## Proposal Summary

Posttraumatic Stress Disorder (PTSD) is a highly prevalent and chronic psychiatric disorder in veterans and the broader US population and is often associated with significant stigma, diminished psychosocial functioning, poor physical health, and lessened quality of life. Despite the impact of PTSD, a precise diagnosis is often difficult: PTSD presents as a multi-faceted illness with variable clinical presentation, is highly comorbid with other psychiatric disorders, and patients often express a myriad of distinct symptoms. A better neurobiological and network level understanding of PTSD can lead to diagnostic clarity and more advanced, targeted and individualized treatments. Finding a unitary biomarker of PTSD has proven difficult. This is likely because of the diversity of presentation, and the potential that different biological subtypes exist within the clinical symptom profile. Recently, advanced computational tools have emerged that can parse this high level of complexity and thus hold significant promise to develop individualized and neurobiologically-based and objective biomarkers of PTSD.

*The primary research objective* of this proposal is to develop an objective brain-based identification that can be used to individualize diagnosis and treatment for patients suffering from PTSD.
**AIM1: Test whether a machine-learning algorithm can link PTSD symptoms with neuroimaging.** Hypothesis: PTSD symptoms can be predicted, using the information in individuals' resting-state fMRI. We propose training machine-learning algorithms (e.g., combination of Principal Component Analysis and Least-Angle Regression, LARS regression) to predict individuals' score on PTSD subdomains based on MRI data.

**AIM 2: Mapping DSM-5 PTSD symptom clusters to brain networks.** Hypothesis: PTSD symptoms at different domains arise from distinct cortical networks, identifiable by resting-state fMRI. We will test whether a machine-learning algorithm can be used to link fMRI-based functional connectivity with severity within different symptom domains. This will enable mapping of network abnormalities to commonly recognized DSM-5 domains of PTSD.

**AIM 3: Developing brain-based symptom clustering.** Hypothesis: Functional connectivity can be used to design an improved PTSD severity scale. We will use the methodology from Aim 1 and 2 but look at relationships between individual symptoms (instead of PTSD symptom clusters, i.e. Intrusion, avoidance, etc.) and connectivity-based networks. We then assess if symptoms can be grouped to make a modified PTSD scale, based on the brain neural networks that correlate with symptoms

In a preliminary study, we have stablished the feasibility of the above approach (for the first two aims). We analyzed resting-state magnetic resonance imaging in a sample (N=50) of PTSD patients and characterized clinical features using the PTSD Checklist for DSM-5 (PCL-5). We compared connectivity among 100 cortical and subcortical regions within the default mode, salience, executive, and affective networks. We then used principal component analysis and least-angle regression (LARS) to identify relationships between symptom domain severity and brain networks.

We found connectivity predicted PTSD symptom profiles. The goodness of fit (R2) for total PCL-5 score was 0.29 and the R2 for intrusion, avoidance, cognition/mood, and arousal/reactivity symptoms was 0.33, 0.23, -0.01, and 0.06, respectively. The model performed significantly better than chance in predicting total PCL-5 score ($p=0.030$) as well as intrusion and avoidance scores ($p=0.002$ and $p=0.034$). It was not able to predict mood/cognition and arousal scores ($p=0.412$ and $p=0.164$).

We would like to use a larger sample from ENIGMA to validate the above results. We would also like to test if by using a larger sample size, we can predict the mood/cognition and arousal symptoms, those that the model did not predict in our initial sample. Finally, we would like to explore Aim 3, using clustering algorithms to group individual symptoms based on similarity of brain networks which invokes them.