UNITED NEUROSCIENCE CAMPUS Lund - Rostock

CTNR Centre for Transdisciplinary Neurosciences Rostock

CTNR/UNC Winter School 2023

January 25th - 27th, 2023

Programme, Information & Abstracts

CTNR UNC WINTER SCHOOL 2023

Finding each other

Rostock & Biohotel Gut Gremmelin, Germany, on January 25th - 27th, 2023

The CTNR Winter School is a platform for getting to know each other and for networking. Senior and junior scientists from Lund and Rostock will come together to present themselves and their research as part of the newly established United Neuroscience Campus (UNC). The Winter School aims to find collaborators for future joint activities, initiatives and exciting research projects. At the Winter School the UNC, its aims, ongoing activities and future plans will be introduced.

A brain preparation course in Rostock will precedes the Gremmelin meeting to deepen neuroanatomical knowledge. At Gut Gremmelin, participants will present the current state of the art, their methods, applications and technologies. The Winter School offers networking opportunities through oral and poster presentations, discussions and scientific networking activities. The two best posters will be awarded with 500 €.

For further information and programme updates please visit our meeting website at:

https://ctnr.med.uni-rostock.de/ctnr-winter-school-2023

We are looking forward to interesting talks, fruitful discussions and an inspiring meeting.

The CTNR Board

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Rüdiger Köhling, Prof.
Physiology, University Medicine Rostock

Angela Kuhla, Prof.
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Alexander Storch, Prof.
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Kevin Peikert, MD
Neurology, University Medicine Rostock

Alexander Storch, Prof.
Neurology, University Medicine Rostock

Brain dissection Course

Wednesday, 25 January 2023 - Rostock		
	Arrival	
Neuroanatomy preparation course I - Institute of Anatomy, Gertrudenstr. 9, 18057 Rostock		
14:00 – 15:30	**Introduction and 3D anatomy**	*Markus Kipp, MD, PhD (Anatomy, Rostock)* *Thomas Freiman, MD (Neurosurgery, Rostock)*
15:30 - 18:30	**Brain dissection I**	
18:30	Dinner at Lecture Hall Anatomy	
	Overnight Stay & Breakfast in Rostock (Hotel MotelOne) for participants from Lund	

Thursday, 26 January 2023 - Rostock		
Neuroanatomy preparation course II - Institute of Anatomy, Gertrudenstr. 9, 18057 Rostock		
08:00 – 11:00	**Brain dissection II**	*Markus Kipp, MD, PhD (Anatomy, Rostock)* *Thomas Freiman, MD (Neurosurgery, Rostock)*
	Transfer to Gremmelin	

CTNR Winter School

Thursday, 26 January 2023 - Gremmelin		
Winter School - Gut Gremmelin, Am Hofsee 33, 18279 Gremmelin		
12:00 - 13:00	Arrival and Lunch	
13:00 - 13:20	Welcome & United Neuroscience Campus Lund - Rostock (UNC)	*Alexander Storch, MD (Neurology, Rostock)* *Per Odin, MD (Neurology, Lund)*
Session I		
13:20 - 13:40	**The deathly cascade of FUS-ALS**	*Andreas Hermann, MD, PhD (Translational Neurodegeneration, Rostock)*
13:40 - 14:00	**Latent factors of neuroinflammation in Alzheimer's disease – association with pathology markers and cognitive decline and challenges in replication between cohorts**	*Stefan Teipel, MD (Psychosomatic Medicine/DZNE, Rostock)*
14:00 - 14:20	**Innate immune pathways in (FUS)-ALS**	*Marcel Naumann, MD (Translational Neurodegeneration, Rostock)*
14:20 - 14:40	**TDP-43 and its impact on the blood-brain barrier in Alzheimer's Disease**	*Jessica Santiago, MD, Master student (Clinical Sciences, Lund)*
14:40 - 15:00	**Blood-brain barrier breakdown after pneumococcal meningitis**	*Irina Pöhner, PhD student (Anatomy, Rostock)*
15:00 - 15:20	**Contacts matter: VPS13 and related proteins in neurodegenerative diseases**	*Kevin Peikert, MD (Neurology, Rostock) & Dajana Großmann, PhD (Translational Neurodegeneration, Rostock)*
15:20 - 16:00	Coffee and Poster Inspection	
Session II		
16:00 - 16:20	**Mechanisms of pallidal deep brain stimulation: cortico-striatal and pallido-thalamic effects**	*Rüdiger Köhling, MD (Physiology, UMR)*
16:20 - 16:40	**Longitudinal trajectories of cognitive reserve in hypometabolic subtypes of Alzheimer's disease**	*Fedor Levin, PhD (DZNE Rostock)*
16:40 - 17:00	**The early cellular phase of Alzheimer's disease**	*Gunnar Keppler Gouras, MD (Experimental Neurology, Lund)*
17:00 - 17:20	**PROSPECT-AD: Early detection of Alzheimer's disease by screening over speech in unselected populations**	*Stefanie Köhler, PhD student (DZNE Rostock)*
17:20 - 17:40	**Biological subtypes of Lewy body disease**	*Julia Schumacher, PhD (DZNE Rostock)*
17:40 - 18:00	**The curvature quantification of Wave I in auditory brainstem responses detects cochlear synaptopathy in the elderly**	*Lichun Zhang, MD (Otorhinolaryngology, Head and Neck Surgery, Rostock)*
18:00 - 18:20	**Characterisation of functional deficits induced by AAV overexpression of alpha-synuclein in rats**	*Andreas Heuer, PhD (Behavioural Neuroscience, Lund)*
18:20 - 19:30	Scientific Networking and Poster Inspection	
19:30	Dinner	

CTNR Winter School

Friday, 27 January 2023 - Gremmelin		
07:00 - 09:00	Breakfast	
Session III and Poster Award		
09:00 - 09:20	**Combining quantitative and qualitative research to assess the effectiveness of a digitally supported care management intervention for family caregivers of people with dementia: Results of the GAIN study**	*Ingo Kilimann, MD (DZNE Rostock)* *Olga Klein, PhD (DZNE Rostock)*
09:20 - 09:40	**Validation of the PD Home Diary for Assessment of Motor Fluctuations in Advanced Parkinson's Disease**	*Matthias Löhle, MD (Neurology, Rostock)*
09:40 - 10:00	**Reliable methods to evaluate both motor fluctuations and non-motor fluctuations among Parkinson disease (PD) patients**	*Carin Janz, PhD student (Neurology, Lund)*
10:00 - 10:20	**Healthcare 3.0: How to transform machine learning prototypes into functional healthcare applications for diagnostic assistance?**	*Martin Dyrba, PhD (DZNE Rostock)*
10:20 - 11:00	Coffee and Poster Inspection	
11:00 - 11:20	**Harmonizing cognitive assessment in memory clinics**	*Marina Boccardi, PhD (DZNE Rostock)*
11:20 - 11:40	**Developing an advisory board with hard-to-reach patients and caregivers: early insights from the PART(icipatory) project**	*Marcel Daum, PhD student (Psychosomatic Medicine, Rostock)* *Olga Klein, PhD (DZNE Rostock)*
11:40 - 12:00	**The effect of pump-based Parkinson treatment on non-motor symptoms**	*Per Odin, MD (Neurology, Lund)*
12:00 - 13:00	Poster Award	
13:00 - 14:00	Lunch	
	Farewell and Transfer	
UNC Board Meeting (for Board members only)		
14:00 - 15:00	UNC Board Meeting	
15:00	Coffee and farewell	

Locations and Travel

Rostock

The old Hanseatic city, which was established in the 13th century, is located at the coast of the Baltic Sea in the north-eastern German state Mecklenburg-West Pomerania. Due to the states low population density there is lots of space for wildlife and biological reserves around the city. Maritime life and maritime attractions have also shaped our city and are on show along the Warnow: from the city port to the river mouth into the Baltic – “Warnemünde”.

Founded in 1419, the University of Rostock is the oldest in the Baltic Sea Region. True to the motto “Traditio et Innovatio”, the University of Rostock has constantly further developed. In contrast to some other German universities founded in the 15th century, Rostock had a medical faculty right from the start.

Travel options to Rostock

Car & Ferry: Lund - Øresund Bridge - Gedser - Rostock:

Combination tickets https://www.scandlines.com/prices/

Train & Ferry: Lund - Trelleborg - Rostock:

Train: Lund - Trelleborg → Ferry: Trelleborg - Rostock (Stena Line, TT-Line)

Flight: Lund - Copenhagen - Hamburg - Rostock:

Airport Hamburg → Train Schedules and Tickets (Deutsche Bahn)

Institute of Anatomy

Gertrudenstraße 9
18057 Rostock

The Institute of Anatomy is close to the City Centre. From Rostock main train station to Gertrudenstraße you can take Tram 6 or Tram 5. Tram schedules and tickets (RSAG)

Information

Hotel Motel One Rostock

Motel One Rostock
Schröderplatz 2
18057 Rostock
Tel.: +49 381 666919-0
Website: https://www.motel-one.com/de/hotels/rostock/hotel-rostock/

A room is reserved for participants from Lund attending the brain dissection course from 25th - 26th January 2023. Check in is possible from 3 pm, check out until 12 noon. Breakfast is included from 6 - 10 am.

Gut Gremmelin (approx. 40 minutes from Rostock by car)

Gremmelin, a village of 150 people, is located on the edge of the Mecklenburger Seenplatte and in the triangle between Hamburg, Berlin and Rostock.

Am Hofsee 33
18279 Gremmelin

https://www.gutgremmelin.de/

- Equipment: TV, telephone, shower room with care products, hairdryer, 1 bottle of free mineral water in the room
- Rooms are available from 3 pm on the day of arrival until 10 am on the day of departure

Arrival by car: Via the A 20 and A 19 as well as the A 24 and A 19. Please take the motorway exit No. 13 "Güstrow-Süd / Teterow" from the A 19. Then please turn left towards Teterow. After approx. 200 m turn left towards Reinshagen. Follow the main road to Gremmelin. At the end of the main street, please turn right onto the cobblestone street. The Gremmelin estate is then on the left. The parking spaces at the hotel are free of charge. **Arrival by train:** To the Güstrow train station, transfer by car/taxi.

Free parking spaces are available around the location area.

General information

Neuroanatomy dissection course

- The language of the course is English.
- For Winter School participants, the CTNR takes over the participation fees.
- Participation in the course is not mandatory for participation in the Winter School.

Oral/Poster presentations

- Participants can prepare a scientific poster (A0). Poster walls will be available on site.
- Participants can present their projects (preferably with potential for cooperation) with talks *(15 minutes + 5 Minutes discussion).*
- The language for the oral and poster presentation is English.

Poster Award

- The UNC Board will vote for the two best posters at the end of the Winter School.
- The winners receive prize money of € 500 for supporting the project presented.

Payment

- All participants from Rostock pay their travel and accommodation costs (Gut Gremmelin: 94€/night incl. breakfast) via "Dienstreiseantrag".
- All participants from Lund pay their travel costs. Accommodation costs will be paid by the CTNR.
- For all Winter School participants (from Lund and Rostock), the CTNR takes over the costs for the participation fees of the neuroanatomy dissection course, location rent, planned meals/beverages and planned social events.

Corona

- The Winter School takes place subject to the then current applicable regulations concerning the coronavirus pandemic.

Organisation and Contact

Virginia Bolowski
Scientific Coordinator

Hannah Güthlein
Student Assistant

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Abstracts - Talks & Posters

Welcome & Session I

Thursday, 26 January 2023, 13:00 - 15:20

United Neuroscience Campus Lund - Rostock (UNC)

Alexander Storch[1,2,3,4] Per Odin[5,6,7,8]

1. Department of Neurology, University Medical Centre Rostock, University of Rostock, Rostock, Germany
2. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Rostock, Germany
3. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany
4. United Neuroscience Campus Lund-Rostock (UNC), Rostock site, Germany
5. Department of Clinical Sciences, Division of Neurology, Faculty of Medicine at Lund University, Lund, Sweden
6. Department of Neurology, Skåne University Hospital, Lund, Sweden
7. Multidisciplinary research focused on Parkinson´s disease (MultiPark), Lund University, Lund, Sweden
8. United Neuroscience Campus Lund-Rostock (UNC), Lund site, Sweden

The United Neuroscience Campus Lund - Rostock (UNC) was founded on the basis of a formal cooperation (Memorandum of Understanding) between the Centre for Transdisciplinary Neurosciences Rostock (CTNR) of the University Medical Centre Rostock at the University of Rostock and the Strategic Research Area "Multidisciplinary research focused on Parkinson's disease" (MultiPark) at the Lund University.

