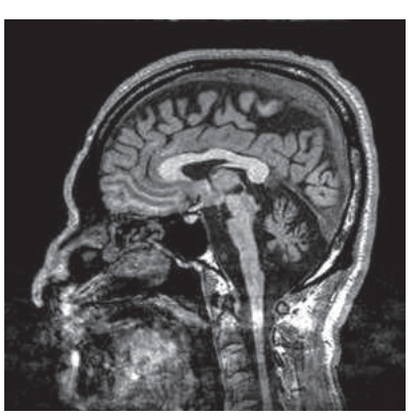
Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with Parkinson's disease and other neurodegenerative diseases.



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).



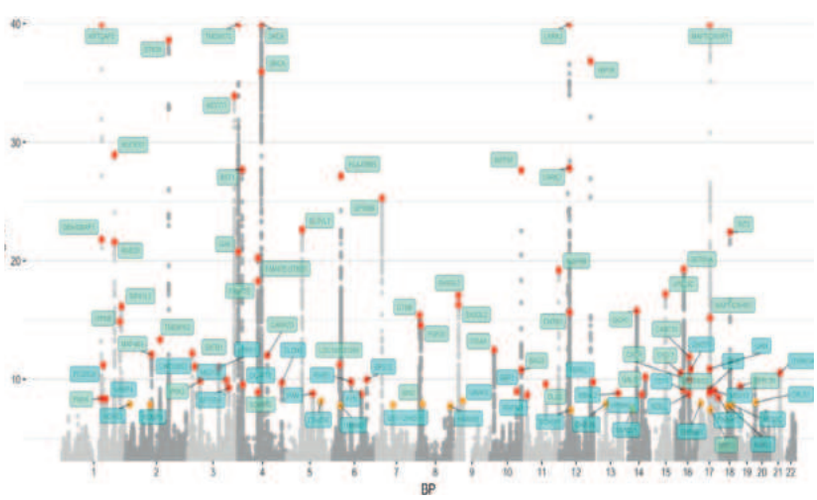
Both, fundamental mechanisms of neurodegeneration in Parkinson's disease and the effects of deep brain stimulation are investgated in Professor Krüger's group.

Parkinson Genetics

Head: Prof. Dr. Thomas Gasser
Team: 7 members
Key words: Parkinson's disease / genetics / association studies / GWAS / mutation / induced pluripotent stem cells / synuclein aggregation assay

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.



The largest genome-wide association study identified more than 80 gene loci that convey a risk to develop sporadic Parkinson's disease (Nalls et al., Lancet Neurology 2019)

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.

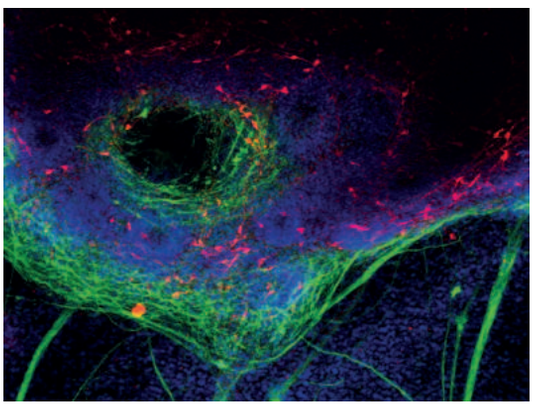
In 2009 we published the result of the first large genome-wide association study (GWAS) in PD, in a collaboration with the laboratory for neurogenetics of the National Institutes of Health (NIH). (Simon-Sanchez et al., Nat Genet 2009). Since this initial study, we have worked with numerous collaborators 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).

More recently, this collaboration has been expanded to the Global Parkinson Genetics Program (GP2), which aims to genotype more than 150.000 PD patients world-wide, particularly from so far underrepresented populations (Kim et al., 2023)

In another international consortium, funded by the Joint Programming in Neurodegenerative Diseases (JPND) program, we have jointly, with partners, genotyped 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 (e.g. Domenighetti et al. 2022, Sugier et al., 2023).

Together with the research group of Kathrin Brockmann and with groups at other sites of the DZNE, we are working on the development of novel synuclein aggregation assays as biomarkers for different genetically stratified forms of PD (Brockmann et al. 2021, Bräuer et al, 2022, Brockmann et al., 2024)

Genetic targets or genetic stratification of patient cohorts are the focus of innovative clinical trials (Pagano et al., 2022; Peterschmitt et al., 2022)



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.

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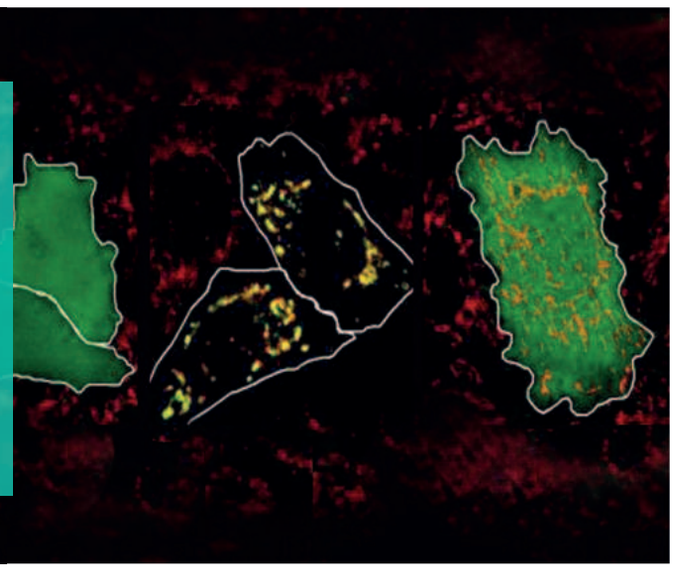
Functional Neurogenetics



Head: Prof. Dr. Philipp Kahle
Team: 5 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 pathological mechanisms underlying aggregation of these proteins and their impact on neural dysfunction. Pathological pathways are modelled 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 pathologische 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 nucleozytoplasmatischen 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.

We completed a transcriptomic study of **α-synuclein** transgenic mice. Having shown previously that high fat diet induced obesity and prediabetic state accelerated the onset of synucleinopathy in (Thy1)-h[A30P] αSYN mice (Rotermund et al. 2014) we performed RNA sequencing of brain tissue in 12 months old animals, an age preceding the onset of synucleinopathy. In the pathologically most affected region, the brain stem, we observed a strong induction mostly of mitochondrial protein coding genes in animals on high fat diet. Remarkably, this response was severely blunted in the (Thy1)-h[A30P]αSYN mice (Kilzheimer et al. 2023). The apparent failure of mitochondrial adaptation to high fat diet might contribute to the development of synucleinopathy in vivo. In a preclinical immune therapy trial, we could reduce classical brain stem synucleinopathy in this transgenic mouse model by treatment with a monoclonal antibody against α-synuclein oligomers/protofibrils (Ekmark-Lewén et al. 2023). Of note, the conspicuous nuclear serine-129 phosphorylated α-synuclein was refractory to such immune therapy, calling for careful assessment of (patho)physiological α-synuclein species in immune therapy attempts.

Post-translational modifications are critically involved in physiological functions of the RNA binding protein TDP-43 and drive the pathological phase separation and aggregation process of this protein (García Morato et al. 2023). We are studying TDP-43 lysine modifications using mass spectrometry in an internal collaboration with the Gloeckner group. We had found an interplay between some lysine ubiquitinylations and pathological phosphorylation (Hans et al. 2018), which is the focus of an ongoing collaboration with Prof. Neumann (Neuropathology, German Center for Neurodegenerative Diseases). Studying such lysine ubiquitinylation sites, we discovered another type of lysine modification, namely acetylation. Interestingly, acetylation of lysine-136 in the RNA-binding domain caused loss of functional RNA interactions and led to liquid-liquid phase separation and TDP-43 aggregation (García Morato et al. 2022). Supported by a Karin Christiane Conradi Foundation Fund for ALS research, Jorge García Morato could establish a miniTurbo-mediated proximity labeling screen for protein interactors of phase separated and

aggregating mutant TDP-43. We are validating putative modulators of TDP-43 unmixing and self-association. In parallel, we use APEX-mediated proximity labeling and RNAseq (Next Generation Sequencing Core Facility Tübingen, Nicolas Casadei) to screen for RNAs differentially interacting with phase-separating TDP-43. This combined protein/RNA screening approach may lead to a comprehensive understanding of the environment of phase separating and aggregating TDP-43, perhaps eventually even leading to the discovery of novel therapeutic targets.

The most common recessive Parkinson's disease gene products PINK1 and parkin regulate mitochondrial functions. We continue to characterize mitophagy defects upon genetic PINK1 deficiency in internal collaboration with the group of Julia Fitzgerald. The mitochondrial protein kinase PINK1 together with the ubiquitin ligase parkin mediates the autophagic removal of damaged mitochondria (mitophagy). In the framework of DFG Research Training Group RTG2364 "MOMbrane", we performed systematic mass spectrometry analyses of phospho-proteomes and ubiquitinylomes throughout the time course of mitophagy in HeLa cells stably expressing wild-type and catalytically inactive mutant parkin (Zittlau et al. 2022). Further validating the apparent outside-in cadence of mitochondrial protein removal upon mitochondrial membrane potential breakdown, we confirmed the initial importance of proteasomal degradation of a distinct subset of parkin-ubiquitinylated mitochondrial outer membrane (MOM) proteins (e.g. mitofusin-1 or TOM70). Interestingly, another subset of MOM proteins (exemplified by TOM20) appeared to detach from depolarized mitochondria to be separately targeted for autophagic removal, not only in parkin-expressing HeLa cells but also in neural precursor cells (Lechado Terradas et al. 2022). Resulting MOM rupture could be seen by electron microscopy in apposition to autophagosomes. Surprisingly, the remaining inner mitochondrial cargo (containing e.g. COX4, citrate synthase and SSBP1) required a second proteasome-dependent step to become later fully degraded via autophagy (Lechado Terradas et al. 2022). Such parkin-dependent degradation pathways of ubiquitinylated mitochondrial material depended on ubiquitin-binding autophagy adaptors. Interestingly, we found that one of these autophagy adaptors, TAX1BP1, which usually plays a relatively minor role in mitophagy compared to the more dominant p62/SQSTM1 or optineurin (Geisler et al. 2010; Lechado Terradas et al. 2021), is modified during mitophagy. When expressing TAX1BP1 as the sole autophagy receptor, this modification appears to direct non-canonical cellular mitophagy degradation pathways (Lechado Terradas et al. manuscript in preparation). The fascinating cellular network of mitochondrial quality control and its most complex interplay with proteasomal and lysosomal degradation machineries is an ongoing topic deserving great attention, not only from a basic cell biology point of view but also due to the association of several key players with neurodegenerative diseases.

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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 ataxias, hereditary spastic paraplegias and leukodystrophies. We use whole genome sequencing along with transcriptomics and proteomics if necessary to provide a definite diagnosis for our patients and opens windows into pathogenesis and potential interventions early in the disease process. Our specialized outpatient clinics provide best medical care and offer interventional trials from phase 1 to 3. In clinical studies we establish new progression markers and biomarkers indicating disease activity that help to monitor therapeutic effects. In the lab we generate induced pluripotent stem cells (iPSC) and re-differentiated them into neurons and human brain organoids which are genetically identical with our patients. This helps us to study most early steps in pathogenesis, identify new targets for therapeutic approaches and screen compounds for therapeutic interventions. Within the Tübingen gene and RNA therapy center (GRTC) we develop novel strategies for allele-specific antisense oligonucleotide approaches and AAV-based gene replacement.

Die Sektion Klinische Neurogenetik ist auf translationale Forschung bei monogenetischen Erkrankungen wie zerebellären Ataxien, hereditären spastischen Spinalparalysen und Leukodystrophien fokussiert. Diagnostisch nutzen wir einen genome first Ansatz, gegebenenfalls kombiniert mit Transkriptom- und Proteomanalysen, um bei dem Großteil unserer Patienten eine molekulare Diagnose zu sichern und Einblicke in die Pathogenese und frühe Interventionsmöglichkeiten zu gewinnen. Unsere Spezialambulanzen bieten Patienten eine best-mögliche medizinische Versorgung und interventionelle Studien der Phasen 1 bis 3 an. In der Klinik entwickeln wir Progressions- und Biomarker, die Krankheitsaktivität anzeigen und ein optimales Monitoring von Therapieeffekten erlauben. Im Labor generieren wir induzierte pluripotente Stammzellen (iPSC) aus Hautbiopsien unserer Patienten und untersuchen an humanen Neurone und Hirnorganoide, die genetisch mit unseren Patienten identisch sind, frühe pathogenetische Veränderungen und testen neue Therapieansätze. Im Rahmen des Tübinger Gen- und RNA-Therapiezentrums (GRTC) entwickeln wir neue Strategien für Allel-spezifische Antisense Oligonukleotide und AAV-basierte Gener-satztherapien.

Ataxia

Concerning genetic diagnostics, we identified a large intronic GAA repeat expansion in FGF14 as a common cause of late onset spinocerebellar ataxia (SCA; Pellerin et al. NEJM 2023; Hengel et al. Mov Disord 2024). SCA27B is clinically characterized by a slowly progressive pancerebellar syndrome, partly combined with afferent sensory deficits (55%) and dysautonomia (28%) whereas cognitive impairment is infrequent (Wilke et al. Brain 2023). Within the EU funded ESMI consortium that is setting up a trial ready cohort for the most frequent genotype, SCA3, we coordinate the movement recording project that strives for an objective and sensitive outcome measure for interventional trials. We proved our motion capture system to be superior 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. Mov Disord 2022). In a comprehensive analysis of fluid and imaging biomarkers we established a staging model of SCA3 that provides objective indicators of neurodegeneration before ataxia onset (Faber et al. Ann Neurol 2024). Further, transcriptional alterations in blood were shown to reflect early changes that start before clinical onset and might serve as peripheral biomarkers in clinical and research settings (Raposo et al. Brain 2023).

In the European Friedreich's Ataxia consortium for Translational Studies (EFACTS) we found cardiac arrhythmia, neurological disability and diabetes mellitus to influence the overall

survival in FA. A survival prognostic score has been developed to identify patients meriting closer surveillance and who may benefit from early invasive cardiac monitoring and therapy (Indelicato et al. Mov Disord 2023). Taking advantage of induced pluripotent stems cells generated from fibroblasts of SCA3 patients we were able to screen antisense oligonucleotides for their capacity to selectively target mutant ataxin-3 in human neurons that are genetically identical to the patients (Hauser et al. Mol Ther Nucleic Acids 2022).

Hereditary spastic paraplegia (HSP)
Early interventions in neurodegenerative diseases require objective and quantifiable measures of the disease process prior to the development of manifest deficits. We established the preSPG4 cohort of first-degree relatives of patients with the most common subtype of hereditary spastic paraplegia (SPG4) who carry a 50% risk to have inherited the SPG4 mutation and to develop a spastic gait disorder. Whereas gait speed and two-minute walking distance as well as expert appraisal of gait did not differ between mutation carriers and healthy controls we found neurofilament light levels but not tau or Aβ to rise in CSF of mutation carriers when approaching the time point of predicted disease manifestation. Digital motion recording found an altered gait pattern in prodromal mutation carriers with reduced angles of the foot and heel ground clearance as well as reduced range of motion for the foot. As gait analysis is able to quantify changes in prodromal SPG4 patients, gait features constitute promising motor biomarkers characterizing the subclinical progression of spastic gait and might help to evaluate interventions in early disease stages (Rattay et al. Brain 2023; Lassmann et al. Mov Disord 2022).
To explore the pathogenesis of SPG4 in human neuronal tissue we generated a heterozygous and a homozygous SPAST knockout induced pluripotent stem cell (iPSC) line from a healthy control iPSC line using CRISPR/Cas9 technology. These knockout lines and their isogenic control will help to study loss of function effects of spastin and identify early molecular and morphological changes in cortical neurons and axons as well as other neural cell types of this most common subype of HSP (Korneck et al. Stem Cell Res 2022).

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. For metachromatic leukodystrophy (MLD) hematopoetic stem cell transplantation is a therapeutic option when performed early in the disease. MLD is caused by loss of function mutations in arylsulfatase A (ARSA gene). In collaboration with the children's hospital we could show that ARSA activity in leukocytes and the ARSA genotype can predict the age of disease onset and the dynamic of disease progression in most of the early onset forms. This knowledge is relevant for patient counseling and to guide treatment decisions, especially when identifying pre-symptomatic individuals, e.g., in newborn screening (Santhanakumaran et al. Mol Genet Metab 2023).

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Deep Brain Stimulation

Head: Prof. Dr. Daniel Weiß
Team: 10 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 neuronal 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 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.

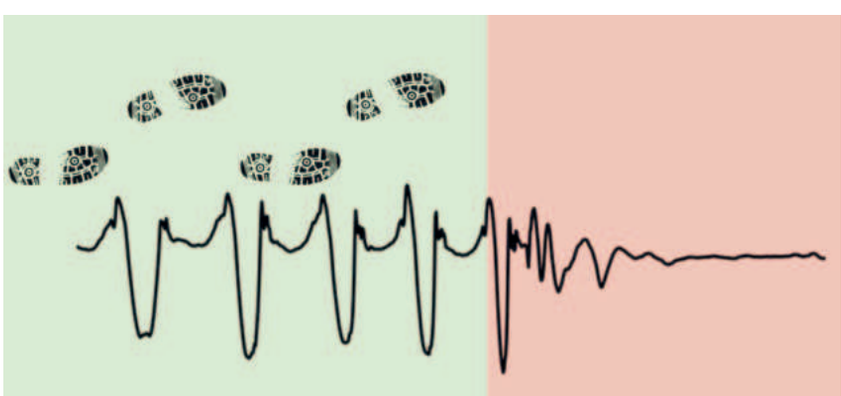
Clinical studies: making DBS available for resistant axial symptoms

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 [1]. 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.

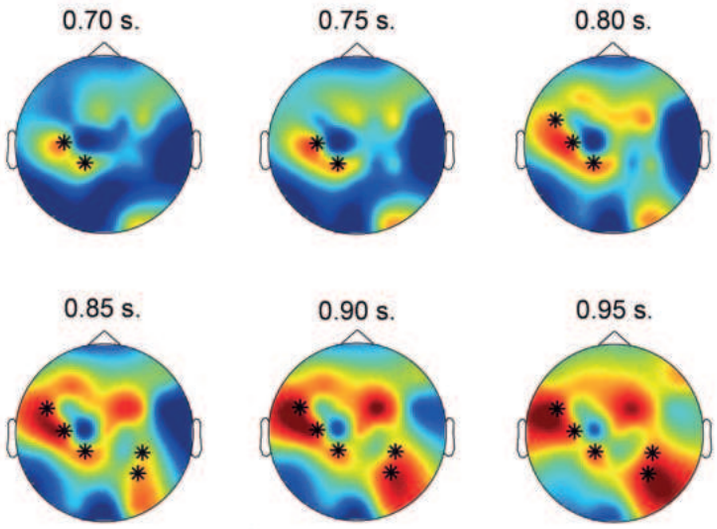
In this framework, we take advantage to co-stimulate the substantia nigra pars reticulata in addition to the subthalamic nucleus as distal electrode tip of a subthalamic lead. First clinical observations were made between 2009 and 2011 [2], and further substantiated by a monocenter randomized controlled trial. This trial pointed to an additional effect of nigral co-stimulation to attenuate otherwise resistant freezing of gait [3]. The Tübingen working group for "deep brain stimulation" coordinated and finished a randomized controlled multicentre trial with 12 DBS expert centres (ClinTrials.gov: NCT02588144). Albeit there was no significant group level effect, the trial indicated that up to 30% of the patients can achieve clinically meaningful improvement by reprogramming STN or STN+SNr parameters.

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 [1].



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, local field potential recordings from the basal ganglia and videotaping in freely moving PD patients. 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 [4-8]. Even more important, we are increasingly able to characterize the transition periods between regular gait and freezing in PD patients. As such, we can identify both activation abnormalities of the STN and of STN-muscular synchronization of the antagonistic leg muscles. In particular, we showed that a failure of reciprocal inhibition is relevant to FoG and that this stems from erroneous supraspinal influence on the antagonistic leg muscles [9]. This is of utmost importance to develop freezing forecasts, i.e. to predict the disruption of locomotion several seconds before the network disturbance becomes clinically apparent in terms of freezing of gait.



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Clinical Parkinson Research

Head: Prof. Dr. Kathrin Brockmann
Team: 13 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 multi-factorial 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]. Knowledge of these phenotypical trajectories are essential in order to plan clinical trials with disease-modifying therapies.

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 $PD_{GBA\_wildtype}$ [6]. 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 [7, 8] but seems rather caused by neocortical alpha-synuclein/Lewy body pathology represented by decreased CSF levels of alpha-synuclein [9]. 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 [10]. Recently, the ultrasensitive seed-amplification assays (SAA) have been introduced. These assays exploit the seeding capacities of prion or prion-like proteins using an amplification strategy to reveal minute amounts of disease-specific protein aggregates in CSF. Both methods show a high sensitivity of 88-96% and specificity of 83-98% for PD and DLB compared to controls. We assessed CSF alpha-synuclein seeding activity in PD and DLB patients with GBA mutations to serve as proxy for pronounced alpha-synuclein pathology and in PD patients with recessively inherited mutations in parkin, PINK1 and DJ1 as representatives for nigral degeneration with sparse alpha-synuclein aggregation. Our results show that PD and DLB patients with GBA mutations present a predominant alpha-synuclein-driven CSF profile which mirrors the prominent alpha-synuclein pathology found post-mortem [11, 12]. These findings allow in vivo patient stratification for clinical trials targeting alpha-synuclein.

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. Adeno-associated Virus (AAV) -based gene therapies that provide neurons with a fully working copy of the GBA gene.
iii. Substrate reduction therapies
iv. Based on the key finding that PD patients with GBA mutations predominantly show an alpha-synuclein-driven CSF profile that is associated with the development of dementia and during lifetime mirrors the widespread Lewy body pathology known from autopsy studies. As different proteins (amyloid-ß, tau, alpha-synuclein) have been shown to be associated with dementia in PD patients and antibody and antisense oligonucleotide therapies are emerging, our findings allow for patient stratification based on the predominantly alpha-synuclein-driven CSF profile. Such an approach will maximize effect sizes in clinical trials [13].

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Mitochondrial Biology of Parkinson's Disease

Head: Dr. Julia Fitzgerald
Team: 6 members
Key words: Parkinson's disease / atypical parkinsonism / mitochondria / PINK1 / MIRO1 / TRAP1 metabolism / neurochemistry / biomarkers

We study the molecular mechanisms of proteins acting at the mitochondria such as PINK1 and Miro1. Our focus is on how mitochondrial proteins and mitochondrial metabolism regulate the development and function of dopaminergic neurons. To achieve this, we are using established biochemical, molecular biology and imaging methods and have long standing experience in transcriptomics, proteomics and metabolomics. We have expertise in mitochondrial phenotyping, bioenergetics, calcium imaging and gene editing. We utilise a wide range of model systems including neural cells, fibroblasts, induced pluripotent stem cells (IPSCs) models and mouse tissue. In parallel, we are working to identify robust mitochondrial-related biomarkers for Parkinson's disease. To do this we work closely with our clinical colleagues to collect patient-derived biomaterials including blood and exosomes.

*Wir untersuchen die molekularen Mechanismen von Proteinen, die in den Mitochondrien wirken, wie PINK1 und Miro1. Unser Schwerpunkt liegt darauf, wie mitochondriale Proteine und der mitochondriale Stoffwechsel die Entwicklung und Funktion dopaminerger Neuronen regulieren. Dazu setzen wir etablierte biochemische, molekularbiologische und bildgebende Verfahren ein und verfügen über langjährige Erfahrung in Transkriptomik, Proteomik und Metabolomik. Unsere Expertise liegt in den Bereichen mitochondriale Phänotypisierung, Bioenergetik, Kalzium-Imaging und Gene Editing. Wir verwenden eine breite Palette von Modellsystemen, darunter Nervenzellen, Fibroblasten, Modelle mit induzierten pluripotenten Stammzellen (IPSCs) und Mausgewebe. Parallel dazu arbeiten wir daran, robuste mitochondrienbezogene Biomarker für die Parkinson-Krankheit zu identifizieren. Zu diesem Zweck arbeiten wir eng mit unseren klinischen Kolleg*innen zusammen, um von Patient*innen stammende Biomaterialien wie Blut und Exosomen zu erfassen.*

Mitochondrial Protein Miro1 in Health and Parkinson's Disease

Miro1 is attached to the outer mitochondrial membrane, where it has three important roles; it binds calcium, it anchors the mitochondria to the microtubules for their movement and it is a mediator of classical Pink1-Parkin mitophagy. These functions make it a key player in neuronal health due to spatial positioning of mitochondria at synapses and dendrites and the energetics of neurotransmission. Not surprisingly, Miro1 knockout is post-natal lethal in mice and mutations affecting Miro1 function are rare. To understand the contribution of Miro1 in Parkinson's disease pathways, we introduced the heterozygous Parkinson's disease patient RHOT1/Miro1 variant R272Q and a homozygous phospho-null S156A mutation at a putative PINK1 phosphorylation site in IPSCs. This work has led us to better decipher the roles of mitophagy and calcium homeostasis in post-mitotic neurons and highlighted the involvement of another Parkinson's disease protein LRRK2 in these mechanisms. We have also performed a replication study for The Michael J Fox Foundation, looking at Miro1 retention at the mitochondria upon depolarization, which occurs in >80% of all sporadic Parkinson's disease fibroblasts tested. We are also testing several compounds targeting Miro1 and calcium channels for their potential to reverse these phenotypes. A follow up study will focus on blood cells with the aim to validate the Miro1 assay as a marker of mitochondrial PD.

Mitochondrial-Related 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 we now explore further two potential biomarkers for Parkinson's disease in living patients and are developing novel digital PCR and sequencing methods to identify dried blood spot markers that are retained in the blood as well as in the brain.

