



Activity Report 2017 - 2018

Joining Forces for Rostock Neurosciences



Centre for
Transdisciplinary
Neurosciences
Rostock




Centre for Transdisciplinary Neurosciences Rostock (CTNR)

Activity Report 2017 - 2018

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Joining Forces for Rostock Neurosciences

The first two years

In the last two years, the Centre for Transdisciplinary Neurosciences Rostock (CTNR) at the University Medical Centre Rostock has become an integral part and major driving force of the Neuroscience Community in Rostock with its focus on translational neurosciences. We join Rostock's strengths and forces in medicine, clinical and experimental neurosciences, bioinformatics and bioengineering to find innovative strategies and solutions for patients suffering from neurodegenerative diseases.

Two years after its foundation, the CTNR can boast several pivotal achievements:

- More than 580 peer-reviewed publications from the member research groups with an increase of collaborative publications of CTNR members by two-fold
- Increase of approved third-party funded projects by 1.5-fold with three successful major joint applications to non-commercial funding agencies by CTNR members
- Initiation of a neuroscience qualification program for young neuroscientists including a career & funding service
- Joint development of the Clinician Scientist Program at the University Medical Centre Rostock together with the two other scientific areas oncology and biomaterial research

This image brochure presents the development of the CTNR in the first two years after its foundation and a snapshot of ongoing activities at the CTNR. I hope that you will find them interesting and accompany us on a journey into translational neurosciences.



Alexander Storch
Speaker CTNR





CTNR at a Glance

- ✓ Mission and Objectives
- ✓ Governance
- ✓ Member
- ✓ Funding
- ✓ Publications
- ✓ Research Environment

CTNR at a Glance

Mission and Objectives

The University Medical Centre Rostock (UMR) has a strong focus on transdisciplinary research in resilience and prevention of neurodegenerative diseases, and is one of the few institutions in Germany to systematically develop and use methods of participatory innovation in neurodegenerative brain diseases research.

In November 2017, the Centre for Transdisciplinary Neurosciences Rostock (CTNR) was founded to bundle the scientific activities of neurosciences and to improve the visibility and outcomes of the University Medical Centre in the field. The centre focuses on “Resilience in Neurodegeneration – from model to patient to population” and represents one of the three main scientific areas (Forschungsschwerpunkte) at the University Medical Centre. The CTNR creates an interface between clinical and basic research and improves its translational approach. Its future concepts of educational training for clinician and medical scientists and funding programs will cover the needs of the neuroscience community in Rostock.

The overall scientific aim of the CTNR is to **identify and target resilience mechanisms in neurodegeneration** to implement innovative therapeutic concepts for primary and secondary neurodegenerative processes. Resilience, in this context, is understood as an integrated concept for physical, cognitive and psycho-social resistance against neurodegenerative insults and/or their impacts. The concept thus ranges from neuroprotective and neuroregenerative factors on the molecular and cell biology level and cognitive and physical resources on the patient level to psycho-social and health system aspects on the population level.

The detailed knowledge of these resilience factors provides new perspectives for disease-modifying therapeutic interventions in primary and secondary neurodegeneration. The CTNR is organized into **three tightly connected topics** to boost qualitative leaps in three dimensions:

1. Mechanisms of resilience and their interplay with neurodegenerative processes
2. Concepts of precision medicine to neurodegenerative disease care to establish predictors for cerebral resilience
3. Bi-directional translation pathways for the development of new treatments for and preventions of neurodegenerative insults.

The CTNR board developed a **policy paper** defining the short and long term objectives for research, education and training, transfer/translation and infrastructures, and the necessary measures. The overall strategic aims are to:

- increase the visibility by defining the unique selling point,
- aim for excellence by bundling and strengthening clinical research,
- encourage innovations by networking and translation,
- support young scientists by generating the appropriate environment and internationalisation,
- achieve sustainability by the expansion of equal opportunities,
- foster the transfer of knowledge by the development of concepts for infrastructure and exploitation.

Governance

The CTNR is a scientific unit of the University Medical Centre Rostock and is supervised by the CTNR Board. It has its own bylaws and organisational structure under the head of the regulations of the UMR. The decision body is composed of three entities: the Member Assembly, the CTNR Board and the Speaker/Co-speaker. In addition, a scientific coordinator is responsible for members requests and the support of the Board.

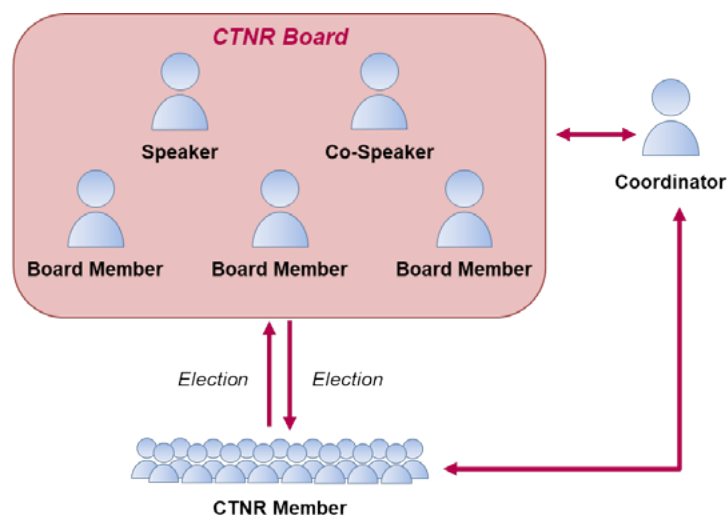


Fig. 1: Organisational Structure of the CTNR.

Member Assembly

The CTNR Member Assembly is composed of core group leaders of the UMR campus with a visible work in the field of neurosciences. Entry into the CTNR Member Assembly must be approved by application to the CTNR Board. One task of the CTNR Member Assembly is to elect the CTNR Board members and the Speaker/Co-Speaker. The members are also obliged to participate in the conceptual and organisational work, the support of young scientists and gender equality in accordance with the bylaws.

The CTNR Board

Members of the Board are elected every 3 years by the CTNR Member Assembly and include the CTNR Speaker, Co-Speaker and three elected research area leaders.

Tasks of the CTNR Board are:

- Decision on the admission of members
- Development of the scientific program and concepts for the support of young scientists, gender equality and infrastructure
- Preparation of applications for collaborative projects
- Program changing funding measures
- Preparation and organisation of CTNR events

Current CTNR Board members are:

- Prof. Dr. med. Alexander Storch (Speaker), Department of Neurology, UMR
- Prof. Dr. med. Rüdiger Köhling (Co-Speaker), Oscar-Langendorff-Institute of Physiology, UMR
- Prof. Dr. med. Stefan Teipel, German Center for Neurodegenerative Diseases (DZNE), Department of Psychosomatic and Psychotherapeutic Medicine, UMR
- Prof. Dr. med. Andreas Wree, Institute of Anatomy, UMR
- Prof. Dr. med. Uwe Zettl, Department of Neurology, Section Neuroimmunology, UMR

CTNR Speaker

The Speaker of the CTNR is a core research institute professor who represents the CTNR both within and outside of the UMR and executes the decisions made by the CTNR Board. The Speaker is the chairman of the CTNR Board and heads the coordination team.

Members

Anyone who belongs to the University Medical Centre Rostock (UMR), the University of Rostock (UR) or to an external research institution in Rostock (e.g. DZNE) can become a member of the CTNR.

In addition, the member must be qualified to do independent scientific work (usually after completion of the doctorate, leading a working group with publication and third party funding activities) in the field. Prerequisite for the membership is the proven expertise in neuroscience research.

Since the foundation of the CTNR in November 2017, the **number of members** has risen to 38 by the end of 2018 (see Fig. 2).

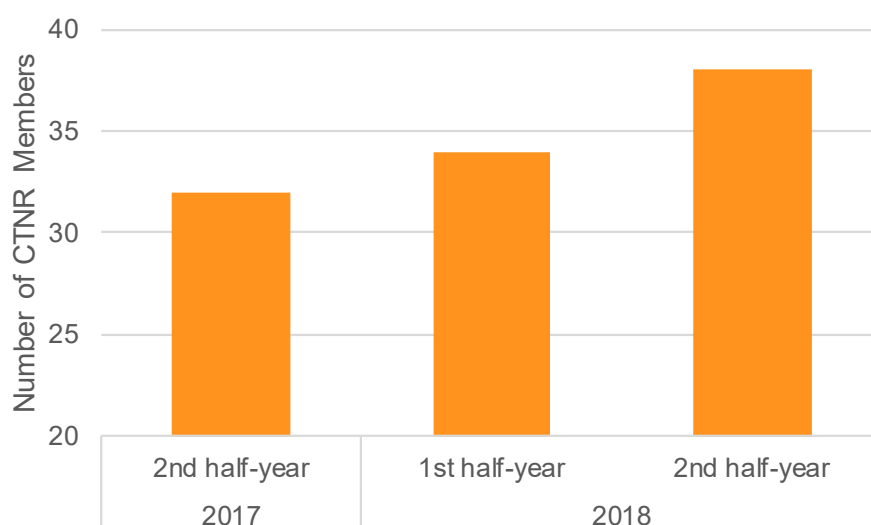


Fig. 2: CTNR Membership Recruitment.

The **sum of citations** in Figure 3 was calculated from the entire publication record of all CTNR members for the years 2015-2018.

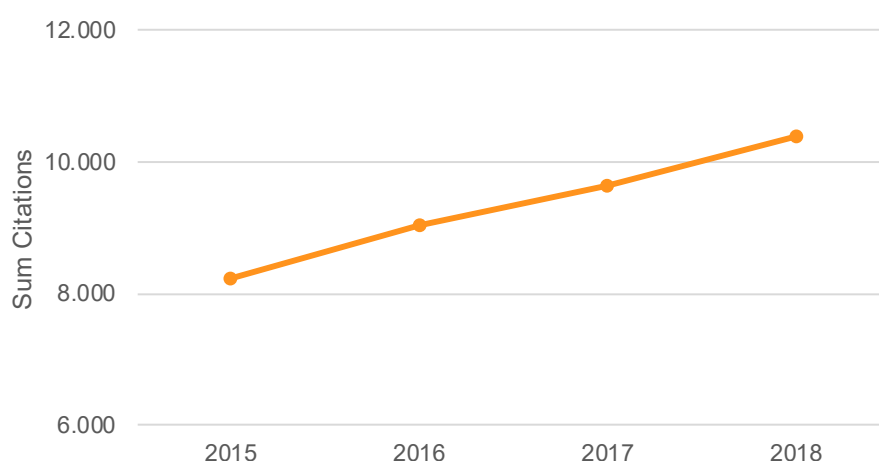


Fig. 3: Sum Citations of the CTNR Members 2015-2018. Source: Scopus, without self citations.

Table 1 shows the CTNR members, their institutions and main research topics.

| Member | Institute | Research Topic |
|-----------------------|--|--|
| Altiner, Attila | Institute of General Practice | Rational pharmacotherapy, respiratory infections and antibiotics |
| Baltrusch, Simone | Institute of Medical Biochemistry and Molecular Biology | Peripheral diabetic neuropathy |
| Berger, Christoph | Department of Psychiatry, Neurology, Psychosomatics, and Psychotherapy in Childhood and Adolescence | EEG and fMRI in psychiatry |
| Bertsche, Astrid | Department of Neuropaediatrics/Neuropaediatric Research Group | Drug therapy safety in epileptology |
| Buchmann, Johannes | Department of Psychiatry, Neurology, Psychosomatics, and Psychotherapy in Childhood and Adolescence | Motor development, pain |
| Büttner, Andreas | Institute of Forensic Medicine | (Forensic) Neuropathology |
| Frech, Moritz | Albrecht-Kossel-Institute for Neuroregeneration | IPSC based disease models |
| Fuellen, Georg | Institute for Biostatistics and Informatics in Medicine and Ageing Research | Health, disease, ageing and senescence |
| Grothe, Michel | German Center for Neurodegenerative Diseases | Neuroimaging patterns of dementia |
| Holzmann, Carsten | Institute of Medical Genetics | Neurodegenerative diseases |
| Jürgens, Tim | Department of Neurology | Pathophysiology & treatment of headaches |
| Kipp, Markus | Institute of Anatomy | De- and remyelination |
| Kirschstein, Timo | Oscar-Langendorff-Institute of Physiology | Novel antiepileptogenic treatments |
| Köhling, Rüdiger | Oscar-Langendorff-Institute of Physiology | Models of chronic neurological diseases |
| Krause, Bernd Joachim | Department of Nuclear Medicine | Molecular imaging of neurodegenerative diseases |
| Kronenberg, Golo | Department of Psychiatry and Psychotherapy | Biological psychiatry |
| Kropp, Peter | Institute of Medical Psychology and Medical Sociology | Non-medical treatment in migraine |
| Kuhla, Angela | Rudolf-Zenker-Institute for Experimental Surgery | Hallmarks of neurodegenerations |
| Lange, Falko | Oscar-Langendorff-Institute of Physiology | Glioma-associated epilepsy and ageing |
| Langner, Sönke | Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology | New techniques in neuroradiology |
| Lukas, Jan | Albrecht-Kossel-Institute for Neuroregeneration | Novel drugs in rare hereditary diseases |
| Luo, Jiankai | Albrecht-Kossel-Institute for Neuroregeneration | Neurodegeneration in NPC1 disease |
| Pützer, Brigitte M. | Institute of Experimental Gene Therapy and Cancer Research | Antineurogenic therapies in cancer |
| Reis, Olaf | Department of Psychiatry, Neurology, Psychosomatics, and Psychotherapy in Childhood and Adolescence | Developmental psychopathology |
| Schmitt, Oliver | Institute of Anatomy | Dynamics of neurodegenerative diseases |
| Spittau, Björn | Institute of Anatomy | Microglia functions |
| Storch, Alexander | Department of Neurology, German Center for Neurodegenerative Diseases | Novel treatments in Parkinson's |
| Teipel, Stefan | Department of Psychosomatic and Psychotherapeutic Medicine, German Center for Neurodegenerative Diseases | Dementia diagnosis and treatment |
| Thierfelder, Kolja M. | Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology | Functional cross sectional imaging |
| Tiedge, Markus | Institute of Medical Biochemistry and Molecular Biology | Mitochondria in type 2 diabetes |
| Völlm, Birgit | Forensic Psychiatry | Forensic psychiatry |
| Vollmar, Brigitte | Rudolf-Zenker-Institute for Experimental Surgery | Hallmarks of neurodegenerations |
| Walter, Uwe | Department of Neurology | Neurodiagnostics in parkinsonism and stroke |
| Weber, Marc-André | Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology | Multimodal dedicated imaging |
| Witt, Martin | Institute of Anatomy | Olfaction and neurodegeneration |
| Wolkenhauer, Olaf | Institute of Computer Science, Department of Systems Biology and Bioinformatics | Systems biology & bioinformatics |
| Wree, Andreas | Institute of Anatomy | Intrastriatal botulinum neurotoxin-A |
| Zettl, Uwe | Department of Neurology | Molecular research in multiple sclerosis |

Tab. 1: CTNR Members in 2018.

Funding

To increase the visibility of neurosciences in Rostock by defining the unique selling point and to aim for excellence by bundling and strengthening the clinical research, the CTNR and its members submitted several third-party proposals and collaborative projects during the last years.

In 2017 and 2018, four **collaborative research applications** (with applicants from more than one CTNR institute) have been prepared and submitted under the supervision of the CTNR (see Tab. 2).

| Funding Body | Funding Initiative | Project Title | Principal Investigator | CTNR Institutes involved |
|---|--|---|---|--------------------------|
| German Research Foundation (DFG) | Collaborative Research Centre: CRC 1270 ELAINE - Electrically Active Implants | Subproject C03 - Deep brain stimulation in dystonia models: Biological implementation, approximation of stimulation parameters and analysis of mechanisms Subproject C04 - Effects of deep brain stimulation on adult neurogenesis in a rat model of Parkinson's disease: Mechanisms of action, stimulation parameters and correlation with behaviour Integrated Research Training Group (IRTG) | Rüdiger Köhling Alexander Storch Alexander Storch | 2 |
| Federal Ministry of Education and Research (BMBF) | Systems medicine research consortia, "e:Med – Paving the Way for Systems Medicine" | Senescence-Associated Systems diagnostics Kit for cancer and stroke (SASKit) | Georg Fuellen | 3 |
| University Medical Centre Rostock | Intramural support for the preparation of collaborative research grants | Preparation of a proposal for a DFG Research Training Group | Stefan Teipel | 10 |
| European Regional Development Fund | Excellence Program | New forms of therapy through translational research approaches | Rüdiger Köhling | 5 |

Tab. 2: Submitted CTNR collaborative research projects in 2017 and 2018.

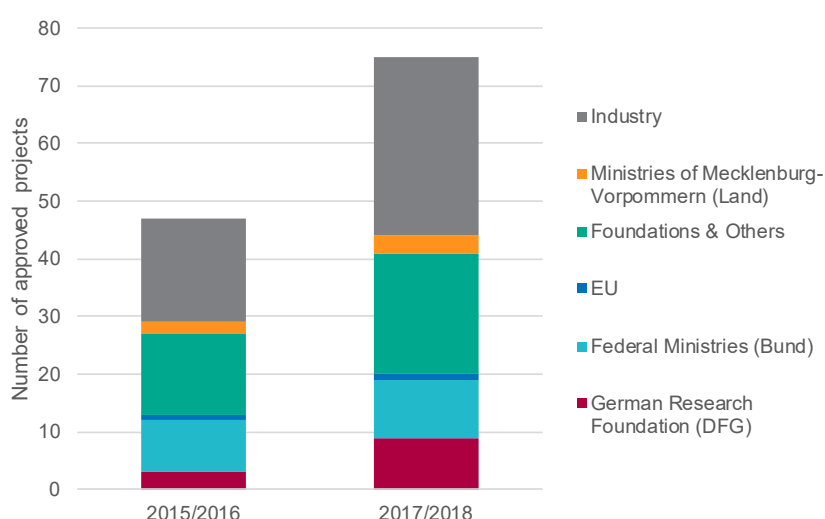


Fig. 4: Number of approved third-party projects of the CTNR members by funding bodies in 2015/2016 and 2017/2018.

During 2015 - 2018 the CTNR members submitted several **third-party fund proposals**. Figure 4 shows the number of approved projects by funding bodies. To foster joint initiatives between CTNR members, overarching research designs that combine methods and issues from basic research and clinical research are necessary. Thus, the CTNR will continue to bring the scientists together to cross interdisciplinary boundaries.

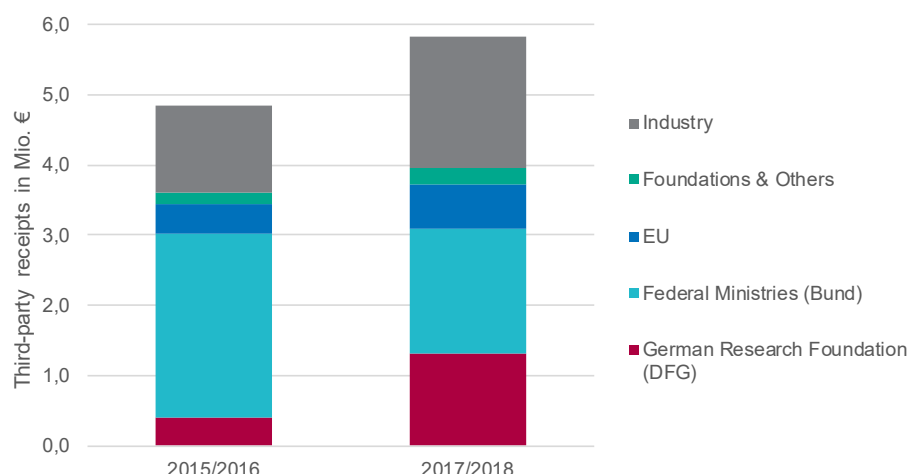


Fig. 5: Third-party receipts of the CTNR members in 2015/2016 and 2017/2018 (in Mio. €).

The **annual funding volumes** of the CTNR members from third-party grants of different funding bodies in the years 2015/2016 and 2017/2018 are shown in Figure 5.

In addition to the submitted collaborative research grants (Tab. 2) various single third-party funding projects in the field of neuroscience were acquired by CTNR members in 2017 and 2018 (a selection of these is given in Table 3).

| Funding Body | Project Title | Principal Investigator | Funding Amount | Project Number |
|--|---|--------------------------------|----------------|----------------|
| German Research Foundation (DFG) | Cerebral FGF21-resistance as cause of the obesity-associated neurodegeneration | Angela Kuhla | 221,000 € | KU3280/1-2 |
| German Research Foundation (DFG) | Activation of the unfolded protein response in multiple sclerosis | Markus Kipp | 230,000 € | KI1469/8-1 |
| Innovationsfonds des Gemeinsamen Bundesausschuss | Smartphone supported Migraine therapy as new form of care (SMARTGEM) | Tim Jürgens | 327,000 € | 01NVF17038 |
| Innovationsfonds des Gemeinsamen Bundesausschuss | CARE-FAM-NET – Children affected by rare disease and their families – network | Astrid Bertsche Peter Kropp | 217,000 € | 01NVF17028 |
| European Union/DZNE | Is prion like propagation of alpha synuclein aggregation associated with a ferroptotic cell death | Alexander Storch Uwe Walter | 500,000 € | CoEN4007 |
| European Union/ Horizon 2020 | Blood Biomarker-based Diagnostic Tools for Early Stage Alzheimer's Disease (BBDiag) | Stefan Teipel | 249,000 € | ID 721281 |
| European Union/ Horizon 2020 | Ageing with elegans, drug screening for Healthspan extension in worm, mouse and human | Georg Fuellen | 7,305,000 € | 633589 |

Tab. 3: Approved third-party projects of CTNR members in 2017 and 2018 (a selection).

In 2015/2016, CTNR members raised 58,000 € funds within the **intramural funding program FORUN** (Forschungsförderung der Medizinischen Fakultät der Rostocker Universität) of the University Medical Centre Rostock. The aim of the program is to develop and promote competitive research projects and research structures for the sustainable improvement of third-party funding. The receipts of FORUN funds of CTNR members increased in 2017/2018 to 79,000 €. From 2015 to 2018, eight CTNR members gained from another intramural funding program of the UMR for the **support of the preparation of collaborative research projects** (Förderung der Verbundforschung) and were part of it as coordinators or sub project leaders.

Publications

To raise the publication activities of the CTNR members in terms of excellence and interdisciplinarity is one of the overall aims of the CTNR.

Figure 6 shows the **number of publications** of the CTNR members in 2015/2016 and 2017/2018 concerning to the impact factors (IF). In addition, the sum of journal impact factors (IF) calculated from the publication record of the CTNR members in 2015/2016 and 2017/2018 is indicated.

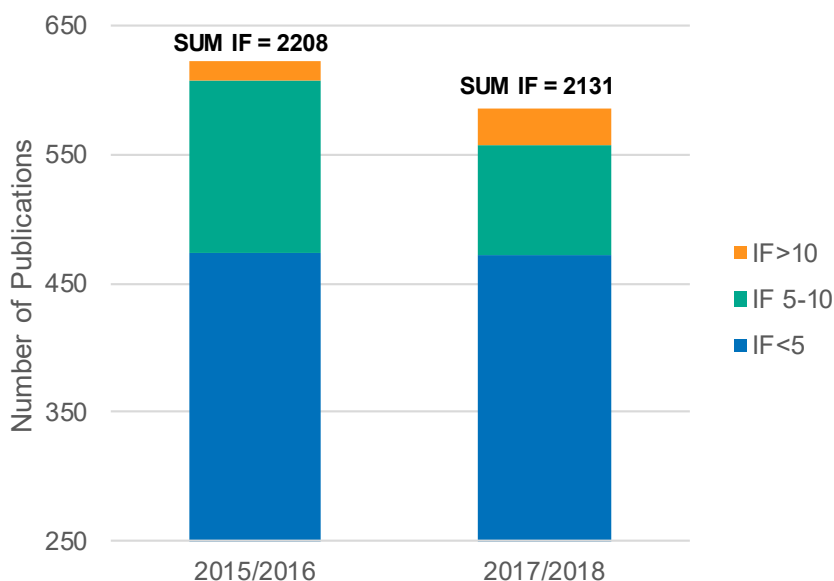


Fig. 6: Number of publications of the CTNR members (2015/2016, 2017/2018) and sum of journal impact factors. Based on the LOM (Leistungsorientierte Mittelvergabe) Database of the UMR (May 2019).

Inter- and transdisciplinary publications are important to increase visibility, to define the unique selling point and to aim for excellence in the field of neurosciences. Thus, they are a main indicator for the evaluation and the success of the CTNR. Figure 7 shows the number of **joint publications** between CTNR members of more than one institution.

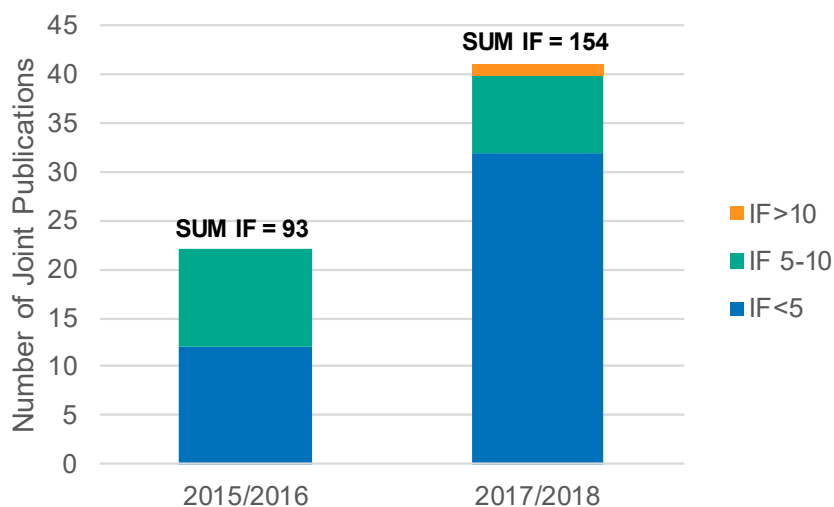


Fig. 7: Number of joint publications between CTNR members (from different institutions) and the sum of the journal impact factors (IF) for the years 2015/2016 and 2017/2018.

The following illustration (Fig. 8) shows the increase in **networking between CTNR members** by collaborative publications. While in 2015 and 2016, before the foundation of the CTNR, members of different disciplines published less together and more bilaterally (black lines), in 2017 and 2018 an increase in publications among members from two (green lines) and three (red lines) institutions can be observed.

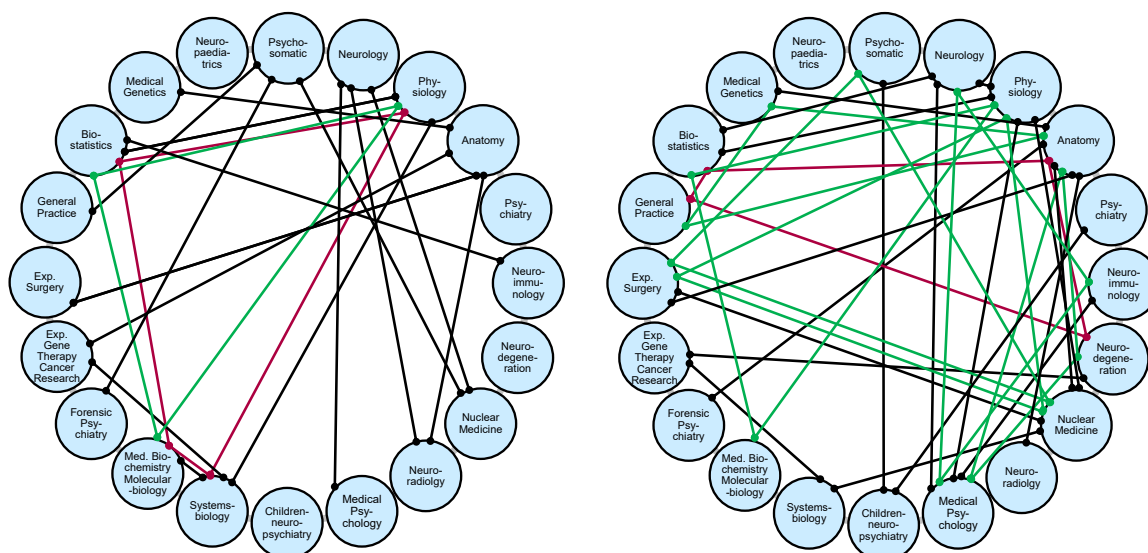


Fig. 8: Interdisciplinary publication activities in 2015/2016 (left) and 2017/2018 (right) between CTNR members from two (black line), three (green line) and four (red line) different institutes.

Selected collaborative publications between CTNR members (bold) of more than one institution in 2017 and 2018:

- Markus-Koch A, **Schmitt O**, Seemann S, **Lukas J**, Koczan D, Ernst M, **Fuellen G**, **Wree A**, Rolfs A, **Luo J** (2017). ADAM23 promotes neuronal differentiation of human neural progenitor cells. *Cell Mol Biol Lett.* 22(16), eCollection 2017.
- Lukas J**, Cozma C, Yang F, Kramp G, Meyer A, Neßlaue AM, Eichler S, Böttcher T, **Witt M**, Bräuer AU, **Kropp P**, Rolfs A (2017). Glucosylsphingosine Causes Hematological and Visceral Changes in Mice-Evidence for a Pathophysiological Role in Gaucher Disease. *Int J Mol Sci.* 18(10).
- Stenzel J, Rühlmann C, Lindner T, Polei S, Teipel S, Kurth J, Rominger A, Krause BJ, Vollmar B, Kuhla A (2018). [¹⁸F]-florbetaben PET/CT Imaging in the Alzheimer's Disease Mouse Model APPswe/PS1dE9. *Curr Alzheimer Res.* 16(1), 49-55.
- Antipova V, **Wree A**, **Holzmann C**, Mann T, Palomero-Gallagher N, Zilles K, **Schmitt O**, Hawlitschka A (2018). Unilateral Botulinum Neurotoxin-A Injection into the Striatum of C57BL/6 Mice Leads to a Different Motor Behavior Compared with Rats. *Toxins (Basel)* 10(7).
- Reichart G, Mayer J, Zehm C, **Kirschstein T**, Tokay T, **Lange F**, **Baltrusch S**, **Tiedge M**, **Fuellen G**, Ibrahim S, **Köhling R** (2018). Mitochondrial complex IV mutation increases reactive oxygen species production and reduces lifespan in aged mice. *Acta Physiol (Oxf).* 225(4).

Selected publications of CTNR members (bold) in 2017 and 2018 in the field of neurosciences:

- Zöller T, Schneider A, Kleimeyer C, Masuda T, Potru PS, Pfeifer D, Blank T, Prinz M, **Spittau B** (2018). Silencing of TGFβ signalling in microglia results in impaired homeostasis. *Nature communications* 9, 4011.
- Teipel SJ**, Cavedo E, Lista S, Habert MO, Potier MC, **Grothe MJ**, Epelbaum S, Sambati L, Gagliardi G, Toschi N, Greicius MD, Dubois B, Hampel H (2018). Effect of Alzheimer's disease risk and protective factors on cognitive trajectories in subjective memory complainers: An INSIGHT-preAD study. *Alzheimer's & dementia the journal of the Alzheimer's Association* 14, 1126–1136.
- Naumann M, Pal A, Goswami A, Lojewski X, Japtok J, Vehlow A, Naujock M, Günther R, Jin M, Stanslowsky N, Reinhardt P, Sternecker J, Frickenhaus M, Pan-Montojo F, Storkebaum E, Poser I, Freischmidt A, Weishaupt JH, Holzmann K, Troost D, Ludolph AC, Boeckers TM, Liebau S, Petri S, Cordes N, Hyman AA, Wegner F, Grill SW, Weis J, **Storch A**, **Hermann A**. (2018). Impaired DNA damage response signaling by FUS-NLS mutations leads to neurodegeneration and FUS aggregate formation. *Nature communications* 9, 335.
- Khan, FM, Marquardt S, Gupta SK, Knoll S, Schmitz U, Spitschak A, Engelmann D, Vera J, **Wolkenhauer O**, **Pützer BM** (2017). Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. *Nature communications* 8, 198.

Research Environment

To foster the transdisciplinary work within the scientific areas of neurosciences at the University Medicine Rostock and to develop an identity, the Centre for Transdisciplinary Neurosciences provides an excellent research environment. For the scientific and educational program, the CTNR has the necessary infrastructure including theoretical and clinical institutes, departments and working groups. The CTNR also acts as a catalyst for new research collaborations beyond the current environment.

At the end of 2018, the CTNR comprised of 38 members from 18 different institutes of the University Medical Centre, 1 external institute (DZNE) and 1 institute of the University Rostock. The members' institutes of the

CTNR are shown in Figure 9. To foster and ensure the interaction between all members of the CTNR, several activities are organised and planned in the future to improve the translation of basic research results into clinical applications. Further information about these measures can be found in the chapters of educational and transfer activities of the CTNR.

The joint forces of the pre-clinical campus including Anatomy, Physiology, Bioinformatics, Proteomics and Genomics and the Clinical Centre for Brain Diseases are particularly focused on translational research in neurodegenerative diseases. This is underpinned by an active interlocking of clinical and preclinical institutions via an exchange of young PIs.

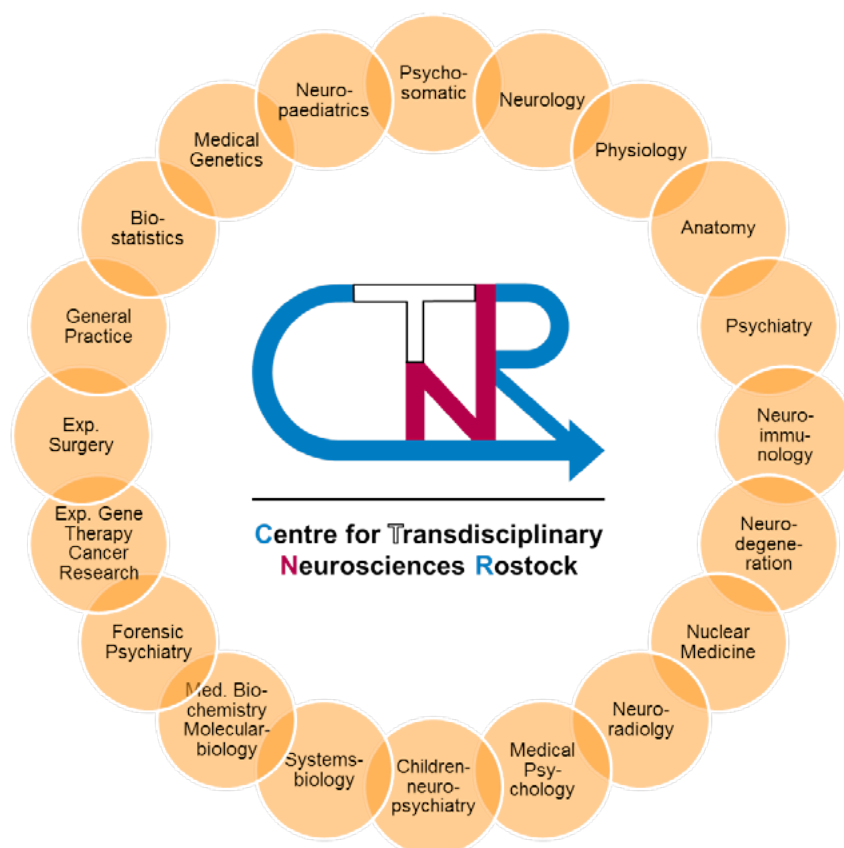


Fig. 9: The CTNR and its affiliated institutes.

The Collaborative Research Centre 1270 “Electrically Active Implants” (ELAINE) funded by the German Research Foundation (DFG) is also firmly embedded in the CTNR research environment. Scientists from the fields of electrical engineering, computer science, mechanical engineering, material science, physics, biology, and medicine are working together in an interdisciplinary manner to understand and improve deep brain stimulation in neurodegenerative disease animal models.

The CTNR has a close collaboration with the German Centre for Neurodegenerative Diseases (DZNE) Rostock/Greifswald in the Helmholtz Society with a strong focus on research of mechanisms of resilience in people with Alzheimer’s disease and other dementias which is based on human imaging studies, intervention clinical trial as well as phase IV trials in primary care populations. In 2017, the implementation of the DZNE/CTNR research group “Non-motor symptoms in Parkinson’s disease” (group leader Prof. Dr. med. Alexander Storch) is a first step for the extension of further collaborations.

In 2018, the UMR has established an overall clinician scientist program (“Strukturprogramm Clinician Scientist”), with a research protected time of two years within the specialist/subspecialist training time to conduct a theoretical research project. The CTNR is strongly connected to the University of Rostock and its full spectrum of supporting infrastructure such as the Graduate Academy and the virtual Interdisciplinary Faculty (INF).



CTNR Research

- ✓ Concept
- ✓ Member Profiles

CTNR Research

Concept

The CTNR is organized into three tightly connected topics to lead to a qualitative leap in three dimensions:

1. Strong focus on mechanisms of resilience and their interplay with neurodegenerative processes to overcome the current standstill in the development of causative treatments for major neurodegenerative diseases.
2. Adoption of the concept of precision medicine to neurodegenerative disease care to establish predictors for cerebral resilience in primary and secondary neurodegeneration in humans.
3. Adoption of continuous bi-directional translation pathways where patient centeredness and patient-relevance and sustainability for the care system are the guiding principles for the development of new treatments and preventions for neurodegenerative insults.

Ad 1. Mechanisms of resilience and their interplay with neurodegenerative processes

This topic is established in various research groups of the theoretical and clinical departments of the University Medical Centre Rostock in strong cooperation with engineer-science institutes of the University of Rostock. This strong connection of biomedical research and engineering science is exemplarily demonstrated by the Collaborative Research Centre (CRC) 1270 “Electrically Active Implants (ELAINE)”. A strong focus of the Rostock neuroscience community is the research on cell and animal models of neurodegenerative diseases with a clear focus on molecular and cellular mechanisms of resilience of neurons and their systems. The CTNR focuses on rare and mostly monogenetic neurodegenerative diseases, such as Amyotrophic Lateral sclerosis (ALS), Niemann-Pick disease and neuronal ceroid-lipofuscinosis (NCL) and on application-oriented animal models of Parkinson’s disease and dystonia.

Ad 2. Precision medicine to establish predictors for cerebral resilience in primary and secondary neurodegeneration in humans

One key topic of the Rostock site of the German Centre for Neurodegenerative diseases (DZNE) is the development of imaging and biochemical biomarkers of neurodegenerative diseases and potential resilience markers. As an internationally unique selling point for Rostock, the whole developmental pipeline of such markers from multimodal animal imaging, functional imaging in small clinical cohorts to populations-based approaches in primary care settings is established in Rostock. Through the integration into large multicentre studies, such as the European DTI Study in Dementia, the European ADNI study, the European Huntington disease network, the German networks on ALS/FTD and Parkinson’s disease together with the cohort studies of the DZNE, Rostock’s neuroscience research is integrated into national and international networks with high visibility and the possibility of fast and targeted recruitment of patient populations. The joint work offers a strong link to fundamental and applied research in computer and cognitive science to develop information and communication technology based measures of human behaviour and function to monitor the course of neurodegenerative diseases and detect intervention effects on physical and functional patient-centred outcomes.

Ad 3. Adoption of continuous bi-directional translation pathways for development of new treatments and preventions in neurodegenerative diseases

The competence not only in basic science-oriented research in cell and animal models of neurodegenerative diseases as outlined above, but also a strong expertise in clinical research ensures the continuous bi-directional translational process to overcome current translational roadblocks in the development of novel therapeutic interventions. In this context, intervention is seen as a broad concept integrating all treatment approaching to strengthen physical, cognitive and psycho-social resistance against neurodegenerative insults and/or their impacts. The development of dementia assistance systems is one key topic of the Department Ageing of the Individual and of Society at the Interdisciplinary Faculty of the University of Rostock. In addition, the clinical members within the CTNR (clinical departments and the DZNE) are already conducting more than 30 mono- and multicentre trials in parallel, including investigator-initiated trials (IITs) according to the AMG in various indications such as dementias, movement disorders and motor neuron diseases, which together form a strong basis for the overall aim of the CTNR, namely to implement innovative therapeutic concepts for primary and secondary neurodegenerative processes.



