Title: Deep brain optical imaging reveals motivational salience encoding by dorsal raphe dopamine neurons

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Abstract: Although reward and punishment have opposite valence and promote approach and avoidance respectively, both stimuli can enhance arousal and capture attention to guide appropriate behavioral responses. We have previously demonstrated that dopamine (DA) neurons in the dorsal raphe nucleus (DRN), which project densely to the extended amygdala, are wake-active over sleep states, promote arousal, and show robust activation to salient stimuli, irrespective of their hedonic valence [1]. We further examined whether DRN-DA neurons encode motivational salience [2] (n = 6 TH-Cre mice) with fiber photometry [3]. GCaMP6f-expressing mice were subjected to fear memory acquisition and extinction, where sensory cues of originally neutral context gain and lose motivational salience. Before conditioning, DRN-DA neurons showed small activation to the novel sensory cues (conditioned stimuli, CS; house-light and 65 dB 5 kHz tone) and no significant change across repetitive exposures (Pearson's $r = -0.12$, $p = 0.75$). Throughout learning and repeated pairings (10 trials, random ITIs within [70, 110] seconds) of CS and electric footshock (unconditioned stimuli, US; 0.6 mA for 1 sec), DRN-DA neurons gradually developed phasic response to the CS (Pearson's $r = 0.78$, $p < 0.01$). As previously shown [1], US induced robust activation of DRN-DA neurons, which however decreased across repeated exposures (Pearson's $r = -0.90$, $p < 0.001$). In contrast to the learning phase, evoked response to the CS diminished across extinction trials, where sensory cues lost motivational salience (Pearson's $r = -0.83$, $p < 0.0001$). These findings suggest that phasic activation of DRN-DA groups encodes motivational salience and that they are modulated by expectations at the population level. To discriminate between projection-specific functions at the single-cell level, we built a two-photon microscope for deep brain imaging of projection-identified DRN-DA cell bodies during appetitive and aversive conditioning tasks. Taken together, these data deepen our understanding of the functional properties of DRN-DA neurons.

Reference:
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