

# Department of Psychiatry and Psychotherapy

## Chair of Psychiatry and Psychotherapy

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### Research focus

- Depressions
- Dementias
- Addiction disorders
- Clinical neurochemistry and neurochemical dementia diagnostics
- Health Services Research
- Clinical Sensory Perception
- Sensory perception
- Molecular psychiatry

### Structure of the Chair

Professorships: 4  
Personnel: 248  
• Doctors (of Medicine): 36  
• Scientists: 29 (thereof funded externally: 14)  
• Graduate students: 83

### Clinical focus areas

- Depression
- Memory disorders
- Dementia
- Schizophrenia
- Addiction
- Anxiety disorders

### Research

Our research is based on a broad spectrum of methods, ranging from basic clinical research to clinical research and care research.

#### Depressions

Sphingolipids are essential components of the nerve cell membrane and regulate the flow of signals between neurons. We were able to further investigate the relationship between sphingolipids and affective disorders in translational preclinical and clinical studies.

Funding: DFG, BMBF, and IZKF

In a randomized-controlled multicenter study (StudieKuS) to investigate the efficacy of a Boulder Therapy intervention (BPT) in people with depression, BPT was shown to be significantly superior to the active control group and not inferior to Cognitive Behavioral Therapy, improvements are stable over at least 1 year, digitization of the manual was prepared. Funding: OH-DO-KWAN-Foundation

#### Dementias

In the context of clinically oriented basic research

on dementias, further studies were performed to better understand  $\beta$ -amyloid metabolism and the involvement of systemic immunological processes. Thus, it was shown that astrocytes may not only be involved in the clearance of amyloid beta peptides ( $A\beta$ ) in Alzheimer's disease (AD), but appear to produce N-terminally truncated  $A\beta$  ( $A\beta_{n-x}$ ) independently of BACE1, which generates the N-Terminus of  $A\beta$  starting with Asp1 ( $A\beta_{1-x}$ ). A candidate protease for the generation and degradation of  $A\beta_{n-x}$  is cathepsin B (CatB), which could explain the opposite roles of astrocytes in AD. Cell culture experiments of our study indicated that non-lysosomal CatB mediated the production of  $A\beta_{2-x}$  in astrocytes. However, the degradation of  $A\beta_{1-x}$  seemed to be dependent on lysosomal CatB in H4 neuroglioma cells, but not in primary astrocytes. These findings highlight the importance of considering organelle targeting in drug development to promote  $A\beta$  degradation.

In another study, we investigated whether microvesicles in CSF reflect AD and thus may be suitable for dementia diagnostics. Flow cytometric analysis showed that the microvesicular content of tau protein and APP was significantly reduced in Alzheimer's patients compared with controls. The total number of microvesicles and the expression of other antigens did not differ between the cohorts.

Another BMBF-funded collaborative project ("NADIM") in cooperation with the companies INVIGATE GmbH, Quantum Analysis GmbH, Immunotools GmbH and Cytecs GmbH is pursuing the development of a diagnostic system based on the identification of phagocytes recirculating from the brain into the blood. It thus pursues a novel cell- and blood-based approach in dementia diagnostics. The core of the project is the detection of phagocytosed, intracellular biomarkers of neurodegeneration.

In the nationwide, multicenter RCT DemWG, the effect of a complex psychosocial intervention on hospital admissions, falls, cognitive abilities, quality of life, and psychological and behavioral problems in people with dementia and MCI in shared-housing arrangements (abWGs) is investigated. Here, the complex intervention consists of the three components A) advanced training of nursing and care staff in abWGs, B) advanced training of the responsible GPs and C) non-pharmacological, multimodal group intervention MAKS-mk+. Collaborating partners: Institute for Public Health and Nursing Research (IPP) at the University of Bremen. Funding: Innovation Fund of the G-BA.

In the five-year "Digital Dementia Registry Bavaria (digiDEM Bavaria), the long-term course of people with MCI and mild to moderate dementia is investigated since 2019. In addition, various digital support services are being provided. The project is a cooperation of several partners of FAU. Funding: Bavarian State Ministry of Health and Care. In the RCT "MAKS-s", the effects of a multimodal psychosocial training program specially developed for people with severe dementia are being investigated. Funding: GKV Spitzenverband.

In the RCT "Stoppt die Demenz", two computerized cognitive training programs for influencing MCI symptoms are being investigated. Cooperation

partners: TH Nuremberg, genesis Systems gGmbH. Funding: Reinhard Frank Foundation.

In the observational study "Care4All (Ambient Assisted Living)" the use of a social assistance robot within a multimodal psychosocial group therapy for people with mild to moderate dementia is tested. The involvement of the therapy participants and therapists ensures a continuous expansion of the robot's functional range. Cooperation partners: HTW Dresden, Dresden University Hospital, Carus Consilium Dresden, Cognitec Systems GmbH and Cultus Dresden. Funding: European Regional Development Fund of the European Union.