The idea is the institutional networking of two internationally excellent neuroscientific locations with a large translational focus in order to establish a virtual campus beyond the Lund and Rostock locations on key neuroscience topics. The overall goal is to increase the scientific excellence through formal international cooperation beyond borders and standards, bilateral mobility and teaching programs for staff and young scientists, innovative collaborative projects and the use of novel synergy effects.

The overarching strategic goals of the UNC are the promotion of young researchers, internationalization, increasing the visibility of the community, stimulating international collaborative research projects and publications. The added values of the UNC, which strongly demands and promotes international relations, lies in the increase of critical mass for new interdisciplinary and innovative collaborative proposals to create better starting conditions for national highly competitive procedures, increased number of host institutions for research stays of young scientists, promotion of opportunities for scientific and staff mobility, additional range of modules in the qualification, training and continuing education programmes of the respective locations.

Scientific relationships already exist between partners on both sides, e.g. in neurology and clinical memory research. The future cooperation in the United Neuroscience Campus has already been mutually declared.

The United Neuroscience Campus is organisationally managed by an international UNC Board consisting of representatives of the respective collaborations and is supported and administered by UNC Coordinators. The leadership is provided alternately from both locations by election. UNC bylaws serve as the formal basis of the UNC Board and Members Assembly.

The deathly cascade of FUS-ALS

Barbara Szewczyk[1], Marcel Naumann[1], Hannes Glass[1], Dajana Grossmann[1] & Andreas Hermann[1,2,3]

1. Translational Neurodegeneration Section „Albrecht-Kossel“, Department of Neurology, University Medical Centre Rostock, University of Rostock, Rostock, Germany
2. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Rostock, Germany
3. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany

FUS (Fused in sarcoma) is an RNA-binding protein (RBP) that resides predominantly in the nucleus and is involved in various cellular processes such as RNA processing and transport. FUS shuttling between the nucleus and cytoplasm is essential for normal cell function. In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), this shuttling is disrupted along with associated processes. The two C-terminal domains of FUS, the proline tyrosine (PY)-NLS and the RGG-rich domain interact with the nuclear import receptor Transportin 1 (TNPO1), disease causing mutations in these regions show cytoplasmic localization and aggregation of FUS, leading to degeneration of neurons.

Using motor neurons derived from human induced pluripotent stem cells (hiPSCs) we showed that impairment of the PARP-dependent DNA damage response due to mutations in FUS NLS leads to additional cytoplasmic FUS mislocalization, cytoplasmic aggregations, axonal and finally neurodegeneration, and, confirmed that mutant FUS recruits nuclear DDX17 to cytoplasmic granules and affects the DDR. We further showed that proteins involved in the conserved stress response pathways, particularly integrated stress response and heat shock response such as Atf4 and Hsp70, are upregulated in mutant FUS motor neurons by which pathophysiology can be kept in bay in early stages but collapse upon additional stress. We finally identified novel targets for transnosological treatment approaches highlighting mitochondrial membrane integrity as putative overarching individualized treatment approach.

Funding: A.H. is supported by the Hermann und Lilly Schilling-Stiftung für medizinische Forschungs im Stifterverband.

Latent factors of neuroinflammation in Alzheimer's disease – association with pathology markers and cognitive decline and challenges in replication between cohorts

Stefan J. Teipel[1,2,3] Martin Dyrba[1], Luca Kleineidam[4,5], Frederic Brosseron[4,5], Fedor Levin[1], Frank Jessen[4,6,7], Michael T. Heneka[4,5]

1. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Rostock, Germany
2. Department of Psychosomatic Medicine, University Medical Centre Rostock, University of Rostock, Rostock, Germany
3. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany
4. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn, Germany
5. University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/Psychiatry, Bonn, Germany
6. Department of Psychiatry, University of Cologne, Cologne, Germany
7. Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

Background and Objectives: Replication of one's findings is a key requirement for relevant clinical research in dementia. Here, we studied different components of inflammation constructed as latent factors from a set of single markers. The purpose of this study was to investigate the association of different inflammatory mechanisms with markers of Alzheimer's disease (AD) pathology and rates of cognitive decline in the AD spectrum. Employing Bayesian analysis and a replication cohort we directly quantified evidence in favor or against an effect and determined if effects were replicable across cohorts

Methods: We studied 296 cases from the DELCODE cohort, including people with subjective cognitive decline, mild cognitive impairment (MCI), AD dementia, first degree relatives and healthy controls, and a replication cohort of 276 cases of the ADNI study, including MCI, AD dementia and healthy control participants. Using Bayesian confirmatory factor analysis, we constructed latent factors for synaptic integrity, microglia, cerebrovascular endothelial function, chemokine, and complement components of the inflammatory response using a set of inflammatory markers measured in CSF. We used generalized linear mixed effect models in a Bayesian framework to determine associations of inflammation factors with levels of Aβ42 and phospho-tau in CSF and with rates of change in global cognition, memory and executive function.

Results: We found very strong to extreme evidence for an association of synaptic integrity, microglia response, and cerebrovascular endothelial function with CSF phospho-tau and Aβ42 levels with Bayes factors in favor of an effect (BF10) > 50. In addition, we found moderate to strong evidence for an effect of synaptic integrity, microglia response, and cerebrovascular endothelial function with rates of cognitive decline even (BF10 > 3) after controlling for the effects of Aβ42 and phospho-tau levels. We found robust evidence against an association of complement and chemokine factors with AD pathology.

Discussion: Synaptic integrity, microglia activation, and cerebrovascular endothelial function were strongly related to AD pathology and contributed to cognitive decline beyond Aβ42 and phospho-tau pathology. Bayesian analysis can help estimating replicability of findings. However, replication of findings was limited by lack of prospective harmonization of protocols across cohorts. This is an important concern for future joint clinical research activities.

Innate immune pathways in (FUS)-ALS

Marcel Naumann[1], Helene Block[1], Andreas Hermann[1,2,3]

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3. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany

Background: Amyotrophic lateral sclerosis (ALS) is a devastating neurological disease leading to death within 3-5 years. Mutations in Fused in Sarcoma (FUS) were shown to be causative in up to 5% of genetic ALS cases, which has been shown to result in motoneuron demise. However, the critical mechanisms of which remain elusive. Recently, we and others demonstrated a pivotal involvement of impaired DNA damage response (DDR) mechanisms due to mutations in FUS, which makes abundant DNA damage a characteristic of the pathology of FUS-ALS. Furthermore, in years past a growing body of evidence implied a role for innate immunity pathways in neurodegeneration. Specifically, the cGAS-STING (stimulator of interferon genes) pathway, which gets activated by sensing of cytosolic DNA and stimulates an Interferon 1 response, was shown to be upregulated in other genetic forms of ALS. On the other hand, RIG1 (retinoic acid-inducible gene 1) which is another mediator of innate immune mechanisms in response to dsRNA occurrence was also implicated in post-mortem ALS pathology. Thus, manipulation of innate immune pathways poses a new target for therapeutic intervention in ALS.

Aims: To investigate the activation of innate response mechanisms like the cGAS-STING pathway in cell models of FUS-ALS and their impact on the cellular integrity.

Methods: Human induced pluripotent stem cell (hiPSC) derived neurons and patient blood cells (PBMC) were analysed for increased Interferon signatures by qPCR. The activation of the cGAS-STING and RIG1 pathways was analysed by a battery of phosphorylated markers downstream of STING activation including TBK1 and IRF3 by western blotting. Patient specific motoneurons and fibroblasts will be analysed for signs of increased cytosolic DNA by live cell imaging and immune fluorescence.

Results: Increased interferon signatures in PBMCs were detected in 1 of 9 sporadic ALS and 3 of 5 FUS-ALS patients. Similarly, increased interferon signatures were observed in multiple FUS-ALS patient derived spinal motoneuron cell lines compared with controls. In line with that, we saw enhanced phosphorylation of TBK1 and RIG1 in these FUS mutant neurons. Taken together, this suggests an activation of innate immune pathways on the mRNA and protein level in FUS mutant human spinal motoneurons. Interestingly, H151, an established pharmacological inhibitor of STING, did not alleviate this effect. However, inhibition of the DNA-proteinkinase (DNA-PK) partially reversed the increased interferon signature. Currently, the live-cell-imaging and immune fluorescence of cytosolic DNA are established to quantify the rate of self-DNA leaking from the nucleus or from mitochondria in neurons and fibroblasts.

Conclusion: This work suggests a mechanism downstream of the previously published increased DNA damage in FUS-ALS. First evidence for a role of upregulated innate immune pathways could be identified. If this negatively impacts on the neuro-axonal survival needs yet to be investigated.

TDP-43 and its impact on the blood-brain barrier in Alzheimer's Disease

Jessica Santiago[1], Cristina Nuñez-Diaz[1], Dovilė Pocevičiūtė[1], Shorena Janelidze[1], The Netherlands Brain Bank[2], Oskar Hansson[3], Malin Wennström[1]

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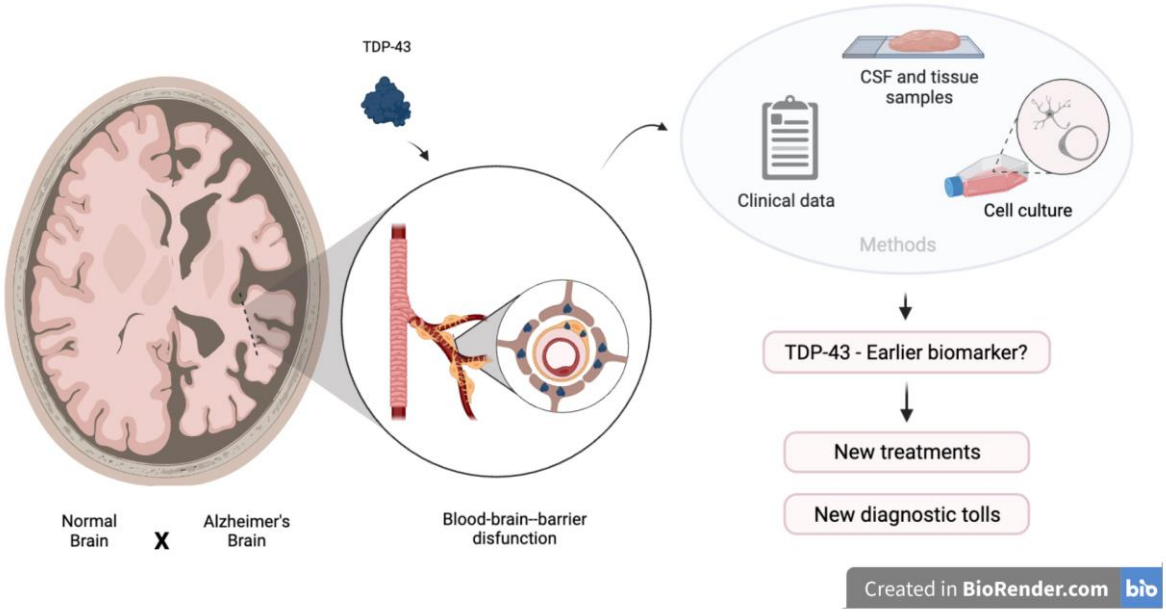
2. Netherlands Institute for Neuroscience, Meibergdreef 47, 1105, BA, Amsterdam, The Netherlands
3. Memory Clinic, Skåne University Hospital, Malmö, Sweden

Talks

Alzheimer's disease (AD) causes progressive memory loss and deterioration of cognitive functions, eventually leading to the inability to perform daily activities without assistance. The disorder affects about 1 in 10 people over 65 years and represents a burden for individuals, families, and society. Nonetheless, AD's mechanisms remain unclear, and no cure or effective treatment to prevent the disease progression is available today.

AD is characterized by the progressive aggregation and deposition of different proteins in the brain, and about 57% of the patients have inclusions of a protein called TAR DNA binding protein 43 (TDP-43) in their hippocampus. Those patients have earlier cognitive impairment and demonstrate a more aggressive course of the disease. Most patients with AD also display impaired blood-brain barrier (BBB) function, and previous studies have demonstrated the deposition of TDP-43 in BBB cells. However, the impact of TDP-43 on the BBB function and how this relates to AD development and progression it is still unclear.

To elucidate this question, we are using postmortem brain tissue to analyse the association of BBB dysfunction with the presence and localization of TDP-43 in pericytes and astrocytes. We are also investigating the correlation of TDP-43 in the cerebral spinal fluid with biomarkers in the blood plasma and with clinical data. Preliminary results showed that pTDP-43 was significantly higher in AD patients than in controls and that the pTDP-43 levels correlated with both mini-mental state examination scores and Qalbumin.



