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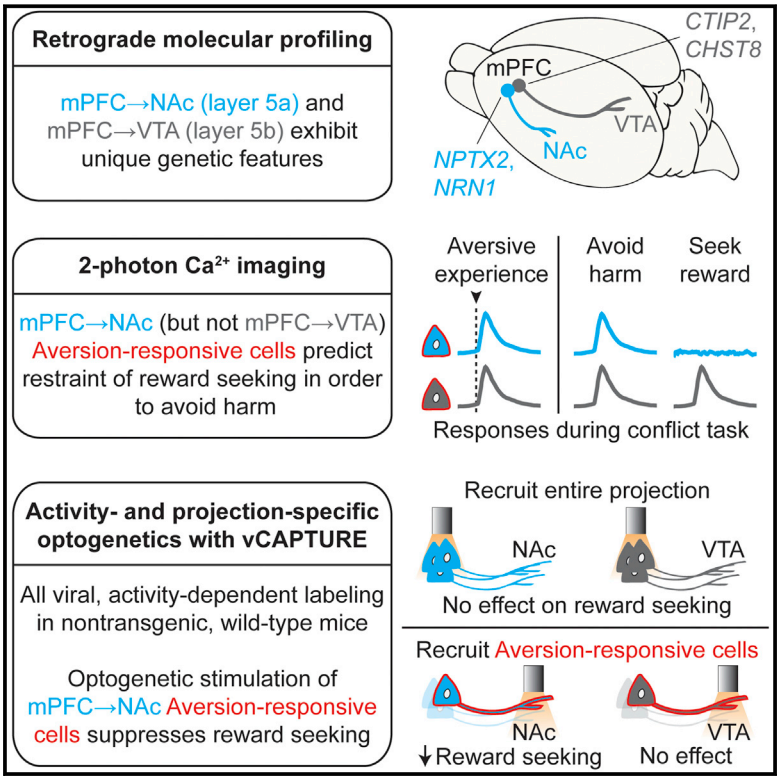
Molecular and Circuit-Dynamical Identification of Top-Down Neural Mechanisms for Restraint of Reward Seeking

Graphical Abstract



Highlights

- Projections from mPFC exhibit unique molecular and laminar phenotypes
- Ca^{2+} imaging reveals that mPFC→NAc shock neurons encode restraint of reward seeking
- vCAPTURE for robust labeling of mPFC→NAc axons active during shock
- Stimulating previously active mPFC→NAc shock neurons can reduce reward seeking

Authors

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In Brief

A population of projection neurons encodes the decision to initiate or suppress reward seeking when faced with punishment.

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Molecular and Circuit-Dynamical Identification of Top-Down Neural Mechanisms for Restraint of Reward Seeking

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SUMMARY

Reward-seeking behavior is fundamental to survival, but suppression of this behavior can be essential as well, even for rewards of high value. In humans and rodents, the medial prefrontal cortex (mPFC) has been implicated in suppressing reward seeking; however, despite vital significance in health and disease, the neural circuitry through which mPFC regulates reward seeking remains incompletely understood. Here, we show that a specific subset of superficial mPFC projections to a subfield of nucleus accumbens (NAc) neurons naturally encodes the decision to initiate or suppress reward seeking when faced with risk of punishment. A highly resolved subpopulation of these top-down projecting neurons, identified by 2-photon Ca^{2+} imaging and activity-dependent labeling to recruit the relevant neurons, was found capable of suppressing reward seeking. This natural activity-resolved mPFC-to-NAc projection displayed unique molecular-genetic and microcircuit-level features concordant with a conserved role in the regulation of reward-seeking behavior, providing cellular and anatomical identifiers of behavioral and possible therapeutic significance.

INTRODUCTION

The complexity of the environment of animals may be contrasted with the unitary nature of action. Many choices involving outcome components of known conflicting-valence (e.g., both reward and punishment) must still be implemented by a single coherent action. To achieve such adaptively important outcomes in the brain, neural circuitry is required to efficiently resolve inconsistencies, select single actions, and transmit the result of this adjudication to motor-output circuitry. Neuroeconomic gain/loss considerations may be of insufficient complexity for the large majority of naturalistic situations, wherein reward and harm are categorically different.

Maladaptive evaluation/selection of such choices is also important in clinical settings (Everitt and Robbins, 2005). For example, physically destructive consequences of substance use (normally aversive and thus effective in deterring behavior) often fail to deter drug-use action plans. Clinically relevant suppression of behavioral responses to aversive stimuli is not limited to substance use; self-injurious behaviors can become of neutral or even positive motivational valence in OCD, borderline personality disorder, and other neuropsychiatric diseases.

Thus requiring neither drug nor dependence, selecting actions with known harmful outcomes arises in diverse adaptive and maladaptive contexts and thus may involve conserved circuitry and neurophysiology with substantial developmental and evolutionary significance. The relevant neural circuitry is incompletely understood from the brainwide to cellular level, but studies of reward and aversion circuitry have identified separate and overlapping networks (Haber and Knutson, 2010). Reward circuitry is heavily dependent upon ventral tegmental area (VTA) dopamine neurons and their targets, which include cortex and nucleus accumbens (NAc) as well as additional corticostriatal circuitry involving the ventral pallidum, anterior cingulate cortex and medial prefrontal cortex (mPFC), and diverse other structures spanning amygdala, hippocampus, thalamus, and habenular and brainstem nuclei (Robbins and Everitt, 1996; Saunders et al., 2015). Processing of aversion (Hayes and Northoff, 2011) can involve many of these same structures as well (Lammel et al., 2011; Lammel et al., 2012; Tan et al., 2012), but with a distinct involvement of lateral habenula, bed nucleus of the stria terminalis, hypothalamus, and periaqueductal gray matter.

Notably, regions shared across reward- and aversion-processing, such as prefrontal cortices and the nucleus accumbens, have been implicated in mediating behavior in approach/avoidance conflict with punishment (reviewed in Orsini et al., 2015a)—a behavior in which the conflicting desires to seek reward and avoid aversion are evaluated to result in a single behavioral choice. Previous studies have highlighted a role of