Decoding complexity

ENGLISH SUMMARY

The current clinical practice in psychiatry relies on the Diagnostic and Statistical Manual of Mental Disorders for categorizing psychiatric disorders based on symptoms. However, this system has limitations, including inconsistent treatment responses and overlooking underlying mechanisms of mental dysfunction. Psychiatric disorders, like major depressive disorder (MDD) or attention deficit hyperactivity disorder (ADHD), are heterogenous and often co-occur with other psychiatric disorders, suggesting the need for more personalized approaches. Traditionally, treatment decisions follow a stepped-care model, but this may not adequately address the complexity of mental health conditions. Transdiagnostic psychiatry proposes a shift towards understanding common factors across disorders rather than rigid diagnostic categories, potentially simplifying treatment protocols and improving outcomes.

Transdiagnostic markers, based on objective measures (e.g. genetic variants or neuroimaging characteristics) can help understand the mechanisms underlying psychiatric conditions and aid in predicting treatment response. Moreover, deep learning, a subtype of artificial intelligence, holds promise in automating identification of markers

from large data.

This thesis aimed to identify transdiagnostic markers from electroencephalography (EEG) data, for predicting treatment response in MDD and ADHD. Hereby, we leveraged large and heterogeneous datasets to capture a broad range of EEG features. Utilizing a data-driven data-reduction method at source level activity, various independent EEG-derived functional brain networks were extracted. Polygenic association analysis was employed to select biologically feasible networks, potentially predictive of treatment outcomes. The results of the proof-of-concept study and follow-up study revealed respectively a slow wave network and posterior alpha network related to age, with sex-specific and medication-specific treatment predictive capabilities for MDD, demonstrating the stratification potential of this innovative approach.

The final study focused on the intersection between biology and neuropsychology, concentrating on objective measures for impulsivity and sleep within the Research Domain Criteria (RDoC) arousal/regulatory domain. Patients with poor impulse control exhibited heightened activity in a frontal beta network. Furthermore, we explored how sleep maintenance problems were related to impulse control on one hand, and to frontocentral EEG beta activity as a marker for hypoarousal on the other. Our findings indicated that spindling excessive beta (SEB) probability, a measure derived through deep learning, is a transdiagnostic state marker for hypoarousal caused by sleep maintenance problems, with concurrent poor impulse control (and is not necessarily a direct marker for impulsivity).

Furthermore, we discovered that frontocentral beta activity has treatment predictive capacities. Specifically, we found that SEB probability predicts treatment outcomes in MDD in a drug-specific manner, while beta power in frontocentral regions is predictive for treatment outcome in girls with ADHD. The results provided insights into the complex interplay among regulatory mechanisms governing sleep, arousal and affect.

In summary, the findings emphasize the potential of employing a network-based and RDoC approach in biomarker research. The integration of objective measures such as EEG, genetics, and sleep data, holds promise for future investigations into biomarkers predicting treatment outcomes. Although this thesis does not directly lead to immediate changes in psychiatric care, it represents a necessary first-step towards future advancements in scientific research on biomarkers. Overall, this doctoral thesis underscores a shift towards more targeted approaches compared to current treatment paradigms, which ultimately may lead to a better understanding of psychiatric disorders and improved treatment outcomes.