Blood-brain barrier breakdown after pneumococcal meningitis

Irina Pöhner[1], Johannes Deutloff[1], Robin Piecha[1], Markus Kipp[1,2], Lars Ove Brandenburg[1,2]

1. Institute for Anatomy, University Medical Centre Rostock, University of Rostock, Rostock, Germany
2. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany

Background: The Gram-positive bacterium Streptococcus pneumoniae is one of the major cause of bacterial meningitis and leads to high morbidity and mortality worldwide; neither the underlying mechanism of migration in the central nervous system (CNS) during infection nor the effects on the blood-brain barrier (BBB) are well understood. In our study, we investigated the time course of BBB breakdown and the following local inflammatory response in bacterial meningitis in the context of members of the innate immune response like pattern recognition receptors (PRR).

Method: A murine model of pneumococcal meningitis by intracranial injection of S. pneumoniae is applied to determine the course of infection and disruption of the BBB. To analyse a possible correlation we performed (immune-) histochemical analysis and FITC-dextran extravasation. In addition, we used murine primary endothelial cells to examine the cellular effect on the BBB in vitro. After treatment with bacterial virulence factors, the effect on the cells was analysed using the endothelial marker Claudin-5 for protein immunoblotting, flow cytometry and fluorescence staining.

Result: Pneumococcal intracranial inoculation caused distinctive symptomatic meningitis in mice within 48 h. The permeability of the BBB increased 30 h post-infection as analyzed by fluorescence detection of FITC labeled dextran. Concurrently, the number of immune cells per mm² within the brain, such as neutrophils and microglia, was increased, indicating a direct correlation. Furthermore, evidence was found for neutrophil-associated phagocytosis. In vitro, detection of Claudin-5 revealed a loss of integrity and morphologic changes of the cells after treatment.

Conclusion: The study clarifies the exact course of pneumococcal infection, the degradation of the BBB, and the invasion of the CNS by the bacteria and immune cells. Our results suggest that formyl peptide receptors, as important representatives of the PRR, play an important role in the maintenance of the BBB and the migration of immune cells into the CNS. In further experiments we would like to investigate the exact influence of the receptors on the interactions between the cells of the CNS and the infecting bacteria.

Contacts matter: VPS13 and related proteins in neurodegenerative diseases

Dajana Grossmann[1] & Kevin Peikert[1,2,3]

1. Translational Neurodegeneration Section „Albrecht-Kossel“, Department of Neurology, University Medical Centre Rostock, University of Rostock, Rostock, Germany
2. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany
3. United Neuroscience Campus Lund-Rostock (UNC), Rostock site, Germany

Only recently, location and function of the members of a hitherto little-known protein family (VPS13 A through D) were unravelled. Located at contact sites of membranes of different organelles (MCS: membrane contact sites), the VPS13 proteins act as conduits for non-vesicular bulk lipid transfer. The corresponding human genes are of considerable interest as mutations in each one of them lead to hereditary neurological disease, such as chorea-acanthocytosis (VPS13A disease), Cohen syndrome (VPS13B disease), familial parkinsonism with Lewy bodies (VPS13C disease) or various ataxic conditions (SCAR4/SCA24/SCASI, now VPS13D disease).

We aim to highlight impaired MCS function and bulk lipid transfer between organelles (via MCS) as a new pathomechanism shared by various neurodegenerative and neurodevelopmental disorders.

MCS play an important role in the function and maintenance of several organelles, including, but not limited to mitochondria, the ER, or peroxisomes. MCS facilitate the exchange of metabolites, ions, proteins or lipids. Furthermore, studies in recent years have shown that certain disease-related proteins are involved in the formation and regulation of MCS. However, it is largely unknown how dysregulation of MCS contribute to the death of neurons and thus to neurodegeneration.

We use patient-derived cellular models harbouring mutations in different proteins that play a role in MCS, e.g., VPS13A, VPS13D and its interaction partner MIRO1, in order to study the effects on mitochondrial function, calcium homeostasis and lipid dynamics. To this end, we label specific types of MCS, organelles and lipids with fluorescent probes for subsequent live cell super resolution imaging. This method allows us to investigate the abundance of specific types of MCS, as well as the effect of MCS-related phenotypes in the context of neurodegeneration.

Funding: Nachwuchsförderung 2021 der Deutschen Gesellschaft für Parkinson und Bewegungsstörungen e.V.: LipiSYN: Untersuchung des Zusammenhangs zwischen Störungen der Membranlipiddynamik und der α-Synuclein-Proteostase. K.P. is supported by the Rostock Academy of Science (RAS).

Session II

Thursday, 26 January 2023, 16:00 – 18:20

Mechanisms of pallidal deep brain stimulation: cortico-striatal and pallido-thalamic effects

Heerdegen M[1], Franz D[1], Santana-Kagelund F[1], Richter A[1], Köhling R[1,2,3]

1. Oscar-Langendorff-Institute of Physiology, University Medical Centre Rostock, University of Rostock, Rostock, Germany
2. Centre for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Centre Rostock, University of Rostock, Rostock, Germany
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Pallidal deep brain stimulation (DBS) is an important option for patients with severe dystonias, which are thought to arise from a disturbance in striatal control of the globus pallidus internus (GPi). The mechanisms of GPi-DBS are far from understood. Although disturbances of striatal, but also thalamic functions are thought to play a role in dystonia, the effects of DBS on these are unknown.

We hypothesised that DBS, via axonal backfiring, or indirectly via thalamic and cortical coupling, alters striatal and thalamic. We tested this hypothesis in the dt^{sz} hamster, an animal model of inherited generalised, paroxysmal dystonia. Hamsters (dystonic and non-dystonic controls) were bilaterally implanted with stimulation electrodes in the GPi. DBS (130 Hz), and sham DBS, were performed in unanaesthetised animals for 3 h or 11 d. Synaptic field potentials (standard and MEA recordings), miniature excitatory postsynaptic currents (mEPSC) and firing properties of neurones were recorded in brain slice preparations obtained immediately after EPN-DBS.

The main findings were as follows: a. short-term DBS increased cortico-striatal evoked responses in healthy, but not in dystonic tissue. b. Commensurate with this, short-term DBS increased inhibitory control of these evoked responses in dystonic, and decreased inhibitory control in healthy tissue. c. Further, short-term DBS reduced striatal mEPSC frequency strongly in dystonic, and less prominently in healthy tissue, showing that also a modulation of presynaptic mechanisms is likely involved. d. long-term DBS, conversely, reduced IPSC frequency in thalamic neurons. e. Lastly, while cellular properties of medium-spiny neurones remained unchanged, the dynamic frequency range of firing in thalamic neurons was increased. e. We conclude that DBS leads to dampening of cortico-striatal communication and restores intrastriatal inhibitory tone, while in the thalamus, inhibitory tone is reduced and the dynamic range of thalamic responses is increased.

Longitudinal trajectories of cognitive reserve in hypometabolic subtypes of Alzheimer's disease

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Background: Previous studies have demonstrated individual resilience to AD-related neuropathology in form of cognitive reserve (CR). In the present study, we characterized differences in cross-sectional and longitudinal estimates of CR between previously identified hypometabolic subtypes of AD-related neurodegeneration.

Methods: We analysed MRI, FDG-PET and cognitive performance data from 59 Aβ-positive cognitively normal (CN), 221 prodromal Alzheimer's disease (AD) and 174 AD dementia participants studied within the Alzheimer's Disease Neuroimaging Initiative (ADNI) from ADNI-1 and ADNI-GO/2 phases, as well as data from 11 Aβ-positive CN, 94 prodromal AD and 43 AD dementia participants from ADNI-3. Participants were classified into the previously identified typical and limbic-predominant hypometabolic subtypes. Cognitive reserve was calculated at baseline and follow-up using a residual approach based on an individual patients' deviance (in W-scores) from the relationship between cognitive performance and AD-typical gray matter atrophy in temporoparietal regions. We evaluated the effects of W-scores on the risk of clinical progression and longitudinal cognitive decline and compared these between the two hypometabolic subtypes.

Results: In line with the CR concept, higher W-scores were associated with a lower risk of prodromal AD participants for progressing to AD dementia and with a slower executive function decline for a combined group of Aβ-positive CN and prodromal AD participants. The protective effect of CR was more pronounced in the typical subtype. The typical and the limbic-predominant subtypes demonstrated similar CR at baseline, but the typical subtype demonstrated faster longitudinal decline of CR in the combined Aβ-positive CN and prodromal AD groups.

Conclusions: Consistent with previous research, CR as assessed by W-scores was predictive of a lower risk of clinical progression and slower cognitive decline. We observed subtype-specific CR effects on cognitive decline as well as different longitudinal CR trajectories. These findings underline the importance of accounting for longitudinal change in CR and may have implications for future research into individual differences in the resilience to AD-related neuropathological changes.

The early cellular phase of Alzheimer's disease

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Alzheimer's disease (AD) has classically been viewed as resulting from the aberrant accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles. However, more soluble forms of amyloid-β (Aβ) are altered 1 to 2 decades before onset off AD symptoms and amyloid plaques are poor correlates of AD progression. The recent clinical benefit, albeit modest, of Lecanemab immunotherapy targeting Aβ oligomers further supports the importance of pre-plaque forms of Aβ. Over the years our group has focused on the pre-plaque alterations that occur in human AD and mouse models of AD. Different cell types and circuits are altered in the brain prior to plaques, some of which can be modeled also in primary brain culture models. Aging leads to early aberrant Aβ accumulation in endosomes, in particular near synapses, in selective brain circuits early with AD pathogenesis. This early Aβ accumulation leads to aberrant tau biology in such neurons, with tau aggregation seen most prominently in selective neuron cell bodies (e.g. entorhinal cortex layer 2) while Aβ aggregates develop at their terminal fields. These subcellular alterations also provide insights into the anatomical separation of plaque and tangle pathologies. Selective synapses are the earliest site of noticeable AD alterations and synapses are also importantly modulated by their complex cellular environment in the brain (astrocytes, microglia, blood vessels, etc.). We hypothesize that such subcellular dissection of the early AD disease process can provide new insights for more effective AD therapy.

PROSPECT-AD: Early detection of Alzheimer's disease by screening over speech in unselected populations

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Background: Early detection of Alzheimer's disease (AD) is essential for medical treatment and tertiary prevention. Impairment of speech is an early indicator for the development of AD. Consequently, the detection and classification of changes in speech and language are promising as digital biomarker for early detection in AD. We designed an easy-access screening tool for people at risk combining automatic data collection via telephone and evaluation of speech data using advanced machine learning modelling. PROSPECT-AD aims to validate and establish this speech biomarker tool to identify early signs of AD.

Methods: The PROSPECT-AD study investigates speech data from telephone calls of well-phenotyped cohorts in Europe (Germany, Sweden, Spain, UK). In Germany, participants of the DELCODE- and DESCRIBE-cohorts of the DZNE are being recruited. These cohorts collect long-term follow-up data of cognitive function (neuropsychological assessments), genetic and environmental risk factors, and biomarkers (CSF, imaging) from healthy adults and people with mild cognitive impairment (MCI) or subjective cognitive decline (SCD). In PROSPECT-AD, the browser-based chatbot "Mili" calls study participants by telephone and collects speech data in a standardized fashion. The study aims at 150 healthy adults and 150 people with MCI or SCD older than 49 years, CDR ≤ 0.5. Mili calls the participants a total of six times every three months and asks them to complete different cognitive tasks such as learning word lists and telling a story. An AI-based self-learning algorithm analyses the speech records in respect to memory function (word list), executive functions (verbal fluency), and psychological and behavioural symptoms (spontaneous free speech). These features will be compared with longitudinal clinical, cognitive, and biomarker data from DELCODE and DESCRIBE. Furthermore, we use semistructured interviews as well as the system usability scale to examine the perceived usability of Mili and participants' acceptance and attitude towards artificial intelligence in medicine.

Results: Until September 2022, we have included 19 of 300 participants (Agemean=72.74 years (range 56-87 years), 8 men) in our study. Seven participants completed at least the first assessment successfully. Further six assessments are scheduled and six are in preparation. At the beginning, two of the participants struggled with Mili at the word list task. We solved the problem by setting a time limit to the word list task. During the first two usability interviews, people described Mili as clear, unambiguous, and well understandable. Both interviewees saw AI as a support for healthcare professionals and scientists but not as substitute for human decision making and consultation. During the first two interviews, people described Mili as clear, unambiguous, and well understandable. Both interviewees saw AI as support for healthcare professionals and scientists but not as substitute for human decision making and consultation.

