Abstract: Background: Stress exposure is a major risk factor for mood disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, some individuals can successfully adapt to stress and do not develop mood disorders. This ability is known as stress resilience. We previously reported that a single injection of ketamine, an NMDA receptor antagonist, prior to stress protects against the development of depressive-like behavior and attenuates learned fear in mice. However, the cellular and molecular pathways underlying ketamine-induced stress resilience are still largely unknown. Methods: Here, we will discuss ongoing work to identify the mechanisms mediating prophylactic ketamine-induced stress resilience. We utilize a combination of behavioral paradigms, drug development, viral strategies, and the ArcCreERT2 mice, a line that allows for the indelible labeling of neural ensembles representing a single behavioral experience. Results: Prophylactic ketamine protected against the development of stress-induced depressive-like behavior and attenuated fear responses. Prophylactic ketamine administration increased deltaFosB expression in a number of brain regions to include the ventral hippocampus (HPC). In a second set of experiments, mice were stereotaxically injected into ventral CA3 (vCA3) with viral vectors in order to upregulate or downregulate deltaFosB expression before prophylactic ketamine administration. Inhibition of deltaFosB only in vCA3 prevented ketamine’s prophylactic effect on fear expression. Current studies are focused on identifying and optogenetically manipulating memory traces following prophylactic ketamine administration. Conclusions: Overall, these data indicate that prophylactic ketamine may induce protective effects by altering aversive memories, specifically in the ventral HPC. Understanding how prophylactic ketamine may prevent stress-induced depressive-like behavior can elucidate both the pathophysiology of depression and provide insights into potential new treatment targets.