Name: Camron D. Bryant, Ph.D. Email: camron@bu.edu

Spectrotemporal USV profiles during neonatal opioid withdrawal in FVB substrains, Zhx2-edited BALB/c substrains, and outbred CFW mice

Kelly K. Wingfield[1], Kayla T. Richardson[1], Teodora Misic[1], Nalia Abney[1], Kaahini Jain[1], Mia B. Rubman[1], Sophia A. Miracle[1], Jacob A. Beierle[1], Kristyn N. Borrelli[1], Emily J. Yao[1], Camron D. Bryant[1]

[1]Laboratory of Addiction Genetics, Department of Pharmacology, Physiology, and Biophysics and Department of Psychiatry, Boston University Chobanian and Avedisian School of Medicine

Opioid use during pregnancy is a growing public health concern, as gestational opioid exposure often leads to neonatal opioid withdrawal syndrome (NOWS) in infants. Current treatments for NOWS involve opioid replacement therapy with methadone or buprenorphine, and interventions promoting maternal care. We use a mouse model for NOWS to assess several phenotypes during spontaneous morphine withdrawal (16hr) on P7 and P14, including ultrasonic vocalizations (USVs) and locomotor activity, and nociceptive testing. Neonatal morphine exposure altered the USV profile, as demonstrated by a significant increase in the proportion of “Complex 3” syllables during withdrawal on P14. The increase in Complex 3 was observed in three inbred FVB substrains, as well as the outbred CFW stock. We also found that naloxone (4 mg/kg, i.p.) was sufficient to increase Complex 3 in morphine-naïve FVB pups. These data suggest that Complex 3 syllables could serve as a therapeutic biomarker for the aversive state of opioid withdrawal in neonates. On P16, we collected brainstem tissue for RNA sequencing and found an upregulation of the kappa opioid receptor (KOR) transcript Oprk1. Given the involvement of KOR activation in dysphoria associated with opioid withdrawal, we hypothesize that dynorphin activation of KOR increases Complex 3 emission. We are currently testing this hypothesis with the KOR antagonist nor-BNI. We are also testing additional substrains (BALB/c) and gene-edited genetic variants in Zhx2 within these substrains. Zhx2 codes for a transcriptional repressor that we recently discovered regulates brain metabolite concentration of oxycodone.