Mitochondrial Parkinson's Disease: 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 mid-brain 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. Here we have identified events at the outer mitochondrial membrane and between mitochondria and ER that influence dopamine homeostasis via metabolic rewiring. We are also Interested in how these mechanisms occur in developing neurons and whether we can restore normal function by intervening in the early stages. Furthermore, we are working with our collaborators to establish both single cell sequencing and spatial (dendrite-axon-soma) proteomics in iPSC-derived neurons. Moreover, we work with genetically modified HeLa cells that are PINK1 and Parkin deficient to Investigate the biochemical Impact of novel PINK1 and Parkin mutations.

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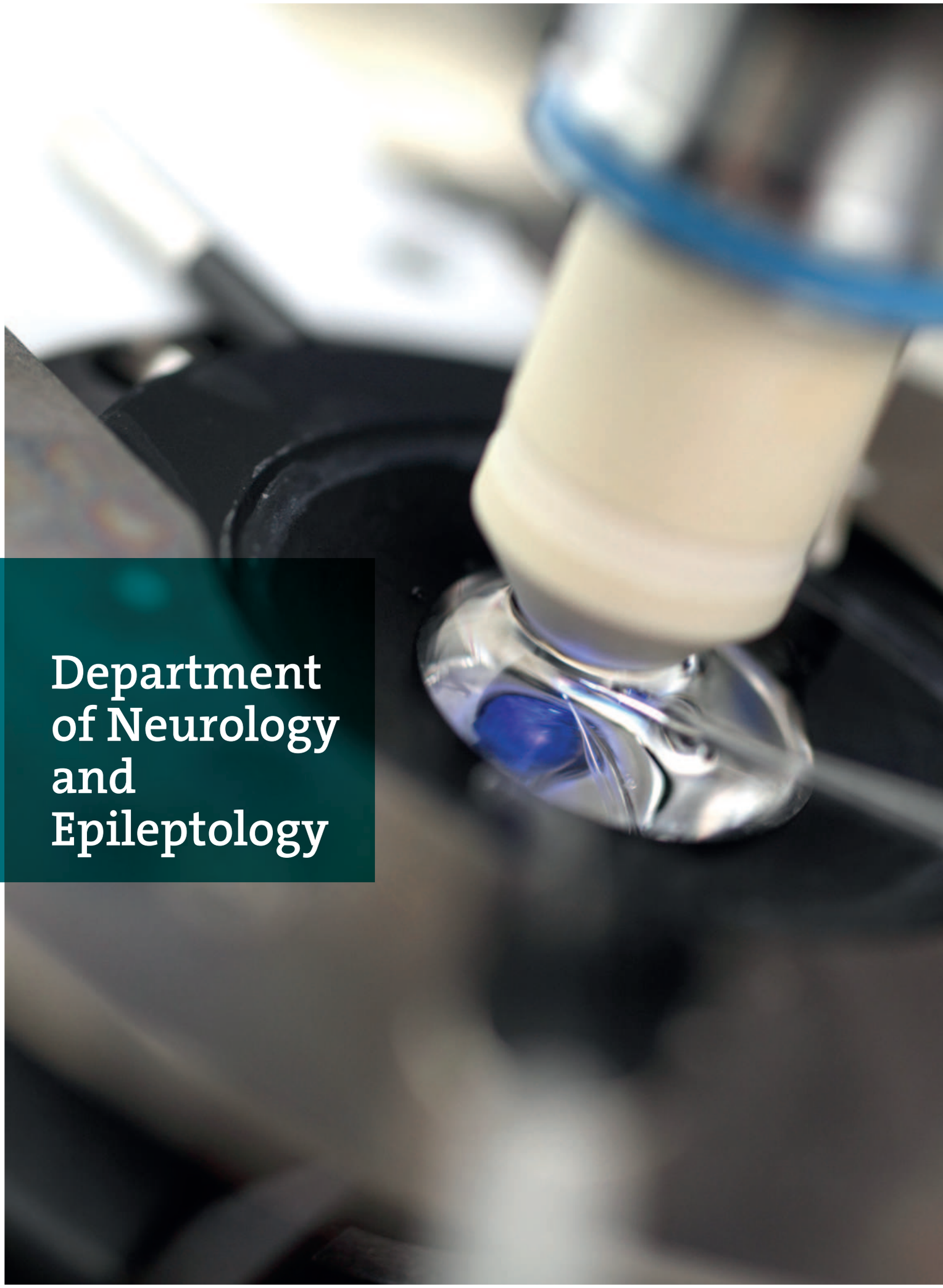
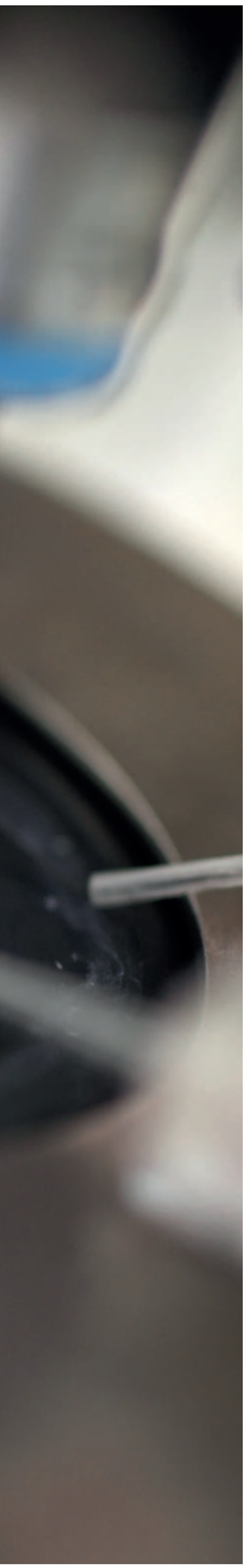


Department of Neurology and Epileptology

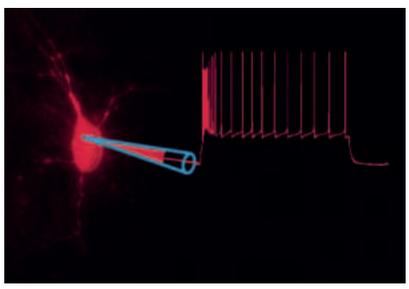


Prof. Dr. Holger Lerche heads the Department of Neurology and Epileptology.

Departmental Structure

As part of the Hertie Center of Neurology and together with the other Neurological Departments, the Department of Neurology and Epileptology is dedicated to provide excellence in patient care for 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 basic and clinical research activities are focused in the fields of epileptology and associated paroxysmal neurological disorders, neuromuscular diseases, headache and pain disorders.

The inpatient unit with 22 beds (Wards 42/43L), running under the supervision of Drs. P. Martin, S. Lauxmann, N. Winter and J. Kegele, includes long-term complex treatment for difficult epilepsy cases and a Video-EEG-Monitoring Unit (headed by Dr. S. Lauxmann), in which inpatients are continuously and simultaneously monitored with video and electroencephalography (EEG) for differential diagnostic and presurgical evaluations. This unit and the epilepsy surgery program, providing effective treatment for patients resistant to anti-seizure medication, vagal nerve and other brain stimulation paradigms are run in close cooperation with the Departments of Neurosurgery (Dr. S. Ethofer, Prof. Dr. J. Honegger, Dr. G. Naros) and Neuropediatrics (Dr. M. Alber).



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

The inpatient service is complemented by a Day Care Clinic, implemented and headed by Prof. Dr. A. Grimm as part of the whole Neurology Clinic, offering diagnostics and therapeutic interventions for patients with a broad spectrum of neurological conditions which can be handled on a day-to-day basis. The electromyography laboratory and nerve and muscular ultrasound of the Neurological Clinic are headed by Prof. Grimm, Dr. Martin and Dr. Winter, the EEG unit by Drs. Lauxmann, Schreiber and Kegele.

Our outpatient clinics offer consulting and treatment in particular for difficult cases and specific questions, such as pregnancy under specific treatments and genetic aspects. They are focused on epilepsy (Prof. Lerche, Drs. Schreiber, Lauxmann and Kegele), headache and neuropathic pain syndromes (Prof. Dr. S. Schuh-Hofer), and neuromuscular diseases (Prof. Grimm, Drs. Martin and Winter), and rare, genetically determined paroxysmal neurological and ion channel disorders (Prof. Lerche, Dr. Lauxmann). We run a clinical study center (Profs. Schuh-Hofer, Grimm, Lerche, Drs. Lauxmann, Kegele) which has been involved in diverse medical trials, including some investigator-initiated trials, to explore novel treatment options, as listed in the Appendix. 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 for Clnical Brain Research with the aim to work on clinically driven basic research questions and rapidly transfer scientific progress into clinical practice, as described in the descriptions of the individual research groups. Our main research topics are:

Our main research topics are

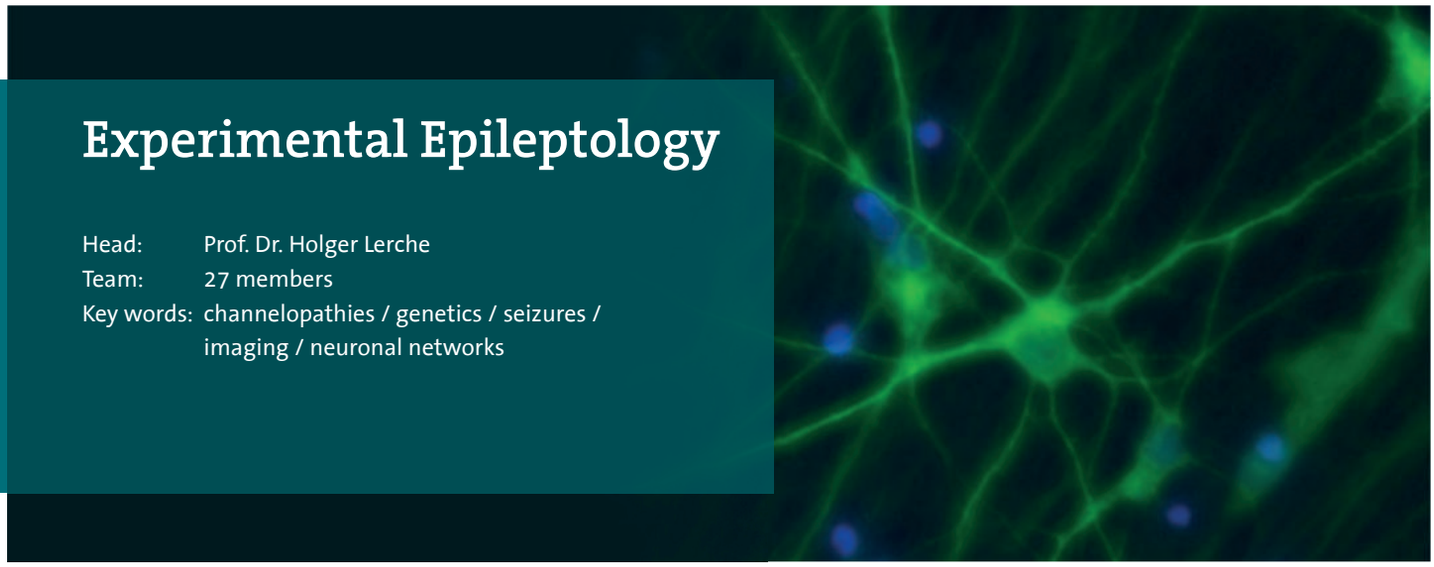
(i) The genetics and pathophysiology, and precision treatments of mainly hereditary epilepsy syndromes and related neurological disorders, such as migraine, pain and paroxysmal dyskinesias, using a wide range of basic science and clinical experimental methods

(ii) Diagnosis, therapy monitoring and personalized therapies of neuromuscular diseases, especially hereditary and immune-mediated polyneuropathies and peripheral nerve injuries using high resolution ultrasound, optoacoustic imaging and MRI (with the Dept. Neuroradiology)

(iii) Structural and functional brain imaging using MRI, EEG and MEG to detect epileptogenic lesions, active foci, and epileptogenic as well as migraine-/pain-related networks in the brain (with the MEG Center and the Depts. Neuroradiology and Neuroimaging)

Experimental Epileptology

Head: Prof. Dr. Holger Lerche
Team: 27 members
Key words: channelopathies / genetics / seizures / imaging / neuronal networks



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

The main 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, analyzing their functional consequences to understand the pathophysiology, and exploring new mechanism-based personalized therapies. We use non-neuronal cells, neuronal cultures including those from induced pluripotent stem cells and human brain slices, and gene-targeted mouse models. We apply machine learning for therapeutic predictions and to develop automated analyses of seizure semiology and EEGs. Finally, we apply clinical neurophysiological and imaging methods to better understand structural and functional aspects of epilepsies and migraine.

Das Hauptziel 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,, untersuchen deren funktionelle Auswirkungen, um die Pathophysiologie zu verstehen, und erforschen neue Therapien, die auf den identifizierten Mechanismen beruhen. Wir verwenden Oozyten oder Säugerzellen, neuronale Kulturen einschließlich induzierter pluripotenter Stammzellen und humanen Hirnschnitten, und genetisch veränderte Mausmodelle. Maschinelles Lernen wird verwendet für Therapievorhersagen und für die Entwicklung automatisierter Analysen der Anfallssemiologie und des EEGs. Schließlich wenden wir klinisch neurophysiologische und bildgebende Methoden an, um strukturelle und funktionelle Aspekte bei Epilepsien und Migräne besser zu verstehen.

Epilepsy affects up to 3% of people during their lifetime, with a genetic component playing a major pathophysiological role in almost 50% of cases. To explore the genetic architecture, mechanisms and new therapies of epilepsy we have initiated national research networks (DFG FOR-2715, BMBF Treat-ION, EKFS Precise.net) and largely contribute to international Initiatives (ILAE consortium on the genetics of complex epilepsies, Epi25, ILAE Genomics). Important examples from the last years are the identification of 4-aminopyridine as a new and specific (precision) treatment for a severe epilepsy with developmental problems of early childhood caused by mutations in *KCNA2* (Hedrich, Lauxmann et al. 2021, with AG Hedrich, HIH best paper of the year award 2022 to Ulrike Hedrich and Stephan Lauxmann), very clear genotype-phenotype correlations with high relevance for clinical management for *SCN8A*-related epilepsies (Johannesen, Liu et al. 2022), and the latest genome-wide association study for epilepsy revealing 26 loci and subtype-specific architectures. In this context, we found out in a whole exome study of rare epilepsy predisposing variants that important functional gene groups of synaptic and ion channels/receptor genes show subtype-specific patterns of disease burden in generalized vs. focal epilepsies (e.g. affecting inhibitory vs. excitatory pathways), and that signals from common and rare variants converge (Koko et al. 2021). With partners in Dianalund/Denmark and Prof. Ludger Schöls (HIH, Neurodegeneration), we also described that defects in a crucial ion channel gene (*SCN8A*), cause rare genetic forms of ataxia (Lyu, Boßelmann et al. 2023). In collaboration with Prof. Nico Pfeiffer (Methods in Medical Informatics, University of Tübingen), we developed multi-task machine learning methods to predict the functional impact of genetic variants in ion channels, which plays a critical role to select specific therapies that either block or enhance the chanels' activity (Boßelmann et al. 2023). C. Boßelmann recently

completed a Research Fellowship at the renowned Cleveland Clinic (Cleveland, OH, USA) and is investigating the role of genetic variants in epilepsy surgery outcomes (Boßelmann et al., under review). In collaboration with the machine learning Excellence Cluster and the Tübingen AI Center, we are developing further methods to apply machine learning tools to clinical datasets and research questions to improve diagnoses and therapy in epilepsy and neuropathies (S. Liebe, N. Winter, H. Lerche with collaborators in EKFS college ClinBrAIn led by Prof. Macke, and in further projects of S. Liebe).

With the aforementioned collaborative projects funded by DFG, BMBF and EKFS, 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 a specific goal to enable precision treatment. Our findings are directly delivered to patients through molecular therapeutic boards attached to the German Academy of Rare Neurological Diseases (DASNE) and the Center for Rare Diseases (ZSEs) in Baden-Württemberg and through a structured process for drug repurposing. Functional implications of selected mutations are examined in neuronal expression systems, such as transfected primary neuronal cultures, genetically altered animal models mimicking human disease, and also iPSC-derived neuronal cultures and native human slices from patients undergoing neurosurgery. To gain insight into the exact mechanisms as to how epilepsy develops as a consequence of a genetic defect, we investigate the electrophysiological properties on both single cell and network levels and apply brain region- and time-specific single cell RNA sequencing in distinct neuronal subpopulations.

We develop and translate advances in structural and functional imaging into clinical applications to improve the understanding of pathophysiology, diagnosis and treatment of structural and genetic epilepsies. We apply several computational, post-processing methods including voxel-based morphometry, machine learning and network analysis based on MRI, MEG, HD-EEG and PET (e.g. Kronlage et al. 2024). Our work is focused on epilepsy but we are active in collaborative projects with other groups in Tübingen and worldwide (e.g. ENIGMA, MELD). A special interest lies in ultra-high field MR imaging in collaboration with the Max-Planck-Institute for Biological Cybernetics (Prof. Klaus Scheffler, Tübingen) and the HIH research group of Prof. Esther Kühn (Translational imaging for cortical microstructure), supported by intramural funding.

Finally, with the support of DFG and UKT intramural research funding, we aim to develop biomarkers for migraine and to unravel pathophysiological mechanisms regarding the strong relationship between sleep and pain. In collaboration with Dr. Dr. R. Helfrich and funded by the DFG (associate project to SFB 1158 from Heidelberg University), we assessed the effects of sleep deprivation on cortical excitability (Lendner JD et al.) and its relation to sleep deprivation induced pain hypersensitivity (manuscript in preparation). Our findings will now be extended to migraine. We have also established a human pain model which enables to unravel the role of CGRP for the prophylactic effects of anti-migraine drugs.

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(*/#equally contributing first/senior authors)

Neuromuscular Imaging

Head: Prof. Dr. Alexander Grimm
Team: 17 members
Key words: nerve ultrasound / immune-mediated neuropathies / polyneuropathies / nerve trauma / nerve disorders

High-resolution ultrasound is a highly efficient method for imaging peripheral nerves and muscles. The aim of our working group is to establish and continuously improve the diagnostics and progression assessment of neuromuscular diseases. Next to the establishment of normative nerve size and echo intensity data, we examine nerve pathology, i.e. nerve enlargement, atrophy, alteration of echo intensity and perineural tissue in neuropathies, nerve traumata, nerve tumors and systemic nerve and muscle disorders, such as motoneuron diseases, lysosomal storage diseases or autoimmune 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 motoneuron diseases, myopathies and radiculopathies as well as in nerve trauma. Here, ultrasound is an important biomarker of muscle changes under therapy. As peripheral nerve disorders are a common problem, we can reach well defined cohorts and thus establish our method in sufficient sample sizes.

Der hochauflösende Ultraschall ist eine hoch effiziente Methode zur Darstellung peripherer Nerven und Muskeln. Ziel unserer Arbeitsgruppe ist es die Diagnostik und Verlaufsbeurteilung neuromuskulärer Erkrankungen zu etablieren und stetig zu verbessern. Hierbei untersuchen wir Patienten mit Polyneuropathien, Nervenverletzungen, -tumoren und Patienten mit Systemerkrankungen, z.B. Motoneuronerkrankungen oder lysosomalen Speichererkrankungen. Sonographisch spielen vor allem Veränderungen der Nervengröße, der Nervenechogenität und des umliegenden Gewebes eine Rolle. Uns interessieren außerdem Veränderungen, die die Regeneration von Nerven nach Operationen oder nach medikamentösen Therapien erklären könnten. Zuletzt sehen wir uns den Muskel an, sei es bei Motoneuronerkrankungen, Myopathien oder auch Wurzel- und Nervenschädigungen.

Different types of polyneuropathies 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 sonomorphological findings and thus simplify an examiner-independent scanning process. Thereof we could now use this scoring tool to further establish nerve ultrasound In other, even rarer neuropathies, e.g. immune-related adverse events or in radiculopathies (1-6).

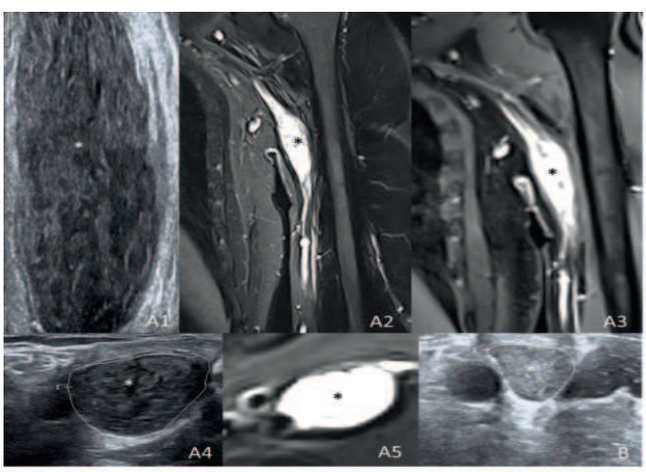
In 2021, we have been able to establish shear wave elastography (SWE) as a new method in our laboratory and since then investigated in several neuromuscular disorder as well as old age (5). In addition to several scientific papers, Dr. med. Benedict Kleiser was awarded the Ulrich Brodeßer FSHD Prize 2023. He comprehensively studied the potential added value of SWE in fascioscapulohumeral dystrophy (FHSD) and characterized the complex interplay between dystrophy and muscle stiffness.
With cooperation partners from i.e. Jena, Basel and others we could publish several works concerning imagning of the peripheral nerves in neuropathies (7-10).

In addition, we were able to further expand our cooperation with the pediatric clinic, neuroradiology neurosurgery and hand, plastic, reconstructive and burn surgery in the Tübinger Nerve Team TNT. Various studies are currently still underway, an interdisciplinary textbook could already be published.

Since 2021 a national network has been established with 8 other centers, among these Charite Berlin, MH Hannover, Göttingen and Cologne - called the Neuritis Netz. This cooperation tries to further elaborate epidemiological data concerning immuno-neuropathies, and establish a clinical diagnostic algorithm. Furthermore, scientific collaboration is ongoing including common grant projects. Some projects have already been finished (9) others are on the way.

An important role of our group is the establishing and collaboration in AWMF guidelines concerning polyneuropathies (DGN, Grimm and Winter), nerve traumata (Winter and Grimm) and nerve tumors (Grimm and Winter) as well as treatment options in immunotherapies (DGN, Grimm).

In the recent past, our group was increasingly involved in innovative clinical trials in neuromuscular disorders (see list of clinical trials in the appendix). Two key studies should be further explained: One study together with ARGENX tries to implement a FcRn (neonatal FC receptor) modulator (Efgartigimod) in patients with autoimmune myositis. FcRn plays an important role in recycling IgG and blocking this receptor leads to depression of IgG antibodies. This leads also to depletion of pathogenic antibodies, which cause myositis. The medication was already established in myasthenia gravis. Another study with Sanofy handles the complement inhibitor Riliprubart in patients with CIDP (chronic immune-mediated neuropathies). Complement deposition is probably one reason of nerve inflammation in CIDP and thus blocking complement cascade might reduce inflammation. This study is important due to the lack of treatment options in many patients suffering from CIDP.



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]).

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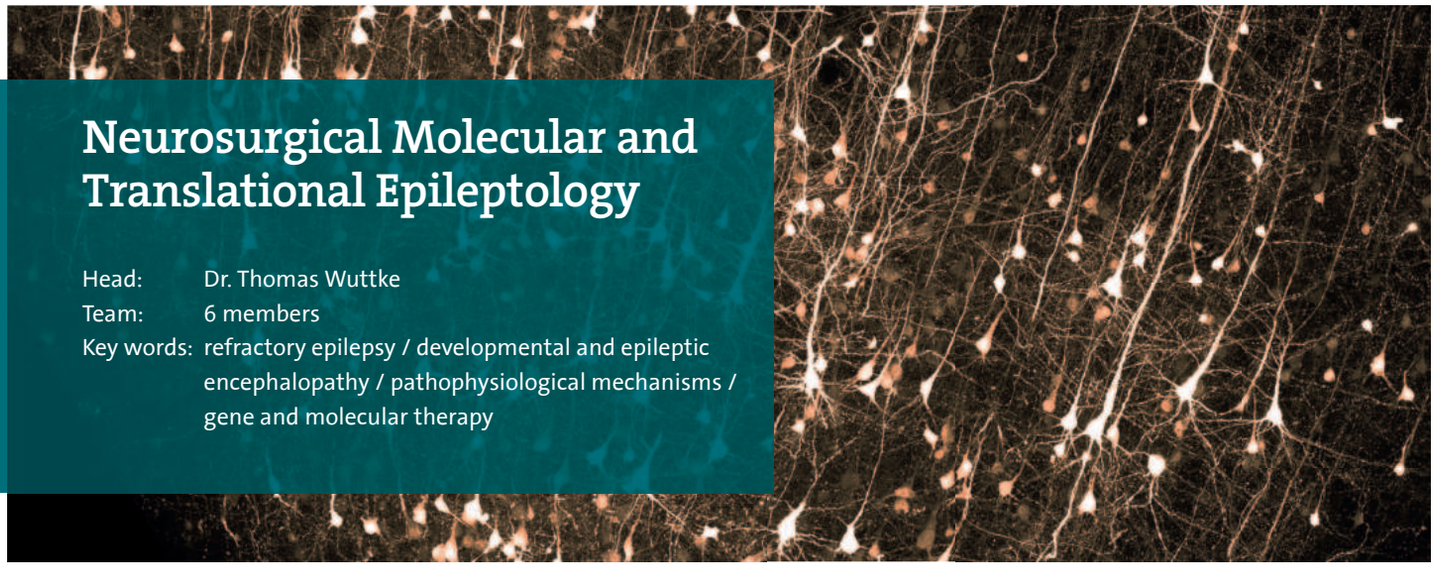
Neurosurgical Molecular and Translational Epileptology

Head: Dr. Thomas Wuttke
Team: 6 members
Key words: refractory epilepsy / developmental and epileptic encephalopathy / pathophysiological mechanisms / gene and molecular therapy



Human cortical brain slice culture transduced with an adeno-associated virus

About 30-50 % of all epilepsies are of genetic origin, while the remaining ones are mainly lesional, inflammatory or of unknown origin. Roughly 30 % of all cases are pharmacoresistant and a large proportion of patients are not amenable to surgical treatment. Our group is interested in developing new treatment options for patients affected by drug resistant seizures and associated encephalopathic syndromes.

