Combinatorial architecture of circuit neuromodulation

Nikolas Karalis[1]

[1]Paris Brain Institute

Internal states and behavior are associated with brain-wide changes in the activity of neuronal circuits. Such global shifts are believed to be implemented by the changes in the neuromodulatory tone. Neuromodulators originate from few neurons and are released widely throughout the brain where they alter the activity and plasticity of target neural circuits.

The amygdala is a core brain region that plays an essential role in the processing of emotional stimuli. Salience and synaptic alterations in this region are critical for emotional processing and learning. The amygdala is innervated by all major neuromodulators, yet we know little about the dynamics of neuromodulator release under physiological conditions and how neuromodulator combinations regulate amygdala circuit activity during different behavioral states and learning.

To address this question, we characterized the neuromodulatory inputs to the amygdala across behavioral states, including exploration, sleep, reward, and aversion learning. Using novel sensors that report the dynamics of neuromodulator release, paired with multi-site, multicolor fiber photometry, we simultaneously measured the activity of all major neuromodulators (dopamine, acetylcholine, serotonin, and norepinephrine) in the amygdala of behaving mice. Using this data, we characterized their release patterns during distinct behaviors and identified the interactions between different neuromodulators.

Further, using simultaneous optical and electrophysiological recordings from the amygdala using high-density silicon probes, we have identified distinct patterns of large-scale neuronal activity that are associated with differential neuromodulator combinations during distinct behavioral states.

In summary, using this novel approach and multi-modal recordings, we are able to jointly characterize the activity of these two core systems and to generate predictions about the causal influence of simultaneous neuromodulation on the activity of downstream circuits during behavior.