Members Research Profiles

Until the end of 2018, 38 members of the University Medical Centre Rostock, the University of Rostock and external institutes are part of the Centre for Transdisciplinary Neurosciences Rostock. Each member is affected by neuroscience contents through publications or projects in the field. Every neuroscience activity contributes to the overall scientific aim of the CTNR: to identify and target resilience mechanisms in neurodegeneration.

To increase the visibility and to strengthen the shared identity of the CTNR members it is important to know each others research aims, technologies and methodologies. Thus, **targeted strategic CTNR member meetings** have been organised and taken place for the first time since July 2018. The result of the meetings was the submission of grant applications in the field of "Deep learning in Biomedicine". Further "get-together" events are planned (e.g. CTNR lecture series, summer school).

In 2018, the implementation and provision of a **CTNR corporate design** (website, slides, logos) and the use of affiliation in publications led to a stronger identification of the members with the CTNR. An **online survey** of members is planned to identify members' needs and suggestions regarding the CTNR. The following pages introduce the research of the CTNR members by individual research profiles.

Basic mechanisms and novel therapeutic approaches in diabetic neuropathy



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State-of-the Art

Approximately 50 % of patients with diabetes mellitus suffer from polyneuropathy, frequently diagnosed too late. Such complications occur both, in type 1 and 2 diabetes mellitus, even though blood glucose is well controlled, and the HbA1c-value normalized. Damage of peripheral nerves can result in disturbed sensation and pain, eventually leading to amputation and reduced quality of life.

Overall Scientific Aim

Affected nerves are mainly A δ und C fibres, which are present in skin, but also in the subbasal nerve plexus of the cornea. Imaging of the subbasal nerve plexus using microscopy techniques allows a very early and objective view of neuropathy, only possible invasively by skin biopsy.

We have used a thy1-YFP mouse strain in which the peripheral nerves are detectable by fluorescence excitation. Using two-photon microscopy we could demonstrate high-resolution three-dimensional images of the corneal subbasal nerve plexus of these mice. We have induced diabetes mellitus in thy1-YFP mice by injection of streptozotocin.

We could show that the increase in blood glucose was paralleled by a loss of subbasal nerve fibres mainly in the centre of the cornea. The subsequent treatment of the animals with insulin normalized the blood glucose and was accompanied by an increase in subbasal nerve fibres.

Projects, Methods & Technologies

Thus, this model is highly suited to investigate the pathogenesis of diabetic polyneuropathy with the aim to develop new causal strategies to treat them. Neuronal damage could be mediated by increased binding of advanced glycation end products (AGEs) to the AGE receptor (RAGE). In various mouse strains we found that the RAGE expression in the cornea is significantly higher than in other tissues.

Curriculum Vitae

1997 State examination and licensure (Approbation) as a pharmacist, Technical University Braunschweig

1997 - 2000 Research assistant at the Institute of Clinical Biochemistry, Medical School Hannover

2000 PhD in pharmacology (Dr. rer. nat.), Technical University Braunschweig

2000 - 2008 Research associate at the Institute of Clinical Biochemistry, Medical School Hannover

2007 Habilitation in Biochemistry, Medical School Hannover

Since 2009 Full Professor of Medical Biochemistry and Molecular Biology, University Medical Centre Rostock

Since 2015 Member of the board of Department Life, Light, Matter, Interdisciplinary Faculty, University Rostock

2016 Ferdinand-Bertram Award of the German Diabetes Association

Our present research focus is to investigate the sub-epithelial corneal nerve plexus in the recently developed thy1-YFP -RAGE knockout mice during diabetes manifestation.

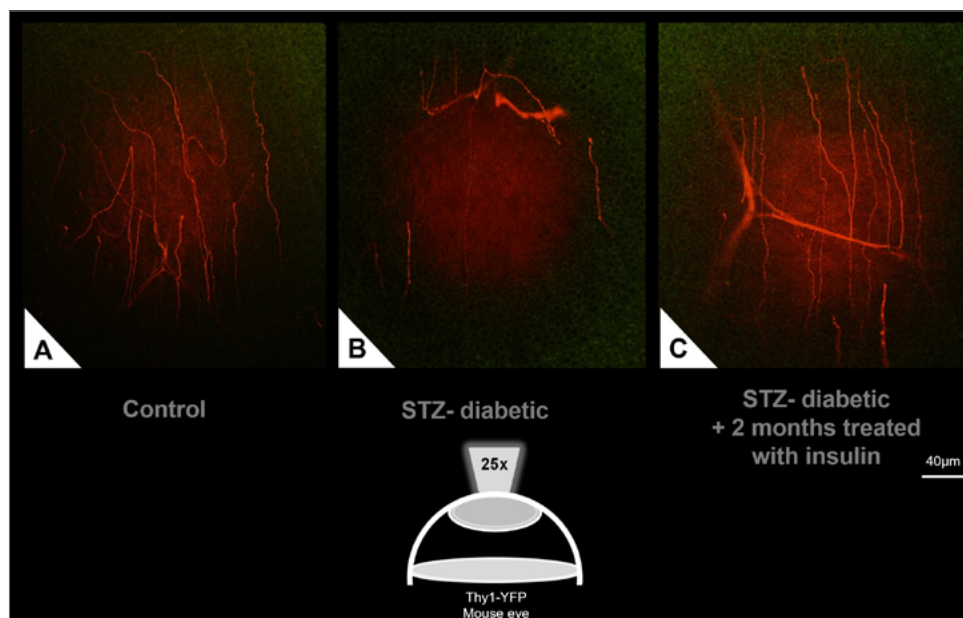


Fig. 1: Subbasal corneal nerves in a healthy, diabetic and treated diabetic thy-1-YFP mouse. [From Baltrusch S (2016). Ophthalmological Monitoring of Diabetic Neuropathy in a Mouse Model. *Klinische Monatsblätter für Augenheilkunde* 233, 1313-1319.]

Selected Publications

- Niemann J, John C, Schroder S, Koch F, Ibrahim SM, Schultz J, Tiedge M, Baltrusch S (2017). An mtDNA mutation accelerates liver aging by interfering with the ROS response and mitochondrial life cycle. *Free Radical Biology and Medicine* 102, 174-187.
- Schultz J, Waterstradt R, Kantowski T, Rickmann A, Reinhardt F, Sharoyko V, Mulder H, Tiedge M, Baltrusch S (2016). Precise expression of Fis1 is important for glucose responsiveness of beta cells. *The Journal of Endocrinology* 230, 81-91.
- Leckelt J, Guimaraes P, Kott A, Ruggeri A, Stachs O, Baltrusch S (2016). Early detection of diabetic neuropathy by investigating CNFL and IENFD in thy1-YFP mice. *The Journal of Endocrinology* 231, 147-157.
- Ehmke T, Leckelt J, Reichard M, Weiss H, Hovakimyan M, Heisterkamp A, Stachs O, Baltrusch S (2016). In vivo nonlinear imaging of corneal structures with special focus on BALB/c and streptozotocin-diabetic Thy1-YFP mice. *Experimental Eye Research* 146, 137-144.
- Baltrusch S (2016). Mitochondrial network regulation and its potential interference with inflammatory signals in pancreatic beta cells. *Diabetologia* 59, 683-687.

Neuro- and electrophysiological correlates of psychiatric disorders



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State-of-the Art

Electroencephalography (EEG) is relatively easy and safe diagnostic tool and has its importance in psychiatric clinical practice mainly for its capability of diagnosis of various neurologic diseases like encephalopathies, focal brain disorders, like tumors and for sleep disorders. EEG is the first line tool to diagnose epilepsy. Beside this use for differentials diagnosis the EEG is a promising source of psychiatric biomarkers, because many of these markers have close neurobiological and behavioral relations. Two examples: the EEG power cordance measure is changeable by antidepressive medication and has a close link to the cerebral blood flow; alpha and theta oscillations are strongly associated with executive functioning and cognition. But meta-analytic reviews show a strong publication bias lacking negative or weak reports, insufficient replications and small sample sizes in many publications. Therefore, EEG has to date not been validated sufficiently to be reliable for guiding psychiatric treatment.

Overall Scientific Aim

It is our aim to analyze EEG derived pattern with links to psychiatric disorders like Depression and ADHD with an emphasis on enlighten reliable links between symptom checklists and EEG markers, and with special focus on validating prior results in higher sample sizes. Furthermore we are interested in replicating the findings from adult studies to psychiatric patients of childhood and adolescent samples. Our research will contribute to a better understanding of neurobiological underpinnings of psychiatric disorders in particular in the context of developmental psychopathology.

Projects, Methods & Technologies

Disturbed regulation of vigilance in wake state seems to play a key role in the development of mental disorders. In one project we are testing whether brain arousal is assessable in pediatric patients with a routine clinical EEG. Vigilance patterns can be derived from EEG via recently developed software VIGALL (University of Leipzig). Resting state EEG measures from two groups of psychiatric patients diagnosed with either ADHD or depression were analyzed. According to the model of Hegerl et al. (2014) we expect a clustering of individual EEG data

Curriculum Vitae

1990 - 1997 graduate engineer in Electrical engineering, University of Rostock

1998 - 2000 IT-project consultant and lecturer, Institute of Maritime Economy, Rostock

2000 - 2004 IT-solutions engineer, T-Systems Nova GmbH, Berlin

2004 - 2013 Scientific Assistant for Neuroscience, Department of Psychiatry, University Medical Centre Rostock

2012 Doctorate in Experimental Psychiatry, University Medical Centre Rostock

Since 2013 Senior scientist and lab engineer, Department of Childhood and Adolescent Psychiatry, University Medical Centre Rostock

into hyper- and hypo-stable vigilance regulation types which should be associated with either Depression or ADHD.

EEG microstates as transient quasi-stable global patterns of EEG topographies have been shown to be altered in adult psychiatric patients with psychosis, with Dementia, with mood and anxiety disorders and also in children with Autism Spectrum Disorder. Beside this, microstates haven't been further investigated in pediatric psychiatry so far. In an explorative study we aim to describe possible alterations in EEG microstate dynamics in a wider sample of clinical routine EEG of Children with psychiatric disorders of our clinic in relation to their diagnosis.

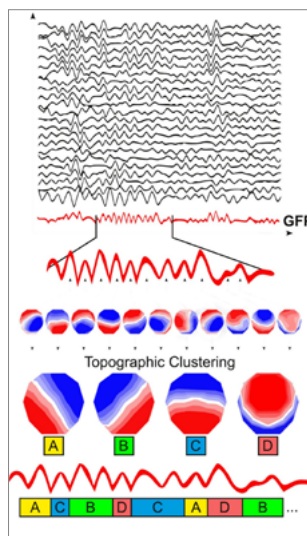


Fig. 1: An illustration of the method of microstate clustering and analysis. [From A. Khanna et al (2015). *Neurosci Biobehav Rev.* 49, 105-13.]. The global field power curve gives a measure of the instantaneous field strength over time. Peaks of the GFP curve represent instances of highest field strength and largest topographic SNR. Electric potential maps of all electrodes were clustered into a small map set based on topographic similarity. Most studies of resting-state EEG microstates find the same set of four cluster maps (labeled A-D)

In a recent study we investigate the efficiency of bright light therapy in pediatric in-house patients beside the relevance for depressive symptoms additionally via potential EEG biomarkers for Depression, in particular the cingulate theta power and vigilance regulation.

Each EEG in clinical routine is accompanied by assessment of ECG according to Einthoven, giving the opportunity to analyze heart rate variability (HRV). Dysregulation of mood, affect and anxiety is associated with dysregulation of autonomic nervous system (ANS), which can be indexed by the loss of HRV. Despite the high amount of adult HRV study reports, the understanding of development of cardiac autonomic nervous system is still very limited. Therefore it's the focus of another project, to how much extent the HRV in pediatric patients with depression is affected by depressive symptoms and how much influences the common developmental HR reduction the HRV.

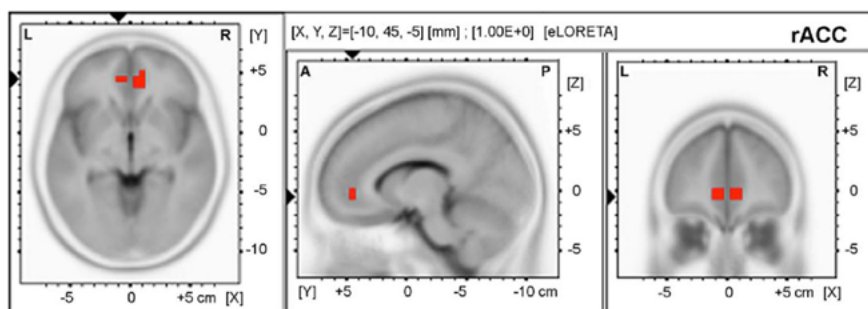


Fig. 2: Region of Interest studying EEG biomarker for depression. [From Arns et al. (2015). *Eur Neuropsychopharmacol* 25, 1190–1200].

Extracted resting state theta power (6.5–8 Hz) from the rostral anterior cingulum using eLORETA. Results of this study: high baseline rACC theta was associated with treatment non-response and low post treatment rACC theta was found in antidepressant responders.

Selected Publications

- Berger C, Müller-Godeffroy J, Marx I, Reis O, Buchmann J, Dück A (2018). Methylphenidate promotes the interaction between motor cortex facilitation and attention in healthy adults: A combined study using event-related potentials and transcranial magnetic stimulation. *Brain and Behavior* 8(12), e01155.
- Brueggen K, Fiala C, Berger C, Ochmann S, Babiloni C, Teipel SJ (2017). Early Changes in Alpha Band Power and DMN BOLD Activity in Alzheimer's Disease: A Simultaneous Resting State EEG-fMRI Study. *Front Aging Neurosci* 9, 319.
- Lischke A, Herpertz SC, Berger C, Domes G, Gamer M (2017). Divergent effects of oxytocin on (para-)limbic reactivity to emotional and neutral scenes in females with and without borderline personality disorder. *Soc Cogn Affect Neurosci*. 12(11), 1783–1792.
- Marx I, Weirich S, Berger C, Herpertz SC, Cohrs S, Wandschneider R et al. (2017). Living in the fast lane: evidence for a global perceptual timing deficit in childhood ADHD caused by distinct but partially overlapping task-dependent cognitive mechanisms. *Front Hum Neurosc* 11, 122.
- Berger C, Domes G, Balschat J, Thome J, Hoepfner J (2015). Effects of prefrontal rTMS on autonomic reactions to affective pictures. *J Neural Transm*. 124, 139–152.

Drug therapy safety and social paediatric aspects in paediatric epileptology



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State-of-the Art

Most epilepsy patients need an anticonvulsive long-term therapy. Drug-related problems, however, endanger the success of therapy under routine conditions. This is the case since a lack of efficacy or the occurrence of preventable adverse drug events (ADE) can limit the possible therapeutic outcome as reported by clinical trial with good internal validity. ADE are usually considered primarily from a medical point of view. The perspective of patients and their relatives is often neglected. However, the latter can have a high influence on adherence. Various projects have shown that, from the point of view of paediatric epilepsy patients and their parents, there are considerable impairments of daily life due to ADE. The participation of children and adolescents with epilepsy and developmental disorders is endangered by the need of long-term medication, possible ADE, disease-related restrictions, necessary safety measures in everyday life and stigmatisation by the environment.

In case of an acute seizure lasting longer than five minutes the use of rescue medication is recommended as the chance of successful termination of a seizure dramatically declines if a seizure lasts longer than five minutes. This rescue medication has to be administered by non-professionals such as parents as an ambulance would take too long to arrive. As most children and adolescents spend most of the day outside their home caregivers such as teachers should as well be able to administer a prescribed rescue medication appropriately.

Overall Scientific Aim

To get deeper insights on the knowledge and perception of epilepsy by the paediatric patients themselves, their parents, peers, teachers, doctors, therapists, pharmacists and the general public. This insight should help to develop programmes to improve safety and participation of paediatric epilepsy patients. Besides, we are aiming at reducing ADE and at helping patients to cope with ADE that are inevitable. To improve safety in case of an acute seizures we develop training programmes on rescue administration for non-professionals such as parents, teachers and therapists.

Curriculum Vitae

1992 - 1999 State exam and Doctorate in Medicine, Ruhr University Bochum

1999 - 2005 Paediatric training, Center of Paediatrics, Charité University Medicine Berlin

2005 - 2009 Neuropaediatric training and senior neuropaediatrician, Department of Paediatric Neurology, Heidelberg University Hospital

2009 - 2010 Senior neuropaediatrician, Department of Neuropaediatrics, Essen University Hospital

2011 - 2017 Senior neuropaediatrician, Leipzig University Hospital for Children and Adolescents

2014 Habilitation in Paediatrics

Since 2018 Full Professor (W2) for Neuropaediatrics, University Medical Centre Rostock

Since 2019 Deputy Director of the Hospital for Children and Adolescents, University Medical Centre Rostock

Projects, Methods & Technologies

We participate in the multicentre project KiDSafe funded by the Federal Joint Committee which aims at reducing ADE by a database which implementation is supported by quality circles. In addition, the spontaneous reporting behaviour of ADE is to be improved by KiDSafe. In our research group in Rostock we perform surveys of parents of epilepsy patients and of the patients themselves to get a deeper insight in the perception of ADE and their impacts on life of paediatric epilepsy patients and their families. The results are to be incorporated into individually tailored training programmes and optimised care concepts.

Besides, we participate in the multicentre project CARE-FAM-NET - Children affected by rare disease and their families – network funded by the Federal Joint Committee. We participate in the project together with colleagues from medical psychology and sociology of the University Medical Centre Rostock. The project is aiming at improving the psychosocial situation of children with rare diseases (e.g. rare epilepsy syndromes) through a psychodynamic-psychosocial intervention (face-to-face) and/or an online intervention based on principles of cognitive-behavioural writing therapy.

To improve safety and participation of paediatric patients with epilepsy we perform surveys on knowledge and attitudes towards epilepsy. Those surveys are addressing the (paediatric) patients themselves, their parents, peers, teachers, doctors, therapists, pharmacists and the general public. In order for training programmes to be effective, we investigate what training needs exist. Training programmes can then be developed to meet the individual needs of the participants. A special focus of our group is in developing practical training programmes for caregivers such as parents and teachers in order to improve the willingness and abilities to correctly administer a prescribed epilepsy rescue medication.

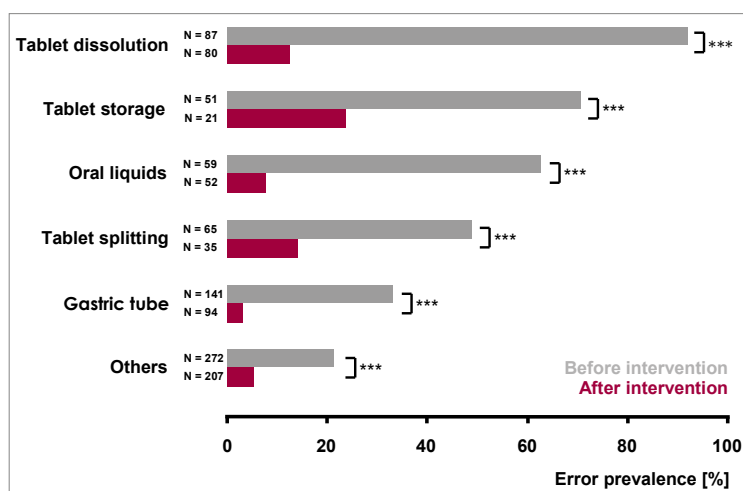


Fig. 1: Reduction of drug administration errors on a neuropaediatric ward after a teaching and training programme for nurses and parents supported by information pamphlets. Grey bars: Administration errors before the intervention. Red bars: Administration errors after the intervention. ***p<0.001. N, total number of observed processes in the respective categories by monitoring on the ward [Figure modified from Bertsche T, Bertsche A et al. (2010) Qual Saf Health Care 19, e26].

Selected Publications

- Bach VA, Neininger MP, Spindler UP, Hotopp LC, Hornemann F, Syrbe S, Merkenschlager A, Kiess W, Bernhard MK, Bertsche T, Bertsche A (2018). How do parents perceive adverse drug events of their children's anticonvulsant medication? Eur. J. Paediatr. Neurol. 22, 427-433.
- Jansen P, Neininger MP, Bernhard MK, Merkenschlager A, Kiess W, Bertsche T, Bertsche A (2017). Knowledge and attitudes about epilepsy: A survey of high school students in Germany. Seizure 51, 139-144.
- Dumeier HK, Neininger MP, Kaune A, Schumacher PM, Merkenschlager A, Kiess W, Bernhard MK, Bertsche T, Bertsche A (2017). Seizure management by preschool teachers: A training concept focussing on practical skills. Seizure 50, 38-42.
- Dumeier HK, Neininger MP, Bernhard MK, Syrbe S, Merkenschlager A, Zabel J, Kiess W, Bertsche T, Bertsche A (2015). Knowledge and attitudes of school teachers, preschool teachers and students in teacher training about epilepsy and emergency management of seizures. Arch. Dis. Child. 100, 851-855.
- Syrbe S et al. (2015). De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat. Genet. 47, 393-399.

Movement disorders in childhood, pain in the musculoskeletal system



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State-of-the Art

Children with mental disorders are very often disturbed in motor development as well. Many of these children also have cognitive limitations and behavioural problems. Often there is a coincidental epileptic syndrome, possibly due to a genetically determined disease. When unfavourable social conditions then occur, the children react accordingly, e.g. with pain, depression or conduct disorders. Adolescents react with self harming. Many of these behaviours are based on impaired impulse control that significantly affect both motor and cognitive and, more broadly, social development.

Overall Scientific Aim

In general, only certain investigation methods can be used in younger children. In our neurophysiological research laboratory, we combine these methods that can be used in this age, e.g. electroencephalography (EEG) and transcranial magnetic stimulation (TMS). We investigate cerebral inhibition and facilitation processes in children with attention deficit hyperactivity disorder (ADHD), Tourette-Syndrome or self-harming adolescents, both with and without medication (see, for example, Fig.1 -ipsilateral silent period and fig. 2 -SICI and LICI in ADHD children).

Projects, Methods & Technologies

TMS over the motor cortex is well suited for the investigation of motor developmental disorders, and this method is very suitable for children. With TMS, inhibition and facilitation processes in the motor cortex can be investigated, which can be the cause for, for example, hyperkinetic behaviour in ADHD or motor tics in Tourette-syndrome. The basis could again be the impaired impulse control. EEG with recording of endogenously evoked potentials (event related potentials = ERP) is also suitable as investigation method for children. Reaction times and reaction types to defined stimuli in specific experimental settings are typical in children with ADHD or in adolescents with self-harm. In paradigm, such as "A not X" can be described by the ERP disturbed cerebral processing in these children. In these experimental settings it is possible to study impulse control in children, regardless of the underlying disease. They are applicable to diseases such as ADHD, Tourette, obsession-compulsive disorder,

Curriculum Vitae

1984 - 1990 State exam in Medicine, University of Rostock

1993 Doctorate in exploratory data analysis in medicine, University Medical Centre Rostock

Since 1995 Specialist in neurology and psychiatry

Since 1998 Senior specialist

Since 2001 Specialist in child- and adolescence psychiatry

2007 Habilitation in Child- an Adolescence Psychiatry, University Medical Centre Rostock

Since 2013 Apl. Professor for Child- and Adolescence Psychiatry, University Medical Centre Rostock

headache (migraine) or motor developmental disorder. The EEG, as polysomnography, could also be used to study sleep in children with these disorders. Disturbed sleep architecture is described in many mental and developmental disorders.

In close collaboration with the sonography laboratory of the Department of Neurology we are investigating in a joint project, inhibiting and facilitating mechanisms in children with ADHD and children with Tourette's syndrome compared to a healthy control group. Morphological data (transcranial sonography) were correlated with data from transcranial magnetic stimulation (short interval cortical inhibition SICI / long interval cortical inhibition LICI / intercortical inhibition ICI) and motor performance (tapping).

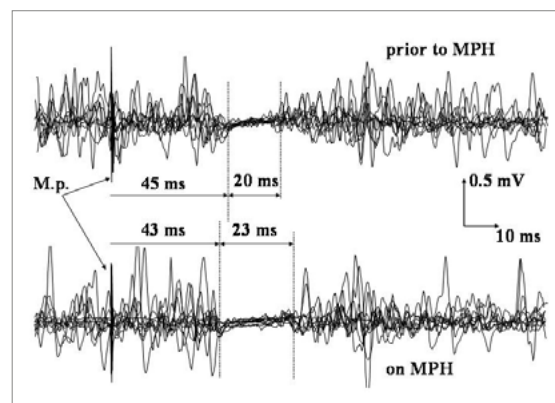


Fig. 1: Ipsilateral silent period.

In other projects, we examine self harming adolescents in their response to pain like stimuli with eeg / erp or the interaction of sleep and behavior as well as sleep and motor performance. These are related to behavioural or depressive symptoms.

Impaired impulse control seems to be an essential mechanism in the development of mental disorders with motor symptoms (ADHD) or motor disorders with obsession-compulsive symptoms (Tourette). The combination of child-adapted neurophysiological investigation methods with e.g. transcranial sonography seems to be a promising approach for the characterization of such diseases.

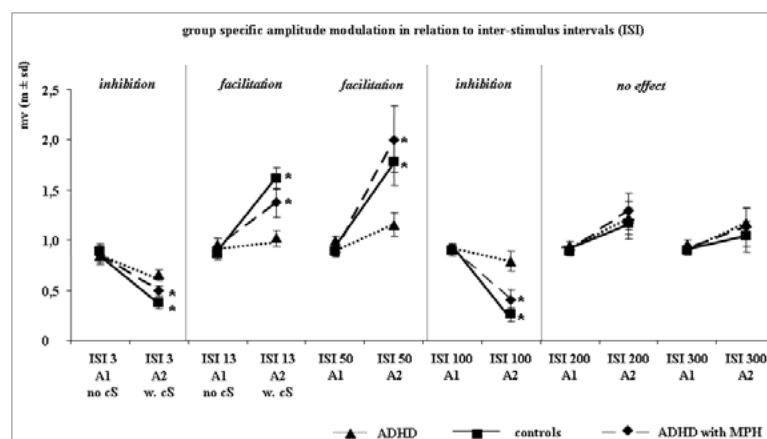


Fig. 2: SICI and LICI in ADHD children.

Selected Publications

- Berger C, Muller-Godeffroy J, Marx I, Reis O, Buchmann J, Duck A (2018). Methylphenidate promotes the interaction between motor cortex facilitation and attention in healthy adults: A combined study using event-related Potentials and transcranial magnetic Stimulation. *Brain and behavior* 8(12):e01155.
- Wittstock M, Buchmann J, Walter U, Rosche J (2018). Vagus Nerve Stimulation and External Defibrillation during Resuscitation; a Letter to Editor. *Emerg (Tehran)*. 6(1), e27.
- Reinhardt M, Wunsch K, Weirich S, Massier F, Buchmann J (2018). Electroconvulsive Therapy (ECT) of a 15-year-old female patient suffering from a severe delusional depression: a case report. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie* 46(6), 536-541.
- Bolz M, Korber S, Reimer T, Buchmann J, Schober H, Briesse V (2017). The Treatment of Illnesses Arising in Pregnancy. *Dtsch Arztebl Int.* 114(37), 616-626.
- Levene R, Günther O, Rothkötter HJ, Bitterlich N, Buchmann J (2014). Treatment of myofascial lumbar dorsal pain : Effective clinical diagnostics and therapy. *Schmerz*. 28(6), 573-583.

(Forensic) Neuropathology



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State-of-the Art

Post-mortem studies of the human central nervous system are of tremendous importance for the exact diagnosis and clinical-neuropathological correlation of deceased patients. In addition, human tissues obtained from these cases provide the possibility of profound histological, immunohistochemical, and molecular studies for research.

Forensic Pathology as one of the main working area in Forensic Medicine determines through gross external and internal examination (autopsy), as well as additional histological and toxicological examination, how diseases and injuries affected the deceased. The primary objective is the determination of the cause of death and the manner of death (natural, accidental, suicide, homicide, undetermined).

The analyses are accomplished through examination of physical evidence at the crime scene, police and medico legal investigative reports, and the medical record. Besides, we perform clinical autopsies after informed consent of the relatives as part of the internal quality control of the medical therapy at the Rostock University Medical Centre.

Forensic neuropathology is a sub-specialty, which mainly focuses on traumatic injuries to the central, and peripheral nervous system. However, due to the composition of our autopsy cohort a broad spectrum of neurological and neurodegenerative diseases are encountered which also requires profound knowledge in general neuropathology.

Overall Scientific Aim

Due to the aging society the rate of neurodegenerative diseases are increasing, rendering the opportunity to conduct research on human brain tissues that will be obtained during autopsy.

Curriculum Vitae

1983 - 1988 Autopsy technician, Institutes of Pathology, Haar, Berlin, Munich

1988 - 1994 Medical School, Ludwig-Maximilians-University (LMU) of Munich

1994w Doctorate in Neuropathology, LMU Munich

1994 - 1996 Institute of Neuropathology, Neurosurgical Clinic, LMU Munich

1997 - 2009 Institute of Legal Medicine, LMU Munich

2004 Habilitation in Legal Medicine, Medical Faculty, LMU Munich

Since 2009 Full Professor (W3) and Director of the Institute of Legal Medicine, University Medical Centre Rostock

Since 2010 Chairman of the Ethical Commission, University Medical Centre Rostock

Projects, Methods & Technologies

Within the CTNR our institute holds the autopsy service from the donor program of the Rostock University Medical Centre in collaboration with the DZNE. We conduct professional sampling of the brain and spinal cord after informed consent of the donors or their relatives for subsequent neuropathological examination. Especially in well-characterized patients, clinical-neuropathological correlation with exact morphological classification of the disease will be beneficial for improving diagnosis and therapeutic options. Furthermore, as the head of the ethical commission and the commission on patient safety of the Rostock University Medical Centre, all research applications are verified ensuring that all studies of the CTNR will be performed according to the international ethical guidelines and the respective laws of the Federal Republic of Germany.

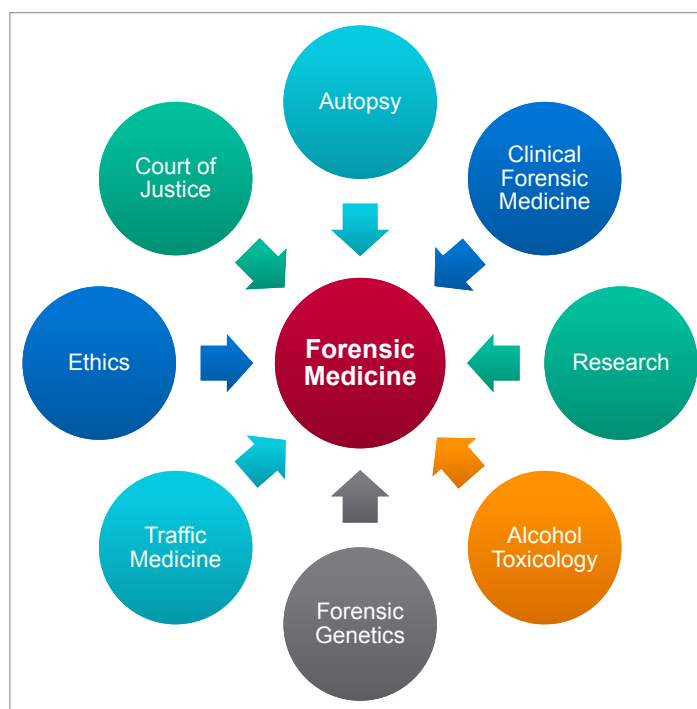


Fig. 1: Activities in Forensic Medicine.

Selected Publications

- Fichtl A, Büttner A, Hof PR, Schmitz C, Kiessling MC (2018). Delineation of subregions in the early postnatal human cerebellum for design-based stereologic studies. *Front. Neuroanat.* 11, 134.
- Weis S, Büttner A (2017). Neurotoxicology and drug-related disorders. In: Kovacs G., Alafuzoff I. (Ed.). *Handbook of Clinical Neurology. Volume 145. Neuropathology.* Elsevier, Amsterdam, Chapter 14, 181-192.
- Büttner A (2017). The neuropathology of drug abuse. *Curr. Opin. Behav. Sci.* 13, 8-12.
- Matschke J, Büttner A, Bergmann M, Hagel C, Püschel K, Glatzel M (2015). Encephalopathy and death in infants with abusive head trauma is due to hypoxic-ischemic injury following local brain trauma to vital brainstem centers. *Int. J. Legal Med.* 129, 105-114.
- Büttner A (2011). The neuropathology of drug abuse. *Neuropathol. Appl. Neurobiol.* 37, 118-134.

IPSCs for disease modelling and drug discovery in lysosomal storage diseases



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State-of-the Art

The group of lysosomal storage diseases (LSDs) comprises more than 60 disease. The largest proportion of LSDs is inherited autosomal recessive. The phenotypical characteristics of LSD includes defects in degradative and synthetic enzymes, lysosomal membrane defects, disorders of lysosome biogenesis and endosome-lysosome trafficking. The various defects result in cellular storage of the substrates of the defective enzymes and consequently to dysfunction in different cell types of the nervous system, eye, bone or inner organs such as lung, spleen and liver. Such perturbations of cellular processes ultimately lead to cell death and organ-specific clinical manifestations. For most of the LSDs no appropriate treatment is available. Thus, a sound knowledge of the pathogenic mechanisms of LSDs is essential to evolve new therapeutic approaches. Against this background we study pathophysiological features of the LSD Niemann-Pick type C1 (NPC1). NPC1 is a rare autosomal recessive lysosomal lipidosis, with an incidence of 1: 120,000 and thus classified as a rare disease. Mutations in the NPC1 gene result in the expression of non-functional or functionally reduced protein. The dysfunction of NPC1 protein leads to an accumulation of unesterified cholesterol in late endosomes and lysosomes. These accumulations can be detected using the Filipin test, displaying a clinical diagnostics tool. NPC1 is defined as neurovisceral disease, with visceral and neurological symptoms occurring at different times and degrees. Visceral dysfunctions are observed in the liver, spleen and lung. Neurological symptoms include motor dysfunctions such as dystonia and cerebellar ataxia. However, the link between the accumulation of cholesterol and the progressive neurodegeneration is yet not well understood. A variety of cellular and animal models are used to elucidate pathogenic mechanism of NPC1. However, studies on human neuronal tissues are limited to postmortem biopsies and thus exclude functional studies. Here, human induced pluripotent stem cells represent an excellent opportunity to expand the range of in vitro disease models for NPC1 and thus the opportunity to gain a deeper understanding of pathophysiological processes underlying NPC1.

Overall Scientific Aim

A detailed understanding of mechanisms contributing to neurodegeneration is prerequisite to develop new therapeutic strategies. Thus, one aim is to develop cellular NPC1 disease model systems based on NPC1 patient

Curriculum Vitae

1991 - 1997 Studies in Biology, University of Kaiserslautern

1998 - 2001 Doctorate in Biology, Max-Planck-Institute for Brain Research, Frankfurt a.M.

2001 - 2003 Postdoc, J.W.Goethe-University, Frankfurt a.M.

2003 - 2006 Lab Head, Grünenthal GmbH, Aachen

Since 2007 Group Leader "Cellular Neurophysiology", University Medical Centre Rostock

specific-iPSCs. Using cellular derivatives of these iPSCs, such as neuronal cells and hepatocyte-like cells, we seek not only to gain a better understanding of the pathogenic mechanisms of NPC1, but we utilize such cell models to discover compounds attenuating pathophysiological features of NPC1 and thus representing a base to develop new treatment strategies.

Projects, Methods & Technologies

Disease Modelling

Recent work on the NPC1 patient specific-iPSCs focused on the evaluation of pathophysiological hallmarks of NPC1 on a cellular level. These studies have proven different NPC1 phenotypical signs amongst others accumulation of cholesterol and gangliosides, gliosis and oxidative stress. Current projects aim to broaden the description of further pathological marks of NPC1 to demonstrate on the one hand the feasibility of the iPSCs for disease modeling and on the other hand to gain a deeper understanding of pathophysiological mechanisms. Against this background we are interested in the impact of intracellular transport deficits on the transport of mitochondria, autophagosomes and lysosomes. An impairment of these basic cellular processes might contribute to the imbalance of autophagy observed in NPC1 and other neurodegenerative diseases. In turn such aberrations can induce or intensify other pathophysiological features like oxidative stress. It is our understanding not only to dissect the malfunction of single cellular processes, but to elucidate how one effects the other.

Drug Discovery

A causal therapy of the Niemann-Pick type C is currently not available. At present, Miglustat (n-butyldeoxynojirimycin, NB-DNJ) is the only drug approved by the European Medicines Agency for NPC therapy. Miglustat is a reversible inhibitor of glucosylceramide synthase and has been approved for the treatment of Gaucher type disease as a substrate reduction therapy. Other potential therapeutic approaches, such as treatment with cyclodextrin, histone deacetylase inhibitors and pharmacological chaperones, are currently under discussion. Pharmacological chaperones (PCs) assist misfolded proteins in correct folding, resulting in an increased amount of functional NPC1 proteins in the late endosomes/lysosomes. Previously tested chaperones contained various oxysterol derivatives, such as 25-hydroxycholesterol, which showed a reduction in cholesterol content in fibroblasts and an improvement in the NPC1 phenotype. Using in silico docking simulations, in a collaborative research project with the PePPP young investigator group of Dr. Jan Lukas, we aim to identify potential pharmacological chaperones. Effective compounds will stabilize misfolded NPC1 protein, subsequently leading to an increased amount of NPC1 protein in the lysosomal compartment. Thus, such compounds should contribute to a reduction

of the cholesterol overload. Besides the approach using PCs, we aim to alleviate pathophysiological characteristics like hypo-/hyperphosphorylation of intermediate filaments, oxidative stress, or malfunction/misplacement of ion channels, to relieve neurodegeneration in NPC1.

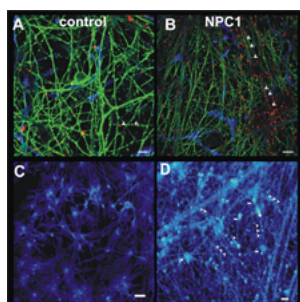


Fig. 1: β III-tubulin staining (green) of iPSC derived neurons of a control cell line derived from fibroblasts of a healthy control (A) and of fibroblasts of a NPC1-patient (B). One can observe the presence of the ganglioside GM2 (red in A and B) in both cell lines, wherein the amount of GM2 is higher in the NPC1-cell line, depicting an pathophysiological hallmark of NPC1. Detection of cholesterol using a Filipin staining (blue in C and D) demonstrate the typical accumulation of cholesterol in NPC1-deficient cells.

Selected Publications

- Rabenstein M, Peter F, Rolfs A, Frech MJ (2018). Impact of reduced cerebellar EAAT expression on purkinje cell firing pattern of NPC1-deficient Mice. *Sci Rep*; 8(1), 3318.
- Trilck M, Peter F, Zheng C, Frank M, Dobrenis K, Mascher H, Rolfs A, Frech MJ (2017). Diversity of glycosphingolipid GM2 and cholesterol accumulation in NPC1 patient-specific iPSC-derived neurons. *Brain Res*. 1657, 52-61.
- Peter F, Trilck M, Rabenstein M, Rolfs A, Frech MJ (2017). Dataset in support of the generation of Niemann-Pick disease type C1 patient-specific iPS cell lines carrying the novel NPC1 mutation c.1180T>C or the prevalent c.3182T>C mutation – analysis of pluripotency and neuronal differentiation. *Data Brief*. 12, 123-131.
- Peter F, Rost S, Rolfs A, Frech MJ (2017). Activation of PKC triggers rescue of NPC1 patient specific iPSC derived glial cells from gliosis. *Orphanet J Rare Dis*. 12(1), 145.
- Rabenstein M, Peter F, Joost S, Trilck M, Rolfs A, Frech MJ (2017). Decreased calcium flux in Niemann-Pick type C1 patient-specific iPSC-derived neurons due to higher amount of calcium-impermeable AMPA receptors. *Mol Cell Neurosci*. 83, 27-36.

