Wolfgang Kelsch, RG Developmental Biology of Psychiatric Disorders

Narrative academic profile: I studied Medicine and received a doctoral degree in cellular neurophysiology in Heidelberg. Following Postdoctoral training at the Max-Planck-Institute of Psychiatry and the Massachusetts Institute of Technology, I set up a DFG Emmy-Noether-Group at CIMH in 2012. In parallel to my work as a Board Certified Psychiatrist with focus on affective disorders, I am leading the RG Developmental Biology of Psychiatric Disorders at the Dept. of Psychiatry at CIMH. In 2019, I was additionally appointed W2-Professor at the Dept. of Psychiatry at the University Medical Center of the Johannes Gutenberg University Mainz and group leader of the RG Systems Neuroscience and Mental Health.

My research focus are basic brain plasticity mechanisms relevant to social and reward prediction learning. Why? Both social memories of and coping with stress as well as individual's perception of rewards are two main risk factors for triggering stress-related disorders like depression. Importantly, these response factors are accessible to be modified by interventions. These factors have a great potential for development of transdiagnostic interventions, but the neurobiology and the interactions between these factors are incompletely understood. Animal models offer the great advantage that neuronal mechanisms can be directly causally tested in the brain. There are however a number of challenges with current approaches that my group tries to address to facilitate true progress in this field. Two main challenges shall be highlighted here. Firstly, we need more ecologically relevant models for stress-related disorders and thereby increase their translational value. Secondly, we need comparable functional read-outs that can be directly translated between translational animal models and humans. fMRI is of great value here for humans, but fMRI in mice during cognitive tasks and awake imaging was not available.

My long-term vision is therefore dual-fold. Firstly, we aim to develop more humane and ecologically valid assays for social-stress responses that also allow to study complex interactions between behavioral domains. Secondly, we aim to fully develop behavioral mouse fMRI combined with mechanistic molecular and circuit manipulations and cell physiology to identify brain mechanisms that can be exploited to develop novel, rationale clinical interventions.

Critical steps achieved since 2020:

1. In 2019, we have started working on a maze for mice that allows to track them 24/7 in multiple behavioral domains over weeks and month. No experimenter intervention shall be necessary during this time. The maze now consists of multiple components. We have developed an automated social hierarchy test that is built into the connecting tubes of the maze and thereby continuously tracks the hierarchy relations in the colony. Social hierarchy stress is the strongest predictor for development of depressive symptoms and evolutionary conserved. Other modules have been established and are continuously refined like complete surveillance of social behavior with tracking through an RNN-based automated analysis pipeline. Another important aspect was to optimize the reliability of the stability of the system and the reward learning module. These goals were achieved by the strong computational and engineering competence in the group and a close cooperation with the Fraunhofer Institute. The further development and validation of the system termed NoSeMaze is funded since 2021 by a BMBF 3R Alternatives to Animal Experiments consortium that I coordinate. The system is currently prepared for publication as a first of its kind full open source platform that can be broadly adapted and

used for behavioral brain research questions. These activities are embedded by membership in the BMBF National 3R Network and the EU cost action Teatime coordinating developments of naturalistic mouse habitats.

