Submitter Name: Pamela Kennedy
Submitter Email: pkennedy@psych.ucla.edu

Epigenetic mechanisms mediating cocaine-induced shifts from hippocampal to dorsolateral striatal behavioral learning and control

Eric Harvey[1] & Pamela J. Kennedy[1,2]

[1]Department of Psychology, University of California Los Angeles; [2]Brain Research Institute, University of California Los Angeles

Learned behaviors are regulated by both cognitive/goal-directed and habit memory systems in the brain. Disruption in the balance between these two systems is a persistent symptom of the addicted phenotype that may contribute to the maintenance of drug addiction and therapeutic challenges. Whether maladaptive behaviors characteristic of drug abuse are supported by enhancements in habit memory systems, impairments in flexible, goal-directed memory systems or a combination of both remains poorly understood. While functional changes in cortico-striatal circuits have been largely implicated in behavioral adaptations associated with chronic cocaine exposure and relapse, less is known about the long-term effects of drugs of abuse on the hippocampus (HPC), a major component of the medial temporal lobe memory system which flexibly encodes information to support goal-directed behaviors. Using a dual-solution navigation task that can be solved with either HPC- or dorsolateral striatal-dependent (DLS) learning strategies we show that following prolonged cocaine abstinence new behavioral learning is acquired by the DLS "habit" memory system *in lieu* of the HPC. This memory system bias is associated with downregulation of brain-derived neurotrophic factor (BDNF) and transcriptionally permissive histone acetylation (AcH3) in HPC and upregulation in DLS, suggesting impaired and enhanced plasticity in these two learning systems, respectively. Our data further suggest that these behavioral and molecular adaptations may be mediated through kappa opioid receptor (KOR) signaling and a common transcriptional regulatory event involving upregulation of the X-linked transcriptional repressor methyl CPG binding protein 2 (MeCP2) in both the DLS and HPC.