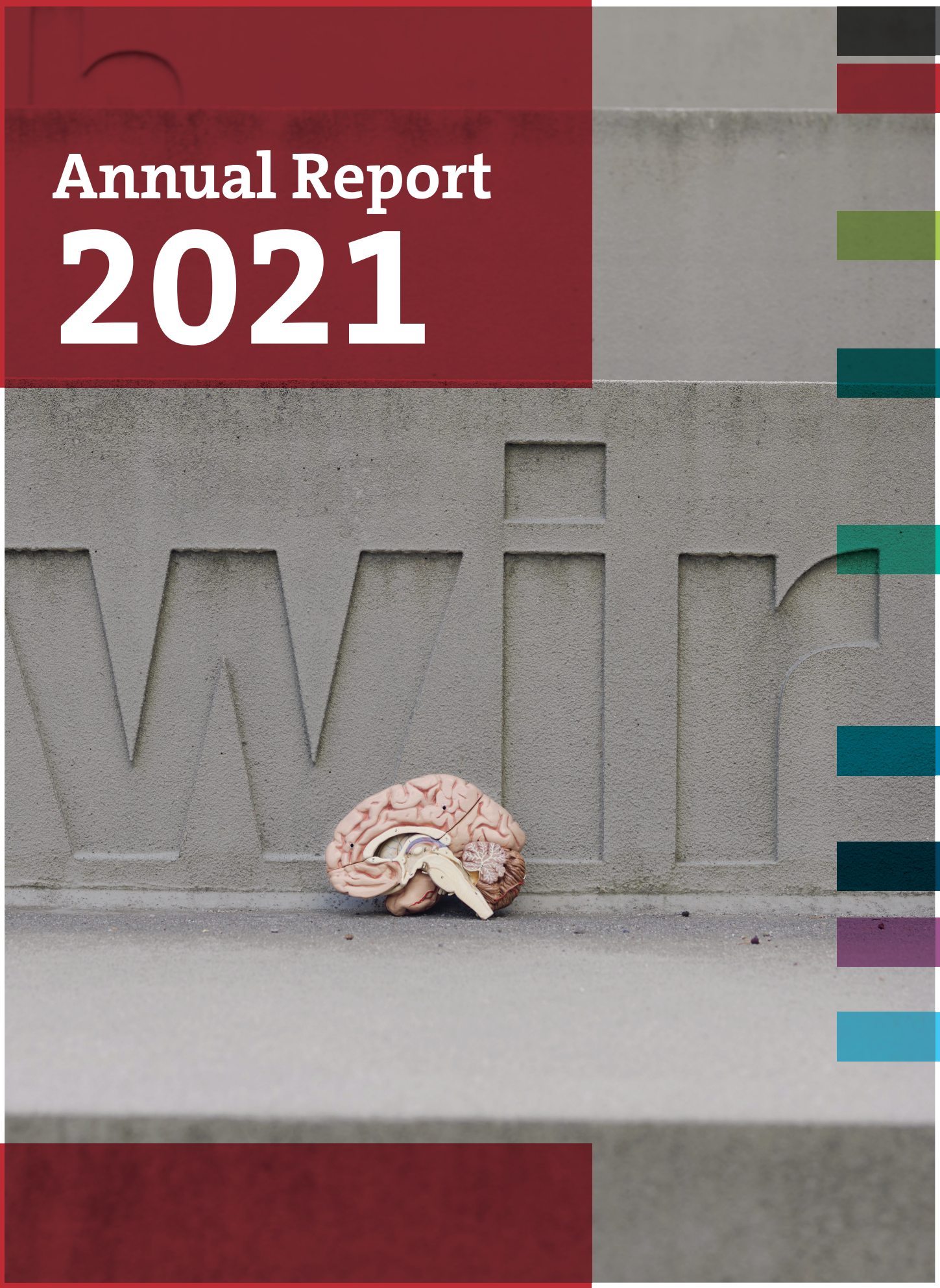
CENTER OF NEUROLOGY
TÜBINGEN

Annual Report 2021



CENTER OF NEUROLOGY TÜBINGEN

Annual Report 2021

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 Center of Neurology

The Center of Neurology

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

The Center of Neurology presently consists of six departments: 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 Center of Neurology from other neuroscience institutions. In particular, the close interaction between basic science and patient care at the HIH and the University Hospital's Clinical Neurology Department was seen as a role model for clinical and translational research in Germany by the German Council of Science and Humanities (Wissenschaftsrat).

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

Das Zentrum setzt sich aus zwei eng verbundenen Institutionen zusammen, der Neurologischen Klinik und dem Hertie-Institut für klinische Hirnforschung (HIH). Die Aufgaben des Zentrums liegen sowohl in der Krankenversorgung durch die Neurologische Klinik als auch in der wissenschaftlichen Arbeit der im HIH zusammengeschlossenen 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.

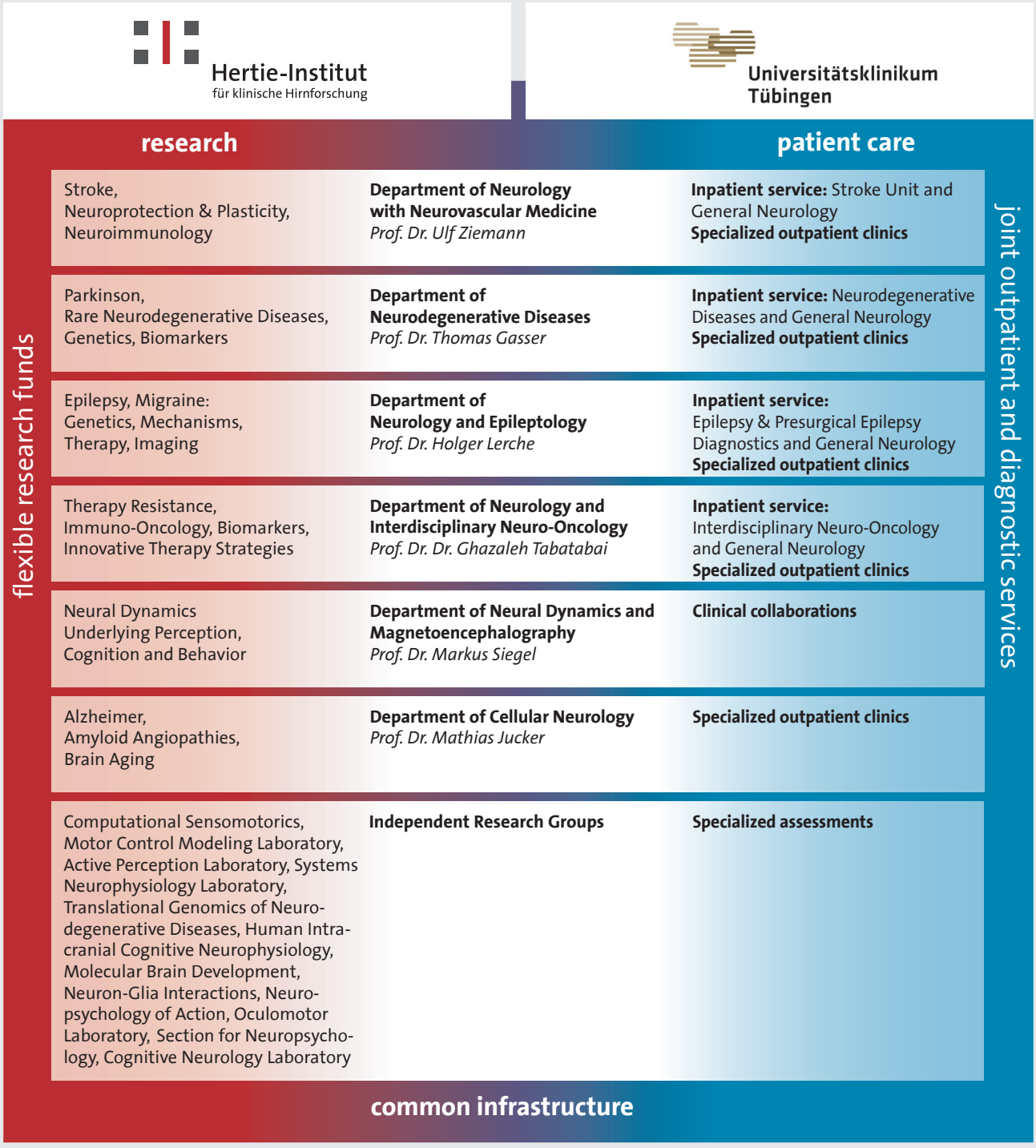
Das Zentrum besteht aus sechs Abteilungen: der Abteilung Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen (Prof. Dr. Ulf Ziemann), der Abteilung Neurologie mit Schwerpunkt neurodegenerative Erkrankungen (Prof. Dr. Thomas Gasser), der Abteilung Neurologie mit Schwerpunkt Epileptologie (Prof. Dr. Holger Lerche), der Abteilung Neurologie mit interdisziplinärem Schwerpunkt Neuroonkologie (Prof. Dr. Dr. Ghazaleh Tabatabai), 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 beteiligt. Die klinischen Abteilungen sind für die Versorgung von Patientinnen und Patienten mit der gesamten Breite neurologischer Erkrankungen gemeinsam verantwortlich. Die Einheit der Neurologischen Klinik in Lehre, Ausbildung und Krankenversorgung wird dabei durch eine gemeinsame Infrastruktur (Patientenaufnahme, Behandlungspfade, Poliklinik, diagnostische Labors, Bettenmanagement, Pflegedienst) gesichert. Die Neurologische Klinik besteht daher nach innen und außen weiterhin als einheitliche Struktur. In den klinischen Abteilungen werden pro Jahr rund 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.

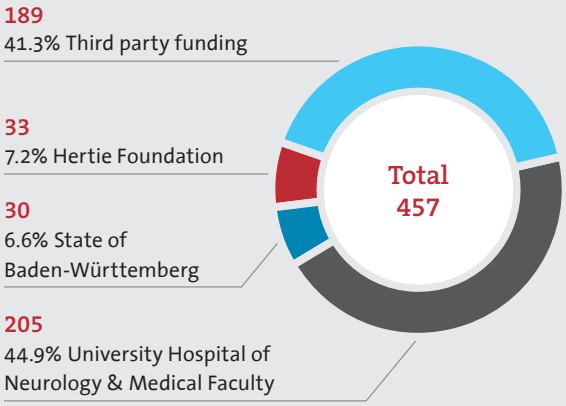
Facts & Figures

CENTER OF NEUROLOGY



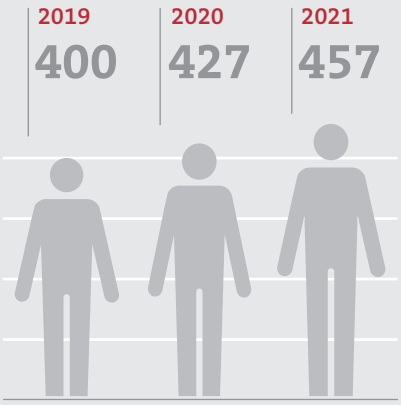
NUMBER OF STAFF IN 2021

Center of Neurology without nursing services (by headcount)



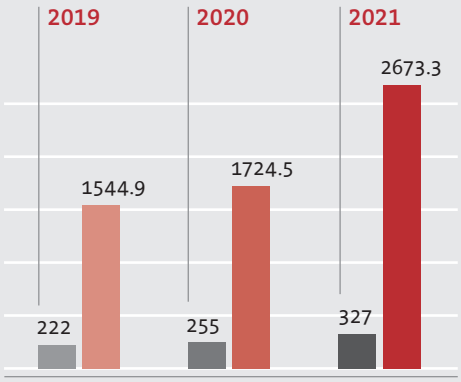
DEVELOPMENT OF STAFF

Center of Neurology (by headcount)



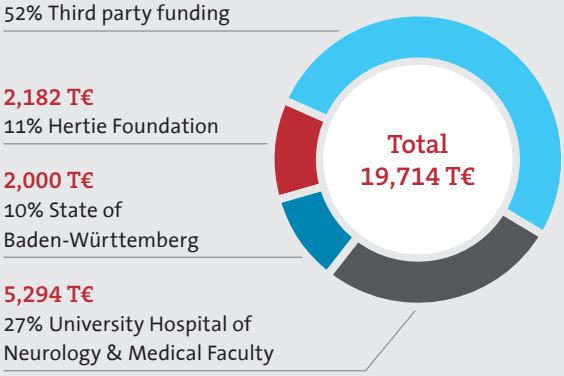
NUMBER OF PUBLICATIONS IMPACT FACTORS

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



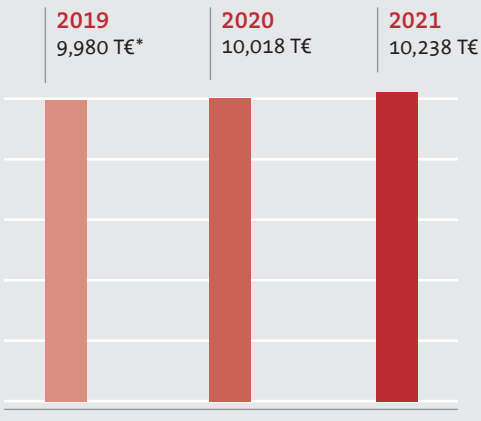
TOTAL FUNDINGS IN 2021

Center of Neurology



THIRD PARTY FUNDING

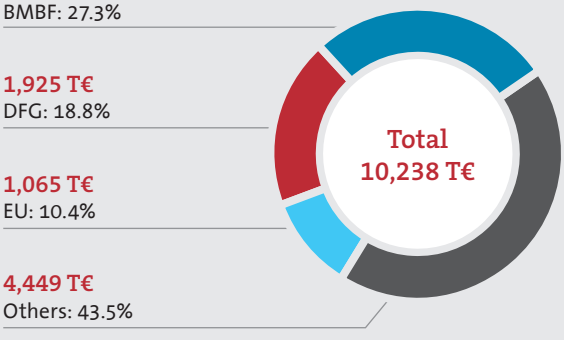
Center of Neurology



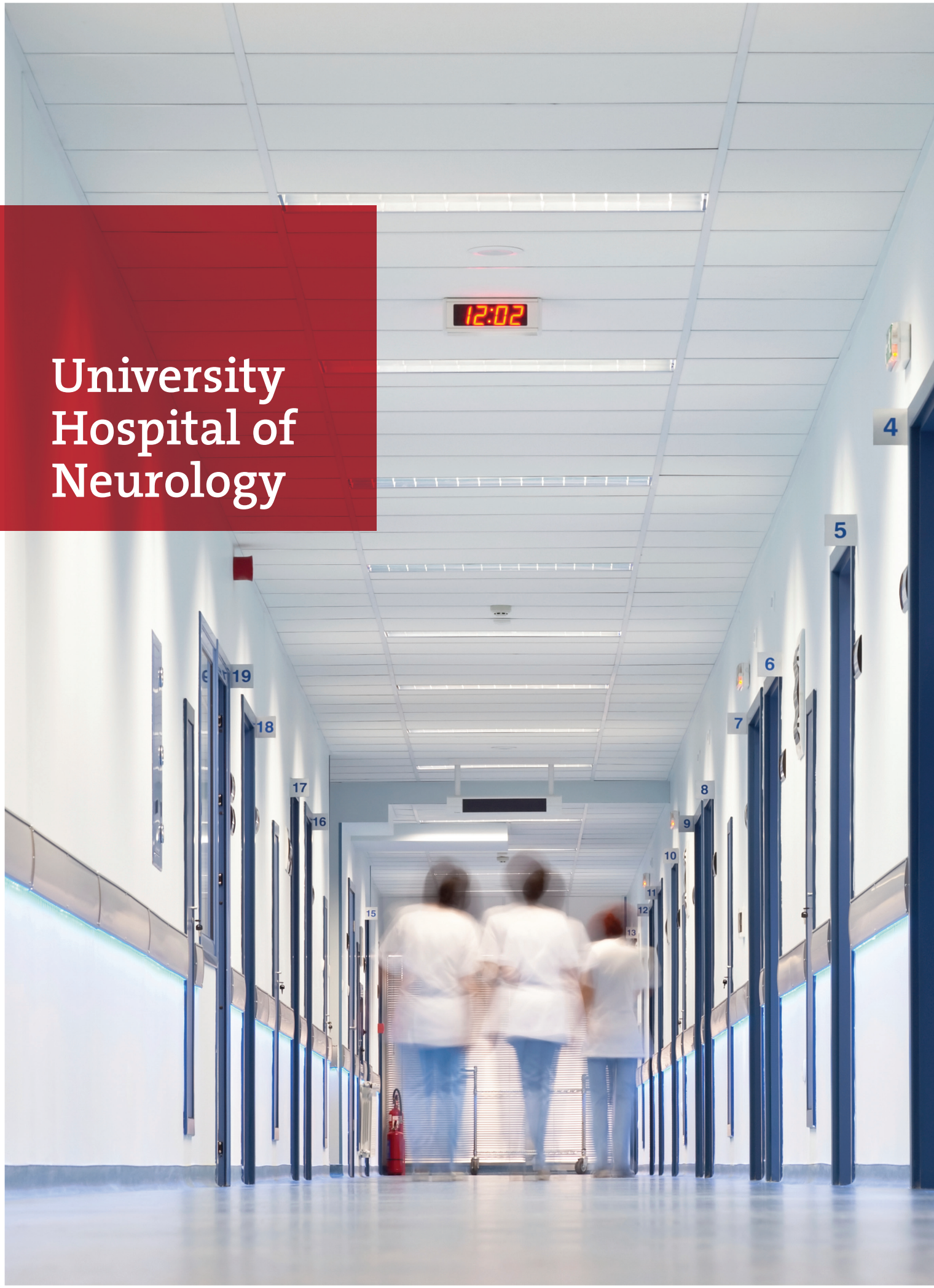
* includes 1 Mio € from the state of Baden-Württemberg

THIRD PARTY FUNDING IN 2021

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

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 15,000 patients (including diagnostic procedures) are examined and treated every year, most of them in specialty clinics which are directed by recognized specialists in their respective fields. The day clinic newly opened by the end of 2021 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 in einem kooperativen Modell auf Intensivstationen im Universitätsklinikum behandelt. Daneben gibt es eine spezielle Einheit zur kontinuierlichen Langzeit-Video-EEG-Ableitung (EEG-Monitoring) für Patienten mit schwer behandelbaren Epilepsien oder solchen mit unklarer Diagnose einer paroxysmalen Erkrankung.

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 15.000 Patienten (inkl. diagnostischer Prozeduren) ambulant betreut, die meisten davon in Spezialambulanzen, die von ausgewiesenen Experten für die jeweiligen Erkrankungen geleitet werden. Die Ende 2021 eröffnete 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 nearly 6,000 patients in 2021.

NUMBER OF ADMISSIONS

5,962

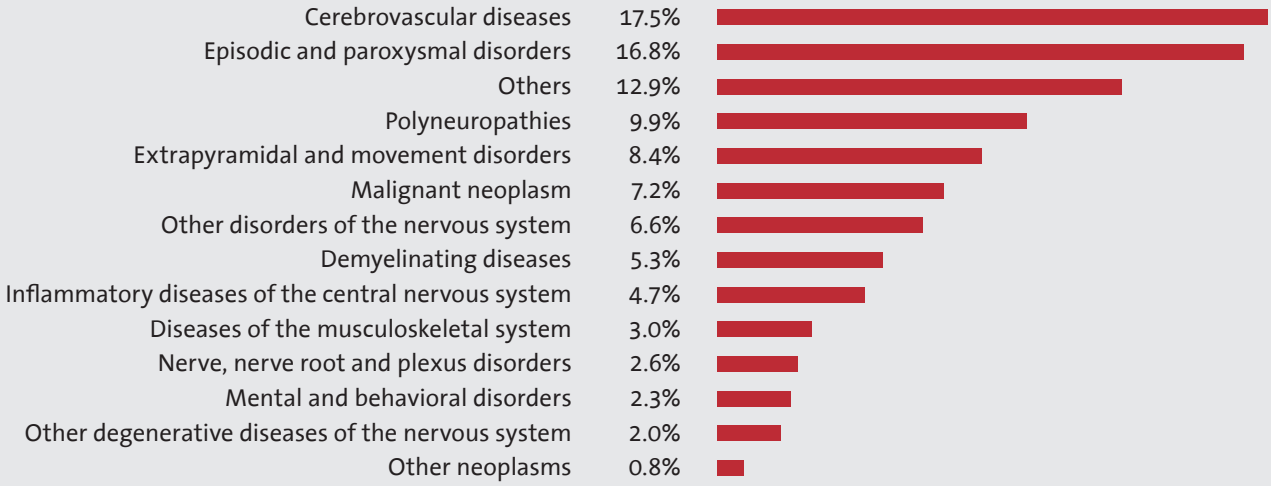
LENGTH OF STAY (IN DAYS)

4.1

CASE-MIX-INDEX 2021

0.95

INPATIENT DIAGNOSIS GROUPS



OUTPATIENT CARE

NUMBER OF CONSULTATIONS
(including diagnostic procedures)

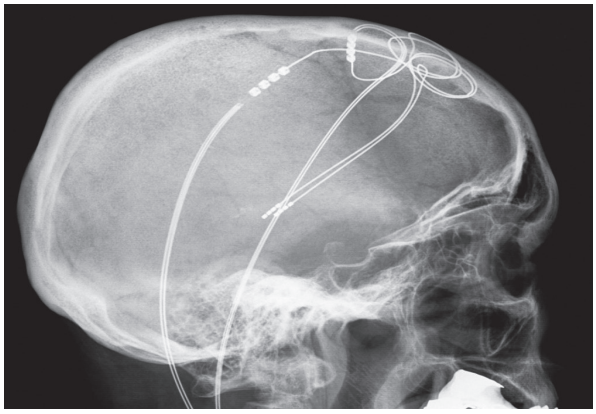
15,229

Outpatient Clinics

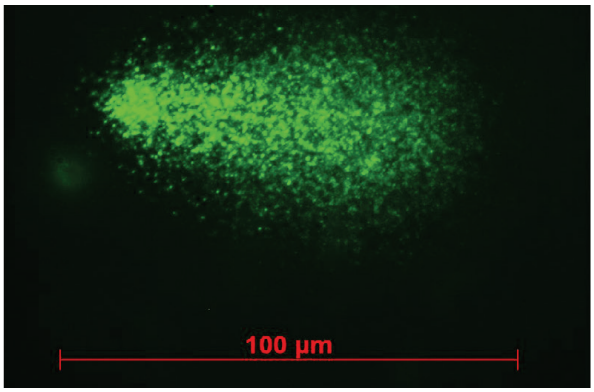
ATAXIA

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 follows a stringent path towards trial-readiness. Together with Dr. W. Ilg and Prof. Dr. M. Giese from the Center for Integrative Neuroscience (CIN) we developed digital-motor outcome measures based on advanced movement recording and wearables technology, allowing to assess motor performance in ataxia patients' real-life. TThese 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. 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.



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. 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. C. Wilke and is supervised by Prof. Dr. M. Synofzik and Prof. Dr. L. Schöls.

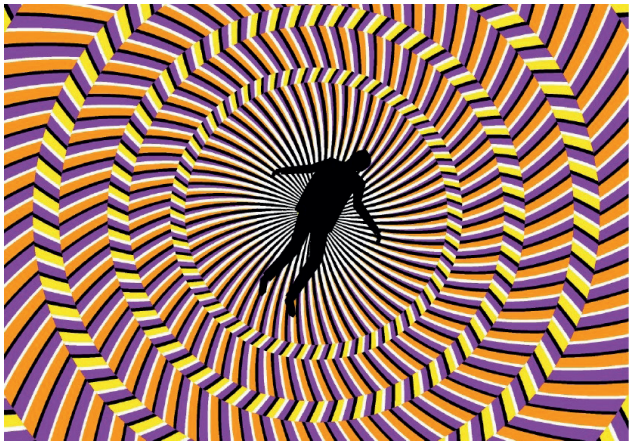
DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is considered the most significant progress in the treatment of neurodegenerative movement disorders over the last decades. As a novel treatment option DBS has been implemented in Tübingen in cooperation with the Department of Neurosurgery already in 1999. The concept of treatment and medical attendance developed by the network for deep brain stimulation of the University Clinic of Tübingen (BrainStimNet; www.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 two days per week in the outpatient clinic for DBS. Additionally, telemedicine counseling are increasingly used in order to facilitate long-term care of DBS patients. Further, the Tübingen site was the first centre to apply the remote DBS programming platform (Neurosphere, Abbott) in 10/2021 in Europe. Patients are seen by a specialized PD nurse (F. Chmell), and expert neurologists, namely Dr. I. Cebi, M. Hormozi, Dr. P. Klocke, M. Löffler, and Prof. Dr. D. Weiß.

Outpatient Clinics



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.

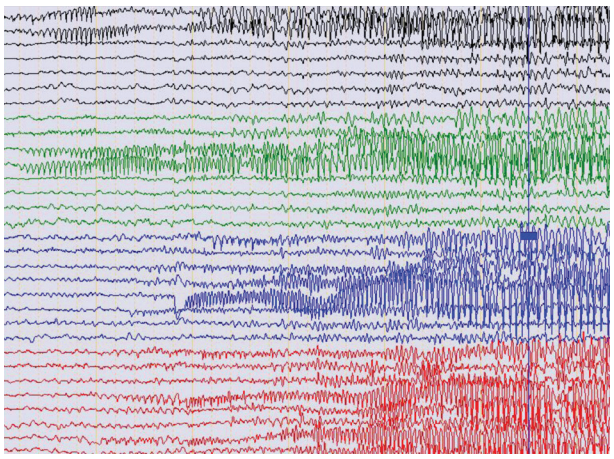
DYSTONIA AND BOTULINUM TOXIN TREATMENT

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).



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

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 episodic ataxias, narcolepsy and paroxysmal movement disorders.

The epilepsy outpatient clinic (Prof. Dr. H. Lerche, Dr. S. Lauxmann, Dr. M. Schreiber) offers consulting and treatment in particular for new-onset patients and those that are difficult to diagnose or difficult to treat, and for specific questions including contraception and pregnancy under antiepileptic treatment and genetic aspects. The study center offers medical and other clinical trials to explore novel treatment options.
The inpatient unit with 22 beds (Ward 42/43L), running under the supervision of Prof. Dr. A. Grimm, Dr. P. Martin and Dr. M. Schreiber, includes acute care for epileptic seizures and status epilepticus, longterm complex treatment for difficult cases, and a Video-EEG-Monitoring Unit which is operated in cooperation with the Department of Neurosurgery. Within this unit, inpatients are continuously and simultaneously monitored with video and electroencephalography (EEG) for differential diagnostic and presurgical evaluations. Epilepsy surgery, an effective treatment for patients resistant to anti-epileptic medication, deep brain stimulation of the thalamus and vagal nerve stimulation are provided in close cooperation with the Department of Neurosurgery (Dr. S. Rona, Prof. Dr. J. Honegger, Dr. G. Naros). Altogether we treat about 2,000 adult epilepsy patients per year.

Outpatient Clinics

Neuro-geriatric patients receive physiotherapy for mobility training.

FRONTOTEMPORAL DEMENTIA AND EARLY-ONSET DEMENTIAS

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

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 diease The clinic is run by Dr. C. Wilke, Dr. L. Beichert and Dr. D. Mengel and supervised by Prof Dr. M. Synofzik.

HEADACHE AND NEUROPATHIC PAIN

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

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

The Headache/Pain unit organizes teaching sessions for medical professionals as well as local patient education events and serves as a platform to provide access to ongoing clinical studies including both multi-center trials as well investigator-initiated pilot trials. 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. Schubert, Dr. S. Straub and Dr. S. Thewes). Patients should be referred preferably by neurologists or pain specialists.

Outpatient Clinics

LEUKODYSTROPHIES IN ADULTHOOD

Leukodystrophies are usually regarded as diseases of infancy and childhood. However, adult-onset forms are increasingly recognized in many leukodystrophies. In cooperation with the Institute of Medical Genetics and Applied Genomics in Tübingen we established whole genome sequencing as standard in genetic diagnostics for our patients. This helps us to identify the cause of disease in more than 2/3 of adult patients in our leukodystrophy cohort. In cooperation with the Department of Neuropediatrics in the Children's Hospital we assess the natural course of metachromatic leukodystrophy and cerebrotendinosis xanthomatosa as an essential prerequisite for therapeutic trials. To prepare for interventional trials in CSF1R-related leukodystrophy we participate in an international biomarker analysis and a run-in natural history study. We follow healthy carriers of CSF1R mutations to identify liquid and imaging biomarkers that indicate that indicate the shift from the prodromal state to manifest disease as the optimal time point for stem cell transplantation. To this end we collaborate with the Department of Neuroradiology and use high-end MRI techniques and MR spectroscopy to disclose characteristic MRI patters and progression markers. Within the European Reference Network for Rare Neurological Diseases (ERN-RND) we develop international guidelines for metachromatic leukodystrophy in collaboration with the European Academy of Neurology (EAN). To support radiologists and neurologists in every day practice in the identification of patients with hereditary leukodystrophies, we develop a tool based on 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 Helath (BMG). A correct molecular diagnosis becomes increasingly important as for an increasing number of these neurometabolic disorders treatment by enzyme replacement, substrate inhibition, stem cell transplantation or gene therapy becomes available. Patients are seen by Dr. S. Hayer, Dr. H. Hengel and Prof. Dr. L. Schöls.

