Urs Andreas Braun

1. **Narrative academic profile, 1200 words:**
   -

   The complexity of mental disorders results in a critical need for clinician scientists trained in both basic research and clinical practice to enable translational research from which patients genuinely benefit. I was lucky to have the possibility to receive outstanding training in both domains at one of the leading institutions in Germany, the Central Institute of Mental Health in Mannheim, under the supervision of Professor Andreas Meyer-Lindenberg. During my residency in psychiatry, I have acquired expertise in the field of adult psychiatry and psychotherapy while, in parallel, my scientific work has focused on developing, implementing, and applying innovative methods from the field of network theory to neuroimaging datasets of both healthy and clinical populations as well as cross-species. This was supported by long and fruitful cooperation with Professor Danielle S. Bassett from the University of Pennsylvania, starting in 2015 with my first visit to her lab to work with her on dynamic network approaches in psychiatric disorders, leading to a series of publications in peer-reviewed journals.

   The stepwise convergence of these two pillars, clinical work and computational neuroscience, has remained the focus of my work in the past years.

   In 2020, I started my own lab at the CIMH, focusing on complex systems approaches in clinical neuroscience. My lab relies on cutting-edge computational techniques to construct increasingly realistic models of brain function and mental disorders. Guided by the perspective that human behavior, the brain, and psychiatric disease can be best understood as complex, interacting multilevel networked systems, my group applies novel methods derived from complex systems theory and network neuroscience to tackle scientific questions at the intersection of psychiatry, neurobiology, and social science. To this end, we employ advanced computational strategies and pharmacological manipulation experiments targeted at the integration of data modalities to develop more realistic models of cognitive (dys)function across psychiatric populations. Despite the challenging endeavor to start a lab during a pandemic, we have grown to now host seven members, ranging from Ph.D. students to master students, with two more people incoming this year.

   As a senior psychiatrist, I currently implement a novel transdiagnostic ambulatory service for all clinical departments at the CIMH. The main goal of this unit is to provide an integrated and standardized clinical and scientific transdiagnostic assessment of every individual entering the psychiatric services of the Central Institute of Mental Health. This will enable the development of data-driven, individualized therapeutic pathways and the acquisition of clinically meaningful data for big data analytical endeavors.

   The lab's main focus remains in Network Neuroscience, an emerging field to which I have contributed over the last years, which holds great promise for developing advanced and realistic models of (dis)ordered cognitive processes. Network models represent the brain as a set of nodes and their mutual relationships (edges), rendering them accessible to advanced topological analysis approaches such as graph theory. However, even these traditional graph approaches are static and, therefore, rather descriptive, often failing to identify (patho-)physiological mechanisms that link system-level phenomena to the multiple hierarchies of brain function. Consequently, my lab and I have pioneered in applying novel tools to overcome those limitations, focusing on time-varying functional connectivity and network control

approaches in cognition. In our work, we explicitly integrate several observational levels, combining neuroimaging data with (epi-)genetic & ambulatory assessment data and use pharmacological interventions to gain a more mechanistic understanding of the underlying (patho)physiological processes. We continue this line of work and are currently broadening our portfolio of methods to harness the possibility of modern machine learning and AI applications to gain direct insight into the underlying dynamic systems' properties in close collaboration with the Department for Theoretical Neuroscience (Daniel Durstewitz and Georgia Koppe) and the Translation Bioinformatics research group headed by Emanuel Schwarz.
The three main themes around our research revolve around include:

1) <u>Models of cognitive processes</u>:
Studying the brain's system dynamics across a broad range of functional domains of cognitive and emotive processing and linking it to monoaminergic signaling in healthy control and psychiatric populations. This can be best achieved by leveraging large, open-access datasets, like the human connectome project, that provide excellent resources for discovering novel brain mechanisms in health and subsequently probing these potential mechanisms in smaller interventional and longitudinal patient studies. By integrating ambulatory assessment and mobile sensor data to validate neurobiological mechanisms, this approach aims for a translational strategy close to the everyday life of patients, laying the foundation for potential biomarkers of therapeutic interventions. Our work in this field has been widely recognized internally and externally, resulting in the reception of the NARSAD Young Investigator Award 2019, the CIMH Young Investigator Award 2019 or the DGPPN.

2) <u>Artificial Neural networks (NN) as preclinical models of cognitive dysfunction</u>:
ANNs are algorithms of neural networks that can be trained with empirical behavioral data to emulate in silico how the brain performs complex cognitive or behavioral tasks. This training is achieved by adapting a complex topological structure optimized to perform algorithmic computations. The resulting network structure adapted by the ANN can be analyzed with tools from network neuroscience to gain insights into the neural mechanisms of high-order cognition. Training ANNs with performance data from healthy subjects and patients offers the possibility to study the difference in resulting network architecture and allows (1) to study causal relationships between network topology and behavior, (2) directly probe these relationships by lesioning and altering network structure to study the direct consequences on cognitive performances and (3) to investigate single unit and small-circuits properties of human cognition and clinical phenotypes otherwise not accessible in humans. The Boehringer Ingelheim Exploration grant currently funds this line of work.

3) <u>Measuring and Modulating Human Social Interaction</u>:
A third evolving interest of our group has been the study of social interactions in everyday environments and clinical populations. Novel mobile sensor technologies like RFID sensors enable us to measure proxies of social interactions in routine clinical settings passively. Such high-density interaction data allow for studying group-wide, naturalistic interaction profile trajectories during the course and treatment of illnesses. They might help identify optimal windows and the course of therapeutic interventions. Hence, in a pilot study, we have begun to develop and test such devices and their feasibility for collecting interaction data in routine clinical settings in collaboration with Dusan Hirjak at the Soteria. Further, building on this approach, we have acquired funding from the International Foundation to test the impact of Oxytocin, a prosocial peptide, on social interaction and symptomatology in psychosis patients.