Ungefähr 30-50 % aller Epilepsien haben einen genetischen Ursprung, die übrigen sind meist läsionell oder entzündlich bedingt, oder die Ursache bleibt unbekannt. Etwa 30 % aller Betroffenen sind pharmakoresistent und einem großen Teil dieser Patienten kann keine epilepsiechirurgische Behandlung angeboten werden. Das Ziel unserer Gruppe ist es neue Behandlungsoptionen für Patienten mit medikamentenresistenten epileptischen Anfällen und assoziierten enzephalopathischen Syndromen zu entwickeln.

Developmental and epileptic encephalopathies (DEEs) are genetically determined brain-wide disorders, which are considered one of the leading causes of pharmacoresistant epilepsy in children. DEEs delineate a spectrum of neurological syndromes with early childhood-onset of intractable seizures, neurodevelopmental delay or regression and clinical features of autism spectrum disorder. Notably, these latter symptoms can also arise independent of epileptic seizures. Standard anticonvulsant treatment has only limited impact on the course of disease and there are no established therapies available preventing the emergence of neurodevelopmental deficits.

In adults, drug resistant epilepsy is mostly associated with different types of structural alterations such as tumors, gliotic scars or hippocampal sclerosis. Additional pathologies include cortical architectural, cytological and migrational abnormalities (cortical dysplasias and periventricular gray matter heterotopias), which like DEEs also account for a significant proportion of pediatric cases with intractable epilepsy. Particularly when multilocular, bilateral or when localized in subcortical regions, eloquent areas of the CNS or when extending across multiple cortical gyri, surgical treatment becomes increasingly challenging or impossible.

Our work investigates the mechanistic underpinnings of DEEs on both neuronal network- and molecular levels, explores strategies for modulation of hyperexcitable states and seeks to derive new therapies for non-genetic focal epilepsy and DEE. Toward these goals, we are employing a wide range of state-of-the-art electrophysiological, imaging and omics-based techniques (Layer et al. 2021, Layer et al. 2023, Bayraktar et al. 2023, Wuttke et al. 2018). These approaches are complemented by analyses in neurosurgically resected tissue to investigate the applicability of pathophysiological and therapeutic concepts to human CNS (Schwarz et al. 2019, Bak et al. 2024, Yuste et al. 2020).

Regarding DEE, our research interests are driven by the dissection of the underlying pathophysiological correlates of DEE (such as Dravet syndrome; funded within the DFG research unit FOR 2715) and by investigation of the therapeutic potential of brain-wide and local circuit modulation by chemogenetics and cell replacement (funded by the DFG). Furthermore, we seek to identify entirely new targets for Dravet syndrome based on transcriptomic studies (Layer et al. 2023, Yuste et al. 2020). A second focus is on providing pre-clinical evidence for different types of targeted treatments aimed at improving the developmental outcome of KCNQ-related encephalopathies. This work is conducted within the Joint Transnational Call of the European Joint Program Rare Disease (EJP RD) as part of a nationally funded (by BMBF for Germany) consortium with partners in Belgium, France, Italy and Germany.

Lesional focal epilepsy on the other side is tackled with collaborators at UNSW Sydney and in several project lines with industry. Together we are exploring both viral and non-viral gene therapeutic concepts. This work is based on several model systems including ex vivo culturing of ethically sourced tissue derived from epilepsy surgery to directly address questions of translatability to the human brain.

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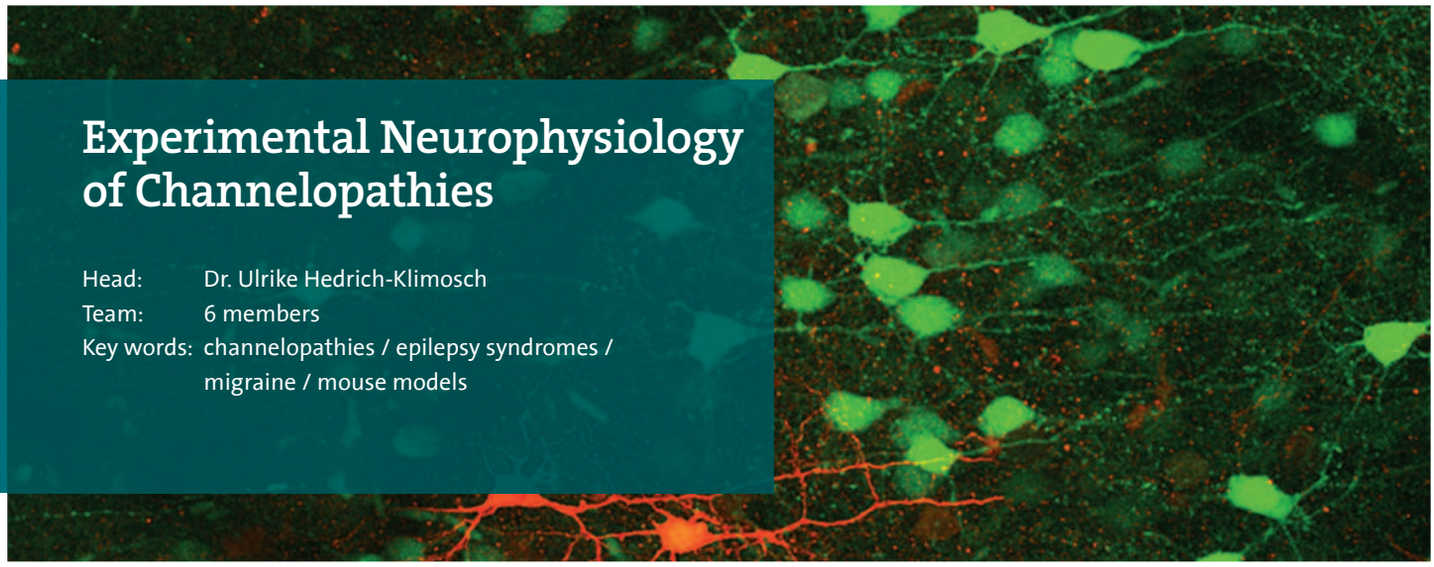
Experimental Neurophysiology of Channelopathies

Head: Dr. Ulrike Hedrich-Klimosch
Team: 6 members
Key words: channelopathies / epilepsy syndromes / migraine / mouse models



In utero electroporated cortical layer 2/3 pyramidal neurons

Our group is interested in understanding the molecular mechanisms of so-called channelopathies, diseases caused by genetic variants in ion channel genes, including epilepsies and migraine, two of the most common neurological diseases, and to develop therapeutic interventions.

Unsere Gruppe ist daran interessiert, die molekularen Mechanismen der so genannten Kanalopathien zu verstehen, d. h. Krankheiten, die durch genetische Varianten in Ionenkanalgenen verursacht werden, darunter Epilepsien und Migräne, zwei der häufigsten neurologischen Krankheiten, und therapeutische Interventionen zu entwickeln.

Epileptic seizures result from spontaneous, synchronous electrical activity of groups of neurons in the brain, manifesting in a wide range of clinical symptoms, such as tingling in an extremity to impaired consciousness, complex actions, or generalized seizures. Migraine attacks often begin with an aura, which classically manifests as visual complaints. These auras are due to cortical spreading depolarization (CSD), a wave of neuronal depolarization that travels slowly across the cerebral cortex. Thus, both diseases are associated with pathological electrical activity, epilepsy with a fast, migraine with a slow propagation of abnormal activity. Interestingly, defects in the same gene can cause epilepsy and migraine, and both diseases can also occur in the same patient and trigger each other. We aim to understand the relationship between genetic variants and rare ion channel diseases at the molecular, cellular and network level and the underlying mechanism of hyperexcitability of these diseases (epileptic seizures vs. CSD) to develop new therapies. Besides this, we are involved in modeling approaches (in collaboration with Prof. Jan Benda; Koch et al., 2023), the functional characterization of specific disease-causing variants (Seiffert et al., 2022), and therapy development (Müller et al., 2023) and in developing a chimeric brain slice culture model to study neurological diseases (in collaboration with Dr. Deborah Kronenberg-Versteeg).

A primary focus of our research is to unravel the epileptogenic mechanisms underlying *KCNA2*-associated encephalopathies (Syrbe, Hedrich et al., 2015). This involves employing in utero electroporation techniques to introduce *KCNA2* variants and the use of newly developed knock-in mouse models harboring gain- or loss-of-function variants, a collaborative effort with Th. Ott from the IZKF-Core Facility Transgenic Animals. Collaborating with O. Garaschuk from the Institute of Neurophysiology, we investigate the critical time windows of vulnerability associated with *Kcna2* variants, along with studying the dysfunction and miswiring of developing neural networks in our mouse models within the DFG Research Unit FOR2715 (Li et al., 2023). Single nuclei RNA sequencing is performed to identify transcriptional changes in these newly developed mouse models. In addition to exploring the pathophysiology, our research also focuses on identifying new treatment options for patients with *KCNA2* gain-of-function variants using 4-aminopyridine, assessing its efficacy across various gain-of-function variants through experiments conducted on *Xenopus laevis* oocytes (Hedrich, Lauxmann et al., 2021). Our work in this area was recognized with the Eva-Luise-Köhler Prize for rare diseases in 2018. Furthermore, we are actively developing efficient *Kcna2* antisense oligonucleotides, which have undergone testing in HEK cells stably expressing $K_V1.2$ subunits as well as in primary neuronal cultures. These oligonucleotides will soon be employed in our knock-in gain-of-function mouse model to selectively downregulate $K_V1.2$.

As part of the BMBF-funded Treat-ION consortium on Neurological Ion Channel and Transporter Disorders, our research is centered on understanding the pathophysiological mechanisms of hemiplegic migraine (HM), a severe monogenic subtype of migraine characterized by unilateral motor weakness during the aura. This condition is caused by variants in genes such as *SCN1A*, which encodes voltage-gated sodium channel $Na_V1.1$, and *SLC1A3*, encoding the glutamate and chloride transporter EAAT1. We use transgenic mouse models to investigate these mechanisms. We have conducted comprehensive studies on the pathomechanisms underlying cortical hyperexcitability in HM using a transgenic *Scn1a* knock-in HM mouse model. Through multimodal analysis, we have observed increased susceptibility to cortical spreading depression (CSD) in heterozygous mice. Additionally, we have noted hyperactivity of inhibitory interneurons and elevated extracellular potassium levels in the early phase of CSD in brain slices of heterozygous mice. These findings suggest a potential mechanistic link between interneuron hyperactivity and the initiation of CSD (Auffenberg, Hedrich et al, 2021). Our ongoing research endeavors include the characterization of epileptic seizures and CSDs in *Slc1a3* mutant mice, funded by the BMBF project Treat-ION. We are also investigating personalized treatment approaches using allele-specific antisense oligonucleotides and exploring the differential pathophysiology of migraine compared to epilepsy in *Scn1a* knock-in mouse models, funded by the Bridging Grant Funding Program of the Hertie Institute for Clinical Brain Research.

Moreover, our interest lies in exploring a novel aspect of Dravet Syndrome (DS) pathophysiology: the interactions between neurons and oligodendrocytes. In a significant proportion of DS patients, *SCN1A* variants have been pinpointed, leading to the loss of function of the $Na_V1.1$ channel, the primary Na^+ channel in inhibitory neurons. Consequently, there is a decrease in inhibition due to reduced action potential initiation and propagation. Teaming up with F. Pfeiffer from the Institute of Neurophysiology and I. Nikić-Spiegel from the Research Group Molecular Mechanisms of Axonal Injury, CIN, we are delving into the effects of *SCN1A* variants on neurons, oligodendrocyte precursor cells (OPCs), and oligodendrocytes. These cell types all express the $Na_V1.1$ channel, share common embryonic origins, and are deeply interconnected during development. Additionally, we are interested in morphological alterations in the axon initial segment and axons and to explore myelination in *Scn1a* mutant mice. This research project is funded by the Gruppo Famiglie Dravet Associazione ONLUS, in collaboration with other European Dravet Foundations. Within the European Joint Program on Rare Diseases (EJP RD), as part of a consortium funded nationally by DFG in Germany, we develop targeted treatments for Dravet Syndrome. Our approach involves knock-in animal models as well as human disease models, with partners in France, Italy, Belgium, the Netherlands, and Germany.

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Department of Neurology and Interdisciplinary Neuro-Oncology

Prof. Dr. Dr. Ghazaleh Tabatabai heads the Department of Neurology and Interdisciplinary Neuro-Oncology.

Departmental Structure

The Department of Neurology and Interdisciplinary Neuro-Oncology treats patients with common neurological diseases and patients with neurooncological diseases.

The clinical and scientific expertise of the Department of Neurology and Interdisciplinary Neuro-Oncology (Director: Prof. Dr. Dr. Ghazaleh Tabatabai) covers complex neurooncological diseases, i.e. patients with primary or metastatic diseases in the nervous system and patients with neurological syndromes caused with cancer therapies. With its outreach activities, the department provides impetus for the region.

Specialized outpatient clinics and clinical trials office offer expert counseling of patients and the best available therapy. Clinical trials are an integral part of the clinical care of this department. Consequently, the outpatient clinics and the clinical trials office of the Department are realized by overlapping persons. The Department is very closely connected with the Departments of Neurosurgery and Radiation Oncology, e.g. by a shared ward and shared outpatient clinics.

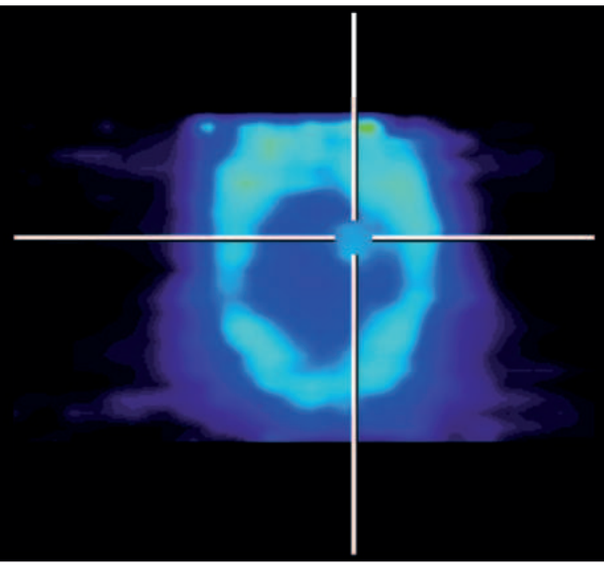
Neuro-Oncology is also represented and a major area in the Comprehensive Cancer Center Tübingen-Stuttgart. The Center of Neuro-Oncology forms a multidisciplinary network of all clinical disciplines, and the Department of Neurology with Interdisciplinary Neuro-Oncology is an integral part of the CNO, Prof. Dr. Dr. Tabatabai furthermore acts as the spokesperson of the CNO.

The Department of Neurology and Interdisciplinary Neuro-Oncology provides the clinical basis and the roof for three research groups at the Hertie Institute for Clinical Brain Research. All research groups have a strong interest in bridging basic science and health care in translational research concepts. Currently, three research groups exist: Health Care Research in Neuro-Oncology (PD Dr. Mirjam Renovanz), Experimental Pediatric Neuro-Oncology (Dr. Daniel Merk), and Clinical and Experimental Neuro-Oncology (Prof. Dr. Dr. Ghazaleh Tabatabai). The research laboratories are located in the Hertie Institute for Clinical Brain Research, i.e. near the hospital. Close collaborations exist with the other departments and research groups at the Hertie Institute and at the Medical Faculty. The Tabatabai Lab is a founding member in the Cluster of Excellence 2180 “Image-guided and Functionally Instructed Tumor Therapies” (iFIT).

The Department of Neurology and Interdisciplinary Neuro-Oncology offers lectures and seminars for medical students, physicians in training and nursing staff. A monthly interdisciplinary Neuro-Oncology Tübingen Curriculum has been initiated in 2020 and covers current topics and new insights into all fields of neuro-oncology. Furthermore, the department contributes to the lectures of the Center of Neurology, e.g. lectures within the Medical Curriculum or postgraduate education in scientific colloquia and in therapy seminars. All these activities are frequently evaluated by the students and by participants. Recently, the Department has published a book in the field of “Neurooncology” (Kohlhammer Verlag) with the aim to facilitate a systematic approach to this interdisciplinary field.

Experimental and Clinical Neuro-Oncology

Head: Prof. Dr. Dr. Ghazaleh Tabatabai
Team: 32 members
Key words: molecular neuro-oncology / acquired resistance to therapy / treatment-induced vulnerability / rational combination therapies / early phase clinical trials



Tumors in the central nervous system either arise from CNS-resident cells (primary CNS tumors) or are metastases from tumors outside the CNS. Metastatic disease in the CNS can present as parenchymal lesions or leptomeningeal disease. Our group investigates basic science, translational, and clinical questions. We investigate clinical questions in basic science projects. Conversely, we translate current research results from basic science into clinical studies. Furthermore, we have recently started to address the topic of diversity in Neuro-oncology leadership within the DivINe commission of the NOA (scientific association of Neuro-Oncology). Selected selected projects are presented below.

Tumoren im zentralen Nervensystem entstehen entweder aus ZNS-residenten Zellen (primäre ZNS-Tumoren) oder sind Metastasen von Tumoren außerhalb des ZNS. Metastasierende Erkrankungen im ZNS können als parenchymale Läsionen oder als leptomeningeale Erkrankung auftreten. Unsere Arbeitsgruppe untersucht grundlagenwissenschaftliche, translationale und klinische Fragestellungen. Wir untersuchen klinische Fragstellungen in grundlagenwissenschaftlichen Projekten. Umgekehrt überführen wir aktuelle Forschungsergebnisse aus der Grundlagenwissenschaft in klinische Studien. Zudem widmen wir uns relevanten gesellschaftliche Themen, wie Chancengleichheit, in diesem Kontext analysierten wir geschlechtsspezifische Unterschiede in Leitungsfunktionen, im Bereich der Neuroonkologie. Einige ausgewählte Projekte werden im Folgenden vorgestellt.

The scientific objectives of our group are

(i) To understand treatment-induced immunological and molecular vulnerabilities
(ii) To design rational novel combination therapies
(iii) To discover molecular markers that can serve as biomarker in the clinical setting
(iv) To establish novel preclinical models
(v) To accomplish continuous forward and backward clinical translation, i.e. to conduct innovative phase I clinical trials and to design preclinical research projects based on the clinical experience
(vi) Social commitment in Neuro-Onkology

Treatment-Treatment of recurrent H3 K27M–mutant diffuse midline glioma (DGM) with ONC201 (Dordaviprone)

Histone 3 (H3) K27M mutation is common in diffuse midline glioma (DMG) and associated with a poor median overall survival (OS) of approximately 1 year from diagnosis. Radiotherapy remains the standard of care, no systemic therapies have proven to be effective, and bona fide responses have rarely been reported in the recurrent setting. As a highly clonal, disease-initiating mutation, H3 K27M may provide a vulnerability for targeted therapy. ONC201 (dordaviprone) is an oral, blood-brain barrier penetrant, small-molecule bitopic antagonist of dopamine receptor D2/3 (DRD2/3) and allosteric agonist of the mitochondrial protease caseinolytic mitochondrial matrix peptidase proteolytic subunit (ClpP). Both DRD2/3 and ClpP have been suggested to play a role in gliomas. DRD2 is overexpressed in multiple cancers, including glioblastoma where it was required for tumor growth in vivo and linked to a poor prognosis. Downstream mitochondrial effects of ONC201 include altered tumor cell metabolism resulting in reversal of pathognomonic loss of H3 K27me3 in H3 K27M–mutant glioma cells. In preclinical in vivo brain tumor models, including H3 K27M–mutant glioma single-agent ONC201 has shown antitumor efficacy. In a pooled analysis of data from five separate clinical trials of ONC-201 as a monotherapy in patients with recurrent or progressive H3K27M DGM we could demonstrate that the single-agent responses by ONC201 were very durable, clinically efficient and well tolerated. Thus, ONC-201 is a leading candidate for further study.

Imaging biomarker in patients with intracranial meningioma

There are no effective medical therapies for patients with meningioma who progress beyond surgical and radiotherapeutic interventions. Somatostatin receptor type 2 (SSTR2) represents a promising treatment target in meningiomas. We conducted a multicenter, single-arm phase II clinical study (NCT03971461) to evaluate the SSTR2-targeting radiopharmaceutical 177Lu-DOTATATE for its feasibility, safety, and therapeutic efficacy in these patients. This study revealed that treatment with 177Lu-DOTATATE was well tolerated. The predefined PFS-6 threshold was met in this interim analysis, thereby allowing this multicenter clinical trial to continue enrollment. 68Ga-DOTATATE PET may be a useful imaging biomarker to assess therapeutic outcome in patients with meningioma.

Functionally-instructed modifiers of response to ATR inhibition in experimental glioma

The DNA damage response (DDR) is a physiological network preventing malignant transformation, e.g. by halting cell cycle progression upon DNA damage detection and promoting DNA repair. Glioblastoma are incurable primary tumors of the nervous system and DDR dysregulation contributes to acquired treatment resistance. Therefore, DDR targeting is a promising therapeutic anti-glioma strategy. Here, we investigated Ataxia telangiectasia and Rad3 related (ATR) inhibition (ATRi) and functionally-instructed combination therapies involving ATRi in experimental glioma. We used acute cytotoxicity to identify treatment efficacy as well as RNAseq and DigiWest protein profiling to characterize ATRi-induced modulations within the molecular network in glioma cells. Genome-wide CRISPR/Cas9 functional genomic screens and subsequent validation with functionally-instructed compounds and selected shRNA-based silencing were employed to discover and investigate molecular targets modifying response to ATRi in glioma cell lines in vitro, in primary cultures ex vivo and in zebrafish and murine models in vivo.
ATRi monotherapy displays anti-glioma efficacy in vitro and ex vivo and modulates the molecular network. We discovered molecular targets by genome-wide CRISPR/Cas9 loss-of-function and activation screens that enhance therapeutic ATRi effects. We validated selected druggable targets by a customized drug library and functional assays in vitro, ex vivo and in vivo. In conclusion, our study leads to the identification of novel combination therapies involving ATRi that could inform future preclinical studies and early phase clinical trials.

Towards more diversity in Neuro-oncology leadership - the DivINe Initiative

In the past decade, there has been an increasing awareness of career disparities based on gender, ethnic, socioeconomic, and other diversities. While the proportion of female medical students in Germany has steadily increased to 67% (https://de.statista.com), less than 50% of practicing physicians and only 19–35% of full professors in the medical profession are women. A recent study on gender disparity in the neurosurgical specialty reported that women represent 35% of neurosurgery residents and 34% of board-certified neurosurgeons at academic medical centers in Germany but hold only 9% of neurosurgery leadership positions. The term “leaky pipeline effect” has been coined for the observation that there is a disproportionally higher drop-out rate of females as opposed to males over the course of an academic medical career. This phenomenon has been described in various medical disciplines, including neuro-oncology. With the objective to evaluate the gender distribution in leadership positions among neuro-oncology centers in Germanspeaking countries (Germany, Austria, and Switzerland; acronym: D-A-CH), we conducted a web-based study. While, in general, our results reflect data from previous surveys, the extent of gender disparity in neuro-oncology leadership within D-A-CH, especially in the top echelon, was remarkable. Not only are the vast majority (81%) of leadership positions held by men, but men are also more likely to be of higher academic rank and to have top leadership roles. To address these disparate career opportunities and professional inequities for women in neuro-oncology within D-A-CH, the “Diversity in Neuro-oncology” (DivINe) initiative was implemented as a regular NOA commission in 2021. Through tailored programs, we offer mentorship, peer support, and professional collaborations to female members of the neuro-oncology community.

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Experimental Pediatric Neuro-Oncology

Head: Dr. Daniel Merk
Team: 3 members
Key words: pediatric brain tumors / functional genomics / CRISPR-Cas9

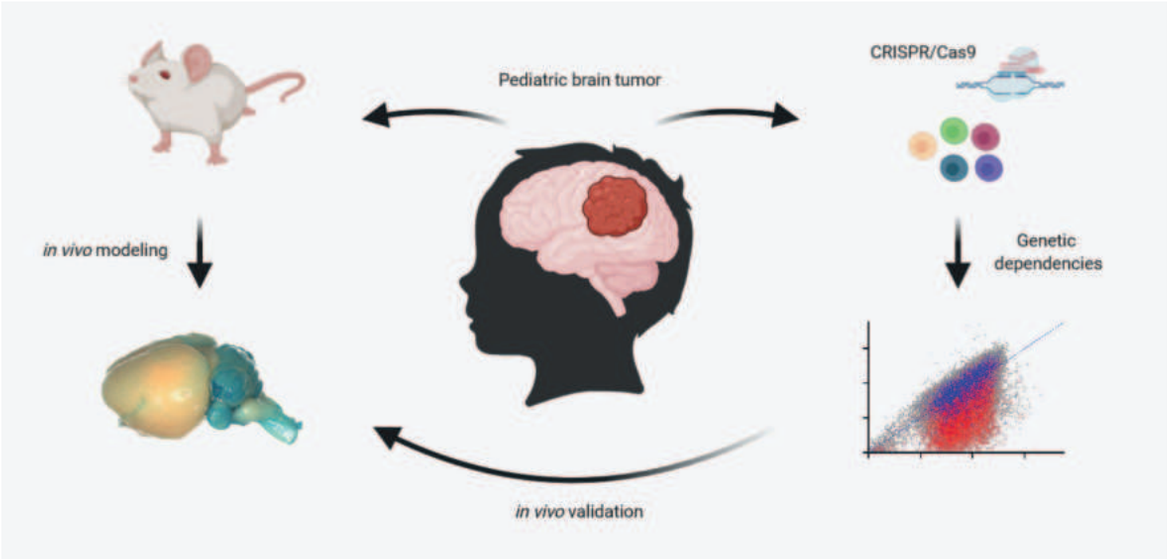
Our objective is to develop targeted therapies for rare brain tumors preferentially arising in young children. To this end, we are employing functional genome-wide screens to identify genomic vulnerabilities that will potentially guide the development of novel therapeutic interventions for these tumor entities.

