Trends in Neurosciences

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Spotlight

Invariant inhibition to calculate prediction errors?

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The ventral tegmental area (VTA) has a pivotal role in motivated behavior. Much of the research on the VTA has focused on the mesocorticolimbic dopamine projections and their role in the computation of a 'reward prediction error' (RPE) for reward-guided learning. In a recent study, Zhou *et al.* report that VTA GABA neurons, the axons of which innervate the ventral pallidum (VP), have a unique role in signaling reward value to the basal ganglia and guiding reward seeking.

Unexpected rewards activate dopamine neurons of the VTA, which project to the nucleus accumbens (NAc). When a cue predicts the reward, after a few repetitions, the latter leads to a phasic activity burst, while the cells continue to fire at baseline when the reward is eventually delivered. Conversely, if the now-conditioned cue is presented, but reward delivery is omitted, baseline firing is inhibited. Moreover, mimicking dopamine burst firing by selective optogenetic stimulation of these neurons is sufficient to reinforce behaviors preceding the stimulation. Together, these observations align with the hypothesis that VTA dopamine firing serves as a RPE signal in reinforcement learning models of behavior, but little is known about how RPE is calculated in the brain.

Exciting recent findings reported by Zhou *et al.* [1] point to a role for a specific population of GABAergic neurons in the VTA in this RPE calculation. Using head-mounted microscopes, Zhou *et al.* measured calcium fluorescence as a proxy of activity from VP-projecting VTA GABA neurons. They found that some GABA neurons of the VTA, similarly to dopamine neurons, were activated by a surprising reward. However, unlike dopamine neurons, this activation persisted after several pairings with a cue (e.g., light or sound). Even when reward delivery was fully predictable, delivering the reward activated these VP-projecting GABA neurons. Therefore, GABA transmission remained invariant during the learning process, whereas dopamine activation shifted to the cue predicting the reward. While there is agreement among many scholars that RPE drives learning, which eventually manifests as synaptic plasticity in the regions targeted by dopamine, the processes behind RPE calculation in the brain remained unclear. In a prior study that traced RPE signals in brain regions other than the VTA, a subset of neurons of the VP stood out [2]. VP firing rates also encode the subjective value of experienced rewards that need to be incorporated for these estimates [2,3]. Zhou *et al.* concluded their study with the intriguing hypothesis that the absence of the reward devaluation in the signal transmitted from VTA GABA neurons to the VP contributes to local RPE calculation, which then feeds back to VTA DA neurons to compute the RPE.

GABA neurons in the VTA are heterogeneous. There are cells in the VTA and adjacent rostrotegmental nucleus (RMTg), which constitute a disinhibitory motif important in physiology. GABA neurons projecting within the VTA project onto, and inhibit, VTA dopamine neurons. These cells receive excitatory afferents from the lateral habenula, which can cause potent inhibition of dopamine neurons in response to an aversive stimulus [4]. Locally projecting VTA GABA neurons are activated by aversive stimuli to support behavioral avoidance. These neurons are also the target of some addictive drugs, including opioids, which cause hyperpolarization and a decrease of release probability through μOR signaling, thus disinhibiting dopamine neurons and promoting behavioral reinforcement. By contrast, VTA GABA neurons targeting the NAc selectively inhibit cholinergic interneurons in response to salient stimuli, regardless of the valence of those stimuli [5]. VTA GABA projection neurons also innervate the hippocampus [6]. Activation of these NAc- or hippocampus-projecting GABA neurons has no effect on ongoing appetitive behavior [6,7]. These functional profiles stand in sharp contrast to the VP-projecting GABA neurons reported by Zhou *et al.*, which, when optogenetically activated, convey information related to the subjective value of the reward, strengthen motivation, and promote learning.

At the cellular level, Zhou *et al.* used pseudo rabies tracing and optogenetic-assisted circuit mapping with patch-clamp electrophysiology to determine that VTA GABA neurons impinge on multiple neurochemical VP subpopulations (Figure 1). This raises the question of how this invariant reward value signal is integrated within the VP. The VP also contains neurons activated by aversive stimuli, the so-called 'negative valence neurons' (NVNs), which map onto the glutamatergic subpopulation [8]. Rewarding stimuli and reward-predictive cues inhibit NVMs, and their activity suppresses reward seeking, mainly when the cost is high [8,9]. An intriguing possibility is that GABAergic inputs from the VTA to the VP directly inhibit NVMs to drive these reward-related inhibitions and promote reward-seeking. By contrast, the firing of nearly half of the VP neurons reflects the subjective value of rewards [2]. Arkypallidal neurons constitute a subpopulation with this functional profile. These neurons project to the NAc, broadly inhibiting neurons coding for suppressing competing actions, thus promoting reward consumption once initiated [10]. An open question is whether these value signals are synthesized