Our success in developing personalized diagnostic and treatment approaches that can be readily translated into clinical practice will ultimately depend on our ability to acquire large, standardized, richly phenotyped clinical and healthy cohort datasets. Joint efforts can only achieve this, requiring a standardized and harmonized data assessment across studies and clinical services. As outlined above, I have implemented a unit at the CIMH that provides a transdiagnostic assessment of all individuals entering psychiatric services at the CIMH. Once fully implemented, this unit will provide transdiagnostic datasets of up to 12.000 patients annually, openly accessible to all researchers at the CIMH.

2. **Key output of the years 2020-now**

Network neuroscience in psychiatry

Graph theory has greatly contributed to establishing the view of mental disorders as dysfunctions of distributed circuits and networks, to which I have continued to contribute by applying innovative tools from complex systems to current clinical and basic neuroscience questions (1.1). In particular, my group's recent efforts concentrate on the investigation of altered brain dynamic in schizophrenia, using the framework of network control theory in combination with multimodal imaging, genetic analyses and pharmacological manipulation. We show that brain-wide altered transitions between activity patterns in schizophrenia can be meaningfully traced by network control properties that are constraint by the underlying structural network and dopaminergic signaling (1.2).

In parallel, we investigated network mechanisms leading to altered structural connectomes in schizophrenia using generative network models. These models helped us to identify spatial constraints and local topological structure as two interrelated mechanisms contributing to the development of abnormal connectomes in schizophrenia that are linked to the genetic risk for schizophrenia (1.3).

1.1 Zhang X, Braun U, Tost H, & Bassett DS. 2020. Data-Driven Approaches to Neuroimaging Analysis to Enhance Psychiatric Diagnosis and Therapy. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.

1.2 1.2 Braun U, Harneit A, Pergola G, Menara T, Schafer A, Betzel RF, Zang Z, Schweiger JI, Zhang X, Schwarz K, Chen J, Blasi G, Bertolino A, Durstewitz D, Pasqualetti F, Schwarz E, Meyer-Lindenberg A, Bassett DS, & Tost H. 2021. Brain network dynamics during working memory are modulated by dopamine and diminished in schizophrenia. Nat Commun, 12(1), 3478. DOI:10.1038/s41467-021-23694-9

1.3 1.3 Zhang X, Braun U, Harneit A, Zang Z, Geiger LS, Betzel RF, Chen J, Schweiger JI, Schwarz K, Reinwald JR, Fritze S, Witt S, Rietschel M, Nothen MM, Degenhardt F, Schwarz E, Hirjak D, Meyer-Lindenberg A, Bassett DS, & Tost H. 2021. Generative network models of altered structural brain connectivity in schizophrenia. Neuroimage, 225, 117510. DOI:10.1016/j.neuroimage.2020.117510

Socio-environmental risk and resilience factors for psychotic disorders

Many socio-environmental exposures shape the developing and developed brain and impact human mental health. Importantly, these exposures can be increasingly quantified in real-life and real-life using ambulatory assessment (AA) techniques. Combining AA in combination with brain imaging and other methods, we have investigated the impact of several risk and resilience factors on brain functioning. Specifically, we were able to show that the amount from which subjects benefit in their emotional well-being from everyday motor activity is moderated by key brain regions involved emotion regulation and strongly altered in affective disorders (1.4). These findings provide important insights into brain mechanisms underlying resilience to mental disorders and provide explicit targets for future interventional efforts. Further, we have investigated the impact of physical non-exercise activity on mood dimensions (1.5) and, in a series of publications, have provided review of the current status and perspectives for future applications of these methods in clinical neuroscience (1.6, 1.7).

1.4 Reichert M, Braun U, Gan G, Reinhard I, Giurgiu M, Ma R, Zang Z, Hennig O, Koch ED, Wieland L, Schweiger J, Inta D, Hoell A, Akdeniz C, Zipf A, Ebner-Priemer UW, Tost H, & Meyer-Lindenberg A. 2020. A neural mechanism for affective well-being: Subgenual cingulate cortex mediates real-life effects of nonexercise activity on energy. Sci Adv, 6(45). DOI:10.1126/sciadv.aaz8934

1.5 Koch ED, Tost H, Braun U, Gan G, Giurgiu M, Reinhard I, Zipf A, Meyer-Lindenberg A, Ebner-Priemer UW, & Reichert M. 2020. Relationships between incidental physical activity, exercise, and sports with subsequent mood in adolescents. Scand J Med Sci Sports, 30(11), 2234-2250. DOI:10.1111/sms.13774

1.6 Reichert M, Gan G, Renz M, Braun U, Brussler S, Timm I, Ma R, Berhe O, Benedyk A, Moldavski A, Schweiger JI, Hennig O, Zidda F, Heim C, Banaschewski T, Tost H, Ebner-Priemer UW, & Meyer-Lindenberg A. 2021. Ambulatory assessment for precision psychiatry: Foundations, current developments and future avenues. Exp Neurol, 345, 113807. DOI:10.1016/j.expneurol.2021.113807

1.7 Reichert M, Braun U, Lautenbach S, Zipf A, Ebner-Priemer U, Tost H, & Meyer-Lindenberg A. 2020. Studying the impact of built environments on human mental health in everyday life: methodological developments, state-of-the-art and technological frontiers. Curr Opin Psychol, 32, 158-164. DOI:10.1016/j.copsyc.2019.08.026