Übergeordnetes Ziel unserer Arbeitsgruppe ist es, neue zielgerichtete Therapieansätze für seltene Hirntumore im Kindesalter zu entwickeln. In unserem Labor nutzen wir funktionelle Genomanalysen um Schwachpunkte im Genom dieser Tumore zu charakterisieren, welche als Ansatzpunkte für neue Therapieverfahren validiert werden.

Brain tumors are the leading cause of cancer-related deaths in infants, children, and adolescents. Our lab is mostly focusing on embryonal brain tumors including medulloblastoma, atypical teratoid rhabdoid tumors, and embryonal tumors with multilayered rosettes. Due to the lack of targeted therapies for these tumors, survival rates remain poor. The primary aim of the lab is to identify novel targeted therapies for children with brain tumors that will result in improved survival rates and fewer long-term side effects.

In the past, we have mostly relied on genetic mouse models to understand the pathology and molecular biology of medulloblastoma, the most common embryonal brain tumor in children. These studies have provided a better understanding of the cellular origin of these tumors (Grammel et al., Acta Neuropathologica, 2012). Additionally, we have provided further mechanistic insights of how CREBBP and EYA1, two genes which have long been known to be associated with medulloblastoma formation, contribute to the pathogenesis of these tumors (Merk et al., Developmental Cell, 2018; Merk et al., Developmental Neuroscience, 2020).

Recently, we have been focusing our efforts to identify actionable targets in embryonal brain tumors in order to improve therapeutic interventions for these tumors entities. We could previously show that inhibition of a specific subgroup of histone deacetylases is highly efficacious in inhibiting tumor growth of medulloblastoma cells (Pak et al., 2019). We are now expanding our analyses onto the entire genome by employing the CRISPR-Cas9 system which enables efficient and precise genome editing. Here, our primary focus is to use genome-wide loss-of-function approaches in order to identify genetic vulnerabilities that might serve as novel targets for therapy. Using this method, we were able to generate a comprehensive overview of genetic dependencies in atypical teratoid rhabdoid tumors, another type of pediatric brain tumor. Based on these results, we have generated a custom drug library that preferentially inhibits growth of these specific tumors, including several clinically approved drugs such as CDK4/6 inhibitors which would enable rapid translation of our findings to the clinic.



Functional genomic screening is used to identify genetic dependencies in human tumor cell cultures derived from embryonal brain tumors. Promising hits can be validated in suitable in vitro models and in vivo mouse models..

Resistance to anti-cancer treatments is a major obstacle to a cure for many brain tumor patients. We are therefore also interested in tumor-drug interactions, and how those relate to novel combination therapies and potential resistance mechanisms that will allow cancer cells to overcome targeted therapies. To this end, we are using both loss-of-function and gain-of-function approaches using the CRISPR-Cas9 system in a genome-wide fashion to investigate modulators of response to promising targeted treatments. In an ongoing project, we have provided evidence for substantial heterogeneity in response to CDK4/6 inhibition in atypical teratoid rhabdoid tumors, arguing that these tumors will present distinct mechanisms of resistance to this drug. Further evaluation of these findings will potentially influence the generation of novel combinatorial treatment options for these tumors.

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Health Care Research in Neuro-Oncology

Head: Prof. Dr. Mirjam Renovanz
Team: 4 members
Key words: neuro-oncology / health care research / patient-centered outcomes / targeted assessment

Neuro-oncological patients face the double burden of an oncological disease and neurological as well as psychological deficits over the disease trajectory. Adequate assessment of health-related quality of life (HRQoL), psychosocial burden and unmet needs remain challenging in neuro-oncological patients, because many instruments have been developed for general cancer patients. Furthermore, neuro-oncological patients might not be able to undergo a standardized assessment due to their unique symptom profile. At the same time is adequate assessment necessary for adequate support. Therefore, we evaluated alternative assessment methods, e. g. the direct assessment of unmet needs during the patient-doctor consultation in high-grade glioma patients (GLIOPT), as well as the development of an app-based assessment of health-related quality of life (TRACE). Furthermore, we prospectively evaluate the effect of psychological Interventions In patients and caregivers regarding compliance to tumor specific therapy (COCOON).

*Neuroonkologische Patienten sind gleichzeitig mit einer onkologischen Diagnose, neurologischen Symptomen sowie psychologischer Belastungen konfrontiert. Wir konnten in mehreren Arbeiten zeigen, dass neuroonkologische Patient*innen unabhängig von der Tumorentität belastet sind und, dass sie aufgrund ihres speziellen Symptomprofils auch spezifizierte Erhebungsinstrumente benötigen. Daher untersuchen wir neue Methoden der Bedarfserfassung, z.B. im Rahmen einer multizentrischen Studie ein direktes Assessment des Unterstützungsbedarfs im Arzt-Patienten-Gespräch bei Patienten mit höhergradigen Gliomen (GLIOPT) und wir entwickelten eine App-basierten Erhebung der Lebensqualität für Patient*innen in speziellen Behandlungssituationen (TRACE). In einer weiteren Studie untersuchen wir prospektiv den Effekt von psychologischen Intervention auf die Therapietreue.*

The scientific objectives of our group are

(i) To understand unmet needs of neuro-oncological patients and caregivers
(ii) To develop targeted assessment strategies to allow adequate support disease - but also situation specific
(iii) To develop innovative methods of psychosocial support
(iv) To validate our methods in clinical trials

Glioma patients in outpatient care-optimization of psychosocial care in neuro-oncological patients (GLIOPT)

We assessed in preliminary work the unmet needs of patients with brain tumors especially with high-grade gliomas. Subsequently we enrolled a prospective study to investigate whether a systematic implementation of signaling questions into the routine outpatient consultation will be helpful to provide adequate support for patients with high-grade gliomas.
It is was multicenter cluster randomized study with two arms. The intervention included an assessment of psychosocial distress of patients in doctor-patient conversation compared to assessment of psychosocial distress via questionnaire (control, standard of care). In total, 763 HGG patients were enrolled and 506 were included in the final analysis.

The assessment conducted directly by attending doctors was as effective than an assessment via a questionnaire regarding referral to psychosocial care. The trial is terminated and the results currently under evaluation.
Trial registration: German Clinical Trials Register, DRKS00018079.

Cancer patients under targeted therapy: App-based assessment of patient-reported outcomes (TRACE)
Cancer patients under targeted therapy are a heterogeneous patient group, mostly in later disease trajectory. After extended molecular diagnostics and discussion in the Molecular Tumor Board, they start with the recommended therapy. For patients in precision oncology trials, the main outcome is the PFS ratio, defined as the PFS interval associated with the molecularly instructed therapy of the individual patient (PFS 2) divided by the PFS interval associated with the last prior systemic therapy (PFS1). However, patient-reported outcomes are not considered so far.

We therefore developed an app for the assessment of health-related quality of life, psychosocial and symptom burden of the patients under molecular based therapy. It includes inter alia the following instruments: European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (disease specific), Distress Thermometer, Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH). The first part of the study proved usability and feasibility (Dörner L Neurooncol Pract. 2024). The next step is an application study in the Center of Personalized Medicine, Tübingen, which Is currently under development (Center for Personalized Medicine – App-based remote patient monitoring for optimization of health care, COAT).

Coaching for coping in glioblastoma patients and caregivers and its association with compliance to TTFields (COCOON)
Patients diagnosed with a glioblastoma and their family caregivers are mainly impaired by the poor prognosis and the high symptom burden. Caregivers report impaired health-related quality of life and high distress. The addition of tumor-treating fields (TTFields, alternating electrical fields, biophysical therapy) to standard therapy, has been shown to prolong the overall survival in patients with newly diagnosed glioblastoma. Several studies showed an association of the daily compliance rate in TTFields with OS and progression-free survival (PFS). Family caregivers' support might be associated to the patients' compliance. However, so far rare supportive programs for patients and their caregivers have been established.

It has been shown that delivery of supportive care via telehealth is feasible, however studies examining the effectiveness, adoption and maintenance of telehealth interventions in glioblastoma patients and family caregivers are still lacking. The aim is to improve patients' compliance to TTFields therapy by a psychological video intervention in a multicenter randomized controlled trial.

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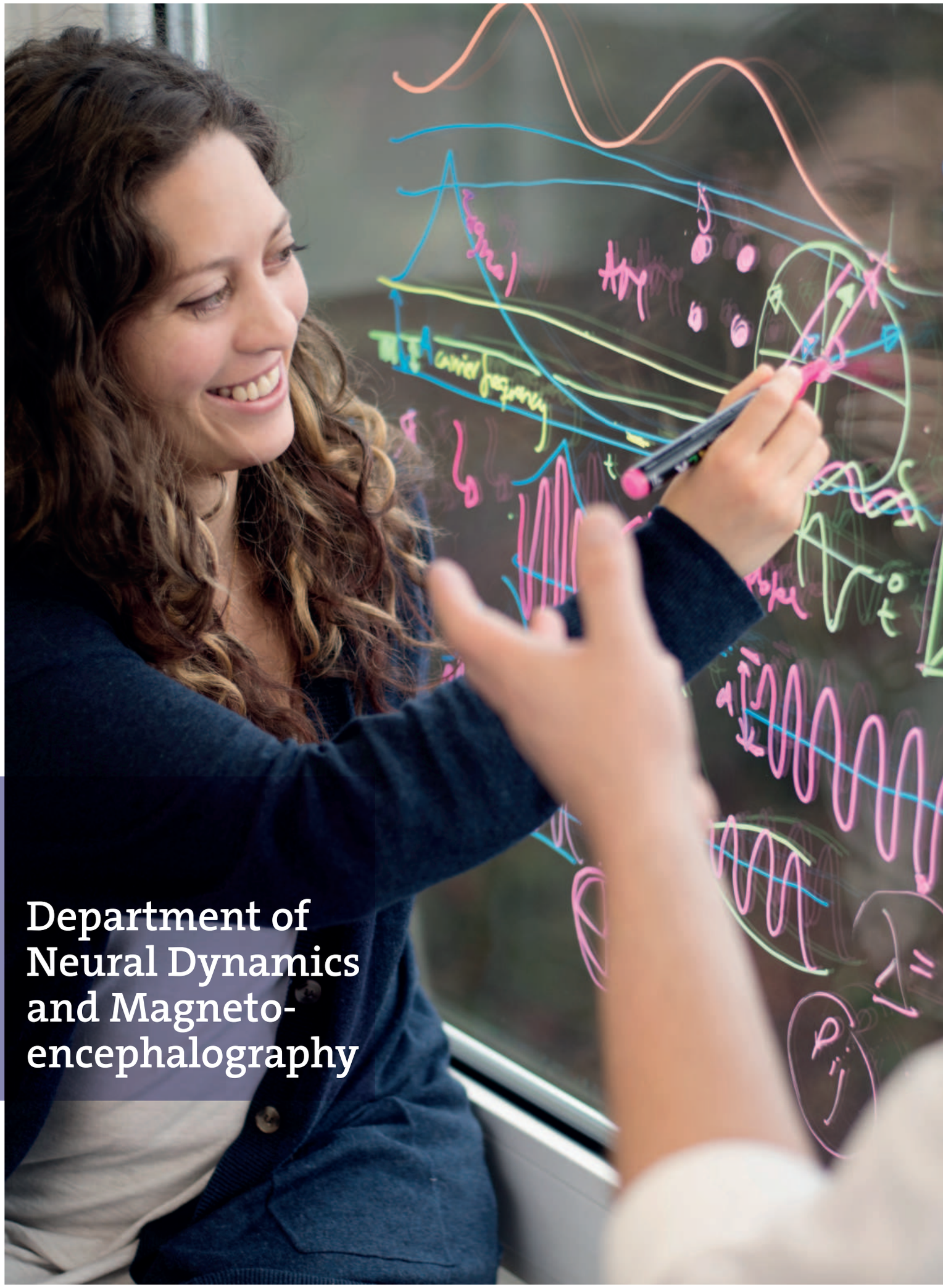
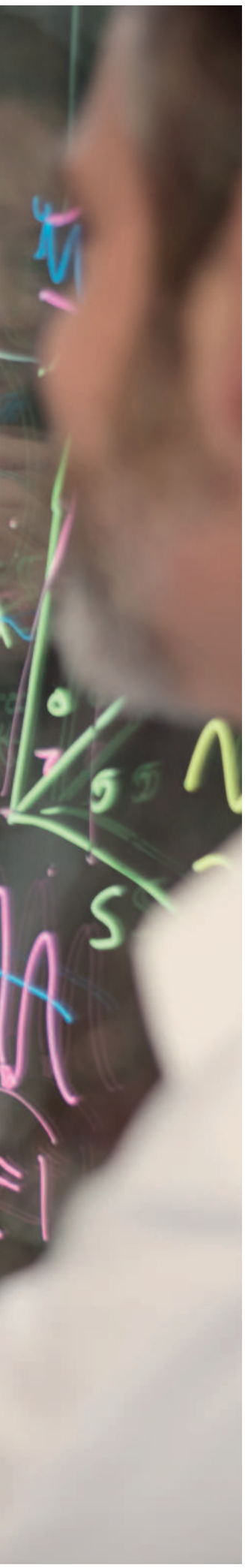


Department of Neural Dynamics and Magneto-encephalography



Prof. Dr. Markus Siegel heads the Department of Neural Dynamics and Magnetoencephalography.

Departmental Structure

The Department of Neural Dynamics and Magnetoencephalography was founded in 2020 and is headed by Professor Markus Siegel. The department pursues a comprehensive and interdisciplinary approach towards understanding the neural dynamics underlying human brain function and their disturbances in the diseased brain. The department is also part of Tübingen's Center for Integrative Neuroscience (CIN).

The brain's internal dynamics and their interactions with the environment are the basis of our ability to dynamically think and act. Accordingly, neurological and psychiatric diseases are often accompanied by disturbances of brain dynamics. Neural dynamics unfold across a wide range of temporal and spatial scales. Temporally, they range from fast cellular interactions on the millisecond scale to slow processes unfolding across years. Spatially, these dynamics range from single neurons to the entire central and peripheral nervous system and its interactions with the environment.

To address all these levels, the department applies an interdisciplinary approach that integrates a broad spectrum of methods ranging from single cell electrophysiology and EEG recordings in animal models, over non-invasive electrophysiology (MEG and EEG) and brain stimulation (tES) in humans, to magneto- and electromyography (MMG and EEG), psychophysical experiments, machine learning and computational modeling. These approaches are applied to investigate the neural dynamics underlying a broad set of brain functions and their disturbances, including sensory perception, learning, memory, decision-making, and motor behavior.

The translational perspective of the department is fostered through a variety of collaborative research projects with other departments of the Hertie Institute for Clinical Brain Research and with partners from the Centre for Integrative Neuroscience, the Institute of Medical Psychology, the Department of Otolaryngology, the Centre for Ophthalmology and the Department of Psychiatry and Psychotherapy.

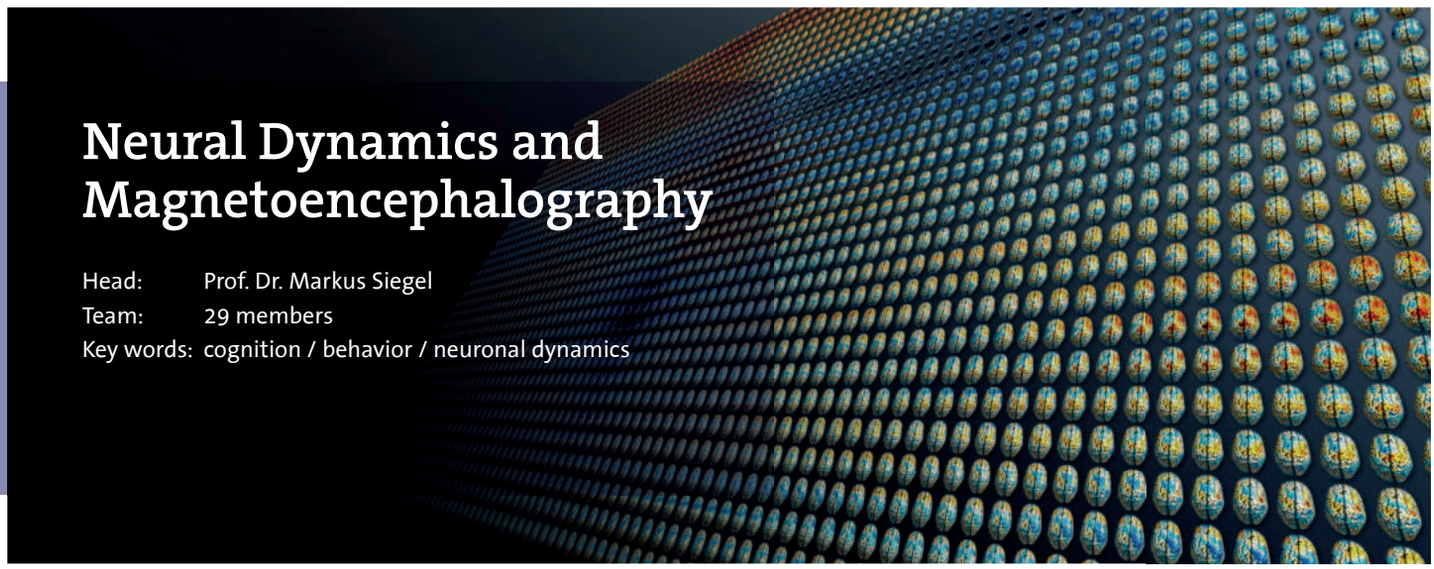
In addition to its primary research group, the department operates the Tübingen MEG Center, which provides state-of-the-art MEG techniques and services to the entire Tübingen neuroscience community. The MEG Center hosts a 275-channels whole-head MEG system, psychophysical setups, high-density EEG, transcranial electrical stimulation, highly precise audiovisual and somatosensory stimulation, various response systems and non-contact binocular eye-tracking.

The Department of Neural Dynamics and Magnetoencephalography provides a stimulating and collaborative environment for researchers from all academic levels, including interns, master students, MD and PhD students, as well as postdoctoral researchers. With scientists from more than 8 nations the department is highly international and diverse.

MEG system installed at the Tübingen MEG Center that allows for measuring the magnetic fields generated by brain activity

Neural Dynamics and Magnetoencephalography

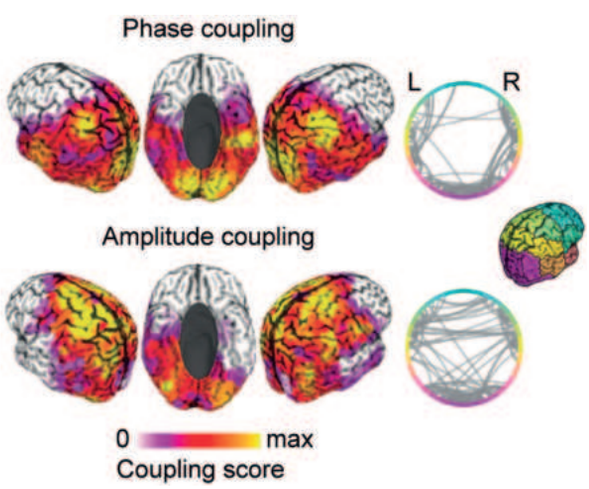
Head: Prof. Dr. Markus Siegel
Team: 29 members
Key words: cognition / behavior / neuronal dynamics



Cortical dynamics of neuromodulation identified with simultaneous MEG and pupillometry.

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.



The phase coupling (top) and amplitude coupling (bottom) of distinct brain networks imaged with MEG is altered in early stage Multiple Sclerosis patients. Adapther from Siems et al., Neuroimage (2022).

The brain is a highly dynamic and distributed system. How do sophisticated cognitive processes such as perception, memory, decision-making, and motor behavior emerge from dynamic interactions across the brain? What is the temporal and spatial structure of brain dynamics? Which neural mechanisms coordinate neuronal interactions and how are they disturbed in neurological and psychiatric diseases?

To address these questions, we link large-scale population measures of neuronal activity to circuit and cellular-level mechanisms. We combine human magneto- and electroencephalography (MEG and EEG), animal electrophysiology, magneto- and electromyography (MMG and EMG), psychophysics, computational modelling, and sophisticated analytical techniques.

Brain Rhythms of Normal and Diseased Brain Function

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

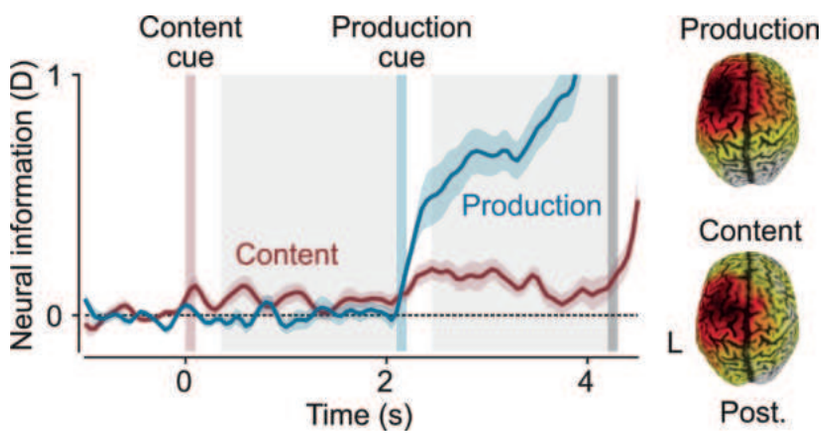
In one line of research, we investigate the dynamics of brain activity with MEG in the resting human brain. We investigate how networks of brain regions spontaneously coordinate their oscillations at different frequencies and how these large-scale oscillatory interactions are altered in the diseased brain. Our recent results show that brain rhythms are tightly coupled to neuromodulatory processes and that their spatial correlation structure is linked to non-rhythmic neuronal processes. Furthermore, in collaboration with the Dept. of Neurology and Neurovascular Medicine we identified the rhythmic coupling of brain networks as a novel biomarker of early-stage Multiple sclerosis (Fig. 1). Furthermore, we investigate the causal and temporal microstructure of different brain rhythms, how they are linked to neural information coding and 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 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. E.g., we recently showed that planned vocalizations can be non-invasively decoded from the human brain (Fig. 2). Together with our clinical collaborators (University Clinic for Psychiatry and Psychotherapy, University Eye Hospital, Department of Otolaryngology), we investigate alterations of neuronal dynamics during pathological conditions, such as e.g. dyslexia in children, schizophrenia, depression, and spatial hearing in cochlear implant users.

Magnetomyography

The development of so-called optically pumped magnetometers (OPM) allows the contact-free measurement of biomagnetic signals without the need of cryogenic cooling. This has enabled the new field of magnetomyography (MMG), i.e. the measurement of magnetic fields generated by muscle activity. Together with our collaborators (Physikalisch-Technische Bundesanstalt Berlin, University of Stuttgart, Frauenhofer IPA Stuttgart) and clinical partners (Dept. of Neurology and Epileptology), we investigate MMG for basic research, prosthetic control and clinical applications.



When subjects are sequentially cued about the content (one of two vowels) and production (overt or imagined) of a vocalization, the content and production of the planned vocalization can be decoded from left lateralized brain activity several seconds before the vocalization using MEG. Adapted from Voigtlaender et al., PNAS (2023).

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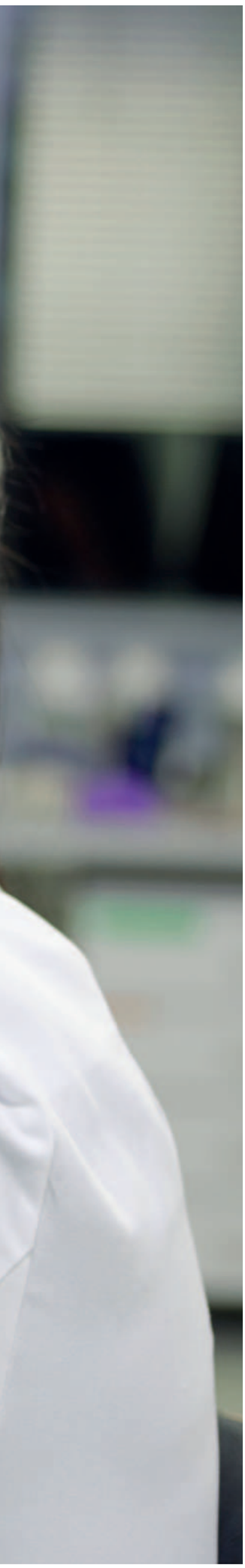
Department of Cellular Neurology



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

Departmental Structure

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.

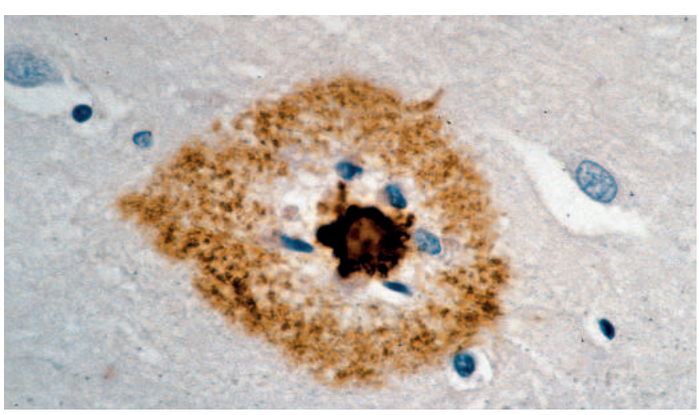
We also coordinate the international Dominantly Inherited Alzheimer Network (DIAN) study in Germany, which aims to understand the rare genetic forms of Alzheimer's disease by longitudinal analysis of gene mutation carriers and non-mutation carrier siblings. Understanding this type of Alzheimer's disease 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 five research groups.