Conclusion: We found the chatbot for screening people in preclinical and prodromal stages of AD feasible and well accepted by the users. The ongoing study will tell us if such speech based biomarker can usefully be employed to predict longitudinal cognitive decline and AD biomarker status. Of note, participants see such technology not as a replacement but as a support of human interaction regarding medical decisions, consultations, and treatments.

Biological subtypes of Lewy body disease

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Lewy body disease (LBD) is characterised by large heterogeneity across patients. Most research to date has focused on studying group average differences (e.g. between patients and cognitively unimpaired controls or between two patient groups), thereby implicitly assuming within-group homogeneity. This may have slowed our understanding of pathophysiological mechanisms and impacted outcomes of clinical trials. A shift towards a more individualised approach is therefore needed in LBD research.

Several neurotransmitter systems have been implicated in the pathophysiology of LBD with dopaminergic and cholinergic systems being the most widely studied to date. There is also evidence for an involvement of the serotonergic and noradrenergic systems, but these have been less widely studied in vivo.

The overall hypothesis underlying the proposed project is that the relative involvement/breakdown of different neurotransmitter systems in individual patients may explain some of the heterogeneity across patients in terms of their clinical presentation, disease progression, presence of Alzheimer's disease (AD) co-pathology, and treatment response.

In the first part of the project, we aim to estimate imaging markers that can serve as proxy measures for the integrity of different neurotransmitter systems. For the cholinergic system, structural MRI data will be used in conjunction with a cytoarchitectonic map of the cholinergic basal forebrain to assess the volume of the nucleus basalis of Meynert, the main source of cholinergic input to the cortex. In addition, acetylcholinesterase sensitive PET data may be used to characterize the functional integrity of the cholinergic system. Furthermore, diffusion-weighted imaging data will be used to assess the integrity of the brainstem pedunculopontine nucleus which provides the main source of cholinergic input to the thalamus. For the dopaminergic and serotonergic systems, FP-CIT SPECT data will be used. While FP-CIT primarily binds to dopamine transporters (DAT) in the striatum, its binding in extrastriate areas reflects serotonin transporter (SERT) availability. FP-CIT binding in DAT-rich areas (caudate nucleus, putamen, and nucleus accumbens) will therefore be used as a measure of dopaminergic system integrity while FP-CIT binding in SERT-rich areas (Raphe nucleus, amygdala, hippocampus, and thalamus) will be used to assess the serotonergic system.

In the second part, these different measures will be combined to identify biological subtypes in LBD patients. To this end, the Subtype and Stage Inference (SuStaIn) algorithm will be applied which can uncover disease phenotypes in a data-driven manner. The SuStaIn algorithm combines aspects from cluster analysis and disease progression modelling to not only uncover different disease subtypes, but also characterise their temporal progression trajectories, using cross-sectional data. It thereby allows to probabilistically assign every individual to a subtype and an associated disease stage.

Finally, the different subtypes will be investigated and compared with respect to their clinical characteristics (absence/presence of the core Lewy body symptoms, symptom severity), presence and severity of AD co-pathology (using CSF biomarkers), and disease progression in patients with longitudinal follow-up data.

The curvature quantification of Wave I in auditory brainstem responses detects cochlear synaptopathy in the elderly

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Age-related hearing loss is the most common sensory disorder in the elderly. During the early-stage elderly listeners oft complain of degraded speech perception in adverse listening environment. Animal studies suggested that a cochlear synaptopathy might be one of the main mechanisms. A decreased Wave I amplitude in supra-threshold auditory brainstem response (ABR) could diagnose this pathology non-invasively. However, the interpretation of the Wave I amplitude in humans is controversial. Recent work has established a robust and reliable mathematic algorithm, i.e. curve curvature quantification, in mice with promising results. The current study aimed to determine whether the curve curvature has also sufficient test-retest reliability to detect cochlear synaptopathy in aging human. Twenty-nine subjects with normal hearing were included into this study. All of them accepted an extended pure tone audiogram examination ranged from 0,125 to 16 kHz and an ABR with a stimulus of 80 db nHL click. The amplitude, curvature at the peak and the area under the curve (AUC) of Wave I were calculated and analysed. The Pearson correlation analyses clearly demonstrated a significant negative correlation between age and curvature (R= -0,33, p= 0,015), as well as between curvature and high-frequency thresholds (R= -0,36, p= 0,009). Additionally, there is also a negative correlation between the high-frequencies thresholds and AUC of the Wave I (R= -0,32, p= 0,02). Thus, these results suggest that curvature quantification and AUC of Wave I can be reliably used to diagnose a cochlear synapthopathy in aging human. It may be applied in the daily routine to diagnose early degenerations of the auditory nerve.

Characterisation of functional deficits induced by AAV overexpression of alpha-synuclein in rats

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Background:

In the last decades different preclinical animal models of Parkinson's disease (PD) have been generated, aiming to mimic the progressive neuronal loss of midbrain dopaminergic (DA) cells, relevant behavioural impairments in motor and non-motor domains as well as histopathological changes that resemble the pathology seen in human PD patients.

Objectives:

The goal with this work was to characterize the impairment in motor and non-motor domains following nigrostriatal overexpression of h-aSYN and correlate the behavioural deficits with histological assessment of associated pathology.

Methods:

In a series of experiments, we characterised the sequelae of AAV vector-based overexpression of human alpha-synuclein in the midbrain of rats. The animals were assessed on a series of simple and complex behavioural tasks probing motor and non-motor domains. Post-mortem neuropathology was analysed using immunohistochemical methods.

Results: Overexpression of h-aSYN led to progressive degeneration of DA neurons of the SN and axonal terminals in the striatum (STR). We observed extensive nigral and striatal pathology, resembling that of human PD patients as well as the development of stable progressive deficit in simple motor tasks, as well as in the non-motor domains such as deficits in motivation and lateralized neglect.

Session III

Friday, 27 January 2023, 09:00 – 12:00

Combining quantitative and qualitative research to assess the effectiveness of a digitally supported care management intervention for family caregivers of people with dementia: Results of the GAIN study

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Background: A dementia diagnosis has an effect on an entire family who often takes on carer responsibilities. Digitally supported complex interventions to minimise carer strain and burden of family caregivers have the potential to be time-efficient and ensure prompt service provision. To evaluate these, mixing methods provides a beyond the scale understanding of effects and hurdles of an intervention and ensure that study findings are grounded in participants' experiences. In this cluster randomised controlled trial (cRCT, GAIN study), our aim was to test the effectiveness of a digitally supported care management intervention to reduce unmet needs and improve quality of life of dementia family caregivers.

Methods: As part of the cRCT we embedded qualitative components within the design to collect further data regarding the acceptance and effectiveness of the cRCT. The digital system comprised a tablet with an unmet needs assessment as well as a care management monitoring system for study nurses. In the cRCT, primary outcomes were the number of unmet needs after intervention and the quality of live using the EQ-5D. For the quantitative analysis, we applied a generalized linear mixed effects model with random effect intercept using the library "lmer" in R. With respect to the acceptance of the digital, tablet-based system, we conducted telephone interviews with caregivers, general practitioners (GPs), practice staff, and study nurses and the data analysed thematically using MAXQDA. All four groups were in contact or used the system for either the unmet needs assessment or the dementia care management intervention.

Results: In cooperation with 24 General practitioners (GPs) and 6 memory clinics, we recruited 192 participants into the trial who were evenly split into intervention (n=96) and control group (n=96). The mean age was 65 years (SD=12.1) and 75% were women. More than half (58%) were the caregiver for their spouse (53%) or partner (5%), 33% for their mother or father, 2% for their mother/father-in-law, and 6,5% for a relative (6%) or acquaintance (0.5%). On average, the system identified 8,67 unmet needs at baseline and 4,88 at follow-up. The quantitative analysis of the primary outcome parameter showed a statistically significant higher reduction of unmet needs in the intervention group compared to the control waiting group (p=0.0088). There was no group difference for the EQ-5D (p=0.335). Out of the sample of 192 participants, we further recruited 17 participants comprising all groups who came into contact with the digital care management system, namely caregivers (n=6), GPs (n=5), practice staff (n=2) and study nurses (n=4). The results of the interviews showed that caregivers did not have problems self-completing the assessment on the tablet and that the time was feasible in clinical practice. Clinical staff reported that it helped when one person was primarily taking care of the tablet with respect to preparation and handing it over to caregivers. Study nurses suggested further improvements with respect to the intervention monitoring. Results of the cRTC and the interviews will be presented in more detail.

Conclusion: Our results showed that the digitally supported care management programme significantly reduced caregivers' unmet needs compared to the control group. The reduction was driven by unmet needs who were connected to the caregivers' care responsibilities. Participants at baseline had a high scoring on the EQ-5D, which might have led to a ceiling effect. With respect to the system, some parts, such as the unmet needs assessment could potentially be used in clinical practice, while others (e.g., the monitoring system) would need some further improvements.

Validation of the PD Home Diary for Assessment of Motor Fluctuations in Advanced Parkinson's Disease

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Objective: To determine the validity of the Parkinson's disease (PD) home diary for quantification of motor states in patients with advanced PD and motor fluctuations.

Background: The PD home diary has been frequently used in clinical studies to assess effects of novel treatments on motor fluctuations in advanced PD. However, the diary has not been extensively validated against direct clinical observation, which ultimately remains the gold standard for objectifying motor fluctuations.

Methods: We performed a prospective, observational cohort study (VALIDATE-PD) in 51 PD patients with motor fluctuations, who screened negative for dementia on the Montreal Cognitive Assessment. Patients were instructed to complete the PD home diary half-hourly for three consecutive days. After one day of diary training, participants were observed by a trained physiotherapist, who independently evaluated motor states half-hourly throughout daytime supported by a 7-meter Timed Up and Go Test. Simultaneously, disease severity was judged by patients and observer using the Patient Global Impression Scale (PGI) and Clinical Global Impression Scale (CGI), respectively.

Results: We included 51 patients (26 males, 25 females) with a median age of 65 years and disease duration of 11 years, who had been suffering from motor fluctuations since 61 months. Overall agreement (Cohen's kappa) between patient and observer diary entries was 59.8% (0.387). Patients documented more On without dyskinesia (52.3% vs. 38.9%, P<0.001) and less On with dyskinesia (21.5% vs. 34.2%, P<0.001), whereas proportions for Off intervals were not different between patient and observer diaries (26.2% vs. 27.0%, P=0.97). Temporal agreement between diary ratings was unsatisfactory, particularly for On with dyskinesia. The analyses of PGI and CGI moreover revealed profound discrepancies in the judgement of disease severity between patients and observer across individual motor states and were suggestive of an altered perception of normality in PD patients, who regarded themselves to be normal during 10.1% of Off intervals and 27.5% of On with dyskinesia.

Conclusions: Our study suggests that the PD home diary insufficiently reflects actual motor states compared to direct clinical observation. Future studies should investigate whether wearable sensor technology can substitute patient diaries to assess motor states more objectively.

Reliable methods to evaluate both motor fluctuations and non-motor fluctuations among Parkinson disease (PD) patients

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Objectives: Reliable methods to evaluate both motor fluctuations and non-motor fluctuations among Parkinson disease (PD) patients are important. Two studies validating ways to monitor PD symptoms will therefore be presented. One study evaluates the PD Home Diary (HD) and the other evaluates the Parkinson´s Kinetigraph (PKG). Recent studies showed only fair agreement between observer and patients motor state assessments on the HD. This could possibly be explained by the patients' insufficient knowledge about motor fluctuations. Therefore, the study aim was to investigate the effect of structured training concerning motor fluctuations on the agreement between observer and HD ratings and daily motor state times. The aim of the second study was to evaluate if PKG is a useful tool when monitoring sleep and daytime sleepiness in PD patients and to further investigate whether rotigotine has beneficial effects on sleep and daytime sleepiness. PKG is an actigraphy designed for PD patients and initial studies measuring sleep with PKG show great promise, but more studies are needed to further investigate whether PKG can be an alternative to polysomnografi.

Methods: In the first study, participants from a previous validation study of the HD were invited back for a study extension. This interventional study consisted of a screening visit including a structured training concerning motor fluctuations and one day of motor ratings on-site during which observer and patient simultaneously and independently evaluated the patients motor state half-hourly. In the second study, an observational study was conducted including patients selected for rotigotine treatment and with sleep disturbances (CGI-S ≥ 3). A PKG registration period, 24h/day for 6 days, took place before and during rotigotine treatment. Furthermore, the patients rated their complaints on questionnaires (PDQ-8, ESS, PDSS-2 and EQ-5D-5L) before and during treatment and the clinician rated them on CISI-PD, CGI-S and CGI-I.