MOTONEURON DISEASE

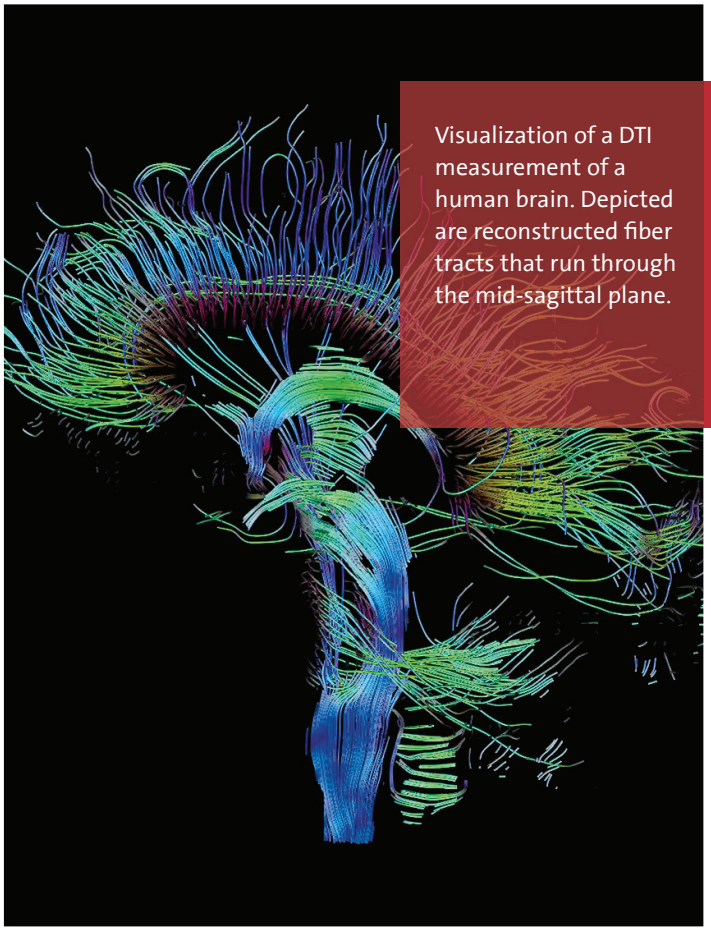
Motoneuron diseases are caused by degeneration of motor neurons in the cerebral cortex (upper motor neuron) and/or the ventral horns of the spinal cord (lower motor neurons). The most common form of motoneuron disease – amyotrophic lateral sclerosis (ALS) – affects both upper and lower motor neurons.

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

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 if tolerated electrophysiologically. In the clinic the indication to further necessary investigations such as MRI or muscle biopsy is provided. The therapy is tailored to the individual patient and his particular type of the disease and usually includes a medicated as well as physiotherapy regimen. The neuromuscular clinic is run by 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).



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

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 2021, the outpatient clinic was run by Dr. R. Kemmner (specialist), Dr. J. Dünschede (resident), Dr. C. Ruschil (resident), and supervised by PD Dr. M. Kowarik (attending physician, with special expertise in MS and other immune-mediated neurological disorders), and Prof. Dr. U. Ziemann (director).

Outpatient Clinics

NEURO-ONCOLOGY

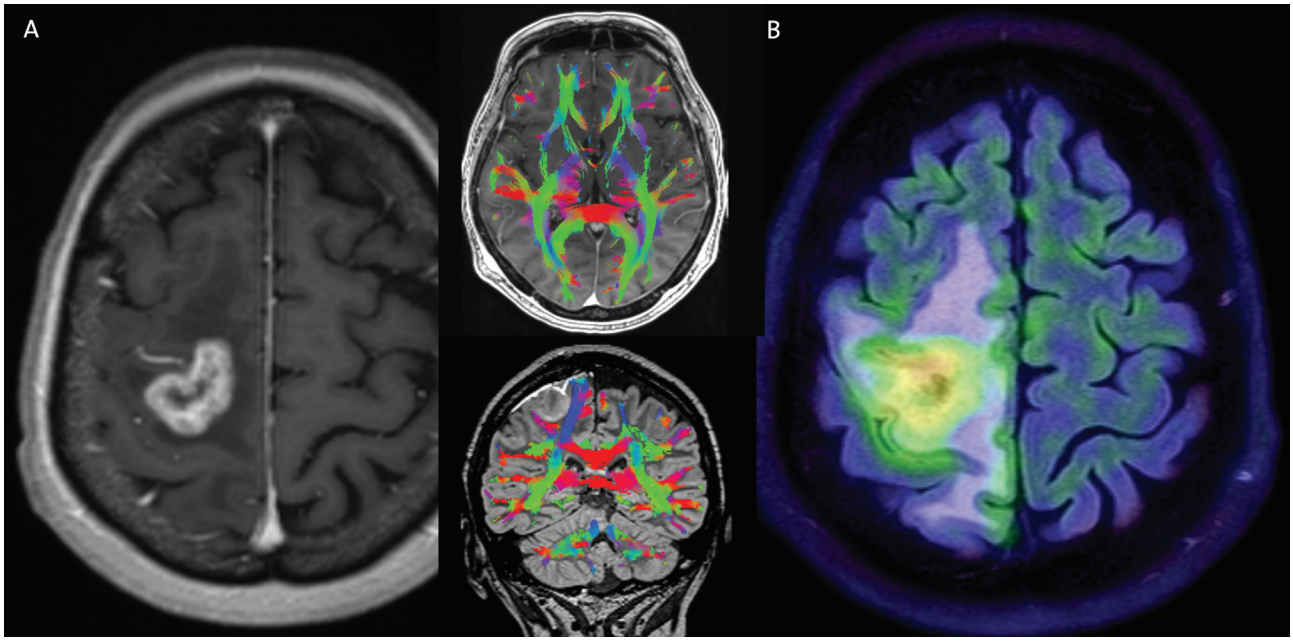
The clinical management of neuro-oncological patients requires an interdisciplinary approach for offering guideline-based therapies and clinical trials. This task is organized and coordinated in the Department of Neurology & Neuro-Oncology with clinical partners.

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 recently received the certificate of the German Cancer Society (DKG) and is the largest Neuro-Oncology center among the DKG-certified centers.

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

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

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

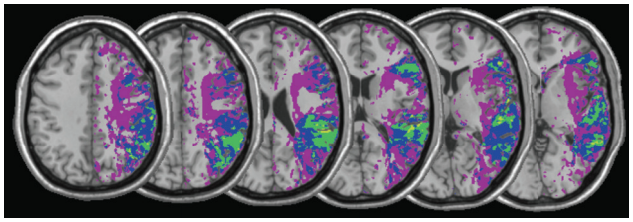


Multimodal imaging for glioma patients: A| contrast enhanced MRI with preoperative tractography for planning the surgical approach in an eloquently located glioma (right precentral gyrus), B| positron-emission-tomography (PET) with the amino-acid tracer 18F-Fluoro-Ethyl-Tyrosine (18F-FET) allows for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

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).

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 Dr. A. Mengel and PD Dr. S. Poli, and Prof. Dr. U. Ziemann.

Outpatient Clinics

PARKINSON'S DISEASE

Outpatient Clinic (Head Brockmann)
The Center of Neurology at the University of Tübingen runs the largest outpatient clinic for patients with Parkinson syndromes in Southern Germany. More than 120 patients are seen every month. A major focus of the clinic is the early differential diagnosis of different Parkinson syndromes. The development of transcranial sonography by members of the department draws patients from all over Germany to confirm their diagnosis which, if necessary, is substantiated by other tests, like the smelling test or neuroimaging investigations with SPECT and/or PET. Genetic testing is offered to patients and relatives with familial Parkinson syndromes who may obtain genetic counselling in cooperation with the Department of Medical Genetics. The Department of Neurodegeneration is one of two German centers that participate in the international Parkinson Progression Marker Initiative (PPMI), a 10-year follow-up of de novo Parkinson patients to better understand aetiology and disease progression and the P-PPMI-(prodromal-PPMI) study, which follows individuals at high risk for PD to better understand the early phase of neurodegeneration. Both studies are supported by the Michael J Fox Foundation. Additionally, large scale longitudinal national and international studies are being performed to better understand the different phases of neurodegeneration as well as symptom development and progression to finally enable more specific, individualized therapies. Importantly, we take part in the world-wide first clinical trials aiming at specific Parkinson-associated pathways: Epi589-15-002 by BioElectron, MitoPD, BP39528_ Pasadena by Roche, and ACT14820/MovesPD by Sanofi. Of note, our centre is the leading clinical site for Germany and PDGBA patients from our outpatient clinic are part of this first pathway-specific clinical trial in PD (ACT14820/MovesPD). Appointments are scheduled daily in the outpatient clinic of the Center of Neurology.

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

In this context, special interest lies in genetically associated forms of the disease such as patients carrying a mutation in the GBA or LRRK2 gene. Moreover, we focus on one of the most important 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.

Outpatient clinic for deep brain stimulation and continous application (Head Weiß)
Another focus is the treatment of patients in later stages of the disease with severe non-motor symptoms or drug-related side effects. In some of these patients, treatment may be optimized in co-operation with the Ward for Neurodegenereative Diseases by intermittent or continuous apomorphine or duodopa application, which is supervised by a specially trained nurse. Other patients are referred for deep brain stimulation (DBS). Various multicenter drug trials, for patients in different stages of Parkinson's disease but also atypical Parkinsonian syndromes offer the possibility to participate in new medical developments. Moreover, close cooperation with the outpatient rehabilitation center 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.

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.

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. R. Berger, S. Willikens, M. Schühle, and Prof. Dr. A. Grimm. We perform several treating and observational studies concerning imaging and electrophysiology of the peripheral nerve system. Also rare polyneuropathies, such as the hereditary TTR-amyloidosis or the POEMS syndrome are diagnosed and treated. There is a broad cooperation with other University hospitals, i.e. Aachen, Jena and Basel as well as with internal partners, i.e. the department of human genetics and neuropediatrics.

Further, we installed the peripheral nerve lesion team, which gives us the possibility for interdisciplinary patient examinations twice a week together with the department of neurosurgery and reconstructive surgery of the BGU hospital. The Tübinger Nerve Team is an interdisciplinary staff, which is an innovative group, that handles therapeutic concepts and organizes observational studies concerning peripheral nerve traumata. Our department is involved with three colleagues (Prof. Dr. A. Grimm, Dr. J. Stahl, 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, geneticists and neuroradiologists. If substantial indicators for a rare disease are evident, recommendations of additional investigations, an outpatient visit or admission to the ward are prepared including specific neurological assessment, genetic diagnostics or neuroimaging. The clinic is run by Dr. L. Zeltner and Prof. Dr. L. Schöls.

SPASTIC PARAPLEGIAS

The outpatient clinic for for Hereditary Spastic Paraplegias (HSP) offers specialized differential diagnostic workup, counselling and management for patients and families with HSP. To meet the challenges presented by the extreme genetic heterogeneity of the disease we are employing whole genome sequencing as first line diagnostic tool. 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'.

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 Butolinum 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 PD 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. The HSP clinic is run by Dr. M. Wayand, Dr. C. Kessler, Dr. T. Rattay and supervised by PD Dr. R. Schüle and Prof. Dr. L. Schöls.

TREMOR SYNDROMES

Essential tremor is with a prevalence of 1 to 5 % among the most frequent movement disorders. Diagnosis and especially differential diagnosis is often challenging. In the outpatient clinic for tremor a thorough standardized assessment battery has been established to facilitate diagnosis and decision for therapeutic strategies. Beyond pharamcological treatment and ergotherapy, deep brain stimulation is considered in resistant tremor. 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.

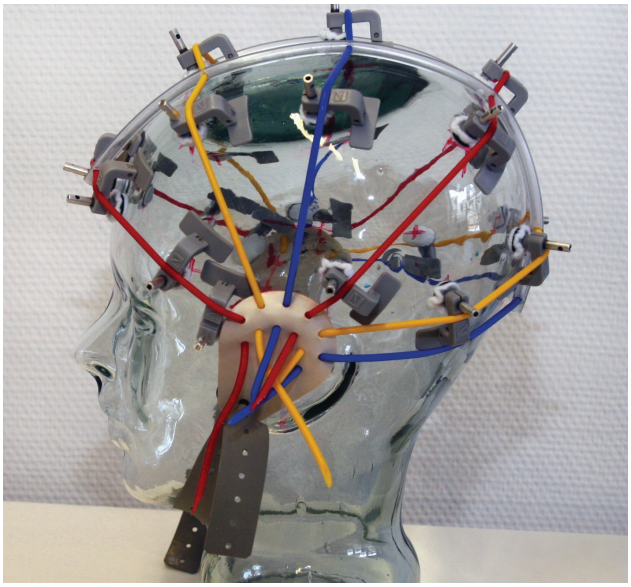
TMS

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. To this end, working closely with the center for clinical trials, it provides the expertise and infrastructure to design and perform large-scale multi-center scientifically-led clinical TMS trials. 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

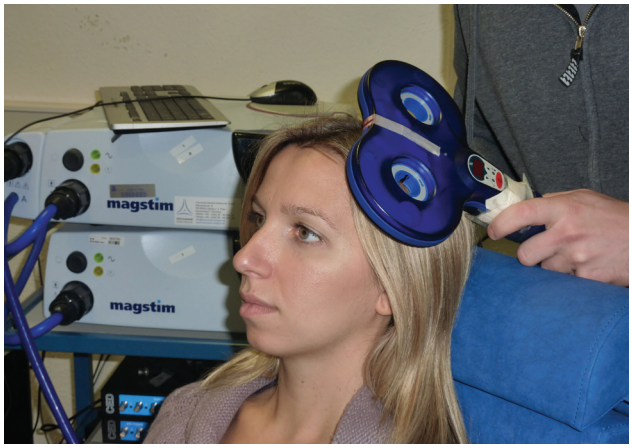
The Clinical Chemistry Laboratory collects more than 1800 samples of cerebrospinal fluid (CSF) per year throughout the University Medical Center. Oligoclonal bands in CSF and serum are detected by isoelectric focusing and silver staining. Junior staff are routinely trained to perform basic CSF examination techniques and the interpretation of results as part of their speciality training. The laboratory takes part in quality management activities of CSF parameters. Immunopathology includes the determination of a set of autoantibodies for the diagnosis of certain neuroimmunological disorders: autoantibodies to acetylcholine receptors, muscle specific tyrosine kinase (MuSK), titin (myasthenia gravis), aquaporin-4 (NMOSD), MOG ("MOGAD"), autoantibodies associated with neurological paraneoplastic syndromes and autoimmune encephalitis, myositis-associated antibodies, and autoantibodies to gangliosides for immunoneuropathies. Cell populations in CSF and blood samples are examined by flow cytometry using a FACScalibur cytometer. These include determination of CD20+ cells in patients under B cell depleting therapies, CSF CD4/CD8 ratio in patients suspected to have neurosarcoidosis, assessment of CD4+CD62L+ cells in patients treated with natalizumab as well as detailed immunophenotyping in patients with complex inflammatory diseases of the nervous system. In addition, CSF-levels of amyloid beta42, tau, phospho-tau and NFL are measured to differentiate various forms of dementia/neurodegenerative diseases. In case samples that have to be sent to external reference laboratories (e.g. CSF JCV testing for natalizumab-associated PML in reference center), the neurochemical laboratory takes care of preparing and sending the samples, as well as organizing the reports. The laboratory is supervised by PD Dr. R. Schüle and PD Dr. M. 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, R. Mahle, K. Vohrer (staff technicians), Dr. M. Schneider and Dr. S. Lauxmann (heads of the laboratory).



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

ELECTROMYOGRAPHY, NEUROGRAPHY AND NEUROMUSCULAR ULTRASOUND

The EMG Laboratory offers all the standard electromyography and neurography procedures for the electrodiagnosis of neuromuscular diseases including polyneuropathies, entrapment neuropathies, traumatic nerve lesions, myopathies, myasthenic syndromes, and motor neuron diseases. In selected cases, polygraphic recordings for tremor registration, registration of brainstem reflexes, exteroceptive reflexes and reflexes of the autonomous nervous system are performed. In addition, the new diagnostic tool of high resolution ultrasound (Phillips Epiq 7, 18 MHz Probe and Mindray T7, 14 MHz Probe) was introduced in 2015. With the ultrasound of the peripheral nervous system as well as of the muscles, several neuromuscular disorders, e.g. polyneuropathies, motoneuron diseases, myopathies, nerve tumours, entrapment syndromes and traumata can be visualized.

Since 2020 we have a new high-resolution probe of up to 24 MHz (Canon Medical Systems Aplio 800i). In 2021 more than 2000 ultrasound examinations were performed. This tool amplifies the interdisciplinary cooperation with the colleagues from the Nerve Surgery Department of the UKT as well as of the BG Hospital for Traumatology. 2018 the Tübinger nerve team was funded, consisting of medical staff of Neurosurgery (Prof. Dr. M. Schuhmann and Dr. S. Wang) of the BG hospital (Prof. Dr. A. Daigeler, Prof. Dr. J. Kolbenschlag, Dr. J. Heinzel and Dr. C. Prahm), Neuroradiology (Dr. T. Lindig) and our team (Dr. J. Stahl, Dr. N. Winter, and Prof. Dr. A. Grimm). Prof. Dr. A. Grimm is the vice president of the German ultrasound society, department Neurology (DEGUM). Further DGKN/DEGUM certified colleagues are Dr. T. Rattay, Dr. C. Ruschil, Dr. V. Ruschil, Dr. N. Winter, Dr. J. Marquetand and Dr. N. Dammeier.

The laboratory is equipped with three digital systems (Cadwell Summit 3.1). In 2021, more than 3100 patients were seen. In most cases (approximate 70 %), a combination of neurography and electromyography is requested. In addition, a Neurosoft Evidence 9000MS stimulator is available for transcranial magnetic stimulation and recording of motor evoked potentials in approximately 800 patients per year. Further, 2000 patients were examined by neuromuscular ultrasound in 2021.

In 2021, the EMG Laboratory was run by a team of technical assistants (A. Deutsch, V. Servotka, J. Wittlinger, I. Köhnlein), residents (Dr. J. Stahl, Dr. V. Stadler, B. Zrenner, Ch. Kessler, Dr. Z. Fleszar, Dr. E. Pichler, Ch. Lipski) under the supervision of Prof. Dr. A. Grimm, Dr. N. Winter and Dr. P. Martin. In 2021 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

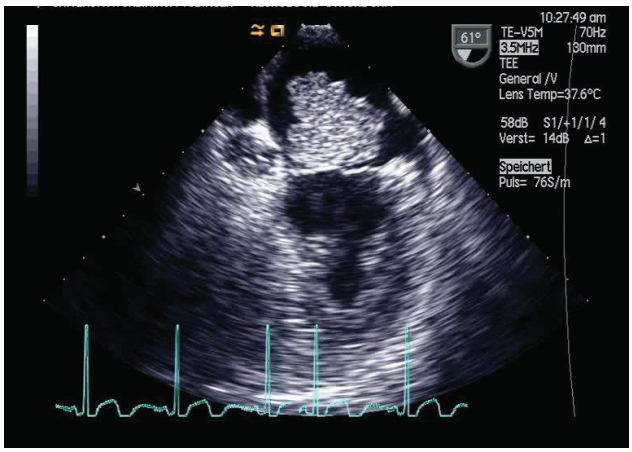
EVOKED POTENTIALS (EP) LABORATORY

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. Fuhrer and I. Köhnleinand are supervised by Prof. Dr. A. Grimm, Dr. P. Martin and Prof. L. Schöls. The EP recordings are analyzed and interpreted during daily conferences according to the guidelines of the German Society for Clinical Neurophysiology (DGKN), and visited by up to four interns.

NVOM LABORATORY (FORMER ENG LABORATORY)

With the formation of the "Tübinger Zentrum für Schwindel- und Gleichgewichtserkrankungen (TüSG)" (also see Dizziness Service) the former ENG laboratory became part of the laboratory for Neuro-Vestibular and Oculo-Motor diagnostics (NVOM). This NVOM laboratory covers the whole spectrum of medical tests established to recognize functional deficits of the vestibular and oculomotor system. For example, caloric and rotatory stimuli with distinct accelerations are used (chair rotation, head-impulse-test, head-shaking). Eye movements are usually studied by deploying video-oculography, 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



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

multivariate analyses. The NVOM laboratory is led by Dr. J. Pomper (Neurology) and Dr. S. Wolpert (ENT). The recordings are conducted by a team of technical assistants. Prof. Z. Hafed and Prof. U. Ilg (both HIH) contribute their expertise in the study of eye movements and eye movement-related vision to clinical research projects.

NEUROCARDIOLOGY LABORATORY

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

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

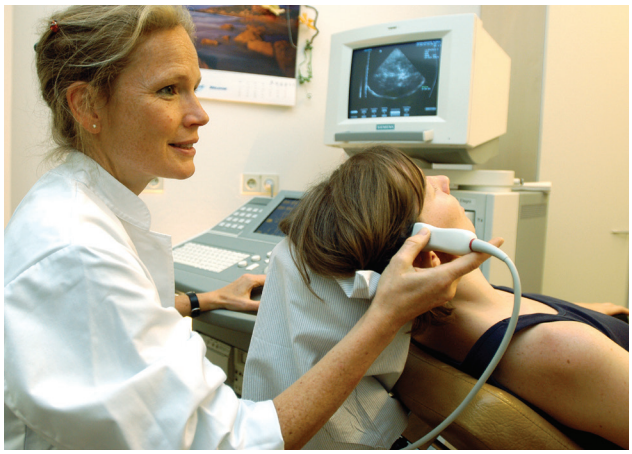
investigations as well as contrast-enhanced echocardiography for the detection of intracardiac shunts or intracardiac thrombi is provided. All patients on our Stroke Unit receive continuous ECG monitoring. Selected stroke patients undergo additional conventional 24-hour Holter ECG, 7-day event recorders and implantable cardiac event recorders for the detection of atrial fibrillation. Since 2015, we are able to offer advanced long-term cardiac monitoring to patients with embolic stroke of undetermined source and suspected atrial fibrillation (AF). We have so far implanted over 300 cardiac event recorders. Close follow-up is guaranteed through the use of daily home monitoring. Due to a risk factor-based selection algorithm, we were able to achieve a one-year AF-detection rate in excess of 30%. Other diagnostic tools include 24-hour blood pressure monitoring, and selection of patients for cardiac MRI or CT in cooperation with the department of radiology. For invasive diagnostic and/or treatment, patients are referred to the department of cardiology.

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

Yearly, we conduct approximately 1,500 echocardiographic examinations are performed, and over 1,200 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 Philips CX50. Additionally, two portable CW/PW Doppler systems – a DWL Multi-Dop pro and a DWL Multi-Dop T digital – are available. Neurovascular ultrasound examinations are performed by the ultrasound assistants N. Ruckwied and J. Wittlinger as well as two neurovascular residents under supervision of the consultant stroke neurologists, Dr. A. Mengel and PD Dr. S. Poli who is DEGUM-certified ultrasound trainer.



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., persistent foramen ovale), and continuous Doppler monitoring of the cerebral blood flow and for testing vasoreactivity (e.g., before, during and after neuroradiological interventions) or for detection of cerebral microembolisms (high-intensity transient signals) are also routinely performed.

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

Occupational, Physical and Speech Therapy

OCCUPATIONAL THERAPY

The treatment program is focused on patients with handicaps from acute strokes, brain tumors, inflammatory diseases, movement disorders, neurodegenerative diseases and disabilities from disorders of the peripheral nervous system. In 2021, 2,404 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 2021, 2,878 patients were treated.

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

SPEECH THERAPY

Neurological patients with swallowing and speech/language disorders receive speech therapy while staying in hospital. The main focus within the team of 14 speech therapists under the supervision of MSc Natalie Rommel lies on the assessment and treatment of patients with dysphagia.

Every acute stroke patient receives a bedside and, if necessary, a video-endoscopic or video-fluoroscopic swallowing examination. This allows for early identification of dysphagia, prevention of aspiration pneumonia and efficient treatment planning. Every acute stroke patient also receives a bedside speech and language examination. The aim of speech therapy in these patients is to improve their communication ability. In 2021, 2.140 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 20 years ago, the Hertie Institute has grown to more than 450 employees at all levels, from technicians to PhD students to full professors. The institute's achievements include discoveries related to the molecular, genetic and physiological basis of a number of major neurologic diseases.

The institute presently consists of six departments. They combine basic and clinical research with patient care, albeit to different degrees and with variable emphasis: 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 20 professors and 29 research groups. Seventeen belong to the aforementioned departments, twelve are led as independent research groups.

In 2021, scientists at the Center of Neurology obtained more than 10 million Euros in third party funding and published more than 320 papers in peer-reviewed journals.

In the same year, the HIH celebrated its 20th anniversary. On this occasion, the institute announced that in the future it will develop strategies for the early detection, prevention and rehabilitation of neurological diseases to an even greater extent than before. The focus will be on systems-based neurology and so-called personalized medicine. Systems-based neurology neuromedicine aims to treat the brain or nervous system as a whole, for example by using neural prosthetics. In contrast, personalized medicine targets the underlying cause of a disease, such as a genetic defect, in a way that is tailored to the patient's individual profile. As advances in modern biomedicine rely on the use of ever-increasing amounts of data in the laboratory and clinic, the HIH will also strengthen the area of digitalization and integrate methods of machine learning and artificial intelligence. The anniversary was celebrated with a digital celebration week in October; the on-site ceremony was postponed to the following spring due to the pandemic.

Tübingen is one of six top research locations in Germany of 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.

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)

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 derzeit 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 20 Professorinnen und Professoren und mehr als 450 Mitarbeitende in 29 Arbeitsgruppen tätig, wovon 12 unabhängige Forschungsgruppen darstellen.

Die Arbeitsschwerpunkte des HIH liegen im Bereich neurodegenerativer und entzündlicher Hirnerkrankungen, der Schlaganfallforschung, Epilepsien und der Erforschung der Grundlagen und Störungen von Wahrnehmung, Motorik und Lernen. Zu den bedeutenden Forschungserfolgen des HIH zählen die Entdeckung wichtiger genetischer und molekularer Grundlagen der Entstehung und Progression neurologischer Erkrankungen und die Charakterisierung der Funktion von neuronalen Netzwerken in der Hirnfunktion. Das HIH, ein Modellprojekt für Public Private Partnership, hat auch im Jahr 2021 rund 10 Millionen Euro an Drittmitteln eingeworben und mehr als 320 Veröffentlichungen in wissenschaftlichen Fachzeitschriften publiziert. Diese Zahlen belegen die wissenschaftliche Leistungsfähigkeit des Zentrums. Die Gemeinnützige Hertie-Stiftung wendete bisher mehr als 60 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

In den Abteilungen sind zurzeit 20 Professorinnen und Professoren und etwa 450 Mitarbeitende in 29 Arbeitsgruppen tätig. Die Gemeinnützige Hertie-Stiftung wendete bisher mehr als 60 Millionen Euro für das HIH auf und plant ihre Förderung fortzusetzen.

Im Jahr 2021 feierte das HIH sein 20-jähriges Bestehen. In dem Zusammenhang gab das Institut bekannt, dass es künftig stärker als bisher Strategien zur Früherkennung, Prävention und Rehabilitation neurologischer Erkrankungen entwickeln wird. Der Fokus liegt dabei auf der systembasierten Neuromedizin sowie der sogenannten personalisierten Medizin. Der erste Ansatz zielt darauf ab, das erkrankte Gehirn oder Nervensystem als Ganzes zu behandeln, etwa mit Hilfe von Neuroprothesen. Im zweiten Ansatz hingegen wird die zugrundeliegende Krankheitsursache – etwa ein Gendefekt – auf die erkrankte Person zugeschnitten therapiert. Da Fortschritte in der modernen Biomedizin auf die Nutzung immer größerer Datenmengen in Labor und Klinik beruhen, wird das HIH zudem den Bereich der Digitalisierung stärken und Methoden des Maschinellen Lernens und der Künstlichen Intelligenz integrieren. Das Jubiläum wurde im Oktober mit einer digitalen Festwoche begangen, der Festakt wurde aufgrund der Pandemie auf das folgende Frühjahr verlegt.

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.

