Emanuel Schwarz, Ph.D

My scientific interest focuses on the development and application of artificial intelligence methods to complex psychiatric illness, in order to elucidate illness mechanisms and provide the basis for novel diagnostic and predictive tools. For this purpose, my Emmy-Noether research group at the Central Institute of Mental Health is developing modern machine learning approaches for integrative analysis of high-dimensional omics, neuroimaging and clinical data. For example, as co-coordinator of the FP7 project IMAGEMEND (www.imagemend.eu) I was able to perform one of the largest machine learning studies using brain structural data in schizophrenia, bipolar disorder and ADHD. This study was awarded the 2019 DGPPN research award for predictive, preventative and personalized medicine in psychiatry and neurology. I am currently coordinating the e:Med systems medicine alliance COMMITMENT ("COMorbidity Modeling via Integrative Transfer machine-learning in MENTal illness") that focuses on identifying the biology of comorbidity between psychiatric and somatic illness. For this, we are developing and implementing advanced transfer learning and subgroup identification procedures that capture shared pathomechanisms and that can inform treatment decisions, in order to reduce morbidity and mortality in psychiatric patients due to somatic illness. We are implementing these computational methods as part of a novel IT framework for geographically-distributed multi-task learning, to circumvent the requirement for data to be pooled in a single storage solution. I am further coordinating the ERA-PerMed network IMPLEMENT ("IMproved Personalized medicine through machine LEarning in MENTal disorders") that aims to identify subgroups of patients with psychosis that can predict improved response to existing and novel treatment modalities, in particular repetitive tanscranial magnetic stimulation. For this, we have developed a novel, biologically-informed machine learning procedure that utilizes gene-annotation data to facilitate pathway-specific algorithm learning from high-dimensional data and that integrates such pathway-specific algorithms into systems-level classifier. Using this procedure, we were able to identify a reproducible blood DNA methylation signature in schizophrenia that predicted DNA methylation differences in brain samples from patients, as well as inter-individual differences in DLPFC-HC connectivity, a neural intermediate phenotype for schizophrenia. We were able to show that the methylation signature indexed epigenetic effects specific for schizophrenia and utilized large-scale genome-wide association data, as well as data from unaffected first-degree relatives to demonstrate that these effects were likely not a secondary to the underlying genetic risk architecture. In addition, we have developed several computational methods for advanced characterization of biological hallmarks in psychiatric illness, including (I) an approach for modeling the longitudinal development of gene expression variability and its association with genetic risk, (II) a novel network-based approach for functional analysis of genetic high-risk variants, and (III) a normative modeling approach to capture physiological genetic co-expression at a genome-wide scale, and quantify deviations thereof in mental illness. Finally, we have developed advanced machine learning tools and provided these to the scientific community through CRAN, Bioconductor, as well as github, and these include the first fully automated pipeline for imputation and quality control of genome-wide association data (Gimpute), as well as the first R library for multi-task learning (RMTL).

These examples reflect my core interest in the development of advanced computational and artificial intelligence tools to advance our understanding of the biology of psychiatric illness, and to utilize these towards translation of research into novel clinical applications.

Key output of the years 2020-now

1. Rieg T, Schwarz E, From mechanistic insight towards clinical implementation using normative modeling, Nature Computational Science volume 2, pages278–280 (2022)

This article provides on overview of concrete steps that should be taken to advance the concept of normative modeling towards a framework that provides deeper mechanistic insight and can be used as a basis for precision medicine approaches in mental health.

2. Cao H, Zhang Y, Baumbach J, Burton PR, Dwyer D, Koutsouleris N, Matschinske J, Marcon J, Rajan S, Rieg T, Ryser-Welch P, Späth J, The COMMITMENT consortium, Herrmann C, Schwarz E. dsMTL - a computational framework for privacy-preserving, distributed multi-task machine learning. bioRxiv, doi: https://doi.org/10.1101/2021.08.26.457778

Manuscript describing the development of federated multi-task learning, developed as part of the e:Med systems-medicine network COMMITMENT. This approach allows the identification of comorbidity-related signatures, and other translational research, on geographically distributed data sources, without the need to bring these together into a single storage solution.

3. ***** Chen J, Zang Z, Braun U, Schwarz K, Harneit A, Kremer T, Ma R, Schweiger J, Moessnang C, Geiger L, Cao H, Degenhardt F, Nöthen MM, Tost H, Meyer-Lindenberg A, **Schwarz E.** Association of a Reproducible Epigenetic Risk Profile for Schizophrenia With Brain Methylation and Function. JAMA Psychiatry. 2020 Jun 1;77(6):628-636.

This article describes a multimodal, multi-site effort to discover and characterize a DNA-methylation signature of schizophrenia, coordinated by E Schwarz. It shows that using a novel, biologically-informed machine learning approach, developed in Dr. Schwarz's group, such signature could be identified and validated, and was associated with schizophrenia-relevant brain function.

4. ***** **Schwarz E**, Alnæs D, Andreassen OA, Cao H, Chen J, Degenhardt F, Doncevic D, Dwyer D, Eils R, Erdmann J, Herrmann C, Hofmann-Apitius M, Kaufmann T, Koutsouleris N, Kodamullil AT, Khuntia A, Mucha S, Nöthen MM, Paul R, Pedersen ML, Quintero A, Schunkert H, Sharma A, Tost H, Westlye LT, Zhang Y, Meyer-Lindenberg A. Identifying multimodal signatures underlying the somatic comorbidity of psychosis: the COMMITMENT roadmap. Mol Psychiatry. 26, 722–724 (2021).

This article describes the e:Med systems medicine consortium COMMITMENT, coordinated by the applicant (Co-PI: Prof. Meyer-Lindenberg). The project focuses on the development and application of innovative machine learning tools for identification of the biology underlying somatic comorbidity in mental illness.

5. Chen J, Schwarz K, Zang Z, Braun U, Harneit A, Kremer T, Ma R, Schweiger J, Moessnang C, Geiger L, Cao H, Degenhardt F, Nöthen MM, Tost H, Meyer-Lindenberg A, **Schwarz E**, Hyper-Coordinated DNA Methylation is Altered in Schizophrenia and Associated with Brain Function, *Schizophrenia Bulletin Open*, Volume 2, Issue 1, January 2021, sgab036

This article describes a new machine learning approach to quantify physiologically-occurring coordination effects of DNA methylation at biologically-related genes. The resulting coordination networks are then used to identify schizophrenia-related signatures of alteration, which are subsequently linked to brain functional differences. This methodology and identified changes are of significant relevance, as they offer a new perspective on how environmental risk effects may be biologically encoded and subsequently contribute to an increase of illness susceptibility.

6. ***** Chen J, Cao H, Kaufmann T, Westlye LT, Tost H, Meyer-Lindenberg A, **Schwarz E**. Identification of Reproducible BCL11A Alterations in Schizophrenia Through Individual-Level Prediction of Coexpression. Schizophr Bull. 2020 Mar 31;46(5):1165-1171.

This article describes the development of an innovative normative modeling technique using machine learning applied to genetic co-expression networks, and its use to identify reproducible biomarker candidate of schizophrenia.