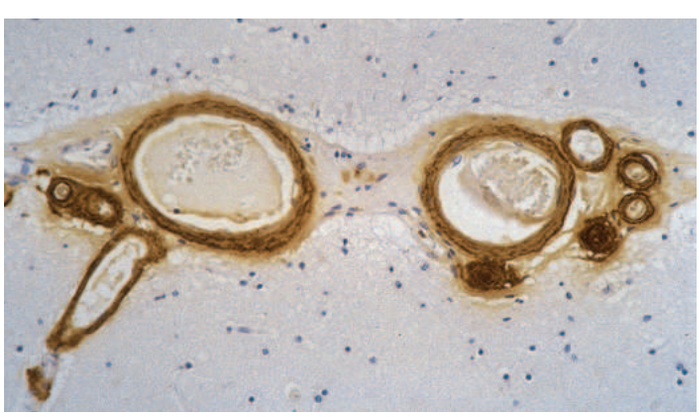
- Experimental Neuropathology
- Experimental Neuroimmunoloy
- Glia Cell Biology
- Molecular Biomarker unit
- Dementia Research unit (clinical)

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.



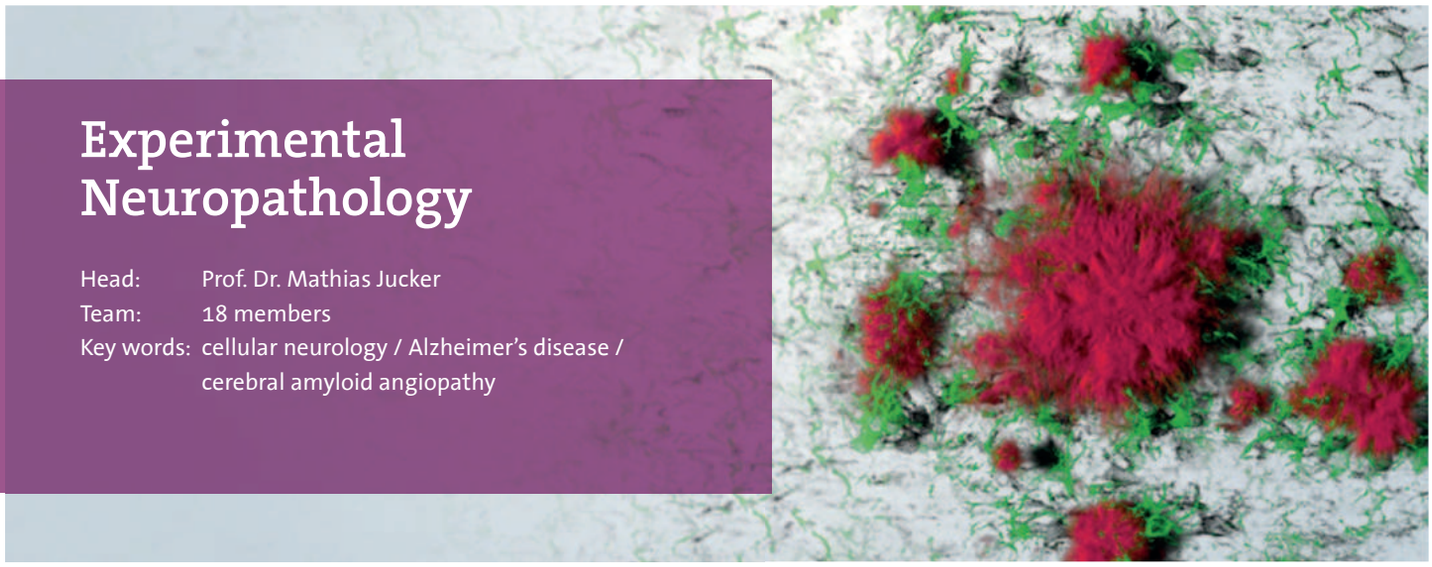
Amyloid plaque (Aβ immunochemistry) in an Alzheimer brain.



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.

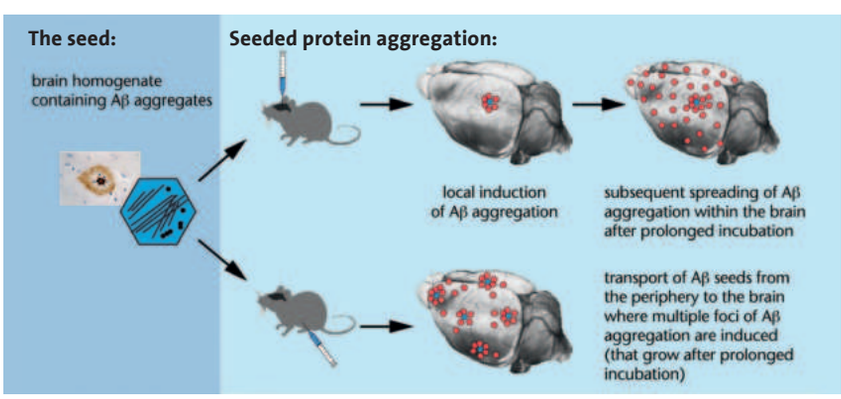
Misfolded proteins are the cause of many neurodegenerative diseases. How these proteins misfold and what the initial trigger is for the misfolding and their subsequent aggregation is, however, largely unknown. Furthermore, it remains unclear why the aging brain is a risk factor for neurodegenerative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

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.

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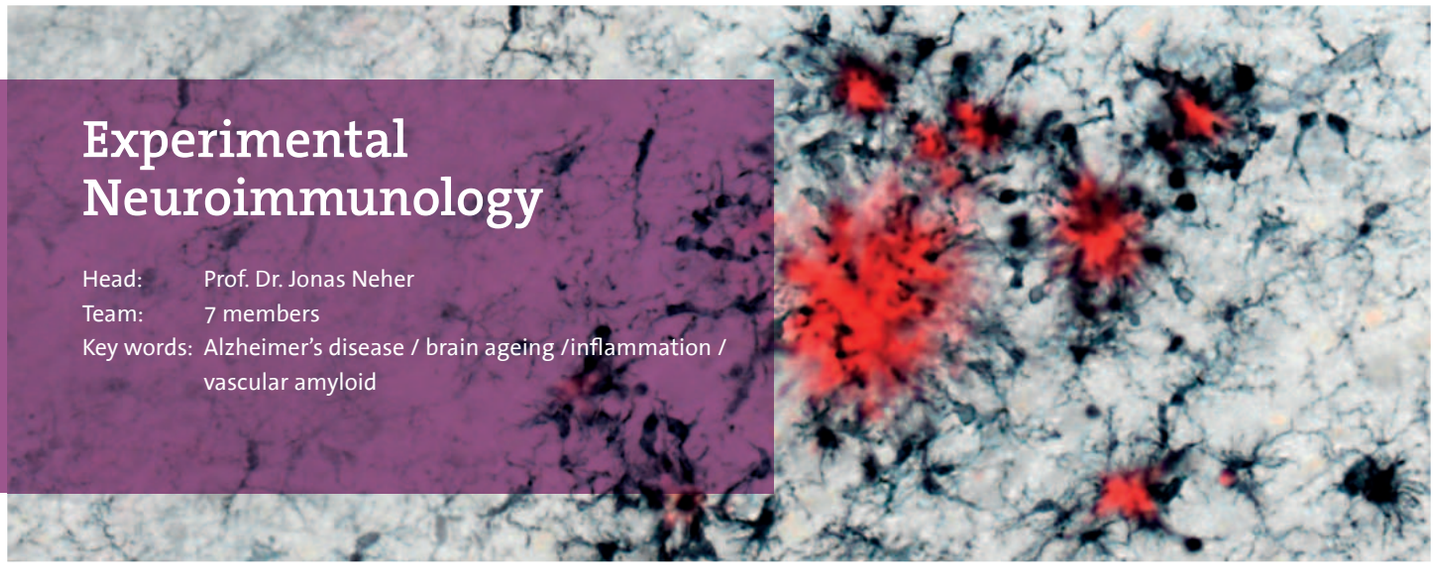


Experimental Neuroimmunology

Head: Prof. Dr. Jonas Neher
Team: 7 members
Key words: Alzheimer's disease / brain ageing /inflammation / vascular amyloid

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

Our objective is to understand how aging and amyloidosis affect the brain's immune system and its blood vessels, and how these alterations contribute to the pathogenesis of Alzheimer's disease. A better understanding of the molecular and cellular processes involved may eventually allow us to develop novel therapeutics.

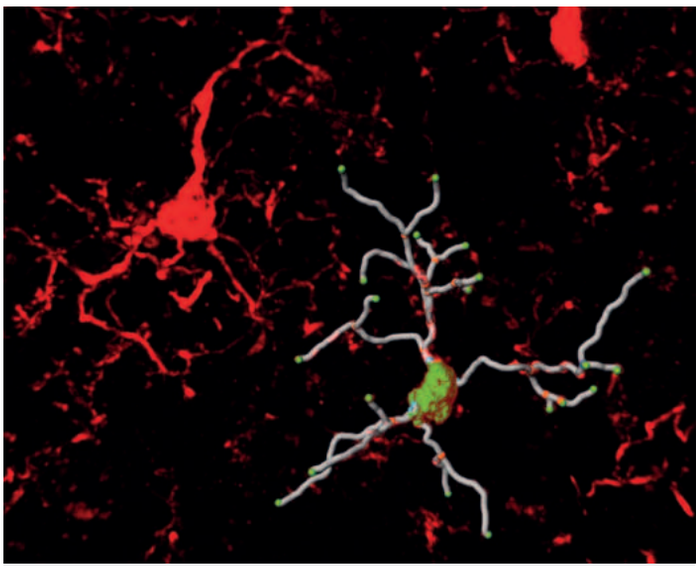
Unser Ziel ist es, die pathogenen Mechanismen der Alzheimer-Erkrankung zu verstehen, um aus diesen Erkenntnissen therapeutische Interventionen zu entwickeln.

An immune response is part of most neurological diseases, and the development of late-onset Alzheimer's disease (AD) has been linked to immune related genes, indicating an important role of the immune system in this neurodegenerative disease. The major population of immune cells in the brain are microglia (brain macrophages), which are attracted to and surround Amyloid-β deposits in the AD brain. However, various aspects of the microglial role in amyloid plaque homeostasis and AD pathogenesis remain unclear.

We recently demonstrated that microglia are capable of retaining a long-lasting epigenetic memory of peripheral inflammatory insults, which are known risk factors for late-onset AD. Importantly, this epigenetic memory changed how microglia responded to much later developing AD pathology and, in turn, affected how AD hallmarks developed in mouse models. These findings indicated that microglia are capable of "innate immune memory" (Wendeln et al., Nature, 2018). We are actively working on understanding the mechanisms of microglial epigenetic reprogramming in response to peripheral inflammation by analysing mouse and human tissue on a single cell basis, and by studying its effects on different forms of neurodegenerative diseases.

Amyloids are proteins that form insoluble deposits in tissue, where they often lead to disruption of tissue function and cause disease. The best-known example is Amyloid-β, whose deposits in the brain are a cardinal feature of Alzheimer's disease.

However, we recently found that the amyloid medin, which is the most common amyloid known in humans, accumulates in blood vessels in the periphery and brain and disrupts their function during ageing in the brain of mice (Degenhardt et al., PNAS, 2020). Moreover, in follow-up work we demonstrated that medin can directly interact with Amyloid-β and thereby promotes vascular Aβ aggregation and damage (Wagner et al., Nature, 2022). Thus, our work as well as independent studies highlight medin amyloid as a novel therapeutic target for restoring vascular health in aging and Alzheimer's disease (Madine et al., Nature Aging, 2023).



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

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Glial Cell Biology

Head: Dr. Deborah Kronenberg-Versteeg
Team: 5 members
Key words: neurodegeneration / glia / stem cells / immunometabolism

Our objective is to understand how glial cells (microglia and astrocytes) contribute to the pathogenic mechanism of neurodegenerative diseases.

Unser Ziel ist es, zu verstehen, wie Gliazellen (Mikroglia und Astrozyten) zu den pathogenen Mechanismen neurodegenerativer Erkrankungen beitragen.

Glial cells are highly abundant in the mammalian brain, yet many questions regarding their development, function, and involvement in disease remain unanswered. Neuronal health is closely intertwined with that of the glial cells surrounding them and we hypothesize that aging-associated neuronal dysfunction and vulnerability to neurodegeneration are driven by glial changes.

We recently developed a chimeric brain slice culture model, combining stem cell derived glial cells and brain slice cultures, providing the opportunity to address how cell-autonomous and non-cell-autonomous factors modulate neuronal vulnerability to neurodegeneration. Importantly, these models allow to investigate the dynamics and molecular mechanisms of human cells in a brain tissue environment. We could demonstrate that the stem cell-derived microglia in these brain slice cultures adopt diverse aging and disease-associated transcriptional states reminiscent of *in vivo* human microglia. We are currently actively working on understanding the mechanisms of glial activation in the context of different neurodegenerative disease pathologies.

Alterations in lipid metabolism have been implicated in many neurodegenerative diseases and we hypothesize that changes in lipid metabolism are the underlying cause of compromised immunoregulatory functions of microglia in neurodegeneration. To this end, we are investigating a potential lipid-immunomodulatory signaling axis also as a potential new treatment angle.

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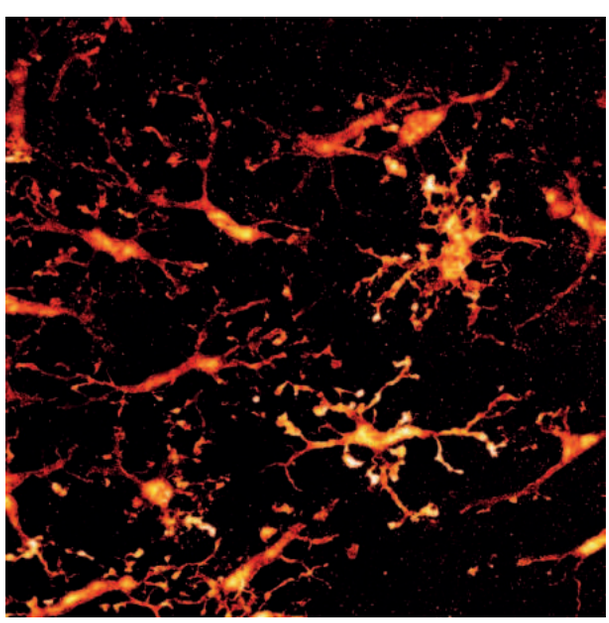


Human stem cell-derived microglia (red) in a brain slice culture

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.

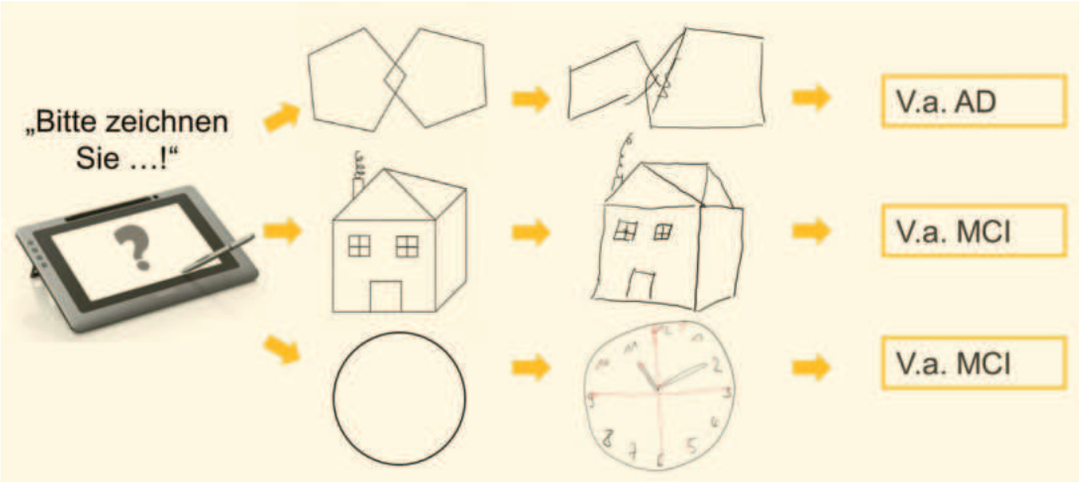
Die Unit Demenzforschung ist eine gemeinsame klinische Forschungsgruppe der Abteilung für Zellbiologie neurologischer Erkrankungen und der Universitätsklinik für Psychiatrie und Psychotherapie. Die Unit arbeitet eng mit der Gedächtnisambulanz der Universitätsklinik zusammen.

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), a new treatment arm with Lecanemab (antibody against β-amyloid) and E2814 (antibody against Tau) vs. placebo will be launched during 2022. 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.



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Independent Research Groups

The HIH attempts to implement flat hierarchies and an organizational structure in which responsibility for research, clinical care and economic performance is shared cooperatively and on an equal footing, without a traditional hierarchical structure. This also includes the element of independent research groups that are not assigned to any department. These research groups are led by appointed professors or other senior scientists.

Independent research groups are free to form “alliances”, depending on their research interest. For example, some are grouped together in the field of Neurorehabilitation, Neuroprosthetics, Neurotechnology (“N3”).

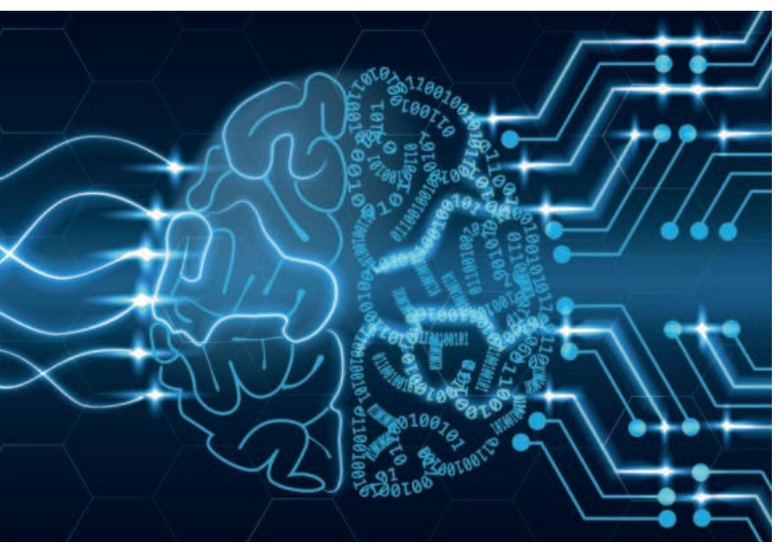
Junior research groups can be independent with their own budget already early in their careers.

Together they cover a broad spectrum of clinical neuroscience and contribute significantly to the success of the Hertie Center of Neurology.

Research Area N3

Neurorehabilation | Neuroprosthetics | Neurotechnology

RESEARCH AREA N3 NEUROREHABILITATION | NEUROPROSTHETICS | NEUROTECHNOLOGY 116



Research Area N3

Neurorehabilitation | Neuroprosthetics | Neurotechnology

The interdisciplinary research area N3 (Neurorehabilitation / Neuroprosthetics / Neurotechnology) integrates basic research in neuroscience with technical applications in the field of clinical brain research. It also establishes close links between the HIH and the fields of machine learning, artificial intelligence, and physical intelligence at the Universities of Tübingen and Stuttgart and the Max Planck Institutes for Biological Cybernetics and Intelligent Systems.

The Research Area N3 is formed by four groups with complementary expertise, all of which have a strong interest in systems neuroscience and clinically relevant applications. The method spectrum ranges from experimental research in animals, including rodents, nonhuman primates, experimental research in humans and patients, to approaches from theoretical neuroscience, biomechanics, and engineering including machine learning. The complementary expertise of these groups allows to develop novel approaches and technology to address questions about aspects of neurological and psychiatric disorders.

The **Section Theoretical Sensomotorics** (headed by Prof. M. Giese) focuses on theoretical neuroscience and on quantitative methods for the characterization and modeling of body motion, and non-invasive neural stimulation. One focus of the work is the development of disease-specific, everyday-relevant motor performance measures for rare neurodegenerative diseases. Further work together with the department of psychiatry contributes to the quantitative assessment of stressor stimuli in obsessive-compulsive disorders exploiting multi-sensor systems in real-world situations. A focus in the context of the ERC Synergy grant RELVANCE is the study of neural and computational mechanisms of the perception of body motion. This involves also the development of novel methods for tracking and computer animation of highly realistic animal avatars. Further technical work provides the basis for single-cell recordings during single-pulse Transcranial Magnetic Stimulation (TMS) in rats, which presently is exploited to study the underlying electrophysiological mechanisms and pathways.

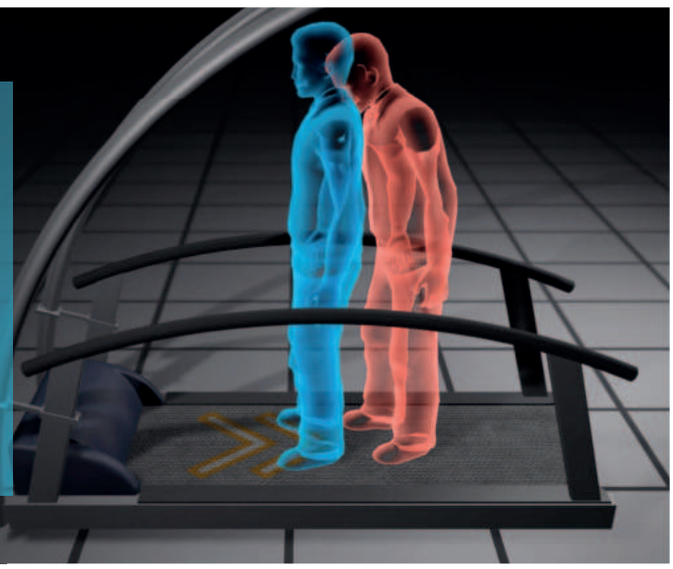
The group **Motor Control Modeling** (headed by Prof. D Häufle) focusses on neuromechanics and rehabilitation robotics. The group develops computer models and simulations of the neuro-musculoskeletal system. In a multi-level approach, they consider the different hierarchical levels contributing to movement generation. This interdisciplinary approach is mainly based on biophysics, biomechanics, and computational motor control. They investigate fundamental neuromechanical control mechanisms and their dysfunction in neurological disease. A deeper understanding of dynamics, impaired control and interaction will serve as a basis for the development of functional assistive devices.

The group **Systems Neurophysiology** (headed by Prof. C. Schwarz) studies the sensorimotor system in rodents (whisker and paw movements) on the neuronal and behavioral level, using state of the art behavioral observation, neural recording and stimulation, as well as imaging on the single and sub-neuronal level. Their aim is the elucidation and differentiation of predictive neuronal systems. In recent work they were able to successfully delineate two presumptive predictive systems, state estimation and sensory gating, with different localization in cerebellum and neocortex, which both very similarly attenuate the tactile flow in movement dependent ways. The overarching motivation to study the delineation and overlap of such systems is the hope that it will allow to substitute one such system by the enhancement of the other in case of neurological disease. This work is funded (amongst other sources) by the DFG Schwerpunktprogramm SPP 2411. The group has also long-standing interest in neurostimulation. Together with Alia Benali (group Giese), we investigate the neuronal underpinnings of TMS, as well as have engaged in the development of nanoparticle-based highly specific stimulation of neuronal tissue, a project that is a central element in the HIH-led cluster-proposal (speaker Giese) within the current Excellence Initiative (Bionic Intelligence for Health).

The **Active Perception Laboratory** (headed by Prof. Z. Hafed) investigates the neurophysiological mechanisms underlying active sensing in animal models, as well as the links of these investigated mechanisms to human perceptual and cognitive performance. The group employs techniques for monitoring and focally perturbing neural activity in individual brain circuits, in order to understand the functional contributions of specific circuits and anatomical pathways in coordinating perception and behavior. Their results are relevant for understanding disorders of attention and distractibility, as well as for understanding and improving the efficacy of interventional brain stimulation protocols as a function of ongoing internal brain state modulations.

A recent achievement of the Research Area N3 has been the successful preproposal ‘Bionic Intelligence for Health’ in the German Excellence Initiative. This proposal, which is coordinated by M. Giese together with researchers from the University of Stuttgart, integrates important contributions of all members of the research area N3. The researchers of the Research Area N3 are members of national and international research networks, and networks fostering industrial partnerships. M. Giese is member of the board of the Bernstein Center (BCCN) of Tübingen, co-speaker of the Else Kröner Medical Scientist Kolleg ‘ClinBrAIn: Artificial Intelligence in Clinical Brain Research’, as well as a board member of the’ Competence Center Biointelligence’ of the Fraunhofer Institute for Process Automation (Stuttgart) with many industrial partners. D. Häufle was appointed as Prof. at Heidelberg University (in April 2023) and is member of Cyber Valley and Faculty of the Max-Planck-Research School for Intelligent Systems. He leads and participates in several projects bridging HIH, CIN, University of Tübingen, University of Stuttgart, and MPI for Intelligent Systems. C. Schwarz chairs the board of the Graduate Training Center for Neuroscience, and is member of DFG SPP 2411. Z. Hafed is member of the SFB 1233 (‘Robust Vision’) and the Cognitive Science Center (CSC) of the University of Tübingen. He is also part of multiple Special Priority Programmes (SPPs) of the Deutsche Forschungsgemeinschaft (DFG), exploring topics related to internal state modulations in active organisms.

Computational Sensomotorics



Head: Prof. Dr. Martin Giese
Team: 32 members
Key words: social perception / neural models / movement modeling and quantification / motor learning and rehabilitation / neurostimulation

The Section Computational Sensomotorics investigates theoretical principles of the perception and control of complex motor behavior and associated technical applications.