Results: Observer and 20 patients completed 316 pairs of motor state assessments. The overall agreement was 68% before training and 76% after training (P = .093) and Cohen's κ increased from .438 to .559 (P = .320). There was no significant improvement in the correlation/reliability of HD-documented daily motor state time when compared with observer ratings. Moreover, before training the agreement in observed "on with dyskinesias" was 58% and after training it was 80% (P = .074). There are yet no definitive results from the PKG study, as it is still ongoing. Results from 12 included patients shows that the patients' sleep improved with rotigotine according to CGI-S (p = 0.037). However, nighttime PKG-scores deteriorated, especially nighttime immobility (p = 0.021) and percent time asleep (p = 0.028). There was a significant reduction of daytime sleepiness (PTID), percent time tremor and percent time bradykinesia. Neither PDSS-2 and sleep score nor PTID and ESS correlated.

Conclusion: Our structured patient training in motor fluctuations did not significantly improve the agreement between observer and HD or the reliability of daily times spent in the different motor states as an aggregate measure of the HD in this PD patient group. However, there are indications on an improvement in the participants ability to detect dyskinesias. No conclusion regarding whether PKG is a useful tool when monitoring sleep and daytime sleepiness in PD patients or whether rotigotine has beneficial effects on sleep and daytime sleepiness can yet be drawn.

Healthcare 3.0: How to transform machine learning prototypes into functional healthcare applications for diagnostic assistance?

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As the number of elderly people is rapidly increasing, we are faced with the challenge that the incidence of age-related diseases is also rising and diagnostic services are demanded more frequently. At the same time, however, the actual number of medical centres and available experts remains almost constant such that tools for diagnostic assistance are urgently needed in order to improve the effectiveness of healthcare. One example is the time-intensive examination of brain MRI scans by neuroradiologists for the diagnosis of neurodegenerative diseases. We developed a deep learning application for the detection of atrophy patterns of dementia, highlighting diagnostically relevant brain areas for further evaluation by the neuroradiologists. In four externally funded projects, we will investigate aspects and strategies of how machine learning prototypes systems can be translated into functional healthcare applications.

In the ongoing project “ExplAInation” funded by the German research foundation (DFG), we are developing an artificial neural network framework to generate visual and textual explanations in order to improve the comprehensibility and interpretability of deep learning models. This effort includes participatory research with clinical users to provide valuable information on expectations, key requirements and the functional utility of different approaches. In the complementary project “TESIComp” funded by the Federal Ministry of Education and Research (BMBF), we will investigate ethical and social aspects of the emerging field of computational psychiatry. Patients, caregivers, and medical doctors will be interviewed and the interviews qualitatively analysed with regards to changes and challenges in the doctor’s role and responsibilities.

Within the German Medical Informatics Initiative, we will contribute the dementia diagnostic assistance prototype to the project “Open Medical Inference”, which plans to develop a registry of distributed machine learning evaluation services. This framework will allow participating university medical centres to use specific services remotely, without the need to operate all the tools locally. We participate in the international “Computer-aided Diagnostics” consortium, which receives funding from the European Baltic Sea Region Interreg program. Here, we will explore the overarching process of integrating machine learning prototypes and commercial tools into the hospital, with specific focus on the involved stakeholders and departments, regulatory aspects, implementation strategies, and staff training. Finally, this information will be used to develop best practice guidelines.

Interested members of the CTNR are invited to participate in these exciting activities.

Harmonizing cognitive assessment in memory clinics

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Standard procedures are a basic requirement in translational research, but heterogeneous patient selection keeps introducing unwanted variability in dementia research. Its detrimental effect on data pooling, results comparisons and on the overall validation of innovative procedures can hardly be overcome post-hoc. Interoperability in clinical centres would also increase reliability and reduce costs and effort to patients and health payers. However, this is also not yet guaranteed in the dementia field.

In 2021, we published a consensus standard battery for European memory clinics (the clinician's Uniform Dataset, cUDS), based on the most widespread existing standard (i.e., the UDS-3, required for US-NACC centres' funding eligibility). The consensus also defined the methodology to produce normative values across tests and languages. An Italian translation of the battery with normative values based on the consensus recommendations has been published in 2022. Meanwhile, two feasibility analyses highlighted hurdles and facilitators in academic and non-academic memory clinics. At the European level, academic clinicians (N=51) expressed concern with implementation issues (64%) (e.g., lack of time, finances and material) and would be facilitated by the provision of cUDS material and evidence of actual diagnostic performance (24%). At a national level, Italian academic and non-academic clinicians (N=62) envisioned no specific obstacles (45%), except finances (18%), although 34% of them would welcome a greater number of neuropsychologists and clinical training, as facilitating the implementation of a standard assessment.

Ideally, providing cultural adaptations and norms of the consensus standard assessment for the different European countries would align all research and clinical centres with a common standard. This would benefit research, patients and health systems, and align clinical practice with scientific results. However, awareness on the need of harmonization is still low among researchers. Mechanisms facilitating the production as well as the uptake of harmonized methods are not yet in place. To get there, the required efforts go beyond typical research grant framework, involving transdisciplinary participation and action from very different stakeholders, that do not usually work together in translational research. The Italian example is indeed an exception, due to close networking between translational research networks and funders including the Ministry of Health. Future steps should entail both bottom-up (i.e., from researchers) and top-down (from governmental institutions) actions to converge on theoretical prerequisites and on specific action required for more efficient translational research. Meanwhile, researchers sensitive to the topic may converge and proceed in this direction.

Developing an advisory board with hard-to-reach patients and caregivers: early insights from the PART(icipatory) project

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Background: Participatory research or patient and public involvement refer to the process of actively involving people with lived experience of a condition into the research process to improve its relevance, quality, and impact. Participatory health research has the potential to reduce health inequalities and can initiate social change [1]. Moreover, evidence indicates that engaging patients in research increases recruitment rates and supports researchers in obtaining funding, developing study protocols, and selecting appropriate outcome measures [2]. The challenge is to establish a sustainable structure to include patient groups which are underrepresented yet, e.g. patients with mental illness or neurodegenerative diseases.

Objective: We plan to develop, implement, and evaluate a patient advisory board (the "PARTBeirat") facilitating involvement in research at Rostock University Medical Centre and serving as a blueprint for future patient involvement in research in Germany.

Methods: The project consists of three phases over three years. The first phase involves establishing the PART-project's organizational structure, creating a systematic review of current research in this field, developing key documents and procedures, and raising awareness via professional networks, workshops and both traditional and social media. In the second phase, we will connect people with lived experience with researchers to establish topic-specific PART-advisory boards. People with lived experience will be active in mental health and neurodegenerative disease-related projects. In the third phase, we will increase the number of projects within the PART-Beirat, monitor their progress to revise procedures and share best practices across the research landscape through guidelines and publications.

Results: The project started in May 2022 with the initial establishment of the organizational structure. We are further developing our professional networks. The awareness-raising campaign to highlight participatory research is ongoing and we are currently developing a website as well as a short introduction film about the project. Regarding the systematic review of current research, we have finalized the search strategy and preliminary results will be presented.

Conclusion: At present, we are underway to develop the organizational structure of a patient advisory board to involve hard-to-reach patients and caregivers. Some first steps are already finished and currently ongoing. With the input of people with lived experience we aim to establish a structure of participatory research to facilitate the exchange between researchers and people with lived experience.

References

[1] Allweiss, Theresa; Cook, Tina; Wright, Michael (2021): Wirkungen in der partizipativen Gesundheitsforschung: Eine Einordnung in die Diskurse zum Forschungsimpact Research impact and participatory health research: an international debate. In: Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 64, S. 215–222. DOI: 10.1007/s00103-020-03268-8.

[2] Domecq, Juan Pablo; Prutsky, Gabriela; Elraiyah, Tarig; Wang, Zhen; Nabhan, Mohammed; Shippee, Nathan et al. (2014): Patient engagement in research: a systematic review. In: BMC Health Services Research 14 (1), S. 89. DOI: 10.1186/1472-6963-14-89.

The effect of pump-based Parkinson treatment on non-motor symptoms

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The non-motor symptomatology is an integral part of Parkinson´s disease (PD), with high relevance for quality of life of both patients and caregiver. When the disease advances the non-motor load becomes even more pronounced. Pump-based PD therapies can significantly improve both “off-time” and dyskinesias in patients with advanced PD. A number of clinical studies now also confirm substantial effects also on the non-motor symptomatology. This includes improvements on for example sleep, day-time sleepiness, mood and anxiety. There is a correlation with improvements in health-related quality of life. These effects might even be part of the indication for these therapies. The non-motor effect profile might also be important in the choice of advanced therapy for the individual patient.

Posters

26th & 27th January, 2023

Lipidomics analysis of erythrocytes from patients with VPS13A disease

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Posters

VPS13A disease (chorea-acanthocytosis) is an ultra-rare disease caused by pathogenic variants in in the VPS13A gene. The disorder is characterized by neurodegeneration mainly in the basal ganglia causing a Huntington’s disease-like phenotype and by the presence of misshaped red blood cells referred to as acanthocytes. As shown very recently, VPS13A is a bridge-like protein located to membrane contact sites connecting the endoplasmic reticulum, mitochondria and lipid droplets mediating bulk lipid transfer. The exact function and regulation of this protein, however, remains elusive.

In this study, we therefore aimed to assess the overall lipid composition of patient-derived cells. Erythrocytes were collected from 5 VPS13A disease patients and 12 healthy control subjects for mass-spectrometry analysis (lipidomics analysis). While we found no significant differences on the lipid class level, alterations in certain subspecies were detected, particularly within the class of phosphatidylethanolamines. In this class, species with longer fatty acid chains tended to be increased, while species with shorter fatty acid chains tended to be decreased.

Our results point to alterations of the composition of particular lipid subspecies in erythrocytes of VPS13A disease patients. Further studies are needed to unravel the role of lipid distribution in the pathophysiology of VPS13A disease and, more general, of a new group of related disorders with disturbed bulk lipid transfer between organelles.

Funding: This study was funded by the MeDDrive grant (TU Dresden). K.P. is supported by Rostock Academy of Science (RAS). A.H. is supported by the Hermann und Lilly Schilling-Stiftung für medizinische Forschungs im Stifterverband.

Investigation of the effect of mutations in RHOT1 or VPS13D on mitochondrial-ER contact sites and lipid metabolism

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The pathogenesis of Parkinson´s disease (PD) is highly complex, including dysfunction of multiple organelles like mitochondria, lysosomes, ER, and cellular processes such as calcium homeostasis, proteostasis, and autophagy. To understand all these processes involving different organelles, research has turned in recent years to the study of organelle contact sites, and specifically to mitochondria-endoplasmic reticulum contact sites (MERCS). Some studies suggested an involvement of peroxisomes in PD as well, however, the role of peroxisomes in neurodegenerative diseases has hardly been studied so far. In this context, MIRO1 is a protein of particular interest because it is involved in transport of mitochondria and peroxisomes, regulation of mitochondrial calcium uptake, fusion and fission of mitochondria and peroxisomes, and regulation of MERCS. Recently, we have described heterozygous mutations in the RHOT1 gene, encoding MIRO1, in four PD patients. MIRO1 has been identified as a direct interaction partner of VPS13D, a protein that serves as a lipid transfer protein at MERCS, and at contact sites between the ER and peroxisomes. However, a comprehensive understanding of how PD-related mutations in MIRO1 affect peroxisomes and how the MIRO1/VPS13D complex mediates lipid transport is currently lacking. Therefore, we are using iPSC-derived neurons from PD patients with mutations in RHOT1 and patients with mutations in VPS13D, leading to ataxia, to study the effects of mutant MIRO1 and VPS13D on the interplay of mitochondria, ER and peroxisomes and the effects on neuronal function. For this purpose, high resolution live cell imaging, Western blot analysis and immunostainings will be used. As a more complex picture of impaired lipid metabolism and mitochondrial dysfunction has emerged in PD research, our study of the MIRO1/VPS13D complex may help to investigate the missing link between these mechanisms in the diverse pathology of neurological diseases.

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Failure of translocator protein ligand (TSPO) to reflect changes in neuroinflammation upon weight-reducing interventions in HFD mice

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Objective: Obesity has been identified as a risk factor for neuroinflammatory processes, and thus for neurodegenerative disorders. In this in vivo study, the influence of different weight loss interventions on high-fat diet (HFD)-induced neuroinflammation was investigated primarily using non-invasive small animal imaging methods e.g. positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) to establish longitudinal approaches with a high translational potential for classification of biomarkers.