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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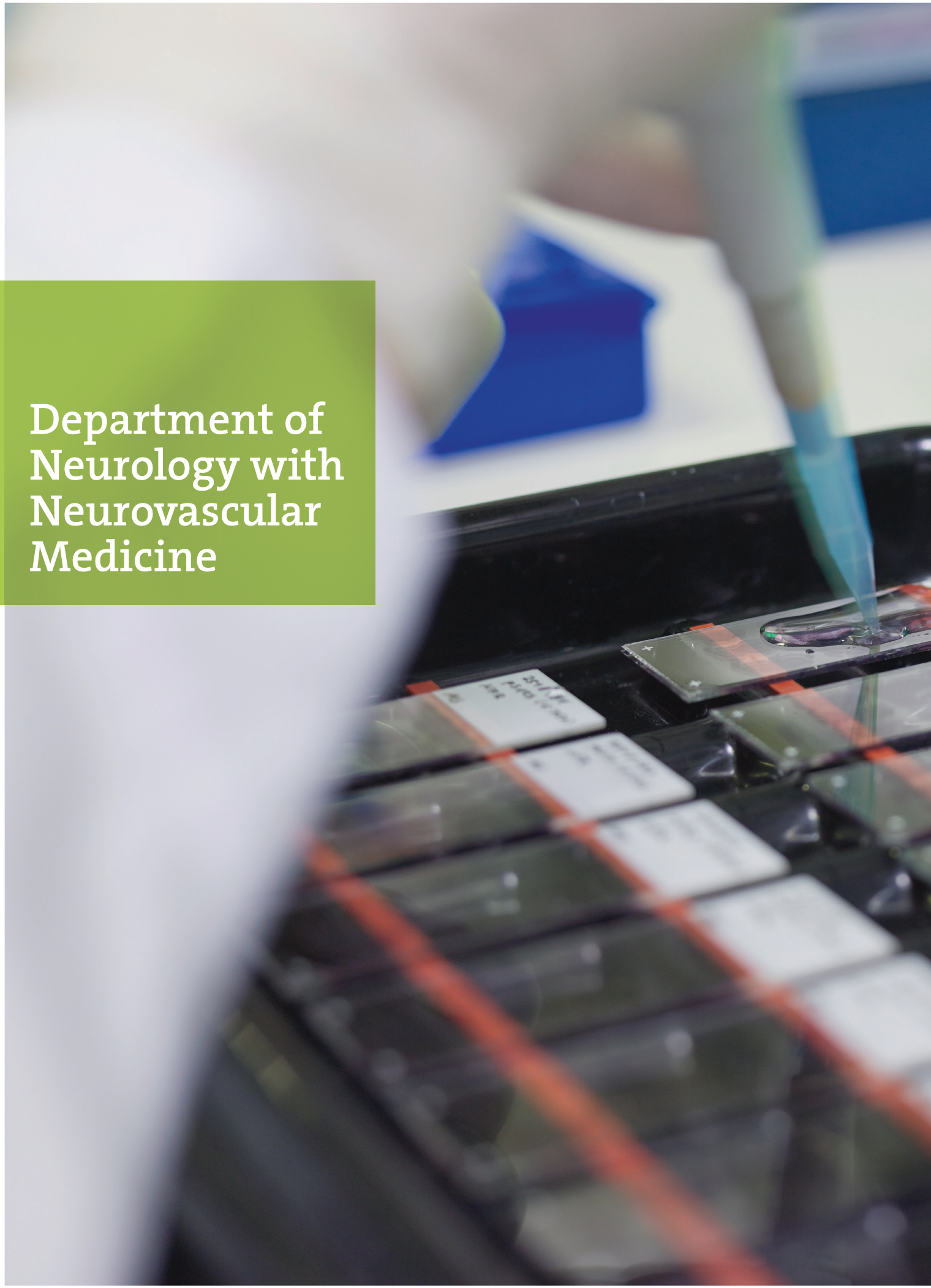
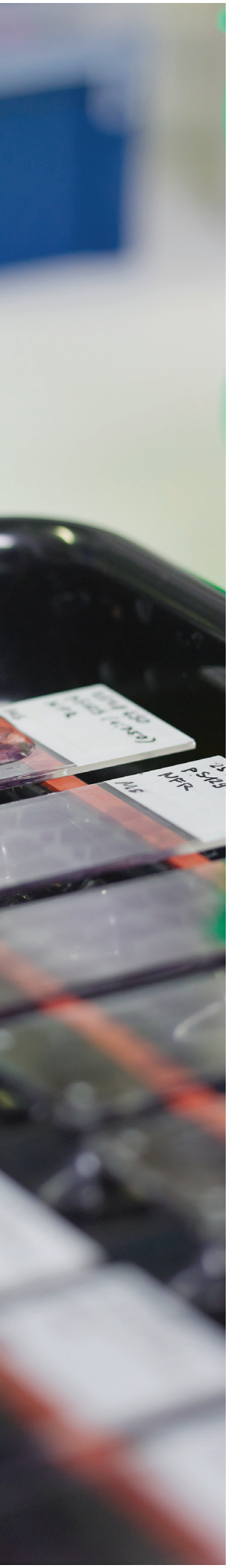
Department of Neurology with Neurovascular Medicine





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 complex neurovascular diseases (ischemic stroke, intracranial hemorrhage, cerebral vasculitis, vascular malformations, rare neurovascular diseases such as endovascular lymphoma, paraneoplastic coagulopathy, or reversible cerebral vasoconstriction syndrome), neuroimmunological disorders (multiple sclerosis, neuromyelitis optica, 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) to provide emergency care for acute stroke patients. This structure has been certified by the German Stroke Society as a Neurovascular Network. 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 (PD 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 closely with the physiotherapy department at the University Medical Center (Zentrum für ambulante Rehabilitation), which has a focus on physiotherapy for stroke rehabilitation.

The Department of Neurology with Neurovascular Medicine offers lectures for medical students, physicians in training, nursing staff, physiotherapists and speech therapists. The neurology scientific colloquium features guest researchers who present their current work that typically covers translational aspects of brain research, and is of broad interest for clinicians, clinician scientists and medical scientists alike. The neurology therapy seminar gives up-to-date overviews on recent advances in neurology, internal medicine, neurosurgery, neuro-ophthalmology, neuroradiology and other areas relevant to the treatment of patients with neurological diseases. The lectures of basic and clinical neurology, the seminar on neurology, and the training course on neurological examination skills are integral parts of the Medical School curriculum and are regularly honored by the evaluation of the students.

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

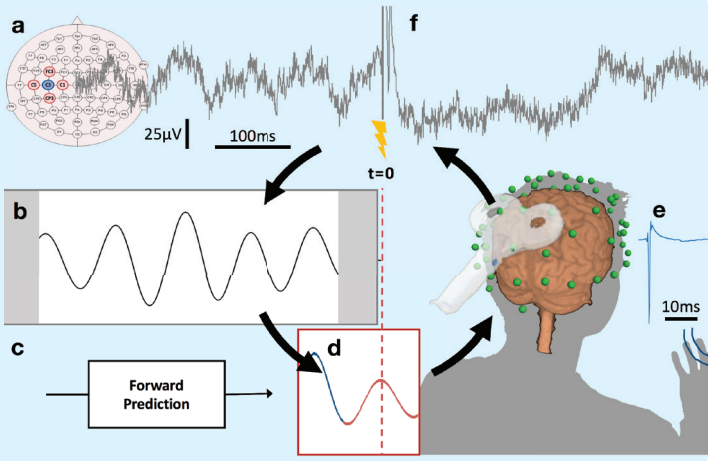
Neuroplasticity

Brain Networks & Plasticity (BNP) Laboratory

Head: Prof. Dr. Ulf Ziemann

Team: 32 members

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



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

The human brain has an amazing capacity to reorganize, which ensures functional adaptation in an ever-changing environment. This capacity for neural plasticity becomes even more important for rehabilitation after cerebral injury such as stroke. Our group focuses on understanding principles of neural plasticity in the human cortex, and on applying novel techniques of non-invasive brain stimulation, in particular personalized stimulation using information of instantaneous brain states based on real-time EEG analysis to 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. The approach of EEG-triggered TMS has the potential to significantly improve

therapeutic brain stimulation in the near future by taking the current brain state into account. This will enable individualized modulation of neuronal networks of the human brain with the necessary precision in space and time.

Translational Clinical Research Toward Personalized Therapeutic Brain Stimulation

A major goal in the BNP lab is to translate the insights gained from innovative fundamental research 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 (BOSSFRONT) and one in subacute stroke patients (STROKE-BOSS). 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 currently also experimentally address the problem that TEPs are contaminated by peripherally evoked potentials due to somatosensory stimulation of the scalp and auditory stimulation by the TMS pulse. We do this by developing a realistic sham condition and repeating pharmaco-TMS-EEG experiments. The aim is to provide TEPs that represent a "clean" brain response to TMS.

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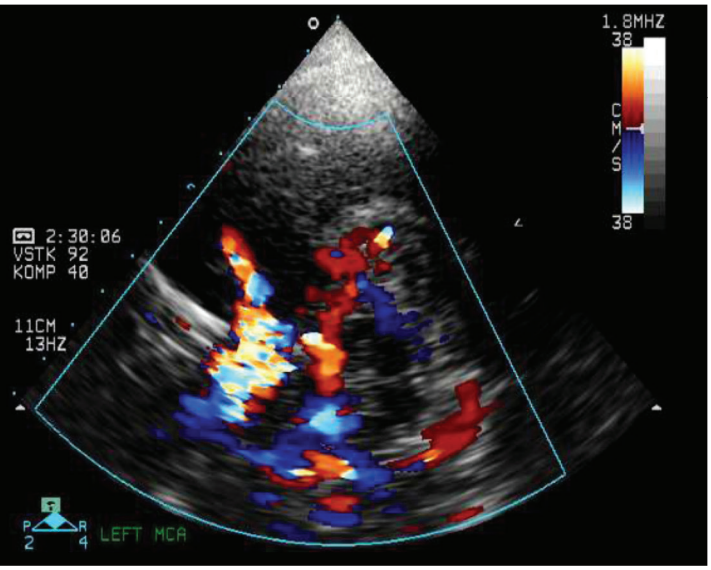
Stroke and Neuro-protection Laboratory

Head: PD Dr. Sven Poli
Team: 12 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 and diagnostics.

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

The focus of our preclinical stroke research is on identification, evaluation and optimization of neuroprotective strategies that might help to minimize brain damage after experimental ischemic and 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.

Furthermore, for clinical stroke research, we run a neurovascular trial unit, which is a globally leading recruitment center in several international multi-center trials. More than 1.200 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 PD Dr. Sven Poli) which was re-certified according to DIN EN ISO 9001:2015 in 07/2021. We have initiated and run a broad spectrum of clinical trials on cooling technologies, hyperoxygenation in thrombectomy candidates, neurosonology, detection of atrial fibrillation, secondary prevention after cryptogenic stroke, thrombolysis in acute central retinal artery occlusion, hemostasis in intracerebral hemorrhage, point-of-care coagulation testing in DOAC-treated patients, and others. We cooperate at an international level.

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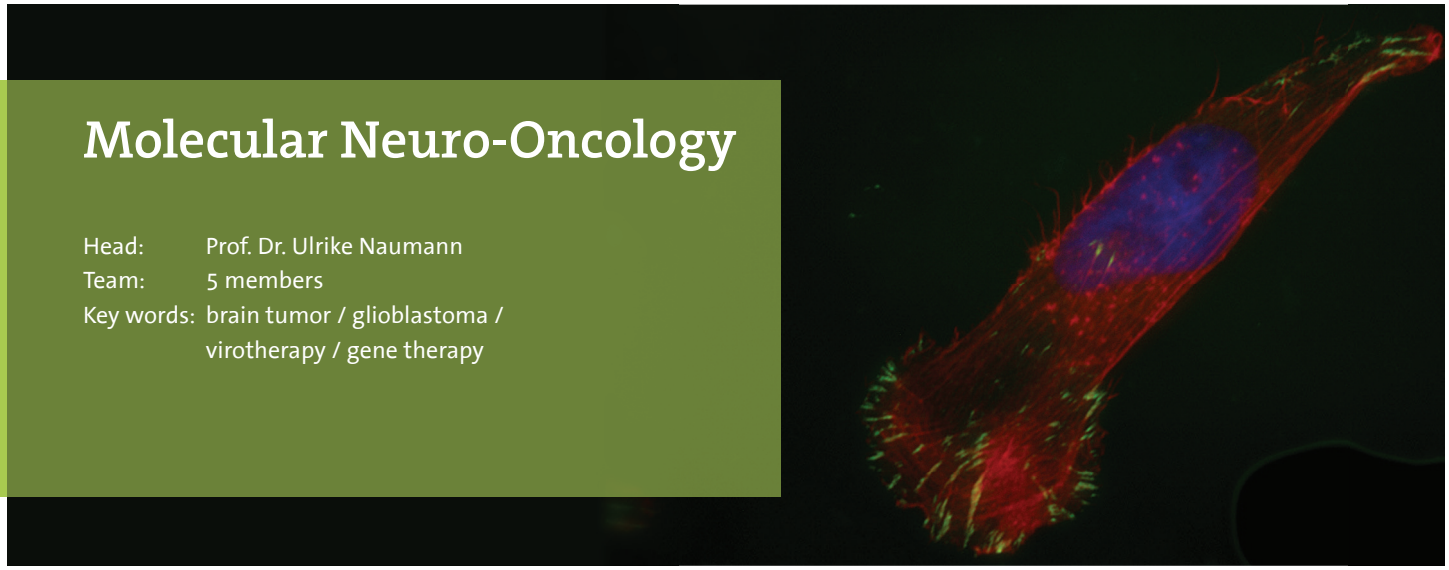
Molecular Neuro-Oncology

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



Migrating glioblastoma cell

The Research Group Molecular Neuro-Oncology is interested in various aspects of the biology of glioblastomas (GBM), the most frequent and 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 combine oncovirotherapy and immune checkpoint inhibition. 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 an 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 glioma that grew in the contralateral hemisphere and that have never been treated with OAVs. The manuscript containing data from this project has been submitted to OncoImmunology (under review).

To further optimize the impact of OAVs we used virus-loaded cells as “Trojan Horses” to shuttle XVir-N-31, via intranasal application, towards infiltratively growing glioma cells that cannot be directly tareted by the intratumoral injection of OAVs. We developed an optimized shuttle cell line with high migratory capacity that addionally contains HSV-TK as a safety gene. Intranasal delivery of XVir-N-31-loaded shuttle cells leads 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 leads to a significant survival prolongation of GBM bearing mice (work in progress).

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 these altered gene expression are exclusively found on glioma-associated vessels. We have identified TGF-ß as a central GBM-secreted cytokine that influences the function of pericytes regarding their metabolic activity, proliferation and motility and their function as a guardian of the integrity of vessel structur and BBB (Wirsik et al, 2021 and manuscipt in the re-review process at PlosOne).

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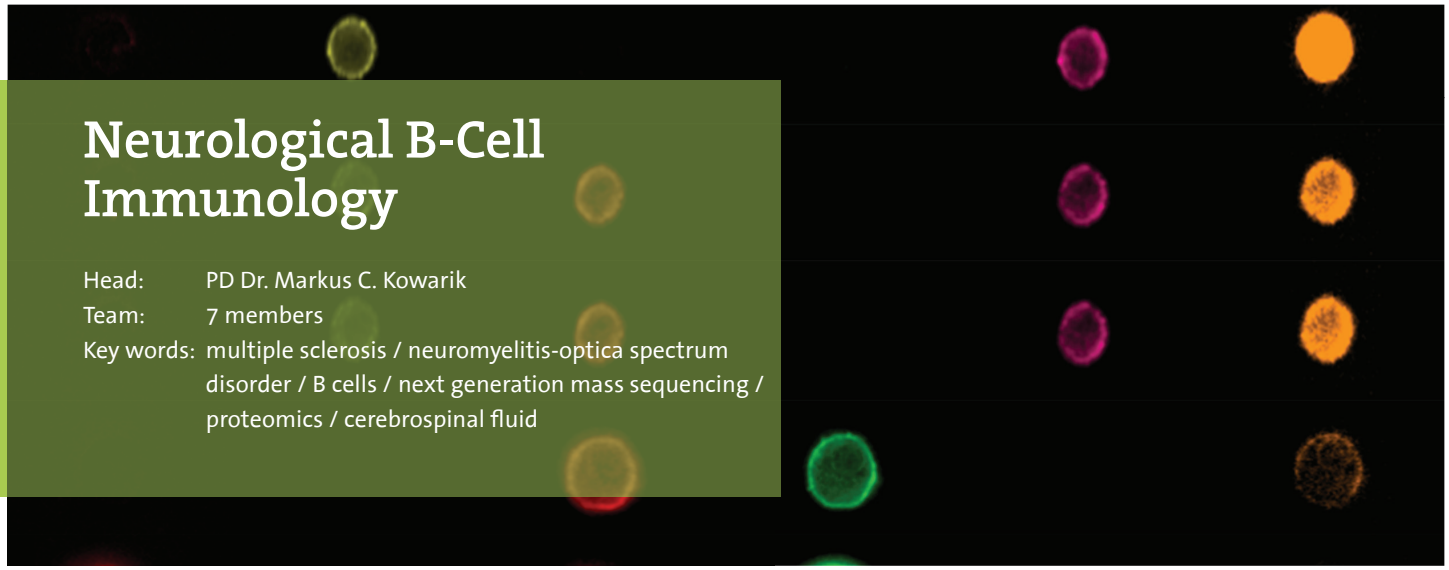

Neurological B-Cell Immunology

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

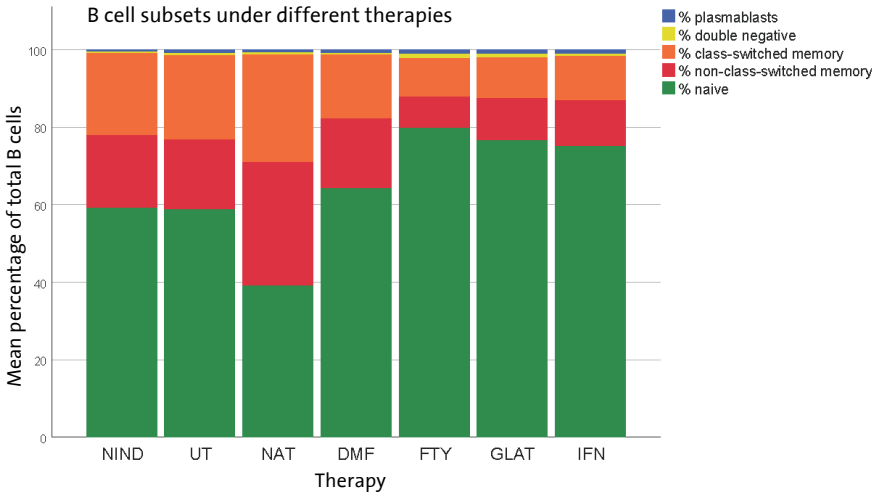

Figure 1: Displayed are the percentages of the B cell subsets among the total CD19+ B cell pool (NIND=non-inflammatory neurological disease, UT= untreated MS patients, NAT= natalizumab, DMF= dimethyl fumarate, FTY= fingolimod, GLAT= glatiramer acetate and IFN= interferon-ß treated MS patients).

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 (Janina Geißert) 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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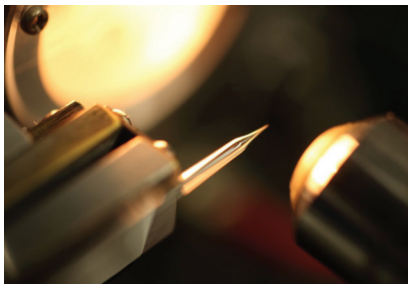
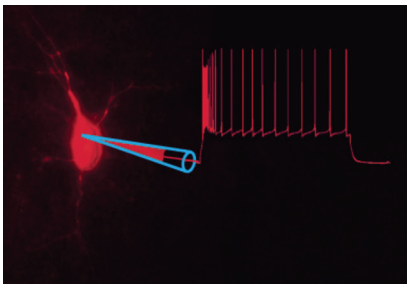
Department of Neurology and Epileptology

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

Departmental Structure

As part of the Center of Neurology and together with the other Neurological Departments, the Department of Neurology and Epileptology is responsible for the clinical care of all neurological patients at the University Clinic Tübingen. A team of nurses, therapists and physicians trained for neurological disorders is available for the inpatient and outpatient clinics. The department's activities have been focusing on effective structures to successfully support basic and clinical research in the field of epileptology and associated paroxysmal neurological disorders, neuromuscular diseases, headache and pain disorders, and provide excellence in patient care. The clinic offers the whole spectrum of modern diagnostic and therapeutic procedures for all neurological disorders. The inpatient unit with 22 beds (Wards 42/43L), running under the supervision of Prof. Dr. A. Grimm, Dr. M. Schreiber, and Dr. P. Martin, includes acute care for epileptic seizures and status epilepticus, longterm complex treatment for difficult cases, and a Video-EEG-Monitoring Unit (headed by Dr. S. Lauxmann) which is operated in cooperation with the Department of Neurosurgery. Within this unit, inpatients are continuously and simultaneously monitored with video and electroencephalography (EEG) for differential diagnostic and presurgical evaluations. Epilepsy surgery, an effective treatment for patients resistant to anticonvulsive





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).

medication, vagal nerve and other brain stimulation paradigms are provided in close cooperation with the Department of Neurosurgery (Dr. S. Ethofer, Prof. Dr. J. Honegger, Dr. G. Naros). The epilepsy outpatient clinic (Prof. Dr. H. Lerche, Dr. M. Schreiber, Dr. S. Lauxmann) offers consulting and treatment in particular for difficult cases and specific questions including pregnancy under antiepileptic treatment and genetic aspects. The other outpatient clinics are focused on headache and neuropathic pain syndromes (Prof. Dr. S. Schuh-Hofer), on neuromuscular diseases (Prof. Dr. A. Grimm, Dr. P. Martin), and rare, genetically determined paroxysmal neurological and ion channel disorders (Prof. Dr. H. Lerche, Dr. S. Lauxmann). Specific genetic diagnostic testing using next generation (whole exome/genome) sequencing is performed in cooperation with the Institute of Medical Genetics and Applied Genomics (Medical Faculty/UKT, Prof. O. Riess and Dr. T. Haack). The department's study center has been involved in diverse medical trials to explore novel treatment options. The department's study center has been involved in diverse medical trials to explore novel treatment options. The department supports the medical and neuroscientific education at the University of Tübingen by providing a comprehensive offer of lectures, seminars and courses.

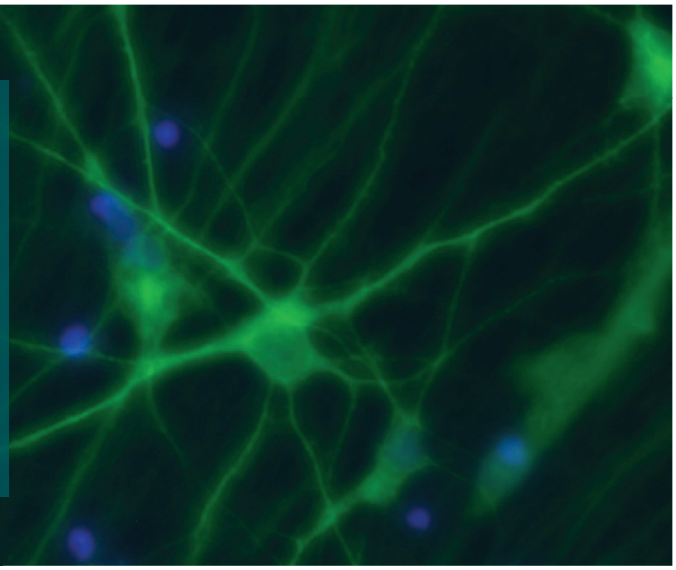
The department stimulates synergies between physicians in the Neurological Clinic and basic research groups in the Hertie Institute with the aim to work on clinically driven basic research questions and rapidly transfer scientific progress into clinical practice.

Our main research topics are

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

Experimental Epileptology

Head: Prof. Dr. Holger Lerche
Team: 25 members
Key words: channelopathies / genetics / seizures / imaging / neuronal networks



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

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

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

Epilepsy affects up to 3% of people during their lifetime, with a genetic component playing a major pathophysiological role in almost 50% of cases. To analyze the genetic architecture of epilepsy we have initiated running national research networks (Treat-ION, DFG FOR-2715) and have initiated or been part of still ongoing European (ESF: EuroEPINOMICS, FP7: EpiPGX, ERANet Neuron: SNAREopathies) and international (ILAE consortium on the genetics of complex epilepsies, Epi25, ILAE Genomics) networks confined to the recruitment of large cohorts of affected individuals and/or families and their genetic analyses. Major achievements in the last years were the prolongation of our DFG-Research Unit FOR 2715, entitled Epileptogenesis of Genetic Epilepsies, establishing Treat-ION, a BMBF-funded network for rare ion channel disorders in 2019 (prolongation pending), and founding ILAE Genomics to collect all available exomes sequenced in epilepsy patients wolrdwide. Important examples from recent studies 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. Sci Transl Med 2021), the identification of a new mechanism for migraine aura in an *Scn1a* mouse model (Auffenberg, Hedrich et al., JCI 2021), and very clear genotype-phenotype correlations with high relevance for clinical management for *SCN8A*-related epilepsies (Johannesen, Liu et al., Brain 2021). A bioinformatic study in a large dataset of whole exomes from more than 8000 affected individuals with common epilepsies revealed that important functional gene groups, such as those of synaptic genes and ion channels / receptors, show specific patterns of enrichment of pathological variants compared to controls in generalized vs. focal epilepsies (e.g. affecting inhibitory vs. excitatory pathways), and also show that signals from common and rare variants converge and contrast in generalized vs. focal epilepsies.

With the BMBF-funded Treat-ION consortium on Neurological Ion Channel and Transporter Disorders we focus on therapeutic studies in cellular, animal and human models, which are complemented by *in silico* searches for new treatments, better predictions for the functional consequences of mutations for therapeutic purposes and cellular drug screens. The use of approved and available 'repurposed' drugs such as 4-aminopyridine is a 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 cneters 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 murine primary neurons, *in utero* electroporated neurons and genetically altered animal models carrying a human mutation (so-called "humanized mouse models"). The advantage of both *in utero* electroporated neurons and gene-targeted mouse models is that altered channels can be studied in their natural environment and additionally, the consequences on intrinsic neuronal properties and network activity can be studied using single cell patch clamp, extracellular recording or multielectrode array (MEA) techniques. We perform 256 electrode MEA recordings and high-resolution electrical imaging (CMOS with 4000 electrodes) to analyze single cell compartments and neuronal network activity in brain slices of transgenic animals and study network dysfunction of our mouse models *in vivo* together with O. Garaschuk (Inst. Neurophysiology) using Ca^{2+} imaging in the frame of the DFG Research Unit. To gain insight into the exact mechanisms as to how epilepsy develops as a consequence of a genetic defect, we investigate brain region- and time-specific RNA expression using single cell RNA sequencing in distinct neuronal subpopulations in mouse models.

Finally, we reprogram fibroblasts obtained from patients carrying different epilepsy-causing mutations in ion channel genes to generate human induced pluripotent cells (hiPSC). Like embryonic stem cells, iPSCs can be differentiated into excitatory and inhibitory cortical neurons and glial cells by addition of different growth factors, defined culture conditions or by overexpression of transcription factors. Thus, it is possible to investigate cortical cells, which were previously inaccessible, from patients carrying genetic diversity or specific mutations of epileptic syndromes. We showed that developmental electrophysiological patterns are similar in iPSC-derived neurons as compared to known data from animals and human tissue and that ipSC-derived neurons represent a study (Rosa et al., Stem Cell Rep 2020). In ongoing work, we characterize firing behaviour and synaptic characteristics of single neurons and networks plated on MEAs. As another human model system, we are using human slice cultures which can be maintained for up to four weeks with good neurophysiological properties when human cerebrospinal fluid (CSF) is used as culture medium. The use of *ex vivo* brain slices derived from adult human neurosurgical-resected tissue allows to probe electrophysiological properties at single cell and network level. We demonstrated robust preservation of neuronal cytoarchitecture and electrophysiological properties of human pyramidal neurons. Further experiments delineate the optimal conditions for efficient viral transduction of cultures, enabling 'high throughput' fluorescence-mediated 3D reconstruction of genetically targeted neurons, and demonstrate feasibility of long term live cell imaging of human cells *in vitro*.

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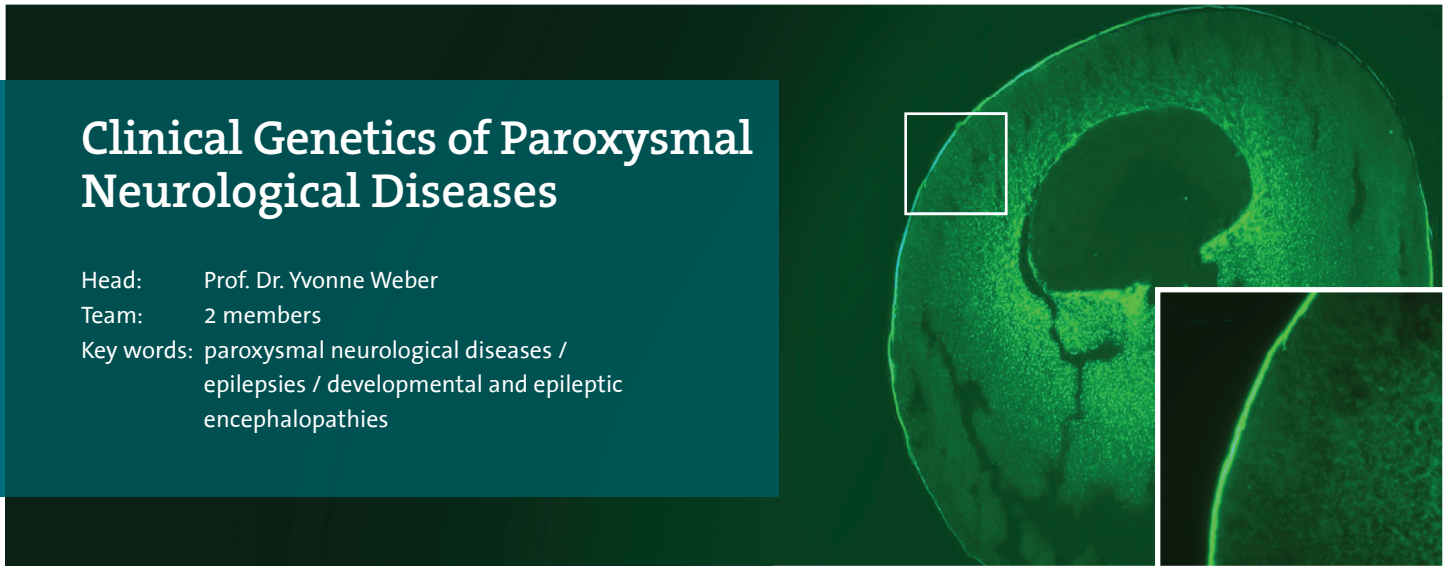
(*/#equally contributing first/senior authors)

Clinical Genetics of Paroxysmal Neurological Diseases

Head: Prof. Dr. Yvonne Weber
Team: 2 members
Key words: paroxysmal neurological diseases / epilepsies / developmental and epileptic encephalopathies



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

Paroxysmal neurological disorders include a broad spectrum of clinical entities. The research group is focused on the clinical genetics of epilepsies and paroxysmal dyskinesias, paroxysmal neurological disorders with overlapping clinical and pathophysiological features. In the last years, the main topics were the analysis of a special type of epilepsies the "Developmental and Epileptic Encephalopathies" (formerly epileptic encephalopathy, EE), the standardization of genetic biomarkers for a precision medicine in epilepsy and the analysis of novel epilepsy genes with a focus on the synaptic metabolism. Additionally, completely novel research fields were started namely the development of a seizure detection system together with a start-up company and a so-called Clinical Decision Support System (CDSS) which provides the practitioners all necessary research information to find an individual therapy for the patient.

