Technical Abstract –Kash / Holmes Proposal

• **Background:** Exposure to stress is a major risk factor for various neuropsychiatric diseases, including Post Traumatic Stress Disorder (PTSD). However, susceptibility to stress varies considerably between individuals, in part due to the modulating influence of genes. Reflecting this, recent reports estimate that while significant proportion of soldiers serving in Operations Iraqi Freedom/Enduring Freedom exhibit symptoms of PTSD, the majority do not. This implies that some individuals are susceptible to the deleterious impact of stress, while others are resilient. Despite being the subject of enormous research efforts, the genetic and neurobiological factors underlying stress susceptibility and resilience remain poorly understood. Studying these factors is extremely difficult in human populations given the myriad genetic, lifestyle, and environmental differences between individuals. Animal models, and mouse models in particular, are an extremely powerful tool for parsing the relative influence of genes and stress on risk for PTSD. In keeping with this, we have recently demonstrated that different genetic strains of mice differ in their anxiety-related responses to chronic (restraint) stress, and that these behaviors are related to differences in glutamate receptor gene expression in the amygdala, a brain region critical for regulation of anxiety-like behavior. These findings are intriguing because the glutamate has been strongly implicated in the pathophysiology and treatment of PTSD. The research idea in this proposal is to systematically study whether differential stress responsivity is mediated by either of two major components of the glutamate system in the amygdala (*N*-methyl-D-aspartate and kainate receptors).

• **Objective/Hypothesis:** Functional alterations in two key glutamate receptors, NR1 and GluR5, determine how chronic stress produces alterations in amygdala neuronal excitability, and whether chronic stress leads to either an active or a passive coping response to stress.

• **Specific Aims:**

<u>Specific Aim 1:</u> Elucidate the neuronal site of stress-induced NR1 upregulation in the BLA of C57BL/6J.

<u>Specific Aim 2:</u> Evaluate effects of NR1 modulation on stress-induced active and passive coping behavior.

<u>Specific Aim 3:</u> Elucidate the neuronal site of stress-induced GluR5 down-regulation in the BLA of C57BL/6J.

<u>Specific Aim 4:</u> Evaluate effects of GluR5 modulators on stress-induced active and passive coping behavior.

• **Study Design:** We will use a multidisciplinary approach to test our hypothesis. Specifically, we will evaluate the impact of modulation of glutamate signaling in the amygdala on restraint-induced anxiety-like behavior using micro-injection methods. Further, we will probe the impact of repeated restraint on amygdalar synaptic transmission and plasticity using *ex vivo* slice physiology.

• **Impact:** The results stemming from the research proposed could provide insights into the neurobiological and genetic basis of susceptibility and resiliency to stress. This could one day lead to new screening tools for at-risk soldiers, for example via testing for at-risk glutamate gene variants and biomarkers, or neuroimaging for patterns of amygdala activation indicative of risk. In the more immediate term, this research could inform the development of therapeutics for soldiers suffering from PTSD, by refining existing understanding of glutamatergic mediation of stress susceptibility and pointing to the right mechanisms to target with drugs. Thus, this proposal has the potential to significantly impact the prophylactic and palliative care of military populations.