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Functional Consequences of Alternative Splicing in Polysubstance Use

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Tight regulation of transcription is required for appropriate neural plasticity and memory formation. This regulation can be dynamically and persistently perturbed by psychostimulant use and includes the process of alternative transcript splicing. Alcohol use is associated with alternative splicing in humans, non-human primates, rats, mice, chicks, and flies, suggesting it is a fundamental mechanism through which alcohol affects the molecular composition and function of cells. However, the functional consequences of the alternatively spliced isoforms, and how it can affect subsequent psychostimulant use are almost entirely unknown. We found that lasting memory for an odor associated with the stimulant properties of alcohol results in a switch in expression of transcript isoforms. These switches included alternative start sites, intron retention, exon skipping, and alternative donor and acceptor sites, and occurred in a variety of different genes including the Dopamine-2-like Receptor (Dop2R) and the only Drosophila signal transducer and activator of transcription (STAT) gene. We hypothesized that alcohol-induced alternative splicing would cause functional changes to the plasticity of memory circuits and response to other psychostimulants including nicotine and methamphetamine. Using a combination of functional in vivo imaging and newly developed high resolution behavior assays to test the rewarding properties of volatile psychostimulants, we demonstrate that alternative splicing changes memory circuit plasticity and behavioral decisions that impact psychostimulant preference. The conservation of alcohol and drug-induced alternative splicing from flies to humans suggests it is likely a fundamental mechanism through which addictive substances affect the function of memory circuits and consequent behavioral responses.