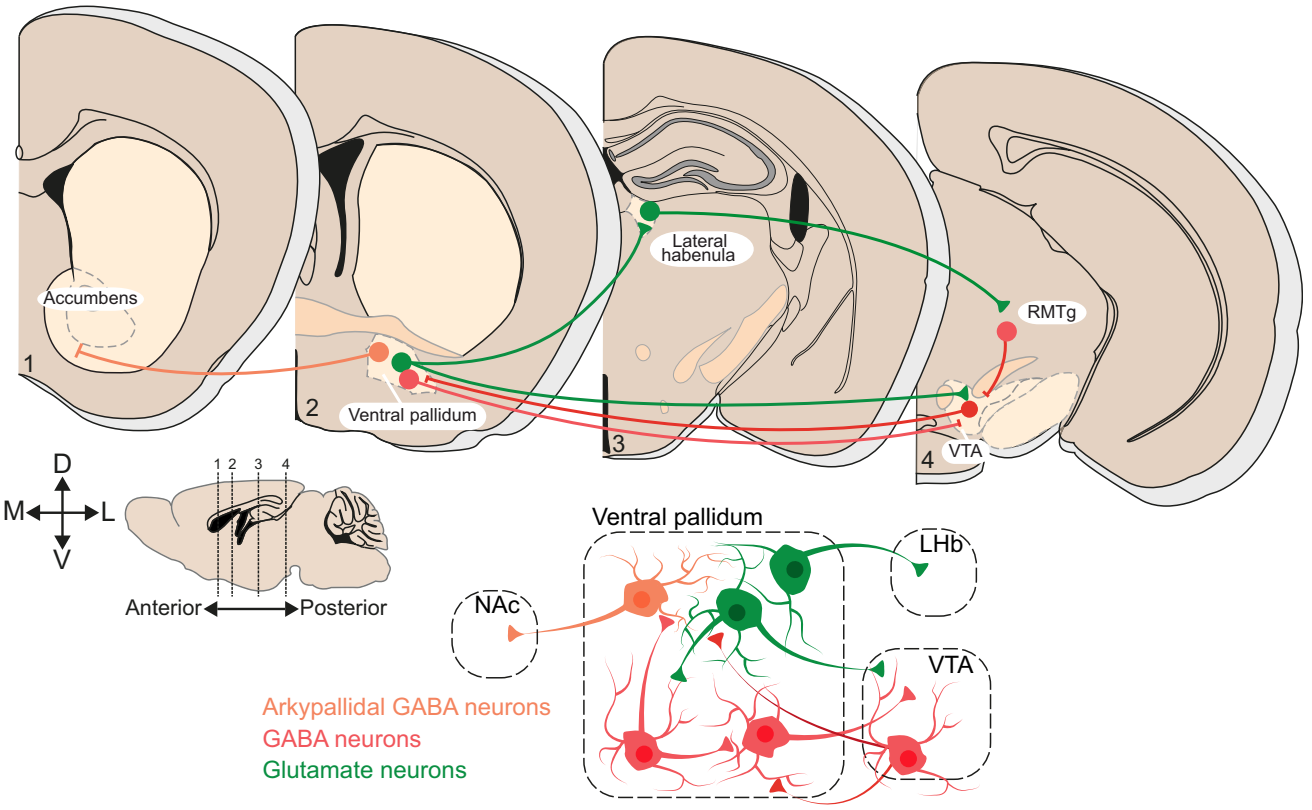

Figure 1. Circuit diagram including GABA and glutamate projections to and from the ventral pallidum (VP). In a recent study, Zhou *et al.* [1] characterized a GABA projection from the ventral tegmental area (VTA) to VP, here shown (putatively) as reciprocal inhibitory connections. There are also excitatory axons allowing the information to travel directly from VP to VTA, and via the lateral habenula (LHb). Inset highlights the diversity of VP neurons. Since the VTA-to-VP GABA projection does not adapt when a reward is fully predicted, it may contribute to reward prediction error (RPE) calculations in the VP. Abbreviations: D, dorsal; L, lateral; M, medial; NAc, nucleus accumbens; RMTg, rostrotegmental nucleus; V, ventral.

at the level of the VP or whether they are inherited from elsewhere. Just as with arkypallidal neurons, Zhou *et al.* found that calcium activity in VP-projecting VTA GABA neurons scaled with the palatability of the experienced reward. This raises the exciting possibility that the invariant reward signal from VTA GABA neurons contributes to these value signals. How would inhibition from VTA GABA neurons lead to reward-related excitation in the VP? While the microcircuits of the VP are not extensively explored, anatomical organizational principles borrowed from the dorsal segment of the globus pallidus suggest that long-range inhibitory inputs impinge on prototypical VP neurons, a type of GABA neuron, which in turn inhibits arkypallidal cells. In this way, VTA-GABA neurons are poised to contribute to excitatory reward-value responses through polysynaptic disinhibition.

The exciting findings reported by Zhou *et al.* add a new dimension to how reward signals are instantiated at the level of the VTA and how these signals are integrated at the level of the VP to guide reward seeking; they also raise an intriguing possibility that VP signals are transmitted back to the VTA dopamine neurons for RPE calculation. This study also opens important questions regarding how changes in motivational state or exposure to stress or addictive drugs may alter activity or plasticity in this pathway and how this may contribute to altered reward processing in these disorders. Ultimately, incorporating these VP-projecting GABA neurons into models of information flow in the mesolimbic reward circuits adds a critical layer to understanding the computation and expression of reward learning.

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Declaration of interests

The authors declare no conflicts of interest in relation to this work.

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