Understanding the molecular basis of health, disease, ageing and senescence



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State-of-the Art

Ageing is defined by all processes that reduce well-being, which is best defined as the composite of health and survival. For a long time, it was known that caloric restriction tends to counteract ageing processes and increase lifespan. Around 30 years ago, it was shown in model species that targeted interventions increase lifespan. Only recently, it was shown in model species that ageing can be partially reversed by senotherapy: by killing senescent cells. In 2019, the first human pilot studies of senotherapeutic compounds demonstrated that the targeted killing of senescent cells improves function in a variety of diseases (idiopathic pulmonary fibrosis, osteoarthritis). It is conceivable that natural compounds such as fisetin (found in strawberries) or quercetin (found in a variety of fruit and vegetables) can, given in the right dose and combination, have senotherapeutic effects. Ultimately, biomarkers are needed to personalize senotherapies, to prevent or treat a wide array of diseases, from cancer to neurodegeneration. The senescence status of a person will be an important tool for predicting progression for many diseases, and for intervening. We thus use molecular measurements (lab values and omics data) to investigate the connection between individual senescence-related biomarker scores & other disease related biomarker measurements, and disease diagnosis/prognosis. Biomarkers are usually identified by machine learning, aided by network biology tools.

Overall Scientific Aim

At the Institute for Biostatistics and Informatics in Medicine and Ageing Research (IBIMA), we are specifically interested in health and prevention, investigating the molecular basis of ageing processes. Generally, we strive to better understand diseases, to propose means for their prevention, to support existing treatments and to develop new strategies to help patients. We support the process of transfer of existing knowledge into medical practice. Thereby, we perform a valuable contribution to the continuous improvement of patient care in the university hospital and beyond. One clinical feature connecting most of the diseases is that these occur more frequently in older populations. We want to find out, what it is on a molecular level that makes some people age more quickly and less healthy than others. One flagship is our current EU funded project "Ageing with Elegans" in which we investigate the effect of ageing on the transcriptome and how this can be modulated. Ongoing work is a

Curriculum Vitae

1992 Diplom in Computer Science, University of the Saarland
 1992 - 1993 Visiting Scientist / Graduate Student, MIT, Cambridge, USA
 1993 Master of Science in Chemistry, MIT, Cambridge, USA
 2000 Doctorate, University of Bielefeld
 2000 - 2001 Scientific Staff, Chair for Systematic Zoology, University of Bochum
 2001 - 2006 Assistant Professor (Wiss. Assistant, C1), Medical Faculty, University of Münster
 2006 - 2008 W2-Professor, Bioinformatics, Institute of Mathematics and Computer Science, University of Greifswald
 Since 2008 W3-Professor and Director, Institute for Biostatistics and Informatics in Medicine and Ageing Research (IBIMA), University Medical Centre Rostock

community effort to map health span pathways and to specify the terminology to describe health. On a molecular level we are interested in molecular pathways contributing to senescence and fibrosis as age-associated cellular phenotypes.

Projects, Methods & Technologies

A core element of our work is to identify new biomarkers. In population studies this may be genetic variations. For patients this may be a particular profile of the transcriptome that is seen in conjunction with clinical phenotypes. The challenge is to constrain an avalanche of data from patients and from public resources towards a much smaller set of molecular interactions that can be experimentally investigated. Along these lines, the IBIMA has developed concepts ("Focus Heuristics", "Expr Essence") to map disease expression data to public molecular network data and then derive a condensed network. We are also interested to learn how to adopt these principles to best compare changes to the transcriptome of diseases with changes known to be induced by drugs, and further by combinations of drugs. We have a local pipeline of tools for the semi-automated processing of Next-Generation Sequencing data that feeds into above routines for condensing networks. These we apply on data from clinical collaborators. We strive to integrate image analyses towards "radio genomics" and have supported investigations of the immune repertoire. As part of our interdisciplinary approach we strive to make science accessible to the public and participate in events such as "Lange Nacht der Wissenschaft". Therefore, we put value to a pronounced competency of our staff members to cooperate with medical research partners.

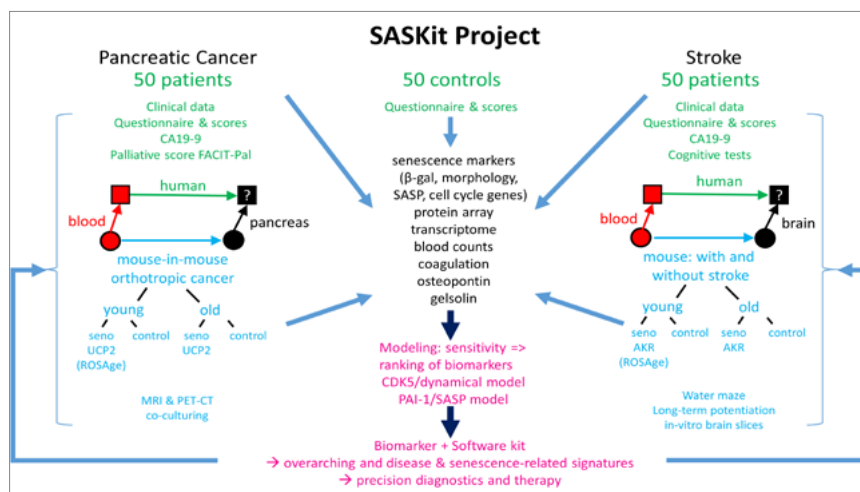


Fig. 1: Graphical abstract of the SASKit project. Pancreatic cancer and ischemic stroke are studied in human and mouse, including senescence-prone ("seno") strains already studied during a predecessor BMBF project (ROSAge). For machine learning and modelling with the aim of a diagnostic/prognostic biomarker kit, human and mouse data are then integrated by the parallelogram approach that extrapolates inter-species data if three of four corresponding data sets are known. Dynamical models are developed specifically with a focus on PAI-1, CDK5 and p16/p21 (CDKN2A/1A). β -gal denotes the senescence associated (SA) form of β -galactosidase. The figure also lists the core measurements done by all sub projects (centre), and the measurements done only by some sub projects (below and above the parallelograms).

Selected Publications

- Fuellen G, Jansen L, Cohen AA, Luyten W, Gogol M, Simm A, Saul N, Cirulli F, Berry A, Antal P, Köhling R, Wouters B, Möller S (2018). Health and Aging: Unifying Concepts, Scores, Biomarkers and Pathways. *Aging Dis.* 10(4), 883-900.
- Hamed M, Gladbach Y, Möller S, Fischer S, Ernst M, Struckmann S, Storch A, Fuellen G (2018). A workflow for the integrative transcriptomic description of molecular pathology and the suggestion of normalizing compounds, exemplified by Parkinson's disease. *Sci Rep.* 8(1), 7937.
- Cohen AA, Legault V, Fuellen G, Fülöp T, Fried LP, Ferrucci L (2018). The risks of biomarker-based epidemiology: Associations of circulating calcium levels with age, mortality, and frailty vary substantially across populations. *Exp Gerontol.* 107, 11-17.
- Ernst M, Du Y, Warsow G, Hamed M, Endlich N, Endlich K, Murua Escobar H, Sklarz LM, Sender S, Junghanß C, Möller S, Fuellen G, Struckmann S (2017). FocusHeuristics - expression-data-driven network optimization and disease gene prediction. *Sci Rep.* 7, 42638.
- Fuellen G, Schofield P, Flatt T, Schulz RJ, Boege F, Kraft K, Rimbach G, Ibrahim S, Tietz A, Schmidt C, Köhling R, Simm A (2016). Living Long and Well: Prospects for a Personalized Approach to the Medicine of Ageing. *Gerontology* 62(4), 409-16.

Topographic neuroimaging patterns of neurodegenerative dementias



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State-of-the Art

One of the most intriguing features of neurodegenerative disease pathologies, such as aggregates of misfolded amyloid or tau proteins in Alzheimer's disease (AD), is that they typically progress in stereotyped patterns along specific vulnerable neuronal systems. Although these typical pathologic progression patterns are already widely used in neuropathological staging schemes, the underlying neurobiological mechanisms that cause these distinct regional vulnerabilities remain largely unknown. Novel PET and MRI-based neuroimaging techniques now allow monitoring diverse types of neurodegenerative brain changes in the living human brain, but the topographic information on pathology spread is not yet commonly assessed in imaging-based in-vivo assessments.

Overall Scientific Aim

To characterize brain-wide neuroimaging patterns of molecular, structural, and functional brain changes that underlie cognitive decline and dementia in the elderly, to study the potential clinical use of these patterns as topographic imaging biomarkers for early detection and staging of neurodegenerative disease, and to explore the specific molecular-functional properties of the affected neuronal systems that may underlie their selective vulnerability to pathology accumulation. Our research outcomes contribute to the development of novel diagnostic and prognostic frameworks based on individual neuroimaging patterns of pathologic brain alterations, and further provide novel insights into the complex molecular-functional mechanisms driving regionally-specific formation and progression of neurodegenerative disease pathology in the human brain.

Projects, Methods & Technologies

Our general research approach is based on the advanced computational analyses of PET and MRI neuroimaging data from large-scale observational cohort studies of older individuals with varying degrees of cognitive impairment, who are characterized by diverse cognitive, molecular, and genetic variables in addition to the neuroimaging assessments.

Curriculum Vitae

2003 - 2009 Diploma in Biology, Department of Biology, University of Cologne

2009 - 2011 MR Image Analyst, German Competence Network for Dementia (KND)

2011 - 2014 PhD (Dr.rer.hum.) in Experimental Psychiatry, Rostock University Medical Center

2014 - 2017 Post-doctoral Researcher at the German Center for Neurodegenerative Diseases (DZNE), Rostock

Since 2017 Principal Investigator at the German Center for Neurodegenerative Diseases (DZNE), Rostock

Using a novel analytic approach for characterizing topographic neuroimaging patterns of progressive pathologic brain alterations, we could demonstrate for the first time the feasibility of in-vivo staging of regional amyloid deposition in amyloid-sensitive PET imaging data. Our analyses indicated that PET-measured amyloid deposition follows a predictable regional sequence that resembles previous neuropathological estimates and can be used analogously to neuropathological approaches for staging an individual's pathologic state along this sequence. Advanced in-vivo amyloid stages were most frequent in AD dementia patients, but were also observed in patients with mild cognitive impairment and even in cognitively normal older participants where they associated with subtle memory impairments (Fig. 1). An important implication of this finding is that PET-based in-vivo staging of amyloid deposition may be used for improving clinical prognosis of individuals in predementia stages of AD.

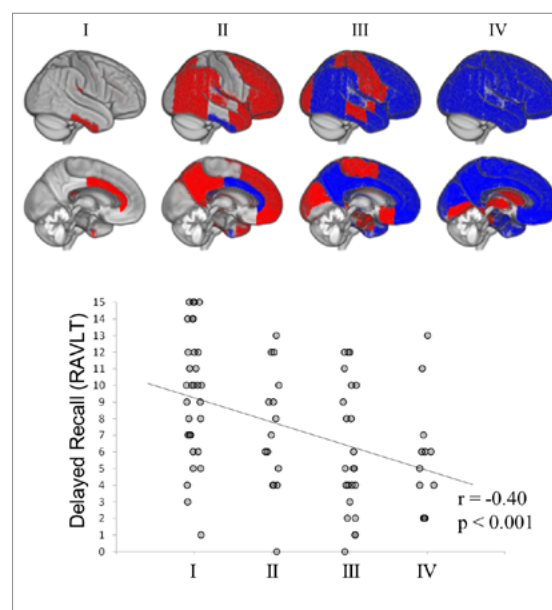


Fig. 1: In-vivo stage model of regional cerebral amyloid progression derived from amyloid-PET data. Advanced amyloid stages associate with worse memory performance among cognitively normal individuals.

In addition to amyloid-PET imaging, tau-sensitive PET imaging techniques have recently emerged, and in a collaboration with Harvard Medical School (Dr. Jorge Sepulcre) we used sophisticated computational methods to analyze distinct regional patterns of amyloid and tau pathology distribution in a unique dataset of multimodal PET acquisitions from the Harvard Aging Brain Study. The study revealed that associations between these two pathologic hallmark pathologies of AD are not global, but primarily observed between specific regional deposition patterns of the respective proteins. These in-vivo neuroimaging analyses not only add important novel information to long-standing neuropathologic observations on amyloid-tau interactions in the human brain, but will now also provide the distinct advantage of studying these interactions longitudinally.

In a complementary line of research we have developed a new method for characterizing molecular brain tissue properties underlying regional vulnerability to AD pathology, which is based on the study of AD-typical neuroimaging patterns in relation to regional gene expression profiles in the human brain. Applying this method to cross-sectional and longitudinal neuroimaging estimates of regional pathology progression, we could demonstrate that brain regions with high expression levels of the amyloid precursor protein (APP) and other synaptic proteins are prone to elevated amyloid accumulation in advanced age. By contrast, brain regions with high expression levels of tau protein and other molecules involved in neuronal plasticity tend to show higher levels of tau-related neurodegeneration in later life. These findings highlight that the regionally selective vulnerability to AD pathology relates to specifically enriched molecular pathways in the affected neural systems, which point to novel candidate genes that now warrant further exploration in genetic association studies.

Selected Publications

- Sepulcre J, Grothe MJ, d'Oleire Uquillas F, Ortiz-Terán L, Diez I, Yang H-S, Jacobs HIL, Hanseeuw B, Li Q, El Fakhr G, Sperling RA, Johnson KA (2018). Neurogenetic contributions to amyloid beta and tau spreading in the human cortex. *Nat Med.* 24(12), 1910-1918.
- Grothe MJ, Sepulcre S, Gonzalez-Escamilla G, Jeliustratova I, Schöll M, Hansson O, Teipel SJ (2018). Molecular properties underlying regional vulnerability to Alzheimer's disease pathology. *Brain* 141(9), 2755-2771.
- Ray NJ, Bradburn S, Murgatroyd C, Toseeb U, Mir P, Kountouriotis GK, Teipel S, Grothe MJ (2018). In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's Disease. *Brain* 141(1), 165-176.
- Grothe MJ, Barthel H, Sepulcre J, Dyrba M, Sabri O, Teipel SJ (2017). In-vivo staging of regional amyloid deposition. *Neurology* 89(20), 2031-2038.
- Grothe MJ, Villeneuve S, Dyrba M, Bartres-Faz D, Wirth M (2017). Multimodal characterization of older APOE2 carriers reveals selective reduction of amyloid load. *Neurology* 88(6), 569-576.

Basic research on neurodegenerative diseases



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State-of-the Art

Systemic application of anticholinergic drugs ameliorates symptoms of Parkinson's Disease (PD), but it is hampered by severe side-effects due to activity in hypocholinergic brain areas and the peripheral nervous system. It is well known, that BoNT-A blocks the cholinergic transmission in the peripheral nervous system. Local application of BoNT-A into the striatum should ameliorate symptoms caused by hypercholinism in PD and avoid side effects by its spatial limited action. During our research we investigated the general possibility of unilateral and bilateral injection of BoNT-A into the striatum of rats as well as mice and checked these animals for alterations in motor and cognitive abilities as well as emotional changes. We performed a thorough behavioural analysis including motor, emotional and cognitive dimensions in a longitudinal test regime to determine both the progressive development of the disease and the transient or longer-term effect of the therapeutic option under study. Main findings of our studies were that intrastratially injected BoNT-A abolishes pathological apomorphine induced rotation behaviour in rats. The intracerebral BoNT-A injection is tolerated well by the animals and does not lead to cytotoxicity, neuronal loss or inflammation reactions in the brain. The application of BoNT-A in the striatum leads to swellings of catecholaminergic and cholinergic nerve fibres. Intracerebral applied BoNT-A leads to a reduction of the striatal D2 and D3 receptor density in 6-OHDA hemilesioned rats. The intrastratial injection of BoNT-A in rats does not lead to cognitive impairments and we found hints for an anxiolytic and antidepressive effect, suggesting that intrastratially applied BoNT-A could serve as a new alternative in the therapy of PD associated symptoms.

Overall Scientific Aim

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder, characterized by motor, cognitive, and psychiatric deficits as well as neurodegeneration and brain atrophy beginning in the striatum and the cortex. Recently a HD transgenic rat model using a human bacterial artificial chromosome (BAC), which contains the full-length HTT genomic sequence with 97 CAG/CAA repeats and all regulatory elements. Of 21 founder rats, 18 possessed the full-length HTT gene. Two lines (TG5 and TG9) were characterized in Tübingen, a further line (TG22) is under investigation in a collaborative research project (Rostock, Tübingen, Bochum).

Curriculum Vitae

1988 - 1992 Study of biology, University of Cologne

1992 - 1993 Diploma thesis at the Institute of Genetics, University of Cologne

1994 - 1998 Doctorate, Institute for Molecular Human Genetics, Ruhr University Bochum

Since 1999 Scientist at the Institute of Medical Genetics, University Medical Centre Rostock

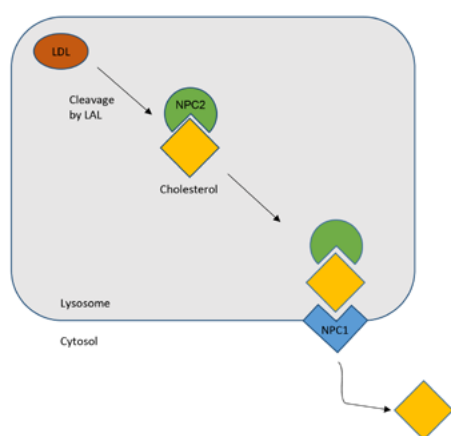


Fig. 1: Schematic outline of the normal cholesterol trafficking via NPC2 and NPC1 interaction. LAL, lysosomal acid lipase [courtesy of René Thieme, modified].

For behavioural characterization performed a thorough behavioural analysis including motor, emotional and cognitive dimensions in a longitudinal test regime to determine both the progressive development of the disease. BACHD transgenic rats display an early onset and progressive phenotype including motor deficits, anxiety-related symptoms and a late onset mild impairment of the reference memory but not of the working memory. Neuropathological, the distribution of neuropil aggregates and nuclear accumulation of N-terminal mutant huntingtin in BACHD rats (TG5 and TG9) is similar to the observations in human HD brains. Interestingly, although clearly symptomatic, the BACHD line TG22 shows no aggregates, neither in the neuropil nor in the nucleus. Currently, dopamine receptor density, microglia activation and glucose turnover are being investigated by in vivo imaging at the Core Facility Multimodal Small Animal Imaging. Our data suggest that this transgenic BACHD rat line may be a valuable model for further understanding the disease mechanisms and for preclinical pharmacological studies.

Projects, Methods & Technologies

Niemann-Pick Type C1 (NPC1) is an autosomal recessive inherited neurodegenerative disorder characterized by accumulation of cholesterol and glycosphingolipids. In close cooperation with the Institute of Anatomy and the Rudolf-Zenker-Institute of Experimental Surgery we evaluated the pharmacological effects on the behaviour of a mouse model of Niemann-Pick type C1 disease using a battery of behavioural tests consisted of accelerated, Morris water maze, elevated plus maze, open field and hot-plate tests. BALB/cNtr-Npc1m1N/-J mice treated with miglustat, cyclodextrin and allopregnanolone generally performed better than untreated mice. However, combination-treated mutant mice displayed worse cognition performance compared to sham-treated ones. Therefore we evaluated effects of these drugs in healthy BALB/c mice. Motor capabilities and spontaneous motor behaviour were unaltered in both drug-treated groups. Miglustat-treated wild-type mice displayed impaired spatial learning compared to sham- and combination-treated mice. Both combination- and miglustat-treated mice showed enhanced anxiety in the elevated plus maze compared to sham-treated mice. Our results suggest that allopregnanolone/cyclodextrin ameliorate most side effects of miglustat in wild-type mice. Currently we investigate the effects of each single drug on disease progression as well as their side effects on other organs.

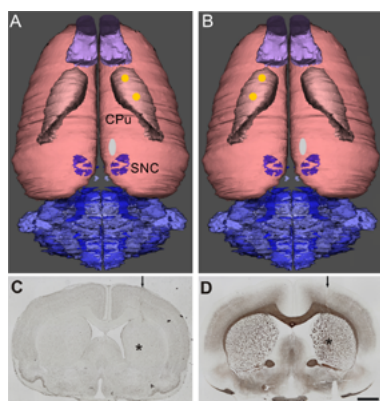


Fig. 2: Dorsal view of reconstructed rat brains. The location of the right side 6-hydroxydopamine (6-OHDA)-injection site in the medial forebrain bundle (MFB; white oval) anterior to the substantia nigra pars compacta (SNC) and the two injection sites of botulinum neurotoxin A (BoNT-A) or vehicle (yellow spots) in the caudate putamen (CPu) ipsilateral (A) and contralateral (B) to 6-OHDA are indicated. Adjacent 20 µm coronal sections of a rat brain stained for cell bodies (C) according to Merker or for myelin (D) according to Gallyas depict the needle tract (arrow) and the needle tip (asterisk) of a BoNT-A-injection ipsilateral to the 6-OHDA-application (9 months survival). Scale bar applies to (C,D): 2 mm.

Selected Publications

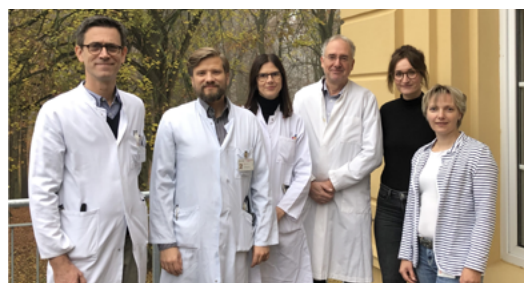
- Antipova A, Wree A, Holzmann C, Mann T, Palomero-Gallagher N, Zilles K, Schmitt O, Hawlitschka A (2018). Unilateral Botulinum neurotoxin-A injection into the striatum of C57BL/6 mice leads to a different motor behavior compared to rats. *Toxins* 10(7), E295.
- Antipova V, Holzmann C, Schmitt O, Wree A, Hawlitschka A (2017). Botulinum Neurotoxin A Injected Ipsilaterally or Contralaterally into the Striatum in the Rat 6-OHDA Model of Unilateral Parkinson's Disease Differently Affects Behavior. *Frontiers in Behavioral Neuroscience* 11, 119.
- Meyer A, Wree A, Holzmann C, Schmitt O, Rolfs A, Witt M (2017). Increased regenerative capacity of the olfactory epithelium in Niemann-Pick disease type C1. *Int J Med Sci* 18, 777.
- Schlegel V, Thieme M, Holzmann C, Witt M, Grittner U, Rolfs A, Wree A (2016). Pharmacologic treatment assigned for Niemann-Pick type C1 disease partly changes behavioral traits in wild type mice. *Int J Med Sci* 17, 1866.
- Teipel SJ, Ehlers I, Erbe A, Holzmann C, Lau E, Hauenstein K, Berger C (2016). Structural Connectivity Changes Underlying Altered Working Memory Networks in Mild Cognitive Impairment: A Three-Way Image Fusion Analysis. *Journal of Neuroimaging* 25, 634–642.

Epidemiology, comorbidities, neurophysiology and treatment of primary headaches



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State-of-the Art

Primary headaches represent some of the most disabling conditions among neurological and non-neurological conditions. Despite recent advantages in the understanding of the most prominent headache disorders, migraine and cluster headache, many aspects of their pathophysiology remain enigmatic. Apart from the relevant role of CGRP as a pivotal neurotransmitter other pathophysiological factors such as cortical hyperexcitability, differential regulation of the trigemino-vascular system by supraspinal structures such as the hypothalamus contribute to a complex network. Several comorbidities, especially depression, share biological features and complicate therapeutical approaches. At present, patients who do not respond to established oral preventive drugs may benefit from onabotulinumtoxinA or the newly developed CGRP respectively CGRP receptor antagonists. Alternatively, neuromodulatory approaches have shown efficacy which focus on peripheral cranial nerves. As a recent development, internet and smartphone based interventional therapies have emerged but have yet to show efficacy in randomized controlled trials.

Overall Scientific Aim

To examine factors contributing to the pathophysiology of migraine and cluster headache with emphasis on cortical hyperexcitability and examine efficacy of novel treatments with a focus on neuromodulation.

Projects, Methods & Technologies

Afterimages and cortical hyperexcitability:

An abnormal cortical excitability along with dysfunctional habituation in patients with migraine has been discussed for a long time. In addition, altered sensory functioning has been reported. In a previous population-based study, we could show that colour vision as well as smell and taste were altered in participants suffering from migraine with aura in comparison to those with migraine without aura and healthy controls. As visual acuity and basic functioning of the auditory system did not differ between these groups, no evidence of a clinically relevant general interictal sensory dysfunction was found. The disturbed colour vision may be due to a mitochondrial

Curriculum Vitae

2001 State Exam in Medicine, Heinrich Heine University Düsseldorf

2005 Doctorate in Medicine (Molecular Neurobiology, Dept. of Neurology, Heinrich Heine University)

2002 - 2008 Junior Neurologist, Dept. of Neurology, University Hospital Regensburg

2008 - 2014 Research Fellow (including Board Exam in Neurology and Specialized Pain Therapy)

2014 Habilitation in Neuroscience, University Medical Center Hamburg-Eppendorf

2014 - 2015 Senior Neurologist, Dept. of Neurology, RegioKlinikum Pinneberg

Since 2015 Senior Neurologist, Department of Neurology, University Medical Centre Rostock

Since 2016 Medical Head of Headache Centre North-East, Dept. of Neurology and Institute of Medical Psychology and Sociology, University Medical Centre Rostock

dysfunction in the primary visual cortex in patients with migraine with aura. Other complex visual disturbances have been reported increasingly, such as the phenomenon of visual snow as well as palinopsia and afterimages, with the latter being closely connected but nevertheless regarded as distinct entities. In a pilot study on medical students with self-reported migraine we could show that afterimage duration is prolonged in those with aura. Based on these findings, we conducted a controlled trial among patients of our Headache Centre suffering from migraine with aura (n=30), migraine without aura (n=53) and matched healthy controls (n=81). As shown in Figure 1, duration

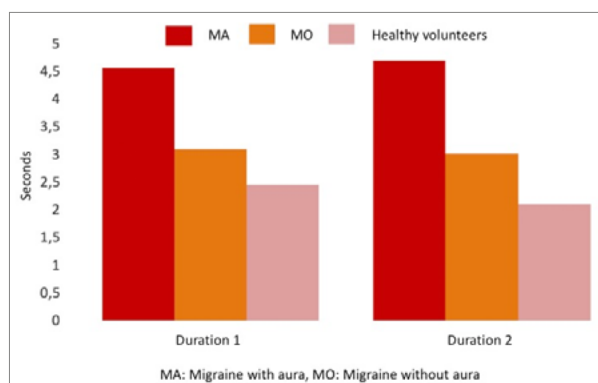


Fig. 1: Duration of afterimages.

of afterimages immediately after presentation of an image rich in contrast for 30 min (duration 1) and after reactivation by blinking (duration 2) shows a statistically significant difference with longest duration in patients suffering from migraine with aura ($p < 0.05$). As no difference was found between red and black images our results point to an altered subcortical (thalamic) or cortical excitability of the visual system in migraine patients with aura. Alternatively, a dysfunctional thalamo-cortical regulation could be causal. The modulation of afterimages by preventive therapies is currently examined in our Headache Centre.

Comorbidities:

Depression is a relevant comorbidity with a bidirectional effect on migraine. However, little is known on loneliness in patients with migraine which could be due to migraine-specific seclusion or comorbid depression. We sought to disentangle both phenomena in a case-control trial. Participants with migraine had higher levels of self-reported loneliness and depression. Depression was a predictor of loneliness although a multivariate regression analysis did not yield specific effects. Thus, loneliness could be a dimension of depression in migraine patients and controls. Further studies will elucidate the extent of loneliness in other headaches.

Neuromodulation:

In recent studies, we could show a beneficial effect of acute and preventive invasive stimulation of the sphenopalatine ganglion on chronic cluster headache. However, non-invasive neuromodulatory approaches (such as peripheral nerve stimulation and transcranial direct current stimulation) have yielded ambiguous results in patients with migraine and cluster headache. We are currently conducting studies using a novel stimulation paradigm based on the transcranial administration of alpha waves in patients with migraine and refractory facial pain.

Smart-phone based interventions:

We are currently participating in an ongoing large multi-centre randomized controlled study examining the efficacy of a smartphone based intervention in patients with migraine (SMARTGEM, funded by Innovationsfonds, Gemeinsamer Bundes-Ausschuss, funding reference 01NVF17038).

Selected Publications

- Gebhardt M, Kropp P, Jürgens TP, Hoffmann F, Zettl UK (2017). Headache in the first manifestation of Multiple Sclerosis - Prospective, multicenter study. *Brain Behav.* 7(12), e00852.
- The impact of Parkinson disease on patients' sexuality and relationship. Buhmann C, Dogac S, Vettorazzi E, Hidding U, Gerloff C, Jürgens TP (2017). *J Neural Transm (Vienna)* 124(8), 983-996.
- Jürgens TP*, Barloese M*, May A, Láinez JM, Schoenen J, Gaul C, Goodman AM, Caparso A, Jensen RH (2017). Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia.* 37(5), 423-434.
- Luedtke K, Rushton A, Wright C, Jürgens T, Polzer A, Mueller G, May A (2015). Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. *BMJ.* 350, h1640.
- Jürgens TP, Berger K, Straube A, Khil L (2015). Migraine with aura is associated with impaired colour vision: Results from the cross-sectional German DMKG headache study. *Cephalalgia.* 35(6), 508-15.

Regulation of de- and remyelination in the central nervous system



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State-of-the Art

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) associated with the development of large demyelinated plaques, oligodendrocyte destruction and axonal degeneration. This pathology is paralleled by activation of astrocytes and microglia as well as the recruitment of peripheral immune cells to the site of tissue injury. The feature which distinguishes MS from other inflammatory and neurodegenerative disorders is the formation of large confluent plaques of primary demyelination. For this reason, any pathogenetic concept of MS has to provide an explanation for this highly specific destruction of myelin and oligodendrocytes. Furthermore, it is currently unknown why in some patients remyelination occurs whereas in others this regenerative process fails. Of note, viable oligodendrocytes and the intact myelin sheath are indispensable for neuronal health.

Overall Scientific Aim

In the recent years our laboratory has published several studies showing that intoxication with the copper chelator cuprizone induces a fast and reproducible perturbation of oligodendrocyte metabolic function leading to oligodendrocyte apoptosis and demyelination. While the precise mode of action during cuprizone-induced oligodendrocyte apoptosis is still not fully elucidated, induction of oxidative stress, release of diverse chemokines, as well as the breakdown of the translational machinery have all been functionally linked to the cuprizone-induced pathology. If we understand which factor(s) trigger(s) oligodendrocyte degeneration, amelioration of oligodendrocyte injury might not just preserve the myelin-axon unit but at the same time decrease relapse frequency and severeness in MS.

Projects, Methods & Technologies

Cellular stress pathways: The unfolded protein response (UPR) represents a signaling pathway well known for restoring cellular homeostasis. Although UPR activation can aid cells in adapting to stress, it can also trigger apoptosis. It is currently not known how the UPR selects between cytoprotective and proapoptotic outputs. Such mechanisms may regulate oligodendrocyte pathology and, in consequence, neurodegeneration, especially

Curriculum Vitae

1999 - 2006 State exam in Medicine, Eberhard-Karls University Tübingen and RWTH Aachen

2008 Doctorate in Medicine, Institute of Anatomy, RWTH Aachen

2010 Habilitation in Anatomy and Cell Biology, Medical Faculty, RWTH Aachen

2011 Doctorate in Biology, Institute of Anatomy, RWTH Aachen

2012 - 2015 Associate Professor (W1) for Neurodegenerative Diseases, Institute of Anatomy, RWTH Aachen

2015 - 2018 Full Professor (W2) for Histology and Neuroanatomy, LMU Munich University

Since 2018 Full Professor (W3) for Anatomy and Director of the Institute of Anatomy, University Medical Centre Rostock

during the progressive stage of MS, which is currently refractory to any therapy. There is accumulating evidence that inflammatory mediators as well as metabolic disturbances activate the UPR. We utilize noninflammatory and T cell-dominated experimental autoimmune encephalomyelitis models of MS, which are suited for studying individual and defined pathogenetic disease mechanisms (i.e., metabolic- and immune-mediated oligodendrocyte degeneration). State of the art technologies are applied to quantify the extent of tissue damage, among design-based stereology, 3D-single cell reconstructions (Neurolucida360), and high speed ventral plane videography (DigiGait).

Sphingosine-signalling: The majority of individuals with relapsing-remitting MS ultimately enter a secondary progressive disease stage, which is characterized by the gradual accumulation of physical disability independent of clinical relapses. The cellular and molecular basis for this transition is unclear, and the role of inflammation during the secondary progressive disease stage is a subject of intense and controversial debate. We try to understand what triggers the peripheral immune cell recruitment during both disease stages, by which anatomical pathways are the peripheral immune cell recruited into the brain parenchyma, and to what extent pharmacological manipulation of these pathways allows amelioration of the disease. In particular, we try to understand the relevance of Sphingosine 1-phosphate (S1P) signaling for MS-related inflammation and neurodegeneration. Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that regulates a variety of physiological processes including lymphocyte recirculation and neuroinflammation. Most S1P effects are mediated via five G-protein-coupled S1P receptor subtypes referred to as S1P1–5. These receptors are expressed on various cell types, including lymphocytes and neuronal cells such as microglia and astrocytes. We assume that the modulation of these receptors exerts a combined anti-inflammatory and neuroprotective effect.

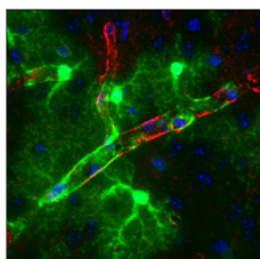


Fig. 1: Perivascular astrocyte extending processes to the perivascular space. The water channel protein Aquaporin 4 (AQP4) is shown in red. Injury of these astrocytes contribute to the recruitment of peripheral immune cells.

Digital patient monitoring: The development costs of new pharmaceuticals have increased many times over the last decades. More than 50 percent of all expenditures are now channeled into clinical development. Using mobile technology and wearables is an attractive approach to make clinical research safer and improve financial viability. Our Institute has now entered into a project alliance with the Neurology Department to investigate

how this could work in practice. During the WeSeniMuS clinical study (Wearable Sensors in Multiple Sclerosis) volunteers and MS patients will be given different types of sensors, and their cognitive and physical performance will be tracked.

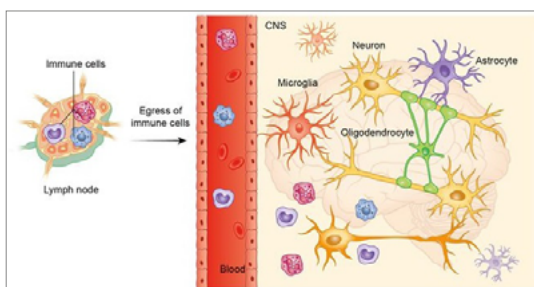


Fig. 2: Proposed mode of action of siponimod: Schematic illustrating our proposed mode of action of siponimod. Note that following this concept, the anti-inflammatory activity of siponimod is at least in part due to direct interactions with brain cells. The copyright license of this illustration is with the authors.

Selected Publications

- Rüther BJ, Scheld M, Dreymueller D, Clarner T, Kress E, Brandenburg LO, Swartenbroeckx T, Hoornaert C, Ponsaerts P, Fallier-Becker P, Beyer C, Rohr SO, Schmitz Ch, Chrzanowski U, Hochstrasser T, Nyamoya S, Kipp M (2017). Combination of cuprizone and experimental autoimmune encephalomyelitis to study inflammatory brain lesion formation and progression. *Glia* 65(12), 1900-1913.
- Holtman IR, Bsibsi M, Gerritsen WH, Boddeke HW, Eggen BJ, van der Valk P, Kipp M, van Noort JM, Amor S (2017). Identification of highly connected hub genes in the protective response program of human macrophages and microglia activated by alpha B-crystallin. *Glia*. 65(3), 460-473.
- Scheld M, Rüther BJ, Grosse-Veldmann R, Ohl K, Tenbrock K, Dreymueller D, Fallier-Becker P, Zendedel A, Beyer C, Clarner T, Kipp M (2016). Neurodegeneration Triggers Peripheral Immune Cell Recruitment into the Forebrain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 36(4), 1410-5.
- Clarner T, Janssen K, Nellessen L, Stangel M, Skripuletz T, Krauspe B, Hess FM, Denecke B, Beutner C, Linnartz-Gerlach B, Neumann H, Vallieres L, Amor S, Ohl K, Tenbrock K, Beyer C, Kipp M (2015). CXCL10 triggers early microglial activation in the cuprizone model. *Journal of immunology*. 194(7), 3400-13.
- Slowik A, Schmidt T, Beyer C, Amor S, Clarner T, Kipp M (2015). The sphingosine 1-phosphate receptor agonist FTY720 is neuroprotective after cuprizone-induced CNS demyelination. *Br J Pharmacol*. 172(1), 80-92.

Basic mechanisms in symptomatic focal epilepsies



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State of the Art

Epilepsy is one of the most common chronic neurological diseases. Major clinical needs constitute novel targeted treatment options for temporal lobe epilepsies, for autoimmune-associated epilepsies and tumour-linked ones.

Scientific Aim

To understand chronic neurological diseases, appropriate animal models are essential for experimental investigations into the basic mechanisms. We focus on the characterisation and analysis of the pathomechanisms of diseases of the CNS using animal models for temporal lobe epilepsy, tumour-associated epilepsy or autoimmune-encephalitis.

Projects, Methods & Technologies

We use electrophysiological, behavioural, imaging and molecular approaches to address the underlying mechanisms of epilepsy. We currently focus on three subprojects:

1. Mechanisms of temporal lobe epilepsy (TLE): Our group is currently engaged in analysing synaptic and intrinsic changes in chronic hippocampal epilepsy of the rat, using a model which closely mimics TLE in patients. We are interested in solving the following questions: To what extent and within which time-frame does cognitive function change at the behavioural and network plasticity level? How can performance improvements be achieved? Which signal transduction mechanisms play a role here? Further, since we have previously identified Ca²⁺-activated potassium channels as powerful modulators of neuronal activity to be functionally

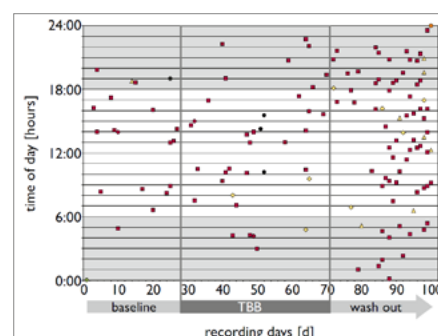


Fig. 1: The individual seizure burden in experimental epilepsy can be documented by video-EEG analysis. Here, we recorded 100 days and applied a test drug (the casein kinase 2 inhibitor TBB) during the indicated period (see time axis below). Each symbol represents a single seizure (yellow: focal seizures, red: generalized seizures). TBB, however, had no anti-seizure effects [Bajorat et al., 2018].

