Personalized Treatment for PTSD: Leveraging Trait-Like and State-Like Biomarkers in Prediction of Prolonged Exposure Therapy Treatment Outcome
(Authors: Fatima, Lu, Bradley, Or, Sigal, Ilan, Yuval)

Post-Traumatic Stress Disorder (PTSD) is a multifaceted condition, marked by a wide range of clinical manifestations and underlying neurobiological mechanisms. The heterogeneity of PTSD symptoms, often overlapping with other psychiatric disorders, complicates both diagnosis and treatment. Currently, treatments are largely guided by subjective symptom reports, which overlook critical neurobiological factors that could offer deeper insights into the disorder's pathophysiology. Without objective biomarkers, effective personalized treatments remain elusive, leading to inconsistent treatment responses.

This study aims to identify and integrate trait-like and state-like biomarkers to predict treatment outcomes for Prolonged Exposure Therapy (PE), an evidence-based therapy for PTSD. Trait-like biomarkers, such as genetic, epigenetic factors, and baseline brain structure, help identify individuals at risk for PTSD, while state-like biomarkers, which reflect dynamic changes in brain structure and function, can track the progression of the disorder and the brain's response to treatment. By combining these biomarkers, this study seeks to personalize PTSD treatment, making it more precise and effective.

Aims of the Study:

1. **Identify trait-like biomarkers** that predispose individuals to PTSD, providing insights into genetic, epigenetic, and brain structural factors that increase vulnerability to the disorder.
2. **Track state-like biomarkers** that reflect changes in brain structure and function over the course of PE therapy, offering a real-time measure of treatment efficacy and progression.
3. **Integrate trait-like and state-like biomarkers** to develop predictive models that can forecast treatment outcomes and guide personalized therapeutic interventions.

For Study 1, we will first compare group differences between individuals with PTSD and controls to identify baseline biomarkers that can distinguish PTSD-specific changes. We will then examine the interaction between baseline measures of specific regions of interest (ROIs) and changes in those ROIs during treatment to predict treatment outcomes. Specifically, we will use multiple linear regressions to test the interaction between pre-treatment brain volume and post-treatment volume changes in predicting symptom reduction. For Study 2, we will replicate this analysis, emphasizing the interaction between baseline predictors and treatment-induced changes in brain regions that relate to symptom reduction. In both studies, we will also generate state-like biomarkers by comparing brain changes across treatment sessions. This will allow us to highlight mechanisms of change in key brain areas affected by PTSD and treatment.

Using these findings, we will develop models that integrate both trait-like and state-like biomarkers to predict treatment outcomes. Cross-validation techniques will be applied to assess the performance and generalizability of these predictive models, while Bayesian networks will

be used to represent the probabilistic relationships between predisposing traits, treatment-induced changes, and treatment outcomes.

The identification of both trait-like and state-like biomarkers can greatly enhance the precision of PTSD treatments, providing clinicians with objective, neurobiological measures to guide therapeutic decisions. By understanding the interplay between these biomarkers, this study aims to improve personalized treatment approaches, optimizing the chances of treatment success and reducing the risk of relapse or inadequate responses.