Die Sektion Theoretische Sensomotorik erforscht die theoretischen Prinzipien der Erkennung und Steuerung komplexer motorischer Handlungen und assoziierter technischer Anwendungen.

A major amount of work has been dedicated to the organization and preparation of a preproposal for the Excellence Cluster Initiative 2026. The Transregio Excellence-Cluster preproposal 'Bionic Intelligence for Health' has been successful. M. Giese is the speaker for Tübingen, and S. Schmitt and S. Ludwigs for the University of Stuttgart. The goal of the proposed highly Interdisciplinary cluster Is the development of new methods for treatment and diagnosis of neural diseases by Integration of physical, software and human intelligence as parts of closed-loop systems. The cluster would Integrate the MPIs for Intelligent Systems and Biological Cybernetics, and it would embed the HIH further in the Cybervalley and the AI/technology ecosystem in the region Tübingen-Stuttgart. In addition, we have continued our work in the following four research fields:

Movement analysis of everyday life behavior in neurodegenerative movement disorders

In the field of cerebellar ataxia, we have developed gait measures that have a significantly higher sensitivity for ataxia-specific changes than the commonly used clinical scores. This enables conclusive clinical studies for these rare diseases with a substantially reduced number of patients. An important challenge for progression and therapy evaluation with high ecological validity is the quantification of movement behavior in everyday life. We have studied such everyday-relevant behaviors in cerebellar ataxia and hereditary spastic paraplegia in collaboration with Profs. M. Synofzik and L. Schöls (Dept. of Neurodegeneration). Based on inertial sensor data, combined with machine learning approaches, we have devised sensitive measures for motor deficits and training success in patient's real life. For the worldwide harmonization and standardization of gait assessments and measures for cerebellar ataxia, we are coordinating a working group in the Ataxia Global Initiative (AGI). Complementing this work, in the project I-AssistADL project, together with D. Häufle and S. Schmitt (University of Stuttgart), we are investigating the online detection of upper limb movement impairments (e.g. intention tremor, dyskinesia) during activities of daily living in neurological patients for the development of an assistive robotic device.

Intelligent wearable support systems for diagnosis and training in psychiatric diseases

Many psychiatric diseases result in deficits of everyday capabilities. An example is Obsessive-Compulsive Disorders (OCD), where patients might be suffering from anxiety that is caused by specific trigger stimuli in everyday situations that result in compulsive behavior. Sometimes such stimuli are not even conscious, making it desirable to analyze the patient's behavior automatically in an everyday context, and to identify post-hoc which stimuli caused anxiety or compulsive behavior. In collaboration with Prof. T. Renner (Dept. of Psychiatry) we explore wearable systems that integrate video recording, wearable movement sensors, eye tracking and the online assessment of physiological measures such as heart rate, allowing a monitoring of such patients outside the laboratory, e.g. in home-based environments. We successfully developed multimodal and robust markers for stress detection, combining physiological measures such as heart rate variability, body movement energy, and eye fixation behavior. The mid-term goal Is to exploit such markers for personalized bio-feedback systems for behavioral training, ultimately

integrating humans with an intelligent environment that combines behavioral and physiological sensing, aiming at improving diagnosis and treatment of a psychiatric disease.

Neural and computational principles of social perception

As part of the ERC SYNERGY grant RELEVANCE we have worked together with our collaboration partners at the KU Leuven and the University of Maastricht on neural mechanisms of the representation of bodies in body patches in the superior temporal sulcus of monkey cortex, and in body areas of the human cortex. One challenge is the generation of highly-controlled visual body stimuli. Standard technologies, such as motion capture are not applicable for body motion tracking in monkeys, who do not accept reflecting markers on their bodies. Therefore, we developed a new marker-less motion capture approach and a pipeline for the animation of a highly realistic monkey avatar model. Our markerless method works with a very small number of hand-labelled keyframes. However, it reaches the high level of accuracy that is required for 3D animation of realistic body models.
Using this new approach, we demonstrated for the first time that monkeys experience an uncanny valley for bodies: They perceive avatar stimuli generated with our animation software as just as realistic as real videos, and disfavor stimuli of medium degrees of realism. We also have developed neural network models for the behavior of body shape-selective cortical neurons, and machine learning methods for the analysis of population data from premotor cortex (with the group of P. Thier). Beyond this, we developed a neural network architecture, based on insights form face representations in primate visual cortex, that accounts for the spontaneous recognition of facial expressions from non-human head shapes, such as monkey heads. This task Is extremely hard for AI (DNN) architectures, but easy for humans.

Physiological mechanisms of cortical TMS

A. Benali has developed together with the laboratories of C. Schwarz, U. Ziemann and A. Oeltermann (MPI for Biological Cybernetics), a novel technology for the simultaneous recording of single cell activity in rats immediately after single pulse TMS with a time loss below one millisecond after the pulse. As core of the method, we developed various types of novel amplifiers that suppress or subtract the strong signals caused directly by the TMS pulse, combined with removal of capacitive and electrotribal artifacts. This enabled experiments to study the neural basis of the TMS response components in the motor cortex. While direct electrical stimulation effects persist only for a few milliseconds, peripheral stimulation elicits a multiphasic neuronal response pattern after about 10 milliseconds. Present studies investigate the exact physiological basis of these components.
The setup has been extended to study the physiological effects of nanoparticle-based stimulation, exploiting particles that transduce magnetic or acoustic fields into local electrical signals. This approach has a much higher spatial accuracy than TMS, and allows to reduce the strength of the magnetic field massively compared to TMS. As part of this work, we have established a small 'Nano-laboratory' for the realization of rodent in-vivo studies that test and develop improve nano agents, developed by Prof. M. Sitti, MPI for Intelligent Systems / Koç University, Istanbul) which interact with the neural system. This is a central topic in the planned Excellence Cluster 'Bionic Intelligence for Health' (s.a.).

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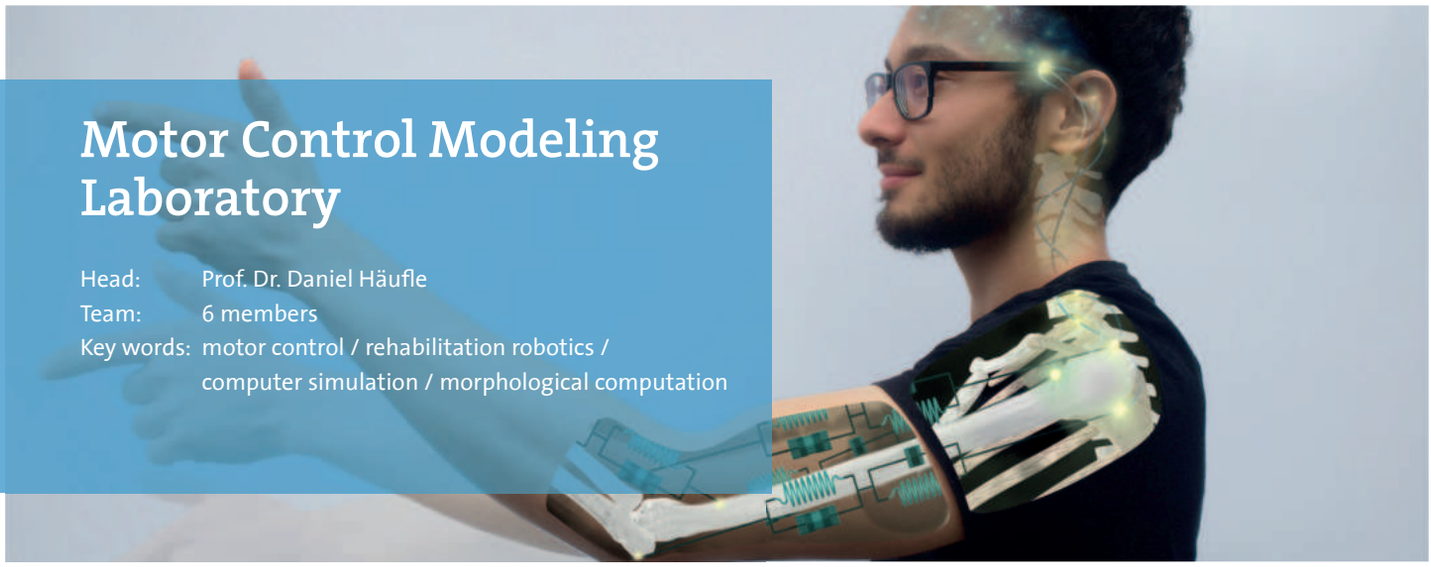
Thierfelder A, Seemann J, John N, Harmuth F, Giese M, Schule R, Schols L, Timmann D, Synofzik M, **Ilg W** (2022) Real-Life Turning Movements Capture Subtle Longitudinal and Preataxic Changes in Cerebellar Ataxia. *Movement Disorders* 37:1047-58



Motor Control Modeling Laboratory

Head: Prof. Dr. Daniel Häufle
Team: 6 members
Key words: motor control / rehabilitation robotics / computer simulation / 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 and provides a scientific link between the Hertie Institute and the Cyber Valley research environment.

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. Unser interdisziplinärer Ansatz integriert Konzepte der Biophysik, Biomechanik und Motorik und stellt einen wissenschaftlichen Link zwischen Hertie-Institut und Cyber Valley Forschungsverbund her.

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 muscles. 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 human locomotion. 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.

In a collaborative effort within the HIH with sections for Computational Sensomotorics (Giese) and Clinical Neurogenetics (Schöls), we were able to develop a model that predicts gait changes in prodromal subjects and patients with Hereditary Spastic Paraplegia. By introducing known motor control dysfunctions like muscle weakness and hypersensitive reflexes, we were able to predict the gradual decline of walking kinematics which is associated with the progression of the neurodegenerative condition.

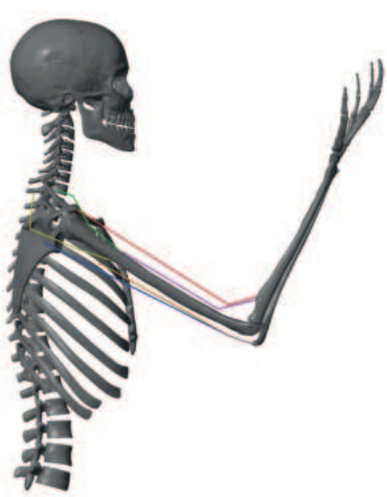
Wearable assistive devices for rehabilitation
The research on motor control dysfunction may be the starting point for the development of functional assistive devices. With the neuromusculo-skeletal models we are able to predict required assistive forces. Here, we collaborate with several researchers within Cyber Valley and received funding from the BW-Foundation for a project "iAssistADL: Intelligent assistive device for patients with neurodegenerative movement disorder: detecting and correcting pathological movement in daily activities". Our group is leading this project as we integrate the robotic hardware, simulation and experimental analysis and prediction of healthy and impaired movements.

Furthermore, together with Prof. Ulf Ziemann and Prof. Lorenzo Maisa (Heidelberg), we started a project to develop a novel mirror-therapy paradigm based on a robotic exoskeleton.

Biorobotics
We develop robotic platforms as tools to study concepts on biological motor control together with the University of Stuttgart and the MPI for intelligent Systems. These tools support the computer simulations and transfer the concepts into the real world, where biological experiments are not possible.

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

The group is part of the regional research alliance “Bionic Intelligence Tübingen Stuttgart”. Our goal is to link the neuroscientific expertise in Tübingen with the expertise in computer simulation at the University of Stuttgart. Daniel Häufle was appointed Full-Professor at Heidelberg University in 2023 and continued to run the projects and the group at HIH Tübingen to ensure the fruitful progress of the numerous collaborations.



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.

One core objective of the group is to develop novel control strategies for assistive devices

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Systems Neurophysiology Laboratory

Head: Prof. Dr. Cornelius Schwarz
Team: 11 members , 4 associate members
Key words: neocortex / tactile coding and perception / active scanning / cerebellum / predictive coding / motor coding and movements / associative learning

Rodents deploy their whiskers to explore their environment.

Our focus is the study of the function of the neocortex and its extensive interaction with brainstem and cerebellar circuits. Our main interest is to understand the neuronal mechanisms underpinning perception, cognition and generation of movement. We use precise quantification of rodent behavior together with monitoring and stimulation of neuronal signals on the multiple single cell level based on electrophysiology and optical methods.

Unser Schwerpunkt liegt auf der Untersuchung der Funktion des Neokortex und seiner umfassenden Interaktion mit Hirnstamm und Kleinhirn. Im Mittelpunkt des Interesses liegt dabei das mechanistische Verständnis von Wahrnehmung, Kognition und der Bewegung. Wir nutzen die präzise Quantifizierung des Verhaltens von Nagetieren zusammen mit der Überwachung und Stimulierung neuronaler Signale auf der Ebene mehrerer Einzelzellen mittels elektrophysiologischer und optischer Methoden.

Learning

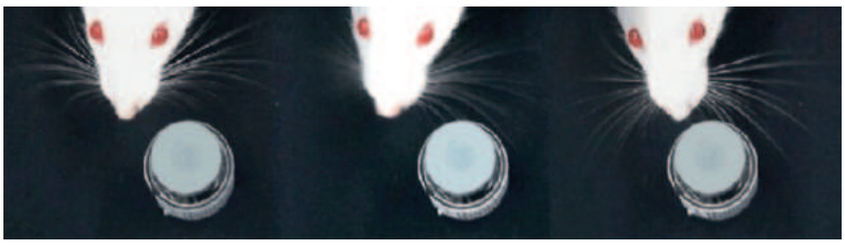
The mammalian brain uses several learning systems that cooperatively adapt behavior to the needs of the individual and to the constraints of the world. Explicit learning is a neocortex-based form of either unsupervised learning, driven by coincidences or correlations, or supervised learning based on 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.

Predictive Systems

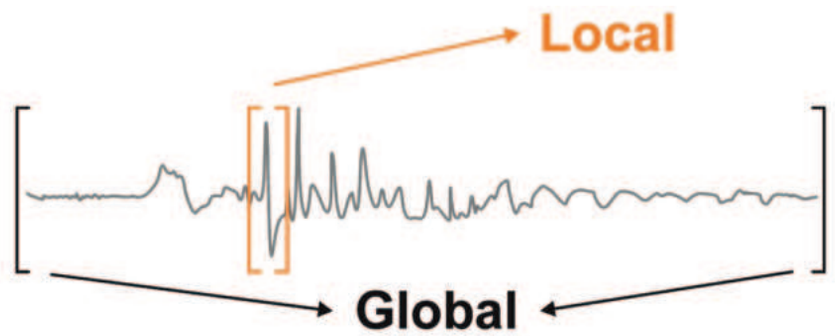
We hypothesize that primary somatosensory cortex is involved in two forms of predictive coding. The first is called state estimation and combines tactile predictions calculated from internal sources, like contextual information intrinsic to the brain (e.g. movement plans and motor commands), and external 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 .in the brainstem. We have developed an experimental model that allows us to simultaneously demonstrate the two predictive systems, state estimation and sensory gating, together with neuronal analysis in cerebellum and brainstem 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 and electrophysiological data present strong evidence for local codes..



Active tactile exploration of the environment using vibrissae.



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).

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Active Perception Laboratory

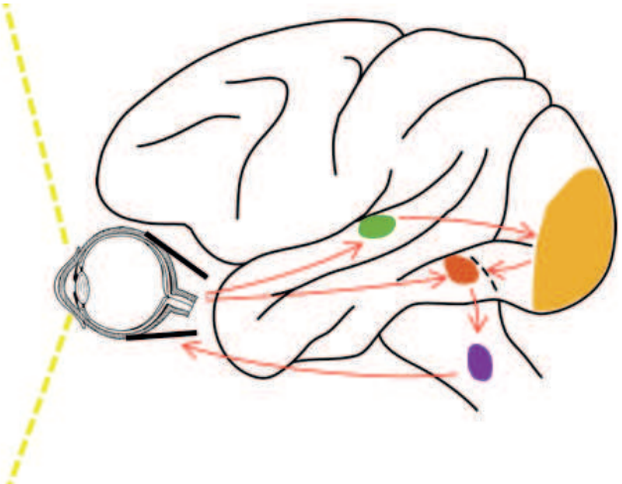
Head: Prof. Dr. Ziad Hafed
Team: 12 members
Key words: visual perception / eye movements / brainstem control of eye movements / perceptual stability / visual field representations

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 zugrunde liegen. 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 Verhaltensweisen 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).

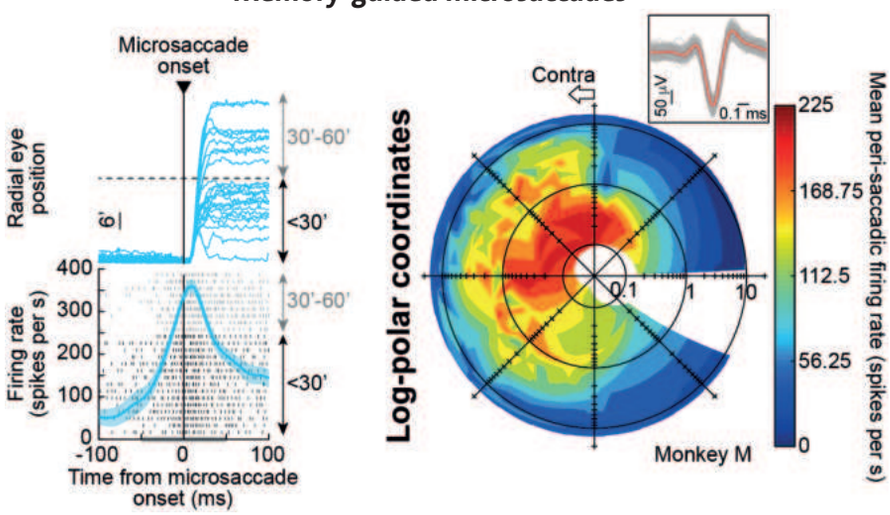
There are two main classes of eye movements that are employed by humans in everyday life: saccades, which are rapid changes in eye position that align gaze on peripheral objects, and smooth pursuit eye movements, which are smooth movements that stabilize the image of a moving object on the retina. Associated 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.

Memory-guided microsaccades

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.



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Independent Research Groups

Flat hierarchies and a uniquely close integration of basic and applied research in the clinical neurosciences distinguish the HIH from many other institutions. Part of the flat hierarchies are independent research groups. Independent research groups aim to establish new or continue to develop existing focus areas.

INDEPENDENT RESEARCH GROUPS 128

Section for Neuropsychology

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

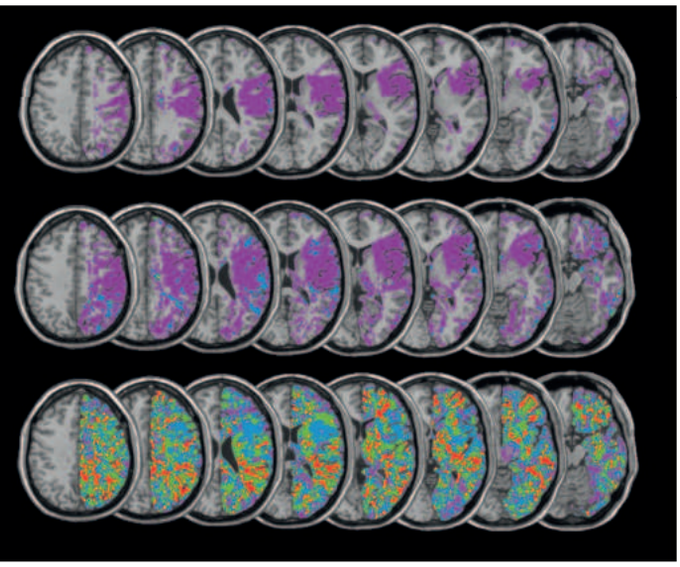

Figure 1: Nowadays, different anatomical atlases exist for the anatomical interpretation of the results from neuroimaging and lesion analysis studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function. A major problem with the use of different atlases in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

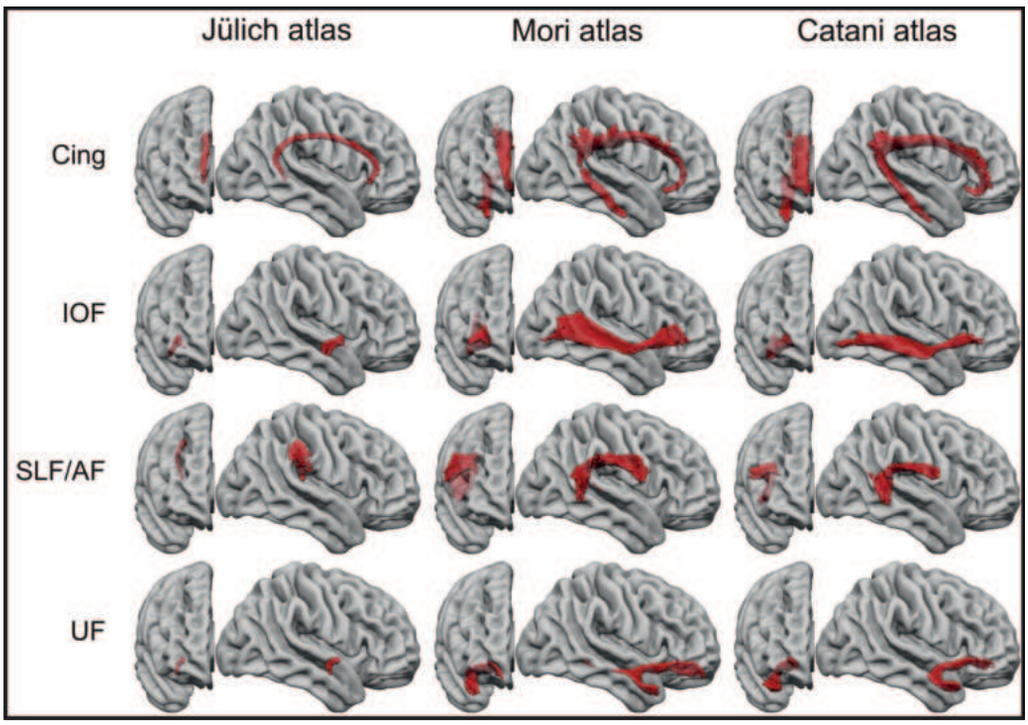

Figure 1

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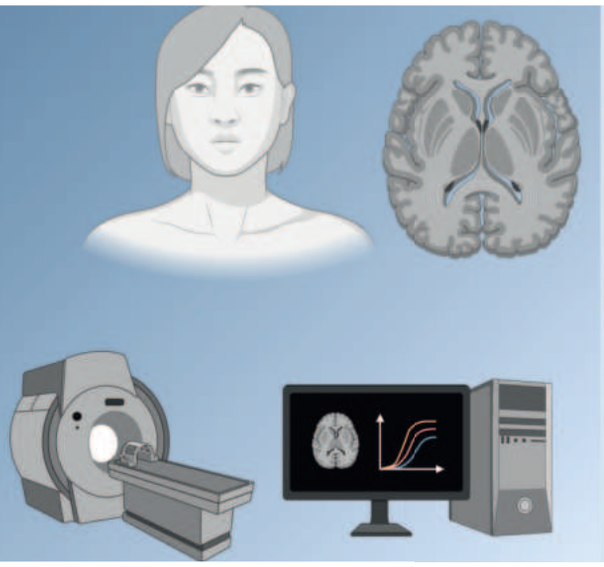
Translational Imaging of Cortical Microstructure

Head: Prof. Dr. Esther Kühn
Team: 8 members
Key words: human neuroimaging / in-vivo microscopy / aging / neurodegeneration / neurological disorders / sensorimotor system



The Group Translational Imaging of Cortical Microstructure investigates the in-vivo microstructure of the human cortex in health and disease by using MR-based neuroimaging. Our recent research addresses three problems:

Die Gruppe Translationale Bildgebung kortikaler Mikrostruktur untersucht die Mikrostruktur des menschlichen Kortex in Gesundheit und Krankheit unter Zuhilfenahme von MRT-basierter Bildgebung. Unsere Forschung konzentrierte sich dabei auf drei Themen:

The microstructural architecture of the sensorimotor cortex

Microstructural imaging, in particular when using ultra-high field MRI > 3T, allows unprecedented insights into the inner architecture of the human cortex in-vivo. Whereas standard 3T MRI does not offer the necessary spatial resolution, histological investigations in humans are restricted to post-mortem samples, where brain organization cannot be directly linked to its function or dysfunction. The microstructural architecture of the living human cortex is therefore still relatively unexplored, in particular with respect to its relation to function or dysfunction. To overcome this limitation, we use a combination of structural and functional ultra-high resolution MRI to characterize the microstructural architecture of the human cortex in-vivo.

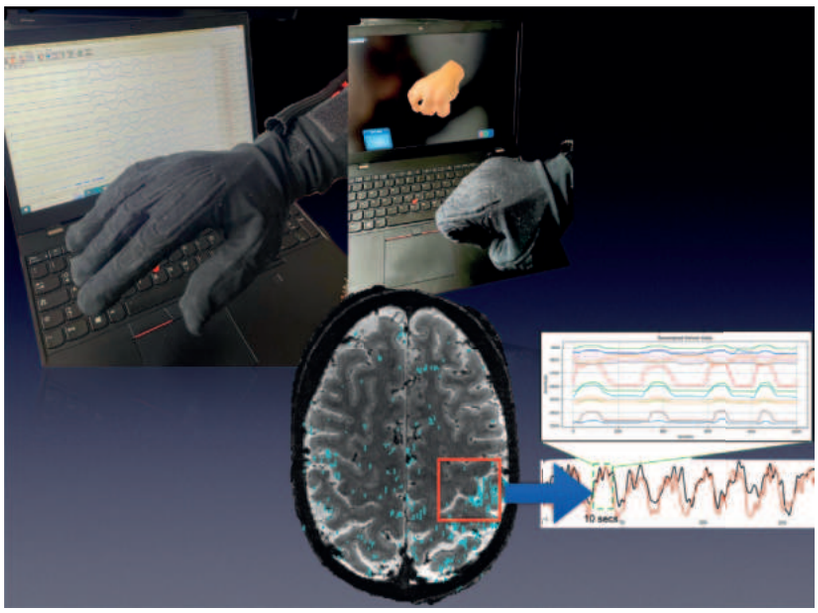
We concentrate on the human sensorimotor cortex given its involvement in a range of neurodegenerative and neurological disorders, such as stroke, motor neuron disease, multiple sclerosis, and frontal lobe dementia, in psychiatric disorders, such as somatoform disorder, and its reduced functionality in aging. A particular focus is to understand the 3D architecture of the human sensorimotor cortex, that is, its architecture parallel to the cortical surface (dimensions 1 and 2) and in depth (dimension 3). This approach incorporates the natural architecture of the cortex into cortical columns and cortical layers. With respect to cortical columns, we develop new technology to describe the organization of functional columns in the human cortex in-vivo. To identify basic units of information processing and their malfunction, we develop algorithms that allow functional data aggregation parallel to the cortical surface based on shared response modelling (SRM). This allows an automated clustering into relevant functional processing units, and their alterations in aging or neurodegeneration. We also develop novel pipelines and analyses techniques to characterize the layers as basic processing units of the human cortex in-vivo. Together with functional (columnar) imaging, this allows us to investigate the 3D architecture of the human sensorimotor cortex, and to precisely identify where dysfunction occurs. The identification of novel mechanisms of cortical dysfunction forms the basis for novel interventions to stop or reverse associated processes.