Curriculum Vitae

1993 - 2000 State exam in Medicine, University of Mainz and University of Bonn

2001 Doctorate in Physiology, University of Mainz

2000 - 2004 Neurology training, Department of Epileptology, University of Bonn

2005 - 2009 Physiology training, Institute of Physiology, University Medical Centre Rostock

2009 Senior Physiologist, Institute of Physiology, University Medical Centre Rostock

2009 Habilitation in Physiology, University Medical Centre Rostock

2017 Associate Professor of Physiology, University Medical Centre Rostock

downregulated in epilepsy, in a DFG-funded project we now investigate which mechanisms lead to this downregulation, with the final aim to find therapeutic interventions.

2. Auto immune-encephalitis-associated epilepsies are an emerging concern. Although it is known that autoantibodies are involved, the mechanisms of these often deleterious events are largely unknown. In our group we established animal models of autoimmune-encephalitis using icv patient CSF injections, and identified novel targets of autoantibodies, as well as biomarkers of hyperexcitability changes. Our final goal is to pave the way for novel, specific therapy approaches.
3. Glial brain tumours are often associated with excitability changes in neuronal structures, which can eventually lead to epileptic seizures and thus to additional clinical complications. The mechanisms of these excitability changes are not yet sufficiently understood. In this Damp-Trust-funded project, we aim to characterise the functional and molecular underlying these processes and to develop therapeutic strategies that synergistically antiepileptic and antitumoural.

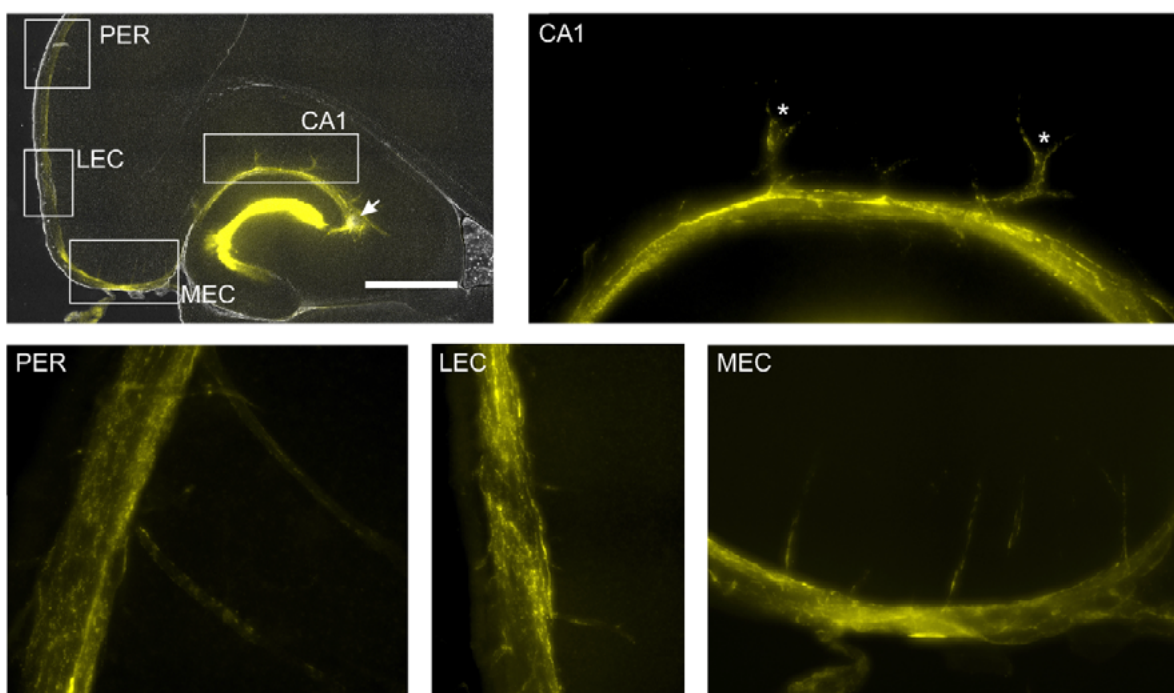


Fig. 2: In order to study the pathophysiology of autoantibodies involved in autoimmune encephalitis, we perform stereotactic injections of patient-derived cerebrospinal fluid or serum into the hippocampus of rats (see arrow). Here, the micrographs show the immunofluorescent dye dispersion in the hippocampus 1 hour after injection into CA3 stratum radiatum (see arrow), magnification 20x. The dye intensely diffuses into the dentate gyrus, but also reaches CA1 and the parahippocampal gyrus. The white boxes indicate the positions of enlarged micrographs (magnification 200x): CA1, Cornu Ammonis 1; MEC, medial entorhinal cortex; LEC, lateral entorhinal cortex; PER, perirhinal cortex. The scale bar indicates 1000 μ m.

Selected Publications

- Müller S, Guli X, Hey J, Einsle A, Pfanz D, Sudmann V, Kirschstein T, Köhling R (2018). Acute epileptiform activity induced by gabazine involves proteasomal rather than lysosomal degradation of KCa2.2 channels. *Neurobiol. Dis.* 112, 79-84.
- Bajorat R, Porath K, Kuhn J, Goßla E, Goerss D, Sellmann T, Köhling R, Kirschstein T (2018). Oral administration of the casein kinase 2 inhibitor TBB leads to persistent KCa2.2 channel up-regulation in the epileptic CA1 area, but lacks antiseizure efficacy in the pilocarpine epilepsy model. *Epilepsy Res.* 147, 42-50.
- Blome R, Bach W, Guli X, Porath K, Sellmann T, Bien CG, Köhling R, Kirschstein T (2018). Differentially altered NMDAR dependent and independent long-term potentiation in the CA3 subfield in a model of anti-NMDAR encephalitis. *Front. Synaptic Neurosci.* 10, 26.
- Würdemann T, Kersten M, Tokay T, Guli X, Kober M, Rohde M, Porath K, Sellmann T, Bien CG, Köhling R, Kirschstein T (2016). Stereotactic injection of cerebrospinal fluid from anti-NMDA receptor encephalitis into rat dentate gyrus impairs NMDA receptor function. *Brain Res.* 1633, 10-18.
- Hackert JK, Müller L, Rohde M, Bien CG, Köhling R, Kirschstein T (2016). Anti-GAD65 containing cerebrospinal fluid does not alter GABAergic transmission. *Front. Cell. Neurosci.* 10, 30.

Basic mechanisms of chronic neurological diseases and ageing processes



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State-of-the Art

Dystonia is the second most common group of movement disorders. At the same time, treatment perspectives are not ideal, with the best options being muscular inactivation using toxins in focal dystonias, and deep brain stimulation (DBS) in more generalised ones. While toxin treatment has an obviously limited field of application, DBS enigmatically often acts with delay, or even fails. Neither the mechanism, nor the causes of failure or delayed action are known.

Epilepsy is one of the most common chronic neurological diseases. Major clinical needs constitute novel targeted treatment options for temporal lobe epilepsies, for autoimmune-associated epilepsies and tumour-linked ones.

Cognitive decline is one of the factors of CNS ageing, although it is by no means clear who will be affected, and why. We therefore need biomarkers of CNS ageing phenotypes, to identify treatment necessity and specificity early on. One innovative approach to tackle this aim is to integrate experimental data into a bioinformatics-systems biology modelling framework.

Overall Scientific Aim

To understand chronic neurological diseases, appropriate animal models are essential for experimental investigations into the basic mechanisms. Our group focuses on the characterization and analysis of the pathomechanisms of diseases of the CNS using animal models for dystonia, temporal lobe epilepsy, tumour-associated epilepsy or autoimmune-encephalitis, as well as ageing-associated diseases such as stroke.

Projects, Methods & Technologies

We use electrophysiological, behavioural, imaging and molecular approaches to address the underlying mechanisms of dystonia, epilepsy and CNS ageing in three project groups:

1. Mechanisms and biomarkers of dystonia DBS treatment: This project, as part of the CRC 1270 ELAINE, aims to clarify the mechanisms of action of deep brain stimulation in dystonia, to narrow down stimulation

Curriculum Vitae

1984 - 1991 State Exam in Medicine, Medical School of the Westfälische Wilhelms-Universität Münster

1991 Doctorate in Neurophysiology, Westfälische Wilhelms-Universität Münster

1998 Habilitation in Physiology, Westfälische Wilhelms-Universität Münster

2003 - 2004 Research group leader, Department of Epileptology, University of Bonn

2004 Full Professor and Chair in Physiology at the University of Rostock

2007 - 2009 President of the German Epilepsy Society

Since 2015 Dean of the Interdisciplinary Faculty, University of Rostock

Since 2017 Co-Speaker of the Centre for Transdisciplinary Neurosciences Rostock (CTNR)

targets and paradigms, and to identify therapeutic success markers in chronic animal models of dystonia. We hypothesise that deep brain stimulation, depending on target structure/stimulation parameters, improves pathophysiological processes of dystonia, in particular synaptic/cellular plasticity, inhibitory tone and network oscillations. Together with our modelling and engineering partners of the CRC, we aim to unravel the mechanisms underlying DBS, to optimise stimulation parameters, to identify early biomarkers of therapeutic success and to predict the effects of DBS on the basal ganglia network (Fig.1).

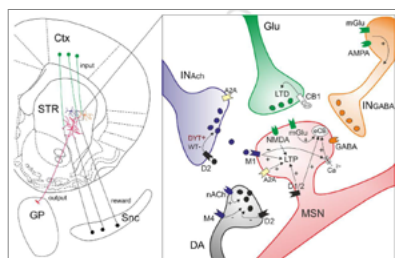


Fig. 1: Mechanisms of Dystonia. Schematic overview on synaptic transmission and plasticity in the striatum. Key elements are intra-striatal cholinergic as well as GABAergic interneurons (INACh and INGABA respectively). In dystonia, the balance of dopamine effects might be shifted to overstimulation of M1 cholinergic receptors, with resulting increase in synaptic plasticity. Further, deficits in fast spiking INGABA could provide another mechanism [adapted from Richter F, Richter A (2014). Genetic animal models of dystonia: common features and diversities. *Prog Neurobiol.* 121, 91-113.].

2. Novel therapeutic interventions in epilepsies: In the field of epilepsy research, we currently focus on three subprojects:
 - i. Mechanisms of temporal lobe epilepsy (TLE): Our group is currently engaged in analysing synaptic and intrinsic changes in chronic hippocampal epilepsy of the rat, using a model which closely mimics TLE in patients. We are interested in solving the following questions: To what extent and within which time-frame does cognitive function change at the behavioural and network plasticity level? How can performance improvements be achieved? Which signal transduction mechanisms play a role here? Further, since we have previously identified Ca^{2+} -activated potassium channels as powerful modulators of neuronal activity to be functionally downregulated in epilepsy, in a DFG-funded project we now investigate which mechanisms lead to this downregulation, with the final aim to find therapeutic interventions.
 - ii. Autoimmune-encephalitis-associated epilepsies are an emerging concern. Although it is known that autoantibodies are involved, the mechanisms of these often deleterious events are largely unknown. In our group we established animal models of autoimmune-encephalitis using icv patient CSF injections, and identified novel targets of autoantibodies, as well as biomarkers of hyperexcitability changes. Our final goal is to pave the way for novel, specific therapy approaches.
 - iii. Glial brain tumours are often associated with excitability changes in neuronal structures, which can eventually lead to epileptic seizures and thus to additional clinical complications. The mechanisms of these excitability changes are not yet sufficiently understood. In this Damp-Trust-funded project, we aim to characterise the functional and molecular underlying these processes and to develop therapeutic strategies that synergistically antiepileptic and antitumoural.
3. Ageing Mechanisms - an experimental and modelling approach: The weakening of cognitive abilities is one of the typical signs of aging. Our group has identified biomarkers of mitochondrial ageing in rodent models of mitochondrial genome mutations. Currently, in this BMBF-funded project, we search for senescence-associated biomarkers in stroke models in a parallel patient and animal model approach, linked by systems biology and bioinformatics modelling. Using this parallelogram approach, we aim for translational implementation in the clinical context.

Selected Publications

- Reichart G, Mayer J, Zehm C, Kirschstein T, Tokay T, Lange F, Baltrusch S, Tiedge M, Fuellen G, Ibrahim S, Köhling R (2018). Mitochondrial complex IV mutation increases reactive oxygen species production and reduces lifespan in aged mice. *Acta Physiologica* 225, 4.
- Müller S, Guli X, Hey J, Einsle A, Pfanz D, Sudmann V, Kirschstein T, Köhling R (2018). Acute epileptiform activity induced by gabazine involves proteasomal rather than lysosomal degradation of $\text{K}(\text{Ca})_{2.2}$ channels. *Neurobiol Dis.* 112, 79-84.
- Li S, Kumar T P, Joshee S, Kirschstein T, Subburaju S, Khalili JS, Kloepper J, Du C, Elkhail A, Szabó G, Jain RK, Köhling R, Vasudevan A (2018). Endothelial cell-derived GABA signaling modulates neuronal migration and postnatal behavior. *Cell Res.* 28(2), 221-248.
- Köhling R, D'Antuono M, Benini R, de Guzman P, Avoli M (2016). Hypersynchronous ictal onset in the perirhinal cortex results from dynamic weakening in inhibition. *Neurobiol Dis.* 87, 1-10.
- Mayer J, Reichart G, Tokay T, Lange F, Baltrusch S, Junghanss C, Wolkenhauer O, Jaster R, Kunz M, Tiedge M, Ibrahim S, Fuellen G, Köhling R (2015). Reduced adolescent-age spatial learning ability associated with elevated juvenile-age superoxide levels in complex I mouse mutants. *PLoS One* 10(4).

Molecular imaging of neurodegenerative diseases



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State-of-the Art

Multimodality imaging represents an increasingly accepted approach to exploit the differing imaging performances of existing imaging technologies for the improved in-vivo characterization of human neurodegenerative diseases and brain malignancies. The multimodality imaging platform at UMR comprises morphological and functional magnetic resonance tomography (MRI) as well as molecular imaging with PET-hybrid Imaging. The experience in Rostock at UMR involves both methodological aspects of MRI and PET imaging as well as preclinical and clinical applications in neuro-oncology/oncology and neurodegenerative diseases. In addition, the radiopharmaceutical group of the Department of Nuclear Medicine supports the development of new molecular PET imaging biomarkers in neurodegeneration and oncology.

Overall Scientific Aim

To exploit pathomechanisms of neurodegenerative disorders and brain malignancies. To develop molecular PET imaging biomarkers - radiopharmaceuticals - for the in-vivo imaging and quantification of specific target structures in neurodegenerative disorders and neuro-oncology with a focus on translational PET hybrid imaging. Our achievements will not only contribute to the understanding of neuro-pathologic mechanisms of neurodegenerative diseases and brain malignancies by means of molecular imaging, but also allow to monitor in-vivo quantitatively the signal of molecular imaging biomarkers (i.e. amyloid, Tau, amino acids) due to novel therapeutic approaches by means of PET hybrid imaging.

Projects

In the field of neuro-oncology the team of the Department of Nuclear Medicine of the UMR has an interdisciplinary expertise in multimodal imaging and image guided therapy of brain tumours. This includes the evaluation of existing imaging modalities for primary diagnosis, treatment planning as well as follow up examination of brain tumours. The application of PET-radiopharmaceuticals (i.e. [18F]O-(2-[18F]-fluoroethyl)-L-tyrosine (F-18-FET)) in addition to established structural imaging procedures (MRI, CT) for radiation treatment planning has been established at the Departments of Nuclear Medicine and Radiation Therapy at UMR. A method for automatic

Curriculum Vitae

1985 - 1990 Studies and state examination in Medicine, Johann Wolfgang Goethe University, Frankfurt/Main
1993 Doctoral thesis in nuclear medicine, Department of Nuclear Medicine, Johann Wolfgang Goethe University, Frankfurt/Main
2000 Habilitation in Nuclear Medicine, Medical Faculty, University of Düsseldorf
1998 - 2003 Senior nuclear medicine physician, Department of Nuclear Medicine, University Medical Center, Düsseldorf
2003 - 2005 Full Professor (C3) for Nuclear Medicine, Department of Nuclear Medicine, Medical Faculty, University Ulm
2005 - 2010 Associate Professor for Nuclear Medicine, Department of Nuclear Medicine, Medical Faculty at the Technical University Munich
Since 2011 Full Professor for Nuclear Medicine and Director of the Department of Nuclear Medicine, University Medical Centre Rostock
Since 2014 Vice-Dean, University Medical Centre Rostock

image fusion (RayStation, RaySearch) of CT/MRI data and F-18-FET-PET data for stereotactic radiotherapy has been established. Our group has demonstrated that F-18-FET can be successfully used for early assessment of the resection status in patients with high-grade gliomas. Patients in whom information of F-18-FET-PET was used for assessment of the resection status the resection status could be predicted by PET-hybrid imaging. A second example for the existing expertise in multimodality neuroimaging and related interdisciplinary cooperation at UMR can be found in the field of Multimodal Imaging in Neurodegeneration. This group is based on a multi-disciplinary collaboration and it includes members of different clinical departments of UMR and external collaboration partners (e.g. Nuclear Medicine / German Centre for Neurodegenerative Diseases (DZNE) / Psychiatry / Neurology / Radiology). Studies comprise preclinical and clinical studies for Alzheimer's disease as well as participation in multi-centre studies (BMBF - AgeGain Study - and DZNE - DELCODE Study).

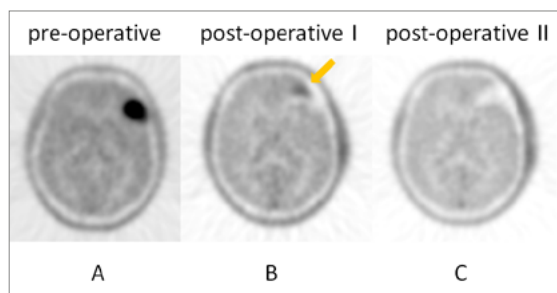


Fig. 1: Residual glioma tissue detected by [^{18}F]FET-PET – Re-resection. Transaxial slices. A: Pre-operative PET with intense focal uptake in the left frontal lobe. B: Early postoperative PET with focal uptake at the cranio-medial border of the resection cavity, leading to re-resection. C: Early postoperative PET after re-resection showing the resection cavity with no focal uptake in the border region, consistent with complete resection. Histopathology confirmed GBM.

Methods and technologies

Imaging biomarkers for the research in the neurosciences are important for tracer development and delivery. There will be a focus on the development, production and the delivery of PET tracers. The radiopharmacy unit of the Department of Nuclear Medicine of the UMR will provide laboratory equipment, personnel, expert knowledge and state-of the art GMP radiopharmaceutical production facilities. Radiopharmacy will collaborate with other projects of the research consortium for the development, production and delivery of novel as well as established PET tracers. Radionuclide production at the University of Rostock are carried out with a cyclotron (DFG GZ: INST 2268/3-1 LAGG) with a F-18 and a C-11 target. A state of the art GMP laboratory has been installed. Quality control procedures for PET tracers have been implemented in a quality management system. All hot cells are equipped with state-of-the art fully automated synthesis modules. These modules will allow the production of PET tracers on a small scale for pre-clinical imaging and on a large scale for clinical PET/CT examination. The radiopharmacy unit of the Department of Nuclear Medicine of the UMR holds a number of manufacturing licenses for PET radiopharmaceuticals. The imaging facility provides experienced personnel, in depth knowledge and support in molecular imaging for all projects involving pre-clinical and clinical imaging. The facility will also be supported by a group that focuses on instrumentation with the view towards standardization, quantitative imaging, kinetic modelling, as well as data analysis techniques to allow for optimized image quality in the projects involving imaging. The imaging facility will collaborate with the groups involved in the research consortium to provide adequate imaging technology. This also includes small animal PET/CT, CT, as well as small animal magnetic resonance imaging. The UMR has a small animal imaging core facility with a small animal 7T MRI (EFRE, GZ: UHROM 16), as well as a small animal PET/CT (DFG GZ: INST 2268/6-1 FUGG).

Selected Publications

- Mann T, Kurth J, Hawlitschka A, Stenzel J, Lindner T, Polei S, Hohn A, Krause BJ, Wree A (2018). [^{18}F]fallypride-PET/CT Analysis of the Dopamine D_2/D_3 Receptor in the Hemiparkinsonian Rat Brain Following Intrastriatal Botulinum Neurotoxin A Injection. *Molecules* 23(3), 587.
- Kuhla A, Rühlmann C, Lindner T, Polei S, Hadlich S, Krause BJ, Vollmar B, Teipel SJ (2017). APPswe/PS1dE9 mice with cortical amyloid pathology show a reduced NAA/Cr ratio without apparent brain atrophy: A MRS and MRI study. *Neuroimage Clin* 15, 581-586.
- Buchmann N, Kläsner B, Gempt J, Bauer JS, Pyka T, Delbridge C, Meyer B, Krause BJ, Ringel F (2016). ^{18}F -fluoroethyl-L-tyrosine (FET) PET to delineate tumor residuals after glioblastoma resection: A comparison to standard postoperative MRI. *World Neurosurg.* 89, 420-426.
- Teipel SJ, Kurth J, Krause BJ, Grothe MJ (2015). The relative importance of imaging markers for the prediction of Alzheimer's disease in mild cognitive impairment – Beyond classical regression. *Neuroimage Clin* 8, 583-593.
- Kläsner B, Buchmann N, Gempt J, Ringel F, Lapa C, Krause BJ (2015). Early [^{18}F]FET-PET in Gliomas after surgical resection: Comparison with MRI and histopathology. *PLOS one* 26, 10(10):e0141153.

Pathophysiology, non-medical treatment of headaches



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State-of-the Art

Migraine is a disabling and great problem for the individual and the society. There is a need to apply and evaluate effective therapeutic treatment strategies.

We are involved in the field of headache research, especially pathophysiology of migraine and non-medical treatment of headaches in common. For this purpose we use standardized procedures to record slow cortical potentials (contingent negative variation, CNV). These potentials differ best between normal controls and migraine patients.

Overall Scientific Aim

Special treatments of migraine may lead to reduced amplitudes of CNV. Therefore recording CNV enables us to quantify the therapeutic effect of our treatments. Figure 1 shows the effect of relaxation training on CNV-amplitudes and migraine activity.

Moreover, these potentials enable us in some circumstances to predict migraine attacks. Figure 2 shows the course of the CNV of a female migraine patient just before and after a migraine attack.

Projects, Methods & Technologies

- Recording CNV in migraine patients before and after treatment of prophylactic medication
- Recording CNV in patients with non-medical treatment procedures

CNV recordings will be applied at t0, t1, and t2 and consist of a standardized protocol (Kropp et al. 2002, 2014). Recordings are based on 32 trials in which the subjects have to react to a target stimulus (GO-response). In order to keep the subjects in a vigilant state, eight trials will be randomly presented where no reaction is expected (NO-GO response). S1 for the GO-response has a frequency of 1000 Hz and lasts 100 ms with an intensity of 75 dB(a). S1 for the NO-GO-response has a frequency of 200 Hz. The target stimulus S2 (f = 2500 Hz) lasts a

Curriculum Vitae

1986 Diploma, Department of Psychology, University of Tübingen

1987 - 1991 Thesis (Dr. rer. soc.), Institute for Medical Psychology, University Medical Centre Kiel

2002 Habilitation in Medical Psychology, University Medical Centre Kiel

2002 - 2005 C2 Lecturer, Institute for Medical Psychology, University Medical Centre Kiel

Since 2008 Head of Department in Medical Psychology, University Medical Centre Rostock

Since 2016 Full Professor (W2) for Medical Psychology and behavioural headache treatment, University Medical Centre Rostock

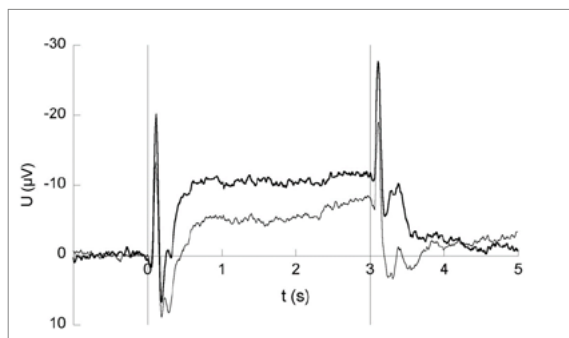


Fig. 1: CNV of migraine patients (upper line) and healthy controls (lower line).

maximum of 1500 ms and is deactivated by pressing a key. CNV will be recorded over Cz with linked mastoids as reference with an electrode resistance of approximately 10 kOhm.

The EEG (bandpass: 0.03 to 35 Hz) will be digitalized with a sampling rate of 100 Hz for each channel. The length of each recording is 6 s, with a randomized interval of 6 to 10 s between trials. Recordings begin 1 s before S1 and end 2 s following onset of S2. The interstimulus-interval between S1 and S2 lasts 3 s. NO-GO-trials are not analyzed. In addition, we record a vertical electrooculogram (EOG). CNV recordings containing eye blinks or artefacts will be discarded.

The periods between recording onset and S1 are used as the baseline for each trial. The CNV session is finished after 40 artefact-free trials (32 GO, 8 NO-GO-trials). For all subjects the 32 GO-trials of each CNV session are grand averaged. The overall-CNv (oCNV) is the grand averaged mean amplitude between onsets of S1 and S2. The initial component (iCNV) is calculated according to a proposal made by Böcker et al. (1990). The terminal CNV (tCNV) consists of the average amplitude of the last 200 ms before S2.

Reaction time is defined as the time between S2 and pressing the key. Habituation of iCNV is calculated by eight consecutive blocks of four trials each. Mean amplitudes of each block serve as measurement for habituation by a linear regression.

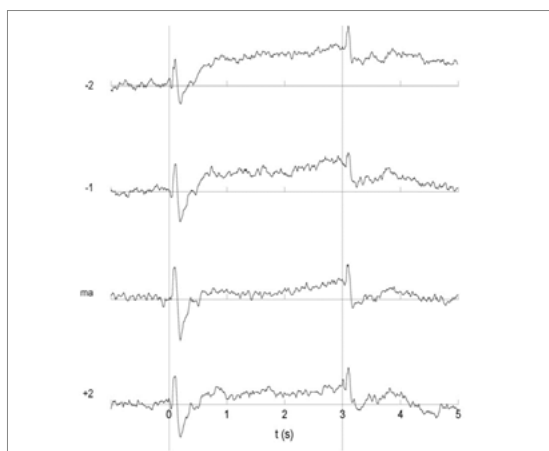


Fig. 2: CNV-recordings two days before a migraine attack (-2), one day before (-1), during (ma), and after two days of the attack (+2).

Selected Publications

- Hilgendorf I, Schumacher H, Stüwe S, Kropp P, Glass A, Freitag S, Greger N, Freund M, Junghanss C (2018). A prospective, randomized evaluation of the feasibility of exergaming on patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 53(5), 584-590.
- Mueller-Hilke B, Hahn H, Kropp P, Kirschstein T, Ruecker G (2017). Test anxiety in medical school is unrelated to academic performance but correlates with an effort/reward imbalance. *PLOS one* 12(2), e0171220.
- Kropp, P, Meyer B, Dresler T, Fritsche G, Gaul C, Niederberger U, Förderreuther S, Malzacher V, Jürgens TP, Marziniak M, Straube A. (2016). Entspannungsverfahren und verhaltenstherapeutische Interventionen zur Behandlung der Migräne. *Leitlinie der Deutschen Migräne- und Kopfschmerzgesellschaft*. *Schmerz* 31(5), 433-447.
- Keller A, Meyer B, Wöhlbier HG, Overath CH, Kropp P. (2016) Migraine and Meditation: Characteristics of Cortical Activity and Stress Coping in Migraine Patients, Meditators and Healthy Controls-An Exploratory Cross-Sectional Study. *Appl Psychophysiol Biofeedback*. *Appl Psychophysiol Biofeedback*. 41(3), 307-313.
- Meyer B, Keller A, Wöhlbier HG, Overath CH, Müller B, Kropp P (2016). Progressive muscle relaxation reduces migraine frequency and normalizes amplitudes of contingent negative variation (CNV). *J Headache Pain* 17, 37.

Basic mechanisms of glioma and tumour-associated epilepsy and ageing processes



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State-of-the Art

High-grade glioma and glioblastoma have one of the lowest survival rates of all common human tumour diseases. In addition to cancer burden, patients often suffer from tumour-associated epileptic seizures, depending on the glioma grade. Multiple mechanisms have been proposed to play a role in tumour progression and generation of seizures.

Overall Scientific Aim

With our experimental models we focus on the characterisation of pathomechanisms that may drive both glioma-associated seizures and tumour progression. Our studies shall contribute to a better understanding of the integration of both diseases.

Projects, Methods & Technologies

Project 1: In glioma patients, peritumoral glutamate levels were found to be elevated up to 100-times higher than in unaffected brains. On the one hand, high levels of glutamate may lead to epileptic discharges and eventually excitotoxicity via calcium influx and therefore allow tumor bulk expansion. On the other hand, glutamate can act in an autocrine manner by promoting proliferation and migration of the tumour cells themselves. Based on this pathophysiological knowledge, it is conceivable that some certain anti-seizure medication could be more preferable than others in the sense of a combined anti-convulsive and anti-tumoral approach. In a DAMP-Stiftung-funded project we investigate the effects of glutamate receptor antagonists like perampanel on brain tumour models and their role as anticonvulsants in glioma-associated epilepsy.

Project 2: In a second project I contribute to investigations of our group to elucidate ageing concepts by experimental and modelling approaches. The weakening of cognitive abilities is one of the typical signs of aging. Our group has identified biomarkers of mitochondrial ageing in rodent models of mitochondrial genome mutations. Currently, in this BMBF-funded project, we search for senescence-associated biomarkers in stroke models in a parallel patient and animal model approach, linked by systems biology and bioinformatics modelling. Using this parallelogram approach, we aim for translational implementation in the clinical context.

Curriculum Vitae

2003 - 2008 Study of life sciences, Faculty of Mathematics and Natural Sciences, University of Rostock

2008 - 2013 Scientific assistant at Department of Systems Biology and Bioinformatics, University of Rostock and
Department of Medicine II, Division of Gastroenterology, Rostock University Medical Centre Rostock

2013 Doctorate in Biochemistry, University of Rostock

Since 2013 Scientific assistant at Oscar-Langendorff-Institute of Physiology, University Medical Centre Rostock

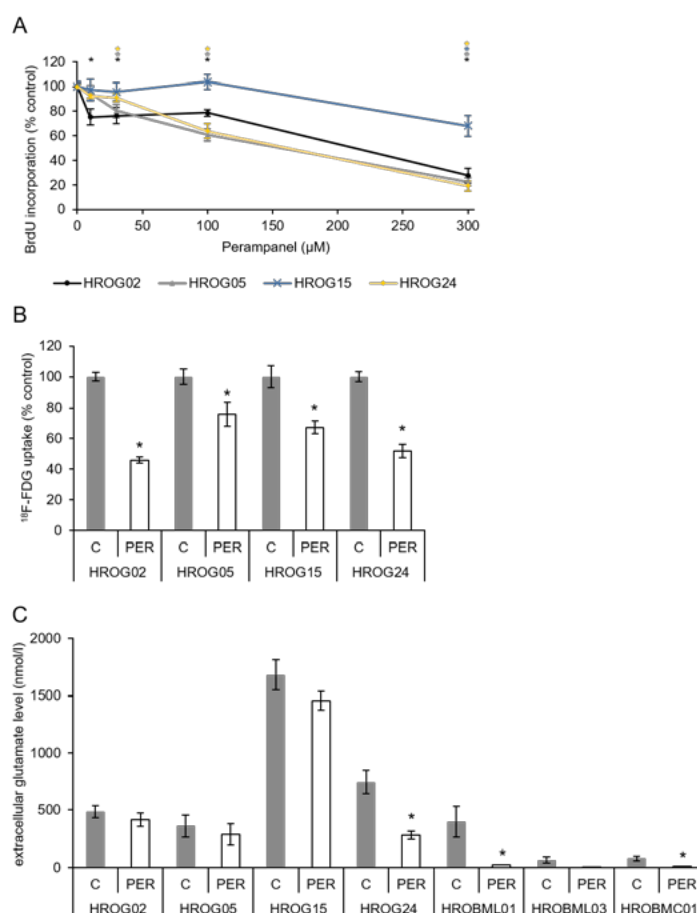


Fig. 1: Effects of AMPA receptor antagonist perampanel on brain tumour cells.

[A] Effects of perampanel on DNA synthesis. Glioblastoma cells (HROG02, HROG05, HROG15, HROG24) were treated with perampanel for 48 h, before DNA synthesis was assessed with the BrdU incorporation assay. One hundred percent BrdU incorporation corresponds to cells cultured without anticonvulsant. Data are presented as mean \pm SEM ($n \geq 12$ separate cultures); * $p < 0.05$ versus control cultures (Kruskal-Wallis test with post hoc Dunn's test). [B] FDG uptake of glioblastoma cells in vitro. Glioblastoma cells were labelled with ^{18}F -FDG, and tracer uptake was quantified. Counts per minute were normalized to the protein content of the samples. One hundred percent ^{18}F -FDG uptake corresponds to solvent-treated tumor cells ($n = 9$; mean values \pm SEM); * $p < 0.05$ versus control cultures (Mann-Whitney U test). [C] Glutamate release of glioblastoma and brain metastasis cells. In subconfluent cell cultures, supernatants (w/o FCS) were collected for a total of 24 hours (\pm perampanel) and glutamate levels were determined. Extracellular glutamate levels were normalized to total protein levels of the cells. Data are presented as mean \pm SEM ($n \geq 14$); * $p < 0.05$ vs. solvent control (Mann-Whitney U test). Multiple comparisons versus control groups (two-Way ANOVA with Bonferroni t-test) demonstrated an overall higher glutamate level in the supernatant of glioblastoma cells than in the supernatant of metastasis cells (HROBMx; $p < 0.001$). Additionally, perampanel attenuates extracellular glutamate level in both cell cohorts ($p = 0.046$).

Selected Publications

- Reichart G, Mayer J, Zehm C, Kirschstein T, Tokay T, Lange F, Baltrusch S, Tiedge M, Fuellen G, Ibrahim S, Köhling R (2018). Mitochondrial complex IV mutation increases ROS production and reduces lifespan in aged mice. *Acta Physiol (Oxf)* 225(4), e13214.
- Gock M, Mullins C, Bergner C, Prall F, Ramer R, Goeder A, Krämer OH, Lange F, Krause BJ, Klar E, Linnebacher M (2018). Establishment, functional and genetic characterization of three novel patient-derived rectal cancer cell lines. *World J Gastroenterol* 24(43), 4880-4892.
- Rohde S, Lindner T, Polei S, Stenzel J, Borufka L, Achilles S, Hartmann E, Lange F, Maletzki C, Linnebacher M, Glass A, Schwarzenböck SM, Kurth J, Hohn A, Vollmar B, Krause BJ, Jaster R (2017). Application of in vivo imaging techniques to monitor therapeutic efficiency of PLX4720 in an experimental model of microsatellite instable colorectal cancer. *Oncotarget* 8(41), 69756-69767.
- Smita S, Lange F, Wolkenhauer O, Köhling R (2016). Deciphering hallmark processes of aging from interaction networks. *Biochim Biophys Acta* 1860 (11 Pt B), 2706-2715.
- Hirose M, Schilf P, Lange F, Mayer J, Reichart G, Maity P, Jöhren O, Schwaninger M, Scharffetter-Kochanek K, Sina C, Sadik CD, Köhling R, Miroux B, Ibrahim SM (2016). Uncoupling protein 2 protects mice from aging. *Mitochondrion* 30, 42-50.

Novel diagnostic and interventional techniques in neuroradiology



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State-of-the Art

Neuroradiology is an emerging subspecialty which is not only focused on new diagnostic imaging techniques but also on new interventional techniques. Endovascular neuroradiological therapy is an established treatment option for intracranial vascular malformations, e.g. coil embolization for intracranial aneurysms in patients with subarachnoid hemorrhage or with an incidental aneurysm. Coil embolization may be performed alone or in combination with balloon remodeling of the aneurysm harboring vessel or in combination with intracranial stent placement. In patients with recurrent ischemic stroke despite optimal medical treatment due to severe intracranial stenosis, intracranial stent placement is an appropriate therapy. However, intracranial stent placement requires life-long antiplatelet treatment with all its side effects.

Analyses of drug distribution and the effects of repeated drug administration in animal models is usually based on ex vivo biochemical analyses or histological work-up. Ultra-high MR microscopy is an emerging MR technology allowing longitudinal studies in animal studies as well as quantitative and qualitative imaging analyses.

Overall Scientific Aim

The scientific aim of the neurovascular study group is to develop new intracranial endovascular devices for the treatment of neurovascular disease. The scientific aim of the neuroimaging study group is the development of new in vivo imaging techniques for preclinical and clinical imaging studies for the monitoring the effects and distribution of medical therapy in neurological disorders.

Projects, Methods & Technologies

My neurovascular study group is focused on the development of a model of the intracranial vasculature using 3D printing techniques. The models are based on individual datasets and are used for the development of a biodegradable scaffold for the intracranial vessels to improve endovascular therapy of intracranial aneurysms.

Curriculum Vitae

1994 - 2001 State exam in Medicine, Christian-Albrechts-University Kiel

2002 Doctorate in Medicine, Institute for Legal Medicine, Christian-Albrechts-University Kiel

2010 Specialisation in Neuroradiology

2012 Habilitation in Neuroradiology, Medical Faculty, University Greifswald

2018 Associate Professor in Neuroradiology, Medical Faculty, University Greifswald

2010 - 2017 Head of Neuroradiology, Universitymedicine Greifswald

Since 2017 Head of Diagnostic and Interventional Neuroradiology, Institute for Diagnostic and Interventional Radiology, Pediatric and Neuroradiology, University Medical Centre Rostock

Furthermore, we are studying intravascular and intra-aneurysmal hemodynamics in patients harboring an intracranial aneurysm to predict. The aim is to develop a matrix for the prediction of aneurysm growth and rupture.

Drug distribution can be analysed using Ultra-high field MR microscopy. We therefore established a small animal model for in vivo imaging of the chicken embryo in ovo at 7T. We analysed the effects of repeated anaesthesia and exposure to ultra-high magnetic fields on the embryonal development. Furthermore, our study group developed different techniques for the visualization of drug distribution in this animal model. My study group has also dealt with the implementation of functional MR imaging techniques, such as sodium-23 MRI, for MR microscopy in small animal and human imaging.

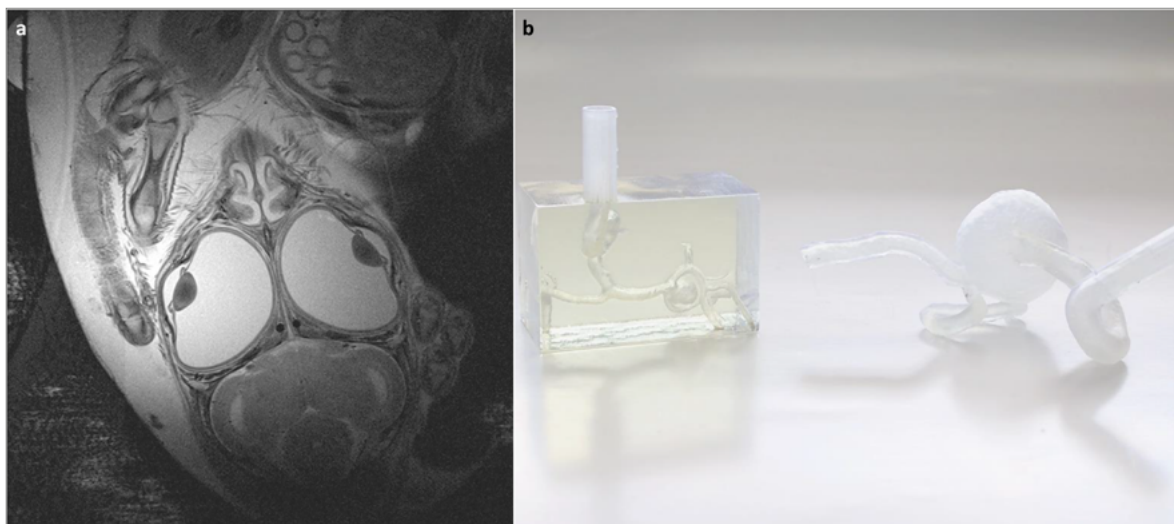


Fig. 1: a) Qualitative in ovo MR microscopy of the chicken embryo in vivo for the analyses of the effects of repeated exposure to ultra-high magnetic fields and repeated anaesthesia on the normal fetal development. b) 3D printed individualized models (scale 1:1) of the intracranial vessels from patients harboring an aneurysm. These models are used for the development and testing of biodegradable intracranial scaffolds.

