Cortico-Accumbens Regulation of Approach-Avoidance Behavior Is Modified by Experience and Chronic Pain

Graphical Abstract

Highlights
- Activity in parallel infralimbic-NAc circuits predicts approach-avoidance choice
- Learned suppression of avoidance during a reward modifies infralimbic-NAc circuitry
- Avoidance during a pain predictive cue is reinstated in a model of chronic pain
- Exogenous modulation of infralimbic-NAc circuitry is sufficient to regulate avoidance

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In Brief
Schwartz et al. establish that an approach-avoidance choice is regulated by cortico-accumbens activity, and that learning, chronic pain, or targeted manipulations of this circuit determine whether approach or avoidance occurs.
Cortico-Accumbens Regulation of Approach-Avoidance Behavior Is Modified by Experience and Chronic Pain

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SUMMARY

Although optimizing decisions between drives to avoid pain and to obtain reward are critical for survival, understanding the neuronal circuit activity that regulates choice during approach-avoidance conflicts is limited. Here, we recorded neuronal activity in the infralimbic (IL) cortex and nucleus accumbens (NAc) during an approach-avoidance task. In this task, disruption of approach by a pain-predictive cue (PPC-avoidance) is extinguished by experience and reinstated in a model of chronic pain. In the IL-NAc circuit, the activity of distinct subpopulations of neurons predicts the extent of PPC-avoidance observed. Furthermore, chemogenetic and optogenetic manipulations establish that IL-NAc circuitry regulates PPC-avoidance behavior. Our results indicate that IL-NAc circuitry is engaged during approach-avoidance conflicts, and modifications of this circuit by experience and chronic pain determine whether approach or avoidance occurs.

INTRODUCTION

Pain engages an aversive behavioral drive and punishes actions resulting in tissue damage. Consequently, we learn to avoid pain by associating contextual cues that predict painful outcomes and then modulate future behaviors in response to these cues. Despite the protective role of pain-predictive cues (PPCs), they are a potentially disruptive component of many essential reward-directed behaviors. Therefore, successful reward-directed behavior often entails learning to suppress PPC-elicited avoidance (Atlas et al., 2010; Broom, 2001; Diekhof et al., 2011; Durn and Herz, 1984; Fields, 2004; Keltner et al., 2006; Roy et al., 2012). Human studies have established that PPCs that modulate pain are encoded by circuitry encompassing the ventro-medial prefrontal cortex and ventral striatum, corresponding to the infralimbic cortex (IL) and nucleus accumbens (NAc) in rodents. Of note are the observations that circuits engaged by PPCs are dissociable from those directly activated by nociceptive stimuli, that ventromedial prefrontal cortex (vmPFC)-NAc circuitry is engaged during both the revaluation of aversive cues and approach-avoidance conflicts, and that it exhibits changes that correlate with the transition to chronic pain (Baliki et al., 2012; Jensen et al., 2003a; Milad and Quirk, 2002; Mobbs et al., 2007; Ploghaus et al., 1999; Ren et al., 2016; Schiller et al., 2008; Schlund et al., 2016; Schwartz et al., 2014; Talmi et al., 2009; Woo et al., 2015). Despite these observations, the neuronal activity in IL-NAc circuitry, its contribution to the regulation of PPC-avoidance, and the changes within it that could lead to increased pain-related interference in the pathology of chronic pain (Fields, 2004; Jensen et al., 2003b, 2012; Vlaeyen and Linton, 2000; Wiech and Tracey, 2013) have not been studied directly.

RESULTS

A Pain-Predictive Cue Disrupts Reward-Directed Behavior

We designed a simple task in which a pain-predictive cue decreases net sucrose consumption (PPC-avoidance) (Figures 1A and 1B). At a pseudorandom interval in this task, animals are cued to the availability of a trial. A lick in response to this first auditory cue initiates a trial. During a trial, each lick delivers ~10 μL of either a small or a large sucrose reward at a maximum rate of 10 Hz. One and a half seconds after the first rewarded lick and on 85% of trials, a second different auditory cue is played; sucrose delivery in response to licks then continues for 2 s; however, if the lick rate is <1.25 Hz the trial ends and the inter-trial-interval (ITI) of 45–90 s begins (all trials are separated by this ITI). These criteria apply to all sessions. Therefore, as detailed in the Experimental Procedures, the pattern of licking during a trial regulates the volume of sucrose delivered. Notably, this imposed pattern of sucrose delivery does not match the natural licking pattern of rats (Weijnen, 1998), therefore, pre-training sessions are run with all auditory cues until lick rates are stable for the duration of the trials (Figures 1D and 1F). Next, the noxious stimulus is introduced; in these trials, 1 s after the second cue and on ~30% of trials, a noxious heat stimulus (an infra-red laser) aimed at the animal’s fore-shoulder is delivered (Figures 1A, 1B, and S1).

To investigate approach-avoidance behavior, we monitored licking during training sessions after introduction of the noxious stimulus. Early in training, animals learn that the second auditory cue during consumption predicts the noxious heat stimulus (i.e., is a PPC), and the cue disrupts licking of both rewards (Figures 1D and 1F). Notably, the disruption of licking initiated by the PPC occurs during two epochs when no noxious heat
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