In-vivo pathology maps to characterize cortical dysfunction

Aging and cortical pathologies, such as motor neuron disease, are assumed to affect the inner architecture of the cortex. Cortical changes contribute to disease progression, are related to disease mechanisms, and signal symptom severity. However, the precise inner architecture of the living cortex has so far not thoroughly been described in humans due to limitations in methodology and/or imaging technology. The basic mechanisms that characterize a malfunctioning cortex, in particular at early disease stages, are therefore still poorly understood.

We apply novel imaging and analyses techniques to better understand cortical alterations that characterize the aging or degenerated cortex. Older adults and patients are investigated with ultra-high field MRI together with descriptions of their behavioral profile, for example their hand dexterity or grip strength, their disease state, their clinical profile, and their behavioral impairments. In-vivo pathology maps are computed by extracting structural and functional tissue characteristics from each layer and each cortical field of the sensorimotor

cortex. These in-vivo pathology maps, recorded using non-invasive techniques, are subsequently related to the individual disease state of the patient, or the individual impairment of the older adult. This allows fundamental insights into the cortical profiles that relate to an impaired phenotype. We identify cortical fields in the sensorimotor cortex that are particularly vulnerable to age-related degeneration, and describe in detail which layers are affected in aging and pathology. This approach takes important steps towards an individualized medicine in which the precise individual cortex architecture is taken into consideration for diagnosis, treatment, and recovery.



Wearable tools for diagnosis and behavioral training in neurological diseases

Changes of movement behavior in aging or neurodegenerative disorders are typically studied using highly controlled laboratory situations, and exploiting simplified tasks, such as walking or goal-directed arm movements. This has the advantage of a simple control and parameterization of the behavior. However, more complex real-world behaviors might be more sensitive to disease- and age-specific signatures of movement degeneration and learning.

We use MR-compatible glove systems to characterize the patterns of hand movements in naturalistic settings, during typical everyday movements, in younger and older adults, as well as in patients with motor neuron disease. The goal is to develop diagnostic and training tools that are closer to the real life behavior of the participant or patient, and that allow to track disease progression and motor learning in realistic scenarios. We train algorithms to recognize a range of different hand movements automatically, and investigate associated neuronal networks in the MR scanner. This research provides an important basis for developing diagnostic and training tools that are closer to the real life of the participant and patient.

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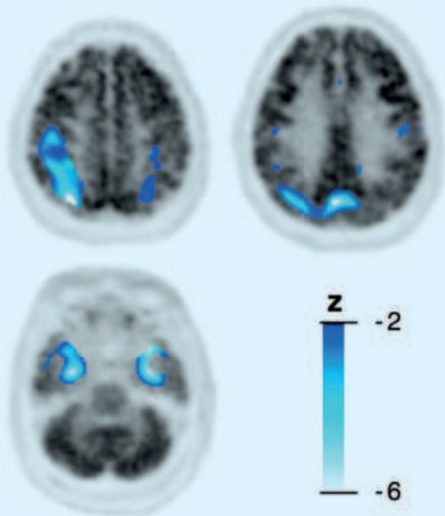
Translational Genomics of Neurodegenerative Diseases

Head: Prof. Dr. Matthis Synofzik
Team: 18 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 / antisense oligonucleotide (ASO) therapy programs



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

The translational research of our Research Division is fully geared by a systematic translational pipeline of developing therapy strategies for a broad range of genetically stratified neurodegenerative diseases. It proceeds from discovering the genetic basis, via fluid and digital biomarkers to paradigmatic first-in-human therapy approaches in

- **ataxia and ataxia-overlap diseases, in particular genetic ataxias, spastic paraplegias, neurometabolic diseases, and rare complex movement disorders**
- **Frontotemporal Dementia, Alzheimer's Disease, and other complex dementias (e.g. early-onset dementias, rare and atypical 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 Sektion verfolgt systematisch eine translationale Pipeline zur Entwicklung von Therapiestrategien für ein breites Spektrum genetisch stratifizierter neurodegenerativer Erkrankungen. Sie geht aus von der Entdeckung der genetischen Grundlagen, über Fluid- und digitale Biomarker bis hin zu paradigmatischen First-in-Human-Therapieansätzen bei

- *Ataxie- und Ataxie-Spektrumserkrankungen, insbesondere genetische Ataxien, spastische Spinalparalyse, neurometabolische Erkrankungen, und komplexe seltene Bewegungsstörungen.*
- *Frontotemporalen Demenz, Alzheimer Demenz und anderen komplexen Demenzen (u.a. seltene und atypische Varianten der Alzheimer-Demenz, genetische Demenz-Formen)*
- *Motorneuronerkrankungen (Amyotrophe Lateralsklerose, v.a. genetische Formen; ALS-FTD-Spektrum-Erkrankungen; lysosomale Motorneuronerkrankungen).*

The concept

For each these disease clusters, we have implemented a translational pipeline covering a comprehensive methodological spectrum including each systematic step of the pipeline:

- genetic stratification of patients with so far molecularly unsolved diseases, leveraging latest whole exome, whole genome and transcriptome sequencing;
- 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 real-life setting;
- deep clinical, neuropsychological and imaging profiling;
- mechanistic first-in-man treatment studies (e.g. with RNA therapies like antisense oligonucleotides, ASOs).

Ataxias and ataxia-overlap diseases

We are a national and international lead center in degenerative ataxias, leading a multitude of national and international ataxia and ataxia-spectrum consortia and platforms. Building on the prospective longitudinal international multicenter Autosomal Recessive Cerebellar Ataxia and Early-Onset Ataxia registry (ARCA/EOA) established by us in 2012, we were able to establish a large international network with continuous longitudinal progression data of >1000 ataxia patients.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 platform "Ataxia Global Initiative ", which coordinates and harmonizes trial-readiness research on genetic ataxias across the leading centers around all continents (launched in 2019).

We helped to expand and delineate the phenotypic spectrum of >20 ataxia genes, including SYNE1, PNPLA6, STUB1, COQ8A (Traschütz et al, 2020, Ann Neurol) and RFC1 (Traschütz et al, 2021, Neurology). Our large web-based cohort of >2100 ataxia exome data-sets (PREPARE GENESIS), allowed us to identify > 15 novel ataxia/hereditary spastic paraplegia genes, like DNAJC3 , KCNA2 or PRDX3 (Rebelo et al, 2021, Brain).

Frontotemporal dementias, Alzheimer's disease and other complex dementias

We are a site PI in several national and international networks establishing translational programs for genetic and sporadic fronto-temporal dementia (FTD). 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 fronto-temporal 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 (Wilke et al, 2021) as well as other neurodegenerative diseases like Parkinson's disease (Wilke et al, 2020, Mov Disord). This very early-stage disease phase which might be uniquely amendable for molecular treatments will now be characterized molecularly in-depth by our novel European JPND "GENFI-prox" consortium (launched in 2020).

Trial-readiness: establishing the basis for effective treatment trials in neurodegenerative diseases

To establish 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, 2020), thus demonstrating ecological validity as required for regulatory approval as trial outcome measures. This is paralleled by our fluid biomarker work in ataxias, Frontotemporal Dementia, Alzheimer's Disease and ALS, highlighting neurofilament light chain (NfL) as a highly promising progression, stratification and treatment-response biomarker for each of these diseases.

Precision Medicine 2.0: developing patient-customized antisense oligonucleotide (ASO) treatments within a scalable platform approach

Building this fluid and digital-motor biomarker trial-readiness work, we are now running a whole series of first-in-man trials with targeted, mechanistic antisense oligonucleotides (ASO) in various genetic ataxias, FTD, Alzheimer's disease and ALS. This includes a systematic development of a scalable platform approach for preclinical and clinical development of fully individualized ìn-of-1î ASOs, developing and launching mechanistic treatments fully tailored to only single neurological patients and their respective private mutation (1 Mutation 1 Medicine, 1M1M); Synofzik et al, 2022).

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Cognitive Neurology Laboratory

Head: Prof. Dr. Peter Thier
Team: 11 members
Key words: mirror neurons / attention / autism / social cognition / motor learning / fatigue / ataxia / (control of) eye movements

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.

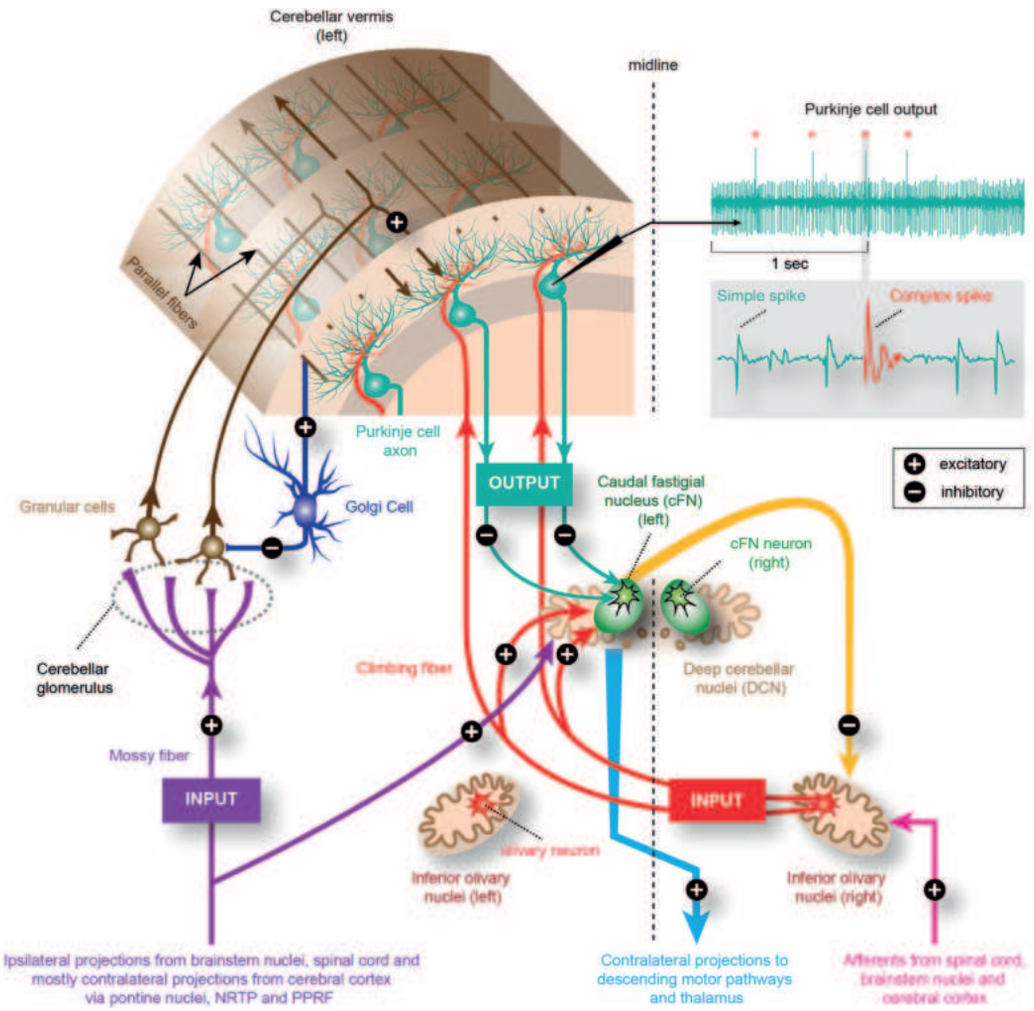
The lab studies of the underpinnings of social interactions and the mechanisms underlying motor learning and their disturbances due to disease.

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

The Cognitive Neurology Laboratory studies 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. The other's eye, head and body orientation are a particularly powerful class of sensory cues revealing the location and object of interest to the other, allowing the observer to shift her/his attentional focus to the same object, thereby establishing joint attention, allowing to map one's own object-related intentions and aspirations onto the other. The cognitive neurology laboratory tries to unravel the neuronal structures and mechanisms affording joint attention and the understanding of the other's intentions as well as information on the other's emotional state as documented by facial expressions. It hypothesizes that malfunction of these structures, which involve larger parts of cortex around the superior temporal sulcus and the neighboring temporoparietal junction, may actually underlie the inability of autistic subjects to efficiently exploit gaze cues when interacting with others.

Complementary work on the underpinnings of social cognition addresses the role of the mirror neuron system in premotor cortex in action understanding and response selection. Mirror neurons are a class of neurons in premotor cortex of monkeys that are activated by specific types of goal-directed motor acts such as grasping a piece of apple in order to eat it. In an attempt to better understand the complex features of mirror neurons, to put the so-called simulation theory to a critical test and to assess alternative concepts such as a role of the mirror neuron system in response selection, the lab is carrying out experiments on premotor cortical area F5. In a nutshell, our past work has shown that this particular area has access to streams of information which are obviously very important for the evaluation of the actions of others such as information on the operational distance between actor and observer or the subjective value, the observed action has for the observer or that observation-related responses of mirror neurons are to some extent viewpoint invariant.

A second major interest of the laboratory pertains to the role of the cerebellum in motor control and motor learning. Using short-term saccadic adaptation, but also smooth pursuit eye movements and goal-directed hand movements as models of motor learning, the group 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. In our most recent work on the role of the cerebellar climbing fiber, traditionally thought to be confined to reporting information on current performance errors, we have been able to establish that this afferent systems taps many other sources of information valuable for learning.

The canonical cerebellar circuit integrating afferent information provided by the two types of afferents, mossy fibers and climbing fibers, and impacting target neurons in the deep cerebellar nuclei by way of the axons of Purkinje cells. The inset at the upper right depicts an exemplary Purkinje cell spike train consisting of simple spikes, which are conventional sodium-potassium action potentials reflecting the collective influence of mossy fiber/parallel fiber activity and various interneurons, and the much rarer and longer-lasting complex spikes, which are released by climbing fiber input from the inferior olive. Abbreviations: cFN, caudal fastigial nucleus; NRTP, nucleus reticularis tegmenti pontis; PPRF, paramedian pontine reticular formation (from Thier & Markanday, Annu Rev Vis Sci, 2019, 5:247-268).

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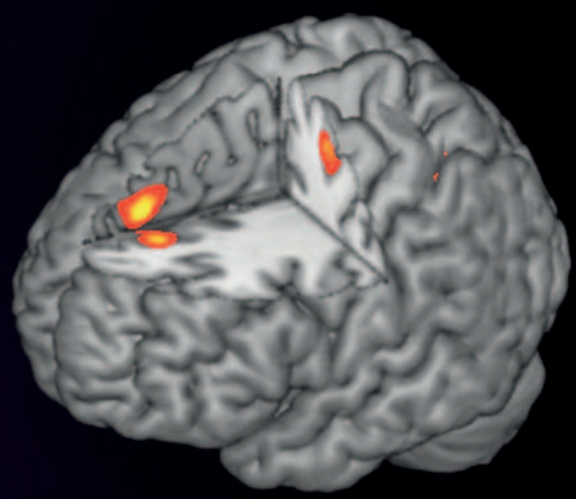
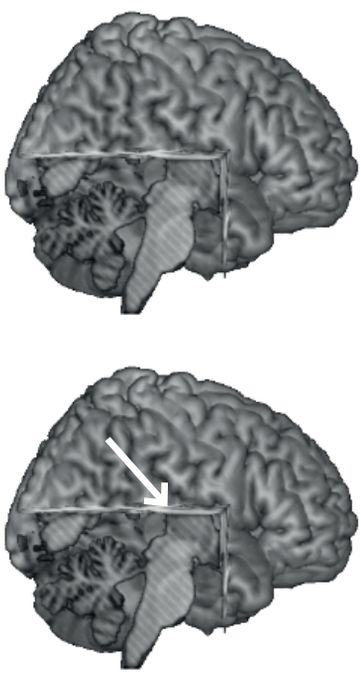
Neuropsychology of Action

Head: PD Dr. Marc Himmelbach
Team: 3 members
Key words: reaching / grasping / brainstem motor functions / UHF fMRI



The Research Group "Neuropsychology of Action" investigates human action control using functional and structural neuroimaging, focusing on subcortical and brainstem structures.

Die Forschungsgruppe „Neuropsychologie der Handlungskontrolle" untersucht die menschliche Handlungskontrolle mit Hilfe funktioneller und struktureller Bildgebung, wobei der Schwerpunkt auf subkortikalen und Hirnstammstrukturen liegt.



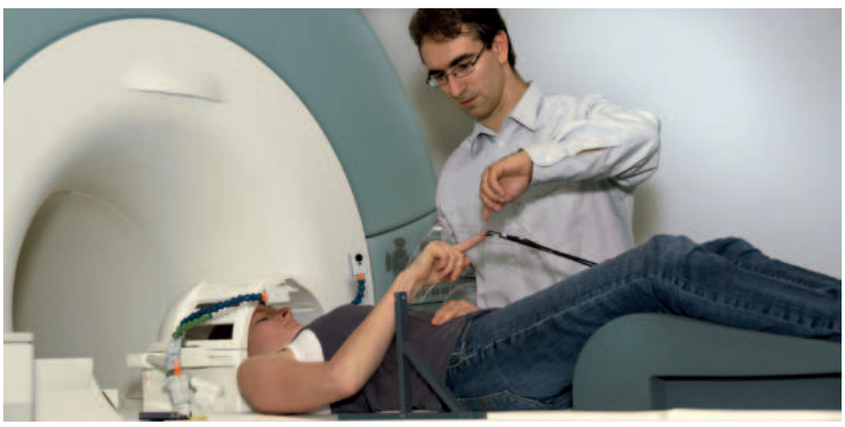
The superior colliculi are part of the tectum which additionally comprises the inferior colliculi right below. Traditionally the superior colliculi have been associated with visual and oculomotor functions.

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 a contribution of the superior colliculi to the control of arm movements also in healthy humans. 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. We extended our work to attentional functions of the superior colliculi and Its interaction with temporal cortex areas.

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.



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

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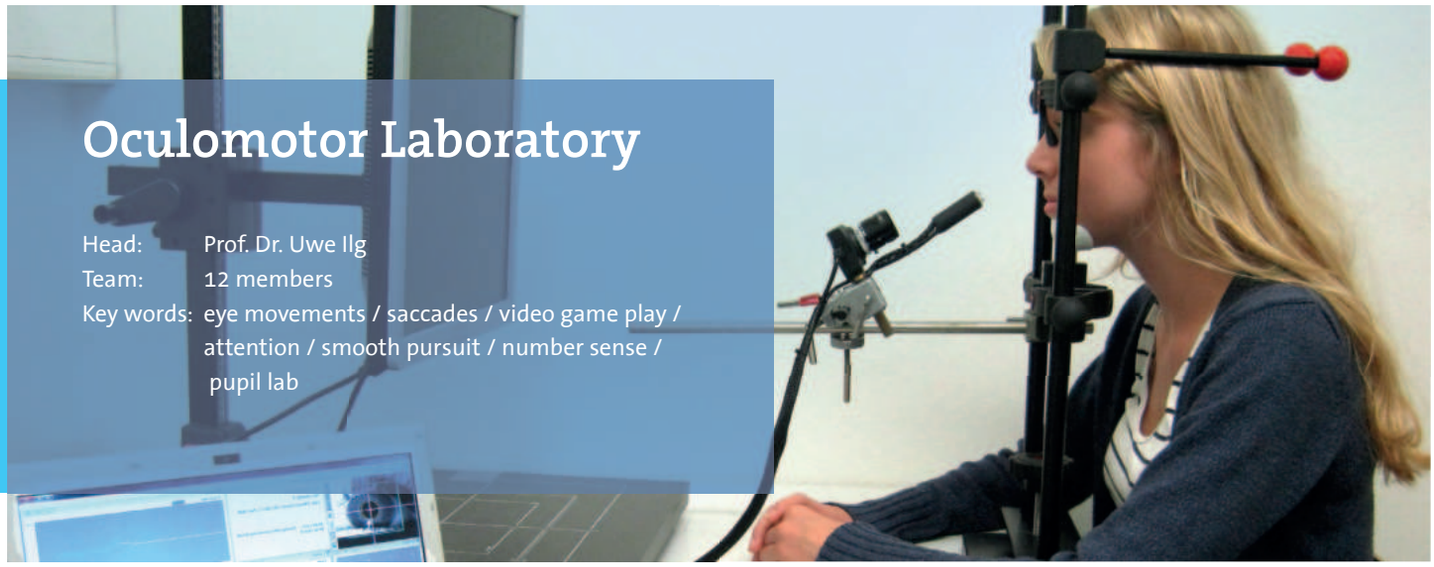


Oculomotor Laboratory

Head: Prof. Dr. Uwe Ilg
Team: 12 members
Key words: eye movements / saccades / video game play / attention / smooth pursuit / number sense / pupil lab

In addition to the two major changes of our society, i.e. the massive increase of the number of older individuals and the ballistic acceleration of the use of digital devices, there Is an increasing lack of trust and knowledge of science within the young part of our society. To understand the effects of age and video game play, we perform various eye movement and perceptual studies. To foster the understanding of Nature of Science as well as to attract future students, we established a pupil lab of Neuroscience. From elementary to high school students perform experiments addressing the mystery of the brain.

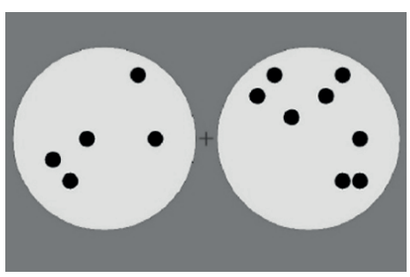
Zusätzlich zu den beiden großen Veränderungen in unserer Gesellschaft, d. h. der massiven Zunahme der Zahl älterer Menschen und der rasanten Beschleunigung der Nutzung digitaler Geräte, mangelt es dem jungen Teil unserer Gesellschaft zunehmend an Vertrauen und Wissen über die Wissenschaft. Um die Auswirkungen des Alters und des Spielens von Videospielen zu verstehen, führen wir verschiedene Augenbewegungs- und Wahrnehmungsstudien durch. Um das Verständnis für die Natur der Wissenschaft zu fördern und zukünftige Studenten anzuziehen, haben wir ein Schülerlabor für Neurowissenschaften eingerichtet. Von der Grundschule bis zur Oberstufe können Schüler Experimente durchführen, die sich mit dem Geheimnis des Gehirns befassen.

Anti-Saccade Paradigm

Under normal conditions, subjects move their eyes towards an unexpected appearance of a visual target (visual grasp reflex). These eye movements (pro-saccades) are extremely fast and performed under ballistic control. During the Anti-Saccade Paradigm, subjects are asked to perform a mirror-like eye movement. If the target appears to 10 degree of sight on the left, the saccade should be directed towards 10 degree right. These anti-saccades are compared with pro-saccades as well as accidentally performed direction errors in separate experimental blocks. There is general agreement that the execution of pro-saccades is regulated by the superior colliculus whereas the execution of anti-saccades is dependent on the frontal eye field (area8).
We performed an age study with close to 600 participants ranging from age 51 to 84. Saccadic reaction time clearly increased with age. However, peak velocity during saccades was not affected by age. Finally. the probability of direction errors expressed as error rate increased with age. Our data reveal a uniform slowing of processing speed independent of the actually performed eye movement. In addition, the data do not support the idea of specific deteriorations of the frontal lobe functions with aging.
In a different study, we asked whether videogame players (VGPs) express differences to non-players (NVGPs) in the anti-saccade paradigm. In the line with earlier studies, VGPs have shorter saccadic reaction times compared to NVGPs. In general, there is a correlation between saccadic reaction time and error rate: subjects with short reaction times tend to have higher error rates. But, to our surprise, the error rate was not different between VGPs and NVGPs. There Is no indication for a reduced executive control function of the frontal cortex In VGPs.

Perception of Numerosity

We are able to estimate the number of objects without counting, at least for small numbers. We compared the number sense of 32 VGPs with 34 NVGPS. For both cohorts, our data clearly show that the precision of the number sense declines from 5 to 10 items. In addition, the precision of the VGPs Is superior to the precision of the NVGPs. However, it should be noted that our definition of VGP was four hours videogame play per week. Negative side effects of extensive videogame play cannot be excluded.



Eye Tracking and Soccer

During a game, soccer players have to perform frequently decisions. We addressed the decision process in the course of an eye tracking study. Subjects were categorized as soccer player (n=19) and non-player (n=20), respectively. We produced 11 videos showing different situations in a soccer game. At the end of each video, the subject had to select the best action out of three possibilities. We tracked eye position as well as pupil size of our subjects. Especially the size of the pupil Indicated that soccer player had a closer and deeper relationship to the task compared to the non-players. In addition, the response latency for the decision was shorter for the soccer players. Our study shed some light into the cognitive processing underlying playing soccer.

