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Narrative academic profile

I am a clinical psychiatrist ("Oberarzt") leading the research group (RG) Animal Models in Psychiatry at the CIMH. My RG develops, establishes and uses rodent models for psychiatric disorders using translational research approaches, especially for affective disorders such as depression and anxiety, but also for schizophrenia and cognitive disorders. For this purpose, we use mice and rats as model organisms. One of the core competences of my RG are behavioral analyses, in the homecage as well as using simple and elaborated mazes or fully-automated complex conditioning systems, like so-called touchscreen boxes. Using these methods and techniques, we often also contribute to collaborative projects using multisystem approaches for gene-function-studies.

On the molecular level, my RG has primarily focused on studying the role of glucocorticoid receptors, the nerve growth factor BDNF, and, more recently, the dopaminergic and the glutamatergic systems. To this end, we often use transgenic animals with targeted genetic alterations, corresponding at best to human genetic variations and/or dysfunctions associated with psychiatric disorders. Pivotal in this context is the role of gene-environment interactions, based on the discovery that usually a genetic predisposition or unfavorable environmental conditions (such as stress, past or current trauma) alone do not lead to psychiatric disorder, but rather the combination of both. This can be modelled in vivo by using transgenic animals with mutations of a chosen risk gene and exposing them to defined stressors at specific points in their development. In contrast, we use environmentally enriched housing conditions to search for resilience factors for a given genetic or molecular risk.

In recent years, the implementation of the 3R principles (Reduce, Refine, Replace) is a central basis for our work. This serves to align animal welfare with the requirements of the respective animal models. A key aspect of this endeavor is the scientific evaluation of stressors implemented in these animal models, which we analyze within the DFG-funded national Research Group FOR 2591 (www.severity-assessment.de). Our aim is to generate an evidence-based assessment of severity and identify the least stressful methods and approaches, to be able to substitute the more stressful ones consequentially, if less stressful ones will lead to the same results and insights.

We envision the following three projects in the next future: Together with the EU consortium UNMET we will study rats with a knockout (KO) of the serotonin transporter (SERT), one of the key genes and molecules in the field of psychiatry, being important both for pathogenesis and therapy. SERT-KO rats exhibit features of depression as well as mania, and our hypothesis is that SERT could be a pivotal molecule for the antidepressant-induced switch from depression to mania.

In the latest editions of classifications of psychiatric disorders, catatonia has been recognized as an own psychiatric entity. Together with the clinical RG of Dusan Hirjak (CIMH) and the translational neuroimaging RG of Alexander Sartorius and Wolfgang Weber-Fahr (CIMH) we

strive to develop a (transgenic) rodent model of catatonia that reflects crucial clinical features and can be used to study anatomical and molecular features of pathogenesis and therapy.

Automated home cage monitoring using physiological parameters like heart rate and body temperature as objective read-outs together with behavioral parameters obtained from permanent camera-monitoring seems the method of choice to study experimental animals under optimized welfare conditions. Together with the national Research Group FOR 2591 we will develop such a system in order to develop severity criteria which will finally enable monitoring of animal welfare and adherence 3R principles. Moreover, this system can contribute to the physiological and behavioral analyses of psychiatric animal models, allowing to study animals under the most natural (i.e. compared to a maze or an arena) or at least undisturbed environmental conditions possible.

Last but not least I try to promote and support young scientists and clinicians. From my RG originate 13 doctoral theses in medicine/biology and 2 habilitations. Together with the respective doctoral candidates I won twice the Hans-Heimann-Prize of the DGPPN (2011 with J. Fuß, 2018 with J. Steinle).

Key output of the years 2020-now

Homberg JR, Adan RAH, Alenina N, Asiminas A, Bader M, Beckers T, Begg DP, Blokland A, Burger ME, van Dijk G, Eisel ULM, Elgersma Y, Englitz B, Fernandez-Ruiz A, Fitzsimons CP, van Dam AM, **Gass P**, Grandjean J, Havekes R, Henckens MJAG, Herden C, Hut RA, Jarrett W, Jeffrey K, Jezova D, Kalsbeek A, Kamermans M, Kas MJ, Kasri NN, Kiliaan AJ, Kolk SM, Korosi A, Korte SM, Kozicz T, Kushner SA, Leech K, Lesch KP, Lesscher H, Lucassen PJ, Luthi A, Ma L, Mallien AS, Meerlo P, Mejias JF, Meye FJ, Mitchell AS, Mul JD, Olcese U, González AO, Olivier JDA, Pasqualetti M, Pennartz CMA, Popik P, Prickaerts J, de la Prida LM, Ribeiro S, Roozendaal B, Rossato JI, Salari AA, Schoemaker RG, Smit AB, Vanderschuren LJMJ, Takeuchi T, van der Veen R, Smidt MP, Vyazovskiy VV, Wiesmann M, Wierenga CJ, Williams B, Willuhn I, Wöhr M, Wolvekamp M, van der Zee EA, Genzel L.
The continued need for animals to advance brain research.
Neuron 109: 2374-2379, 2021

