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Narrative academic profile:

How do we make adaptive choices in changing and novel environments? My main research interest is to understand how subjects make flexible decisions in complex environments. Behavioral flexibility is a hallmark of intelligent behavior and deficits in this cognitive domain are observed in several major neuropsychiatric disorders such as schizophrenia, autism, Parkinson's disease or frontal lobe lesions. This deficit is of major clinical importance because cognitive deficits are one of the strongest predictors of long-term functional outcome (e.g., in schizophrenia), but present treatment options are very limited. In order to develop new therapeutic approaches, we need to understand the underlying (patho-)physiology. However, we still lack a coherent understanding of how correct task rules are identified in an ever-changing environment and how this information is encoded in neural activity. Our group uses a translational approach and performs behavioral and neural recordings in both rats and humans. Our aim is to identify species-conserved mechanisms of behavioral flexibility using a combination of behavioral, computational and electrophysiological analyses.

I have been interested in analyzing translational research questions that require a broad methodological repertoire since medical school. During my thesis work in the group of Professor Draguhn (Institute of Physiology and Pathophysiology, University of Heidelberg), I studied the physiological mechanisms underlying neural oscillations in an acute slice preparation of the mouse hippocampus. This involved the use of several extra- as well as intracellular recording techniques combined with pharmacological interventions, advanced analysis of electrophysiological data as well as histological methods (Both et al., 2008; Wulff et al., 2009; Bähner et al., 2011; Viereckel et al., 2013). We discovered and characterized a physiological correlate of assembly formation during hippocampal high-frequency oscillations (Bähner et al., 2011). Specifically, we could show how neurons that participate in a given network pattern are distinguished from the majority of nonparticipating cells. This work is relevant for the cellular and network mechanisms underlying memory consolidation. During my residency in general psychiatry, I joined the group of Professor Meyer-Lindenberg at the Central Institute of Mental Health (CIMH) in Mannheim to study hippocampal-prefrontal physiology at the systems level in humans. Our aim was to clarify the role of hippocampal-prefrontal interactions in working memory and how they are altered by both genetic variation and in patients with schizophrenia. I established a virtual reality version of a translational spatial working memory task that is widely used in rodents (radial arm maze) within the context of the Bernstein Center for Computational Neuroscience Heidelberg-Mannheim. Within this project, I used various methods that involve processing and analysis of high-dimensional functional MRI data (e.g., general linear models, principal and independent component analysis, multivariate pattern analysis; Demanuele et al., 2015). We could show that hippocampal-

dorsolateral prefrontal BOLD functional connectivity during the performance of a virtual reality task significantly predicted spatial working memory capacity in healthy individuals (Bähner et al., 2015, 2017). This translational approach helps to bridge previous discrepant results and suggests that hippocampal-prefrontal coupling may be a systems-level mechanism of spatial working memory that is conserved across species.

However, many research questions are difficult to answer at the macroscopic level and instead require a complementary analysis of neural microcircuits. I therefore decided to return to a translational rat model to understand the microcircuits underlying cognitive flexibility and started as a PostDoc in an interdisciplinary project of the SPP1665 with Prof. Daniel Durstewitz (CIMH) and Prof. Wolfgang Kelsch (CIMH, Mainz University). In this project, we used a combination behavioral, optogenetic and electrophysiological methods together with advanced time-series analyses to understand the microcircuit mechanisms of sudden transitions in prefrontal rule representations (Toutounji, Bähner et al., *in preparation*).

During that period, I successfully applied for my first DFG grant (BA5382/1-1: *“Verarbeitung präfrontaler und phasischer dopaminerger Signale im ventralen Striatum während eines rule switching-Paradigmas”*, 11/2014-02/2019) and became a Co-PI in the second funding period of the SPP1665 (BA 5382/2-2: *“Netzwerkdynamiken und computationale Mechanismen des Regellernens II”*, 10/2016-09/2019). In 2017, I won the third CIMH Young Investigator Award (*“Friends or food – are there medial prefrontal circuits dedicated to social decision making?”*) which allowed me to establish my own junior research group in the Department of Psychiatry and Psychotherapy. So far, our group has published two experimental papers that focused on methodological issues of the DREADD technology (Ilg et al., 2018) and the effect of an impulsive behavioral phenotype (“sign tracking”) on rat executive functions (Enkel et al., 2019). During that time period, four medical students and two Master students have completed their projects under my direct supervision, four additional medical doctoral theses are still ongoing. Since 2020, my work as a clinician scientist - now as a senior physician (“Oberarzt”) - is supported by the MACS (Mannheim Advanced Clinician Scientist) program (*“Translational models of behavioral flexibility as a tool to understand prefrontal (patho-)physiology”*, mentors: Prof. Meyer-Lindenberg, Prof. Andreas Draguhn).