Der Überbegriff der paroxysmalen neurologischen Erkrankungen beinhaltet ein breites Spektrum an klinischen Entitäten. Der wissenschaftliche Schwerpunkt der Arbeitsgruppe ist die klinisch genetische-genetische Untersuchung von Epilepsien und paroxysmalen Dyskinesien, die häufig pathophysiologische überlappungen zeigen und ebenfalls zum Krankheitsspektrum der paroxyxmalen neurologischen Erkrankungen zählen. In den letzten Jahren lag der Fokus auf speziellen Epilepsieformen, nämlich den entwicklungsbedingten und epileptischen Epilepsien (früher epileptische Enzephalopathien, EE), der Standardisierung von genetischen Biomarkern für eine individualisierte Therapie sowie der Analyse von neuen Epilepsiegenen mit Fokus auf dem synaptischen Metabolismus. Darüber hinaus wurde ein komplett neues Forschungsfeld mit der Entwicklung eines Anfallsdetektors zusammen mit einem Start-up-Unternehmen begonnen sowie die Entwicklung eines sog. Clinical Decision Support Systems, das dem Kliniker alle Informationen zur Verfügung stellt, um eine individualisierte Therapie festzulegen.

Epilepsy is a very common neurological disease with a lifetime incidence of up to 3 % in the general population. Epilepsies are divided in focal and generalized forms as well as in structural (induced by e. g. scars, dysplasias or strokes), infectious, autoimmune, metabolic and genetic forms looking from a pathophysiological point of view. Up to 30 % of epilepsies are genetically determined. Epileptic encephalopathies (EE, development and epileptic encephalopathies) are defined as early onset and pharmaco-resistant epilepsies associated to developmental delay or regression. Several subtypes are known such as West syndrome or Lennox-Gastaut syndrome encompassing syndrome with defined age of onset, seizure types and EEG characteristics.

Epilepsies are commonly related to other diseases such as mental retardation, ataxia or paroxysmal dyskinesias since those diseases can be found in the same family and can be based on the same genetic defect. Paroxysmal dyskinesias can be symptomatic (e. g. multiple sclerosis lesions found in the basal ganglia), but most of the described cases are of idiopathic/genetic origin.

Activities in 2021

Together with others we detected a novel gene for a developmental and epileptic encephalopathy OGDHL which is relevant mitochondrial metabolism (Yap et al. 2021). We extended our work towards a CDSS for epilepsy patients (Zöllner et al. 2021) and underlined the importance of genetic testing especially in the presurgery workup (Bosselmann et al. 2022, Balestrini et al. 2021). Together with our we went more deeply in the analysis of genetic epilepsies (Epi25 2021, Vonderwülbecke et al. 2021, Manivannan et al. 2021).

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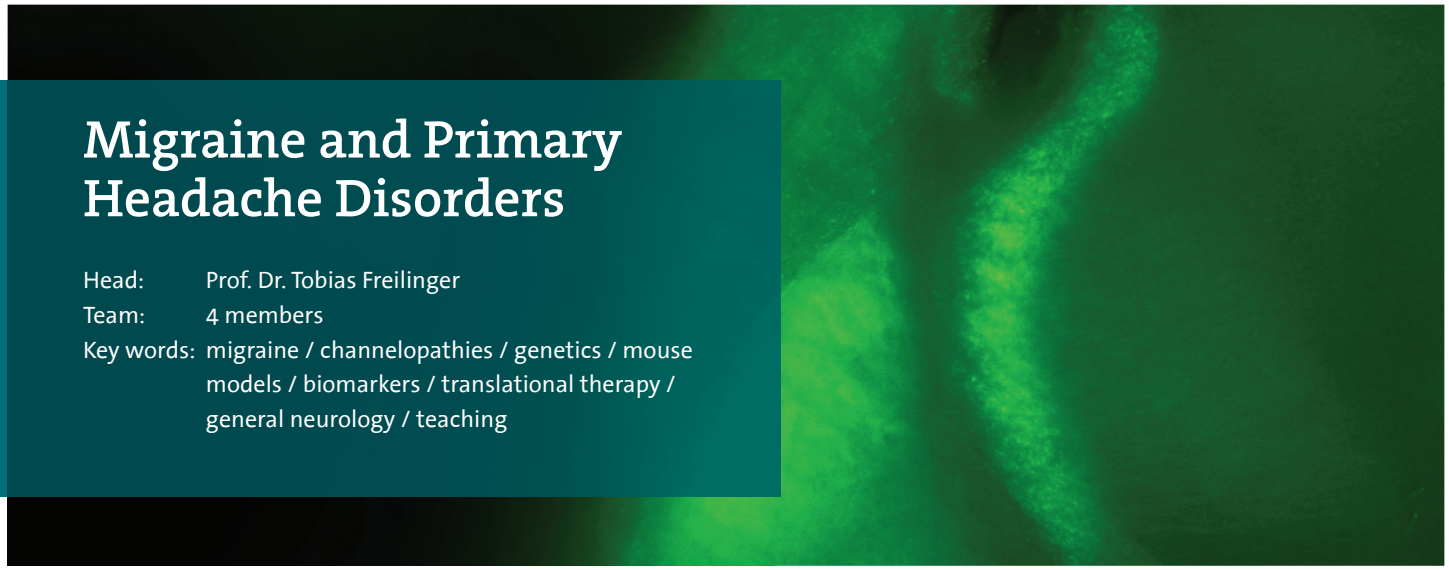
Migraine and Primary Headache Disorders

Head: Prof. Dr. Tobias Freilinger
Team: 4 members
Key words: migraine / channelopathies / genetics / mouse models / biomarkers / translational therapy / general neurology / teaching



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

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

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

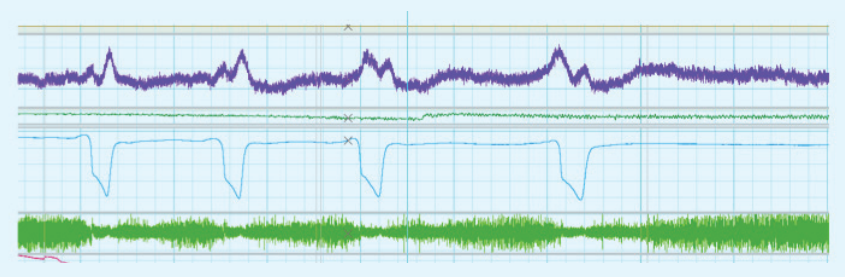
One major focus of our research is hemiplegic migraine (HM), a severe monogenic subtype of migraine with some degree of unilateral motor weakness during the aura. We have access to one of the worldwide largest HM cohorts, which is actively expanded through ongoing recruitment as well as clinical and genetic work-up, with new insights into the mutational spectrum, genotype-phenotype correlations (e.g. Schubert et al. 2018) and imaging findings (Roth et al. 2018). In a sporadic HM patient, we had previously identified a novel missense mutation in SCL1A3, the gene encoding the astrocytic glutamate transporter hEAAT2. In collaboration with C. Fahlke (Jülich) we have comprehensively characterized this novel variant to find a loss-of-function effect, highlighting impaired K+ binding to hEAAT1 as a novel mechanism (Kovermann et al. 2017); functional analysis of a further SLC1A3 variant is ongoing.

To comprehensively study mechanisms underlying cortical hyperexcitabilitiy in HM, we are performing multimodal analysis of a transgenic Scn1a knock-in HM mouse model. By in vivo analyses we could show increased susceptibility to cortical spreading depolarisation (CSD), the likely correlate of migraine aura. Further, this model allowed us to establish increased activity of (inhibitory) interneurons (and a subsequent increase in extracellular K+) as a potential novel mechanism of CSD initiation (Auffenberg et al., 2021). Ongoing analyses focus e.g. on the the differential pathophysiology of migraine vs. epilepsy and stroke susceptibility in migraine (cooperation with N. Plesnila, ISD, Munich).

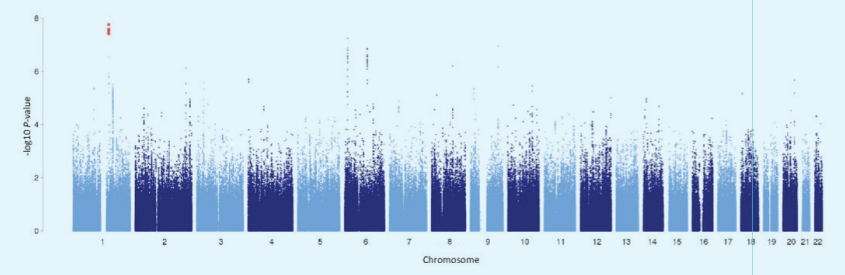
We are also interested in improving clinical care of HM patients. Building on research support from the Centre of Rare Diseases (ZSE) as well as the intramural AKF program, we were able to launch the first mechanism-based translational prospective treatment trial in HM evaluating the role of the sodium channel blocker lamotrigine in preventing HM attacks (HeMiLA, HeMiLa, Prophylactic treatment of hemiplegic migraine with Lamotrigine; EudraCT-Nr. 2016-003223-30).

As a second focus we are interested in the common genetically complex types of migraine. As part of the International Headache Genetics Consortium (IHGC), we were prominently involved in the identification of all currently established risk variants as well as more recent downstream analyses (e.g. Gormley et al. 2018, Yang et al. 2018, Brainstorm Consortium et al. 2018). Our group has a special interest in the migraine – vascular diease connection, and we are looking further into this (e.g. Winsvold et al. 2017), aiming at identification of novel genetic as well as other types of biomarkers.

Finally, our portfolio covers aspects of general clinical neurology (e.g. Auffenberg et al. 2018; Hoffmann et al. 2019; Niller et al. 2020; Ruschil et al., 2021) as well as medical teaching in neurology; a recent pilot project was dedicated to developing a novel interactive learning and teaching toolbox for medical students comprising more than 20 case vignettes on classical neurological disease entities (Neuro-CliPS Tübigen; support from intramural funding).



Representative traces from multiparametric in vivo monitoring of transgenic HM animals



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

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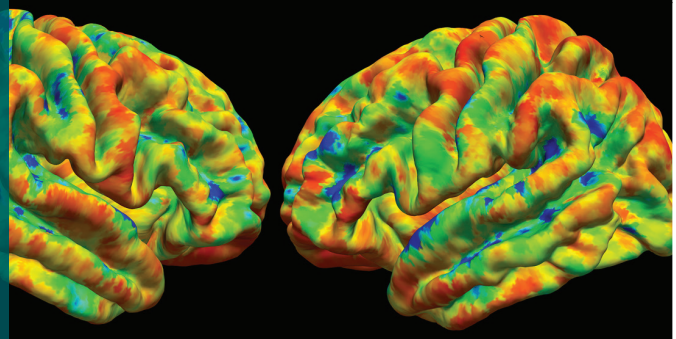
Translational Neuroimaging

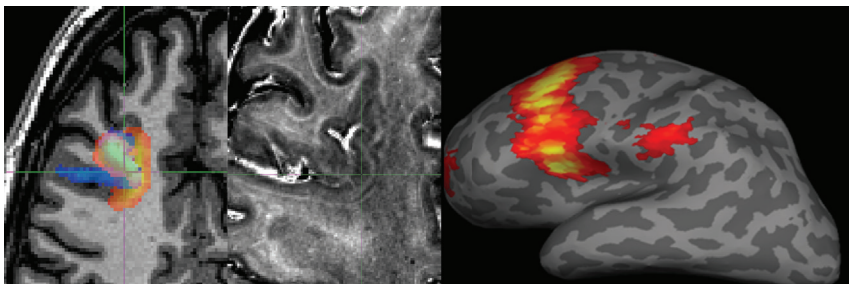
Head: Prof. Dr. Niels Focke
Team: 4 members
Key words: multi-modal imaging / epilepsy / post-processing / classification methods



Cortical structual connectivity derived from whole brain fibre tracking

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

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



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

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

Imaging Modalities

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

Recent results

In patients with idiopathic/genetic generalized epilepsy (IGE/GGE) we could demonstrate microstructural network alterations based on diffusion tensor imaging although routine MR imaging was completely normal (Focke et al., 2014). Moreover, based on functional imaging (MEG) we could show increased network connectivity in IGE/GGE in the resting state (Elshahabi et al., 2015). Siblings of GGE patients showed intermediate patterns of increases MEG and EEG connectivity (Stier et al., 2021). Also, we have worked on integrating and systematically comparing different functional imaging modalities (Klamer et al., 2015a) and improving structural VBM for lesion detection in epilepsy (Lindig et al., 2017, Kotikalapudi et al., 2019) as well as systematically assessing VBM as a tool for presurgical epilepsy diagnostics (Martin et el., 2017). Furthermore, we have worked on assessing and improving the reliability of network analysis based on DTI (Bonilha et al., 2015), MEG/EEG (Marquetand et al. 2019) and enabling ultra-fast fMRI (Sahib et al., 2016 and Sahib et al., 2018).

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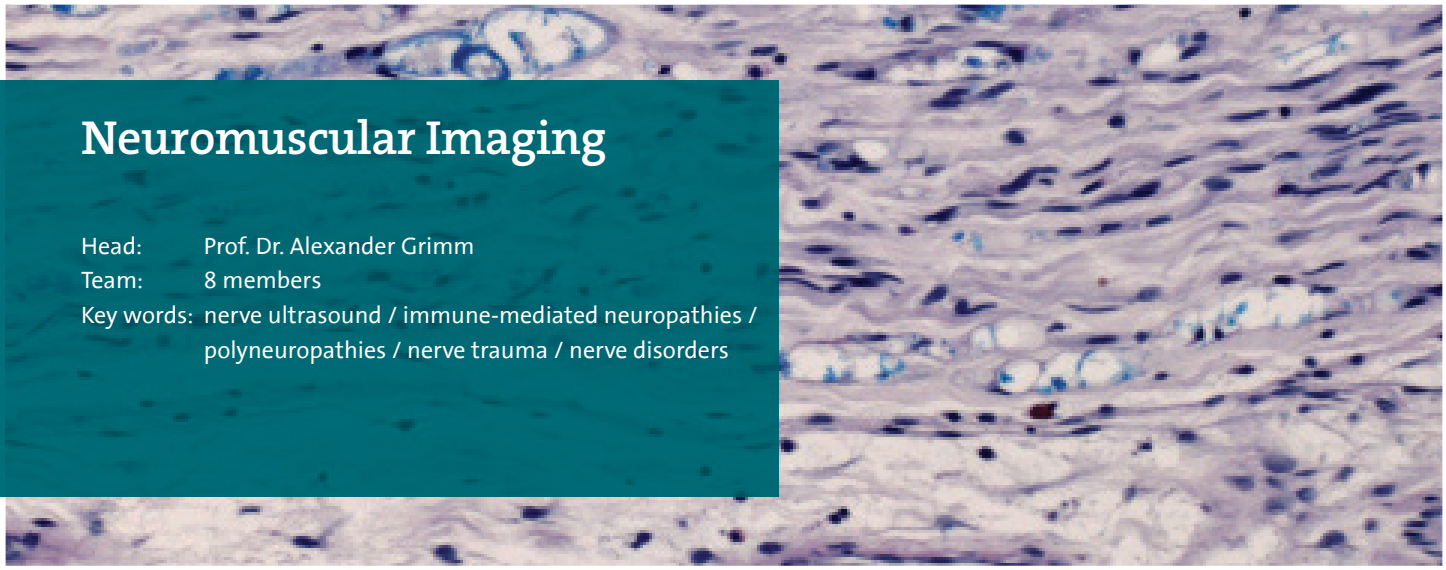


Neuromuscular Imaging

Head: Prof. Dr. Alexander Grimm
Team: 8 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 (Grimm A et al., 2018).

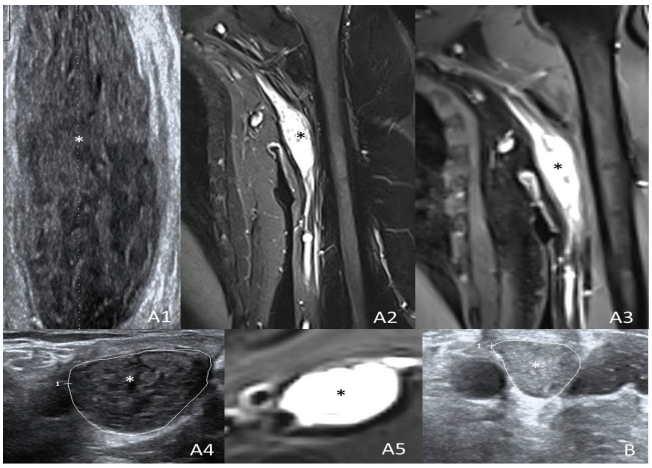
In addition, we successfully established nerve and muscle ultrasound as a new biomarker in the differentiation and follow-up of hereditary neuropathies. We combined three different nerve ultrasound scores, 1) the ultrasound pattern sum score (UPSS) reflecting nerve enlargement at 14 nerve sites of 10 different nerves, 2) the homogeneity score (HS) as a marker of the distribution of nerve enlargement, and 3) entrapment ratios at carpal tunnel and cubital tunnel. Using this combination, it was possible for us to depict characteristic features of nerve alteration for each examined hereditary neuropathy (Winter et al., 2021).

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

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

Ultrasound has been further proven, to detect the inflammatory base of several mononeuropathies of unknown origin (Winter et al. , 2019). So far, the cause of those sporadic mononeuropathies remained often unclear as it only showed axonal damage in electrophysiology without clarifying the underlying pathology. By ultrasound however, our group could find tremendeous nerve swelling and edema, which decreased with treatment and correlated to the clinical improvement (Figure). This finding is emerging for many patients as it might facilitate early therapeutic steps. Ongoing studies handle the huge field of hereditary neuropathies, lysosomal storage diseases and their nerve ultrasound presentation. In 2021, we have been able to establish shear wave elastography (SWE) as a new method in our laboratory. In our studies we could characterize SWE of various limb and truncal muscles, demonstrate the importance of patient positioning, and offer an advanced examination protocol. Furthermore, we provide SWE data for the transducer setup using the Canon Aplio i800 System and 18MHz probe (Romano et al., 2021). In addition to normal values, first applications in patients, e.g. in the detection of muscle changes in patients with myotonia, could also be investigated (Kronlage et al., 2021).

In addition, we were able to further expand our cooperation with the pediatric clinic, neurosurgery and hand, plastic, reconstructive and burn surgery.. Various studies on this are currently still underway.



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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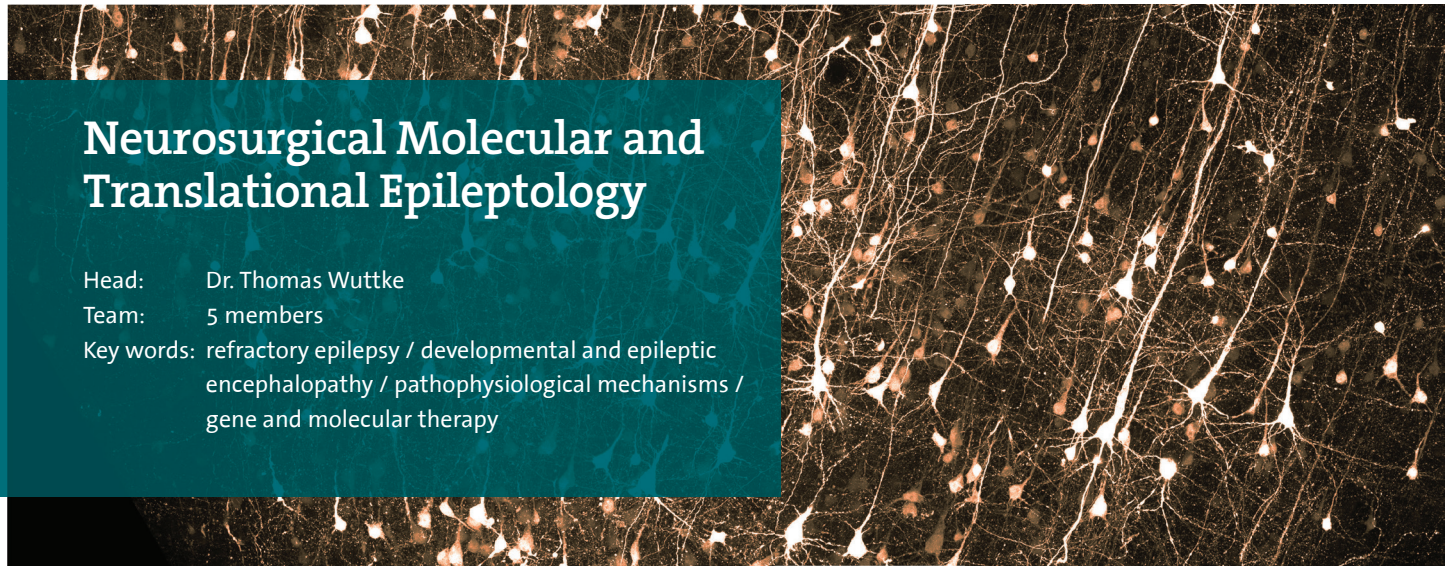
Neurosurgical Molecular and Translational Epileptology

Head: Dr. Thomas Wuttke
Team: 5 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. These approaches are complemented by analyses in neurosurgically resected tissue to investigate the applicability of pathophysiological and therapeutic concepts to human CNS.

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. 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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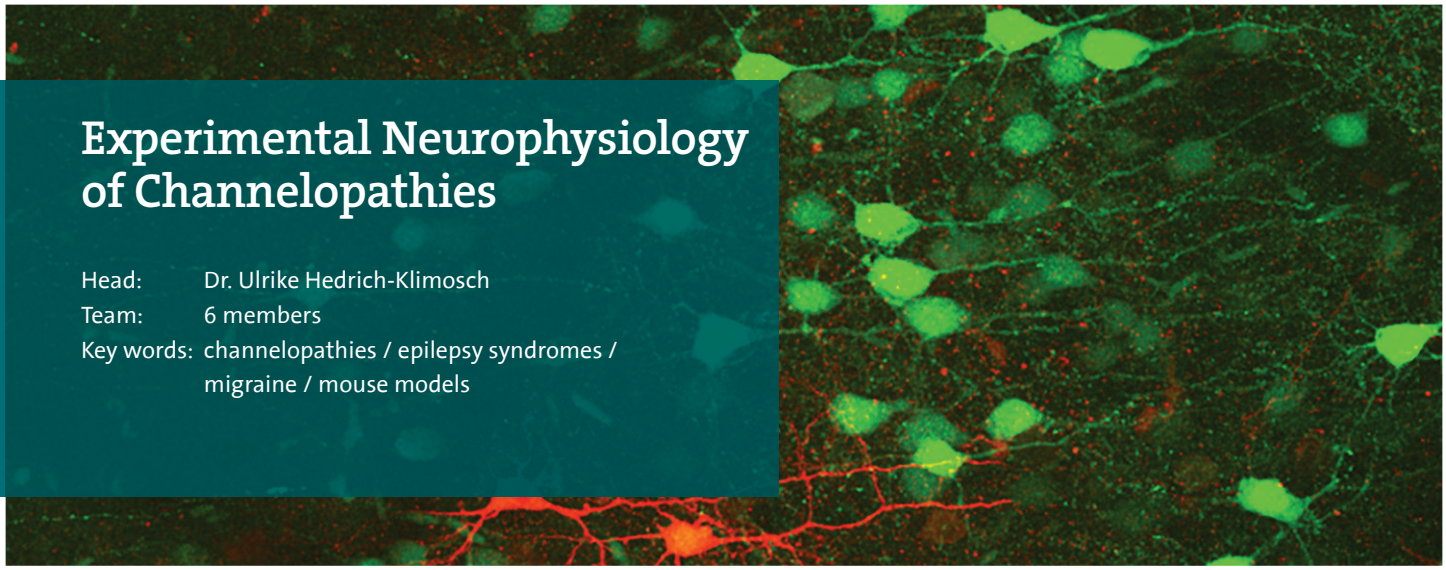
Experimental Neurophysiology of Channelopathies

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) in order to develop new therapies.

One major focus of our research is to understand the epileptogenic mechanism of *KCNA2*-associated encephalopathies using in utero electroporation of *KCNA2* variants and newly generated knock-in mouse models carrying gain- or loss-of-function variants (in collaboration with Th. Ott (IZKF-Core Facility Transgenic Animals)). Together with O. Garaschuk (Inst. of Neurophysiology) we study the vulnerable time windows of *Kcna2* variants and the network dysfunction and miswiring of the developing neural network of our mouse models within the DFG Research Unit FOR2715. Beside studying the pathophysiology, we also focus on the treatment of patients with *KCNA2* gain-of-function variants with 4-aminopyridine and its effect on different gain-of-function variants using *Xenopus laevis* oocytes (Hedrich, Lauxmann et al., 2021), for which we also received the Eva-Luise-Köhler prize for rare diseases in 2018. In addition, we currently develop efficient *Kcna2* antisense oligonucleotides.

Within the BMBF-funded Treat-ION consortium on Neurological Ion Channel and Transporter Disorders we focus on the pathophysiological mechanisms of hemiplegic migraine (HM), a severe monogenic subtype of migraine with some degree of unilateral motor weakness during the aura, among others caused by variants in the brain sodium channel gene *SCN1A* and the glutamate and chloride

transporter gene *SLC1A3* using transgenic mouse models. We comprehensively studied the pathomechanisms underlying cortical hyperexcitability in HM by performing multimodal analysis of a transgenic *Scn1a* knock-in HM mouse model. By *in vitro* and *in vivo* analyses we could show increased CSD susceptibility in heterozygous mice, an increase in activity of inhibitory interneurons and in extracellular K^+ in the early phase of CSD in brain slices of heterozygous mice, likely representing the mechanistic link between interneuron hyperactivity and CSD initiation (Auffenberg, Hedrich et al, 2021). Ongoing analyses focus on the characterization of epileptic seizures and CSDs in *Slc1a3* mutant mice (funded by BMBF project Treat-ION), personalized treatment using allele specific antisense oligonucleotides and the differential pathophysiology of migraine vs. epilepsy in *Scn1a* knock-in mouse models (funded by the Bridging Grant Funding Program of the Hertie-Institute for Clinical Brain Research).

Furthermore, we are interested in a new mechanism in the pathophysiology of Dravet Syndrome (DS), the neuron-oligodendrocyte interactions. For a majority of DS patients, *SCN1A* variants have been identified causing loss-of-function of the $Na_V1.1$ channel, the main Na^+ channel in inhibitory neurons, and thus a loss of inhibition through the reduction of action potential initiation and propagation. In collaboration with F. Pfeiffer (Inst. of Neurophysiology) and I. Nikić-Spiegel (Research Group Molecular Mechanisms of Axonal Injury, CIN) we study the impact of *SCN1A* variants in neurons, oligodendrocyte precursor cells (OPCs) and oligodendrocytes, since these cells all express the $Na_V1.1$ channel, share common embryonic origins and highly interact during development. In addition, we aim to identify morphological changes in the axon initial segment and axons and investigate myelination in *Scn1a* mutant mice. This project is funded by the Gruppo Famiglie Dravet Associazione ONLUS in partnership with other European Dravet Foundations. Within the European Joint Program on Rare Disease (EJP RD) as part of a nationally funded (by DFG for Germany) consortium with partners in France, Italy, Belgium, the Netherlands and Germany, we focus on targeted treatments for Dravet Syndrome using knock-in animal models as well as human disease-models.

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Department of Neuro-degenerative Diseases

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

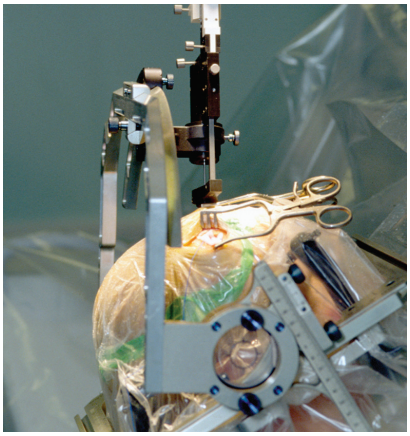
Departmental Structure

The Department of Neurodegenerative Diseases was founded with the support of the Charitable Hertie Foundation and started operations on September 1, 2002. Since 2009, it is also a part of the Tübingen site of the German Center for Neurodegenerative Diseases (DZNE). Prof. Dr. Peter Heutink, speaker of the DZNE Tübingen and head of the Research Group on Genome Biology of Neurodegenerative Diseases, holds an affiliation with the Hertie Institute and is a member of the Department for Neurodegenerative diseases. The department pursues a comprehensive approach towards basic and clinical research in the field of neurodegenerative diseases and movement disorders, from their genetic basis and early diagnosis to innovative treatments and patient care. Through its clinical division, the department cares for patients with neurodegenerative diseases and movement disorders on an inpatient unit of 21 beds (Ward 45) and several specialized outpatient clinics. The clinical work is carried out by specially trained staff on all levels, including nurses, physiotherapists, occupational and speech therapists, as well as neurologists and neuropsychologists. A structured training, the Movement Disorders Curriculum for medical residents in training for board certification has been implemented, that covers a wide variety of movement disorders and rare neurogenetic diseases and includes clinic rotations, talks and journal clubs.