Methods: Mice were fed with HFD for 6 months to induce obesity. Afterwards, the mice were subjected to different interventions, i.e. dietary change to low-fat diet (LFD), treadmill training (TM) and/or time-restricted feeding (TRF) for 6 months. One group remained on HFD as a control group. For imaging glial activity and for direct marking of glial cells, the radiopharmaceuticals 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) and [18F]GE-180, as a marker for translocator protein ligand (TSPO), were used. Percentage of injected dose per mL of tissue (%ID/mL) was calculated for the brain regions cortex, hippocampus and hypothalamus. Neurometabolites such as myoinositol, which indicate increased neuroinflammation, were assessed by MRS. Imaging data were complemented by neuronal mRNA expression analysis of common markers of inflammation (e.g. cytokines and Iba1).

Results: Weight-reducing interventions led to a reduction of neuroinflammatory processes. Compared with the HFD group, a significant reduction in mRNA expression of the inflammatory cytokine IL-1β was observed as a result of TM in combination with TRF. This was also the case for IL-6 mRNA expression, where additionally the dietary change to LFD in combination with TM and TRF induced a significant decrease. Moreover, these interventions caused a large decrease in TNF-α and microglial marker Iba1 mRNA expression. Accordingly, a significant reduction of myoinositol was observed. However, PET/CT data only partially reflected the results mentioned above. TM caused a reduction in [18F]FDG uptake, yet the remaining interventions tended to result in higher uptake of [18F]FDG compared to HFD group. Notably, the combination of TM and TRF, as well as the dietary change, even caused a significant increase in [18F]GE-180 uptake compared to the HFD group. This is partly reflected in higher mRNA expression of TSPO upon TM as well as TM in combination with TRF.

Conclusion: The present study was able to show a reduction in neuroinflammation triggered by weight-reducing interventions in HFD-induced obesity. This was underlined by characteristic markers of inflammation such as cytokines, IL-1β, IL-6 and TNFα. Surprisingly, TSPO assessed by mRNA analysis and [18F]GE-180 PET imaging could not detect the reduced neuroinflammation after weight loss in HFD mice and therefore might not be suitable as a biomarker.

Posters

Investigation of brain networks activity and their association with transfer of cognitive training gains

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Posters

Background: Age-related cognitive decline increases the need for cognitive interventions to maintain cognitive function. Transfer of training gains to untrained tasks is a key indicator for the effectiveness of cognitive training. However, the underlying brain mechanisms need to be further investigated. We implemented a cognitive training study to assess functional connectivity determinants of transfer of training gains.

Method: A sample of 181 healthy older adults (mean age: 68 years) underwent a 4-week cognitive training across three sites. The control group consisted of 54 older adults. To evaluate transfer and training effects, participants underwent a neuropsychological assessment before and after the training. A second follow-up assessment was applied 12 weeks after the training. The training group was divided in subjects who had and who did not have successful transfer, which was defined as higher improvement in cognitive tasks than the control group. We used cognitive scores representing working memory, verbal and visuospatial memory and executive functions. Baseline resting-state functional magnetic resonance imaging was assessed in order to investigate the functional connectivity of brain networks associated with cognitive functions. We extracted brain resting state networks using the Independent Component Analysis (ICA) approach.

Results: We observed successful long-term transfer of cognitive training gains in most of the participants. Our results demonstrated spatially restricted effects ($p<.01$ uncorrected) for the association of transfer of gains with the resting-state connectivity of brain networks, such as the Default Mode Network, Central Executive Network and Visual Network.

Conclusion: Long-term transfer of training gains in aging is possible. A strong association between transfer of gains and resting-state functional connectivity was not identified. A data-driven approach generating brain networks using Independent Component Analysis might be not sensitive in contrast to seed-based approach.

Patient-specific iPSCs for disease modeling in Fatty acid hydroxylase-associated neurodegeneration (FAHN)

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Posters

The Fatty acid hydroxylase-associated neurodegeneration (FAHN), an autosomal recessive condition due to mutations in FA2H, is a disorder that intersects the fields of leukodystrophies and disorders of Neurodegeneration with Brain Iron Accumulation (NBIA). In FAHN, abnormal hydroxylation of cerebrosides appears to lead to myelin instability. The symptoms of FAHN are mostly confined to the central nervous system. Patients present with motor regression with muscle spasticity and dystonia, ocular abnormalities, progressive gait instability, intellectual impairment and seizures. In addition, patients display abnormal myelination, cerebellar atrophy and some have iron deposition in the central nervous system. The FA2H gene encodes a 43 kDa membrane bound protein residing in endoplasmic reticulum. It catalyses the hydroxylation of fatty acids at position 2 of the N-acyl chain to form 2-hydroxy-free fatty acids, which is a precursor for ceramide synthesis, a principle component of sphingolipids and myelin. Pathogenic FA2H variants have been shown to lead to decreased protein abundance or enzyme activity. Loss of FA2H function in mice causes demyelination in the spinal cord and optic nerves accompanied by axonal loss, as well as changes of Purkinje cells. However, the pathophysiology of FAHN is poorly understood so far. A deeper understanding of the pathophysiological mechanisms would provide both, new clues to elucidate the neurodegeneration in FAHN, and further open up new possibilities for therapeutic approaches.

The main objective of this project is to research and understand FAHN disease by studying FAHN in human cell models using induced pluripotent stem cells (iPSCs) derived from fibroblasts of different FAHN patients, as well as iPSCs carrying FAHN mutations inserted by CRISPR/Cas9 technology. Here we describe the generation of a human iPSC line derived from fibroblasts of a female patient carrying the compound heterozygous mutation p.Gly45Arg/c.p56A>G (c.133G>A/p.His319Arg). The generated iPSCs provide the basis to obtain neurons, astrocytes and especially oligodendrocytes. Analysis of iPSC derived oligodendrocytes demonstrated the maturation of neural progenitor cells into oligodendrocyte precursor cells and mature oligodendrocytes. Furthermore, a co-culture of neurons and oligodendrocytes revealed myelinating oligodendrocytes, shown by the detection of the myelin basic protein. Regarding the expression of the FA2H enzyme, we found a reduced protein level in FA2H-deficient cells, demonstrated by western blot.

This disease model of FAHN will allow us to systematically characterize the pathophysiology within neurons and oligodendrocytes and their interactions to gain a better understanding of the detailed pathophysiological mechanisms underlying FAHN-related demyelination and neurodegeneration.

Project run time: Project was started in January 2021 and will be continued at least until March 2023. Funding: The study was funded by the NBIA Disorders association. Fatima Efendic is funded by the Centre for Transdisciplinary Neurosciences Rostock (CTNR). Andreas Hermann is supported by the Hermann und Lilly Schilling-Stiftung für medizinische Forschung im Stifterverband.

Food restriction in mice induces food-anticipatory activity, circadian rhythm-related activity changes, and glial cell alterations in the hypothalamus

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Anorexia nervosa (AN) is a debilitating psychiatric disorder characterized by severe emaciation, hyperactivity, and amenorrhea. Severe brain volume atrophy was found in AN patients which was linked to neuropsychological deficits, while its underlying pathophysiology remains unclear. To what extent AN-related symptoms are primarily due to food restriction or neuronal dysfunction is also unclear. Therefore, we aim to understand the relevance of food restriction on AN-related symptoms such as hyperactivity and amenorrhea. In addition, disrupted circadian rhythms and glial cell disturbances in the arcuate nucleus (ARC) of the hypothalamus in which eating **behaviour** is regulated were hypothesized to contribute to the pathophysiology of eating disorders.

We hypothesized that starvation leads to hyperactivity, amenorrhea, and a changed circadian rhythm. In addition, brain volume loss could be associated with glial cell changes in the ARC.

Starvation was induced by restricting food access of either early adolescent or adolescent (4/8 weeks old) mice to 40% of their baseline food intake until a 20% weight reduction was reached (acute starvation). To mimic chronic starvation, the body weight was maintained for another 2 weeks. Locomotor activity was investigated using running wheel sensors, whereas a change in circadian rhythm-related activity was measured using a newly developed, infrared-sensory-based home-cage tracking system (Goblotrop). Amenorrhea was determined by histological examination of vaginal smears. Immunohistochemical stainings were used to quantify the density of microglia and astrocytes in the ARC.

All cohorts showed an increase in locomotor activity up to 4 hours before food presentation (i.e. food-anticipatory activity; FAA). Whereas amenorrhea was present in all groups except in early adolescent acutely starved animals, hyperactivity was exclusively found in chronically starved groups. Of note, adolescent chronically starved mice showed a decrease in circadian rhythm-related activity at night. In parallel with brain weight reductions, acute starvation did induce an increase of IBA1+ microglia cells, while chronic starvation demonstrated a decrease of microglia cell numbers in the ARC. Further, starvation led to a decrease in the number of GFAP+ astrocytes in this region.

Chronic starvation most closely mimics AN-related behavioural changes. Further, the circadian activity changes might underlie the pathophysiology of AN. Besides that, acute starvation might be paralleled with microgliosis in the ARC, potentially due to inflammation and astrocytosis. The characterization of glia cell alterations can identify new targets for the treatment of AN and thereby contribute to the understanding of pathologic processes in the brain of patients with AN.

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Posters

Calcium phenotype in cellular models of VPS13A disease

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VPS13A is a membrane protein located at membrane contact sites (MCS) involved in lipid exchange between the endoplasmic reticulum (ER) and mitochondria and between lipid droplets and mitochondria, respectively. Mutations in the respective gene cause chorea-acanthocytosis/VPS13A disease, a neurodegenerative disorder of the young adulthood. Furthermore, in VPS13A deficient cells, calcium homeostasis via ORAI1-mediated store operated calcium entry (SOCE) is disturbed, although the exact mechanism has not been completely discovered yet. Since the MCS between ER and mitochondria are of particular importance for cellular calcium homeostasis, we hypothesize that MCS dysfunction in absence of VPS13A contributes to impaired calcium homeostasis, consequently contributing to neurodegeneration. To this end, we used patient-derived cells (fibroblasts and iPS-derived neurons) with VPS13A deficiency compared to cells from healthy donors. The cells were transfected with a specific marker for mitochondria-ER contact sites (MERCS) and with the ER marker BFP-KDEL. Subsequently, cells were stained with MitoTracker deep red and the calcium dye Rhod2-AM. Using super resolution live cell imaging (LSM900 confocal microscope with Airyscan 2 module, Zeiss), images were acquired over 2 minutes before and after treatments with Thapsigargin or Ru360. Thapsigargin is an inhibitor of the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA), preventing calcium uptake by the ER, while Ru360 is a specific inhibitor of the mitochondrial calcium uniporter (MCU), thereby blocking calcium uptake by the mitochondria. We observed that VPS13A deficient cells responded with a stronger increase of MERCS to Thapsigargin-induced calcium stress compared to control cells. Furthermore, in contrast to control cells, VPS13A-deficient cells showed a MCU-independent mitochondrial calcium influx upon combined treatment with Thapsigargin and Ru360, suggesting alterations in cellular calcium homeostasis. To date, little is known about the interplay of lipid metabolism and calcium homeostasis. Our study may contribute to the understanding of these mechanisms and how their disruption in VPS13A deficiency is involved in neurodegeneration.

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Diagnosing Patients with a Migration background in Europe: an exploratory analysis

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Posters

Background: the detection rate of dementia is low (20-50%) even in highly developed countries. In Europe, one of the barriers to timely diagnosis is a migration background, which has been shown to limit access to specific assessments and care due to language and cultural barriers. To learn more about actual ongoing practices, we asked specific questions about the assessment of Patients with Migration Background (PwM) to specialized clinicians.

Methods: we investigated the frequency and modalities of assessment of PwM within two surveys exploring the feasibility of implementation of a standard cognitive assessment in memory clinics. A European survey collected responses from 51 academic clinicians (78% neuro-psychologists) from 46/72 centres of the European Alzheimer's Disease Consortium located in 16/18 European Union (EU) and 2 non-EU countries. A national survey collected answers from 30 academic and 32 non-academic clinicians (72% neuro-psychologists) belonging to the Italian Society of Neurology (N total of affiliated members = 382) and working in 14/20 Italian regions.

Results: 82% of European academic clinicians (N=51) reported assessing PwM mostly on a monthly (24/51) and a yearly basis (18/51). The majority (69%) declared to translate local tests and less than half (39%) use cultural and language-specific tests. Only 10% reported using always an interpreter. Similarly, 76% of Italian academic/non-academic clinicians (N=62) reported yearly (33/62) and monthly visits (14/62) for PwM, but 24% reported none (15/62). 47% declared to translate tests (29/62) and 10% use adaptations for culture and language (6/62). Just 5% reported always using an interpreter (3/62).

