Mesolimbic dopamine modulation of stress resilience

Background: Resilience is maintaining mental health or rapid recovery when facing adversity. The underlying mechanisms of resilience remain elusive, and no efficient treatments for stress-related mental disorders are available. Based on observations in humans, we have have modelled resilience by chronically stressing mice with aggressors of a distinct strain. Some mice showed threat-safety discrimination avoiding only the aggressors' strain, while others generalised fear, also avoiding safe strains. Notably, only mice that display discrimination are responsive to extinction of social avoidance. Our preliminary data suggests that dopamine in the nucleus accumbens (NAc) promotes discrimination and extinction in our model. In addition, we previously have shown that learning to cope with mild social defeat builds resilience against future stressors, which the mesolimbic system may also modulate.

Hypothesis: Threat-safety discrimination and responsiveness to extinction are modulated by accumbal dopamine.

AIM1: Observe NAc dopamine levels between resilient and susceptible individuals
AIM2: Optogenetically manipulate NAc dopamine levels to establish causality in resilience outcomes
AIM3: Deploy a learning-to-cope training to build resilience (prevention strategy)
AIM4: Boost dopamine levels with L-DOPA to reverse susceptibility-associated symptoms (treatment strategy)

Experimental approach: We will implant optic fibers to monitor the fluorescence of genetically encoded dopamine sensors. For optogenetic manipulations, we will transfect DAT-Cre mice with AAV vectors to express a floxed version of excitatory & inhibitory opsins in ventral tegmental area DA neurons. Our preliminary data provide proof of feasibility and principle.

Impact: The project will establish the mesolimbic circuit's role in stress resilience. Our findings will help identify biomarkers and develop rational prevention and treatment strategies for stress-related mental disorders. Repurposing L-DOPA is original and novel.