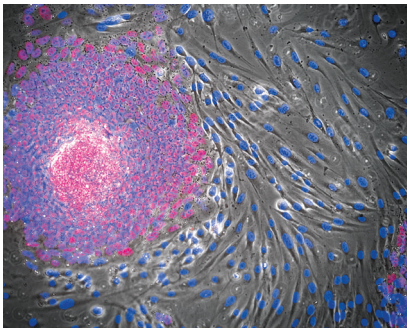
The clinical branch of the department offers specialized and up-to-date diagnostic procedures for neurodegenerative diseases, including transcranial sonography of the brain parenchyma and genetic testing. Innovative treatment for patients with Parkinson's disease (PD) and other movement disorders include deep brain stimulation (in close collaboration with the Department of Neurosurgery), but also continuous apomorphine or levodopa infusion treatment in Parkinson's patients with severe fluctuations, or botulinum toxin treatment in patients with dystonias and spastic gait disorders. 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 other rare neurogenetic disorders allows highly individualized patient management. The equally close interaction of clinicians with basic scientists within the Hertie Institute for Clinical Brain Research and the DZNE, on the other hand, allows truly translational research. This innovative concept includes active education and training of scientific and clinical junior staff. In 2020, the clinical department was named for the sixth time in a row as one of Germany's Top Ten hospital departments in Parkinson's Disease by the Magazine Focus.

Research is currently organized within 9 research groups and four associated groups. The group of Prof. 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 PD 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, while PD Dr. Rebecca Schüle focuses on the genetic basis of spastic paraplegias, also spanning the entire translational spectrum from gene identification to individualized treatments. In 2016, Dr. Ebba Lohmann has joined the department to run the outpatient unit for botulinum toxin treatment of dystonias and spasticity, linking this clinical approach with the search for the genetic basis of these hyperkinetic movement disorders. Dr. Julia Fitzgerald has become junior group leader, studying the mitochondrial biology of PD. Two research groups with a primary affiliation with the DZNE, Jun-Prof. Dr. Dr. Michela Deleidi, and PD Dr. Johannes Gloeckner are also members of the Department. Two previous members, Prof. Dr. Daniela Berg and Prof. Dr. Rejko Krüger, have both accepted chairs for Neurology at the University of Kiel and Luxembourg, respectively. They both still hold affiliations at the Department and provide their expertise in research and teaching and closely collaborate in a number of externally funded projects. Finally, the group of Prof. Dr. M. Synofzik, which applies systems neurobiologic and genetic approaches to elucidate the basis and develop novel treatments of rare complex movement disorders including ataxias, but also dementias and motor neuron diseases, is now an independent research group at the HIH, but continues to pursue all patient work, including outpatient clinics, the characterization of patient cohorts and innovative clinical trials, within the Department of Neurodegenerative Diseases.

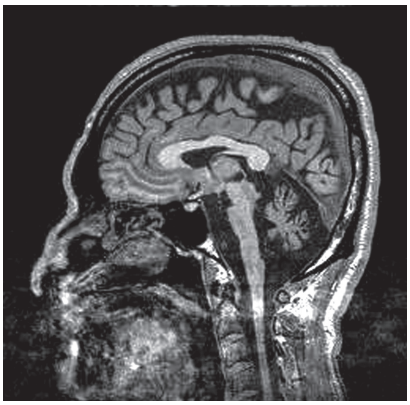
Thus, the wide spectrum of activities in the department covers all aspects from basic research to highly competent care of patients with Parkinson's disease and other neurodegenerative diseases.



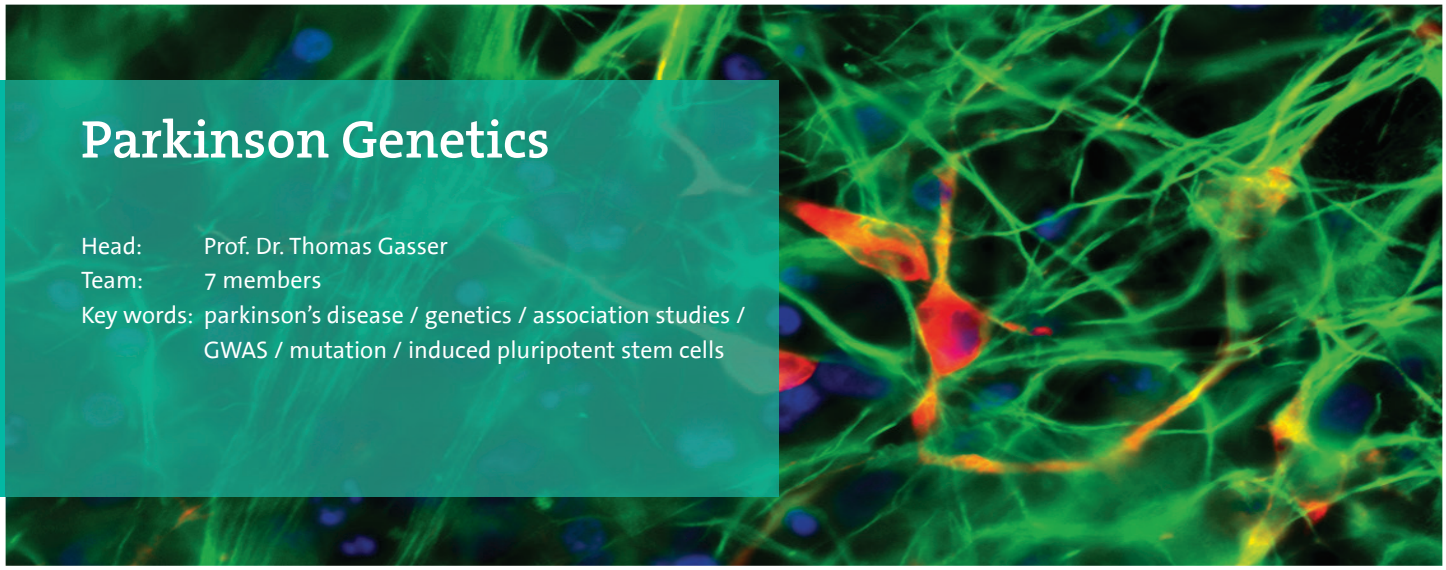
Insertion of an electrode during deep brain stimulation for Parkinson's disease.



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.

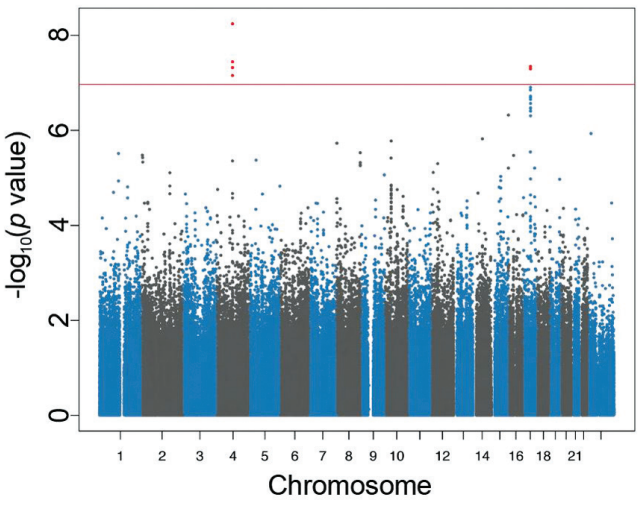


Parkinson Genetics

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

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

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

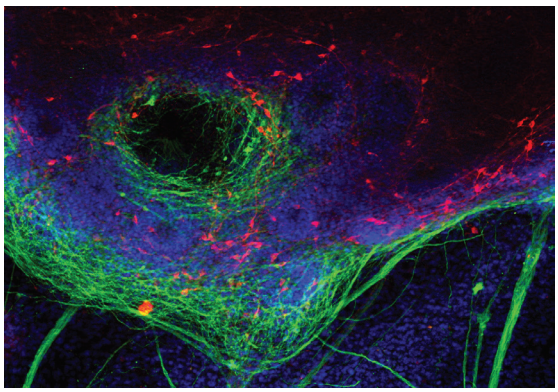


A large genome-wide study identified two genetic risk loci for sporadic PD. One is MAPT, containing the gene for the microtubule associated protein tau.

As in most complex neurodegenerative disorders, specific mutations in some genes can cause rare inherited forms of Parkinson's disease (PD). Mutations in the LRRK2-gene, for example cause the most prevalent autosomal-dominant form of PD, which was discovered by us and collaborators in 2004 (Zimprich et al., Neuron 2004). A contribution of more common genetic sequence variants, often called single nucleotide polymorphisms (SNPs), in the etiology of the much more common sporadic (=non-familial) form is now equally well established.

In 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).

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



As genome-wide association studies only capture relatively common variants, a significant proportion of the total genetic risk remains to be discovered. This is sometimes called the "missing heritability" and thought to be conferred mainly by rare genetic variants of moderate effect size. In order to identify the relevant variants, we are participating in IPDGC efforts of whole-exome sequencing studies. Recently, these studies provided insight into the genetic architecture of Lewy body dementia, which shares risk profiles and pathways with Alzheimer's disease and Parkinson's disease (Chia et al., 2021).

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. Grover et al., 2021).

Knowing the genetic underpinnings of a complex neurodegenerative disorder such as PD is important, but the study of individual families is still important. In collaboration with a Greek research group we were able to identify novel mutations in the first PD-gene (alpha-synuclein, SNCA). (Liu et al., 2021)

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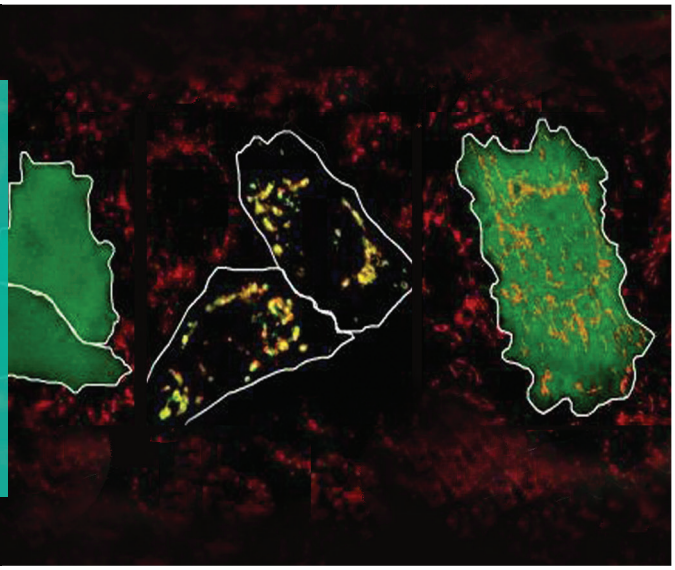
Functional Neurogenetics

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 histopathological mechanisms underlying aggregation of these proteins and their impact on neural dysfunction. Pathological pathways are modeled in cell culture and animal models. Investigated mechanisms include protein aggregation and post-translational modifications, mitophagy, and nucleocytoplasmic protein transport. We wish to understand the molecular basis how intracellular protein aggregation affects particular neuronal functions, which cause the characteristic syndromes of neurodegenerative movement disorders and dementias.

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

The most common recessive Parkinson's disease gene products **PINK1 and parkin** regulate mitochondrial functions. We performed mitophagy assays for PINK1-deficient iPS cells characterized by Bus et al. (2020). Mitophagy is an essential cellular process removing damaged mitochondria in a highly complex pathway that depends on post-translational modifications initiated by the PINK1 phosphotransferase and the ubiquitin ligase parkin (Lechado Terradas et al. 2021). In standard cell culture models, depolarization of the mitochondrial membrane potential prevents the import of nuclear encoded proteins. As a result, PINK1 accumulates at the mitochondrial outer membrane, where it phosphorylates ubiquitin and the ubiquitin-like domain of parkin. Thereby PINK1 activates parkin to ubiquitinylate several mitochondrial proteins in a coordinated process mediating 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 mutant parkin (Zittlau et al. 2022). This comprehensive work provides a rich resource of post-translational modifications potentially identifying novel regulatory steps for the important mechanism of mitophagy. Initial validations indicated an interesting outside-in cadence of mitochondrial protein removal (Zittlau et al. 2022), challenging the prevailing view of wholesale mitochondria autophagy. The characterization of the proteasomal and autophagic fates of distinct mitochondrial subcompartments is subject to current investigation.

For **α-synuclein** we continued to contribute our well-established transgenic mouse model to the study of disease seeding and spreading. Intracranial injection of α-synuclein fibrils not only caused robust synucleinopathy but also microglial activation (Gentzel et al. 2021). Interestingly, microglia contained a novel type of inclusions both in α-synuclein transgenic mouse models (Tanriöver et al. 2021) as well as in long-term slice cultures (Barth et al. 2021). Furthermore, we performed the antibody epitope mapping for a study of medin that showed its aggregation in aging mice to cause cerebrovascular dysfunction (Degenhardt et al. 2020).

The pathogenesis of frontotemporal dementia and amyotrophic lateral sclerosis was inspired in the recent years by the emerging concept of liquid-liquid phase separation. It was found that TDP-43 and FUS, two common hallmarks of these diseases, are RNA-binding proteins able to form hydrogels via their low-complexity domains. Stress granules (SGs) are membrane-less organelles that can be viewed as separate phases in the cytosol. Indeed, SG forming conditions were most powerful inducers of **TDP-43** ubiquitinylation and insoluble protein aggregation. Surprisingly, pharmacological inhibition of SG formation per se did not prevent pathological TDP-43 ubiquitinylation (Hans et al. 2020). Thus, our results do not support the original hypothesis that SGs act as seeds for TDP-43 aggregation, arguably because in SGs TDP-43 is bound to RNA. Rather multiple distinct pathways can directly lead to pathological TDP-43 modifications. In our mass spectrometric analysis of ubiquitinylation sites (Hans et al. 2018) we also discovered another type of lysine modification, namely acetylation. Two functionally important lysine residues were found to regulate key aspects of TDP-43 pathophysiology. Acetylation of K84 in the nuclear localization sequence led to cytoplasmic mislocalization of TDP-43. Acetylation of K136 in the RNA-binding domain caused loss of functional RNA interactions and led to liquid-liquid phase separation and TDP-43 aggregation. The results from site-directed mutagenesis were successfully confirmed by amber suppression mediated introduction of authentic acetyl-lysine at these sites. This together with the development of acetylation-selective antibodies allowed us to identify sirtuin-1 as a powerful deacetylase capable of reverting the pathogenic acetylation effects (Garcia Morato et al, 2022). This research featured within the German Center for Neurodegenerative Diseases is continued to establish the human disease relevance of TDP-43 acetylations and importantly aims to identify the protein and RNA components driving phase separation and TDP-43 aggregation.

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Dystonia

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

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

Dystonia is a movement disorder that involves involuntary muscle contractions that can cause twisting and repetitive movements or abnormal postures. There are several different forms of dystonia that may affect a single muscle, a group of muscles such as those in the arms, legs, or neck, or the entire body. Dystonia can occur at any age and describes a clinical symptom, the origin of which is very often unknown.
There are several genetic causes of dystonia. Symptoms may vary widely in type and severity even among members of the same family. In some instances, people who inherit the defective gene may not develop dystonia. The aim of the group, which brings together clinical experience in the diagnosis and treatment of the dystonias with expertise in molecular genetics, is to define the role of known genes in the etiology of dystonia, but especially to find new genes and therefore gain novel insight into the molecular pathogenesis of the disorder.

Die Dystonie-Erkrankungen gehören zu den Bewegungsstörungen und zeichnen sich durch unwillkürliche Verkrampfungen der Muskulatur aus, welche zu ungewöhnlichen und repetitiven Bewegungen und Körperhaltungen führen. Dystonien treten in ganz unterschiedlichen Ausprägungen auf und können einen einzelnen Muskel, eine Muskelgruppe (z.B. im Arm, Bein oder Halsbereich) oder aber auch die gesamte Muskulatur betreffen. Eine Dystonie kann in jedem Alter auftreten und beschreibt letztendlich zunächst nur ein klinisches Symptom, dessen Ursache häufig ungeklärt ist.
Es gibt jedoch einige Genveränderungen, welche die Entstehung der dystonen Erkrankung mit verursachen können. Die klinischen Erscheinungsformen können jedoch in Schwere und Verteilungsmuster selbst zwischen Familienmitgliedern erheblich variieren. Manchmal entwickeln Personen auch gar keine Symptome, obwohl sie eine entsprechende Genveränderung tragen. Ziel unserer Arbeitsgruppe, welche sich aus Klinikern und molekulargenetisch ausgebildeten Experten zusammensetzt ist es, zum einen die Rolle bereits bekannter Dystonie-Gene besser zu definieren und zum anderen neue Gene zu finden, um die molekularen Mechanismen der Dystonie besser zu verstehen.

Patient recruitment is based on the departmental outpatient clinic for botulinum toxin treatment, which is run by Dr. E. Lohmann since end of 2015. She brought a large number of patient samples from her previous position at the University of Istanbul in Turkey, where she founded a neurogenetics research group and was supported by a Margarete von Wrangell-stipend. Dr. E. Lohmann continued her work with funding from the German Research Foundation (DFG). Detailed phenotyping and a thorough work-up of the families provide the basis for genetic analysis. Interestingly, phenotypes such as parkinsonism, spasticity and motor neuron diseases are often overlapping with genetic forms of dystonia.

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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 ataxia, hereditary spastic paraplegia, choreatic disorders and leukodystrophies. To discover the genetic cause of the diseases we use transciptomics and proteomics beside whole genome sequencing to provide a definite diagnosis for our patients and open windows into pathogenesis and potential interventions in early stages of the disease process. In our specialized outpatient clinics we see many patients with these rare diseases and include them into clinical studies to establish measures of disease progression that can be used to monitor therapeutic effects. We establish biorepositories of DNA, RNA, serum, CSF and fibroblasts for the development of biomarkers indicating disease activity. Clinical studies are matched by basic research generating induced pluripotent stem cells (iPSC) from skin biopsies of our patients. iPS cells are re-differentiated into neurons which constitute cell culture models that are genetically identical with our patients and represent the cell type that is primarily affected by the disease. This helps us to study very early consequences of the disease causing mutations and to identify new targets for therapeutic approaches. These neuronal cell culture models also help to screen new compounds before they are tested in animal models and finally come to the clinic in interventional trials.

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

Ataxia

In preparation for interventional trials in spinocerebellar ataxias (SCA) we are part of the EU funded ESMI problem we established diagnostic consortium that is setting up a trial ready cohort for the most frequent genotype, SCA3. Here we coordinate the movement recording project that is supposed to provide an objective outcome measure for trials. We proved the superiority of this motion capture system over clinical measures in the assessment of disease progression in a multi-center setting and in individuals at risk to develop SCA, i. e. first degree relatives of patients (Ilg et al., in preparation). Further, we performed the first multi-centric assessment on the influence of lifestyle factors on the course of ataxia (Hengel et al. Mov Disord 2022). In the European Friedreich's Ataxia consortium for Translational Studies (EFACTS) we provided natural history data essential for planning of interventional trials in a longitudinal prospective cohort study (Reetz et al. Lancet Neurol 2021). The increasing complexity of autosomal recessive ataxias has been reviewed by our group in Neuron (Synofzik et al. 2019) with a focus on genetics and trial readiness. We clearly show that genetic stratification of

cohorts and quantitative markers of disease activity are key for the development of new therapeutic options in hereditary ataxias.
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)
HSP is a group of neurodegenerative diseases of the spinal cord with the clinical hallmark of progressive spastic gait disorder. Although rare, HSP is highly heterogeneous with more than 80 genetically defined subtypes. We took advantage of a large cohort of >1000 HSP patients seen in Tübingen and collaborative centers to analyse neurofilament light chain as a biomarker in CSF. Levels of CSF NfL were significantly increased in patients with hereditary spastic paraplegia compared to controls (Kessler et al. Ann Clin Transl Neurol 2021). In a genotype specific analysis we found serum levels of NfL to be significantly increased in SPG4 as the most commons HSP subtype especially in younger patients. As serum NfL levels were stable In longitudinal assessment sNfL may be valuable as a therapy response rather than a progression biomarker. (Kessler et al. Ann Clin Transl Neurol 2022)
Many autosomal recessive types of HSP are caused by loss of function mutations in the respective genes. This makes supplementation of DNA (by gene transfer), RNA or protein promising approaches. We set out to explore the therapeutic potential of a RNA-based therapy in SPG5 that is caused by loss of function mutations in CYP7B1 coding for a cytochrome important for oxysterol degradation in the liver (Schöls et al. Brain 2017). In cooperation with the CureVac Company in Tübingen, we tested the application of human CYP7B1 RNA to mice that lack the endogenous Cyp7b1 gene. We found a single-dose injection of CYP7B1 RNA to decrease the amounts of oxysterols drastically in liver as well as in blood within 2 days. Pharmacokinetic studies indicated the effect to last for about 5 days. Repetitive applications of RNA were safe for at least 4 injections and resulted in a significant reduction of neurotoxic oxysterols not only in liver and serum but also to some extend in the brain after 17 days (Hauser et al. Mol Ther Methods Clin Dev 2019).

Leukodystrophies
Leukodystrophies and hereditary leukoencephalopathies are frequently regarded as disorders of childhood. In Tübingen we see more than 300 patients with adult forms of these rare diseases. Cerebrotendinous xanthomatosis (CTX) is a rare multi-systemic leukodystrophy leading to progressive movement disorder and dementia due to loss of function of the cytochrome CYP27A1 in the liver. To improve pathophysiological understanding of disease we performed deep metabolic profiling in serum, cerebrospinal fluid, and brain of patients with CTX and studied therapeutic responses to treatment with chenodesoxycholic acid (Höflinger et al J Lipid Res 2021).

New neurological disease genes
In close collaboration with the Institute of Medical Genetics (Prof. Rieß) and rare disesease networks we were able to prove autosomal recessive mutations in UGDH to cause developmental epileptic encephalopathy (Hengel et al. Nature Comm 2020). We further proved bi-allelic loss-of-function variants in BCAS3 to result in a syndromic neurodevelopmental disorder (Hengel et al. Am J Hum Genet 2021). In a large internation consortium we could show that mutations in ATG7 impair autophagy and lead to severe developmental deficits (Collier et al. NEJM 2021).

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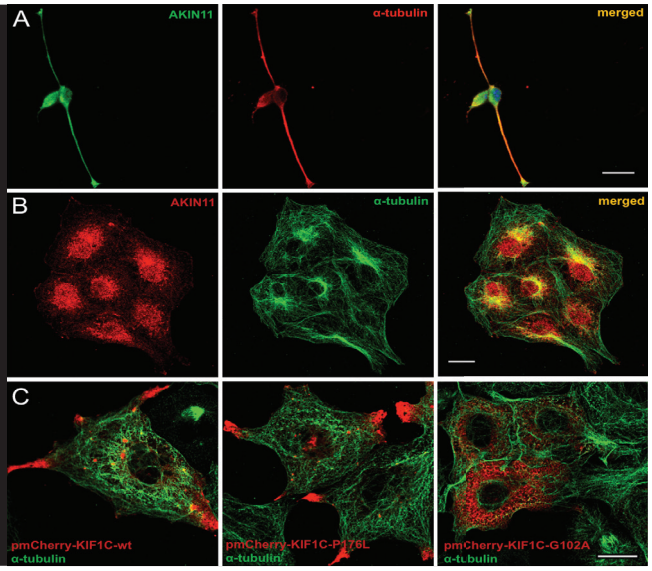
Genomics of Rare Movement Disorders

Head: PD Dr. Rebecca Schüle
Team: 13 members
Key words: rare movement disorders / mutation-specific therapies / antisense oligonucleotides / RNA therapies / genomics and transcriptomics / induced pluripotent stem cells / CRISPR/Cas9 / translational medicine / clinical trials



Subcellular localization of endogeneous and overexpressed KIF1C

Rare disease by definition affect not more than 5 in 10.000 people and yet, about 6-8 % of the population are affected by on of ~6.000 rare disease recognized by the European Union. Yet, 95% or rare diseases lack a curative or disease-modifying treatment option. Inspired by recent technological advances in RNA therapy, we have teamed up with like-minded colleagues from across Europe to launch the 1 Mutation – 1 Medicine consortium (1M1M), seeking to develop mutation-specific RNA therapies for individuals with ultrarare neurological diseases. We furthermore systematically addresses challenges specific to rare diseases, including definition of standard of care, validation of trial outcome parameters, performance of natural history studies, identification of novel disease genes and new therapeutic targets, disease modeling in cell culture and iPS-derived human model systems, preclinical and clinical trials. Supported by the Federal Ministry for Education and Research (BMBF), the European Union, the National Institutes of Health (NIH), the Spastic Paraplegia Foundation Inc. and others, we collaborate internationally to promote trial readiness in rare diseases.

Seltene Erkrankungen betreffen definitionsgemäß nicht mehr als 5 in 10.000 Personen und doch sind ca. 6-8 % der Bevölkerung in der Europäischen Union von einer der rund 6.000 seltenen Erkrankungen betroffen. 95% der seltenen Erkrankungen sind derzeit ohne kurative oder den Erkrankungsverlauf modifizierende Behandlungsmöglichkeiten. Inspiriert durch jüngste Fortschritte in der RNA Therapie haben wir gemeinsam mit Partnern aus ganz Europa das ‚1 Mutation – 1 Medicine' Konsortium (1M1M) gegründet, das mutationsspezifische RNA-Therapien für Individuen mit ultraseltenen neurogenetischen Erkrankungen entwickelt. Des weiteren stellt sich unsere Forschungsgruppe systematisch den Herausforderungen, die einer Therapieentwicklung für seltene Erkrankungen im Wege stehen: Definition von Therapiestandards, Validierung von Zielparametern für klinische Studien, Studien des natürlichen Verlaufes, Identifizierung neuer Erkrankungsgene und Ansatzpunkte für Therapien, Erkrankungsmodellierung in Zellkultur und humanen Stammzellmodellen, sowie die Durchführung präklinischer und klinischer Studien. Gefördert durch das Bundesministerium für Bildung und Forschung (BMBF), die Europäische Union, die amerikanischen 'National Institutes of Health' (NIH), die Spastic Paraplegia Foundation Inc. und andere kooperieren wir hierbei mit Forschungsgruppen aus der ganzen Welt, um 'Trial Readiness' für seltene Erkrankungen zu fördern.

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

Mutations in known genes still explain only about half of the cases. To identify novel mutation types, novel disease genes and ultimately novel therapeutic targets we combine whole exome / genome sequencing with other omics technologies including transcriptomics, metabolomics and proteomics. This work has led to the identification of > 20 novel genes for Hereditary Spastic Paraplegias, Spastic Ataxias and Hereditary Ataxias. Among the recent highlights of the work were the identification of HPDL mutations as a frequent cause of autosomal recessive HSPs. This genomic work is funded by the European Union through funding for the Horizon2020 programme Solve-RD, the BMBF and the NIH in an RO1 grant awarded to Rebecca Schüle and her collaborator Stephan Zuchner from the University of Miami, Florida.

To promote trial readiness in HSP we have initiated and coordinate the TreatHSP translational network for

HSPs and related disorders. TreatHSP is funded by the Bundesministerium für Bildung und Forschung (BMBF). TreatHSP.net concentrates its translation-oriented research approach on pathophysiological key pathways of HSP (mitochondrial – ER/microtubule-related – endo-lyso-autophagosomal related) that unify multiple and frequent forms of HSP. To make substantial progress towards implementation of novel therapies TreatHSP.net (i) is generating a shared infrastructure that provides federated access to clinical data, biological samples and OMICS data for TreatHSP.net and beyond, (ii) is systematically developing and validating outcome parameters for clinical trials including sensor-based, patient- and caregiver-reported as well as molecular outcomes, (iii) is using unbiased high-throughput approaches in murine as well as stem cell-derived human models of HSP to identify shared pathways and novel therapeutic targets, and (iv) prioritizes drug-repurposing strategies to evaluate novel therapeutic approaches in preclinical trials that promise rapid translatability to human trials.

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

The 1 Mutation – 1 Medicine consortium (1M1M) which is jointly coordinated by the Universities of Tübingen and Leiden is dedicated to making mutation-specific ASO therapies available to eligible patients with severely debilitating or life-threatening (SDLT) rare neurological diseases caused by nano-rare cryptic splicing mutations in a sustainable, scalable, time-critical and safe manner. 1M1M has set up a platform to select suitable patients, drawing on large research-driven genomic databases as well as diagnostic pipelines and streamlined preclinical and clinical development of ASO therapies towards first-in-human application, working closely with regulators. This highly innovative platform collaborates closely with the international N-of-1 ASO collaborative.

