

Reverse Engineering for Robust MDD Biomarkers: Unveiling Novel Neural Biotypes for Digital Phenotypes

Despite the availability of effective treatments for depression, the response rate remains at about 50%. In recent years, there has been growing interest in identifying biomarkers that explain the psychopathology underlying depression and could serve as effective treatment targets. While significant progress has been made, including the identification of biotypes that may respond differently to treatments, the implementation of these biomarkers in clinical practice remains challenging due to high costs and scalability issues. In parallel, digital phenotyping has emerged as a promising approach for improving treatment efficacy due to its accessibility, automatic data collection capabilities, and availability to anyone with a smartphone. However, digital phenotyping lacks mechanistic explanations linking it to underlying brain processes.

To bridge the gap between brain research and smartphone-based research using digital technologies, we propose a novel framework to define novel neural biomarkers and their associated digital phenotypes for Major Depressive Disorder (MDD). This biomarker-based digital phenotyping approach has potential for scalable implementation in clinical practice. Our framework leverages large-scale neuroimaging datasets, behavioral measures, and computational approaches, including machine learning and normative modeling, to define novel neural biotypes and associate them with clinical signatures for MDD at the individual level. These signatures can significantly enhance individual-level prediction and clinical decision-making, ultimately improving treatment outcomes.

The proposed framework aims to (1) identify neural biomarkers in MDD using large publicly available neuroimaging datasets, (2) identify biomarker-based digital phenotyping by finding associated behavioral signatures that can be widely applied in clinical practice through local trials that collect both neuroimaging and extensive digital data and (3) conduct randomized controlled trials to prospectively allocate patients to their most effective treatments based on their biomarker-based digital phenotyping.

By reversing the traditional sequence of research, from neurobiological mechanisms to behavioral and clinical markers, we establish valid markers that can be widely implemented in clinical settings. The proposed framework aims to bridge the gap between advanced brain research and the practical needs of clinical decision-making, thereby significantly impacting clinical practice.