Selected Publications

- Wenz D, Kuehne A, Huelnhagen T, Nagel AM, Waiczies H, Weinberger O, Oezerdem C, Stachs O, Langner S, Seeliger E, Flemming B, Hodge R, Niendorf T (2018). Millimeter spatial resolution in vivo sodium MRI of the human eye at 7 T using a dedicated radiofrequency transceiver array. *Magn Reson Med.* 80(2), 672-684.
- Streckenbach F, Klose R, Langner S, Langner I, Frank M, Wree A, Neumann AM, Glass A, Stahnke T, Guthoff RF, Stachs O, Lindner T (2018). Ultrahigh-Field Quantitative MR Microscopy of the Chicken Eye In Vivo Throughout the In Ovo Period. *Mol Imaging Biol.* 21(1), 78-85.
- Langner S, Kromrey ML, Kuehn JP, Grothe M, Domin M (2017). Repeated intravenous administration of gadobutrol does not lead to increased signal intensity on unenhanced T1-weighted images-a voxel-based whole brain analysis. *Eur Radiol.* 27(9), 3687-3693.
- Grothe M, Lotze M, Langner S, Dressel A (2017). Impairments in Walking Ability, Dexterity, and Cognitive Function in Multiple Sclerosis Are Associated with Different Regional Cerebellar Gray Matter Loss. *Cerebellum* 16(5-6), 945-950.
- Minnerup J, Broocks G, Kalkoffen J, Langner S, Knauth M, Psychogios MN, Wersching H, Teuber A, Heindel W, Eckert B, Wiendl H, Schramm P, Fiehler J, Kemmling A (2016). Computed tomography-based quantification of lesion water uptake identifies patients within 4.5 hours of stroke onset: A multicenter observational study. *Ann Neurol.* 80(6), 924-934.

Cellular disease models for drug testing in rare hereditary diseases



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State-of-the Art

The total number of rare monogenic diseases is estimated at over 5000. There is no therapy for most of these diseases. For the few diseases for which there is a therapy, it is not curative and largely insufficient to address all patients equally. Early diagnosis increases the probability of successful therapy. But due to the rarity of the diseases there is a lack of awareness and availability of diagnostic tests. Moreover, the discovery of new individual forms of therapy is beginning to pay off, led to the approval of pharmacological chaperone therapy (PCT) for the lysosomal storage disease Fabry disease in 2016. A pharmacological chaperone is a small molecule that enables the correct folding of a mutant protein and accelerates its maturation and transport to its final cellular target. This therapy depends on the genetics of the patients. Such a PCT is also being investigated in clinical trials for Gaucher disease. The development of personalised medicine for the metabolic disease Wilson's disease has not progressed so far. Since, as with the mentioned diseases, it is a disease with hundreds of different gene mutations in the disease-associated ATP7B gene, an individual approach is still an option.

Overall Scientific Aim

The nature and severity of the underlying gene mutation plays a significant role in the clinical heterogeneity of various monogenic diseases. My group develops cellular disease models to establish relationships between the molecular pathophysiology and the clinical manifestation. In particular, humanized and patient-derived models such as induced pluripotent stem cell-based cells play an important role. Since the underlying pathophysiology for many of the gene variants identified is based on a protein misfolding defect, we aim to identify novel drug candidates by targeting the endoplasmic reticulum protein biosynthesis network.



Fig. 1: Wilson's disease affected amino acid residues in the nucleotide binding domain of the copper transporting ATPase ATP7B. Missense mutations leading to single amino acid substitutions within the nucleotide binding domain of ATP7B cause structural and functional damage. This domain serves us for the computer-aided analysis of drug candidates as potential pharmacological chaperones.

Curriculum Vitae

2000 - 2005 Diploma in Biology, Georg-August-University, Göttingen

2005 - 2007 Research assistant at the Leibniz Institute for Age Research - Fritz Lipmann Institute, Department of Neuroendocrinology, Jena

2014 Doctorate at the Albrecht Kossel Institute for Neuroregeneration, University Medical Centre Rostock

2014 - 2016 PostDoc at the Albrecht Kossel Institute for Neuroregeneration, University Medical Centre Rostock

Since 2017 Work group leader "Medical Genetics" at the Albrecht Kossel Institute for Neuroregeneration, University Medical Centre Rostock

Projects, Methods & Technologies

Our current project deals with an inherited disorder of copper metabolism, Wilson's disease. It is a joint project funded by the European Social Fund within the framework of the Excellence MV. A major innovation of this project is the computer-aided simulation for the identification of binding partners to the Wilson protein (>ATP7B<), which can serve as potential pharmacological chaperones. This makes it possible to screen large substance libraries in high-throughput mode. As receptor we have modeled the nucleotide binding domain of the copper-transporting ATPase ATP7B. Molecular docking is performed using the Glide Software (Schrodinger LLC). The efficacy of the hit compounds from the computer-assisted screening will be tested in cellular and cell-free *in vitro* assays. The thermal shift assay (also known as Differential Scanning Calorimetry) is a cell-free method that refers to the quantification of the variable thermal denaturation temperature of a protein in different environments, salts, pH, and oxidation/reduction. However, the assay can also be used for drug screening. We use the recombinant nucleotide binding domain of ATP7B expressed and purified in *Escherichia coli*. Since Wilson's Disease is mainly a disease of the liver, we created a cellular model that is able to simulate the pathophysiology in this organ. We used the genome editing method CRISPR/Cas9 to produce ATP7B deficient hepatoma cells (HepG2-ATP7B^{-/-}). The cells show a bi-allelic deletion in exon 2 of the ATP7B gene associated with an altered copper metabolism. Using these cells, we investigate affected pathways in Wilson's disease and, hence, try to identify possible new therapeutic targets. We are currently investigating whether knock-in of a human missense mutation into the genome of these liver cell progeny cells is also possible. This would allow us to test for pharmacological chaperones. Further models and substance classes are being investigated in our group revolving around the proteostasis machinery network with the aim to better understand the pathomechanisms of the diseases and identifying improved drugs for rare diseases. We are convinced that our efforts in rare diseases can also lead to a significant increase in knowledge about the more common diseases through their numerous points of intersection.

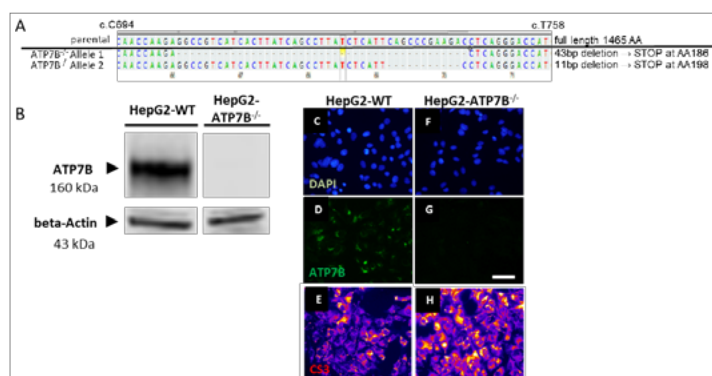


Fig. 2: Detection of ATP7B knockout in human Hepatoma cell line HepG2. A: ATP7B locus information (exon 2) in ATP7B Knockout cells (HepG2-ATP7B^{-/-}). Allele 1 had a 43 bp and allele 2 an 11 bp deletion of indicated nucleotides led to an abnormal gene product. B: Detection of complete ATP7B Knockout using Western blot. Beta-actin antibody was used as a housekeeping control. Comparative cell staining of wild type HepG2 cells (HepG2-WT) and HepG2-ATP7B^{-/-} with the nucleus staining DNA intercalator DAPI (C,F), ATP7B antibody (D,G) and the copper binding CS3 (E,H) under low copper conditions. The absence of ATP7B expression (G) led to an increased loading of the cells with copper (H). Scale bar 50 μm (C-H). Abbreviations: AA, amino acid; bp, basepairs; CS3, Copper Sensor 3; DAPI, 4',6-Diamidino-2-Phenylindole; WT, wild type.

Selected Publications

- Lenders M, Neußer LP, Rudnicki M, Nordbeck P, Canaan-Kühl S, Nowak A, Cybulla M, Schmitz B, Lukas J, Wanner C, Brand SM, Brand E (2018). Dose-Dependent Effect of Enzyme Replacement Therapy on Neutralizing Antidrug Antibody Titers and Clinical Outcome in Patients with Fabry Disease. *J Am Soc Nephrol.* 29(12), 2879-2889.
- Lukas J, Cozma C, Yang F, Kramp G, Meyer A, Neßlauer AM, Eichler S, Böttcher T, Witt M, Bräuer AU, Kropp P, Rolfs A (2017). Glucosylsphingosine Causes Hematological and Visceral Changes in Mice-Evidence for a Pathophysiological Role in Gaucher Disease. *Int J Mol Sci.* 18(10), pii: E2192.
- Bohl C, Pomorski A, Seemann S, Knospe AM, Zheng C, Krężel A, Rolfs A, Lukas J (2017). Fluorescent probes for selective protein labeling in lysosomes: a case of α-galactosidase A. *FASEB J.* 31(12), 5258-5267.
- Lukas J, Scalia S, Eichler S, Pockrandt AM, Dehn N, Cozma C, Giese AK, Rolfs A (2016). Functional and Clinical Consequences of Novel α-Galactosidase A Mutations in Fabry Disease. *Hum Mutat.* 37(1), 43-51.
- Lukas J, Pockrandt AM, Seemann S, Sharif M, Runge F, Pohlers S, Zheng C, Gläser A, Beller M, Rolfs A, Giese AK (2015). Enzyme enhancers for the treatment of Fabry and Pompe disease. *Mol Ther.* 23(3), 456-464.

Mechanisms of neurodegeneration in Niemann-Pick Type C1 (NPC1) disease



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State-of-the Art

Niemann-Pick Type C1 (NPC1) disease is a rare neurodegenerative lysosomal storage disorder caused by mutations in *Npc1* gene, leading to intracellular accumulation of unesterified cholesterol in the late endosome/lysosome. The clinical manifestations of NPC1 are varied in the CNS with typically neurological or psychiatric symptoms, including ataxia, tremor, dystonia, motor control problems and seizures. Neurodegenerative disorders including neuron loss and hypomyelination in certain regions of the CNS have been found in NPC1 patients as well as the NPC1 mutant mouse model.

Studies have confirmed axonal defect and neuron loss in the hippocampus and cortex in NPC1 mutant mice. Upon AMPA stimulation, NPC1 mutant neurons have a higher and more persistent spike amplitude accompanied by an upregulated calcium influx, suggesting an involvement of AMPA receptors in NPC1 disease. Furthermore, some factors have been considered to be involved in hypomyelination in NPC1 disease, e.g., an increase of the PSA-NCAM, and a decrease of Myrf and phosphorylated Fyn. Although NPC1 disease has been studied for decades, the precise mechanism of the neurological disorder is still not fully understood. Therefore, it is interesting to investigate the precise mechanisms referring to neuron loss and hypomyelination in NPC1 disease.

Overall Scientific Aim

The aim of our study is to investigate pathophysiological mechanisms involved in neuron loss and hypomyelination in NPC1 disease. We focus on the effect of NPC1 on cellular internalization in neurons and on myelination in oligodendrocytes in the CNS. Our findings will not only find out the precise mechanisms of NPC1 disease, but also help us achieve new potential treatments for NPC1 disease.

Projects, Methods & Technologies

Cholesterol is essential for normal function of cellular membrane and in this project, we investigate the effect of NPC1 mutations on AMPA receptor internalization of neurons isolated from mutant NPC1 mice using primary neuron culture system. Our data show that the defective internalization of GluR2-containing AMPA receptors

Curriculum Vitae

1982 - 1987 Bachelor in Medicine, Hubei Medical University, China

1989 - 1992 Master in Medicine, Tongji Medical University, China

1996 - 1999 Doctor of Medicine, Ruhr University Bochum

2000 - 2003 PostDoc, Institute of Anatomy, University of Essen

2004 - 2007 Group leader in Institute of Anatomy, University of Jena

2008 Habilitation in Anatomy, Medical Faculty, University of Jena

Since 2007, Group leader in Translational Neurodegeneration Section „Albrecht-Kossel“, Department of Neurology,
 University Medical Centre Rostock

is related to the dysfunction of mGluR1/5 induced by a decrease of cholesterol level in lipid rafts. Applications of DHPG and β -cyclodextrin restore the internalization of AMPA receptors and over-influx of calcium in NPC1 mutant neurons, respectively. Thus, our data imply that abnormal internalization of AMPA receptors is a critical mechanism for neuronal dysfunction and the correction of dysfunctional mGluR1/5 is a potential therapeutic strategy for NPC1 disease.

Cholesterol is a main component of myelin structure and its availability is rate-limiting for myelination in the CNS. The *Npc1*-dependent pathway is essential for the formation and maintenance of myelin in the CNS. In the project, we identify a disruption of oligodendrocyte differentiation in NPC1 mice, as indicated by a significant decrease of the major myelin proteins, which may be caused by a decrease of oligodendrocyte regulatory factors, e.g., *Myrf*, *Olig1* and *Olig2*. Furthermore, NPC1 oligodendrocytes showed a less response to the stimulation of neuron-conditioned medium by in vitro oligodendrocyte cultivation, indicating a defect of oligodendrocyte per se, which can be restored by lovastatin treatment. Thus, these knowledges will help us find out new potential therapy for NPC1 treatment.

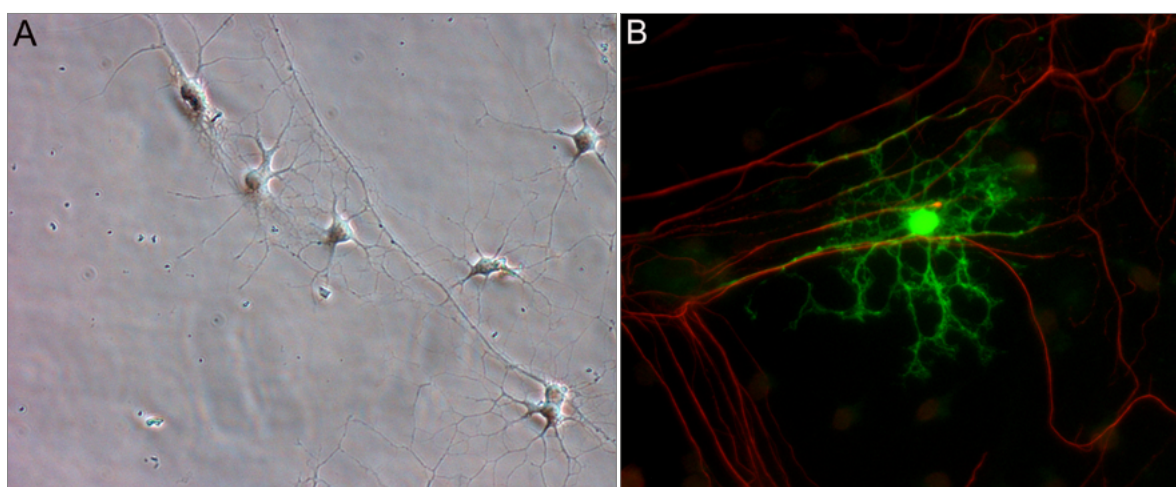


Fig. 1: In vitro co-culture of mouse cortical neurons (red in B; neurofilament) and oligodendrocytes (cells in A, green in B; MBP).

Selected Publications

- Yan X, Wang Z, Bishop CA, Weitkunat K, Feng X, Tarbier M, Luo J, Friedländer MR, Burkhardt R, Klaus S, Willnow TE, Poy MN. (2018). Control of hepatic gluconeogenesis by Argonaute2. *Mol Metab.* 18, 15-24.
- Qiao L, Yang E, Luo J, Lin J, Yan X. Altered myelination in the Niemann-Pick type C1 mutant mouse. (2018). *Histol Histopathol.* 33, 1311-1321.
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- Yang F, Feng X, Rolfs A, Luo J. Lovastatin promotes myelin formation in NPC1 mutant oligodendrocytes. (2018). *J Neurol Sci.* 386, 56-63.
- Markus-Koch A, Schmitt O, Seemann S, Lukas J, Koczan D, Ernst M, Fuellen G, Wree A, Rolfs A, Luo J (2017). ADAM23 promotes neuronal differentiation of human neural progenitor cells. *Cell Mol Biol Lett.* 22, 16.
- Narendra Talabattula VA, Morgan P, Frech MJ, Uhrmacher AM, Herchenröder O, Pützer BM, Rolfs A, Luo J. (2017). Non-canonical pathway induced by Wnt3a regulates β -catenin via Pyk2 in differentiating human neural progenitor cells. *Biochem Biophys Res Commun.* 491, 40-46.

Mechanisms of the nerve-cancer cell cross-talk in cancer progression



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State-of-the Art

Cancer is on the rise not only in Western societies. Metastasis, the ability of cancer cells to spread to distant sites within an organism, marks the onset of the disease's terminal stage. Understanding the processes underlying metastasis could facilitate the development of drugs to prevent progression towards aggressive stages. The hallmarks include formation of new lymphatic and blood vessels to support tumor growth and dissemination.

A similar but far less studied process that occurs in relation to the nervous system involves neoneurogenesis, where nerves are built around the tumor. Analogous to angiogenesis, in which the tumor co-opts vessel formation programs to drive progression to metastatic stages, nervous system-related signaling pathways and factors can be recruited as well. In melanoma, a highly aggressive skin cancer prone for brain metastases, neurotrophic signaling promotes proliferation and migration. Hence, a tumor may achieve its own innervation by producing and excreting neuronal growth factors, neurotrophins and/or axon guidance molecules. Recent findings describe that neural progenitors from the subventricular zone of the central nervous system break the blood-brain barrier, infiltrate the tumor microenvironment and generate new neurons. This reciprocal interaction between nerves and cancer cells provides new insights into the cellular and molecular bases of tumor metastasis and points to the potential utility of antineurogenic therapies.

The transcription factor p73 is a member of the p53 family and implicated in both, cancer progression and neuronal development. The TP73 gene synthesizes a large number of isoforms by alternative splicing or use of an extrinsic and alternative intrinsic promoter, generating transcriptionally active TA isoforms as well as amino-truncated variants that partially or entirely lack the transactivation domain. The latter constitute the DN classes of isoforms. In the context of cancer, TAp73 proteins have been considered anti-oncogenic (Stiewe and Pützer 2000, Nature Genet. 26:464), whereas, DNs are oncogenic, induce stemness and promote metastatic outcomes (Meier et al. 2016, Cancer Res. 76:197; Steder et al. 2013, Cancer Cell 24:512). In addition, neurobiology studies indicate that p73 affects stemness throughout neuronal differentiation (i.e. from neural stem cells to postmitotic neurons). In general, TAp73 is required for neuronal differentiation and maintenance of neural stem cells, while DNp73 is required for neuronal survival, both, during development and in adult neuronal tissues.

Curriculum Vitae

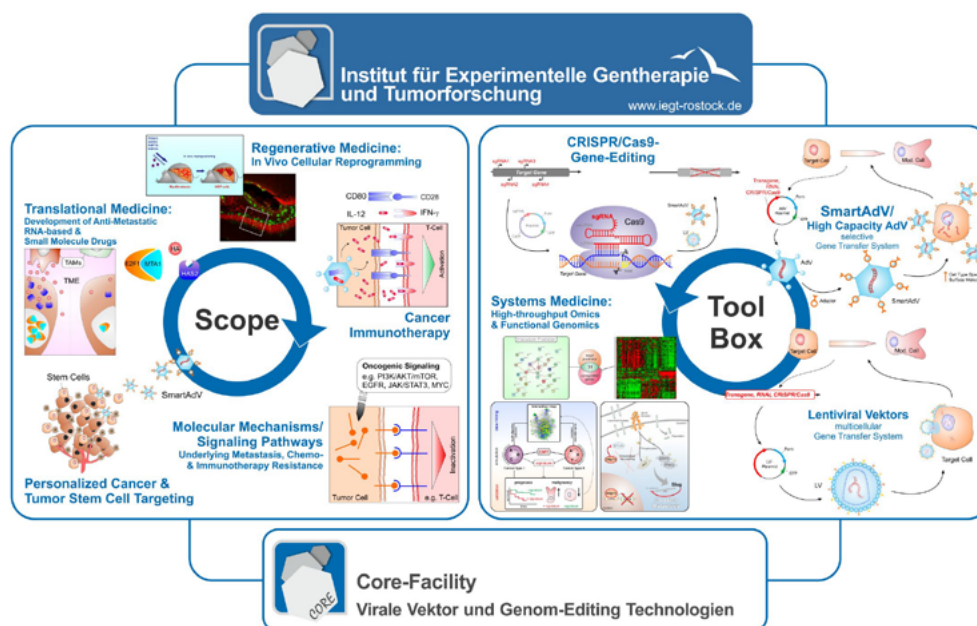
1992 State exam in Medicine, University of Essen
 1994 Ph.D. in Molecular Biology, Department of Molecular Biology (Tumor Research), University of Essen
 1995 - 1996 Research group leader, Department of Molecular Biology (Tumor Research), University Hospital Essen
 1996 - 1998 Postdoctoral Fellow, Department of Biology, McMaster University, Hamilton, Ontario, Canada
 Since 1998 Assistant Professor, Department of Molecular Biology, University Hospital Essen
 1998 - 1999 Visiting Assistant Professor, Center of Molecular Medicine, University Cologne
 2000 Doctorate in Medicine, Department of Molecular Biology (Tumor Research), University Hospital Essen
 2001 Habilitation and Venia legendi in Molecular Biology, Medical Faculty, University of Essen
 Since 2003 Full Professor for Vectorology and Experimental Gene Therapy and Head of the Department for
 Vectorology and Experimental Gene Therapy, University Medical Centre Rostock
 Since 2013 Director, Institute of Experimental Gene Therapy and Cancer Research, University Medical Centre Rostock

Overall Scientific Aim

On the basis of the dual role of p73 isoforms in both, neuronal development and cancer initiation and progression, we hypothesize that p73 isoform(s) may govern mechanisms underlying neurogenesis in cancer. Using melanoma as a representative example, our current studies focus on characterizing established and emerging markers of tumor-induced nerve formation in invasive p73-expressing melanoma cells and define the p73 variants causatively linked to this process. Hence, we decipher proteins which interact with neurogenesis-related p73 isoform(s) in order to modulate gene regulation and/or epigenetic programs towards the activation of neurodifferentiation/neurodevelopmental programs that foster metastatic progression. Beyond this research, further development of strategies to identify inhibitors of protein-protein interactions in conjunction with bioinformatics-based pharmacophore modeling that block growth of nerves will contribute not only to a mechanistic understanding of this poorly understood relationship between tumor progression and the nervous system, but also to the development of innovative therapies preventing metastatic stages. In future, cancer patients with infaust molecular signature will likely benefit from combination treatments.

Projects, Methods & Technologies

Our main research interests are the basic mechanisms and treatment of cancer metastasis, development of stem cell-based therapeutics and cellular programming technologies. We explore molecular signaling networks and epigenetic signatures responsible for apoptosis deficiency, invasiveness, tumor microenvironmental changes as well as causes of chemo- and immunotherapy resistance and thereby focus on the E2F1 transcription factor interactome and the p53 transcription factor family. By high-throughput Omics, we identify molecular alterations in regulatory signaling networks, apply modeling approaches to predict biomarkers and develop custom-made antimetastatic drugs for translational medicine. Particular emphasis in creating new gene therapeutic tools lies on our cell targeting smart-viral-vector systems.



Selected Publications

- Pützer BM, Solanki M, Herchenröder O (2017). Advances in cancer stem cell targeting: How to strike the evil at its root. *Adv Drug Deliv Rev.* 129, 89-107.
- Khan FM, Marquardt S, Gupta SK, Knoll S, Schmitz U, Spitschak A, Engelmann D, Vera J, Wolkenhauer O, Pützer BM (2017). Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. *Nature Commun.* 8, 198.
- Talabattula VAN, Morgan P, Frech MJ, Uhmacher AM, Herchenröder O, Pützer BM, Rolfs A, Luo J (2017). Non-canonical pathway induced by Wnt3a regulates β -catenin via Pyk2 in differentiating human neural progenitor cells. *Biochem Biophys Res Commun.* 491, 40-46.
- Song G, Pacher M, Balakrishnan A, Yuan Q, Tsay H-C, Yang D, Reetz J, Brandes S, Dai Z, Pützer BM, et al. (2016). Direct reprogramming of hepatic myofibroblasts into hepatocytes in vivo attenuates liver fibrosis. *Cell Stem Cell* 18, 797-808.
- Reetz J, Hildebrandt S, Schmidt A, Meier C, Herchenröder O, Gläser A, Witt M, Pützer BM, Wree A (2016). Novel subventricular zone early progenitor cell specific adenovirus for in vivo therapy of central nervous system disorders reinforces brain stem cell heterogeneity. *Brain Struct Funct.* 221, 2049-2059.



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Developmental psychopathology itself is developing towards holistic approaches, ranging “from neurons to neighbourhoods”. In my own research I try to be as holistic as possible.

As the head of the small research department of the Clinic for Child and Adolescent Psychiatry my interests are accommodated to the topics we examine at our unit. They reach from pathophysiological mechanisms of mental disorders, such as ADHD, to the effects of risky neighbourhoods within the town of Rostock. A major part of my research in developmental psychopathology is prevention and longitudinal research. In prevention, I do research about drug abuse and sexual abuse in youth with intellectual disabilities. In longitudinal research, I am heading the Rostock Longitudinal Study which started in 1970 and was conducted the latest time when participants were 38 years old (2008).

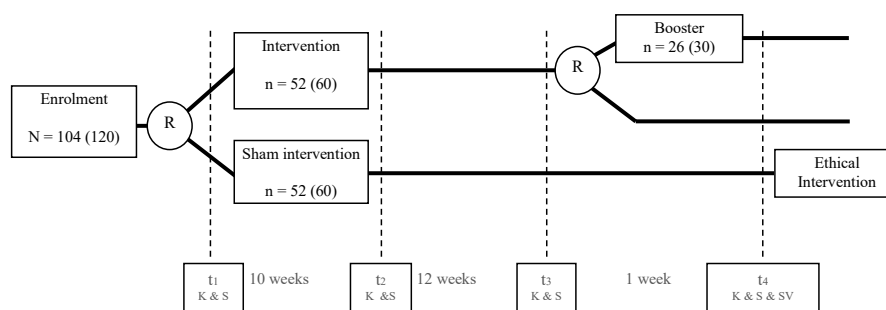


Fig. 1: Study design for the evaluation study. R = Randomization, K & S = Knowledge and Skills, SV = Social Validity (acceptance and unwanted effects). Sample sizes are made according to the power analysis and compensate for the anticipated attrition (in brackets) [From Chodan et al. (2017)].

1984 - 1989 State exam in Psychology, Friedrich Schiller University Jena

1993 Doctorate in Psychology, Faculty of Philosophy, University of Rostock

Since 2003 Senior Researcher, Clinic for Child and Adolescent Psychiatry, University Medical Centre Rostock

2015 Habilitation in Psychology, Faculty of Philosophy, University of Rostock

Projects, Methods & Technologies

This broadness regards the methods I use as well. On the physical end, I participate in electrophysical research (mostly EEG) done at our unit (see also Dr. Berger's work). I also collaborate with Dr. Marx, who runs experimental designs using computer-tasks examining basic patho-mechanisms of ADHD (see DRKS00015760). For my prevention research however, I am using observational data acquired within real settings (see for an example our study on prevention of sexual abuse in girls with intellectual disabilities, DRKS00014673) and data from ecological momentary assessments (see our study on alcohol prevention in boys with mild to borderline intellectual disability, DRKS00014042). On the sociological level I use regionalized data on prevalences of mental disorders, but also micro-social data, such as quotations from extended interviews. For the analysis of meaningful communications I proved hierarchical log-linear models on the contingencies of quotations to be useful (Reis, 2017: Nischen im Wandel, Book, Gießen: psychosozial).



My interest in regional distribution of risks for mental disorder started in 2018, when I analysed the geographical source of patients from our clinic. In this very first step I manually attached one datapoint per patient to a map of Rostock. As visible on the first glance - neighbourhoods turned out to be very different.

Selected Publications

- Kuttler H, Schwendemann H, Reis O, Bitzer EM (2016). Developmental hazards among young alcohol intoxicated patients, *Journal of Adolescent Health* 1, 87-95.
- Grüne B, Piontek D, Pogarell O, Grübl A, Groß C, Reis O, Zimmermann US, Kraus L (2016). Acute alcohol intoxication among adolescents – the role of the context of drinking, *European Journal of Pediatrics* 176, 31-39.
- Groß C, Kraus L, Piontek D, Reis O, Zimmermann US, and RISCA-Group (2016). Prediction of long-term outcomes in young adults with a history of adolescent alcohol-related hospitalization, *Alcohol and Alcoholism* 51, 47-53.
- Dueck A, Berger C, Wunsch K, Thome J, Cohrs S, Reis O, Haessler F (2015). The role of sleep problems and circadian clock genes in attention deficit hyperactivity disorder and mood disorders during childhood and adolescence, *Journal of Neural Transmission* 124, 127-138.
- Häßler F, Thome J, Reis O (2015). Polypharmacy in the treatment of subjects with intellectual disability, *Journal of Neurotransmission* 122 (Suppl 1), 93-100.

Connectomics and proteomics of neurodegenerative diseases



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State-of-the Art

Central and peripheral neuronal connections are essential for transmitting electrochemical signals to control body homeostasis and behaviour. All known connections of an organism can be assembled in a connectome. The granularity of connectome data is large for laboratory rats and mice. These data provide very specific information with regard to orientation and density of neuronal connections because they can be generated with outstanding precise and reliable tract tracing experiments. These connectional information is used to model dynamic processes in connectomes to understand the relation of connectional structure and functional outcome. Moreover, connectomes help to detect differences of signal dynamics in non-lesioned control connectomes and connectomes that were lesioned with regard to connections or regions. A lesion of regions could be the deafferentation of the substantia nigra in Parkinson disease and a lesion of connections could be the demyelination of the somatosensory pathway or interhemispheric connections.

Overall Scientific Aim

The connectome is build of directed connections of variable density and specific features of electrochemical conductance. From a network perspective, information can be transmitted through such a network through different routes having different effects with regard to signal integration on target regions. In the case of degeneration of neuronal connections or neurons such routes can be reconstructed by network modelling and analysis of dynamics. It would be a great advantage to determine those patterns of regions in a connectome which exhibit strongest changes following simulations of lesions in comparison with non-lesioned connectomes. This information would help to predict disease progression and provide patterns of primary and secondary functionally impacted regions.

Projects, Methods & Technologies

In our research group, a framework have been made available to analyse the propagation of dynamic processes through weighted and directed networks and connectomes. Using differential connectomics, control and lesioned connectomes can be directly analysed with regard to functional changes related to connectional disintegration.

Curriculum Vitae

1984 - 1991 State exam in Medicine, University of Lübeck

1991 Doctorate in Anatomy, Institute of Anatomy, University of Lübeck

1992 - 1993 Resident at the clinic of surgery of the district hospital, Heide

1993 Postdoctoral research fellow at the Institute of Anatomy, University of Lübeck

2001 Habilitation in Anatomy, University of Lübeck

2004 Medical specialist for anatomy

2002 - 2007 Assistant professor, University Medical Centre Rostock

2007 - 2019 Adjunct professor, University Medical Centre Rostock

For this, a bilateral tract tracing connectome of the rat, the Allen mouse connectome and CoComac were analysed. These connectomes are based on long term curated metastudies collecting tract tracing information. Moreover, the workflows of our framework are flexible and have been applied to tractographic small animal and human data.

In an ongoing project of Multiple Sclerosis two approaches are applied to better understand myelin pathology of the EAE model and dynamic effects of demyelination in dynamic connectome modelling.

To identify changes of protein patterns the myelin proteome was specifically isolated by using gradient centrifugation. Protein identification will be performed by liquid chromatography-mass spectrometry (nanoLC-HDMS^E). For differential connectome analysis new network diffusion models were realized. The Gierer-Meinhardt and the Mimura-Murray reaction diffusion models turned out to generate stable patterns of oscillations in weighted and directed networks. Using new non-linear weight modulation functions in combination with network-reaction-diffusion we are able to model changes of neuronal weights in analogy to demyelination processes. Recently a reduction of functional activity between thalamic nuclei has been found when miming the progressive relapsing form of Multiple Sclerosis at the level of the spinal cord.

Our group works over many years to provide connectome data and the connectome analysis framework neuroVIISAS to the neuroscience community. Using the analytical workflows of structural and functional connectome analysis supports a substantial understanding of how connectional structure shapes neuronal function in health and diseases.

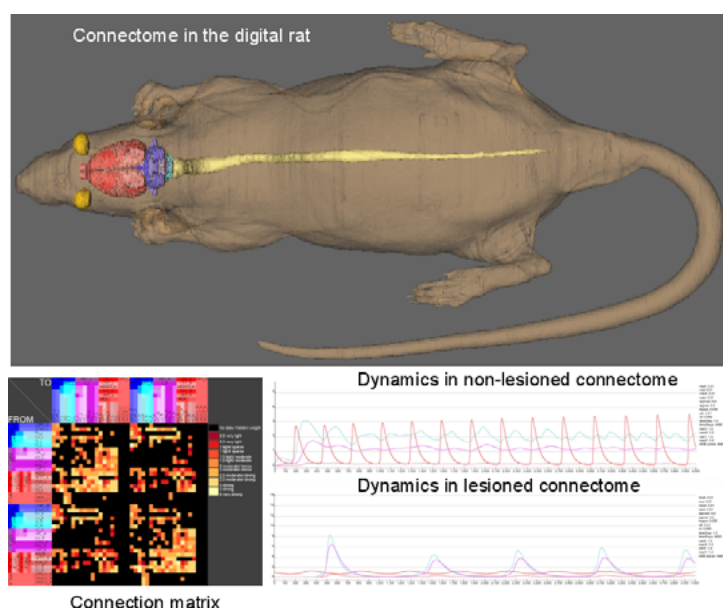


Fig. 1: The connectome in a digital rat and the connectivity matrix were used together with dynamic models to determine changes of functions in the non-lesioned and lesioned connectome.

Selected Publications

- Schwanke S, Jenssen J, Eipert P, Schmitt O (2018). Differential connectomics in neuroVIISAS. *Neuroinformatics* 17, 163-179.
- Schmitt O, Eipert P, Schwanke S, Lessmann F, Meinhardt J, Beier J, Kadir K, Karnitzki A, Sellner L, Klünker A-C, Kuch L, Ruß F, Jenssen J (2018). Connectome verification: inter-rater and connection reliability of tract-tracing based intrinsic hypothalamic connectivity. *Brief Bioinform.* [Epub ahead of print].
- Schmitt O, Badurek S, Liu W, Wang Y, Rabiller G, Kanoke A, Eipert P, Liu J (2017). Prediction of regional functional impairment following experimental stroke via connectome analysis. *Scientific reports* 7, 46316.
- Sinke MRT, Otte WM, Christiaens D, Schmitt O, Leemans A, van der Toorn A, Sarabdjitsingh AR, Joels M, Dijkhuizen RM (2017). Diffusion MRI-based cortical connectome reconstruction - dependency on tractography procedures and neuroanatomical characteristics. *Brain Struct Funct* 223, 2269-2285.
- Schmitt O, Eipert P, Kettlitz R, Lessmann F, Wree A (2016). The connectome of the basal ganglia. *Brain Struct Funct* 221, 753-814.

Regulation of physiological and pathological microglia functions



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State-of-the Art

Microglia are the resident immune cells of the central nervous system (CNS) and have been described to play pivotal roles in virtually all neuropathological conditions. Their stimulation in the course of neurodegenerative diseases is believed to further foster disease progression and to induce bystander neuronal damage by release of cytotoxic factors. Next to these disease-associated functions, microglia have further been implicated in prenatal and postnatal CNS development by regulating neuron survival, supporting neuronal network formations and controlling synapse maturation and function. Moreover, aging has been described to effect microglia and result in impairments of microglial functions. However, how microglia functions are endogenously regulated under physiological and pathological conditions is only poorly understood and need to be further elucidated.

Overall Scientific Aim

Our aim is to increase the understanding of how Transforming Growth Factor beta 1 (TGFβ1) controls microglia functions under physiological and neuropathological conditions. Moreover, we are aiming to elucidate the importance of microglial presence during CNS development, physiological aging processes and during CNS pathologies such as Parkinson's disease (PD) and Alzheimer's disease (AD).

Projects, Methods & Technologies

Using elegant transgenic approaches, we are able to specifically silence TGFβ signalling in microglia in vivo and in vitro. The tamoxifen-inducible Cre/loxP technique allows us to analyse TGFβ1-mediated functions in microglia at defined developmental and adult time points by deletion of the ligand-binding receptor Tgfr2 and the intracellular downstream mediator Smad4. Moreover, these mutant mice are further used to determine the contribution of TGFβ1-regulated microglia activation during dopaminergic neuron degeneration in the toxin-based MPTP mouse model for PD. We have recently demonstrated that microglial TGFβ signalling is essential for microglial homeostasis in adult mice by preventing excessive microglia activation. Moreover, microglial TGFβ signalling seems to be involved in early postnatal microglial differentiation and maturation as a prerequisite for appropriate microglial functions.

Curriculum Vitae

2000 - 2006 State exam in Medicine, Georg-August-University of Göttingen

2007 Doctorate in Medicine (Molecular Cell Biology), Institute of Anatomy, Department of Neuroanatomy, Georg-August-University of Göttingen

2006 - 2008 PostDoc, Institute of Anatomy, Department of Neuroanatomy, Georg-August-University of Göttingen

2008 - 2012 PostDoc, Institute of Anatomy and Cell Biology, Department of Molecular Embryology, Albert-Ludwigs-University Freiburg

2013 Habilitation in Anatomy and Cell Biology, Medical Faculty, University of Freiburg

2012 - 2017 Principal investigator and Research group leader at the Institute of Anatomy and Cell Biology, Department of Molecular Embryology, Albert-Ludwigs-University Freiburg

Since 2017 Full Professor (W2) for Anatomy and Associate Director of the Institute of Anatomy, University Medical Centre Rostock

In order to understand the importance of microglia during CNS development and under pathological conditions, we employ microglia depletion models in vitro and in vivo. The inhibition of microglial CSF1 signalling by either pharmacological blockade or by genetic deletion of the CSF1 receptor result in efficient depletion of microglia from cell culture models and transgenic mice. Using this depletion approach, we are addressing the role of microglia for the establishment of neuronal networks and synaptic maturation. Transgenic mice are further used to address the effect of microglial absence during aging and under neuropathological conditions.

Next to murine model organisms, we are currently establishing a system to induce microglia-like cells from human induced pluripotent stem cells (iPSCs). In collaboration with the Eastern Finland University, we optimise the current induction protocol to improve the phenotype of iPSC-derived microglia. This technique will allow us to analyse microglia phenotypes from patient-derived iPSCs in the future, to further understand whether primary microglia defects and functional impairments could be causative for certain CNS diseases.