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Deep Brain Stimulation

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

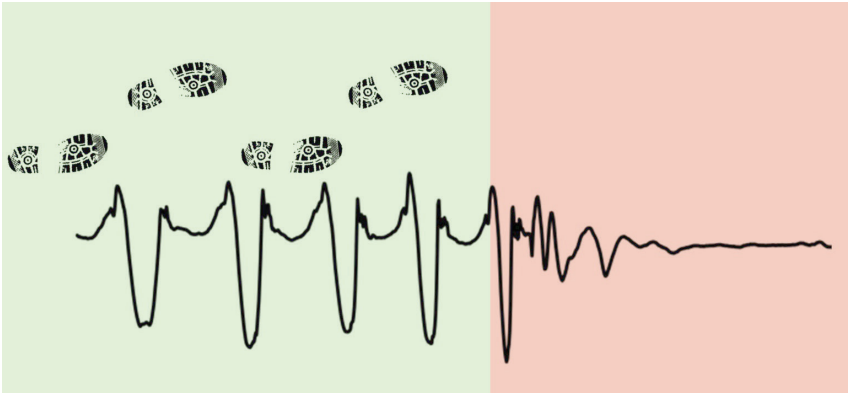
The research group for deep brain stimulation (DBS) strives for refining and expanding neurostimulation therapy for movement disorders therapy by interfering with functional large-scale functional circuits. We give particular emphasis to modulate otherwise resistant axial symptoms of Parkinson's disease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

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

Clinical studies: making DBS available for resistant axial symptoms

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

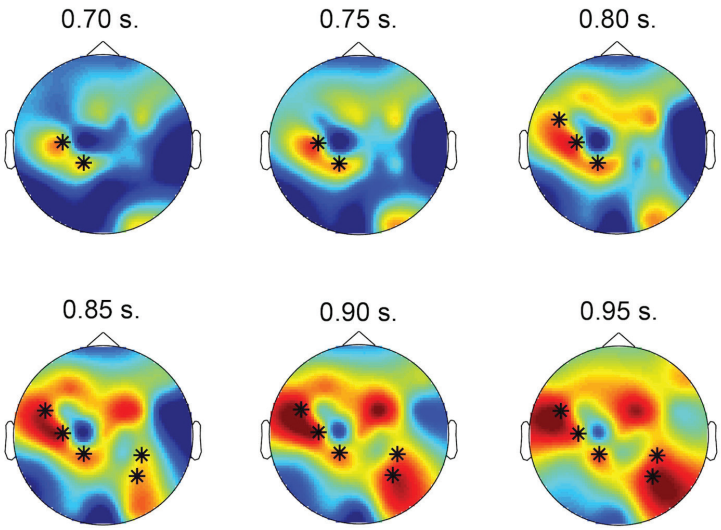
In this framework, we take advantage to co-stimulate the substantia nigra pars reticulata in addition to the subthalamic nucleus as distal electrode tip of a subthalamic lead. First clinical observations were made between 2009 – 2011 [1], and further substantiated by a monocenter randomized controlled trial. This trial pointed to an additional effect of nigral co-stimulation to attenuate otherwise resistant freezing of gait [2]. The Tübingen working group for 'deep brain stimulation' coordinated and finished a randomized controlled multicentre trial with 12 DBS expert centres (ClinTrials.gov: NCT02588144). Moreover, a monocenter trial was finished to study the effect of nigral stimulation with respect to resistant dysphagia in PD. This approach is plausible from pathophysiological reasoning, i.e. nigral overactivity may lead to defective neuronal integration of PD swallowing and oral transport in the substantia nigra pars reticulata – superior colliculus circuit. The ongoing clinical trials have potential to inform future personalized both DBS implantation and re-programming strategies in PD patients.



De-mystifying the pathophysiology of freezing phenomena

Freezing phenomena in Parkinson's disease were paraphrased as 'enigmatic phenomena'. Most obviously, this reflects the profound lack of pathophysiological understanding about the underlying brain and circuit mechanisms (Weiss et al., 2019).

Technological advancement enabled only in recent years to obtain mobile recordings from PD patients during real gait experiments and characterization of defective neuromuscular gait integration on high both temporal and spatial resolution. We conduct fully synchronized and mobile recordings with motion kinematics, EEG, EMG, 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 [3-5]. Even more important, we are increasingly able to characterize the transition periods between regular gait and freezing in PD patients. This is of utmost importance to develop freezing forecasts, i.e. to predict the disruption of locomotion several seconds before the network disturbance becomes clinically apparent in terms of freezing of gait.



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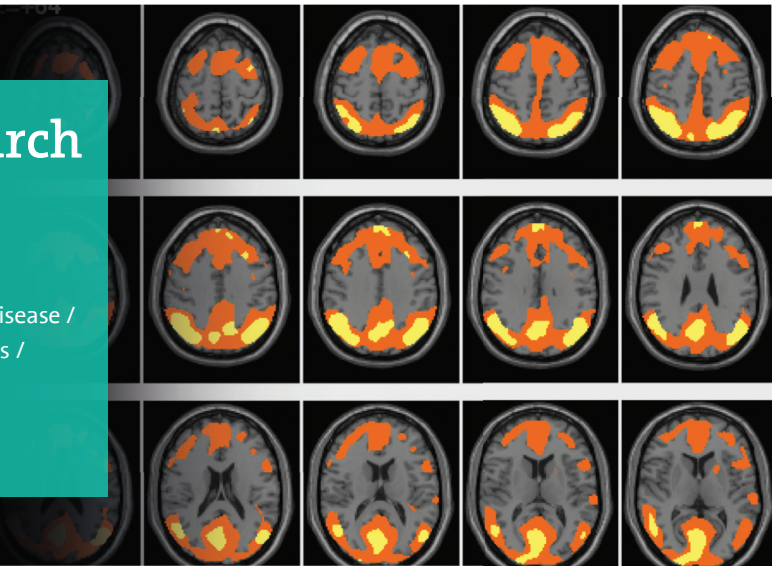
Clinical Parkinson Research



Head: PD 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 real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA) 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 with RT-QuIC 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]. 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 [12].

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Mitochondrial Biology of Parkinson's Disease

Head: Dr. Julia Fitzgerald
Team: 5 members
Key words: Parkinson's disease / atypical parkinsonism / mitochondria / PINK1 / MIRO1 / TRAP1 metabolism / neurochemistry / 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. These models also provide a platform for testing compounds (that target Miro1) as a potential therapy.

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 those markers that are retained in the blood as well as in the brain.

Mitochondrial Parkinson's Disease: Human Dopaminergic Neuronal Models

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

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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.

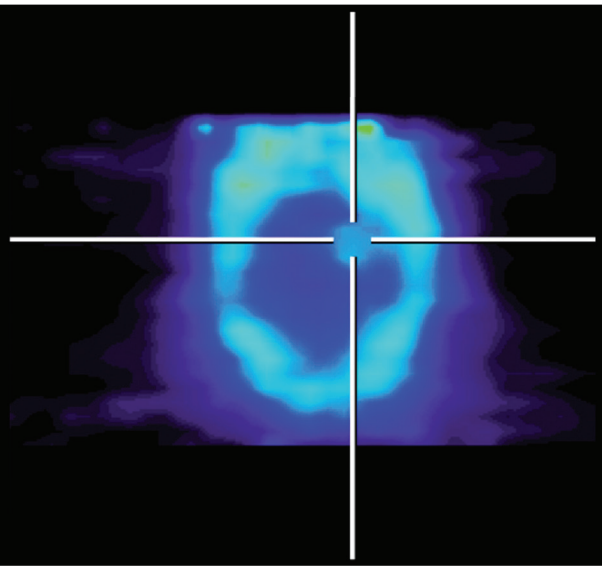
Neuro-Oncology is also represented and a major area in the Comprehensive Cancer Center Tübingen-Stuttgart. The Center of Neuro-Oncology forms a multidisciplinary network of all clinical disciplines, and the Department of Neurology with Interdisciplinary Neuro-Oncology is an integral part of the CNO,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

Experimental and Clinical Neuro-Oncology

Head: Prof. Dr. Dr. Ghazaleh Tabatabai
Team: 22 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. Some 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. 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

Treatment-induced vulnerabilities in glioma

We analyzed molecular and immunological alterations after a combination therapy of radiotherapy and temozolomide or radiotherapy and lomustine with oncolytic measles vaccine virus in vitro, identified the synergistic treatment sequence, performed bulk RNA sequencing and identified a treatment-induced inflammatory phenotype. Furthermore, we identified treatment-induced upregulation of TAP-1 and other relevant components of antigen processing and presentation pathways. Thus, we also analyzed the immunopeptidome and identified a novel treatment-induced new immunogenic MHC-class I peptide. These data could help to evaluate novel therapeutic strategies like using a peptide vaccination with the novel MeV-L peptide (Rajaraman et al., 2018). Another example is our study on targeting the glioblastoma-associated cellular micromilieu including microglia with tumor-promoting effects. Treatment with CSF1R antibody in our syngeneic SMA560/VM/Dk mouse model in vivo resulted in a reduction of macrophages and an increase in tumor-infiltrating CD8+ T cells. The combination of CSF1R and PD1 antibody treatment showed a synergistic anti-glioma effect especially when CSF1R (but not PD1) antibody was administered first. Thus, this new combination therapy could be evaluated in the future for glioblastoma patients (Przystal et al., 2021).

Novel preclinical model: patient-derived microtumors and autologous tumor-infiltrating lymphocytes

In cooperation with the group of Dr. Christian Schmees at the NMI Natural and Medical Sciences Institute in Reutlingen, we developed a new preclinical model of patient-derived microtumors (PDM) and autologous tumor-infiltrating lymphocytes (TILs) that we have successfully used in two recently published studies (Przystal et al., 2021; Walter et al., 2021). This model is particularly interesting because preclinical studies are usually restricted to cell culture models in vitro or mouse models in vivo. Cell culture models are limited by the fact that they do not reflect the entire tissue network. Xenograft models with transplanted human glioma cells in vivo cannot be used to investigate tumor cell/host cell interaction because the recipient CD1nu/nu mice are immunodeficient. Syngeneic glioma mouse models, on the other hand, do not allow the analysis of the behavior of human cell lines. Therefore, we established this 3D microtumor model in which patient-derived microtumors (PDM) can be generated from residual freshly resected tumors. Of note, this process allows the isolation and expansion of autologous tumor-infiltrating lymphocytes (TILs) and consequently, through PDM/TIL co-culture, a new "immune competent" model ex vivo, which closes a methodological gap.

Loss of H3 K27me3 in meningioma

The aim of this study was to assess the prognostic value of H3K27 histone trimethylation and its potential clinical utility in the „Tübingen meningioma cohort." To this end, we investigated tumor tissue of meningioma patients who underwent meningioma resection between October 2003 and December 2015 at the University Hospital Tübingen. Immunohistochemical stainings for H3K27me3 and the proliferation marker MIB1 were assessed and correlated with clinical parameters using univariate and multivariate Cox regressions as well as Pearson's chi-squared and log-rank test. Overall, we analyzed 1268 meningiomas with a female to male ratio of 2.6 and a mean age of 58.7 years (range 8.3-91.0). With 163 cases lost to follow up, 1103 cases were available for further analysis with a mean follow-up of 40.3 months (range 1.1-186.3). Male gender, younger age, intracranial tumor localization, progressive tumor, subtotal resection, higher WHO grade, increased MIB1 rate, and loss of H3K27me3 were significant negative prognostic factors in the univariate analysis. H3K27me3 status and all other prognostic factors, except age and tumor location, remained significant in the multivariate model. Furthermore, adjuvant radiotherapy was an independent positive prognostic factor. We concluded that loss of H3K27me3 combined with MIB1 labeling index are independent prognostic factors in meningioma. These data support the clinical utility of H3K-27me3 immunohistochemical staining in meningioma and its integration into the diagnostic routine (Neuro Oncol. 2021 Aug 2;23(8):1273-1281)

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Experimental Pediatric Neuro-Oncology

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

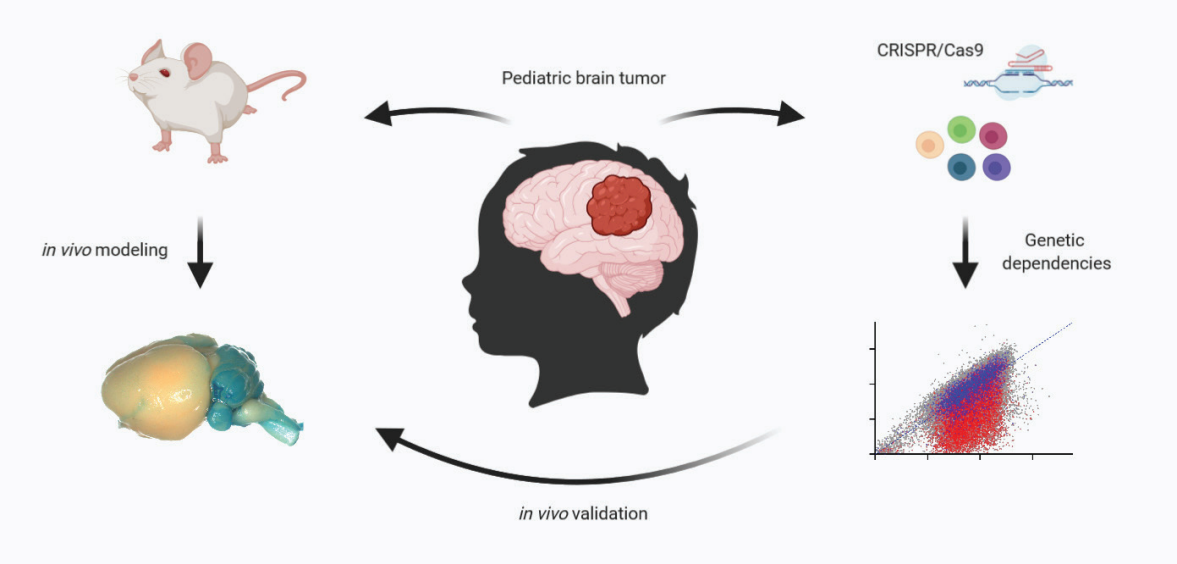
Our objective is to develop targeted therapies for rare brain tumors preferentially arising in young children. To this end, we are employing functional genome-wide screens to identify genomic vulnerabilities that will potentially guide the development of novel therapeutic interventions for these tumor 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. 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: PD Dr. Mirjam Renovanz
Team: 7 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. We could recently show that neuro-oncological patients are highly burdened independent of their tumor entity. However, 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 currently evaluate alternative assessment methods, e. g. the direct assessment of unmet needs during the patient-doctor consultation in high-grade glioma patients, as well as the development of an app-based assessment of health-related quality of life.

*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 und wir entwickeln eine App-basierten Erhebung der Lebensqualität für Patient*innen in speziellen Behandlungssituationen.*

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 a multicenter cluster randomized study with two arms. The intervention includes 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, 600 HGG patients were enrolled so far (intended: 770). The primary outcome is the number of HGG patients with increased psychosocial distress who receive professional support from psychosocial services. Secondary endpoints are inter alia number of patients reporting psychosocial distress and unmet needs detected correctly by the respective method.

Our hypothesis is that an assessment conducted directly by attending doctors and in which the doctors talk to patients with HGG will be more effective than an assessment via a questionnaire, leading to better identifying patients in need of support. This may lead to an improvement of health care in these patients. Further, this method might be implemented also in other brain tumor patients (e.g., patients with brain metastases). 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 is a pilot test including usability and feasibility assessment, which is ongoing. So far, we included 8 patients.

The aim is to evaluate the app in 2022, to optimize it accordingly and to enroll a multicenter application study thereafter.

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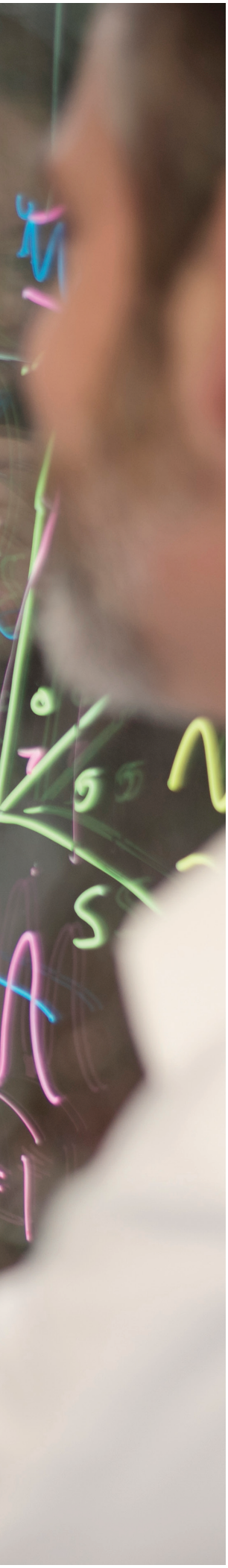
Department of Neural Dynamics and Magneto-encephalography



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, the Department of Psychiatry and Psychotherapy and the Department of Psychosomatic Medicine.

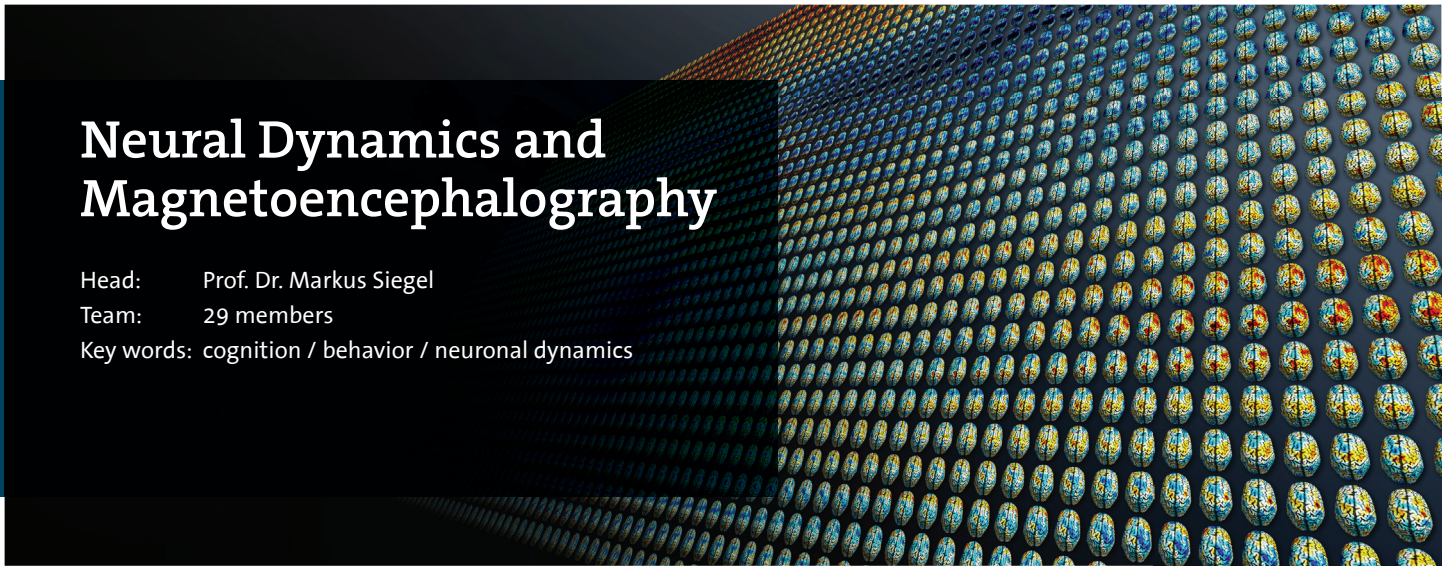
In addition to its primary research group, the department operates the Tübingen MEG Center, which is a core research facility of the Medical Faculty and University Hospital. The MEG Center provides state-of-the-art MEG techniques and services to the entire Tübingen neuroscience community. The MEG Center 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 7 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

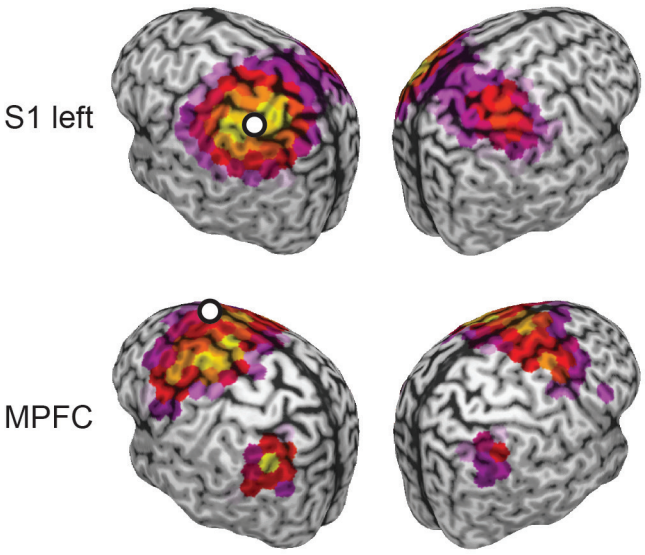
Neural Dynamics and Magnetoencephalography

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



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

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



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

The brain is a highly dynamic and distributed system. How do sophisticated cognitive processes such as perception, memory, decision-making, and motor behavior emerge from dynamic interactions across the brain? Which neural mechanisms coordinate these 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, and sophisticated analytical techniques.

Spectral Fingerprints of Normal and Diseased Brain Function

One focus of the lab are oscillatory dynamics of neuronal activity. Brain activity exhibits oscillations, i.e. periodicity, at 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.

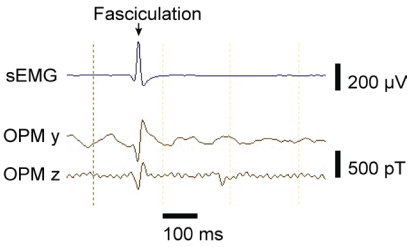
In one line of research, we investigate these spectral fingerprints with MEG in the resting human brain. We investigate how networks of brain regions spontaneously coordinate their oscillations at different frequencies and how these large-scale oscillatory interactions are altered in the diseased brain. Our recent results show that, based on their amplitude and phase, brain rhythms are coupled in two distinct modes that are expressed in different brain networks and with different dynamics. Together with our clinical collaborators, we investigate these rhythmic networks as novel biomarkers of different neurological pathologies, such as e.g. Multiple sclerosis (with the Dept. of Neurology with Neurovascular Medicine) and Epilepsy (with the Dept. of Neurology and Epileptology). Furthermore, we investigate the temporal microstructure of different brain rhythms and 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 recent results show how sensory, cognitive, and motor neuronal information can be non-invasively decoded from the human brain, how this information flows across the brain and how such information relates to cortical spiking activity. Together with our clinical collaborators (University Clinic for Psychiatry and Psychotherapy, University Eye Hospital, University Clinic for Otolaryngology), we investigate alterations of neuronal dynamics during pathological conditions, such as e.g. dyslexia in children, schizophrenia, and spatial hearing in cochlear implant users.

Magnetomyography

A recent focus of our research is on magnetomyography (MMG), i.e. the measurement of magnetic fields generated by muscle activity. The development of so-called optically pumped magnetometers (OPM) has enabled flexible and contact-free MMG without the need of cryogenic cooling. Together with our collaborators (Physikalisch-Technische Bundesanstalt Berlin, University of Stuttgart) and clinical partners (Dept. of Neurology and Epileptology), we investigate OPM-based MMG for basic research and clinical applications.



Simultaneous recording of a muscle fasciculation with traditional surface EMG (sMEG) and with contact-free OPM-based magnetomyography (OPM y/z).

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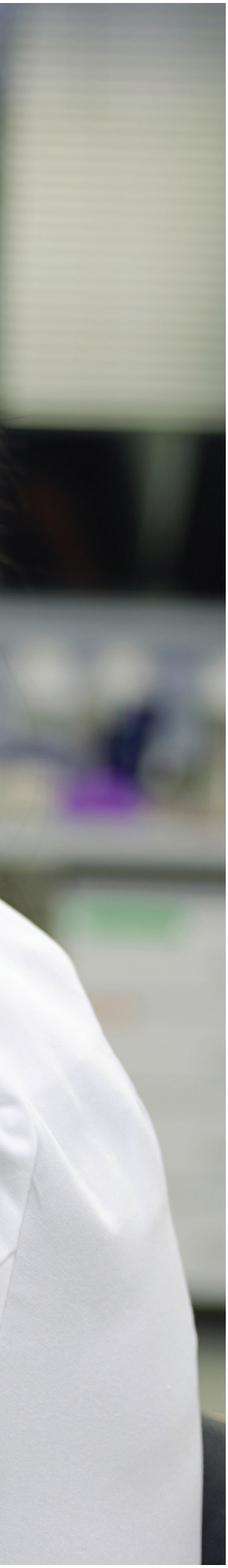
Department of Cellular Neurology



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.

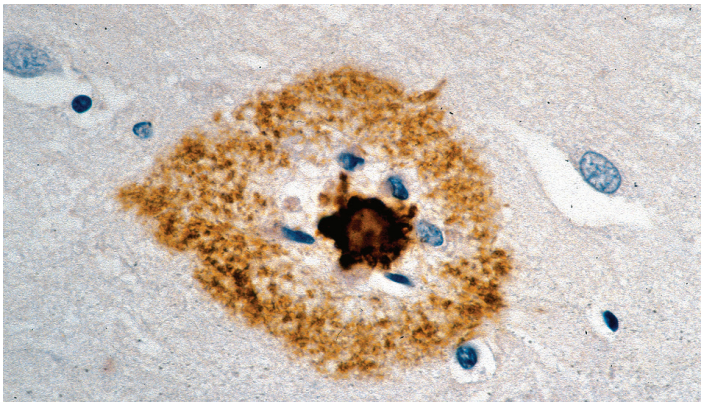
We also coordinate the international Dominantly Inherited Alzheimer Network (DIAN) study in Germany, which aims to understand the rare genetic forms of Alzheimer's disease by longitudinal analysis of gene mutation carriers and non-mutation carrier siblings. Understanding this type of Alzheimer's disease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

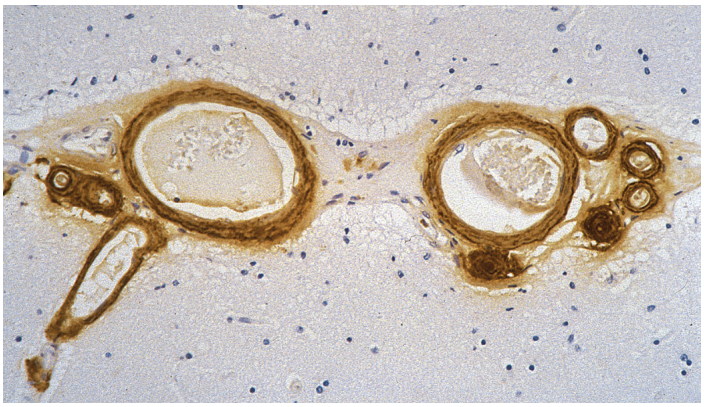
- Experimental Neuropathology
- Experimental Neuroimmunoloy
- Glia Biology unit
- Molecular Biomarker unit
- Dementia Research unit (clinical)

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

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



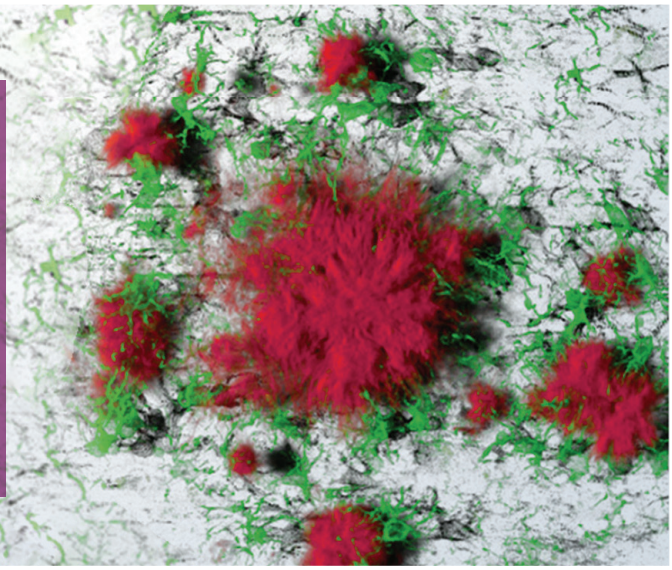
Amyloid plaque (Aβ immunochemistry) in an Alzheimer brain.