This Opinion Paper envisions a dogma of the behavioral neurosciences, i.e. that behavior and behavioral disease states cannot be studied in a dish. At the same time, we try to scientifically evaluate the severity and impact of psychiatric disease models on animals' wellbeing, in order to reduce and refine current and future psychiatric rodent models, since the current severity categorizations are – at least in part – based on anthropomorphic jugdements. Representing the topic and field of psychiatric animal models in a national research group funded by the DFG we could demonstrate by newly established research criteria within this consortium that several commonly used models for depression- or schizophrenia-like endophenotypes are burdened with moderate severity only. This evidence may promote the further use of longstanding behavioral paradigms that have been at risk of elimination due to erroneous severity classifications. The following papers are representitve for our activities in this field.

Mallien AS, Häger C, Palme R, Talbot S, Vogt MA, Pfeiffer N, Brandwein C, Struve B, Inta D, Chourbaji S, Hellweg, R, Vollmayr B, Bleich A, **Gass P**
Systematic analysis of severity in a widely-used cognitive depression model for

mice.
Laboratory Animals: 54: 40-49, 2020

Mallien AS, Pfeiffer N, Brandwein C, Inta D, Sprengel R, Palme R, Talbot SR, **Gass P**
Comparative severity assessment of genetic, stress-based, and pharmacological mouse models of depression.
Frontiers in Behavioral Neuroscience 16: 908366, 2022

Mallien AS, Becker L, Pfeiffer N, Terraneo F, Hahn M, Middelman A, Palme R, Begni V, Riva MA, Leo D, Potschka H, Fumagalli F, Judith R. Homberg JR, **Gass P**
Dopamine transporter knockout rats show impaired wellbeing in a multimodal severity assessment approach.
Frontiers in Behavioral Neuroscience 16: 924603, 2022

While these studies may serve as landmarks for the severity assessment of so-called depression models, we analyze analogously models used in schizophrenia research. In a first study we could demonstrate a moderate burden in a transgenic mouse line (AMPA receptor subunit GluA1 knockout) already in postweaning young animals, demonstrating also the importance to study animal models at different stages of the lifespan.

Reiber M, Stirling H, Sprengel R, **Gass P**, Palme R, Potschka H
Phenotyping young GluA1 deficient mice – a behavioral characterization in a genetic loss-of-function model.
Frontiers in Behavioral Neuroscience 16: 877094, 2022

This manuscript is also part of several cooperations with other groups concerning gene-function-studies on glutamatergic or dopaminergic genes. In the first mentioned below we detected a similar phenotype in mice as in humans with the corresponding single nucleotide polymorphism (SNIP). The second paper demonstrates network studies using the same neuroimaging techniques applied for humans in DAT-KO rats, a novel translational model for human diseases involving aberrant dopamine functions.

Bertocchi I, Eltokhi A, Rozov A, Nguyen Chi V, Jensen V, Bus T, Pawlak V, Serafino M, Sonntag H, Yang B, Burnashev N, Li SB, Obenhaus H, Both M, Niewoehner BU, Single FN, Briese M, Boerner T, **Gass P**, Rawlins JNP, Köhr G, Bannerman DM, Sprengel R
Voltage-independent GluN2A-type NMDA receptor Ca 2+ signaling promotes audiogenic seizures, attentional and cognitive deficits in mice.
Communications Biology 4(1): 59, 2021

Reinwald JR, Gass N, Mallien AS, Sartorius A, Becker R, Sack M, Falfan-Melgoza C, Clemm von Hohenberg C, Leo D, Pfeiffer N, Middelman A, Meyer-Lindenberg A, Homberg JR, Weber-Fahr W, **Gass P**
Dopamine transporter silencing in the rat: systems-level alterations in striato-cerebellar and prefrontal-midbrain circuits.
Molecular Psychiatry 27(4): 2329-2339, 2022

Using neuronal activation and injury markers (c-Fos, Hsp-72) we study signalling effects and potential vulnerability exerted by glutamatergic drugs with the potential to be used as rapid-acting antidepressants in depressive patients. This is one of the fields where intense clinical and preclinical activities in the CIMH are ongoing, in order to improve the mechanistic understanding of pathogenesis and (rapid) therapy of depression.

Vasilescu AN, Mallien AS, Pfeiffer N, Lang UE, **Gass P**, Inta D
Rapastinel alleviates the neurotoxic effect induced by NMDA receptor blockade in

the early postnatal mouse brain.
European Archives of Psychiatry & Clinical Neuroscience 271: 1587-1591, 2021

Vasilescu AN, Pfeiffer N, Terraneo F, Riva MA, Inta D, Lang UE, **Gass P**
Region-specific enhancement of c-fos expression by combined treatment with NMDA receptor agonists and antagonists with antidepressant potential.
International Journal of Neuropsychopharmacology in press

Gass P, Vasilescu AN, Inta D
Rapid-acting antidepressants-neurobiological mechanisms of action.
Der Nervenarzt 93: 233-293, 2022