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Mapping Brain FOS Reactivity in Genetically Diverse Rats Reveals Cortico-Striatal-Thalamic Network Vulnerabilities Associated with Oxycodone Addiction-like Behavior

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Oxycodone use disorder poses a significant public health challenge, contributing to high morbidity, mortality, and societal costs. While traditional research highlights specific addiction-related neural circuits, a whole-brain view during abstinence is needed. Previous studies showed increased Fos reactivity and reduced functional connectome modularity during alcohol and stimulant withdrawal in dependent mice. We hypothesized that protracted abstinence from oxycodone self-administration will similarly decrease whole-brain modularity. Using genetically diverse heterogeneous stock (HS) rats to mirror human variability, this study compares whole-brain Fos reactivity in animals characterized as vulnerable or resilient to addiction-like behaviors after extended intravenous oxycodone self-administration. Characterization is based on a median split of their addiction index, using z-scored measures of escalation, motivation, tolerance, and hyperalgesia. Brains were perfusion fixed, immunolabeled for Fos (activity marker) and NeuN (neuronal marker), cleared with CLEAR+ and SmartBatch+, and imaged via light-sheet microscopy. Images were aligned to the Waxholm Space Rat atlas, Fos+ cells counted, and functional connectomes derived. Vulnerable rats showed higher Fos counts than resilient ones, especially in cortical areas (orbitofrontal cortex, medial prefrontal cortex, insula) and subcortical regions (striatum, hypothalamus). Counts were lower in the hippocampus, thalamus, and pons. No overall modularity reduction occurred, but hyperconnectivity existed among prefrontal-striatal-thalamic regions, including the hypothalamus and limbic/midline thalamus, but not the sensory thalamus. These results indicate that protracted abstinence from oxycodone profoundly restructures whole-brain functional networks. Future studies should investigate whether genetic variants predict whole-brain connectivity changes, or if individual differences in connectivity can serve as a biomarker for treatments or relapse prosperity.