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

Experimental Neuropathology

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



Microglia (green) surrounding an amyloid plaque (red)

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

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

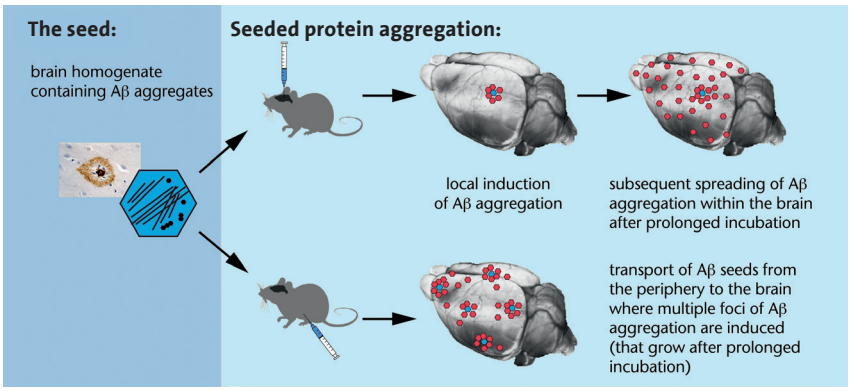
Misfolded proteins are the cause of many neurodegenerative diseases. How these proteins misfold and what the initial trigger is for the misfolding and their subsequent aggregation is, however, largely unknown. Furthermore, it remains unclear why the aging brain is a risk factor for neurodegenerative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

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

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

These observations are mechanistically reminiscent of prion diseases and are now used to develop new therapeutic approaches for Alzheimer's disease and other amyloidoses. First immunotherapy trials in transgenic mice are promising and show that β-amyloid aggregation can be reduced by targeting the initial proteopathic Aβ seeds. Microglia appear to play a crucial role in Aβ immunotherapy and also play an important role in early pathogenesis. To this end, we now use in vivo 2-photon microscopy to track 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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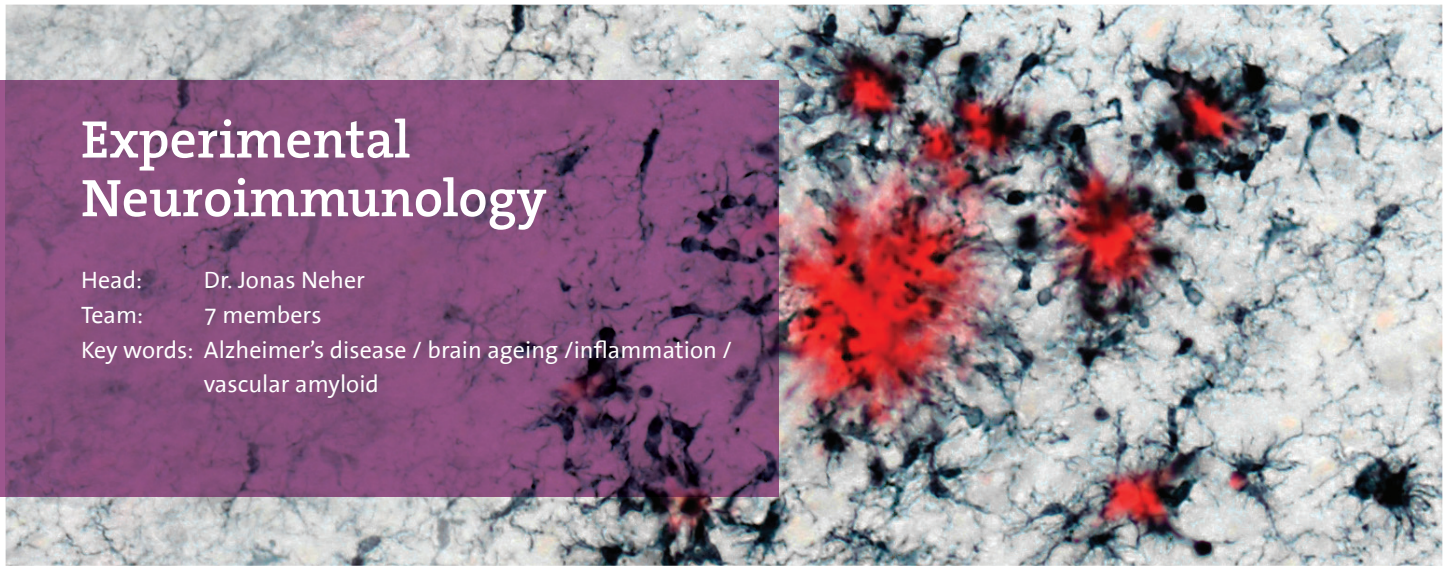


Experimental Neuroimmunology

Head: 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 the brain's immune system contributes to the pathogenic mechanism of neurodegenerative diseases and to develop therapeutic interventions that target the immune system.

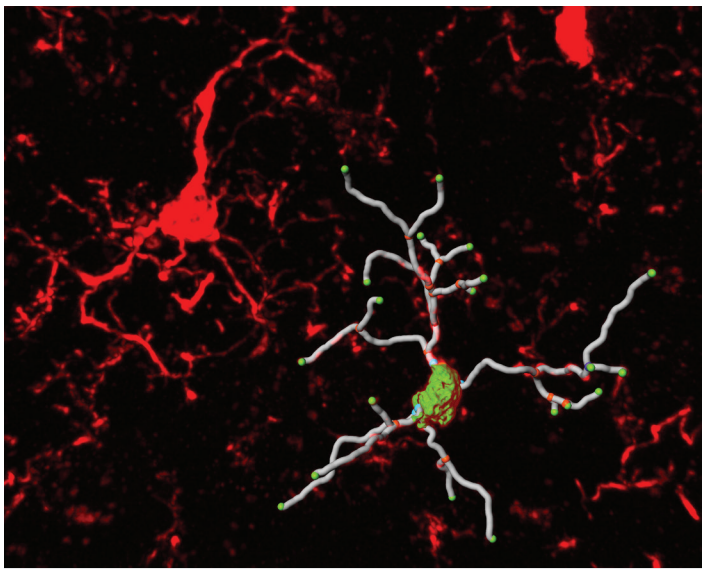
Unser Ziel ist es, die pathogenen Mechanismen der Alzheimer-Erkrankung zu verstehen, um aus diesen Erkenntnissen therapeutische Interventionen zu entwickeln.

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 altered 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 have 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). Because dysfunction of blood vessels is also an important contributor to AD and dementia, we are now working on understanding the role of medin in Alzheimer's disease by studying mouse models as well as human tissue.



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

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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.

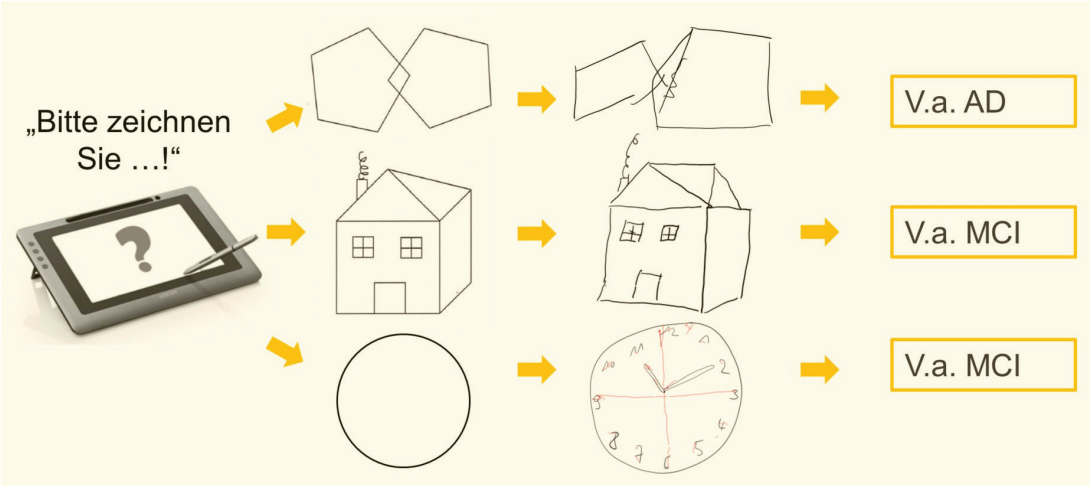
Die Unit Demenzforschung ist eine gemeinsame klinische Forschungsgruppe der Abteilung für Zellbiologie neurologischer Erkrankungen und der Universitätsklinik für Psychiatrie und Psychotherapie. Die Unit arbeitet eng mit der Gedächtnisambulanz der Universitätsklinik zusammen.

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 ▣-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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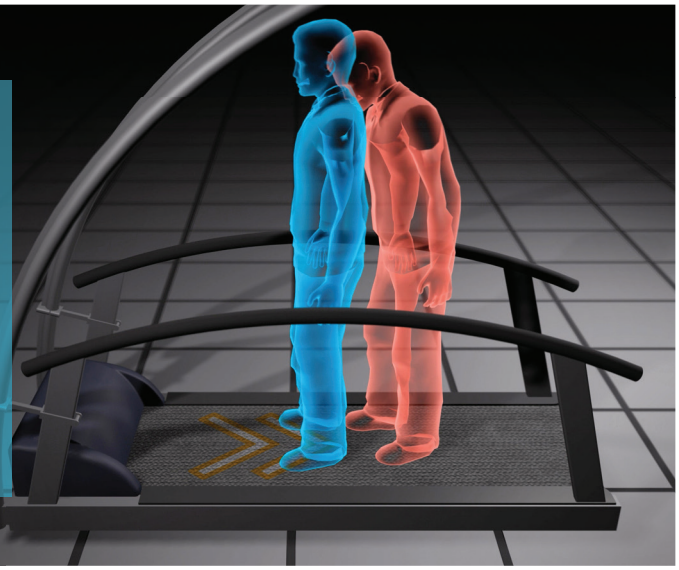
Independent Research Groups

Computational Sensomotorics

Head: Prof. Dr. Martin Giese
Team: 22 members
Key words: sensorimotor control / motor learning and rehabilitation / social perception / neural modeling / technical applications in neurology and psychiatry / neurostimulation



The Section Computational Sensomotorics investigates theoretical principles of the perception and control of motor behavior and associated technical applications. Our recent research addresses four problems:

Die Sektion Theoretische Sensomotorik erforscht die theoretischen Prinzipien der Erkennung und Steuerung motorischer Handlungen und assoziierter technischer Anwendungen. Unsere Forschung konzentrierte sich dabei auf vier Themen:

Movement analysis of everyday life walking behavior in neurodegenerative movement disorders
Changes of movement behavior in neurodegenerative disorders, such as cerebellar ataxia, 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-specific signatures of movement degeneration.

In addition, to serve as progression and treatment outcome biomarker in therapeutical trials, movement measures have to be ecologically valid for regulatory approval. This makes the quantitative characterization of movement behavior and in everyday life an important problem. Such situations include complex forms of locomotion or full body movements like turning, which are typical for everyday activities. Technically, the assessment of such everyday behavior raises fundamental challenges. First, the assessment of the movement has to be realized with wearable devices, such as inertial sensors, which often are less accurate than in-laboratory assessment techniques such as optical motion capture. At the same time, the analysis of the acquired data poses much more difficult problems in terms of pattern recognition. Behavior in natural situations often cannot be categorized easily in terms of prototypical actions. People may realize multiple tasks simultaneously, and individual behaviors might be executed in quite variable individually-specific styles. We have studied the analysis of such everyday-relevant behaviors in cerebellar ataxia patients in collaboration with Profs. M. Synofzik and L. Schöls (Dept. of Neurodegeneration). Based on inertial sensor data, we have developed ecologically valid biomarkers exploiting machine learning methods, which are also useful for the validation of the beneficial effects of motor training in preclinical populations.

Wearable support systems for diagnosis and behavioral training in psychiatric diseases
Many psychiatric diseases result in deficits of everyday capabilities, requiring diagnosis and treatment in situations with relevance for everyday activities. An example are Obsessive-Compulsive Disorders (OCD), where patients might be suffering from anxiety that is caused by specific trigger stimuli in everyday situations, resulting in compulsive behavior.

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

Sometimes these trigger stimuli are not even conscious. This makes it desirable to observe the patient in everyday context and to analyze 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, inertial sensors for movement analysis, eye tracking and the online assessment of physiological measures such as heart rate, allows a monitoring of such patients outside the laboratory. We develop computer vision-based methods for the analysis of the generated data. Such systems have the potential to develop personalized bio-feedback systems for behavioral training, providing online feedback and appropriate behavioral instructions when trigger stimuli are identified in the actual scene. This would be a step towards wearable systems for behavioral training in real-world situations, where training with a psychotherapist is not feasible or cost-efficient.

Neural and computational principles of social perception

In the context of a HFSP project (together with D. Tsao (CALTECH) and A. Martinez (Ohio State Univ.)) we had developed a highly realistic macaque face avatar, which meanwhile can be even operated in real-time exploiting the game engine UNREAL. In collaboration with the laboratory of P. Thier (HIH) this avatar face was tested in monkeys, showing that the avatar is perceived as equally realistic as real movies of monkey expressions. In this 'Uncanny valley' study the same dynamic expressions were shown as real movies, and using the avatar and different degraded versions of it. In a related psychophysical study that showed monkey and human facial expressions, and morphs between them, to human observers. Unexpectedly, we found that the recognition of facial dynamics is largely independent of facial shape. This explains why our participants spontaneously recognized human expressions on monkey faces without prior training, and why we can recognize facial expressions even from highly unnatural comic characters like the 'sponge bob'. We have developed a neural model that explains this face shape-independent encoding of facial expressions. This model reproduces psychophysical data on facial expressions recognition and electrophysiological results from the Superior Temporal Sulcus, obtained by the group of P. Thier. Further extensive work as part of the ERC Synergy project RELEVANCE has been dedicated to the development of technology to realize accurate video tracking of body movements of monkeys (together with R. Vogels, KU Leuven), and to the testing of first neural models that reproduce the invariance properties of neurons in body patches in macaque cortex.

Physiological mechanisms of cortical TMS

In a collaboration with the laboratories of C. Schwarz and U. Ziemann, A. Benali has established a preparation that allows to apply Transcranial Magnetic Stimulation (TMS) to rats and to simultaneously record signals from single cells. The method is based on measures that suppress the artifacts induced by the very strong magnetic field on the electrophysiological recording devices, and specifically on the construction of an amplifier that shortcuts the strong electrical signals induced by the TMS coil. After showing that the neural activation dynamics after single-pulse TMS in rat cortex highly resembles the one in human cortex, present work focuses on a precise analysis of the different cortical and subcortical circuits that underlie the induced excitatory and inhibitory electrical response components in motor cortex.

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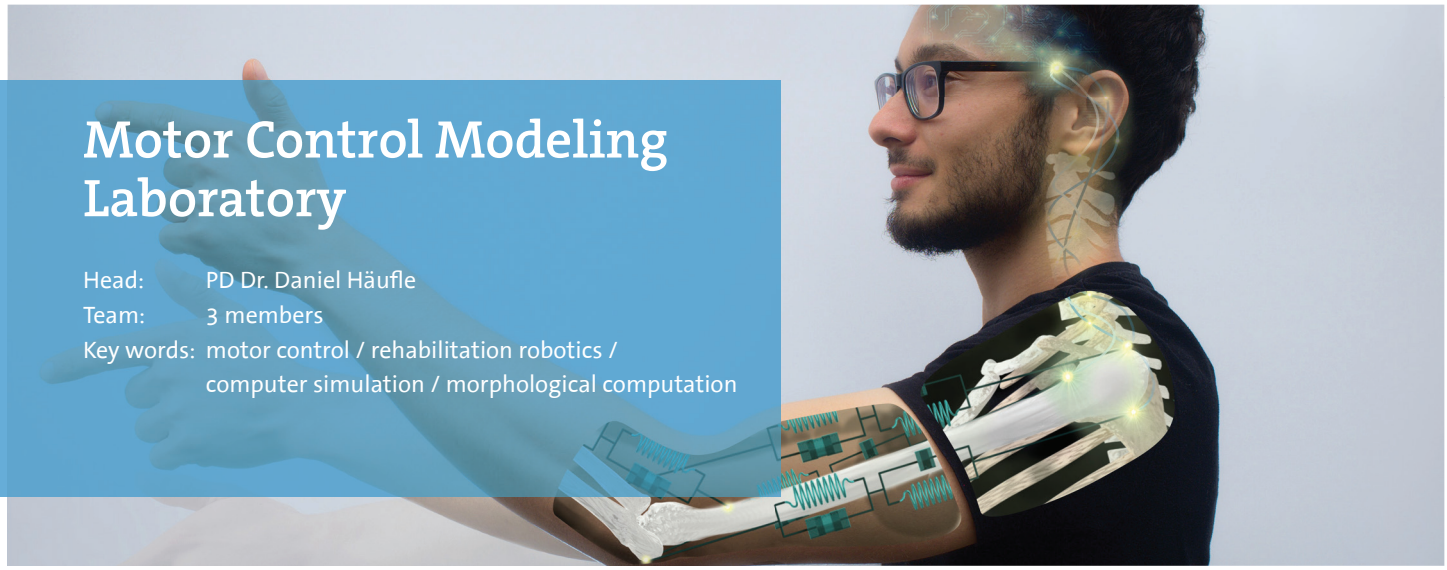


Motor Control Modeling Laboratory

Head: PD Dr. Daniel Häufle
Team: 3 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 the human arm. These models consider the structure of the skeleton with its rather rigid bones and the joints, which allow movement. Muscle models predict forces, which act on the bones via tendons. Other soft tissue models consider passive viso-elastic forces. Finally, a model of sensor signals and spinal neuronal processing allows to estimate a stimulation signal, which controls muscle force and, hence, the movement. All these structures are described by mathematical equations (ordinary differential equations). The benefit of such models is, that we can investigate the contribution of individual structures and neuronal signals to the movement. The goal is to identify the mechanisms of motor control dysfunction and to gain a deeper understanding of the dynamics of impaired control. In this field we work together with the Sections for Computational Sensomotorics (Giese) and Clinical Neurogenetics ((Schöls) and the Department of Neurodegenerative Diseases (Weiß).

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

Biorobotics
We develop robotic platforms as tools to study concepts on biological motor control together with the University of StMPI for intelligent Systems. These tools support the computer

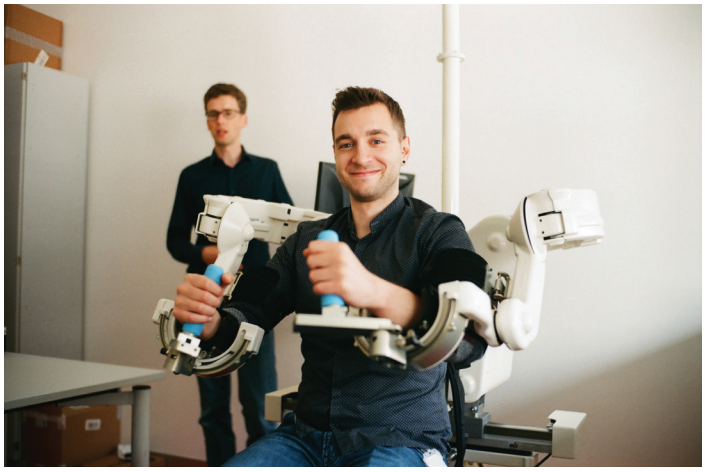
simulations and transfer the concepts into the real world, where biological experiments are not possible.

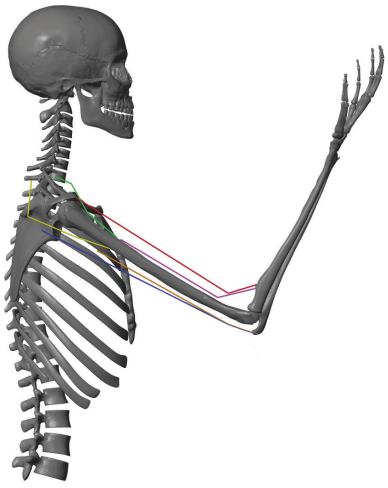
Morphological computation
The concept of morphological computation captures the observation that the physical structures contribute to the control in biological systems. We develop methods to quantify the contribution of the morphology and compare biological systems to robotic systems in computer simulations.

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

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

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





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.

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Active Perception Laboratory

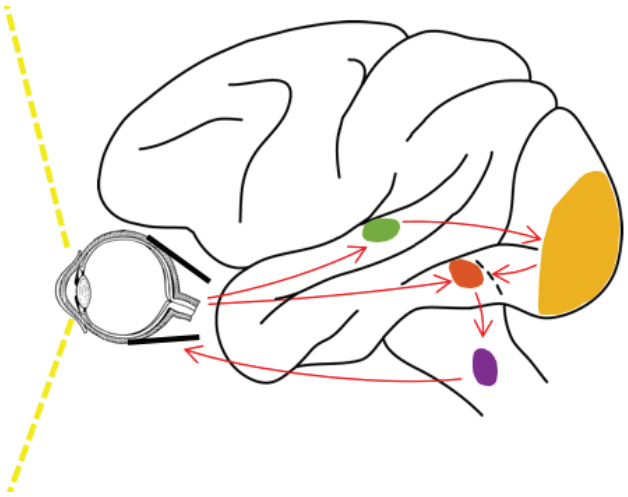
Head: Prof. Dr. Ziad Hafed
Team: 8 members
Key words: visual perception / eye movements / brainstem control of eye movements / perceptual stability / visual field representations

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

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

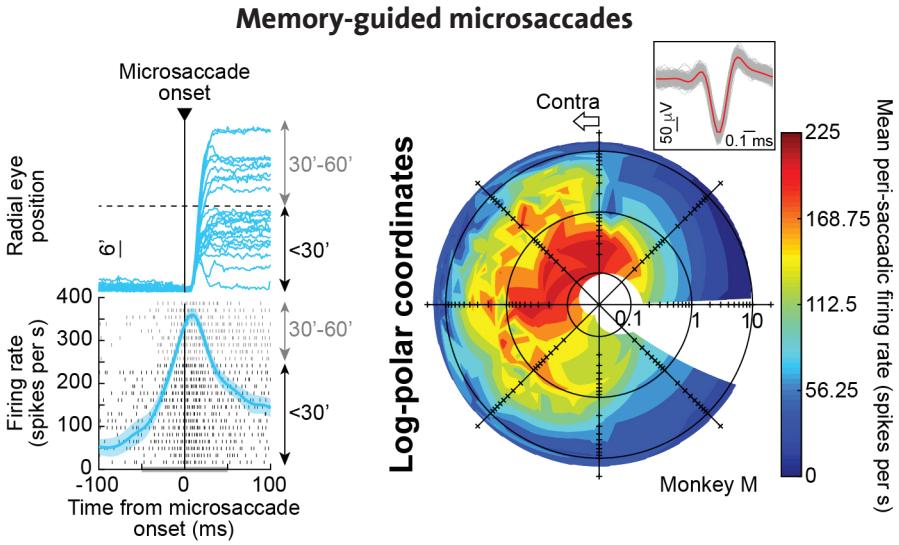
High-resolution vision in humans is only limited to a small area of the visual field. Despite this fact, humans have the perception of a vivid, clear scene throughout the visual field, and this is due to the fact that humans are active observers. By moving their eyes around, humans effectively compensate for the resolution limitations that are inherent in the retina. However, the mere act of moving the eyes creates retinal image shifts and motions that are not present in the real world. The visual brain is therefore perpetually faced with both: 1) a need to move the eyes in order to align the high-resolution portion of the retina with objects of interest, and 2) a need for spurious visual signals caused by eye movements to escape perception in order for us to experience a stable and clear vision of our environment. Our research addresses both of these challenges to visual perception using a multi-disciplinary approach involving human perceptual experiments, invasive neurophysiology in non-human primates, and theoretical modeling. The insights that we gain have strong relevance for understanding clinical orders of stability, balance, and bodily reference frames (e.g. dizziness, vertigo, and so on).

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



Finally, our work investigates action and perception taking into account ecological constraints on brain function. Ultimately, our brain operates in a natural environment and is therefore expected to be optimized to the statistics of this environment. Such intuition implies both anatomical and functional specializations in the eye movement system in order to best serve perception in the natural environment, which we are systematically uncovering.

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



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Systems Neurophysiology Laboratory

Head: Prof. Dr. Cornelius Schwarz
Team: 11 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.

We study the operating principles of the neocortex using modern multi-neuron electrophysiology and optical methods. We have established methods to observe tactile sensorimotor behavior and learning in rodents that let us study neocortical function and its extensive interaction with sub-cortical circuits during highly defined and precisely monitored behavior. The similarity of neocortex in animals and humans suggests that the results will be highly appropriate to inform research on human disease (Alzheimer's, Parkinson's, schizophrenia, and depression).

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

Problem, model system, and methods

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

Research into cortex function requires the combination of a macroscopic and microscopic view – i.e. the study of representation of memories on the cellular level locally and their linkage between cortical areas globally. We employ modern methods of multiple neuron electrophysiology and optical imaging/stimulation and combine it with behavioral observation at highest precision. Our major model for studying these questions is the sensorimotor vibrissal system (vibrissae = whiskers) of rodents. We further study the tactile human fingertip system. Rodents and humans use an 'active' strategy of sampling tactile information about their immediate environment by actively moving their fingertips or vibrissae across objects in their vicinity.

Learning

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

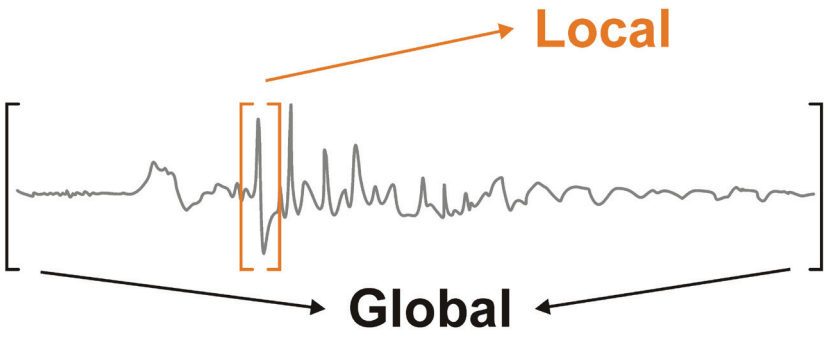
Active tactile exploration of the environment using vibrissae.

Active perception

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

Tactile coding

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



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

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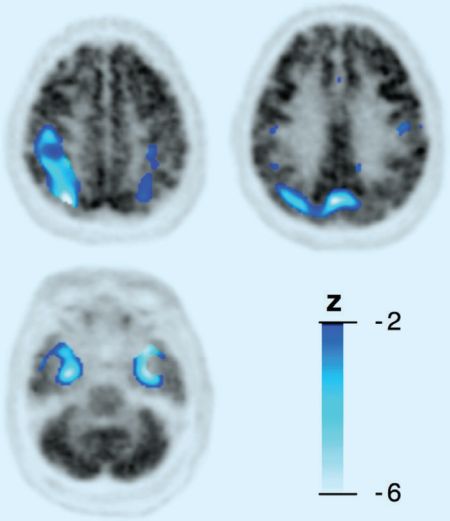
Translational Genomics of Neurodegenerative Diseases

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: preparing and establishing first-in-human treatments for neurodegenerative disease

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.