Discussion: in European and Italian memory clinics requests and modalities for the assessment of PwM, are not frequent nor standardized, independently from the setting (academic/non-academic). Implementing an international standard cognitive assessment could facilitate the diagnosis of PwM through consistent translations and appropriate norms in several languages.

SeMiNd – The impact of senescent microglia on neurodegenerative processes

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Posters

Microglia, the immune guardians of the brain, change their morphology, function and phenotype with age. However, data on the aging process of age-associated microglia populations themselves and its consequences for the surrounding tissue in health and disease are largely unknown. Furthermore, the study of microglia during aging is often limited to pathological conditions and hampered by the fact that microglia, at least in in vivo models, were not exclusively aged but rather the whole body/tissue of interest. Therefore, we here do an extensive characterization of microglial aging by using state-of-the-art models and next-generation sequencing by focusing on the impact of microglial aging on neurodegenerative disease.
The physiological aging of microglia was first investigated in human post-mortem tissue and it was found that microglia develop a dystrophic morphology with increasing age, characterized by deramification and shortening of processes as well as cytoplasmic fragmentation. The survival and function of neurons is greatly affected by glial cells, because their surveillance decreases significantly with age leading to impaired synaptic brain network and poor recovery after damage. Therefore, microglia aging has significant effects on neuron viability and brain homeostasis. However, an extensive characterization of microglial aging, e.g. of morphology, function and gene expression specifically of age-associated microglial populations and their impact on neurodegenerative diseases is lacking.
We hypothesize that microglial aging themselves fundamentally alter their phenotype and function and ultimately affecting brain homeostasis, particularly neurons. This age-associated phenotype change could be sufficient to either directly trigger neurodegeneration, exacerbate pre-existing (sub threshold) neurodegeneration or render specific cells more susceptible to neurodegenerative events. For an intensive characterization of microglia aging, we first developed several state-ofthe-art in vitro and in vivo technologies of inducible accelerated aging. Via an inducible Progerin expression, we are able to (1) selectively age murine microglia in vivo and (2) translate these results in an in vitro model of premature human microglia. Currently, we characterize these models with our proposed age-associated marker panel that have more predictive power then single used aging markers. Via high parameter FACS and next-generation sequencing methods (CITE-Seq, Single-Cell-RNA-Sequencing) we further investigate age-associated microglia populations in a time-curse dependent manner. Moreover, these models and identified age-associated populations can in general give a new opportunity to get a deeper view into the aging processes of brain immune cells and their impact on age-related diseases.

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Glymphatic clearance capacity and its relation to Alzheimer's disease-like histopathology

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Posters

Background: The accumulation of amyloid-β (Aβ) within the brain parenchyma is a main pathological feature of Alzheimer's disease (AD). Clearance of Aβ from the brain occurs largely via the glymphatic system, which mediates an exchange of corticospinal fluid (CSF) and interstitial fluid (ISF). The aim of this study is to use minimal invasive in vivo gadolinium based contrast agent (GBCA) magnetic resonance imaging (MRI) to evaluate glymphatic system capacity in a transgenic model of AD and how this is correlated with Aβ plaque load and neuroinflammation.

Material and Methods: We implemented a GBCA-MRI approach on a 7T small animal ultrahighfield MRI scanner (Bruker BioSpin GmbH, Ettlingen, Germany) to determine glymphatic clearance efficacy. Imaging sessions were performed longitudinally at the age of 9 and 12 months in n=5 APPswe/PS1dE9 (tg) mice and n=5 wild type (wt) littermates. The scan protocol consisted of a highly T1w RARE sequence carried out for 180 minutes. We determined mean voxel values in manually delineated volumes of interest (VOI) in cortex and hippocampus. Additionally in histological samples of a cross-sectional study in n=6 tg and n=6 wt mice at the same age, quantification of Aβ plaques was performed using 6E10 as a marker. Microglial activation was quantified in Iba1 stained samples with focus on total cell number, cell processes and ramification index to evaluate neuroinflammation.

Results: Analysis of MRI data and histological specimens are still ongoing. Preliminary results of the histological evaluation, show a significant effect of age ($F(1,24)=5.718$; $p=0.0250$) and genotype ($F(1,24)=264.7$; $p<0.0001$) on Aβ plaque accumulation in correspondence to existing literature. Signs of aggravated neuroinflammation was only observed in 12 months old tg mice reflected by significantly higher numbers of microglia in the frontal cortex ($p=0.0305$) and a significantly lower ramification index in the hippocampus ($p=0.0463$) compared to wt littermates.

Perspective: Final results of the MRI evaluation may allow to conclude on the feasibility of the used AD model. It will provide further information if there is an effect of age or the AD-like phenotype on glymphatic clearance capacity in this model and if these changes reflect aggravated Aβ plaque formation and neuroinflammation.

The associations between cognitive performance and glucose metabolism in ALS patients

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Background: Around 50% of amyotrophic lateral sclerosis (ALS) patients suffer from cognitive impairments, but the neurological substrates of these impairments have not been satisfactorily described yet. Various structural changes have been documented and some correlations have been found between regional structural degradation and performance on specific cognitive domains. The functional changes associated with patients' general cognitive status have been well described, but the associations between impairments per cognitive domain and brain metabolism have not yet been examined in detail.

Aim: To investigate the associations between the performance on various cognitive domains and the patterns of whole-brain glucose metabolism in ALS patients.

Sample: The neuropsychological, clinical, and imaging data from N=54 ALS patients acquired in the University Medical Center in Rostock will be analyzed.

Materials: Cognitive performance was measured with the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) that assesses 5 cognitive domains (language, verbal fluency, executive functions, memory, and visuospatial processing), and two additional social cognition tests: Faux-pas Test, and Facial Recognition Test. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) scans were acquired to evaluate the patients' glucose metabolism. Furthermore, structural MRI scans were attained to implement the partial volume correction (PVC) on the FDG-PET scans using the Müller-Gärtner (MG) method.

Statistical analyses: The imaging data will be preprocessed with the PET-PVE toolbox in SPM12 and all statistical analyses will be carried out in SPM12 using Matlab. Separate voxel-based analyses of the PV corrected FDG-PET data will be carried out per cognitive domain to examine specific patterns of glucose metabolism related to performance on those domains. Relevant clinical data such as gender, ALS phenotype, onset date, and age at testing will be used as covariates. Any clusters of hypometabolism will be examined and compared to previous findings.

Oxygen and microglia secure appropriate brain development

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Oxygen is a well-known signaling factor affecting brain development. Maternal application of higher doses of oxygen is able to accelerate brain development at specific time points through enhancing proliferation of intermediate progenitors within the cortex leading to an increased amount of layer V neurons. We here used immunohistochemistry to analyze the follow up cortical development of C57BL/6J mice bearing an increased cortex caused by maternal hyperoxygenation. Our analysis revealed a normalization of cortical development including an appropriate cortical layering shortly after birth. Interestingly, this was mediated neither by post-treatment reduced proliferation nor by increased apoptosis of layer V neurons. Instead, we could show that active microglia are able to target and phagocytose layer V neurons. Although, they are known to target neural stem cells without any signs of apoptosis, we here show for the first time that microglia keep this function when invading the cortical plate until the first days of birth and initially regulate the number of neurons. This interaction of an altered cortical development caused by maternal oxygenation with postnatal normalization mediated by active microglia may serve as model system for layer V related neurodevelopmental disorders.

Posters

Intravenously administered gadolinium based contrast agent as a novel approach to longitudinally measure ventricular brain clearance with magnetic resonance imaging in an Alzheimer´s disease model

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Posters

Background: Amyloidopathy, one pathological hallmark of Alzheimer's disease (AD), results from dysbalanced amyloid-β (Aβ) production and clearance. Especially in the more common form of late-onset sporadic AD, disruptions in brain clearance may have a pivotal role as pathogenic drivers. Transgenic mice models of amyloid overproduction are predominantly used models in AD research, yet there are only highly invasive procedures available to study brain clearance. Minimal-invasive in vivo measurement methods would be of great interest to study a possible contribution of impaired brain clearance to amyloidopathy in transgenic models.

Material and Method: We implemented an intravenously administered gadolinium based contrast agent (GBCA) magnetic resonance imaging (MRI) approach on a 7T small animal ultrahighfield MRI scanner (Bruker BioSpin GmbH, Ettlingen, Germany) to determine brain clearance efficacy. Imaging sessions were performed longitudinally at the age of 6, 9 and 12 months in n = 9 APPswe/PS1dE9 (tg) mice and n = 9 wild type (wt) littermates. The scan protocol consisted of a highly T2w Inv. Rec. RARE (FLAIR) sequence carried out recurring for 180 minutes after GBCA administration. We determined mean voxel values in manually delineated volumes of interest in both lateral as well as third and fourth ventricles in axial brain slices using PMOD software.

Results: We created intensity-time-curves and extracted area under the curve (AUC) as well as decay coefficients for invasion and wash-out. The latter were derived from fitting the data with a model function consisting of an exponential convoluted with another exponential. We detected a significant effect of age ($p = 0.0155$, $F(1.492, 20.89) = 5.800$) on AUC pointing to a significant lower GBCA crossing into the ventricular system in 12 month old mice compared to 6 and 9 month old mice, independently of genotype. However, our tg AD model showed no differences neither in ventricular invasion nor wash-out of intravenously administered GBCA compared to wt mice.

Conclusion: The lack of an effect of the transgene suggests that effects on ventricular clearance capacity only play a minor role in the development of the AD-like phenotype in this model of Aβ overproduction. Further experiments will be needed to elaborate on more sensitive AD-like changes in parenchymal invasion and wash-out, representing glymphatic clearance of GBCA.

P73 isoforms hijack the activity of the REST complex on brain-specific subunits of GABA receptors to drive a melanocyte-to-neurogenic phenotype switch and modulate the tumour microenvironment

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The mechanisms of tumour progression differ from those of tumorigenesis. One enigmatic prometastatic process is the recapitulation of pathways of neuronal plasticity at aggressive stages: cancer cells and neurons develop reciprocal interactions via the mutual production and secretion of neuronal growth factors, neurothrophins, and/or axon guidance molecules in the tumour microenvironment. In this study, we aimed to investigate whether products of the p73 gene, a transcription factor with a dual role in neuronal development and cancer, exert their documented role in cancer invasion and metastasis by manifesting their neuronal properties and activating their nervous system-related gene targets in the context of the cancer cell. Moreover, NRSF/REST, a transcriptional repressor of neuronal genes, was predicted to play an important role in regulating GABA receptor subunits in the presence of p73. Our data show that genes involved in neuron development, differentiation, and function are reactivated in tumours and predict poor patient outcomes, as well as provide the basis for exploring the driving forces of neuron-tumour interactions.

The role of HSPB8 in motor neurodegeneration

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HSPB8 is a small heat shock protein (HSP) that binds misfolded proteins in an ATP-independent manner to facilitate their proper folding. HSPB8 is a key component of chaperone assisted selective autophagy (CASA)HS, an autophagic pathway responsible for the recognition of misfolded proteins and facilitates their degradation through the autophagosome-lysosome pathway.

Mutations in HSPB8 gene are an underlying cause of peripheral neuropathy in Charcot-Marie-Tooth disease, where dysfunction of HSPB8 protein leads to accumulation of protein aggregation and neurodegeneration of peripheral neurons. Recent evidence suggests it also as a rare monogenetic cause of amyotrophic lateral sclerosis (ALS). However, the detailed molecular pathways involved in this process are still underexplored.

Therefore, the aim of our study was to investigate the molecular pathomechanisms involved in the neurodegeneration of human motor neurons upon HSPB8 knock-out (KO). For this purpose, we generated an isogenic pair of control and HSPB8 KO human induced pluripotent stem cells (iPSC). We differentiated the cells into motor neurons (MN) and we investigated different molecular aspects of neurodegeneration.

We hypothesized that knocking out HSPB8 can hamper the autophagic flux which in turn might impair the protein sorting/proteolysis pathway resulting in the inevitable aggregation of non-native protein and ultimately promoting neurodegeneration.

Interestingly, our data has shown significant changes in the protein level of chaperones participating in CASA and other co-chaperones participating downstream of this pathway. Additionally reinforcement of autophagy has been observed in HSPB8-KO neurons marked by upregulation of autophagy markers LC3B and p62. This further impacted the autophagic flux through the autophagosome-lysosome pathway eventually causing the autophagosome accumulation in the knock-out condition.