Subjects watched different soccer videos while eye position and pupil size were recorded. At the end of the video, a still image was displayed and the subjects had to indicate by an eye movement what they believed as best solution.

Pupil Lab for Neuroscience

The Pupil Lab for Neuroscience offers a fascinating introduction to the scientific study of causality in neuroscience for elementary to senior high school students from all over Germany. It makes it possible to undertake fascinating experiments related to neuroscience research themes. Since it was established in 2008, the Pupil lab has become well-established as an after-school learning facility not only in southern Germany, attracting a consistent level of visitors (roughly 2,000 school pupils a year). For many years now, either a one-day school visits, special days such as Girls' Day, or Summer academy for an entire week have been fully booked.
But not only students, also teachers participate in the Pupil lab. Annual training sessions provide the possibility for teachers to keep in touch with current research topics.

Finally, the Pupil lab offers the possibility to perform educational research. Strategies to improve the understanding of Nature of Science as well as the competence to derive hypothesis and their experimental verification can be tested here.

Two high-school students examine the brain of a lamb as a model for the human brain.

Visual stimulation during the number sense study. The display was shown for 500 ms only, subjects could not count the number of dots in both displays. They had to indicate the location of the larger numerosity.

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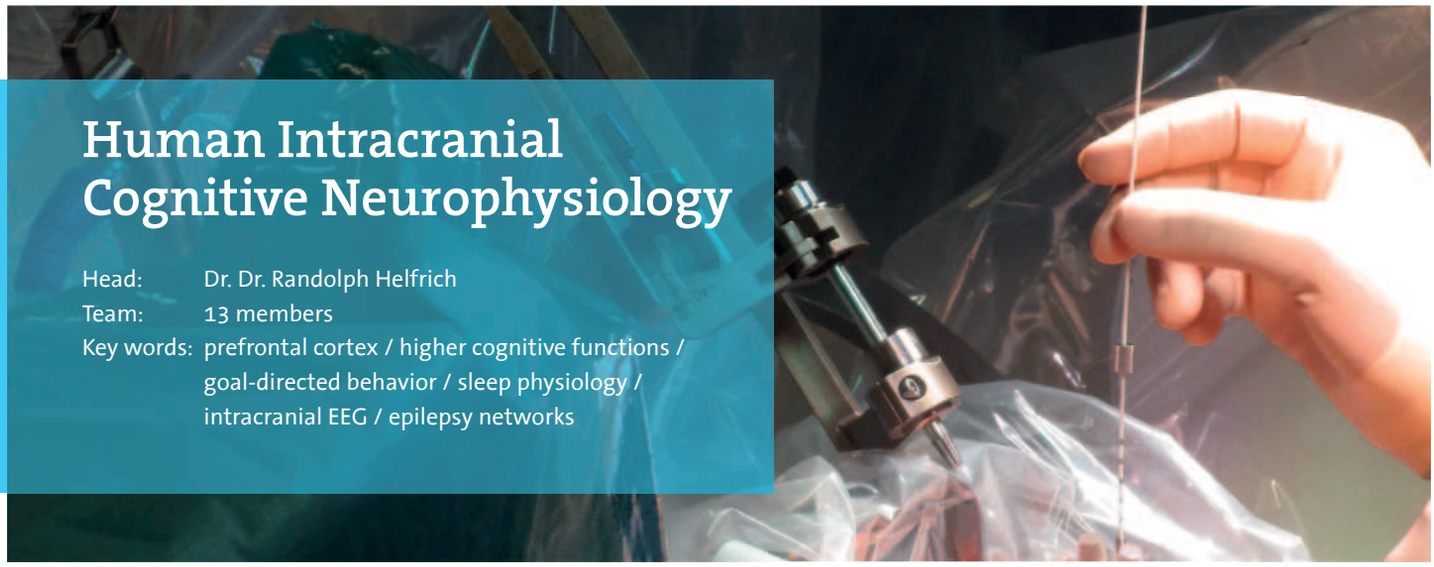
Independent Junior Research Groups

Promoting young scientists is an investment in the future and is therefore high on the Hertie Center of Neurology's list of priorities.

The HIH supports early scientific independence. Independent junior research groups are equal in status to HIH research group leaders. A prerequisite for establishing such a junior research group at the HIH is external funding (ERC grant, Emmy Noether junior research group, etc.). Independent junior research group leaders have the opportunity to actively shaping the future of the institute and taking on responsibility at an early stage. Embedded in the excellent infrastructure of the institute, they can build up their own research program.

INDEPENDENT JUNIOR RESEARCH GROUPS 142

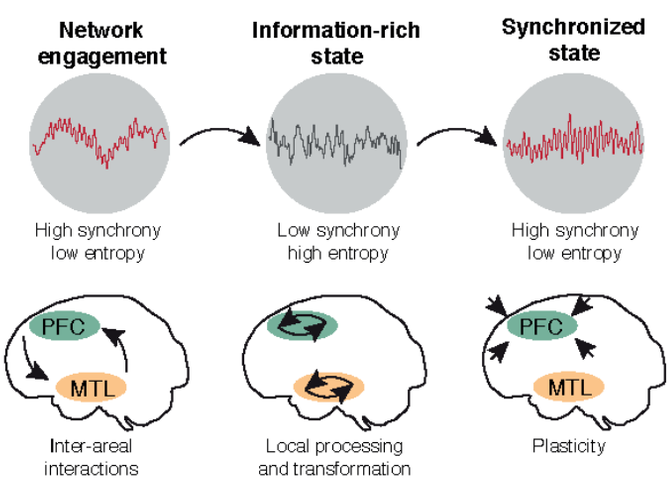


Human Intracranial Cognitive Neurophysiology

Head: Dr. Dr. Randolph Helfrich
Team: 13 members
Key words: prefrontal cortex / higher cognitive functions / goal-directed behavior / sleep physiology / intracranial EEG / epilepsy networks

The goal of our group is to understand the neural network mechanisms supporting higher cognitive functions and their disturbances underlying neuropsychiatric disorders. We study the functional architecture of human cognition with a spatiotemporal resolution spanning single units to large-scale network activity. In particular, we seek to understand context-dependent, goal-directed behavior in humans through the study of neural network dynamics with a particular emphasis on prefrontal cortex (PFC) physiology. The key hypothesis is that context dependent endogenous brain activity shapes cognitive processing in different cortical states, i.e. wakefulness or sleep. A core interest is the systematic investigation of the functional network architecture of cortico-cortical and subcortico-cortical interactions supporting cognitive processes such as attention and memory and their impairment in healthy aging and neurodegenerative diseases.

Unsere Arbeitsgruppe erforscht die neuronalen Mechanismen, die höheren kognitiven Prozessen wie Aufmerksamkeit oder Gedächtnis zugrunde liegen. Insbesondere gehen wir der Frage nach, wie es dem Gehirn gelingt, aus den sich unablässig ändernden Gehirnwellen einen zeitlich zusammenhängenden Sinneseindruck entstehen zu lassen. Unser Interesse konzentriert sich dabei vor allem auf den präfrontalen Kortex, von dem wir vermuten, dass er die entscheidende Rolle bei der Integration, Interpretation und Umsetzung eines daraus folgenden Handlungsplanes spielt. Dazu untersuchen wir vor allem periodische Fluktuationen im Verhalten (z.B. natürliche Schwankungen der Aufmerksamkeit) als direkten Spiegel der zugrundeliegenden neuronalen Oszillationen. Das Verhalten beeinflusst aber auch das Gehirn selbst, so dass sich z.B. neuronalen Oszillationen im darauffolgenden Schlaf verändern und so Erinnerungen abgelegt werden. Sowohl im Wachzustand als auch im Schlaf arbeitet eine Gehirnregion nie allein, sondern immer in einem komplexen Netzwerk aus kortikalen und subkortikalen Strukturen. Eine krankheitsbedingte Veränderung in einer Region oder im gesamten Netzwerk kann diese Zusammenarbeit stören und zu Einschränkungen in Konzentration und Merkfähigkeit führen. Um zu verstehen, wie verschiedene neurologische und psychiatrische Erkrankungen höhere kognitive Prozesse beeinflussen, untersuchen wir neben gesunden Probanden auch verschiedene Patientenpopulationen.



The putative function of synchronized and desynchronized brain states for memory consolidation during sleep. From Helfrich, Lendner, Knight (2021) TiCS.

Currently, much of our understanding of the neural basis of cognition stems from invasive primate recordings or non-invasive recordings in humans. The limited spatiotemporal resolution of non-invasive imaging hampers scientific progress in our understanding of health and disease. Human intracranial electrophysiology has the promise of significant insights into the neural mechanisms that guide behavior. Several clinical procedures provide the unique opportunity to record directly from the human brain at the single neuron or population level. A key goal of our lab is to bridge the gap between different imaging modalities in different species. Translationally, we integrate cognitive and clinical neurophysiology to increase our understanding of cognitive decline and reduced arousal levels such as sleep, anesthesia and coma.

Rhythmic building blocks of human attention: How network oscillations link perception and action

Attention is a fundamental mechanism needed to select and boost behaviorally relevant information to efficiently translate sensory experiences into goal-directed actions. Traditionally, attention has been conceptualized as a continuous process: Once it is allocated, it remains constant until the next environmental stimulus is attended. However, it is unclear how the brain implements constancy when its activity exhibits prominent waxing and waning patterns, also termed neuronal oscillations. Recently, several lines of inquiry probing attention on a fine-grained temporal scale revealed frequency-specific behavioral fluctuations during both covert sampling and overt exploration that aligned with ongoing brain oscillations. This evidence suggests that attention-guided perception might be a rhythmic and not a purely continuous process. In our work, we address the rhythmic basis of attention using detailed behavioral testing with both correlative and causal methodologies. In addition to non-invasive magnetoencephalography in healthy participants, we employ direct brain recordings in epilepsy patients, who are implanted with intracranial electrodes for seizure onset localization. In order to establish causality, we utilize both the neuropsychological lesion approach as well as direct brain stimulation.

(Patho-)Physiology of human memory networks during wakefulness and sleep

In a second line of research, we investigate the functional role of sleep for cognitive functioning. We all experience the positive effects of sleep on our mood, cognitive abilities and physical health. Even one night of sleep loss has devastating effects on our mental and physical well-being. Therefore, it is not surprising that almost every neuropsychiatric disease is associated with impaired sleep and often accompanied by cognitive symptoms, such as memory deficits. Notably, sleep disturbances often precede illness as for instance exemplified by REM sleep disorders in Parkinson's disease, which can occur up to 10 years before any motor symptoms. Our goal is to understand the sleeping brain with high spatiotemporal resolution using intracranial recordings in humans to determine how different temporal scales support memory formation. In particular, we seek to unravel how the precise temporal coordination between the hippocampus and the prefrontal cortex subserves memory formation, i.e. the reactivation, transfer and consolidation of newly acquired information.

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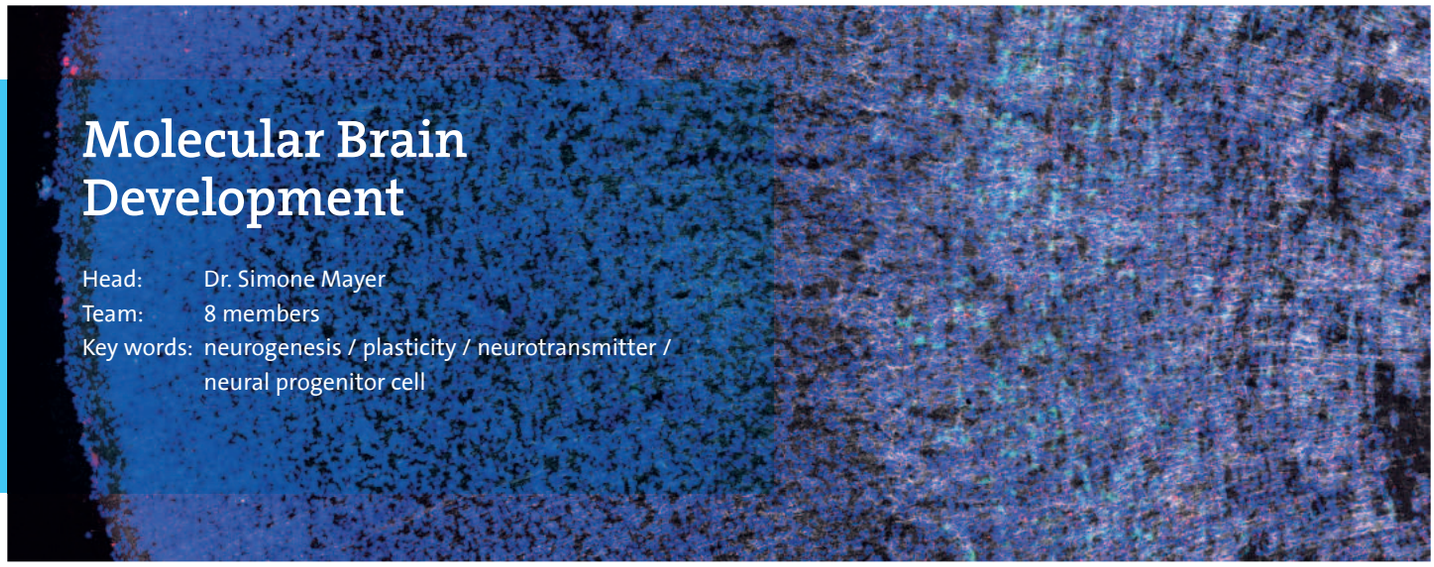


Molecular Brain Development

Head: Dr. Simone Mayer
Team: 8 members
Key words: neurogenesis / plasticity / neurotransmitter / neural progenitor cell

Genetic and environmental factors shape the complex architecture and function of the mammalian brain. Recent progress in stem cell biology allow to recapitulate human brain development in vitro using so-called brain organoids. We use different type of brain organoids in order to generate models of neurodevelopmental disorders with genetic and environmental causes.

Genetische und Umweltfaktoren bestimmen die komplexe Architektur und Funktion des Gehirns von Säugetieren. Jüngste Fortschritte in der Stammzellbiologie ermöglichen es, die Entwicklung des menschlichen Gehirns in vitro mithilfe sogenannter Gehirnorganoide nachzubilden. Wir verwenden verschiedene Arten von Gehirnorganoiden und entwickeln Modelle für neurologische Entwicklungsstörungen die durch Umwelteinflüsse oder genetische Veränderungen hervorgerufen werden.

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 (2D) neural cultures as well as brain region-specific three-dimensional (3D) organoids derived from human induced pluripotent stem cells (hiPSCs). Organoids have 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, 2020). Since their initial development, cerebral organoid protocols have been improved by increasing reproducibility, incorporating long-distance cellular interactions and adding glial cells. By using both 2D and 3D hiPSC models of human brain development, we contribute 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 signaling 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). Due to the large cellular diversity present in brain organoids, single-cell analysis is especially needed in this context, in order to reveal cell type-specific biological processes. Additionally, we perform signaling pathway analysis using classical methods such as immunofluorescence, and Western blotting.

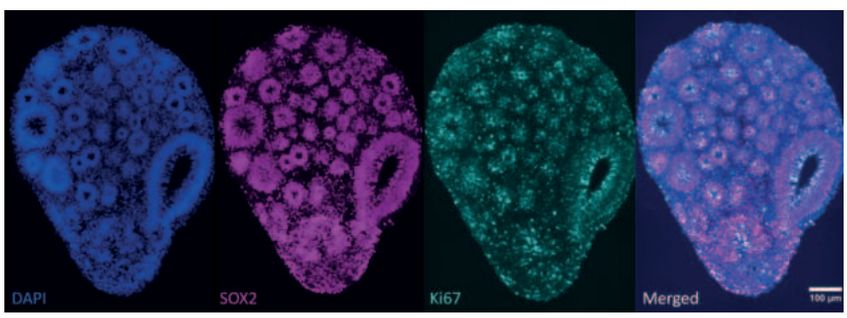
Plasticity in neocortical development in health and disease

Using diverse in vitro models of human neocortical development, we determine how environmental factors can affect neocortical development with a focus on the proliferation and differentiation of neural stem cells. Many environmental impacts including viral infections, substance abuse, and pharmaceuticals have been shown to affect human brain development in organoid models (see our recent review, Sarieva and Mayer, Front Mol Biosci, 2021). For example, in a recent project, we determined the molecular and cellular effects caused and elevated interleukin-6 signaling in the developing human neocortex. We established an organoid model of maternal immune activation and studied changes in organoid biology using a combination of experimental approaches including single-cell RNA-sequencing to show that Interleukin-6 receptor activation specifically

disturbs the proliferation and differentiation of radial glia cells (Sarieva et al., Mol Psych, 2023). We also showed that while changes in gene expression upon treatment with Interleukin-6 were recapitulated in a 2-dimensional neural differentiation protocol, effects on proliferation were only seen in the more complex organoid model, likely because cell-cell Interactions in 3D are required to control complex cellular processes during human neocortical development (Sarieva et al., Disease Models and Mechanisms, 2023). Another on-going project in the lab address how anti-epileptic drugs affect human neocortical development and may thus be molecular causes of the increased risk of such exposures to develop neurodevelopmental disorders, such as autism spectrum disorders.

Revealing the disease mechanisms

Genetic perturbations may also affect human brain development. As a disease model, in cooperation with the Pediatrics department at the University Clinic Tübingen, the Clinical Neurogenetics Section at HIH, the University Hospital Freiburg, and a patient organization, , 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 microcephaly, indicating that neocortical development is also affected by the genetic abnormalities. Understanding the cellular and molecular mechanisms that drive disease progression in the different brain areas may pave the way for treatment approaches. This work is currently supported by a grant from the Chan Zuckerberg Initiative, under the lead of Dr. Simone Mayer. The project on PCH was also honored by the Eva Luise Köhler Research Award to Dr. Simone Mayer in 2023. Importantly, both funders emphasized the importance of collaborating closely with patient parents to address unmet needs in a rare disease.



Representative image of dorsal forebrain organoid (neocortical organoid) on Day 35 of differentiation. Differentiation protocol according to Velasco et al. 2019, Nature. Images were taken by Zeynep Yentür.

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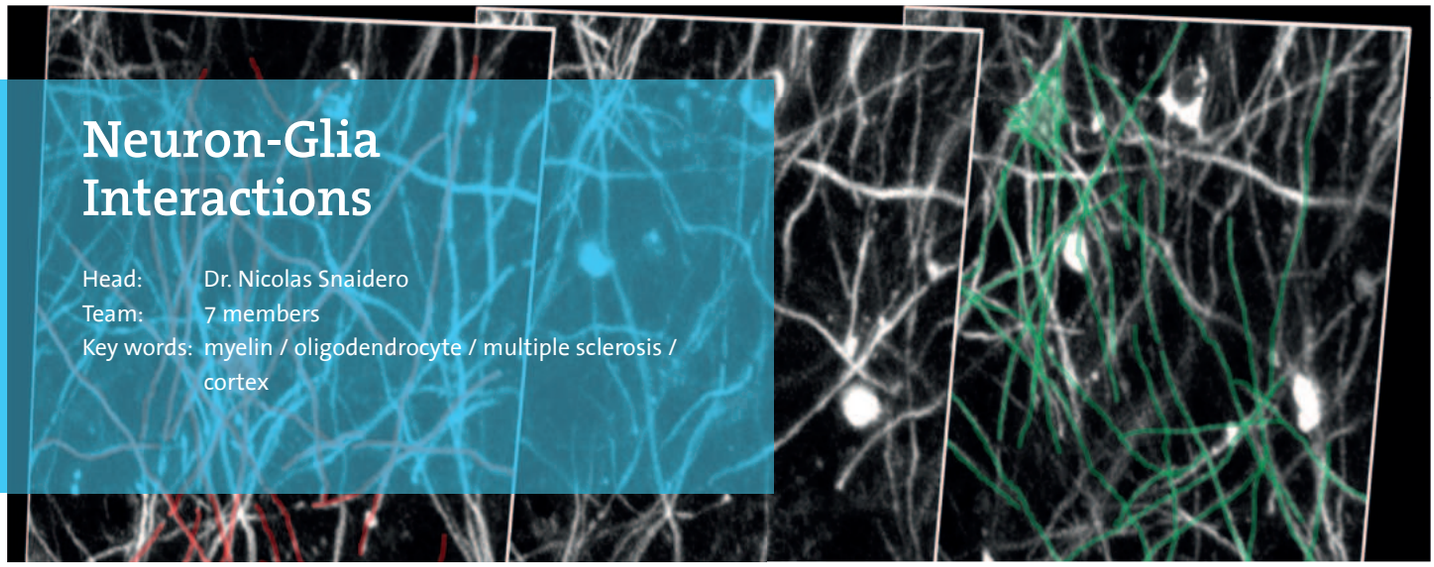


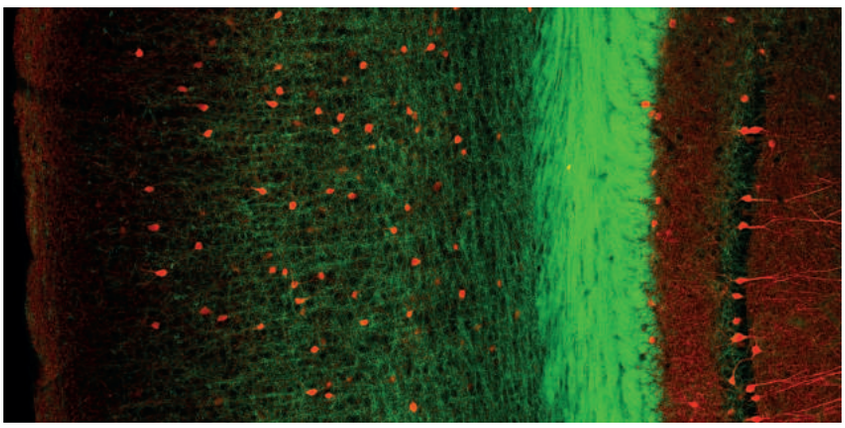
Neuron-Glia Interactions

Head: Dr. Nicolas Snaidero
Team: 7 members
Key words: myelin / oligodendrocyte / multiple sclerosis / cortex

Oligodendrocytes are glial cells that in the central nervous system enwrap several axons simultaneously, enabling fast impulse propagation and providing long term metabolic support. In the cortical grey matter, complex and diverse patterns of myelin can be found along cortical axons that have been shown to be dynamic during adulthood with single sheath plasticity and global increase of myelin content over time. The regulation of this complex "myelinome" offers immense potential for neuronal network plasticity and has already been associated with memory. However, the molecular and functional determinants of this targeted process, its dynamic at a single cell level and the selectivity of the axo-glia units resulting from sparse cortical myelination remain largely unknown. Our newly founded lab is focusing on identifying the mechanisms underlying the cortical adaptive myelination, as well as its dysregulation in aging and inflammatory lesions. Using advance microscopy and correlative structural and omic tools a key goal of the lab is to bridge the cellular, molecular and functional dimensions of targeted cortical myelination to, ultimately, develop new translational approaches for targeted and personalized remyelination therapies.

Oligodendrozyten sind Gliazellen, die im zentralen Nervensystem mehrere Axone gleichzeitig umhüllen, eine schnelle Impulsübertragung ermöglichen und den Stoffwechsel langfristig unterstützen. In der grauen Substanz des Kortex finden sich entlang der kortikalen Axone komplexe und vielfältige Myelinmuster, die sich im Erwachsenenalter als dynamisch erwiesen haben, mit einer Plastizität der einzelnen Hüllen und einer globalen Zunahme des Myelinanteils im Laufe der Zeit. Die Regulierung dieses komplexen „Myelinoms" bietet ein immenses Potenzial für die Plastizität neuronaler Netzwerke und wurde bereits mit dem Gedächtnis in Verbindung gebracht. Die molekularen und funktionellen Determinanten dieses gezielten Prozesses, seine Dynamik auf Einzelzellebene und die Selektivität der Axo-Glia-Einheiten, die aus der spärlichen kortikalen Myelinisierung resultieren, sind jedoch noch weitgehend unbekannt. Unser neu gegründetes Labor konzentriert sich auf die Identifizierung der Mechanismen, die der kortikalen adaptiven Myelinisierung zugrunde liegen, sowie auf deren Dysregulation bei Alterung und entzündlichen Läsionen. Mithilfe fortschrittlicher Mikroskopie und korrelativer struktureller und omic-Instrumente besteht ein Hauptziel des Labors darin, die zellulären, molekularen und funktionellen Dimensionen der gezielten kortikalen Myelinisierung zu überbrücken, um letztlich neue translationale Ansätze für gezielte und personalisierte Remyelinisierungstherapien zu entwickeln.

In order to investigate the complex cellular and molecular dynamics linked with cortical myelin patterning and its dysregulation in inflammatory demyelinating lesions and aging, we are primarily using longitudinal intravital imaging. We are combining advanced genetic and viral labelling to reach a comprehensive labelling of glia cells, neuronal types but also to investigate the functional properties of these cells in relation to their dynamics.



Example of a rodent brain slice where neuronal specific labeling (red) and mature oligodendrocytes (green - with their myelin sheath) depict the complex cortical patterning from the layer 1 to the corpus callosum down to the hippocampus.

One line of projects aims to investigate the cellular and functional determinants of the adult cortical myelin patterning. Here we are building on recent published work to address the mechanisms underlying the preside axonal targeting during adaptive myelination, that has been associated with memory, and homeostatic remyelination, that occurs from very young age in humans and rodents. Here we are using an assay that we recently developed combining longitudinal intravital imaging with single oligodendrocyte ablation. Functional and molecular modulation are performed locally with gene therapy and non-invasive strategies.

On another line of research, the lab is investigating the cellular and molecular causes for failing remyelination in inflammatory lesions. Here we adapted our recently published model for cortical MS lesions in order to investigate the cellular and milieu determinants for the poor remyelination as well as neuronal damages in cortical MS lesions. We aim to develop non-invasive translational strategies to 1) reduce the initial demyelination due to inflammation and immune response 2) potentiate precursor differentiation in a focal manner to achieve complete remyelination 3) protect neuronal damages.

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