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 program of even highly individualized "n-of-1" 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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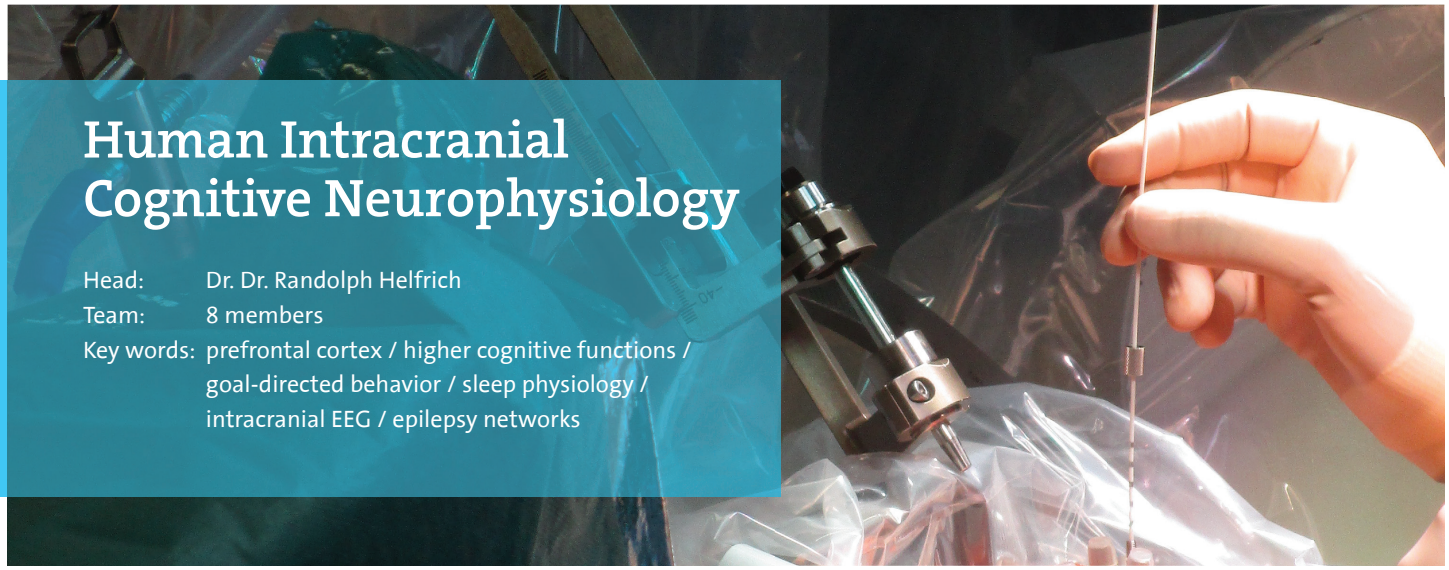


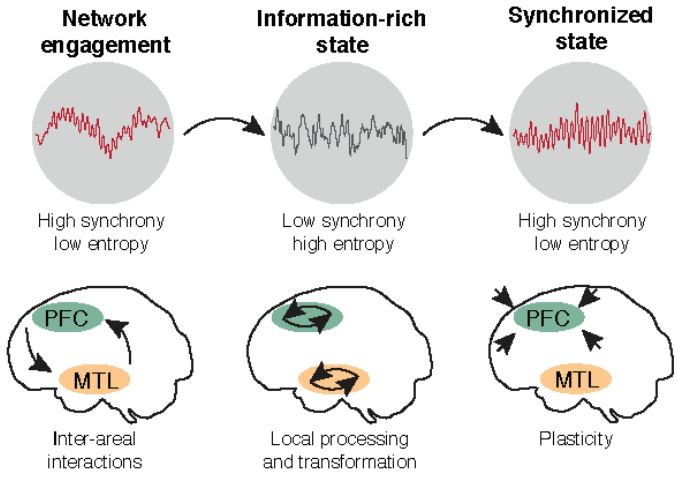
Human Intracranial Cognitive Neurophysiology

Head: Dr. Dr. Randolph Helfrich
Team: 8 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 alleine, 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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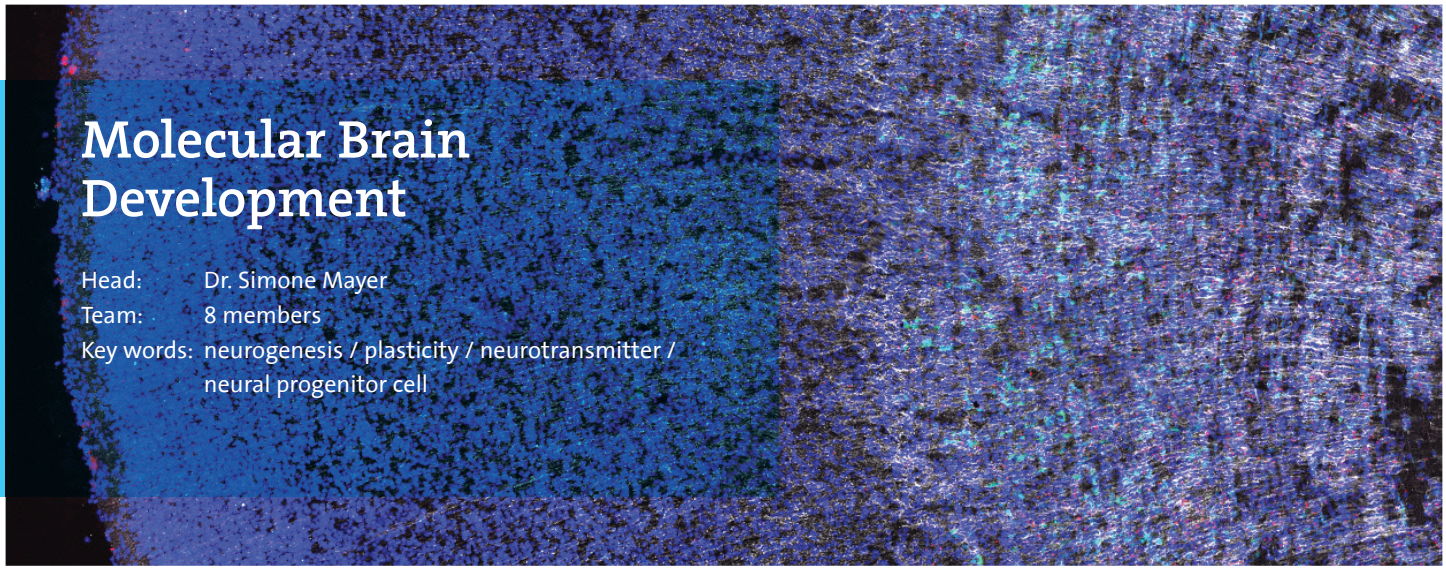


Molecular Brain Development

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

The mammalian brain is a highly complex and spatially heterogeneous structure, which has changed significantly in mammalian evolution. Recent progress in stem cell biology has allowed us to model human brain development in a dish using different organoid protocols giving us unprecedented access to study human-specific features of brain development. In the research group Molecular Brain Development, we are interested in revealing how genetic and environmental factors shape developmental processes in two brain regions, the neocortex and the cerebellum, using organoids. Neocortical networks are at the heart of cognitive function, but their dysfunction is also a cause for a plethora of psychiatric and neurological disorders. While we have gained significant insights into the contribution of genetically "hard-wired" mechanisms of proliferation, differentiation, and maturation in the neocortex, less is known about the degree to which environmental influences affect these processes, especially in humans. We aim to understand how the brain can adapt to perturbations using "plasticity" mechanisms in health and disease. Our long-term goal is to identify factors that boost the resilience of neocortical development and thus help to prevent neurodevelopmental disorders. Moreover, we are interested in revealing human-specific features of cerebellar development, a brain region that has not been studied extensively to date. In collaboration with clinicians, we aim to understand how the development of the cerebellum is affected in a rare pediatric neurological disorder, pontocerebellar hypoplasia.

Das Gehirn ist sehr komplex und besteht aus sehr vielen verschiedenen Regionen. Außerdem hat es sich während der Evolution stark verändert. Jüngste Fortschritte in der Stammzellforschung haben es ermöglicht, die menschliche Gehirnentwicklung in einer Petrischale mit Hilfe verschiedener Organoidprotokolle zu modellieren. Dadurch können wir nun menschenspezifische Merkmale der Gehirnentwicklung auf zellulärer und molekularer Ebene untersuchen. In der Forschungsgruppe Molekulare Hirnentwicklung ist es unser Ziel zu verstehen, wie genetische Faktoren und Umweltbedingungen die Gehirnentwicklung verändern können und untersuchen dies mittels verschiedener Organoide. Insbesondere untersuchen wir zwei Hirnregionen, den Neokortex und das Kleinhirn. Neokortikale Netzwerke sind das Herzstück der kognitiven Funktion, aber ihre Dysfunktion ist auch eine Ursache für eine Vielzahl von psychiatrischen und neurologischen Störungen. Während wir kürzlich bedeutende Einblicke in den Beitrag genetisch „fest verdrahteter" Mechanismen der Proliferation, Differenzierung und Reifung von Nervenzellen gewonnen haben, ist weniger darüber bekannt, inwieweit Umwelteinflüsse diese Prozesse beeinflussen, insbesondere beim Menschen. Unser Ziel ist es zu verstehen, wie Plastizität zur menschlichen neokortikalen Entwicklung beiträgt. Langfristig möchten wir Faktoren identifizieren, die die Resilienz der neokortikalen Entwicklung stärken und so dazu beitragen, neurologischen Entwicklungsstörungen vorzubeugen. Darüber hinaus möchten wir die Entwicklungsprozesse im menschlichen Kleinhirn besser verstehen, da diese Gehirnregion bisher wenig Beachtung gefunden hat, aber für viele Prozesse essentiell ist. In Zusammenarbeit mit Klinikern untersuchen wir, wie die Entwicklung des Kleinhirns in einer seltenen, genetisch bedingten pädiatrischen neurologischen Erkrankung, der pontozerebellären Hypoplasie, gestört ist.

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

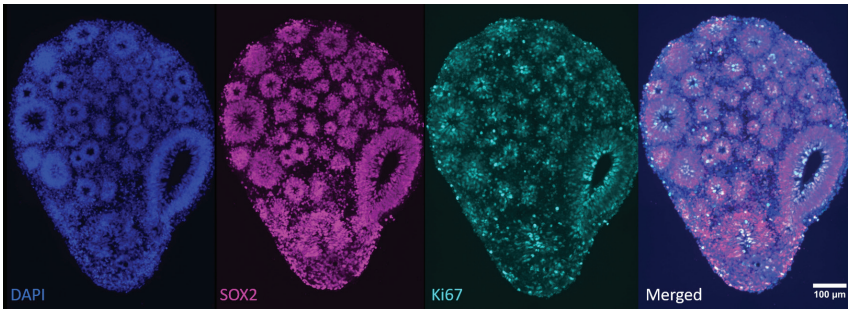
Recent developments in single-cell RNA-Sequencing (scRNA-seq) have emphasized the importance of investigating phenotypes on a single-cell level in order to reveal cell-type-specific signaling pathways (see for example our recent review, Khakipoor et al., Neuroforum, 2019). I have recently developed a 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). Therefore, we aim to employ multimodal single-cell approaches to quantitatively characterize cell type-specific responses to different experimental perturbations with a focus on the transcriptome and epigenome. Additionally, we perform signaling pathway analysis using classical methods such as immunofluorescence,and Western blotting. Additionally, we are currently establishing physiological readouts, to determine neural network activity in organoids.

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). Several on-going projects in the lab address how environmental impacts, such as maternal immune activation, or 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 underlying pontocerebellar hypoplasia

Genetic perturbations may also affect human brain development. As a disease model, in cooperation with the Pediatrics department at Universitätklinikum Tübingen, the Clinical Neurogenetics Section at HIH, and a parents' initiative, we are investigating cellular mechanisms of pathology in pontocerebellar hypoplasias (PCH). PCH are a group of rare neurogenetic disorders that mostly affect the cerebellum and pons resulting in a severely disturbed development of patients during childhood. Additionally, patients develop 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.



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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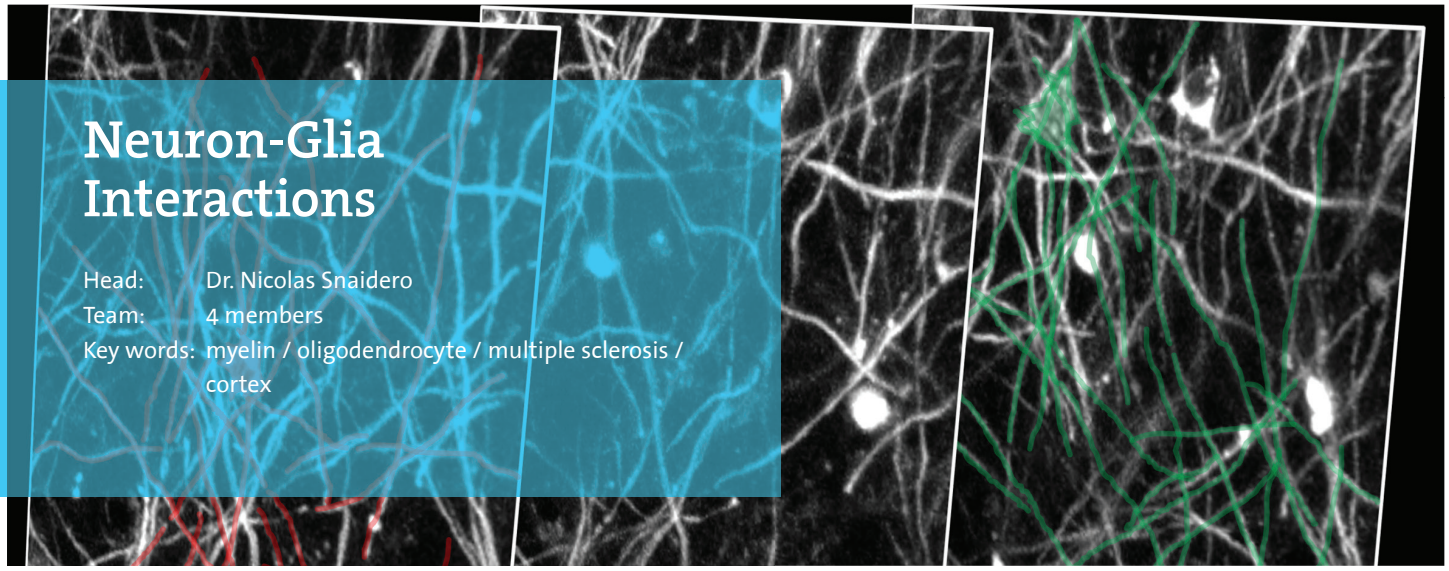


Neuron-Glia Interactions

Head: Dr. Nicolas Snaidero
Team: 4 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.

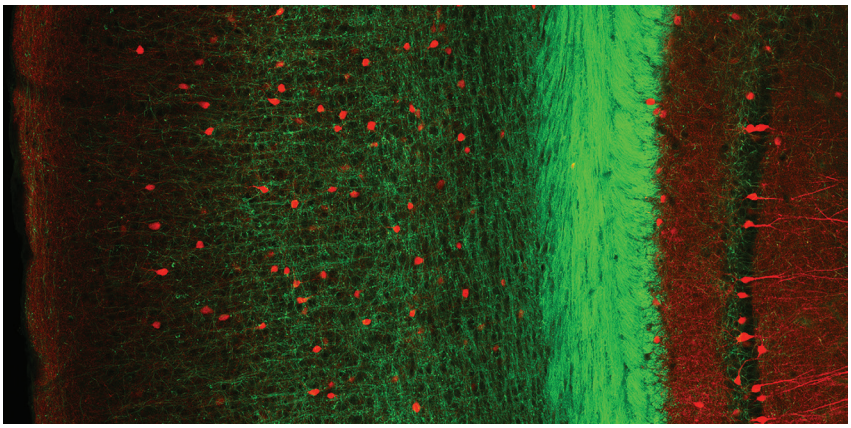
Oligodendrozyten sind Gliazellen, die im zentralen Nervensystem mehrere Axone gleichzeitig umhüllen, eine schnelle Impulsübertragung ermöglichen und den Stoffwechsel langfristig unterstützen. In der grauen Substanz des Kortex finden sich entlang der kortikalen Axone komplexe und vielfältige Myelinmuster, 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 de-myelinating 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.

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 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.

The cortical myelination has recently been shown to be an active and progressing process in young adult. However, this process slows downs dramatically with aging. In the lab we are combining imaging and omics to assess the cellular and molecular dysregulation leading to targeted myelin loss and investigate pro myelination approaches to reduce the cognitive decline.



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.

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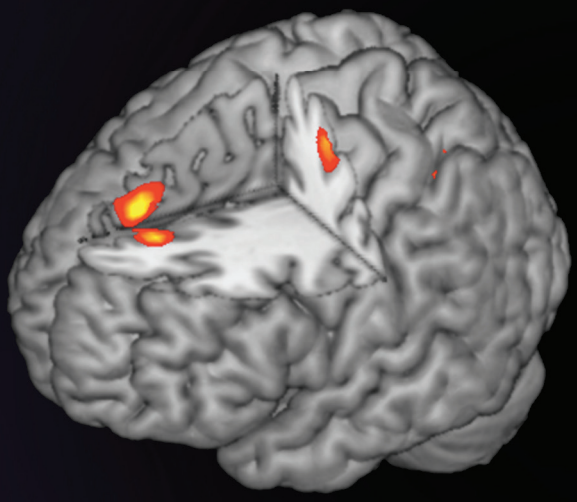
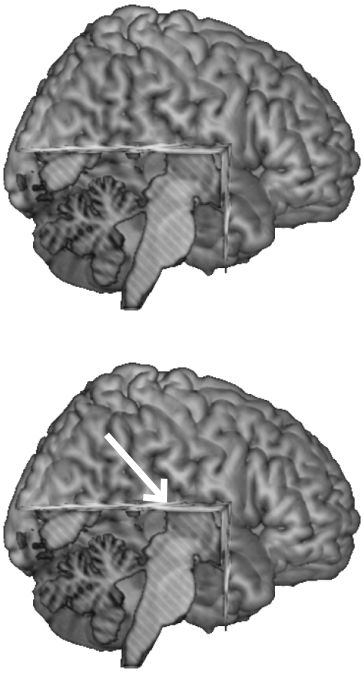
Neuropsychology of Action

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



The Research Group "Neuropsychology of Action" 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.



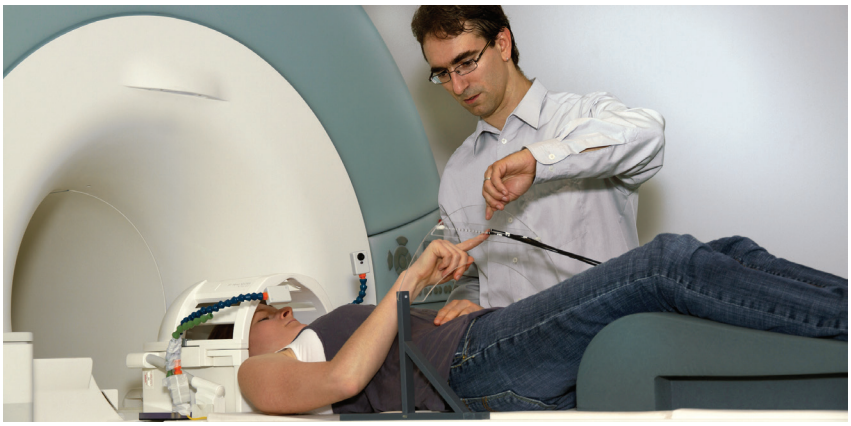
The superior colliculi are part of the tectum which additionally comprises the inferior colliculi right below. Traditionally the superior colliculi have been associated with visual and oculomotor functions.

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

Oculomotor Laboratory

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

Our society is currently marked by two major changes: overall, there is a massive increase of the number of older individuals. In addition, the use of digital devices augments, especially video-games as a wide spread leisure activity. With respect of the video-games, there is a vivid debate about possible consequences, being either positive or negative. In several studies, we used various ocuomotor paradigms including smooth pursuit eye movements and anti-saccades to examine the influence of age as well as video-game on several oculomotor properties. In addition, we also asked whether cognitive abilities such as primitive mathematics are affected by video-games.

Unsere Gesellschaft ist gegenwärtig von zwei großen Veränderungen gekennzeichnet. Einerseits nimmt der Anteil von älteren Menschen massiv zu. Andererseits werden immer mehr digitale Geräte benützt, vor allem Computerspiel in der Freizeit. Es existiert immer noch eine lebhafte Diskussion bezüglich der möglichen positiven oder negativen Folgen der Computerspiele. In einer Reihe von Studien untersuchen wir die Auswirkungen des Alters und der Computerspiele in verschiedenen Augenbewegungsparadigmen. Außerdem untersuchen wir, ob kognitive Fähigkeiten wie zum Beispiel einfache Mathematik von Computerspielen beeinflusst werden.

Nowadays, video games are an omnipresent medium. In Germany, a recent study showed that over 46 % of the teenagers between 12 and 19 are consuming video games on a daily basis. Despite this strong prevalence, the effects of video-game consumption are still under debate. We decided to examine possible effects of video-game play in a wide battery of tests addressing eye movements and the allocation of attention.

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

Pro- and Anti-Saccades and direction errors

We applied a very simple oculomotor task in our first study. We asked our subject to perform a saccade to the mirror position of a visual target. In some cases, the subject is unable to suppress the gaze shift towards the target, triggered by a reflexive shift of attention towards the target. These saccades are directional errors quite similar to the visually-guided saccades called pro-saccades. There is compelling evidence that the fast visual orienting responses (directional errors) are generated by the superior colliculus in the midbrain. In contrast, the cognitively driven anti-saccades are mediated by the frontal eye field (area 8) in the frontal cortex. So the frequency of directional errors can be used as a direct measure for the strength of the executive control function of the frontal cortex upon the midbrain circuit. We tested a total of 55 subjects aged 15 to 31 years in our experiment. All subjects were either classified as VGPs or as non-players depending on their daily gaming time: VGPs (n=35) played at least one hour per day video games.

Firstly, we analyzed the saccadic reaction times of our subjects. A general finding was that the directional errors had about 100 ms shorter reaction times than the correctly executed anti-saccades. More strikingly, the reaction times of both types of saccades were decreased for approximately 10 ms in VGPs compared to non-players. The eye speed during gaze shifts reaches very high values. In our data, the maximal velocity of the eye during a 10-degree saccade is between 350 and 400 degrees/second. In other

In order to reveal the shifts of attention, we measure precisely the gaze movements of our subjects. Depending on the specific experimental question, we are using different eye tracker technologies with and without restriction of the head movements and different temporal sampling rates.

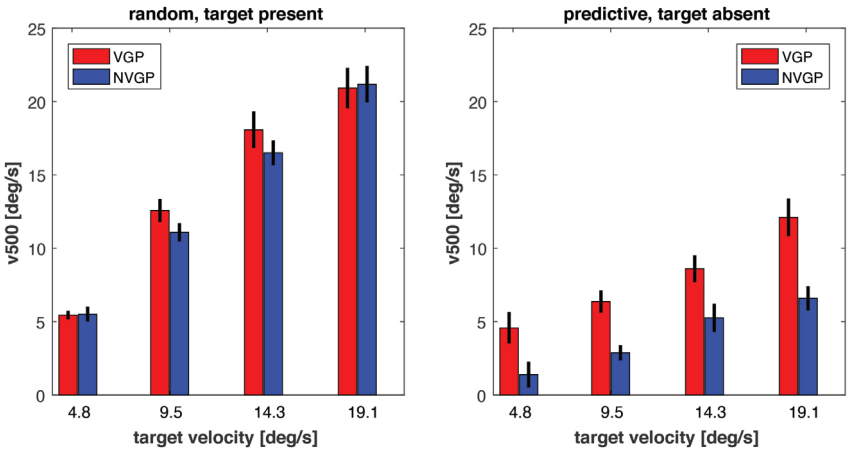
words, if the eyes could rotate without limitations, a complete rotation of the eyeball would occur within one second. As reported by others, direction errors reach higher peak velocities than anti-saccades. Surprisingly, both types of saccades of VGPs reach higher peak velocities gaze shifts executed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

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

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

Number Sense

We addressed the possible correlation between playing video games and numerical cognition. Using a cross-sectional design, we compared psychophysical parameters of video-game players (VGP) and non-players (NVGP) as they estimated the number of briefly displayed items in a two-alternative forced choice paradigm. We used linear regression models to analyze the psychophysical data obtained from 32 VGPs and 34 NVGPs. We did not find differences in the accuracy of numerosities estimation between VGPs and NVGPs. However, sensory precision expressed as the just-noticeable difference (JND) was better in VGPs as compared to NVGPs and was positively correlated with time spent gaming each week. We argue that the superiority of VGPs in number processing is most likely not due to specific differences in the neuronal processing within distinct areas underlying numerical cognition but rather related to more general differences in the attentional system, most likely the top–down attentional processes implemented in the dorsal attention network.



Mean eye velocity (during 100 ms) for 4 different target velocities is not different for VGPs (red) and NVGPs (blue) during visual guided smooth pursuit (left). However, anticipatory eye velocity in total darkness in anticipation of 4 different upcoming target velocities is clearly different for VGPs and NVGPs: VGPs produce much higher eye velocities (right).

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Section for Neuropsychology

Head: Prof. Dr. Dr. Hans-Otto Karnath
Team: 27 members
Key words: cognitive neuroscience / neuropsychology

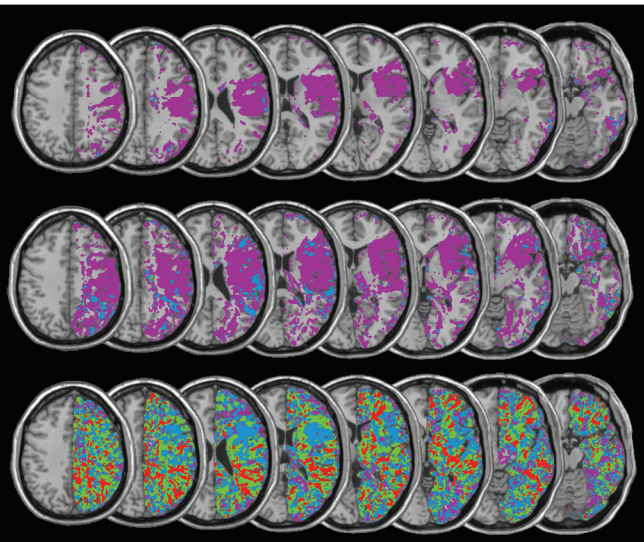

Figure 1: Nowadays, different anatomical atlases exist for the anatomical interpretation of the results from neuroimaging and lesion analysis studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function. A major problem with the use of different atlases in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

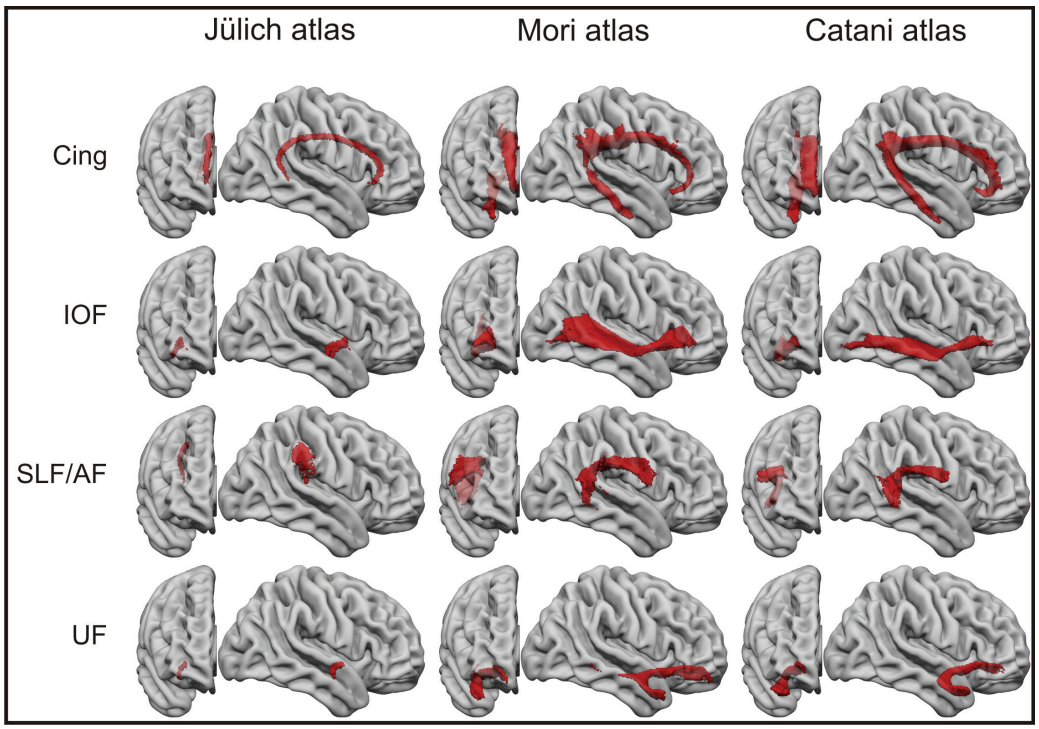

Figure 1

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Cognitive Neurology Laboratory

Head: Prof. Dr. Peter Thier
Team: 13 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.

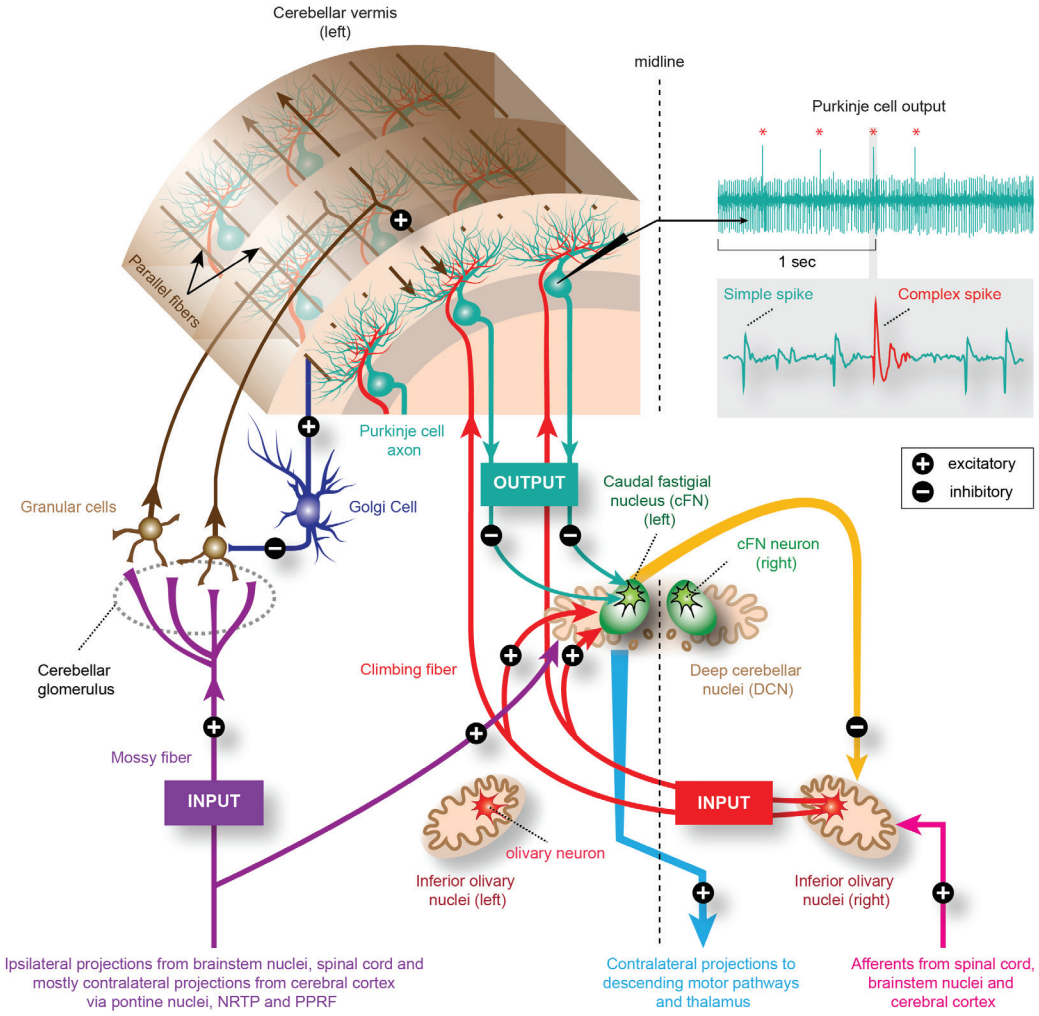
The lab studies of the underpinnings of social interactions and the mechanisms underlying motor learning and their disturbances due to disease.

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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