1. **Background:**

Major depressive disorder (MDD) is a serious illness that occurs in 11% of adolescents (Avenevoli, Swendsen, He et al JAACAP, 2015) and is associated with tragic outcomes including chronic adult disability and suicide. While some evidence-based treatments are available such as antidepressant medication and cognitive behavioral therapy, these interventions are only successful in reducing depression in about half to two-thirds of cases. Research is urgently needed to better understand the biological roots of adolescent depression and to develop improved treatments. In order to facilitate the development of improved, biologically based treatments, fundamental knowledge must first be gained as to the neural underpinnings of depression and neural change that is exerted by existing treatments. Understanding treatment-related changes of brain circuits is the key for evaluating the effectiveness of rehabilitation and monitoring the course of depression. Although there are few reports regarding successful treatments in reducing abnormal functional activities (Crane, 2017; Dichter, 2015), not much is known about changes in inter-regional relationships and network structure from treatment. This project will explore functional network changes exerted by currently-standard treatments. We will apply a set of advanced analytical tools developed in the Parhi's laboratory including network-and-connectivity based analysis, graph theory, and machine learning. We propose to investigate an existing pre-post treatment data set by analyzing functional connectivity and network based brain model with statistical tools.

The adolescent MDD dataset (PI: Cullen) contains resting-state fMRI from 60 adolescent patients with MDD and 35 healthy adolescents under IRB 0804S30542 (now closed, in data-analysis only status), at the University of Minnesota. The subjects underwent diagnostic assessment and multi-modal imaging. 15 of the unmedicated adolescents with depression returned for a second scan after receiving 8 weeks of treatment for depression.

Brain functional networks are created by defining cortical and subcortical regions (as defined using the Desikan-Killiany atlas) as nodes and the functional connectivity as edge weights in graphs. The functional connectivity is usually calculated by the correlation in pattern of spontaneous brain activity between two regions. Graph measures describe properties of global, community, and local topological structures; these include aspects of functional integration (characteristic path length, global efficiency), segregation (clustering coefficient, transitivity), degree, centralities, and smallworldness (Rubinov & Sporns, 2010; Wang et al., 2010). While these graphical tools have shown some promise in application to psychiatric disease including depression (Braun et al, 2015; Peng et al, 2014), they have not yet been applied in adolescent depression, nor in pre-post treatment studies to understand how treatment alters brain networks.

2. **Explain how the project contributes to the body of knowledge on translational research in the use evidence-based prevention interventions:**

The applicant has been collaborating with Dr. Cullen's group to analyze the baseline data of the same dataset using the similar approach for anatomical network estimated from diffusion MRI. In the baseline study, we found that the unmedicated group has higher nodal centrality (connections to the other parts of brain) on right hippocampus than that of the medicated group. In addition, the unmedicated group has increased clustering coefficient and local efficiency on right lateral orbitofrontal (rLOF), which means more complicated and efficient interconnections between the rLOF and its one-hop neighbors. The next step in this collaborative effort is to examine longitudinal change in the 15 subjects where we have usable pre-post treatment data.

In the project, the brain connectivity and network topology will be examined for any changes caused by depression or treatments. Those alterations add the knowledge in better understanding biological roots of adolescent depression, and can be derived into hypothesis for emotion related studies. Furthermore, key biomarkers will be identified from the findings using machine-learning techniques for clinical application design, like patient classification, depression progress monitor and treatment evaluation.

3. **Describe the anticipated outcome of the project:**
   In the short term, the finding will be presented in a conference or journal paper to add the knowledge of adolescent depression. In the long term, the identified biomarkers could be develop into algorithms to monitor treatment effectiveness and course of illness in an automatically way in clinical applications.
4. **Describe the mentoring relationship that will take place between you and your ITR faculty project advisor endorsing this proposal.**
   Bonnie Klimes-Dougan, Ph.D., is professional in neurobehavioral development and emotion/stress regulation system including the assessment of key front-limbic neurocircuitry and associated physiological systems. She will help in the knowledge of depression, emotion regulation and front-limbic circuitry.
   Kathryn Cullen, M.D., is professional in the neurobiology of depression using brain imaging, assessment of the neurobiological stress system and neurocognitive assessment, and depression treatment designs for children and adolescents. She will provide information regarding the data and knowledge of adolescent depression.
   Keshab Parhi, Ph.D., is an expert in digital signal processing, statistical signal processing, machine learning, statistical modeling, and computer architectures for digital signal. He will review the use of statistical tools and machine learning techniques.