In summary, this data clearly indicates an impairment in autophagy as one of the crucial pathways related to neurodegeneration cause by HSPB8 dysfunction. However, further studies are needed to establish the link between CASA, cellular autophagic machinery, lysosomal-degradative pathway and neurodegeneration.

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Starvation in mice induces glial cell alterations in the corpus callosum accompanied by changes in the liver

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The psychiatric disorder Anorexia nervosa (AN) induces a widespread organ dysfunction caused by severe malnutrition. The underlying pathophysiology is poorly understood, despite its potential importance in explaining the neuropsychological deficits and clinical symptoms associated with the illness. Glial cells, which are relevant for maintaining the brain's homeostasis, might be involved in the processes leading to brain atrophy found in patients with AN. The organ dysfunction due to malnutrition includes liver damage such as hepatocyte injury leading to a rise in transaminases indicating that these effects might contribute to the pathophysiology of eating disorders.

We hypothesized that starvation induces glial cell changes in the white matter accompanied by cellular damage in the liver.

4 and 8 weeks old female C57BL/6J mice received a restricted amount of food once a day and had unlimited access to a running wheel. A 20% respectively 25% body weight reduction was maintained for two weeks to mimic chronic starvation. Immunohistochemical stains were then used to analyse glial cell density in the corpus callosum and to detect changes in hepatocyte proliferation. Besides that, liver fat content was analysed using an Oil Red O stain on cryoprotected liver sections and serum alanine aminotransferases (ALT) and aspartate aminotransferase (AST) levels were measured spectrophotometrically.

Concomitant with a reduction of the brain weight, chronic starvation led to a significant decrease in the number of $GFAP^+$ astrocytes in the corpus callosum. Additionally, starvation induced a reduction of $Iba1^+$ microglia cells in this region. These glial cell alterations could be observed in the 20% weight loss group. Beyond, the density of $Ki67^+$ hepatocytes was decreased, indicating a reduced cell proliferation. Moreover, the amount of liver fat was reduced and starvation was associated with mild microvesicular steatosis. While no change in transaminases could be shown in animals with a 20% weight loss, there was a significant increase in AST levels in the 25% weight loss group.

Starvation was accompanied by changes in glial cell density in the corpus callosum. These glial cell alterations might play a role in impaired cognitive function common in AN and could constitute for understanding and treating of AN. Starvation also affected the liver and led to an increase in serum AST. This might be indicating hepatocyte damage. Further research should identify the underlying mechanisms of starvation-induced liver damage.

Posters

Improving convolutional neural network comprehensibility via visual relevance maps and textual explanations

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Although convolutional neural networks (CNNs) achieve high diagnostic accuracy for detecting neurodegenerative diseases based on magnetic resonance imaging (MRI) scans, they are not yet used in clinical routine. One important reason for this is a lack of network comprehensibility. Recently developed visualization methods for deriving CNN relevance maps may help to fill this gap as they allow the visualization and relative scoring of key input image features that drive the decision of the network. In this study, we will investigate computational approaches to realize visual as well as textual explanations assisting clinicians.

Building on previous studies, we will train CNNs for the detection of Alzheimer's disease (AD) and frontotemporal dementia (FTD) in T1-weighted MRI scans. We will evaluate the association of relevance scores and established neuroimaging markers such as hippocampus or frontal lobe volume to assess the clinical validity of this approach. We will extend a previously developed web-app for the interactive visualization of 3D CNN relevance maps, allowing intuitive network inspection. To further improve the network comprehensibility we will develop a computational approach to generate region-specific textual explanations, with the possibility of summarizing findings under a the hierarchal parcellation of brain. The textual explanations will be evaluated using a participatory research approach with clinical users to gain valuable information on key requirements and functional utility expected from different explainability approaches.

With the aim to realize an end-to-end prototype for comprehensible CNNs including interactive visualization of relevance maps and textual explanations, this prototype will provide with knowledge on forms of explanations clinicians find most valuable and how to advance CNN models towards being more likely to be adopted in clinical routine. Our study will serve as a blueprint for a computational framework which can be applied to other similar disease detection or image classification tasks, in order to assist in making CNN models more comprehensible.

Posters

fMRI in harbour seals (Phoca vitulina)

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Harbour seals (Phoca vitulina) are globally one of the most abundant pinniped species and serve as a key species in local food webs, due to their role as both prey and predator. Many aspects of the harbour seal such as their behaviour, physiology, and morphology have been thoroughly researched over the years, yet little in known about their brain, particularly from a functional perspective. In this project, we aim to document brain areas devoted to visual processing in awake and unrestrained harbour seals through functional Magnetic Resonance Imaging (fMRI). fMRI allows to indirectly measure neural activity as response to sensory stimulation. We are interested in how and where different optical stimuli are processed in the seal brain. These data will allow meaningful comparison to other previously studied mammals, such as dogs, monkeys, and humans.

Currently, 2-3 juvenile harbour seals from the Marine Science Center of the University of Rostock, Germany, are trained to voluntarily participate in the fMRI measurements in an MRI mockup installed in the seal enclosure (provided by Siemens Hamburg). The functional MRI scans will be conducted with a 3 Tesla MRI scanner at the MRI Flow Lab of the University of Rostock. The functional MRI scans will be analysed considering the specific neuroanatomy of the harbour seal brain which is currently being investigated in detail in another project in our research group. To our knowledge this will be the first fMRI study conducted on an awake marine mammal and will give a unique insight to the central neural mechanisms underlying sensory processing in the harbour seal, a secondarily adapted mammal.

Long-term deep brain stimulation in a transgenic alpha-synuclein rat model of Parkinson's disease using a fully implantable stimulation device

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases, occurs predominantly in advanced age, and is characterized by a chronic-progressive course. Typical neuropathological hallmarks are the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which leads to cellular and synaptic dysfunctions in basal ganglia and the progressive accumulation of Lewy Bodies containing alpha-synuclein. One successfully used therapeutic option, especially for advanced PD, is deep brain stimulation (DBS), most often applied in the subthalamic nucleus (STN). This therapy is symptom-oriented and currently used for treating motor symptoms, resulting in improved quality of life in PD patients. However, the underlying mechanisms of DBS, also concerning non-motor symptoms, are not fully understood. Therefore, there is an urgent need for further research in which animal models might contribute significantly to the understanding of DBS modes of action.

So far, we have used the 6-hydroxydopamine (6-OHDA) hemiparkinsonian rat model to investigate the effects of STN-DBS on midbrain dopaminergic cellular plasticity and found an increased number of dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) after five weeks of continuous DBS, which could be attributed to neurorestorative effects of STN-DBS. Due to limitations of the 6-hydroxydopamine (6-OHDA) hemiparkinsonian rat model, e.g., its unilaterality, the execution of behavioural studies is limited, for example, due to the interfering sensorimotor neglect. Thus, we plan to use a novel transgenic alpha-synuclein rat model for future studies. This alpha-synuclein rat model is characterized by an ubiquitous overexpression of the human full-length alpha-synuclein. In addition to a generalized deposition of alpha-synuclein, it shows a progressive loss of striatal dopamine and age-related motor impairments. Therefore, it reflects important hallmarks and the typical chronic-progressive course of human PD.

The project aims to further characterize the alpha-synuclein model, mainly by studying disease progression and the influence of bilateral long-term STN-DBS. For this purpose, a fully implantable neurostimulator, developed in cooperation with the Institute of Applied Microelectronics and Computer Engineering at the University of Rostock, will be used. Both the novel alpha-synuclein rat model and the fully implantable stimulator, which does not restrict the animals in their natural behaviour, now allow behavioural experiments.

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Feature-type distributed clustering for patient stratification on tabular clinical datasets

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Patient stratification is a fundamental challenge in clinical data science. It is a common practice to embed high-dimensional clinical data into a low-dimensional embedding using common manifold learning techniques. The low-dimensional embedding reveals patterns in the data which can be used for identifying and characterizing patient subpopulations of interest with respect to a clinical hypothesis.

However, we have noticed a fascinating challenge that arises from the diverse feature types typically present in clinical/epidemiological data. We found that, even though there are a few continuous features in a dataset, they have an overpowering effect while using UMAP for dimension reduction. We provided a solution for this in the form of a feature-type distributed clustering framework using different distance measures for different data types.

From a methodological perspective, we show that for diverse data types, frequent in clinical datasets, feature-type-distributed clustering using UMAP is effective as opposed to the conventional use of the UMAP algorithm. The application of UMAP-based clustering workflow for this type of dataset is novel in itself. Our clustering paradigm applies UMAP separately on continuous, nominal, and ordinal features separately. For each of these feature categories, we create a lower dimensional embedding of the dataset. Finally, we integrate the lower dimensional embeddings to extract clusters from them using the DBSCAN algorithm, a clustering algorithm used for extracting clusters from data based on data density.

Our approach to manifold learning reduces the bias induced by different variable types prevalent in clinical datasets. Therefore, it can have diverse applicability in patient stratification problems in clinical data science.

Downstream Effects of Mutations in SOD1 and TARDBP Converge on Gene Expression Impairment in Patient-Derived Motor Neurons

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Amyotrophic Lateral Sclerosis (ALS) is a progressive and fatal neurodegenerative disease marked by death of motor neurons (MNs) present in the spinal cord, brain stem and motor cortex. Despite extensive research, the reason for neurodegeneration is still not understood. To generate novel hypotheses of putative underlying molecular mechanisms, we used human induced pluripotent stem cell (hiPSCs)-derived motor neurons (MNs) from *SOD1*- and *TARDBP* (TDP-43 protein)-mutant-ALS patients and healthy controls to perform high-throughput RNA-sequencing (RNA-Seq). An integrated bioinformatics approach was employed to identify differentially expressed genes (DEGs) and key pathways underlying these familial forms of the disease (fALS). In TDP43-ALS, we found dysregulation of transcripts encoding components of the transcriptional machinery and transcripts involved in splicing regulation were particularly affected. In contrast, less is known about the role of SOD1 in RNA metabolism in motor neurons. Here, we found that many transcripts relevant for mitochondrial function were specifically altered in SOD1-ALS, indicating that transcriptional signatures and expression patterns can vary significantly depending on the causal gene that is mutated. Surprisingly, however, we identified a clear downregulation of genes involved in protein translation in SOD1-ALS suggesting that ALS-causing SOD1 mutations shift cellular RNA abundance profiles to cause neural dysfunction. Altogether, we provided here an extensive profiling of mRNA expression in two ALS models at the cellular level, corroborating the major role of RNA metabolism and gene expression as a common pathomechanism in ALS.

Glutamate receptor expression in human brain tumors and perampanel action in rodent glioma

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Seizures are a common comorbidity of glioblastoma. Both, glioblastoma and tumor-associated epilepsy share several pathological mechanisms, which drive tumor progression and generation of seizures. On key player is the neurotransmitter glutamate. In glioma, extracellular glutamate levels were found to be elevated up to 100-times higher than in unaffected brains. On the one hand, this may contribute to an increased glioma cell growth and, on the other hand, may lead to epileptic discharges and excitotoxicity, which in turn may facilitate tumor bulk expansion. Several glutamate receptors like mGluR3 are known to be upregulated in glioblastoma. In contrast to glioblastoma, there are hardly any data for brain metastasis.

In our study, we analysed the expression of glutamate receptors in tissues of glioblastoma and brain metastasis obtained from surgical resections. Additionally, clinical data like the presence of seizures were recorded. We were able to identify a panel of genes that are expressed differently between the two cohorts. As expected, mGluR3 was found to be higher expressed in glioblastoma than in samples of brain metastasis, but there are also differences in the group of the AMPA receptors.

Therefore we further asked, if an AMPA receptor antagonist may not only attenuate an epileptic phenotype, but also may affect tumor progression. As shown by our group in vitro, AMPA receptor antagonist perampanel acts in an antiproliferative manner and additionally may attenuate glutamate levels in human glioblastoma cells. To further investigate the role of AMPA receptors in glioma and tumor-associated epilepsy, we employed F98 glioma cells as an orthotopic tumor model in Fischer rats. Perampanel was tested in a monotherapy setting and also in combination with standard radiochemotherapy (RCT). Epileptiform activity was recorded with video EEG monitoring in vivo and in electrophysiological analysis of brain slices bearing F98 glioma in vitro. With respect to F98 gliomas, the tumor size was estimated and expression of AMPA receptors was analysed. In EEG recordings, we could demonstrate that perampanel abolished a tumor-associated epileptogenic phenotype. Furthermore, electrophysiological recordings suggested neuroprotective effects by perampanel in combination with RCT. With respect to the tumor disease, a highly reduced glioma size after RCT was determined whereas additional perampanel substitution had no further effect.

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