Submitter Name: Kristyn N. Borrelli
Submitted email: kristynb@bu.edu
PI Name: Camron. D. Bryant
PI email: camron@bu.edu

Reward sensitivity in *Hnrnph1*$^{+/-}$ mice following acute methamphetamine administration as measured via intracranial self-stimulation

Kristyn N. Borrelli[1], Julia L. Scotellaro[1], Kyra Dubinsky[1], William A. Carlezon Jr[2], Elena H. Chartoff[2], Camron D. Bryant[1]

[1]Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine; [2]McLean Hospital, Department of Psychiatry, Harvard Medical School

Several loci within the mouse genome have been linked to addiction-related behaviors. These implicated loci could provide clinical insight to the contribution of genetic factors in addictive disorders. We previously mapped and validated *Hnrnph1* (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene underlying variance in methamphetamine (MA)-induced locomotor activity. Mice heterozygous for a frameshift deletion in coding exon IV of *Hnrnph1* (*Hnrnph1*$^{+/-}$) display decreased locomotor activity in response to MA compared to their wild-type littermates (*Hnrnph1*$^{+/+}$). Microdialysis studies additionally show reduced MA-induced dopamine release in *Hnrnph1*$^{+/-}$ mice. Intracranial self-stimulation (ICSS), an operant behavioral paradigm commonly used to assess shifts in sensitivity to stimulation of the dopaminergic mesolimbic reward circuit, was implemented to assess changes in ICSS responding following acute MA administration in *Hnrnph1*$^{+/-}$ mice. Subjects underwent stereotaxic surgery to implant a unilateral, stimulating electrode into the medial forebrain bundle (MFB). Activation of these fibers produces robust brain stimulation reward (BSR). Mice were trained on a fixed ratio 1 (FR1) schedule to receive MFB stimulation for each 1/4 turn of a response wheel. Increasing doses of MA were then administered every other day to detect MA-induced changes in BSR-associated reinforcement. We identified a significant reduction in the rate of ICSS responding in *Hnrnph1*$^{+/-}$ mice compared to wild-type littermates following acute MA administration, most notably at 4 mg/kg (i.p.). This supports our previous findings that *Hnrnph1* dysfunction disrupts the rewarding properties of MA, further implicating this RNA binding protein in reward circuitry modulation.