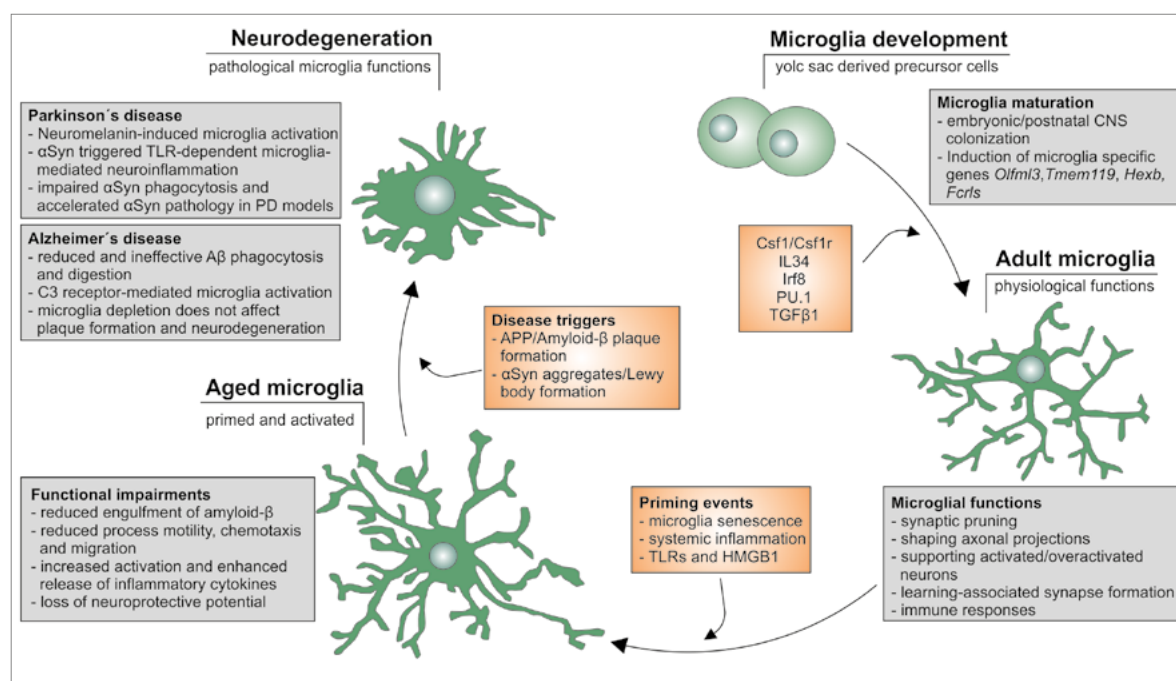


Fig. 1: Schematic overview of the microglial life cycle [from Spittau 2017]. Transgenic mouse models to silence TGF β signalling and microglia depletion models are used to decipher microglial functions at defined points within this cycle.

Selected Publications

- Zöller T, Schneider A, Kleimeyer C, Masuda T, Potru PS, Pfeifer D, Blank T, Prinz M, Spittau B (2018). Silencing of TGF β signalling in microglia results in impaired homeostasis. *Nat Commun.* 9, 4011.
- Attaai A, Neidert N, von Ehr A, Potru PS, Zöller T, Spittau B (2018). Postnatal maturation of microglia is associated with alternative activation and activated TGF β signaling. *Glia* 66, 1695-1708.
- Neidert N, von Ehr A, Zöller T, Spittau B (2018). Microglia-Specific Expression of *Olfml3* Is Directly Regulated by Transforming Growth Factor β 1-Induced Smad2 Signaling. *Front Immunol* 9, 1728.
- Hühner L, Rilka J, Gilsbach R, Zhou X, Machado V, Spittau B (2017). Interleukin-4 Protects Dopaminergic Neurons In vitro but Is Dispensable for MPTP-Induced Neurodegeneration In vivo. *Front Mol Neurosci* 10, 62.
- Spittau B, Rilka J, Steinfath E, Zöller T, Krieglstein K (2015). TGF β 1 increases microglia-mediated engulfment of apoptotic cells via upregulation of the milk fat globule-EGF factor 8. *Glia* 63, 142-153.

Basic mechanisms of novel therapeutic approaches in Parkinson's disease



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Non-motor symptoms in Parkinson's disease
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State-of-the Art

Parkinson's disease (PD) is the second most frequent neurodegenerative disease and represents a major therapeutic challenge because of the so far missing causative therapeutic means. Despite considerable advances in symptomatic pharmacotherapy, levodopa remains the mainstay for treatment of PD due to its superior efficacy and favorable side-effect profile. However, long-term levodopa treatment is associated with motor and non-motor complications, which can substantially impair quality of life. For the advanced stage of the disease, deep brain stimulation and pump therapies for continuous dopaminergic stimulation are established therapeutic options. However, the basic mechanisms of action of deep brain stimulation, particularly on non-motor symptoms, remain in part enigmatic.

Overall Scientific Aim

To dissect the basic mechanisms of treatment approaches in PD with special focus on deep brain stimulation (DBS) on the one hand and on novel therapeutic options for sleep disturbances and non-motor fluctuations on the other hand. Our achievements will contribute not only to the understanding of the various treatment approaches, but also to the generation of novel innovative therapeutic means for motor and non-motor symptoms in late-stage PD.

Projects, Methods & Technologies

In our Collaborative Research Centre ELAINE (CRC 1270) project, we dissect the mechanisms of DBS related to the interplay between cellular plasticity and non-motor symptoms such as depression/anxiety and cognition using the 6-hydroxydopamine rat model of PD. In detail, we focus on the influence of various stimulation parameters and target regions on adult neurogenesis processes such as proliferation, migration and differentiation of neural progenitors. We furthermore investigate the interactions between physiologic regulators (i.e. physical activity) of adult neurogenesis and DBS. The results contribute to the understanding of DBS actions including the pathophysiological mechanisms underlying depression and cognitive dysfunction in neurodegenerative diseases. This knowledge will ultimately help us to optimize implants including stimulation targets and parameters for DBS treatment of motor and non-motor deficits of PD.

Curriculum Vitae

1990 - 1995 State exam in Medicine, Johannes-Gutenberg-University of Mainz and Free University Berlin
1996 Doctorate in Molecular Neurobiology, Institute of Physiological Chemistry and Pathobiochemistry, Johannes Gutenberg-University of Mainz
2001 Habilitation in Neurology, Medical Faculty, University of Ulm
2001 - 2004 Senior neurologist, Department of Neurology, University of Ulm
2004 - 2010 Full Professor (C3) for Neurodegenerative Diseases, Department of Neurology, Medical Faculty Carl Gustav Carus at the Technische Universität Dresden
Since 2011 Research group leader, German Centre for Neurodegenerative Diseases (DZNE)
Since 2015 Full Professor (W3) for Neurology and Director of the Department of Neurology, University Medical Centre Rostock
Since 2017 Speaker of the Centre for Transdisciplinary Neurosciences Rostock (CTNR)

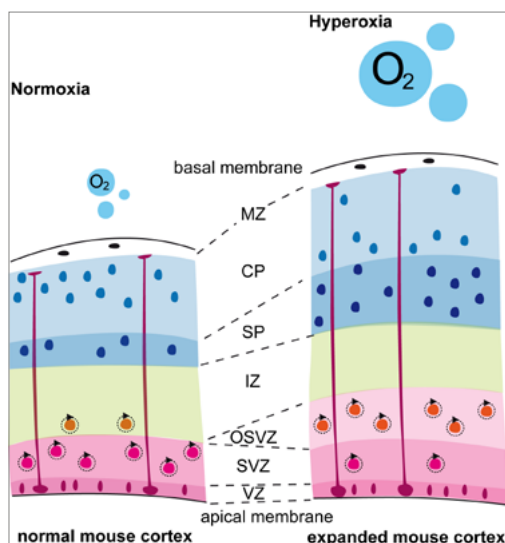


Fig. 1: Schematic of the expansion of the neocortex in response to hyperoxia in mouse [from Wagenführ et al. (2015) *Development* 142(17), 2904-15].

Sleep disorders are common in PD and have an immense negative impact on patient's quality of life. Neurodegenerative processes within sleep regulatory brain circuitries, antiparkinsonian (e.g., levodopa and dopamine agonists) and concomitant medication (e.g., antidepressants) as well as comorbidities or other non-motor symptoms (such as depression) are discussed as causative factors. Management of sleep disorders in PD patients usually starts with optimization of (dopaminergic) antiparkinsonian therapy followed by specific treatment of the sleep disturbances. We studied the dopaminergic effects of the MAO-B inhibitor rasagiline on sleep architecture in PD in a blinded investigator-initiated study and show that objective sleep quality parameters are improved by rasagiline with no effects on the patient's perception of sleep. Aside from these clinical issues of sleep disorders in PD, the concept of REM-sleep behavior disorder (RBD) as an early sign for emerging neurodegenerative diseases is of pivotal interest for our research on biomarkers and neuroprotective treatment strategies of PD.

The role of non-motor symptoms in PD has been a research focus of the group over recent years. Cognitive impairment, depression and psychosis are well-characterized non-motor aspects of PD, with other relatively common complications including anxiety, sleep problems, apathy, and impulse control disorders. The prominence of these symptoms alongside classical motor features has led experts to consider PD as a neuropsychiatric condition. Our group focuses on the phenomenon of non-motor fluctuations in conjunction to motor fluctuations in late-stage PD. By applying the extended ^{18}F Fluorodopa PET protocol to measure the striatal dopamine turnover as a potential disease-intrinsic presynaptic compensatory mechanism in response to the dopaminergic neurodegenerative process in PD, we demonstrate that putaminal dopamine turnover in de novo PD is associated with the risk for motor and neuropsychiatric fluctuations in the later disease course. Since both the extent of dopamine turnover changes and the occurrence of late-stage motor complications in PD depends on specific MAO-B gene polymorphisms and subsequently on MAO-B activity, we describe a new concept of a potentially protective treatment against late-stage complications by MAO-B inhibition.

Cell replacement has raised hope to offer restorative treatment options in PD. Clinical trials have provided "proof of principle" that transplantation of dopamine-producing neurons into the striatum of PD patients can achieve symptomatic relief given that the striatum is sufficiently re-innervated. Various cell sources have been subsequently tested, including fetal ventral midbrain tissue, embryonic stem cells, fetal and adult neural stem cells and, after their ground-breaking discovery, induced pluripotent stem (iPS) cells. Our group works since years on the optimization of stem cell-based dopaminergic cell replacement strategies by understanding the basic mechanisms of dopaminergic stem cell proliferation and maintenance. We thus provide major information on oxygen as a regulatory molecule in corticogenesis and dopaminergic neurogenesis.

Selected Publications

- Löhle M, Mangone G, Wolz M, Beuthien-Baumann B, Oehme L, van den Hoff J, Kotzerke J, Reichmann H, Corvol J-C, Storch A (2018). Functional MAOB gene intron 13 polymorphism predicts putaminal dopamine turnover in de novo Parkinson's disease. *Mov. Disord.* 33(9), 1496-1501.
- Schrempf W, Fauser M, Wienecke M, Brown S, Maaß A, Ossig C, Otto K, Brandt M, Löhle M, Schwanebeck U, Graehlert X, Reichmann H, Storch A (2018) Rasagiline improves polysomnographic sleep parameters in patients with Parkinson's disease: A double-blind, baseline-controlled trial. *Eur. J. Neurol.* 25(4), 672-679.
- Löhle M, Mende J, Wolz M, Beuthien-Baumann B, Oehme L, van den Hoff J, Kotzerke J, Reichmann H, Storch A (2016). Putaminal dopamine turnover in de novo Parkinson's disease predicts later motor complications. *Neurology* 86, 231-240.
- Schurig K, Zieris A, Hermann A, Freudenberg U, Heidel S, Grimmer M, Storch A[#], Werner C[#] (2015). Neurotrophic growth factors and glycosaminoglycan based matrices to induce dopaminergic tissue formation. *Biomaterials* 67, 205-213.
- Wagenführ L, Meyer AK, Braunschweig L, Marrone L, Storch A (2015). Brain oxygen tension controls the expansion of outer subventricular zone-like basal progenitors in the developing mouse brain. *Development* 142(17), 2904-15.

Improving prediction, diagnosis, treatment and care of dementia



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State-of-the Art

Currently, diagnostic markers are available for prodromal and clinical stages of Alzheimer's disease (AD), but have not penetrated into clinical care. The specialized setting of a clinical research experiment is often not able to capture the full range of clinical phenomena that is, however, important for caregivers and patients when considering the impact of dementia diseases or of an intervention on everyday life. In acknowledgement of this fact, major stakeholders such as the Alzheimer's Association, and regulatory authorities have proposed to adopt the concept of real world evidence (RWE) to dementia research. Current treatment trials and development of new treatments will benefit from the use of RWE outcomes using novel digital sensor markers. In addition, the development of novel diagnostic markers and treatments will greatly benefit from consequent involvement of the patients and caregivers into the research process.

Overall Scientific Aim

Our clinical research section has three major research aims:

- Extension of clinical trials to transfer diagnostic markers and interventions from methodological development through experimental settings into routine care.
- Development of digital functional markers for assessing everyday function and providing RWE in clinical trials
- Feasibility, effectiveness, and implementation of dyadic interventions in a participatory design

Projects, Methods & Technologies

Establishing neuroimaging markers in respect to neuropathology gold standard, we have determined associations between MRI based volumetric markers and neuropathological hallmarks of AD and non-AD dementia, based on data from the ADNI cohort and the Rostock autopsy cohort. We also determined molecular underpinnings of the regional distribution of AD lesions using gene expression maps and pattern of atrophy, amyloid and tau deposition. In back translation we have determined the neuropathological features of volumetric and metabolic markers from ultrahigh-field MRI in transgenic models of cerebral amyloidosis. We have contributed to the international Biomarker Roadmap Process to bring novel diagnostic markers from experimental settings to clinical care. This included the development of an international standardized operating procedure for measurement of the hippocampus volume, multicentre resting state fMRI and

Curriculum Vitae

1996 Research Assistant, Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, USA. Head: Prof. Stanley I. Rapoport

1998 - 2003 Post-doctoral Research Assistant, Alzheimer Memorial Center, Neuroimaging and Dementia Section, Department of Psychiatry, University Munich

2000 Doctorate in Psychiatry and Psychotherapy, Medical Faculty, Ludwig-Maximilian University Munich

2003 - 2008 Senior Researcher, Alzheimer Memorial Center, Neuroimaging and Dementia Section, Department of Psychiatry, University Munich

2007 Habilitation in Psychiatry and Psychotherapy, Medical Faculty, LMU, University of Munich

2008 - 2012 Full professor (W2) and Chair in Clinical Experimental Research, University Medical Centre Rostock

Since 2009 Speaker/Deputy Speaker of the DZNE, German Center for Neurodegenerative Diseases (DZNE) Rostock/Greifswald

Since 2015 Full professor (W3) and Chair in Clinical Dementia Research, University Medical Centre Rostock

Since 2017 Steering Board Member of the Centre for Transdisciplinary Neurosciences Rostock (CTNR)

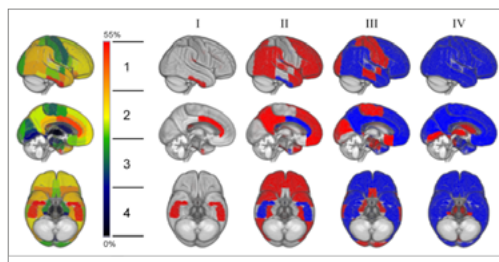


Fig. 1: Stages of amyloid pathology in the amyloid PET study already show the accumulation in predilection areas of Alzheimer's disease in cognitively healthy elderly persons.

We have formulated the framework for the use of ICT technology as RWE in clinical trials. We have worked in the InsideDem study on the use of digital technology to detect behavioural changes in advanced AD, and have studied accelerometric markers of disorientation in the early AD stages in the SinDem study. In SAMi project we combine these technologies to assist people with dementia in institutional care, in the GRAIL study we want to determine neuronal network underpinnings of orientation failures in early stages of AD. In the upcoming project EIDEC we will study ethical implications of the use of monitoring technologies in dementia in a participatory design. In respect to dyadic treatment we explore the use of a digital expert system to identify needs of caregivers of people with dementia in primary care (GAP study, Innovationsfond). To address these needs we cooperate with the German Alzheimer Association, section Mecklenburg Western-Pomerania. Together we have developed and evaluated an education program for caregivers for people with dementia. Extending the scope of this program a new model project, funded by the Land MV, will start in 2020 to implement multimodal caregiver and patient interventions into the current health care system. I am the head of the scientific advisory board of this model project.

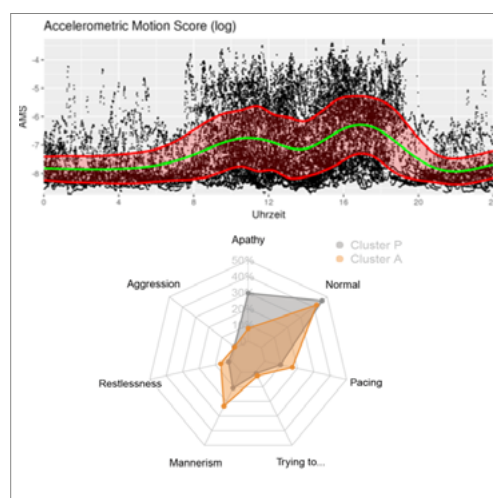


Fig. 2: Extract of an accelerometer profile of a patient with dementia over 24 hours. The cumulative accelerometric values predict individual behavior types (apathetic cluster P vs. agitated cluster A) with a cross-validated accuracy of 88.2%.

We have recognized the need for a more intensive psychologically focused support for a subgroup of care-givers that experience a particularly high level of burden through care-giving. Therefore, we developed and evaluated a care-giver centred psychotherapeutic prevention intervention in a phase 2a trial. We also contribute to a range of phase 3 clinical trials, including anti-amyloid vaccination trials.

Selected Publications

- Teipel SJ, Cavedo E, Hampel H, Grothe MJ (2018). Basal Forebrain Volume, but Not Hippocampal Volume, Is a Predictor of Global Cognitive Decline in Patients With Alzheimer's Disease Treated With Cholinesterase Inhibitors. *Front Neurol.* 9, 642.
- Grothe MJ, Sepulcre J, Gonzalez-Escamilla G, Jelistratova I, Scholl M, Hansson O, et al. (2018). Molecular properties underlying regional vulnerability to Alzheimer's disease pathology. *Brain* 141, 2755-71.
- Teipel S, König A, Hoey J, Kaye J, Krüger F, Robillard JM, et al. (2018). Use of noninvasive sensor-based information and communication technology for real-world evidence for clinical trials in dementia. *Alzheimers Dement.* 14, 1216-31.
- Teipel SJ, Metzger CD, Brosseron F, Buerger K, Brüeggen K, Catak C, et al. (2018). Multicenter Resting State Functional Connectivity in Prodromal and Dementia Stages of Alzheimer's Disease. *J Alzheimers Dis.* 64, 801-13.
- Teipel SJ, Cavedo E, Lista S, Habert MO, Potier MC, Grothe MJ, et al. (2018). Effect of Alzheimer's disease risk and protective factors on cognitive trajectories in subjective memory complainers: An INSIGHT-preAD study. *Alzheimers Dement.* 14, 1126-36.

Functional cross sectional imaging



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State-of-the Art

My Name is Kolja Thierfelder and I am senior executive physician and the head of Functional Imaging at the Institute for Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology of the University Medical Centre Rostock starting in January 2018. I completed a Master of Science in Information Systems at the University of Melbourne and the University of Munster, where I graduated with a diploma thesis about electronic procurement processes in the public health system. I studied human medicine at the Charité – University Medicine Berlin where I completed my doctoral thesis in the field of functional MRI. In 2016, I completed my habilitation thesis about decision support in the acute stroke situation at the Ludwigs-Maximilian University.

I am a board-certified radiologist and published over 60 articles in international peer-reviewed journals focusing on stroke imaging, CT perfusion and dynamic CT angiography, imaging of prostate cancer, musculoskeletal imaging, and health economic effects. I am very grateful that I was awarded a number of national and international prizes, including the Wilhelm Conrad Röntgen Prize for my work on advanced stroke imaging in 2018. Within the framework of a close cooperation with the University of Greifswald, I currently work on different population-based projects, using the data from the Study of Health in Pomerania (SHIP) cohort and the German National Cohort (GNC).

Overall Scientific Aim

Within in the context of neuroradiology, I am particularly interested in functional imaging techniques in stroke and other emergency conditions. During my neuroradiologic research activities in the last years, my aim was not only to determine the diagnostic value of whole-brain CT perfusion and dynamic CT angiography. I am convinced that the task of the Radiologist is not to only produce high-quality images that get more impressive by each year, but to understand the needs of our patients and our clinical partners. We need to closely cooperate with our partners in order to identify the best diagnostic and therapeutic strategy for each individual patient. In the context of stroke imaging, this means that we need imaging methods that offer a fast and comprehensive decision support for the doctor in charge of the patient in order to decide whether to offer intravenous thrombolysis or thrombectomy.

Curriculum Vitae

1999 - 2004 Master of Science of Information Systems, Westfälische Wilhelms-Universität Münster, University of Melbourne, Australia

2005 - 2011 State exam in Medicine, Charité - University Medicine Berlin

2011 Doctorate in Human Medicine, Center of Neurology, Neurosurgery and Psychiatry, Charité - University Medicine Berlin

2016 Board-certified Radiologist, Ludwig-Maximilian University of Munich

2016 Habilitation in Radiology, Ludwig-Maximilian University of Munich

Since 2018 Vice Chair and Head of Functional Imaging, Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology, University Medical Centre Rostock

Projects, Methods & Technologies

During the last years, my research focus in neuroradiology was on advanced imaging techniques, particularly on whole-brain CT and MR perfusion. Perfusion offers vast opportunities of postprocessing, including color-coded CT angiography, Wavelet CTA, Venous Wavelet Reconstructions, and MR-Wavelet. Due to my academic background, I am also familiar with health economics and cost-effectiveness analyses. During the last year, I also focused on Artificial Intelligence and Radiomics not only in neuroradiology, but also in prostate MRI and muskuloskeletal imaging.

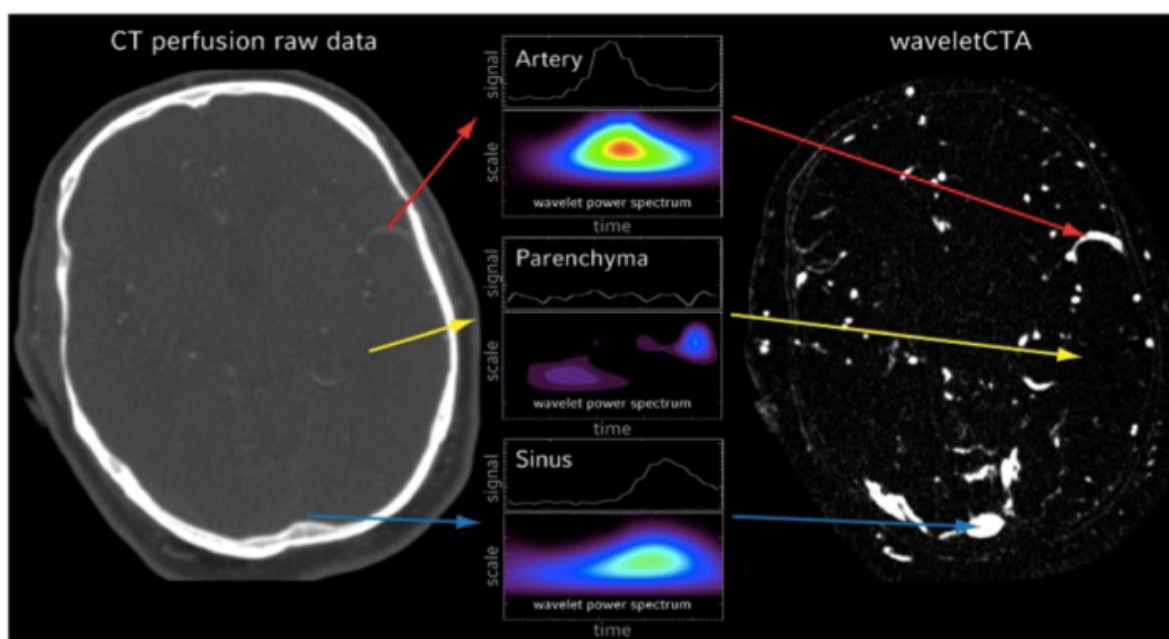


Fig. 1: General principle of Wavelet-based CT angiography in a stroke patient. First, a CT perfusion after the administration of intravenous contrast agent is performed (left). The Wavelet algorithm analyzes the whole shape of the time-signal curve for each voxel (middle). A voxel that covers an arterial (red arrows) or a venous vessel (blue arrows) has a time-signal curve that is similar to a generic bolus curve and is therefore likely to cover a vessel. The wavelet power spectrum is high, and the Wavelet CTA reconstruction yields a high signal in this voxel. In a voxel outside the vessels (yellow arrow), the time-signal curve does not resemble a bolus curve, leading to a low signal in the corresponding voxel of the Wavelet CTA reconstruction. This discrimination leads to a CT angiography with a very high signal-to-noise ratio (right).

Selected Publications

- Reidler P*, Thierfelder KM*, Fabritius MP, Sommer WH, Meinel FG, Dorn F, Wollenweber FA, Duering M, Kunz WG (2018). Thalamic Diaschisis in Acute Ischemic Stroke: Occurrence, Perfusion Characteristics, and Impact on Outcome. *Stroke* 49(4), 931-937.
- Kunz WG, Hunink MG, Dimitriadis K, Huber T, Dorn F, Meinel FG, Sabel BO, Othman AE, Reiser MF, Ertl-Wagner B, Sommer WH, Thierfelder KM (2018). Cost-effectiveness of Endovascular Therapy for Acute Ischemic Stroke: A Systematic Review of the Impact of Patient Age. *Radiology*. 288(2), 518-526.
- Kunz WG, Fabritius MP, Sommer WH, Höhne C, Scheffler P, Rotkopf LT, Fendler WP, Sabel BO, Meinel FG, Dorn F, Ertl-Wagner B, Reiser MF, Thierfelder KM (2018). Effect of stroke thrombolysis predicted by distal vessel occlusion detection. *Neurology* 90(20), e1742-e1750.
- Kunz WG, Sommer WH, Höhne C, Fabritius MP, Schuler F, Dorn F, Othman AE, Meinel FG, von Baumgarten L, Reiser MF, Ertl-Wagner B, Thierfelder KM (2017). Crossed cerebellar diaschisis in acute ischemic stroke: Impact on morphologic and functional outcome. *J Cereb Blood Flow Metab.* 37(11), 3615-3624.
- Kunz WG, Hunink MG, Sommer WH, Beyer SE, Meinel FG, Dorn F, Wirth S, Reiser MF, Ertl-Wagner B, Thierfelder KM (2016). Cost-Effectiveness of Endovascular Stroke Therapy: A Patient Subgroup Analysis From a US Healthcare Perspective. *Stroke* 47(11), 2797-2804.

Mitochondrial ROS generation in the process aging and type 2 diabetes



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State-of-the Art

Reactive oxygen species (ROS) were regarded as a central key element for neurodegenerative diseases, diabetes mellitus and aging. However, ROS are mainly produced as a bypass of the mitochondrial OXPHOS system and its production relies upon the dysfunction of mitochondria itself. Using the model system of conplastic mice we could generate a set of strains with polymorphism of mitochondrially-encoded OXPHOS genes on a common nuclear B6 background. Interestingly, these mice differed in ROS generation in an age-dependent pattern promoting or preventing insulin resistance and hepatosteatosis as the major driver for development of type 2 diabetes mellitus. While high ROS generation in liver coincided with hepatosteatosis at the age of 3 months, ROS generation by the CNS became evident after the age of 2 years. Recent studies showed that disturbed mitochondrial dynamics (fission, fusion, autophagy) are linked to changes in ROS generation. Notably, ROS generation and mitochondrial dynamics develop not in a linear manner due to mitohormetic effects starting at the early adult period of life (3 - 9 months of age, corresponding to 20 - 40 years in humans). Thus, mitochondrial dysfunction during adolescence could be critical for the pathogenesis of degenerative effects on different organ systems such as liver and CNS as exemplified in Figure 1.

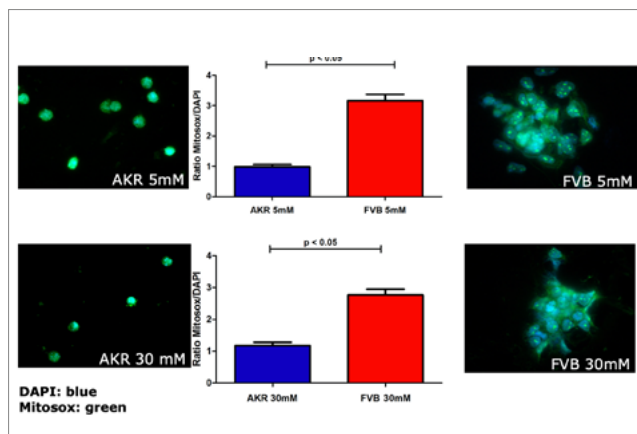


Fig. 1: ROS production in beta cells from control mice (AKR) and polymorphism of the ATP synthase complex (FVB). Cells were incubated with the Mitosox ROS sensor at different glucose concentrations. ROS accumulates independently from glucose concentration.

Curriculum Vitae

1982 - 1988 State exam in Medicine, Georg-August University of Göttingen
1988 Doctorate in Pharmacology, Georg-August University of Göttingen
1988 - 1989 Residency in Internal Medicine, Deaconess Hospital of Bremen
1989 - 1992 Postdoctoral fellow (DFG stipend), Institute of Pharmacology and Toxicology, Georg-August University of Göttingen
1992 - 1995 Postdoctoral fellow
1995 - 2004 Senior scientist, Institute of Clinical Biochemistry, Hannover Medical School
2000 Habilitation and venia legendi in Biochemistry, Hannover Medical School
Since 2004 Full Professor (C4) for Medical Biochemistry and Director of the Institute of Medical Biochemistry and Molecular Biology, University Medical Centre Rostock

Overall Scientific Aim

Our work is focused upon organ-specific pattern of mitochondrial mass and morphology in conplastic strains with high (FVB) or low (ALR) ROS generation as a sign of altered mitochondrial dynamics. It is the major goal of the CTNR project to compare mitochondrial dynamics in pancreatic beta cells, liver, muscle and brain within a timeline between 3 months and 24 months of age. The experimental design will help

- to identify periods of high susceptibility to metabolic mitochondrial stressors (high fat, high caloric diet).
- to characterize mitochondrial morphologies during mitochondrial stress.
- to monitor mitohormetic response by RT-PCR arrays to identify the time point of mitohormetic exhaustion.

Projects, Methods & Technologies

The project is mainly focused on work with our well-characterized conplastic mouse strains differing in ROS production and mitochondrial dysfunction. The strains are kept in the central animal facility and will be available to partners of the CTNR network. Furthermore, our institute will give access to methods of mitochondrial analysis, which will be helpful for functional and morphological characterization. These methods comprise:

- High-resolution microscopy to monitor changes of the mitochondrial network structure (Fig. 2)
- Quantification of in vivo ROS production after in vivo injection of Mitosox stain.
- Measurement of oxygen consumption in tissue samples by highly sensitive fluorescence sensors.
- Blue native gel electrophoresis of OXPHOS complexes.
- Metabolic monitoring of conplastic mice: insulin sensitivity and glucose tolerance tests.

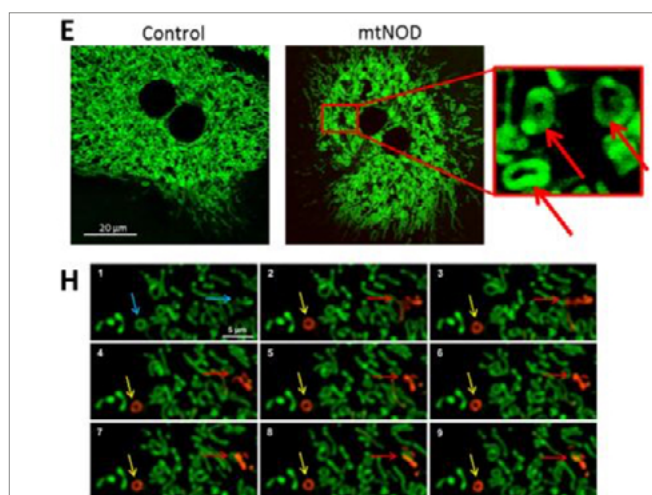


Fig. 2: Figure from Niemann et al. (2017): An mtDNA mutation accelerates liver aging by interfering with the ROS response and mitochondrial life cycle. *Free Radical Biology and Medicine*, 102, 174–187. Mitochondrial network inhomogeneity with immobile loop-shaped mitochondria appears at an earlier age stage in liver tissue sections of mtNOD mice compared with controls. Hepatocytes were stained by Mitotracker green. The dynamics of differently shaped mitochondria were analyzed by means of selective mitochondrial staining with Dendra2, a green-to-red photoswitchable fluorescent protein. By radiation with UV light (blue arrows), green Dendra2 in a straight mitochondrion (red arrow) and a circular mitochondrion (yellow arrow) was photoconverted to the stable red fluorescent Dendra2.

Selected Publications

- Niemann J, John C, Schröder S, Koch F, Ibrahim SM, Schultz J, Tiedge M, Baltrusch S (2017). An mtDNA mutation accelerates liver aging by interfering with the ROS response and mitochondrial life cycle. *Free Radic Biol Med*. 102, 174-187.
- Schultz J, Waterstradt R, Kantowski T, Rickmann A, Reinhardt F, Sharoyko V, Mulder H, Tiedge M, Baltrusch S (2016). Precise expression of Fis1 is important for glucose responsiveness of beta cells. *J Endocrinol*. 230, 81-91.
- Chauhan A, Weiss H, Koch F, Ibrahim SM, Vera J, Wolkenhauer O, Tiedge M (2015). Dissecting Long-Term Glucose Metabolism Identifies New Susceptibility Period for Metabolic Dysfunction in Aged Mice. *PLoS One* 10(11), e0140858.
- Moeller M, Hirose M, Mueller S, Roelf C, Baltrusch S, Ibrahim S, Junghans C, Wolkenhauer O, Jaster R, Kohling R, Kunz M, Tiedge M, Schofield PN, Fuellen G (2014). Inbred mouse strains reveal biomarkers that are pro-longevity, antilongevity or role switching. *Aging Cell* 13, 729-738.
- Tiedge M (2014). Inside the pancreas: progress and challenges of human beta cell mass quantification. *Diabetologia* 57, 856-9.

Forensic psychiatry



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State-of-the Art

Forensic psychiatry provides care for individuals that have committed a crime for which they have been found not fully responsible on account of a mental illness. Typically these individuals pose a risk of harm to themselves or others.

Research predominantly focuses on risk assessment and management, effective psychological interventions, rates of recidivism and more recently on experiences of care, particularly in relation to coercive or restrictive aspects of care.

Recent approaches to research and clinical practice promote strength-based paradigms. These approaches assert that desistance from criminal behaviours and successful recovery from mental illness are a consequence of individuals living a rich, fulfilling life. Research within these paradigms seek to measure clinical outcomes such as symptom alleviation and risk reduction but also patients' satisfaction with care, quality of life, skill development, goal attainment and engagement in social and occupation activities.

Neuroscientific research in the field is slowly gaining prominence. Research focuses on the etiology of psychopathology, the application of neuroscientific techniques to detect psychiatric problems in defendants, and neurobiological correlates of aggression. These investigations have important scientific and legal consequence; the use of neuroscience in judicial proceedings is topical.

Research is hampered by the limited number of potential participants in studies and the ethical or legal considerations around transporting forensic patients to sites where appropriate technologies are available.

Curriculum Vitae

1990 - 1996 State Exam in Medicine, Medical School, University of Witten/Herdecke

2001 Doctorate in Medicine, University of Witten/Herdecke

2002 German Certificate of Completion of Training in Psychiatry and Psychotherapy

2007 Ph.D., University of Manchester, UK

2007 Certificate of Completion of Training in Forensic Psychiatry

2008 - 2018 Professor in Forensic Psychiatry, University of Nottingham and Consultant Forensic Psychiatrist, Rampton Hospital, UK

Since 2018 Director Department of Forensic Psychiatry and Professor of Forensic Psychiatry, University Medical Centre Rostock

Overall Scientific Aim

Our group has three main research themes:

1. Forensic psychiatric service provision

I have a particular interest in types of service provision and outcomes of forensic-psychiatric services. This area of interest has led to a broad portfolio of studies, ranging from evaluation of staff training, audits of prescribing in secure settings, self-harm in prisoners, use of seclusion and forced medication, amongst others. Since moving to Rostock, our group has developed projects to evaluate our new de-escalation training, the implementation of a peer support worker and a follow up study of our out-patient services while developing additional projects, including international comparisons of service provision.

2. Personality disorders

I have gained considerable expertise in the neurobiology of PD which I have investigated using a range of neuropsychological and brain imaging methods leading to high quality publications. I have been successful in recruiting incarcerated offenders to these projects, an achievement only shared by few research groups. In addition, I have used healthy populations to investigate neuropsychological functions relevant to antisocial groups, in particular social cognition. I have also developed a new questionnaire of empathy, the QCAE.

While of theoretical interest in itself, the translational aspects of this theme are of particular interest, e.g.

- i. Oxytocin and social cognition: I have investigated the effect of oxytocin on judgements of trustworthiness and complex social cognition in healthy controls. In addition, I have completed an fMRI study to describe the modulation of neuronal networks following oxytocin administration. The aim was to use these findings to further explore the potential use of oxytocin in personality disordered individuals.
- ii. Transcranial magnetic stimulation (TMS): I have investigated the effects of TMS on the performance on impulsivity and empathy tasks in healthy individuals with a view of later application of the intervention in clinical samples.
- iii. Neuropsychological deficits in ASPD: We currently develop a CANTAB study using neuropsychological markers as predictors for outcome.

3. Systematic reviews

I have been part of a team completing high quality systematic reviews on the treatment of personality disorders, an area of considerable recent policy development. So far four reviews have been completed and published, two on borderline PD (one regarding psychological and one regarding pharmacological interventions) and two on antisocial PD. All of these are currently updated.

Projects, Methods & Technologies

Most of our research uses traditional qualitative interviewing or questionnaire/survey methods. However, we currently have a project using the Cambridge Neuropsychological Test Automated Battery (CANTAB) iPad application. Specifically this explores the link between memory, attention, executive function and social cognition, and patient outcomes such as rates of progression through care and number of incidents in the clinic.

Selected Publications

- Cheng-Chang Y, Khalifa N, Völlm B (2018). Effects of intermittent theta burst stimulation applied to the left dorsolateral prefrontal cortex on empathy and impulsivity in healthy adult males. *Brain and Cognition* 128, 37-45.
- Völlm B, Edworthy R, Huband N, Talbot E, Majid S, Holley J, Furtado V, Weaver T, McDonald R, Duggan C (2018). Characteristics and Pathways of Long-Stay Patients in High and Medium Secure Settings in England: A Secondary Publication From a Large Mixed-Methods Study. *Frontiers in Psychiatry* 9, Article 140.
- Völlm B, Clarke M, Bulten E, Tort V, Seppanen A, Gosek P, Heitzmann J (2018). European Psychiatric Association (EPA) guidance on forensic psychiatry: Evidence based assessment and treatment of mentally disordered offenders. *European Psychiatry* 51, 58-73.
- Völlm B, Foster S, Bates P (2017). How best to engage users of forensic services in research: literature review and recommendations. *International Journal of Forensic Mental Health* 16, 183-195.
- Tiwana R, McDonald S, Völlm B (2016). Policies on sexual expression in forensic psychiatric settings in different European countries. *International Journal of Mental Health Systems* 10, 5.

Mechanistic analysis of gastrointestinal and neurodegenerative diseases



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Our research group focuses on adipositas-associated Alzheimer disease and the understanding of the liver-brain axis. In addition, the group is interested in the pathogenetic understanding of several other neurodegenerative diseases and the elaboration of therapeutic strategies. For this purpose, our institute provides an armamentarium of different mouse models as well as state-of-the art methods and techniques. Here, both the central animal care facility and the multimodal small imaging facility serve as ideal technical platforms for the whole consortium of CTNR. By sharing these technologies and the scientific expertise, fruitful collaborations exist with members of the CTNR, e.g. A. Storch, A. Wree and S. Teipel.

