Submitter Email: Lieselot Carrette Submitted Email: lcarrette@health.ucsd.edu

Characterization of the whole-brain reactivity and functional connectome associated with analgesia through MOR and KOR agonism.

Lieselot Carrette[1], Selene Bonnet-Zahedi[1], Angie Santos[1], Angelica Martinez[1], Brent Boomhouwer[1], McKenzie Pavlich[1], Andres Collazo[2], and Olivier George[1]

[1]Department of Psychiatry, UC San Diego; [2]Beckman Institute, Caltech

A better understanding of the impact of opioids on the brain is essential for the development of improved analgesics with reduced abuse liability. Activation of both the mu or kappa opioid receptors (MOR and KOR, respectively) induces analgesic effects, but MOR agonists are generally rewarding and widely abused, while KOR agonists are dysphoric, which may protect against misuse. To visualize similarities and differences between MOR and KOR agonism, we use single-cell whole-brain imaging of Fos reactivity. Mice (N=8/group, 4M+4F) were treated with the MOR agonist heroin (20 mg/kg), the KOR agonists salvinorin A (2 mg/kg) or U50488 (5 mg/kg), or vehicle, 30 minutes before an open field test to assess locomotion and general condition and a tail immersion test to assess analgesia. The brains were perfusion extracted, 90 min later, immunolabeled and cleared using the iDisco+ protocol, and imaged using light-sheet microscopy. Images were processed using the ClearMap pipeline for cell detection and counting. As expected and previously reported, agonism at both receptors induced analgesia, but resulted in the opposite effect on mobility, increased by heroin and reduced by salvinorin A. This aligned with overall increased Fos activation of the brain by heroin compared to salvinorin A. Here, we will look at regional reactivity and the derived connectomic differences associated with these treatments to improve our understanding of their brain-wide impact and develop predictive network models. In the future, we want to use this approach to look at connectomic differences in genetically diverse animals at baseline and in response to drugs.