#### Addiction disorders

The role of sphingolipids and their regulatory enzymes in the development of alcohol addiction was investigated in translational studies. A central role of ceramides in the brain could be demonstrated. In the emotional centers of the brain, such as the hippocampus and the amygdala, individual ceramides regulate not only alcohol consumption, but also behavior associated with anxiety and depression. Thereby, the local ceramide concentration is controlled by a large number of different enzymes. It could be shown that the activity of acid sphingomyelinase also plays an important role in the development of cocaine addiction in behavioral models in rats and primates. The changes indicate that lipid systems also exhibit a molecular plasticity in the development of addiction, as is typical for normal learning processes. Other enzymes involved in the development of addiction are the neutral and acidic ceramidase. A brain area-specific role in different learning processes could be demonstrated especially for the neutral ceramidase. Furthermore, it could be shown that the neutral ceramidase in the blood is a good predictor for the cognitive performance in rats and primates.

In further studies, the role of 2D: 4D finger lengths, the neuroimmune regulator TANK and the leptin or testosterone levels in the blood as risk factors for alcohol addiction could be confirmed and expanded. In addition, new pharmacotherapies were investigated in preclinical tests. Promising results were found in reducing the amount of alcohol drinking for the FKBP51 inhibitor SAFit2.

Funding: DFG

#### Clinical neurochemistry and neurochemical dementia diagnostics

The analysis of the cerebrospinal fluid (CSF) offers excellent diagnostic possibilities in a variety of neurological and psychiatric disorders, and the Laboratory for Clinical Neurochemistry and Neurochemically Dementia Diagnostics has been an internationally recognized center for neurochemical diagnostics of neurodegeneration for several years now. In spite of global pandemic issues, the Laboratory was 2020 successfully reaccredited and extended its ISO 15189 certificate for the next five years. The Lab continued its efforts in development and validation of new biomarkers of neurodegeneration, including candidate biomarkers from the blood. The Erlangen Score interpretation algorithm, developed in the

Laboratory and reported in details in the previous Report (2019), was further validated, and finally was included as a routine tool for diagnostic application. To that end, a close cooperation with the MIK-Team resulted in a full automatization of the algorithm on the lab's data processing platform (Swisslab). The Erlangen Score algorithm was also recommended in the official S1 guidelines "Lumbar puncture and Cerebrospinal Fluid Analysis" of the German Neurological Society (AWMF-Nr.: 030/141). Following this development, several centers in Germany decided to adopt the algorithm for their routine use. The head of the Laboratory continues his tasks as a member of the advisory board of the German Society of Clinical Neurochemistry and CSF Analysis (DGLN, e. V.), and the Board of the Society accepted our offer to organize the next Conference of the Society in Erlangen, which will be held in May 2021 (most probably as a virtual event). The Lab continues its coordination tasks in the international inter-center proficiency testing scheme for CSF biomarkers biobanking.

### Health Services Research

In cooperation with the Interdisciplinary Pain Center, the care situation of headache patients in the long-term course is examined. The evaluation of the routine data contains courses over a period of 5 years. In cooperation with the MDK Bavaria, a representative study on the situation of informal caregivers was started in order to investigate not only the care needs but also the benefits of home care for the first time. Funding: Leifheit Foundation.

### Clinical Sensory Perception

While sensory information such as touch, vision and hearing is normally primarily processed via the thalamus as the "gateway to consciousness", the olfactory system has a special feature: It partially projects directly into the limbic system without thalamic filtering. We make special use of this feature to investigate anhedonia, the inability to feel pleasure, by olfactory means.

Anhedonia can occur as a severe symptom in depression, and it further defines the subtype of melancholic depression. It has been shown that patients with melancholic depression have an altered olfactory experience (Clepce et al. 2010). In depressed patients, the limbic system shows morphological changes and it is thus also a key structure for the genesis of depression. With specific knowledge about the processing of olfactory information, a basis for the design of an odor-based anhedonia test will be formed.

Our completed study of 61 subjects clearly shows that memories can be effectively triggered by presentation of odors, and that these memories can be efficiently assessed in terms of hedonic value and intensity using our testing algorithm. We attributed the correlation of the hedonic value of an odor with the hedonic value of the memory elicited to a learned affective evaluation of an odor: If an odor is already positively occupied by experience, we also perceive it as more pleasant. For further validation, in an ongoing study depressed and anhedonic patients versus healthy control subjects will be tested with our olfactory anhedonia test. Anhedonia represents a cross-diagnosis phenomenon in psychiatric disorders. Thus, the olfactory approach of our test development could be potentially relevant for a variety of disorders.

### Sensory perception

One focus of our work are multisensory integration studies with respect to food perception. Currently, we are working on the topic of olfactory-visual integration during food intake in different life stages

within the BMBF cluster Enable. Here we investigate the influence of age on sensory integration processes, as well as the influence of a product label on sensory perception using functional imaging.

Olfactory-trigeminal interactions are of particular importance with regard to the masking of unpleasant odor impressions. In an fMRI experiment, we investigated the masking behavior of a eucalyptol-ammonia mixture. The aim was to mask the unpleasant ammonia odor using the fresh eucalyptol odor. It was established that the olfactory component of the ammonia could be masked, but the trigeminal component could not be masked. Trigeminal perception was actually enhanced by the addition of eucalyptol. This enhancement was also reflected in the activation of typical parts of the pain system of the human brain - the insula and the secondary somatosensory cortex.

