# Decoding complexity

## IMPACT PARAGRAPH

While the findings of this work do not directly translate to psychiatric care, this thesis represents a necessary first step forward in shifting from traditional psychiatry towards personalized care (tailoring treatments to each individual's unique neurobiological profile), highlighting an intermediate phase known as stratified psychiatry. In traditional psychiatry, diagnoses like depression typically rely on symptom clusters, which may not comprehensively represent the fundamental underlying mechanisms of mental disorders, given their heterogeneous symptomatology. However, treatment decisions often adhere to a one-size-fits-all approach informed by diagnosis due to the absence of biomarkers reliably predicting treatment outcomes for individual patients. Consequently, this approach yields varied treatment responses and lacks precision in therapeutic interventions.

Central to this thesis is the transition from these diagnostic boundaries to a transdiagnostic approach. Transdiagnostic biomarkers can facilitate in patient stratification, which involves subgrouping patients who are more susceptible to responding to one relative to another treatment, thus potentially improving treatment outcomes. This thesis offers a transdiagnostic framework for future research on biomarkers predicting treatment response.

Here, the focus was on uncovering common brain patterns through electroencephalography (EEG) across various psychiatric disorders. Therefore, objective ('ground-truth') measurements, including polygenic (risk) scores (PRS), actigraphy and continuous performance tasks, were associated to EEG networks and signatures to elucidate the underlying neurobiological mechanisms of treatment response. A novel methodology was introduced for understanding and predicting treatment outcomes in psychiatric disorders, aiming to identify transdiagnostic brain markers to improve treatment response and remission rates. To achieve this, a proof-of-concept "genetics-informed, data-driven data-reduction approach" was presented, where multiple functional brain networks were extracted from EEG data within large and heterogenous cohorts. Subsequently, association analysis with PRS for antidepressant response (the ground-truth)

was performed in order to select biologically meaningful networks that may have genetic underpinnings linked to treatment response. Hereby, the limitations of subjective measures and biases inherent in traditional classification systems were overcome. The approach's value was confirmed through two studies, the proof-of-concept study and follow-up study, both demonstrating the capability of the identified networks for treatment prediction.

Genome-wide association studies (GWAS) typically demand large sample sizes, often ranging from several thousand to tens of thousands of individuals, to achieve sufficient statistical power to find genetic variants associated with specific traits or diseases. In contrast, PRS calculation cumulates the weighted effects of numerous common genetic variants identified through GWAS. Thus, by utilizing ground-truth PRS data extracted from expansive GWAS datasets, we were able to detect biologically plausible networks, even when working with smaller yet still substantial sample sizes for EEG-PRS association analysis.

The age-related posterior alpha network, probably reflecting neurodevelopmental trait characteristics, is interesting as it represents a promising biomarker for stratification, due to its stability over time and predictive capacities for treatment outcomes in depression. Future research should focus on further investigation of this network, as it holds the potential to provide significant insights into the development of targeted interventions that may have long-term prognostic value for psychiatric disorders.

Exploring objective neuropsychological measurements in relation to an EEG signature in frontocentral brain regions, known as spindling excessive beta (SEB), has provided valuable insights into the relationship between SEB, impulse control, and sleep. Results emphasized the significance of addressing sleep maintenance problems in treatment planning for all psychiatric patients. Additionally, it has become evident that frontocentral beta activity holds potential as a transdiagnostic brain marker for predicting treatment outcomes across various psychiatric disorders.

Furthermore, the development of a deep learning algorithm for the automatic detection of SEB presents a promising opportunity to streamline the detection process, alleviating the workload for clinicians and researchers, and facilitating large-scale studies on objectively determined SEB.

At last, our findings notably elucidated sex-specific effects, highlighting the importance of conducting research separately for men and women while considering diverse medications or treatment protocols. Additionally, medication-specific effects emerged not only for treatments with distinct modes of action, but also for medications presumed to be largely comparable, like the selective serotonergic reuptake inhibitors escitalopram and sertraline. Accounting for these potential differential effects in analyses on treatment prediction can pave the way for more tailored and effective interventions.

Looking ahead, I envision stratified psychiatry as a crucial transitional phase toward a more precise and personalized approach. Recognizing the necessity of biomarkers for this objective, I propose shifting away from the current diagnostic boundaries and embracing a research focus on a transdiagnostic approach as introduced in this thesis, which is grounded in objective measures such as genetics. However, it is essential to acknowledge the challenges ahead. Biomarker research in psychiatry faces many obstacles, necessitating collaboration across multiple clinics, large-scale data collection, validation in independent samples, and implementation studies to confirm their clinical utility, enhance predictive accuracy, and ultimately realize their full clinical potential.

Transdiagnostic biomarkers for stratification, when integrated into clinical care, can help clinicians in selecting treatments that are most likely to be effective for a particular patient, which could minimize the trial-and-error process associated with psychiatric treatments and leading to quicker symptom relief and remission. Nevertheless, clinical observation remains a fundamental aspect of psychiatric practice. While biomarkers can guide treatment decisions, they may not capture the full spectrum of an individual's presentation. Clinical observation enables clinicians to see nuances in psychiatric symp-

toms that biomarkers may overlook, and to incorporate other factors, such as social and environmental influences, into the treatment plan to enhance overall well-being.

In summary, this doctoral thesis offers a transdiagnostic framework for future research focused on stratified psychiatry and implementation studies, with the potential to revolutionize our understanding and treatment of psychiatric disorders.