2. The second milestone is to fully establish fMRI in behaving mice to obtain a directly comparable readout to human cognitive and psychiatric research. One important aspect here is that the added value of mice is only leveraged by causal manipulation. Once particular activation brain regions or networks relevant to a cognitive or disease-related process have been identified in fMRI, they can be mechanistically dissected by in vivo recordings and/or interventions. We therefore have established a hierarchical approach that parametrizes behavior to then identify brain regions and functional networks involved in specific cognitive processes. Within this hierarchical approach, the cellular coding mechanisms are dissected in the fMRI-identified regions. The feasibility of this hierarchical approach and novel insights in the updating mechanisms of cue-specific outcome expectations are illustrated in a recent publication from our group together with the Dept.'s RG Translational Imaging (Winkelmeier et al.., 2022; for details see please 'Key outputs' below). This approach can be combined with molecular pharmacology, optogenetics, and novel knock-out strategies that we use in the lab as detailed below in 'Key outputs'. In current work, we use this hierarchical approach for instance either in conjunction with longitudinal studies in mice that live in the NoSeMaze and undergo longitudinal fMRI during tasks, or examine the roles of oxytocin in social recognition and memory formations as in the NSF-BMBF CRCNS project with Prof. Linster at Cornell. Other examples involve a new Leibniz Society-Cooperative Excellence Project „Learning Resilience: Supporting neuronal network state transitions to foster stress resilience (K430/2021)": Brain wide network state for cognitive flexibility in behavioral fMRI (2022-2025) where the hierarchical approach provides the backbone. The work described above requires a multi-disciplinary team. In particular, novel computational frameworks are needed and due to the massive data acquired, innovative data analytics is needed tailored to the specific demands.
3. Here, I am trying to support young scientists to gain early independence in the group. For instance, in the framework of the work above, I could convince in 2020 the Boehringer Ingelheim Foundation to fund a RG Complex Systems in Translational Resilience Research. Through this junior group funding, we could attract a talented Physicist, Dr. Eleonora Russo, as P.I. and collaborate on our overall goal and at the same time develop full independence with now-documented independent publications and a series of invited talks amongst others at the Sainsbury Center at UCL this June.

Key output of the years 2020-now: I would like to illustrate the above research agenda with three key publications from that last two years:

The first research paper by Winkelmeier et al. (2022) established behavioral fMRI fully in mice. So far only one study existed in behaving mice from the Shanghai Institute that however had technical limitations with regards to the BOLD dynamics and task performance in fMRI. In Winkelmeier et al., we established in close collaboration with the RG Translational Imaging awake fMRI based on our experience with head-fix recordings during behavior. We implemented additional habituation and handling steps so that animals performed well during scanning with low levels of stress. In this first study, we then modeled the behavior and could identify regions that were involved in value prediction, prediction error and cue-specific updating of predictions based on recent outcomes. fMRI thus served as a discovery tool. Notably, the small set of regions that fully compute the prediction error in humans, matched

those now identified in mice; arguing for a surprising level of conservation that will help translation. We then validated the computation of this information with multi-site single unit recordings in the fMRI-identified brain regions. These recordings identified multiple co-existing prediction signals that integrate information at different time scales. Their distributed and shared coding mechanisms were dissected. This work has received strong resonance in the field, and will be part of a number of evolving consortia.

This second paper by Ethoki et al. (2021) is a cooperation with the Depts. of Genetics and Neuroanatomy in Heidelberg and highlights the power of combining multiple levels of analyses for understanding the consequences of altered functions of risk genes in neurodevelopmental disorders. We found here bidirectional effects of gene dosing and loss of function point mutations on synaptic function and molecular synaptic profiles. Interestingly, the two mouse lines with elevated or lowered bevels of functional Shank2 expression (derived from human syndromes) altered bi-directionally the neuronal signal-to-noise levels and decoding abilities consistent with phenotypic alterations in social exploration behavior. Notably, the neurodevelopmental phenotypes were rescued by normalizing gene expression in the adult.

The third example (Oettl et al., 2020) directly relates to the first study described above and examined the neuronal mechanisms how animals generate outcome predictions. While prediction coding has been extensively shown to be expressed in dopamine neurons in the VTA and dopamine dependent reinforcement learning is implicated in forming such predictions, the proof of sufficiency for dopamine to induce such reinforcement of sensory cues was missing in awake animals. This is important as such reinforcement-related prediction learning is thought to be a core mechanism in the development of psychosis as well as cognitive bias in depression. We could show here that endogenous dopamine release was sufficient to reinforce stimulus responses in the ventral striatum and that these reinforced ventral striatal responses can drive the learnt prediction response in dopamine neurons in stimulus-outcome learning. This work provides the basis for a number of ongoing studies in which we genetically manipulate the system and explore the consequences for prediction coding, biases, and, complex behavioral phenotypes in social behaviors with the use of NoSeMaze and non-invasive genetic silencing.

References:

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