We are also members of the Global Consortium for Chemosensory Research (GCCR), which is interested in the impact of SARS-CoV-2 infection on the chemical senses. A questionnaire was created to query the subjective assessment of the senses of smell and taste, as well as trigeminal perception during infection. It was found that SARS-CoV-2 infection leads to severe impairment of the senses of smell and taste, and that the loss of the senses of smell and taste during the pandemic should be understood as an alarming symptom of infection.

### Molecular psychiatry

Synaptic transmission plays a key role in neuronal function. The release of neurotransmitter from presynapse depends on highly complex and dynamic interplay of proteins and lipids. The breakdown and dismantling of presynapse is the first hallmark in various neurodegenerative and neuropsychiatric conditions, indicating that presynapse represents the neuronal compartment with highest vulnerability to pathological insults. Over the past years, we investigated the molecular mechanism that control neurotransmitter release and contribute to presynapse integrity. In collaboration with M. Heine (Mainz) we demonstrated that naturally expressed splicing variants of presynaptic voltage gated calcium channels that differ in their anchoring to presynaptic scaffolds and lateral mobility within presynapse also decisively shape plasticity of neurotransmitter release. DFG FE1335/3

We discovered new role of presynaptic scaffolding protein CtBP1 in the retrieval of synaptic vesicles during compensatory endocytosis. DFG GRK2162, IZKF J74

We conducted further studies in the frame of the collaborative project GeNeRARE (German Network of RASopathy research). BMBF GeNeRARE

We described new function of scaffold protein Bassoon in the control of presynaptic protein homeostasis. Bassoon interacts with the core proteasome and via this interaction, it inhibits its catalytic activity. In collaboration with M. Friese (Hamburg) we demonstrated that proteasome activation and Bassoon inactivation are neuroprotective in an animal model of amyotrophic lateral sclerosis. DFG 1335/1

### Teaching

The Department of Psychiatry and Psychotherapy participates with compulsory and elective subjects in the curricular teaching of Medicine and Logopedics. Particularly noteworthy here is the interdisciplinary teaching within the framework of the cross-sectional subjects EKM, Q9 (clinical pharmacology / pharmacotherapy) and Q10

(prevention and health promotion) and in the context of the compulsory elective subject of sexual medicine. Since 2019, the department offers an interprofessional seminar to teach taking a sexual anamnesis to students of medicine and psychology as well as nurses-to-be. The Department has further expanded the simulation program of patients. Students can practice acting in difficult situations with agitated, affective, rejecting and uncooperative patients. In addition, Objective Structured Clinical Examinations (OSCE) stations were developed to validate communication and investigation skills. Induced by the corona pandemic, the classical lecture has been replaced by online case discussions and blended learning. The bed-side teaching has also been shifted to the internet by replacing face to face examinations by video-calls.

Curricular teaching in Medical Psychology and Medical Sociology in the preclinical study section includes a basic lecture, a course and a seminar. During the reporting period, Erlangen's medical students achieved the rank 1 in the written part of the first section of the Medical Examination compared to all other German universities with the same examination format (multiple choice). Bachelor's and Master's theses as well as MD and PhD theses are supervised.

### Selected publications

Baldeiras I, ..., Lewczuk P. Erlangen Score as a tool to predict progression from mild cognitive impairment to dementia in Alzheimer's disease. *Alzheimers Res Ther*, 2019;11(1):2.

Zoicas, I, ..., Kornhuber, J., (2020) Ceramides affect alcohol consumption, depressive-like and anxiety-like behavior in a brain region- and ceramide species-specific way in male mice. *Addiction Biology* 25: e12847.

Parma V et al. (2020) More than smell. COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chemical Senses* 2020 Oct 9;45(7):609-622.

Kratzer, A., ..., Graessel, E. (2020). The DemWG study: reducing the risk of hospitalisation through a complex intervention for people with dementia and mild cognitive impairment (MCI) in German shared-housing arrangements: study protocol of a prospective, mixed-methods, multicentre, cluster-randomised controlled trial. *BMJ Open*, 10(12), e041891.

Karg N, ..., Luttenberger K. (2020) Bouldering psychotherapy is more effective in the treatment of depression than physical exercise alone: results of a multicentre randomised controlled intervention study. *BMC Psychiatry*. 12;20(1):116.

Ivanova D., ..., Fejtova A. (2020). CtBP1-Mediated Membrane Fission Contributes to Effective Recycling of Synaptic Vesicles. *Cell Rep* 30, 2444-2459 e2447.

### International cooperations

Prof. G. Schumann, Institute of Psychiatry Psychology and Neurology, King's College London, London: Großbritannien

Prof. M. Filip, Institute of Pharmacology, Polish Academy of Sciences, Krakow: Poland

Prof. M. Barros, Primate Center, University of Brasilia, Brasilia, Brasilien

Dr. Z. Hassan, Centre for Drug Research, Universiti Sains Malaysia, Penang: Malaysia

Prof. H. Zetterberg, Sahlgrenska Academy, Mölndal: Sweden