State-of-the Art

It is known that obese patients reveal a significant rise of hepatic and systemic FGF21 concentrations. This paradox is interpreted with a FGF21-resistance similar to an insulin- or leptin-resistance because obese patients show due to the low-grade inflammation a reduction of the FGF21 co-receptor, β -klotho, in adipose tissue. If such a FGF21 resistance - mediated by a reduced β -klotho expression - is also present in brain tissue and may cause neurodegeneration via the FGF21-Glut1 axis is currently the focus of our research (see Fig. 1).

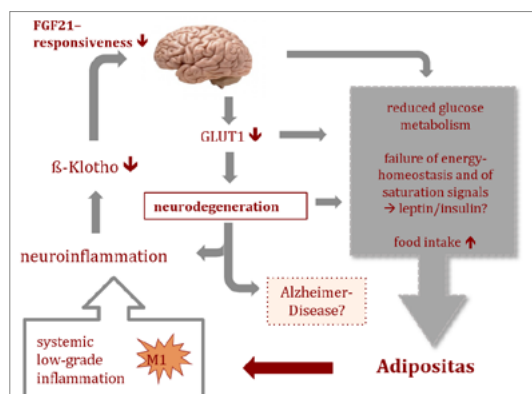


Fig. 1: Schematic representation of the working hypothesis. The focus is on the question of whether systemic low-grade inflammation leads to neuro-inflammation and whether this results in a neurodegeneration via FGF21-GLUT1 pathway.

Curriculum Vitae Brigitte Vollmar

1982 - 1988 State exam in Medicine, Ludwig-Maximilians-University (LMU) Munich

1988 - 1990 Resident, Department of General Surgery, LMU Munich

1991 Doctorate in Experimental Surgery, Institute for Surgical Research, LMU Munich

1991 - 1996 Research assistant, Institute for Surgical Research, LMU Munich, Institute for Clinical & Experimental Surgery, University of Saarland, Homburg/Saar

1996 Habilitation in Experimental Surgery, Medical Faculty, University of Saarland, Homburg/Saar

1996 - 2002 Vice Director, Institute for Clinical & Experimental Surgery, University of Saarland, Homburg/Saar

1998 - 2002 Fellow, Heisenberg Programme, German Research Foundation

Since 2002 Full Professor, Institute for Experimental Surgery with Central Animal Care Facility, University Medical Centre Rostock

Overall Scientific Aim

Our principal research field is adipositas-associated neurodegeneration with the focus on the fasting hormone, Fibroblast Growth Factor 21 (FGF21), which is also known to regulate the carbohydrate and lipid homeostasis. Exogenous FGF21 reduces in obese patients the plasma concentration of triglycerides and cholesterol.

Projects, Methods & Technologies

We have already successfully recruited two research grants of the German Research Foundation (DFG) (1. DFG grant with Module Temporary Position for Principle Investigator for 24 months, KU 3280/1-1, 214.051€ „Fgf21- a key factor of the hepatic-neuronal communication“; 2. DFG grant for 36 months; KU 3280/1-2, 221.736€ „Cerebral FGF21-resistance as cause of the obesity-associated neurodegeneration“). Moreover, together with Andreas Wree (also a CTNR member) we collaborated with several projects. Accordingly, we jointly investigated the impact of caloric restriction on cognition performance in mice and found that a life-long caloric restriction improves the working memory. In addition, we work together on various projects on the Niemann-Pick disease mice and currently published a review article on this topic. Furthermore, we have also a successful collaboration with Stefan Teipel and focus our research on the histological, neurobiological, electrophysiological and behavioral phenotyping of cerebral amyloidosis and hyperexcitability in transgenic models of Alzheimer disease. In this

context, especially morphological, functional and molecular analyses with imaging method were evaluated and already successfully published (see Fig. 2).

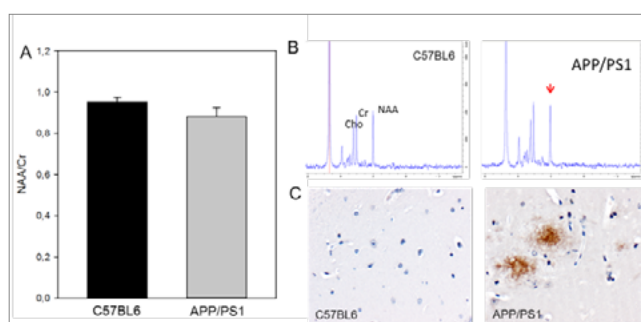


Fig. 2: Quantitative analysis of N-acetylaspartate (NAA) / creatine (Cr) ratio (A) and associated MR spectroscopy (B) of C57BL6 (left) and APP / PS1 (right) mice. Immunohistochemical detection of Aβ plaques (C) in C57BL6 (left) and APP / PS1 (right) mice. Values are given as MW ± SEM.

Selected Publications

- Ebner L, Gläser A, Bräuer A, Witt M, Wree A, Rolfs A, Frank M, Vollmar B, Kuhla A (2018). Evaluation of Two Liver Treatment Strategies in a Mouse Model of Niemann-Pick-Disease Type C1. *Int J Mol Sci.* 19, 972.
- Kuhla A, Rühlmann C, Lindner T, Polei S, Hadlich S, Krause BJ, Vollmar B, Teipel SJ (2017). APP^{swe}/PS1^{dE9} mice with cortical amyloid pathology show a reduced NAA/Cr ratio without apparent brain atrophy: A MRS and MRI study. *Neuroimage Clin.* 15, 581-586.
- Kuhla A, Derbenev M, Shih HY, Vollmar B (2016). Prophylactic and abundant intake of α-lipoic acid causes hepatic steatosis and should be reconsidered in usage as an anti-aging drug. *Biofactors.* 42,179-89.
- Rühlmann C, Wölk T, Blümel T, Stahn L, Vollmar B, Kuhla A (2016). Long-term caloric restriction in ApoE-deficient mice results in neuroprotection via Fgf21-induced AMPK/mTOR pathway. *Aging (Albany NY)* 8, 2777-2789.
- Kuhla A, Ludwig SC, Kuhla B, Münch G, Vollmar B (2015). Advanced glycation end products are mitogenic signals and trigger cell cycle reentry of neurons in Alzheimer's disease brain. *Neurobiol Aging* 36, 753-61

Curriculum Vitae Angela Kuhla

1997 - 2002 Diploma in Biology with focus on Neurobiology, University of Leipzig

2002 - 2007 PhD in Neurobiology, Paul-Flechsig-Institute of Brain Research, University of Leipzig

2006 Stay abroad in Cleveland, Ohio, Case Western Reserve University

2007 - 2014 Postdoc Position, Rudolf-Zenker-Institute for Experimental Surgery, University Medical Centre Rostock

2014 Habilitation in Experimental Surgery, University Medical Centre Rostock

Since 2014 Group leader "Metabolic Syndrom and Neurodegeneration", Rudolf-Zenker-Institute for Experimental Surgery, University Medical Centre Rostock

Neurosonology and multimodal neurodiagnostics in Parkinson's disease and stroke



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State-of-the Art

A) The diagnosis of Parkinson's disease (PD) is currently based on motor symptom criteria which apply only if already the majority of dopaminergic nigrostriatal neurons have degenerated. Therefore international research efforts aim at an earlier diagnosis of PD based on non-motor symptom criteria as well as laboratory and neuroimaging biomarkers. Meanwhile a wide range of potential early markers of PD have been reported, including the increased echosignal of substantia nigra on transcranial ultrasound. However the specificity of single diagnostic markers is low with respect to individual prediction of PD. Moreover, it is unclear yet whether a hyperechogenicity of substantia nigra, reflecting increased iron content, may be reversed by therapy with iron chelating agents.

B) Acute stroke is associated with a varying degree of neuronal death and chronic impairment of general health. Poststroke spasticity, poststroke depression, and accelerated senescence are frequent sequelae following the brain insult. The mechanisms related to faster aging in stroke patients are poorly understood, and there is little knowledge on the long-term predictive value of clinical and laboratory markers of senescence.

Overall Scientific Aim

A) To identify sets of early diagnostic markers (clinical, neuroimaging, neurophysiological) that offer the best-possible prediction of PD in risk cohorts such as patients with severe depression, malignant melanoma, or REM sleep behaviour disorder. In addition we want to explore whether iron chelating therapy can reduce the hyperechogenicity of substantia nigra in early PD.

B) To identify sets of diagnostic markers (clinical, neuroimaging, laboratory) that can predict accelerated senescence over a time period of 2-4 years following stroke. Such a set might become the basis of novel senescence-preventive therapies.

Projects, Methods & Technologies

A) In long-term follow-up studies on local cohorts of patients with depression, malignant melanoma, REM sleep behavior disorder, and early PD, a number of clinical (motor, non-motor) and neuroimaging findings (sonographic substantia nigra echogenicity, sonographic vagus nerve caliber, sonographic pupillometry, iron-related MRI sequences and MR

Curriculum Vitae

1989 - 1995 State exam in Medicine, University of Jena

1991 - 1996 Doctorate in Medical Biochemistry, Institute of Biochemistry, University of Jena

2007 Habilitation in Neurology, University Medical Centre Rostock

2002 - 2008 Senior neurologist, Department of Neurology, University Medical Centre Rostock

Since 2009 Extraordinary Professor for Neurology, Department of Neurology, University Medical Centre Rostock

Since 2011 Vice Director of the Department of Neurology, University Medical Centre Rostock

spectroscopy) are assessed in order to characterize their value for predicting subsequent PD, as well as the course of PD under different therapy regimes. In cooperative studies with local and external partners we compare sonographic measures of brain structures and of vagus nerve with the degree of parasympathetic pupil and bowel innervation. As an innovative tool we develop and use at our department the real-time MRI-ultrasound fusion imaging which allows the direct comparison of echogenicity and MR intensity data of distinct brain structures. This fusion imaging modality is also optimized and applied for the intra- and post-operative monitoring of deep brain stimulation (DBS) electrode position. In the ongoing Center of Excellence in Neurodegeneration Research (CoEN) collaborative project with the University of Lille (Prof. David Devos), the Newcastle Dementia Biomedical Centre (Prof. Nicola Pavese) and the Helmholtz Institute Munich (Prof. Marcus Conrad) we explore the cellular mechanisms of ferroptosis in humans as well as in the animal model by comparing neuroimaging (transcranial ultrasound, MRI, MR spectroscopy) and laboratory (blood, cerebrospinal fluid, genetic) analyses in PD patients on iron chelating or placebo medication, and behavioural as well as histological data obtained in the animal model. In several mono-centre and collaborative bi-centre studies we assess sonographic markers of trace metal accumulation in the brain in a wide range of neurodegenerative diseases.



Fig. 1: Real-time fusion imaging of pre-implantation MRI and post-implantation transcranial sonography (TCS) in a patient with deep brain stimulation (DBS). Left panel: coronal brain TCS image showing the bilateral highly echogenic electrode tips; right panel: MRI-TCS fusion image showing the overlay of electrode sonogram and corresponding MRI.

B) In the Federal Ministry of Education and Research (BMBF) funded SASKit study, coordinated by Prof. Georg Füllen, which comprises six subprojects of several departments at the University Medicine Rostock, one subproject is conducted at our department. In this study, the senescence status of ischemic stroke patients, which is expected to be an important tool for predicting progression for many diseases, is characterized in detail. We lay the foundations by investigating the connection between an individual senescence-related biomarker score & other disease-related biomarker measurements, and disease diagnosis/prognosis in particular. Biomarkers will be judged by their predictive power (cross-validated accuracy/AUC), weighted by statistical significance, effect size, and practical considerations (such as cost). We also aim for biomarkers for early detection of a pancreatic ductal adenocarcinoma (PDAC) comorbid event in patients with stroke and vice versa, going beyond stroke by considering thromboembolic events and going beyond PDAC by considering other cancer entities.

Selected Publications

- Walter U, Tsiberidou P, Kersten M, Storch A, Löhle M (2018). Atrophy of the Vagus Nerve in Parkinson's Disease Revealed by High-Resolution Ultrasonography. *Front. Neurology* 9, 805.
- Walter U, Fernández-Torre JL, Kirschstein T, Laureys S (2018). When is "brainstem death" brain death? The case for ancillary testing in primary infratentorial brain lesion. *Clin. Neurophysiol.* 129, 2451-2465.
- Walter U, Rosales R, Rocco A, Westenberger A, Domingo A, Go CL, Brüggemann N, Klein C, Lee LV, Dressler D (2017). Sonographic alteration of substantia nigra is related to parkinsonism-predominant course of X-linked dystonia-parkinsonism. *Parkinsonism Relat. Disord.* 37, 43-49.
- Walter U, Heilmann E, Voss J, Riedel K, Zhivov A, Schäd SG, Gross GE, Benecke R, Trcka J (2016). Frequency and profile of Parkinson's disease prodromi in patients with malignant melanoma. *J. Neurol. Neurosurg. Psychiatry* 87, 302-310.
- Walter U, Müller JU, Rösche J, Kirsch M, Grossmann A, Benecke R, Wittstock M, Wolters A (2016). Magnetic resonance-transcranial ultrasound fusion imaging: a novel tool for brain electrode location. *Mov. Disord.* 31, 302-309.

Multimodal functional, high-resolution or large-volume imaging



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State-of-the Art

My name is Marc-André Weber and I serve as full professor and chairman of the Institute of Diagnostic and Interventional Radiology, Paediatric and Neuroradiology starting from September 1st 2017. The Institute of Diagnostic and Interventional Radiology, Paediatric and Neuroradiology is the central service provider at the Rostock University Medical Centre in the field of diagnostic imaging, which among others serves as international training centre of the European School of Radiology. Before, I was appointed as vice-chairman of the Clinic of Diagnostic and Interventional Radiology at the University Hospital Heidelberg for 3 years and as section head of musculoskeletal radiology at the University Hospital Heidelberg for 7 years.

I am a board-certified radiologist and neuroradiologist, holding among others European diplomas in Neuroradiology, Spine Interventional Neuroradiology, Emergency Radiology and Musculoskeletal Radiology. I have also passed a Master of Science in Healthcare Management from the University of Heidelberg. My research has led to more than 300 publications in refereed journals, where I serve as author and co-author, and I am author and co-author of more than 35 books and book chapters. I am involved in various activities in national and European scientific associations and educational as well as research projects. As well as the other project partners, I am very happy to serve as member of the CTNR that supports and enhanced collaborative and interdisciplinary initiatives.

Overall Scientific Aim

Radiology is changing and evolving permanently and radiology has, since its foundation as a discipline more than 100 years ago, been one of the technology drivers in medicine. In the next decade, radiology will have to cope with big data and will implement Radiomics, radiology will yield high-resolution morphology and will obtain the functional parameters and biomarkers that really matter in precision or personalized medicine. For this issue, my team and I strive for the implementation of big data analysis by using machine learning and data mining in large population-based cohorts, such as the German National Cohort (GNC) or Study of Health in Pomerania (SHIP). In addition, besides large-volume as well as high-resolution morphologic imaging, such as MR microscopy, we are constantly implementing functional techniques and strive to an early presentation of novel biomarkers to our

Curriculum Vitae

1993 - 1999 Medical School, Philipp-University, Marburg
2000 Doctorate in Anatomy and Cell Biology, Philipp-University, Marburg
2000 - 2004 Business School, Ruprecht-Karl-University, Heidelberg
2007 Habilitation in Radiology, Medical Faculty, University of Heidelberg
2010 Associate Professor of Radiology, University Hospital Heidelberg
2009 - 2015 Head of radiology at the Centre for Orthopaedics, Trauma Surgery and Spinal Cord Injury, University Hospital Heidelberg
2015 - 2017 Medical Vice-Director of the Clinic of Diagnostic and Interventional Radiology and head of radiology at the Centre for Surgery, University Hospital Heidelberg
Since 2017 Full Professor (W3) of Radiology and Chairman, Institute of Diagnostic and Interventional Radiology, Paediatric Radiology and Neuroradiology, University Medical Centre Rostock

clinical and preclinical partners to establish radiology as a core discipline in modern precision medicine.

Projects, Methods & Technologies

The development and the test of algorithms for the (semi-)automatic quantification, segmentation and annotation of clinically important morphological and functional parameters, as well as biomarkers such as tumour growth rate and perfusion on brain tumours on larger data sets has been a research topic of me and my team. These projects are supported as part of the DFG, EU and other funders.

Regarding spine segmentation, collaboration projects comprised the segmentation of intervertebral discs using spine MRI data sets. I am serving as head of the focus group musculoskeletal radiology of the GNC since 2011 and I have actively participated in deciding on sequence protocols, the MRI units and the incidental findings of the GNC. Scientific research areas of me and my research team comprise the implementation of innovative methods for morphologic (e.g. 3D), functional (e.g. biochemical cartilage assessment at 3 and 7 Tesla), multimodal and large-volume musculoskeletal imaging (e.g. in plasma cell diseases), and the implementation of minimal-invasive radiological treatment of diseases of the locomotor system including the spine. Currently, a project on the whole-body image analysis for diagnosing patients with monoclonal plasma cell disorders is funded by the D-A-CH initiative of the DFG (WE 2709/3-1). In addition, my research group has dealt with the implementation of functional imaging techniques, such as sodium-23 MRI at 1.5, 3 and 7 Tesla to detect altered muscle-cell ion homeostasis in several rare muscular channelopathies (see Fig. 1). Recent work led to the implementation of chlorine-35 MRI.

The comprehensive scientific work on functional and morphologic MRI techniques in the field of muscular diseases yielded in a monograph with 32 international and 11 national authors (Weber MA. Magnetic Resonance Imaging of the Skeletal Musculature. Springer, Heidelberg New York Dordrecht London, 2014). My research group has also dealt with multi-parametric tumour imaging for treatment planning and response assessment with a focus on brain tumours (parts of these work have been funded by the German Federal Ministry of Education and Research (BMBF)) as well as with the implementation and assessment of techniques to reduce the radiation exposure in projection imaging with support by the Dietmar Hopp foundation.

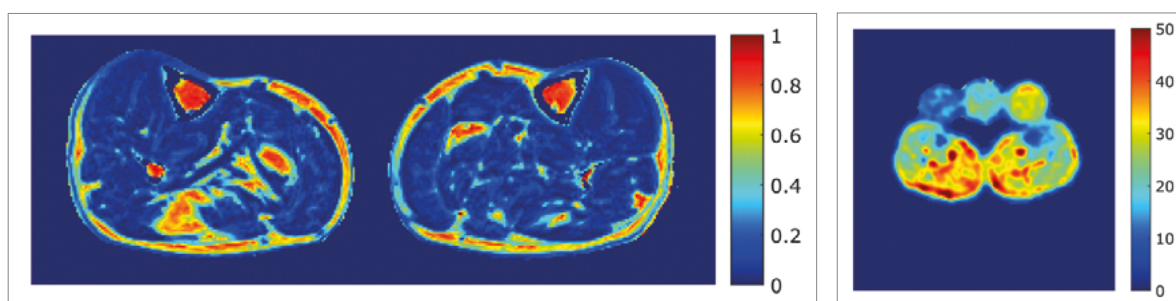


Fig. 1: Illustration of MR imaging findings in a 66-year-old female patient with hypokalemic periodic paralysis (HypoPP). (with the Cav1.1-R1239H mutation), (left) fat fraction maps obtained by using the Dixon-type sequence, (right) 7-T sodium-23 Na MR images (160/0.35). [From Weber et al. (2016)].

Selected Publications

- Wennmann M, Kintzelé L, Piraud M, Menze BH, Hielscher T, Hofmannigler J, Wagner B, Kauczor HU, Merz M, Hillengass J, Langs G, Weber MA (2018). Volumetry based biomarker speed of growth: Quantifying the change of total tumor volume in whole-body magnetic resonance imaging over time improves risk stratification of smoldering multiple myeloma patients. *Oncotarget* 38, 25254-25264.
- Glemser PA, Jaeger H, Nagel AM, Ziegler AE, Simons D, Schlemmer HP, Lehmann-Horn F, Jurkat-Rott K, Weber MA (2017). ²³Na MRI and myometry to compare eplerenone vs. glucocorticoid treatment in Duchenne dystrophy. *Acta Myol* 36, 2-13.
- Regula JU, Jestaedt L, Jende F, Bartsch A, Meinck HM, Weber MA (2016). Clinical muscle testing compared with whole-body magnetic resonance imaging in facio-scapulo-humeral muscular dystrophy. *Clin Neuroradiol* 26, 445-455.
- Weber MA, Nagel AM, Marschar AM, Glemser P, Jurkat-Rott K, Wolf MB, Ladd ME, Schlemmer HP, Kauczor HU, Lehmann-Horn F (2016). 7-T ³⁵Cl and ²³Na MR imaging for detection of mutation-dependent alterations in muscular edema and fat fraction with sodium and chloride concentrations in muscular periodic paralyses. *Radiology* 280, 848-859.
- Simon JJ, Cordeiro SA, Weber MA, Friederich HC, Wolf RC, Weisbrod M, Kaiser S (2015). Reward system dysfunction as a neural substrate of symptom expression across the general population and patients with schizophrenia. *Schizophr Bull* 41, 1370-1378.

The olfactory system in neurodegenerative diseases



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State-of-the Art

Olfactory deficits are observed in many neurodegenerative diseases. As essential olfactory disorders may proceed the outbreak of manifest clinical (motor) symptoms for several years, as seen, for example, in idiopathic Parkinson's disease (IPD), they may be regarded as predictors for accelerated neurodegeneration. Recent studies revealed that after 4 years, 7% of individuals with olfactory loss have developed signs of IPD. Nevertheless, the reason for the early involvement of the olfactory system in IPD remains unclear.

Overall Scientific Aim

Also other neurodegenerative diseases, e.g., Alzheimer's disease, Huntington's disease, Multiple Sclerosis, or rare storage diseases, go along with olfactory dysfunction suggesting that the special cellular and molecular conditions in the peripheral nasal mucosa (highly proliferative) and the central olfactory bulb as well as all subsequent canonical pathway stations (much less proliferative) may have common reasons, although the specific causes of the respective disease may be quite different. Viewed from a practical standpoint, the unique plasticity of the olfactory system may qualify olfactory acuity as a biomarker for potential treatment monitoring.

Projects, Methods & Technologies

We use several animal models that mimic defects occurring in human diseases such as Idiopathic Parkinson's Syndrome, Huntington's disease, Multiple Sclerosis, or Niemann-Pick disease. Most outcomes are based on immunohistochemical, electron microscopical and molecular biology techniques.

1. A rarely revisited system in a rare neurodegenerative disease:

Olfaction and Niemann-Pick Disease Type C1

To illustrate disease-specific dynamics of olfactory dysfunction and its reaction upon therapy, we experimentally demonstrate severe olfactory dysfunction in a transgenic mouse model for a rare lipid storage disease, Niemann-Pick disease Type C1 (NPC1) that can be significantly ameliorated under therapy with, for example, 2-hydroxypropyl- β -cyclodextrin. Especially the highly dynamic olfactory neuroepithelium suffers from severe cell

Curriculum Vitae

1983 State exam in Medicine, University of Hamburg

1986 Doctorate in Anatomy (Pituitary Gland), Institute of Anatomy, Eberhard-Karls University of Tübingen

1990 Research Fellow, Department of Anatomy, Bowman Gray School of Medicine, Winston-Salem, NC, USA

1994 Habilitation in Anatomy (Carbohydrate Histochemistry of Taste Buds), Medical Faculty, University of Tübingen

1994 - 2008 Senior Physician and Extraordinary (apl) Professor, Department of Anatomy and Department of Otorhinolaryngology, Medical Faculty Carl Gustav Carus, Technische Universität (TU) Dresden

2002 Guest Professor, Department of Integrated Biosciences, Faculty of Frontier Sciences, Tokyo University, Japan

Since 2008 extraordinary Professor of Anatomy, University Medical Centre Rostock

2019 Doctor honoris causa, Medical University Karol Marcinkowski, Poznań, Poland

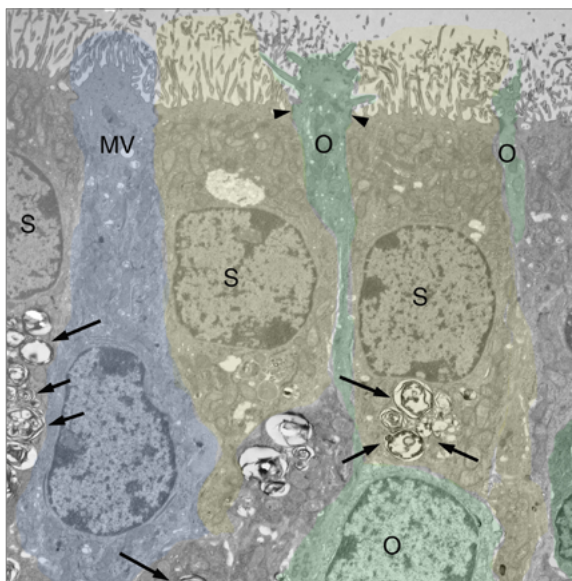


Fig. 1: Transmission electron micrograph of the olfactory epithelium of a Niemann-Pick-disease mutant mouse. Pathologic lipid storage in supporting cells (yellow, arrows). ORN (green) occasionally contain such deposits, but appear normal at the surface [from Hovakimyan et al. (2013), PlosOne].

loss that interferes with olfactory pathway relays in the first CNS structure, the olfactory bulb. Our comparative immunohistochemical, morphometric and molecular biological studies suggest that the olfactory bulb is the most affected brain region, at least in NPC1.

2. Olfaction and dopaminergic pathways in a 6-OHDA rat hemiparkinson model

The relevance of dopaminergic interneurons in the olfactory bulb for the sense of smell is an intriguing question. We tested the hypothesis that an experimentally induced hemiparkinsonism by intoxicating the medial forebrain bundle (MFB) with 6-hydroxydopamine (6-OHDA) may be suitable for describing olfactory deficits in IPD. In an experimental rat model we investigated the impact of dopamine receptor D2/3 availability in the olfactory bulb using PET/CT. Because of the dopaminergic deafferentiation between substantia nigra and striatum we speculate that in the olfactory bulb (OB) dopaminergic imbalance may lead to alterations in the expression of dopamine (D2/D3) receptors. Also the effect of intrastriatal injection of botulinum neurotoxin A (BoNT-A) on dopamine (D2/D3) receptors in the OB has been analyzed, as it normalizes pathologically increased D2/D3 receptors in the CPU of hemi-PD rats and reverses rotational motor symptoms.

3. The cerebral immune barrier and olfaction

The interface between peripheral and central nervous structures is a highly important issue in understanding CNS pathology, as, for example, demyelination processes and disturbed microglia expression may open gateways for invasion of immune cells into the brain. In this respect, the olfactory ensheathing glia along with its accompanying olfactory axons is an interesting candidate to study in animal demyelination models, e.g., for multiple sclerosis.

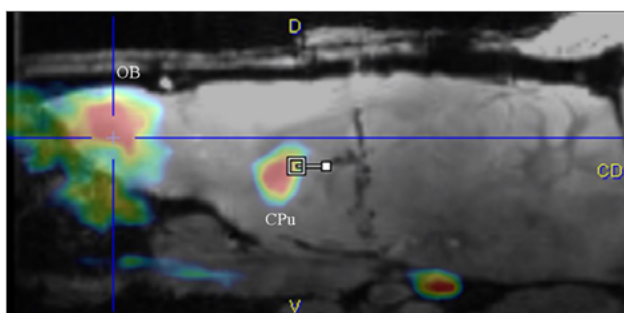


Fig. 2: [18 F]fallypride PET/CT image of a rat brain. Red areas show high D2 receptor availability in the olfactory bulb (OB) and striatum (CPu) [from Mann et al. (2018), Chem. Senses 43: e187].

Selected Publications

- Witt M, Thiemer R, Meyer A, Schmitt O, Wree A (2018). Main Olfactory and Vomeronasal Epithelium Are Differently Affected in Niemann-Pick Disease Type C1. *Int J Mol Sci.*, 19(11), 3563.
- Meyer A, Gläser A, Bräuer AU, Wree A, Strotmann J, Rolfs A, and Witt A (2018). Olfactory performance as an indicator for protective treatment effects in an animal model of neurodegeneration. *Front. Integr. Neurosci.* 12, 35.
- Meyer A, Wree A, Günther R, Holzmann C, Schmitt O, Rolfs A, Witt M (2017). Increased Regenerative Capacity of the Olfactory Epithelium in Niemann-Pick Disease Type C1. *Int J Mol Sci.* 18(4), 777.
- Reetz J, Hildebrandt S, Schmidt A, Meier C, Herchenröder O, Gläser A, Witt M, Pützer BM, Wree A (2015). Novel subventricular zone early progenitor cell specific adenovirus for in vivo therapy of central nervous system disorders reinforces brain stem cell heterogeneity. *Brain Structure & Function* 221(4), 2049-59.
- Witt M, Reutter K (2015). Anatomy of the tongue and taste buds. In: *Handbook of Olfaction and Gustation* (Ed. RL Doty), 3rd ed., John Wiley & Sons, Hoboken, NJ, 639-665.

Mathematical modelling of nonlinear dynamical systems in the life sciences



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State-of-the Art

We are experiencing tremendous technological advances, bringing a steady increase in the generation of data in biology and medicine. How can it be, that these advances do not translate into automated analyses, confident predictions and user-friendly tools? Due to the complexity of living systems, biological and medical data do not speak for themselves. We approach this challenge with the development of data analysis and modelling workflows, in which multiple heterogeneous data sources are integrated and processed by a variety of methodologies. Not only the generation of biological and medical data has become more complicated, the analysis of data cannot be done without an interdisciplinary effort. To this end, we successfully combine a wide range of computational and mathematical approaches in integrated workflows. Our team is multidisciplinary and so is our approach to address problems in biological and medical research. We have twenty years of experience in interdisciplinary research and training, which led to a solid track record of successfully completed projects. Our methodologies and tools are supporting the translation of biological and medical research into real world solutions and practical applications.

Overall Scientific Aim

We analyse data and create meaningful models to improve our understanding of health and disease. Our research thereby contributes to better diagnosis, prognosis and therapy.

Projects, Methods & Technologies

We are data scientists, using mathematics and computational tools to make sense of data. Our work focusses on understanding how the functioning of cellular systems emerge from the interactions between the systems parts, and how these emergent properties of a system as a whole enable or constrain the behaviour of its parts. Despite technological advances, that allow us to identify and characterize cellular components, the principles by which cells and tissues realize their function, remain poorly understood. Our approach combines data-driven modelling with model-driven experimentation, using a wide range of computational and mathematical tools, including machine learning, statistics, systems theory, stochastic processes, and category theory. The results of

Curriculum Vitae

1994 - 1997 Research Associate at the Control Systems Centre UMIST, Manchester, UK
 1997 Ph.D., Control Systems Centre, Dept. Electrical Eng. & Electronics, UMIST, Manchester, UK
 1997 - 2000 Lecturer, Lucas Varsity Research Lectureship, Control Systems Centre UMIST, Manchester, UK
 2000 - 2002 Lecturer, Joint appointment between the Control Systems Centre and the Department of Biomolecular Sciences, UMIST, Manchester, UK
 2002 - 2003 Senior Lecturer, Joint appointment between the Dept. of Biomolecular Sciences and the Dept. of Electrical Engineering & Electronics, UMIST, Manchester, UK
 Since 2004 Adjunct Professor in the Dept. of Electrical Engineering & Computer Science, Case Western Reserve University, Cleveland, Ohio, USA
 2005 Fellow of the Stellenbosch Institute for Advanced Study (STIAS) Stellenbosch, South Africa
 Since 2003 Full Professor (C4/W3), Chair in Systems Biology & Bioinformatics, Faculty of Computer Science & Electrical Engineering, University of Rostock

our daily work support basic biological and medical research.

In addition, the group holds an active role in the development of standards for computational biology, contributing to standardization initiatives like SBML, SBGN, and SED-ML and contributes to the development of the FAIRDOMHub data management platform. The group has developed several integrative computational pipelines for sequencing analysis by combining approaches from systems biology and bioinformatics. I and my group are also experienced in using machine learning and deep learning in the field of image analyses and beyond. His group deals with several ongoing projects such as DeepMRI, DeepBioSeq, FlowML that are exclusively dealing within the domain of Artificial Intelligence and patient specific therapeutic decision-making. The group is participating in multiple BMBF-funded projects for the German network for Bioinformatics Infrastructure (de.NBI) and e.Med on data management and sequencing data analysis. The group also hosts an industry funded three year research program on machine learning for patient data, which started in October 2018.

The Systems Biology and Bioinformatics group, as a member of de.NBI, the European Elixir initiative, and part of the RNA Bioinformatics Center (RBC), has access to a cluster with 86 compute nodes and a total of 2064 compute cores. Each node is equipped with at least 32 GB of RAM and the net storage capacity is approximately 700 TB. With regards to the currently established de.NBI cloud the computational performance will accordingly upscale. In addition, the group hosts a high-performance GPU cluster with around 24,000 computing nodes.

Our expertise at a glance:

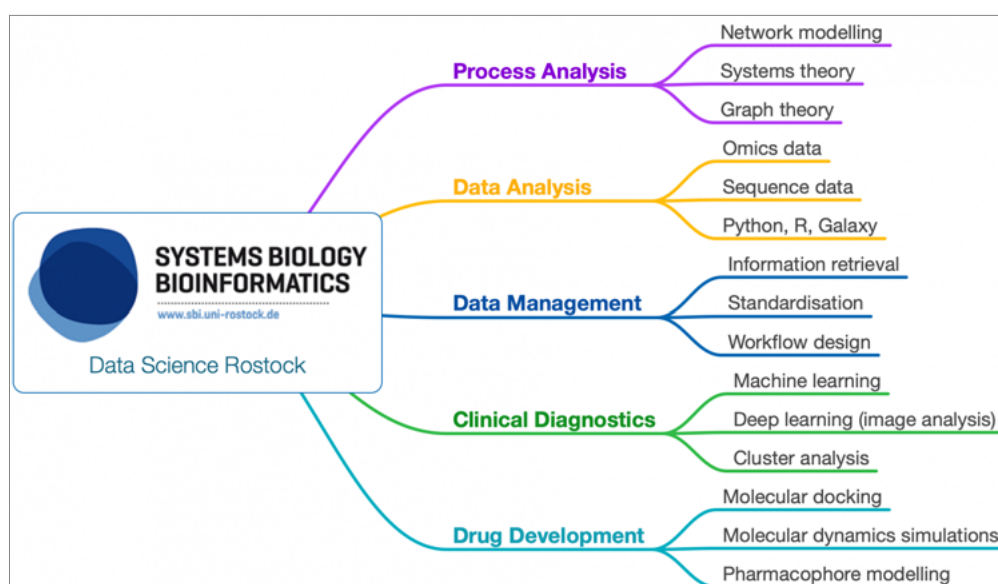


Fig. 1: Mindmap about our primary expertise in the five selected fields of process analysis, data analysis, data management, clinical diagnosis, and Drug development.

Selected Publications

- Winter F, Bludszuweit-Philipp C, Wolkenhauer O (2018). Mathematical analysis of the influence of brain metabolism on the BOLD signal in Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism* 38(2), 304–316.
- Lai X, Gupta SK, Schmitz U, Marquardt S, Knoll S, Spitschak A, Wolkenhauer O, Pützer BM, Vera J (2018). MiR-205-5p and miR-342-3p cooperate in the repression of the E2F1 transcription factor in the context of anticancer chemotherapy resistance. *Theranostics* 8(4), 1106–1120.
- Khan FM, Marquardt S, Gupta SK, Knoll S, Schmitz U, Spitschak A, Engelmann D, Vera J, Wolkenhauer O, Pützer BM (2017). Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. *Nature Communications* 8(1),198.
- Schmitz Y, Rateitschak K, Wolkenhauer O (2013). Analysing the impact of nucleo-cytoplasmic shuttling of beta-catenin and its antagonists APC, Axin and GSK3 on Wnt/beta-catenin signalling. *Cellular Signalling* 25(11), 2210–21.
- Lai X, Schmitz U, Gupta S, Bhattacharya A, Kunz M, Wolkenhauer O, Vera J (2012). Computational analysis of target hub gene repression regulated by multiple and cooperative miRNAs. *Nucleic Acids Research* 40, 8818–8834.

Effects of intrastriatal botulinum neurotoxin-A in hemiparkinsonian rats



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State-of-the Art

In the field of neurodegeneration, our group focusses on three topics: hemiparkinsonian rats, transgenic BACHD rats, mouse mutants of Niemann-Pick Type C1 disease, studying morphological, functional and behavioral parameters in control and diseased animals.

Overall Scientific Aim

Hemiparkinsonian rats: due to the collaboration with the Department of Neurology we developed the intrastriatal injection of botulinum neurotoxin-A (1 ng) to ameliorate motor symptoms in hemiparkinsonian rats. This was done to reduce the striatal hypercholinism that seeming is a major reason of parkinsonian disturbances. Main findings were: BoNT-A injection is well tolerated, do not lead to neuronal degeneration of neurons, especially of cholinergic interneurons, do not induce inflammatory reactions in the brain, however lead to swellings of catecholaminergic and cholinergic nerve fibers. Intrastriatally applied BoNT-A - among influencing the receptor densities of various receptors - leads to a reduction of the striatal D2 and D3 receptor density in 6-OHDA hemi-PD rats. All in all, we suggest the intrastriatal application BoNT-A could serve as an interesting option in the therapy of at least the experimental hemi-PD-associated symptoms. Especially the intensive cooperation with Prof. K. Zilles (Research Centre Jülich, Institute of Neuroscience and Medicine INM-1, Jülich, Germany) and the colleges of the Core Facility "Multimodal Small Animal Imaging", Rostock University Medical Center is essential for our studies.

Projects, Methods & Technologies

Niemann-Pick Type C1 (NPC1): NPC1 is - like HD - a rare disease in humans. NPC1 is an autosomal recessive inherited neurodegenerative disorder characterized by accumulation of cholesterol and glycosphingolipids. In close cooperation with the AKos, the Department of Neurology and the Centogene AG we evaluated the effects of pharmacological intervention (miglustat, cyclodextrin and allopregnanolone in combinations or alone) in wildtype and NPC1 homozygote mutant mice on the behavior (accelerod, Morris water maze, elevated plus maze, open field and hot-plate tests). The BALB/cNctr-Npc1m1N/-J mice treated with miglustat, cyclodextrin and

Curriculum Vitae

1971 - 1977 Studies of human medicine, Christian Albrechts Universität zu Kiel
1977 Doctorate in Neuroanatomy, Anatomical Institute, Christian Albrechts Universität zu Kiel
1978 - 1981 Scientific assistant, Anatomical Institute, Christian Albrechts Universität zu Kiel
1981 - 1987 Scientific assistant, Anatomical Institute, University of Cologne
1986 Habilitation in Anatomy, Medical Faculty, University of Cologne
1987 - 1992 Professor (C2) for Anatomy, University of Würzburg
1992 - 2018 Full Professor (C4) for Anatomy and Director of the Institute of Anatomy, University Medical Centre Rostock
Since 2017 Steering Board Member of the Centre for Transdisciplinary Neurosciences Rostock (CTNR)
Since 2018 Senior Professor, University Medical Centre Rostock

allopregnanolone generally performed better than untreated mutant mice. As the drugs interfere with the general cholesterol metabolism involved in many metabolic pathways of cells, we evaluated the effects of these drugs in healthy BALB/c mice and found unaltered motor capabilities and spontaneous motor behaviour. However, miglustat-treated wild-type mice displayed impaired spatial learning compared to sham- and combination-treated mice. However, both combination- and miglustat-treated mice showed enhanced anxiety in the elevated plus maze compared to sham-treated mice. Our results suggest that allopregnanolone/cyclodextrin ameliorate most side effects of miglustat in wild-type mice. With respect to brain morphology, the most impressive result is, that the combination therapy in mutant mice with miglustat, cyclodextrin and allopregnanolone results in a dramatic inhibition of the otherwise occurring loss of cerebellar Purkinje neurons. Ongoing quantitative studies investigate the fresh volumes of various brain areas of both wildtype and mutant mice after various therapeutic regimes. In cooperation with Prof. K. Zilles and K. Amunts (Research Centre Jülich, Institute of Neuroscience and Medicine INM-1, Jülich, Germany), and the colleges of the “Central Institute of Engineering, Electronics and Analytics, ZEA-3, Research Centre Jülich” and the “Cécile and Oskar Vogt Institute of Brain Research, Heinrich Heine University Düsseldorf” studies evaluating the topographic distribution of densities of the receptors for the most important transmitters and lipids in the brain are ongoing.