Within the context of our work on rule learning in rats, I have always been fascinated by the question how rats actually infer task rules in a complex environment. Intriguingly, rats also show hallmarks of flexible behavior such as sudden transitions in performance or faster learning with prior experience. However, despite a wealth of information about task-related neural firing patterns, necessary brain regions and involved neurotransmitters in the context of rule-switching paradigms, virtually nothing is known about the underlying learning mechanisms in rodents. Based on theoretical work in humans and own experimental observations, we hypothesized that rats test hypothetical rules such as *“don’t press any lever with a bright light regardless of position”*. We call these hypothetical rules behavioral strategies and found preliminary evidence that rats test them sequentially to identify task rules. Because the identification of a species-conserved mechanism of behavioral flexibility would be a major scientific finding, I decided to put all available resources into this project. In order to achieve that goal, we had to broaden our methodological repertoire and I started several national (magnetoencephalography/MEG: Andreas Meyer-Lindenberg, CIMH; multi-site local field potential recordings: Andreas Draguhn, Heidelberg University) and international collaborations (reinforcement learning models: Hazem Toutounji, University of Nottingham, UK; MEG data analysis Tzvetan Popov, University of Zurich, Switzerland).

Our group first developed a novel translational rule-learning task that allowed us to investigate whether rats follow low-dimensional behavioral strategies to test task features for relevance. Using a combination of behavioral, computational and electrophysiological methods, it became clear that rats are indeed able to infer task rules similar to what has been described for humans. For example, we tracked rat head movements and found that rats sequentially focus their attention on different task features while testing strategies and we were able to decode behavioral strategies from rat prefrontal multiple single-unit recordings. We then developed a corresponding human paradigm to verify that rats and humans use similar learning mechanisms in the same task and we further emphasized the cross-species link by showing that behavioral strategies can also be decoded from MEG signals in human prefrontal cortex.

These mechanistic findings provide a foundation for the translational investigation of impaired cognitive flexibility. Current work focusses on understanding pathophysiological processes in a rat model with an environmental risk factor of psychiatric disease (postweaning social isolation; collaboration with Peter Gass, CIMH) and we plan to combine eye tracking and MEG recordings in patients.

Key output of the years 2020-now:

In the last three years, my entire scientific work focused on the identification of a species-conserved mechanism of behavioral flexibility (see above). We investigated >50 human subjects and >200 rats using multiple behavioral, computational and electrophysiological methods in the context of several collaborations. Due to the complexity of this interdisciplinary project, we are only now completing our first manuscript based on this huge data set (Bähler et al., *in preparation*). During that process, we also plan to make the MATLAB code developed in this project freely available on GitHub.

Our group presented this work at different stages of the project both nationally and internationally. I first presented our data in a talk at an international conference (SPP1665 concluding symposium in Hamburg: *"Behavioral strategies guide rule learning in rats: novel behavioral mechanisms and associated prefrontal dynamics"*). We also discussed our data in the context of the ZIHUB in 2021 both as a poster at the ZIHUB Mental Health Alliance Retreat and in a talk (ZIHUB Joint Research Colloquium: *"How do we learn to make good choices: a translational model of cognitive flexibility"*). Our most recent presentations in 2022 include a talk at the virtual 4th Joint DKFZ – ICON Clinician Scientist Network Meeting (*"Translational models of behavioral flexibility as a tool to understand prefrontal (patho-)physiology"*) and a poster at FENS Forum in Paris (*"Selective attention aids rapid learning in complex environments"*).

Moreover, I have always been eager to learn about new topics with translational relevance and together with several colleagues, I recently helped to organize an interdisciplinary conference on the therapeutic potential of psychedelics (IZN Retreat 2022: *"Psychedelics in Neuroscience and Medicine: Hope or Hype?"*).