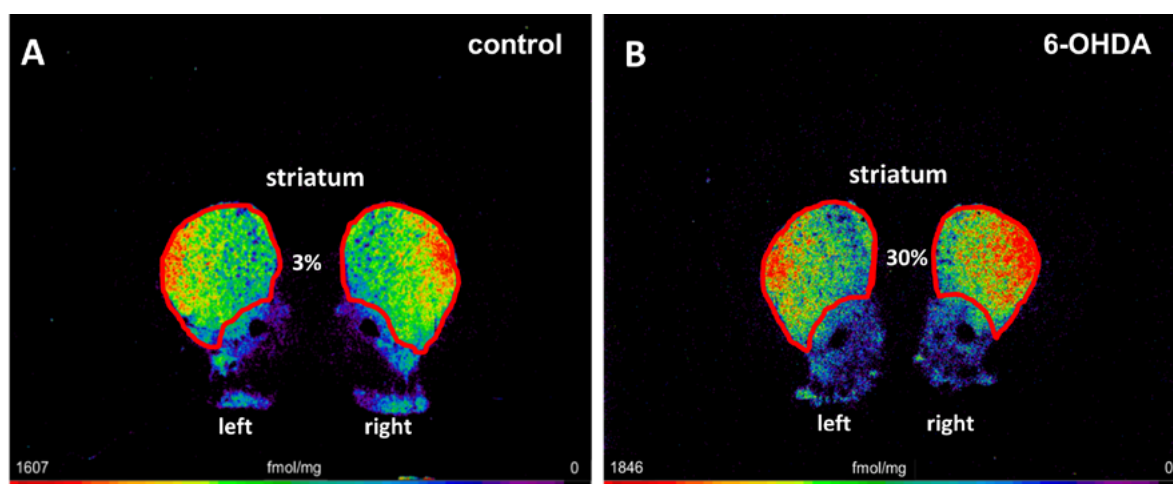


Fig. 1: Contrast-enhanced color-coded autoradiogram using [^{18}F]Fallypride showing the regional striatal distribution of D2/D3 receptor density (fmol/mg protein) in a control rat (A) and (B) after 6-OHDA injection into the right medial forebrain bundle. The interhemispheric difference is 3% in the control (A), and 30% in the hemiparkinsonian rat due to the upregulation of the D2/D3 receptor density in the dopamine-depleted hemisphere.

Selected Publications

- Witt M, Thieme R, Meyer A, Schmitt O, Wree A (2018). Main olfactory and vomeronasal epithelium are differently affected in Niemann-Pick disease type C1. *Int J Mol Sci.* 19(11), 3563.
- Mann T, Zilles K, Klawitter F, Cremer M, Hawlitschka A, Palomero-Gallagher N, Schmitt O, Wree A (2018). Acetylcholine neurotransmitter receptor densities in the striatum of hemiparkinsonian rats following Botulinum neurotoxin-A injection. *Front Neuroanat.* 12(65).
- Hawlitschka A, Wree A (2018). Experimental intrastriatal applications of botulinum neurotoxin-A: a review. *Int J Mol Sci.* 19(5),1392.
- Mann T, Kurth J, Hawlitschka A, Stenzel J, Lindner T, Polei S, Hohn A, Krause BJ, Wree A (2018). [^{18}F]fallypride-PET/CT analysis of the dopamine D2/D3 receptor in the hemiparkinsonian rat brain following intrastriatal Botulinum neurotoxin-A injection. *Molecules* 23(3), 587.
- Mann T, Zilles K, Dikow H, Hellfritsch A, Cremer M, Rösch F, Piel M, Hawlitschka A, Schmitt O, Wree A (2018). Dopaminergic (D1, D2), noradrenergic (alpha1 and alpha2) and serotonergic (5HT-2A) neurotransmitter receptor densities in the striatum of hemiparkinsonian rats following Botulinum neurotoxin-A injection. *Neuroscience* 374, 187-204.

Molecular pathomechanisms and biomarker research in multiple sclerosis



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State-of-the Art

Multiple sclerosis (MS) is a common chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system. The pathological hallmark of MS is the formation of focal lesions in the brain and spinal cord. The individual clinical presentation of patients with MS is very heterogeneous. MS is currently incurable, but there are more than a dozen approved disease-modifying treatments (DMTs) that can reduce disease activity and limit progressive neurologic deterioration. Although the causes of MS are still largely unclear, it has been established that the pathogenic processes are driven by complex interactions of genetic and environmental factors. However, there is a lack of studies aimed at deciphering the functional implications of MS-associated genetic variants.

Overall Scientific Aim

The interdisciplinary neuroimmunological research group in Rostock is engaged in innovative basic and applied research on immune-mediated neurological diseases, in particular MS. One focus is on exploring the molecular mechanisms that contribute to the pathogenesis of MS. Another main objective is the identification of novel biomarkers for improved diagnosis, prognosis and monitoring of the disease. Our research is always with and for the patients (from bedside to bench and back). We usually employ multi-omic approaches by screening various types of molecules (e.g., DNA, RNA and proteins) in different types of patient samples (e.g., blood and liquor cerebrospinalis).

Projects, Methods & Technologies

Two of our currently funded projects address the connection between genetic variants and aberrant RNA processing events in MS. The latest international genome-wide association study (GWAS) revealed more than 200 genetic loci to be associated with an increased risk of MS (Patsopoulos et al., Science, 2019). We hypothesize that several MS-associated single-nucleotide polymorphisms (SNPs) affect the splicing of protein-coding RNAs and the biogenesis of non-coding microRNAs. MicroRNAs are processed from stem-loop precursor RNA sequences via different enzymatic cleavage steps. Mature microRNAs are very small RNA molecules that regulate gene expression by triggering the degradation of complementary transcripts. According to current estimates, over 60% of human protein-coding genes are conserved targets of microRNAs (Bartel, Cell, 2018). Consequently, microRNAs are involved in many physiological processes such as proliferation, differentiation and apoptosis of immune cells. More recently,

Curriculum Vitae

1982 - 1988 State exam in Medicine, Otto-von-Guericke-Universität of Magdeburg and University of Rostock
1990 Doctorate in Microbiology, Institute of Microbiology, Medical Faculty, University of Rostock
1992 - 1994 Research grant Deutsche Forschungsgemeinschaft (DFG) Clinical and experimental Neuroimmunology, Clinic of Neurology; Julius-Maximilians-Universität Würzburg
Since 1994 Research Group Leader Section Neuroimmunology, University Medical Centre Rostock
1997 Habilitation in Neurology, University Medical Centre Rostock
2003 Professor for Neurology / Neuroimmunology, Department of Neurology, University Medical Centre Rostock
Since 2011 Full Professor (W3) for Neurology / Neuroimmunology, Department of Neurology, University Medical Centre Rostock
Since 2017 Visiting Professor Medical University of Vienna, Austria
Since 2017 Steering Board Member of the Centre for Transdisciplinary Neurosciences Rostock (CTNR)

pathological microRNA expression patterns have been discovered. A major part of our research is on blood cells. Therefore, we have established optimized laboratory protocols to separate different lymphocyte populations from blood samples of MS patients. For instance, memory B cells and T helper cells are believed to play distinct roles in the initiation and progression of MS through antigen presentation and secretion of proinflammatory cytokines. Following the biobanking of blood samples, we obtain diverse types of data by employing modern technologies, including quantitative real-time PCR, microarrays and RNA-sequencing. The molecular data and the clinical data are then analyzed in a highly integrative manner by incorporating also information from public databases. The parallel examination of genotypes and microRNAs allows to identify the genetic loci controlling their expression. Such molecular quantitative trait loci (QTL) have become an important asset in the genetic study of complex diseases.

We have previously demonstrated that an MS-associated SNP alters the processing of microRNA-548ac (Hecker et al., PLoS Genet., 2019). We were also the first to show that this microRNA regulates genes, which participate in inflammatory processes and in controlling the balance of protein folding and degradation. Several other microRNAs are similarly encoded within MS-associated genetic loci. Therefore, we are currently expanding our research efforts to discover new insights on these microRNAs and to identify potential biomarkers. An example is shown in figure 1: The MS-associated SNP rs817478 is located downstream of the microRNA-4423 stem-loop sequence. This SNP affects a known sequence motif that is relevant for the enzymatic cleavage of the precursor RNA. Carriers of the MS risk allele A thus express significantly lower levels of this microRNA. Various open questions remain: For instance, the functional roles of many non-coding RNAs and their isoforms are still enigmatic. Novel concepts from the field of systems medicine have to be implemented to better disentangle the causal interactions and the regulatory dynamics

in the complex molecular network. Furthermore, it has to be investigated to which extent RNAs and proteins, which are encoded in disease-associated genetic regions, are suited to distinguish relapsing and progressive forms of MS and to evaluate the individual effects of DMTs. In the long term, a more comprehensive understanding of the biological mechanisms that underlie MS susceptibility will ultimately translate into benefits in the clinical care of our patients.

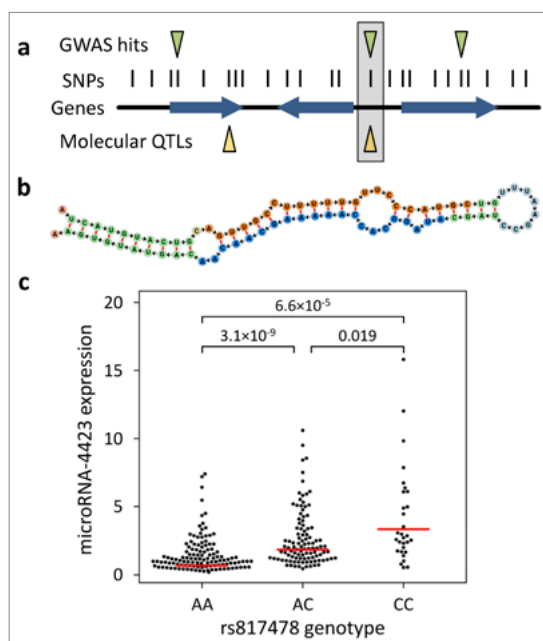


Fig. 1: Functional characterization of genetic MS risk loci with example. (a) Strategy for identification of disease causative variants. MS-associated genetic loci from genome-wide association studies (GWAS) are prioritized by checking for colocalization with molecular quantitative trait loci (QTLs). (b) Secondary structure of the precursor of microRNA hsa-mir-4423. The mature microRNA sequences are highlighted in orange and blue. (c) MicroRNA expression QTL analysis based on RNA-sequencing data obtained for blood-derived cells. The level of microRNA-4423-5p depends on the genotype of the single-nucleotide polymorphism (SNP) rs817478. Significantly lower levels of this microRNA can be observed in individuals with the MS risk allele A (t-test p-values are shown above the brackets).

Selected Publications

Rommer PS, Eichstädt K, Ellenberger D, Flachenecker P, Friede T, Haas J, Kleinschmitt C, Pöhlau D, Rienhoff O, Stahmann A, Zettl UK (2018). Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Mult Scler.* 25(12), 1641-1652.

Angerer IC, Hecker M, Koczan D, Roch L, Friess J, Rüge A, Fitzner B, Boxberger N, Schröder I, Flechtner K, Thiesen HJ, Winkelmann A, Meister S, Zettl UK (2018). Transcriptome profiling of peripheral blood immune cell populations in multiple sclerosis patients before and during treatment with a sphingosine-1-phosphate receptor modulator. *CNS Neurosci Ther.* 24(3), 193-201.

International Multiple Sclerosis Genetics Consortium (2018). Low-Frequency and Rare-Coding Variation Contributes to Multiple Sclerosis Risk. *Cell.* 175(6), 1679-1687.e7.

Zettl UK, Hecker M, Aktas O, Wagner T, Rommer PS (2018). Interferon β -1a and β -1b for patients with multiple sclerosis: updates to current knowledge. *Expert Rev Clin Immunol.* 14(2), 37-153.

Berger T, Elovaara I, Fredrikson S, McGuigan C, Moiola L, Myhr KM, Oreja-Guevara C, Stolarov I, Zettl UK (2017). Alemtuzumab Use in Clinical Practice: Recommendations from European Multiple Sclerosis Experts. *CNS Drugs.* 31(1), 33-50.

Neurobiology of depression, poststroke depression, stress and vascular disease



Alumni - Kronenberg, Golo

Prof. Golo Kronenberg, MD
College of Life Sciences, University of Leicester and
Leicestershire Partnership National Health Service Trust
BHF Research Centre, Glenfield Hospital
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gdk7@leicester.ac.uk

Prof. Kronenberg becomes a CTNR Member in 2017. Since 2018 he is part of the alumni network.

Research fields:

- Mechanisms of neuronal cell death (DNA damage and repair, apoptosis)
- Regeneration and functional outcomes (behavioral endpoints, cellular plasticity, neurogenesis)
- MR Imaging of neuropsychiatric disorders
- Neurobiology of affective disease

Selected Publications

- Kronenberg G, Uhlemann R, Richter N, Klempin F, Wegner S, Staerck L, Wolf S, Uckert W, Kettenmann H, Endres M, Gertz K (2018). Distinguishing features of microglia- and monocyte-derived macrophages after stroke. *Acta Neuropathol* 135(4), 551-568.
- Gertz K, Uhlemann R, Foryst-Ludwig A, Barrientos RM, Kappert K, Thöne-Reineke C, Djoufack P, Kirschbaum C, Fink KB, Heinz A, Kintscher U, Endres M, Kronenberg G (2018). The cytoskeleton in 'couch potato-ism': Insights from a murine model of impaired actin dynamics. *Exp Neurol* 306, 34-44.
- Kronenberg G, Uhlemann R, Schöner J, Wegner S, Boujon V, Deigendesch N, Endres M, Gertz K (2017). Repression of telomere-associated genes by microglia activation in neuropsychiatric disease. *Eur Arch Psychiatry Clin Neurosci* 267(5), 473-477.
- Uhlemann R, Gertz K, Boehmerle W, Schwarz T, Nolte C, Freyer D, Kettenmann H, Endres M, Kronenberg G (2016). Actin dynamics shape microglia effector functions. *Brain Struct Funct* 221(5), 2717-34.
- Kronenberg G, Mosienko V, Gertz K, Alenina N, Hellweg R, Klempin F (2016). Increased brain-derived neurotrophic factor (BDNF) protein concentrations in mice lacking brain serotonin. *Eur Arch Psychiatry Clin Neurosci* 266(3), 281-4.

Curriculum Vitae

- 1998 Doctoral thesis, Institute of Pathology, Ruprecht-Karls-Universität, Heidelberg
- 1998 - 2001 Resident, Central Institute of Mental Health, Mannheim
- 2001 - 2003 Postdoctoral Research Fellow, 'Neuronal Stem Cells' Group, Max-Delbrück-Center for Molecular Medicine, Berlin-Buch
- 2003 - 2007 Postdoctoral Research Fellow, Department of Experimental Neurology, Charité
- 2007 Board Certification 'Psychiatry and Psychotherapy' (Berlin)
- 2008 Assistant Professor (W1), Charite University Medical Center
- 2015 Associate Professor (W2) for Biological Psychiatry, Charite University Medical Center, Berlin
- 2016 - 2018 Deputy Head, Department of Psychiatry and Psychotherapy, University Medical Centre Rostock
- Since 2018 Chair in Adult and Liaison Psychiatry, University of Leicester, and Honorary Consultant, Leicestershire Partnership NHS Trust, Leicester, UK



CTNR Educational Activities

- ✓ Clinician Scientist Program
- ✓ Qualification Program

CTNR Educational Activities

Clinician Scientist Program

In 2016, the German Council of Science and Humanities outlined the increasing problems of Medical Faculties and University Hospitals in recruiting of young medical scientific researchers as well as their specific challenges concerning compatibility of research and clinical work^[1]. Consequently, the currently existing framework conditions for clinical scientists need to be improved in order to create efficient incentives for an academic/research career besides medical training. In 2018, the University Medical Centre Rostock (UMR) has recognised these problems and challenges and established the **Rostock Academy for Clinician Scientists (RACS)**. It contains a general clinician scientist program structured into a junior and an advanced clinician scientist program. The aim of RACS is a targeted recruitment of excellent clinician scientists for all departments and institutes of the UMR. The concept for RACS was initiated and developed by the board of the CTNR.

At the same time, the CTNR board implemented an additional **Clinician Scientist Program in the field of neuroscience** to strengthen the scientific significance of this priority area by the opportunity for two additional physicians to apply for temporary clinician substitute positions ("Rotationsstellen") under the umbrella of RACS and the CTNR. The concept of the CTNR Program is based on the approved recommendations for developing clinical research at German Universities^[2] and the recommendations for the implementation of Advanced Clinician Scientist Programs^[3] by the Permanent Senate Commission of the German Research Foundation.

The key goals of RACS and the CTNR Clinician Scientist Program are to:

- create and structure career paths for physicians during specialist/subspecialist training time,
- ensure equal opportunities for physicians concerning their clinical and scientific career management,
- provide the necessary interdisciplinary research environment and infrastructure for the participating clinician scientists,
- ensure every clinician scientist within his/her specialist training a research protected time for his/her independent research projects,
- generate high-quality trained clinician scientists by an individual clinical, scientific and soft skill educational curriculum offered by excellent scientists and physicians,
- create an interface between pre-clinical and basic research and clinical science to promote translational research at the UMR,
- feature quality management by the implementation of a mentoring scheme and a transparent organization structure,
- improve the expertise and international visibility of the host institution in the three scientific priority areas.

[1] Wissenschaftsrat (2016). Perspektiven der Universitätsmedizin, Weimar.

[2] Deutsche Forschungsgemeinschaft (2015). Etablierung eines integrierten Forschungs- und Weiterbildungs-Programms für "Clinician Scientists" parallel zur Facharztweiterbildung, Bonn.

[3] Deutsche Forschungsgemeinschaft (2018). Etablierung einer wissenschaftsorientierten Personalentwicklung für Fachärztinnen und Fachärzte in der Universitätsmedizin, Bonn.

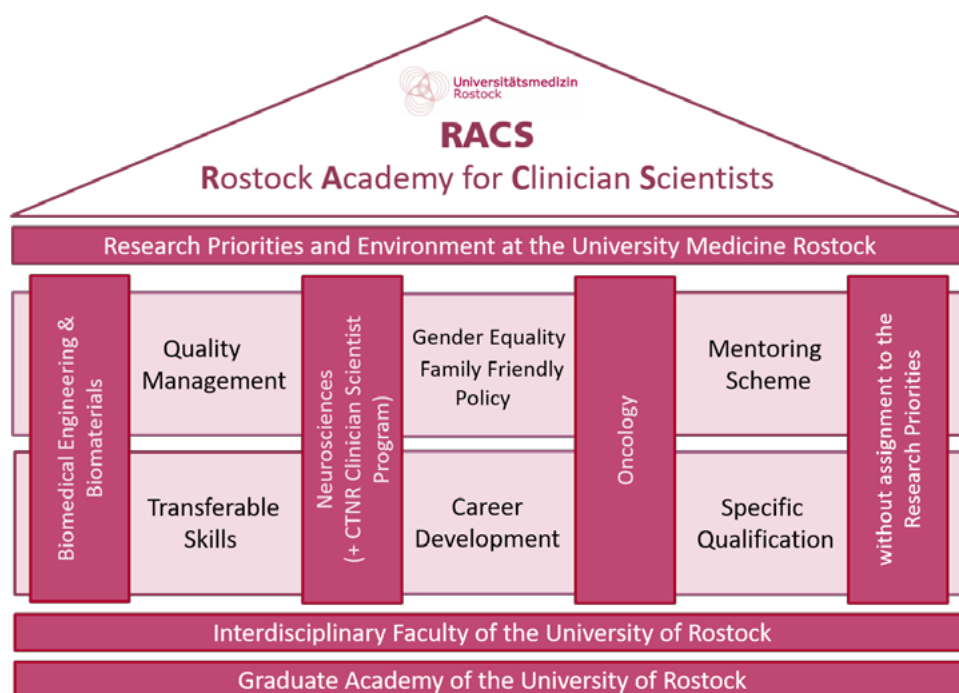


Fig. 1: Research Environment of the Rostock Academy for Clinician Scientists (RACS).

RACS contains an overall Clinician Scientist Program for institutes and departments of the three priority areas or without an assignment to them. The CTNR implemented an additional program with two further positions for clinician scientists in the field of neuroscience.

To achieve a high scientific and educational quality, the key elements (quality management, mentoring scheme, gender equality, career development, topic specific qualification and soft skill modules of the curriculum) are ensured by the excellent expertise and experience of the participating institutions. The clinician scientist programs cover the individual needs of the participating clinician scientists and their research projects in the corresponding area. Clinician Scientists are physicians in specialist training time (at least 50% of the common trunk is passed) or on sub specialisation training. The research protected time is the key element and corresponds in average to 50% of the working hours to exclusively conduct research. Its allocation depends on the individual requirements of the clinician scientist in consultation with the head of the clinical department or institute and can be taken episodic or in total.

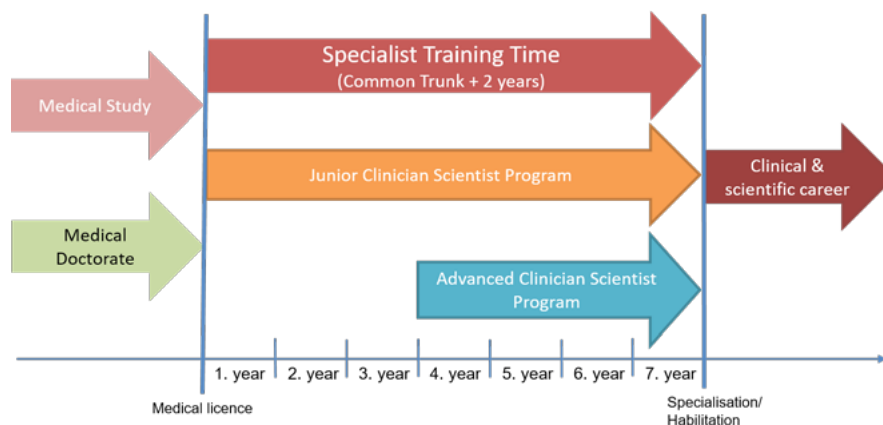


Fig. 2: Junior and Advanced Clinician Scientists.

Structured career path of clinician scientists of the CTNR Clinician Scientist Program (exemplary five years common trunk and two years of research protected time).

Qualification Program

The CTNR strategy contains to bring forward the recruitment and generating of young clinical, medical and scientific researchers and to support them in the development of their careers. Beside the CTNR Clinician Scientist Program an overall educational and qualification program with the contributions of CTNR members was implemented. The educational activities are divided into the **qualification program organised and conducted by the CTNR** and the **activities of the neuroscience community** in Rostock.

In 2018, the CTNR qualification program contained workshops and lectures about funding opportunities for young scientists in Germany:



Workshop: Research Grants at the German Research Foundation - Structure, Content and Process

The aim of the workshop is to support the application for a research grant (Sachbeihilfe) at the German Research Foundation (DFG). Practical exercises and joint non-scientific discussions are tools for the development of a template that can be used as a basis for the submission of a third-party fund proposal.

Lecture: Funding Opportunities for young scientists

The talk provides an overview of the third party funding system in Germany and the EU, introduces the most important funding bodies and gives advices on how to apply.

To bundle the educational activities of all CTNR members a **web-based platform** was implemented. The platform gives an overview of planned seminars, workshops, conferences and events of the institutes of the CTNR members. The CTNR helps to announce the events and to increase the outreach. The following table shows some examples of the educational activities of CTNR members in 2018.

| CTNR Institute | Educational Activities |
|---|---|
| Hospital for Children and Adolescents, Neuropaediatrics | Electroencephalography Workshop |
| Institute for Biostatistics and Informatics in Medicine and Ageing Research | Contribution with sessions on aging at the Hauptstadtkongress Berlin Second Workshop Next Generation Sequencing Consortium Mecklenburg-Vorpommern |
| Oscar-Langendorff-Institute of Physiology | 12th Baltic Sea Summer School on Epilepsy |
| Department of Neurology | International Young Scientist Symposium on the Center of Excellence in Neurodegeneration Research (CoEN) 2018 Scientific Meeting of the MDS NMS PD Study Group: The many faces of Parkinson's disease |
| Institute of Anatomy | 113th Annual Meeting Anatomische Gesellschaft |
| Institute for Experimental Surgery with Central Animal Care Facility | Workshop: Neuro-PET in transgenic mouse models |
| Department of Psychosomatic and Psychotherapeutical Medicine | Lecture: Cognitive problems in people with Multiple Sclerosis: Perceived effectiveness and provision of cognitive rehabilitation |

In 2018, preparations for the **Lectures of Excellence: Pioneers in Neurosciences** were made. The event will start in 2019 and invites excellent scientists of significant discoveries in the field of neuroscience to provide insights into their research. These include, above all, Nobel Prize winners, Leibniz Prize winners or winners of other excellent awards. The lectures are addressed to scientists, physicians and junior scientists working in the field of neuroscience. By presenting their own experiences, the lecturers will awake the interest for innovative solutions and alternative ways of thinking. The audience will get in close contact with interesting personalities and their groundbreaking research.

Further planned measures for 2019 are the implementation of a **CTNR Lectures Series** with financial and organisational support for CTNR members to conduct talks, workshops and symposia with national and international guest speakers, the development and implementation of a **CTNR master program** "Translational Neurosciences" and a **Medical Scientist Program**.



- ✓ Infrastructure Concepts
- ✓ Career & Funding Service

CTNR Transfer Activities

Infrastructure Concepts

The short-term goal of the CNTR in relation to translation is the development of comprehensive research designs which combine methods and issues from basic and clinical research. In the long-term, new therapy and prevention approaches in animal models and in human studies should be evaluated.

Beside the scientific transfer of knowledge and results, the CTNR Board regularly analyses the initial conditions for optimal research and develops infrastructure concepts with suggestions for the improvement of the research environment. These concepts are transferred to the head office of the UMR as part of the **consultancy tasks** of the CTNR. Members of the CTNR are regularly involved into appointment procedures for new professorships and meetings of (research) commissions. The coordinator of the CTNR regularly evaluates conducted CTNR events and analyses the results in terms of needs and suggestions of the participants.

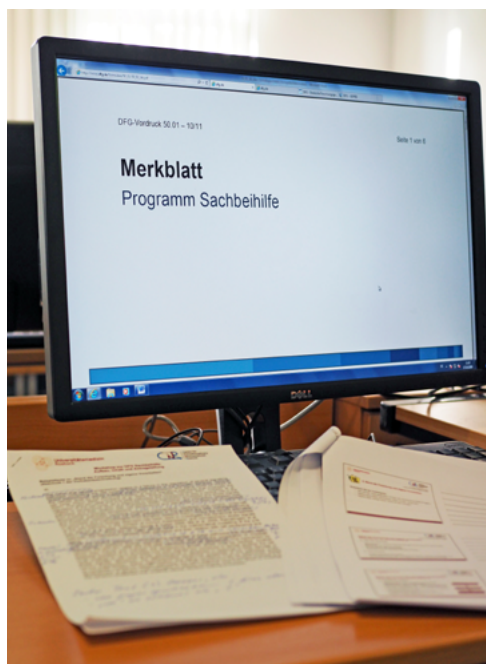
In 2018, as a result the CTNR Board worked out a concept for a **funding program to support the career paths of women after graduation** and a concept for a new **core facility “funding support”** and presented this to the head office of the University Medical Centre Rostock.



Another result of demand-oriented analyses revealed the need for a **clinical research platform for neurosciences** in Rostock. The platform contains the project management in the administrative planning and organisation of commercial and science-oriented clinical studies, taking into account the regulatory and site-specific academic constraints of the neuroscience research area. The definition and further development of the processes at the interfaces between scientists, the Coordination Centre for Clinical Studies (KKS) and the administration of the University Medical Centre Rostock will be important. In 2019, the CTNR will employ a scientific manager to implement the clinical research platform.

Career & Funding Service

To support the transfer of information around and about the neuroscience community in Rostock, the CTNR implemented the **CTNR Newsletter**. Since January 2018, the monthly newsletter provides information about the activities of the CTNR members, recent funding opportunities, awards, training opportunities and events in the field of neurosciences. In addition to the CTNR members, more than 38 external readers subscribed to the newsletter.



The CTNR homepage informs on its “**Career & Funding**” **website** about current open positions in the neuroscience community, the Clinician Scientists Programs and other funding opportunities (e.g. foundations, associations, awards).

For the future, CTNR **Thesis Advisory Committee Meetings** (TAC Meetings) for doctoral students and at least two supervisors are planned to ensure a mentoring scheme and to support young scientists in their career path.

In addition to coordinating the major CTNR collaborative projects, the CTNR scientific coordinator has regularly advised and supported CTNR members in the application of third-party funding projects (e.g. DFG research grants) since the foundation of the CTNR in November 2017. The **CTNR grant writing support** includes the organisation of kick-off meetings for interdisciplinary applications, as well as individual consultation with formal reviews of the proposals and the calculation of project costs. The aim is to increase the number of submitted proposals and the third-party funds in the scientific area of neurosciences.

Since 2017, six proposals have been submitted for consultation at the CTNR coordination office before submitted at the respective funding body (see Fig. 1). Two of them were eventually funded.

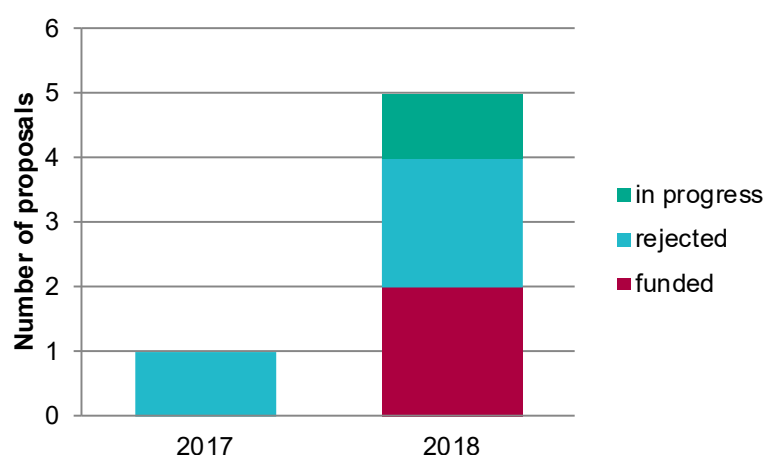


Fig. 1: Number of proposals submitted for consultation at the CTNR in 2017/2018. Two of them were funded in 2018, three of them were rejected in 2017 and 2018. In 2018, one of them is still in progress.

Gallery



Main building of the University of Rostock



Centre for Neurology at the
University Medical Centre



Department of Psychiatry in Childhood and
Adolescence at the University Medical Centre



Institutes for Physiology and Anatomy
at the University Medical Centre



Lecture Hall Schillingallee at the
University Medical Centre



Skyline of Rostock



Appendix

- ✓ List of Publications 2017 - 2018
- ✓ Imprint

Appendix

Publications 2017 - 2018

(Only PubMed-listed publications)

Baltrusch, Simone: Peripheral diabetic neuropathy

- Baltrusch, S. (2017). Konfokal mikroskopisch sichtbarer kornealer Nervenplexus als Biomarker für systemische Erkrankungen
Blick vom kornealen Nervenplexus auf die Erkrankung Diabetes mellitus. *Der Ophthalmologe Zeitschrift der Deutschen
Ophthalmologischen Gesellschaft*, 114, 592–600.
- Baltrusch, S. J., van Dieën, J. H., van Bennekom, C. A. M., & Houdijk, H. (2018). The effect of a passive trunk exoskeleton
on functional performance in healthy individuals. *Applied ergonomics*, 72, 94–106.
- Niemann, J., Johne, C., Schröder, S., Koch, F., Ibrahim, S. M., Schultz, J., Tiedge, M., & Baltrusch, S. (2017). An mtDNA
mutation accelerates liver aging by interfering with the ROS response and mitochondrial life cycle. *Free radical biology
& medicine*, 102, 174–187.

Berger, Christoph: EEG and fMRI in Psychiatry

- Berger, C., Muller-Godeffroy, J., Marx, I., Reis, O., Buchmann, J., & Duck, A. (2018). Methylphenidate promotes the interaction
between motor cortex facilitation and attention in healthy adults: A combined study using event-related potentials and
transcranial magnetic stimulation. *Brain and behavior*, 8, e01155.
- Lischke, A., Herpertz, S. C., Berger, C., Domes, G., & Gamer, M. (2017). Divergent effects of oxytocin on (para-)limbic
reactivity to emotional and neutral scenes in females with and without borderline personality disorder. *Social cognitive
and affective neuroscience*, 12, 1783–1792.
- Villemonteix, T., Marx, I., Septier, M., Berger, C., Hacker, T., Bahadori, S., Acquaviva, E., & Massat, I. (2017). Attentional
control of emotional interference in children with ADHD and typically developing children: An emotional N-back study.
Psychiatry research, 254, 1–7.
- Marx, I., Weirich, S., Berger, C., Herpertz, S. C., Cohrs, S., Wandschneider, R., Hoppner, J., & Hassler, F. (2017). Living in
the Fast Lane: Evidence for a Global Perceptual Timing Deficit in Childhood ADHD Caused by Distinct but Partially
Overlapping Task-Dependent Cognitive Mechanisms. *Frontiers in human neuroscience*, 11, 122.
- Brueggen, K., Fiala, C., Berger, C., Ochmann, S., Babiloni, C., & Teipel, S. J. (2017). Early Changes in Alpha Band Power
and DMN BOLD Activity in Alzheimer's Disease: A Simultaneous Resting State EEG-fMRI Study. *Frontiers in aging
neuroscience*, 9, 319.
- Berger, C., Domes, G., Balschat, J., Thome, J., & Hoppner, J. (2017). Effects of prefrontal rTMS on autonomic reactions to
affective pictures. *Journal of neural transmission (Vienna, Austria 1996)*, 124, 139–152.
- Koo, P. C., Thome, J., Berger, C., Foley, P., & Hoepfner, J. (2017). Current source density analysis of resting state EEG in
depression: a review. *Journal of neural transmission (Vienna, Austria 1996)*, 124, 109–118.
- Dueck, A., Berger, C., Wunsch, K., Thome, J., Cohrs, S., Reis, O., & Haessler, F. (2017). The role of sleep problems and
circadian clock genes in attention-deficit hyperactivity disorder and mood disorders during childhood and adolescence:
an update. *Journal of neural transmission (Vienna, Austria 1996)*, 124, 127–138.

Bertsche, Astrid: Drug therapy safety in epileptology

- Gesing, J., Hoppmann, J., Gebauer, R., Pfäffle, R., Bertsche, A., & Kiess, W. (2018). Diagnosis and Clinical Course of Three Adolescents with Amiodarone-Induced Hyperthyroidism. *Pediatric cardiology*, 39, 1707–1716.
- Fisch, S. M., Neining, M. P., Prenzel, F., Bernhard, M. K., Hornemann, F., Merkenschlager, A., Kiess, W., Bertsche, T., & Bertsche, A. (2018). Experiences, expectations, and fears of adolescents with epilepsy or bronchial asthma. *European Journal of Pediatrics*, 177, 1451–1457.
- Hotopp, L., Spindler, U., Bach, V., Hornemann, F., Syrbe, S., Andreas, A., Merkenschlager, A., Kiess, W., Bernhard, M., Bertsche, T., Neining, M., & Bertsche, A. (2018). How do Parents Perceive the Initial Medical Consultation on their Child's Developmental Disorder? *Klinische Pädiatrie*, 230, 44–49.
- Schumacher, P. M., Kaune, A., Merkenschlager, A., Bernhard, M. K., Kiess, W., Neining, M. P., Bertsche, A., & Bertsche, T. (2018). Optimizing parents' performance in anticonvulsant rescue medication administration. *Epilepsy & behavior* E&B, 84, 37–43.
- Willems, L. M., Bertsche, A., Bosebeck, F., Hornemann, F., Immisch, I., Klein, K. M., Knake, S., Kunz, R., Kurlmann, G., Langenbruch, L., Moddel, G., Müller-Schluter, K., Podewils, F. von, Reif, P. S., Steinhoff, B. J., Steinig, I., Rosenow, F., Schubert-Bast, S., & Strzelczyk, A. (2018). Efficacy, Retention, and Tolerability of Brivaracetam in Patients With Epileptic Encephalopathies: A Multicenter Cohort Study From Germany. *Frontiers in neurology*, 9, 569.
- Neining, M. P., Buchholz, P., Kiess, W., Siekmeyer, M., Bertsche, A., & Bertsche, T. (2018). Incompatibilities in paediatric intensive care - pitfalls in drug information. *Die Pharmazie*, 73, 605–608.
- Nickel, P., Wolfram, C., Pfeifer-Wiegleb, D., Hornemann, F., Kiess, W., Merkenschlager, A., Andreas, A., & Bertsche, A. (2018). Herausforderungen in der psychologischen Diagnostik, Beratung und Therapie bei Kindern und Jugendlichen mit geistiger Behinderung und ihren Familien als interdisziplinärer Bestandteil innerhalb eines Sozialpädiatrischen Zentrums. *Kinder- und Jugendmedizin*, 17, 293–300.
- Bach, V. A., Neining, M. P., Spindler, U. P., Hotopp, L. C., Hornemann, F., Syrbe, S., Merkenschlager, A., Kiess, W., Bernhard, M. K., Bertsche, T., & Bertsche, A. (2018). How do parents perceive adverse drug events of their children's anticonvulsant medication? *European journal of paediatric neurology*, 22(3), 427–433.
- Dumeier, H. K., Richter, L. A., Neining, M. P., Prenzel, F., Kiess, W., Bertsche, A., & Bertsche, T. (2018). Knowledge of allergies and performance in epinephrine auto-injector use: a controlled intervention in preschool teachers. *European journal of pediatrics*, 177, 575–581.
- Bertsche, T., Neining, M., Kaune, A., Schumacher, P., Dumeier, H., Bernhard, M., Syrbe, S., Kiess, W., Merkenschlager, A., & Bertsche, A. (2018). Interdisziplinäre Konzepte von Pädiatrie und Klinischer Pharmazie zur Optimierung der Antikonvulsivatherapie. *Klinische Pädiatrie*, 230, 5–12.
- Zimmer, J., Hartl, S., Standfuß, K., Möhn, T., Bertsche, A., Frontini, R., Neining, M. P., & Bertsche, T. (2017). Handling of hazardous drugs - Effect of an innovative teaching session for nursing students. *Nurse education today*, 49, 72–78.
- Dumeier, H.K., Neining, M.P., Bernhard, M.K., Merkenschlager, A., Kiess, W., Bertsche, T., Bertsche, A. (2017). Providing teachers with education on epilepsy increased their willingness to handle acute seizures in children from 1-10 years of age. *Acta paediatr.* 106, 1811-1816.
- Hoppmann J., Gesing J., Silve C., Bertsche A., Hirsch W., Kiess W., Pfäffle R., Schuster V. (2017). Phenotypic variability in a family with Acrodysostosis Type 2 caused by a novel PDE4D mutation. *J. Clin. Res. Pediatr. Endocrinol.* 9, 360-365.
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