HOT TOPICS
Reinforcing actions through the thalamostriatal circuit

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Glutamatergic cortical inputs to the striatum are well-known drivers of striatal activity and play prominent roles in reinforcement learning [1]. Despite longstanding knowledge that thalamic nuclei also contribute anatomically notable glutamatergic inputs to the striatum, the behavioral roles of this circuitry have received far less attention. Recent reports that thalamic activity elicits dopamine release in striatal regions including the dorsal striatum and nucleus accumbens laid groundwork for new hypotheses regarding the roles of thalamic inputs to the striatum in behavioral reinforcement and action control [2–4]. In the dorsal striatum, glutamate release from thalamic neurons activates cholinergic interneurons to promote acetylcholine release, which in turn triggers dopamine release from local dopamine neuron varicosities through actions on nicotinic acetylcholine receptors [2, 3]. Because striatal dopamine release can drive reinforcement learning [1], and activation of striatal neurons in the dorsomedial striatum (DMS) can also support behavioral reinforcement [5], it stands to reason that thalamostriatal activity could also serve as a reinforcement signal.

To examine a role for thalamic inputs to the DMS in reinforcement learning, we updated the classic intracranial self-stimulation approach using optogenetics to selectively target thalamostriatal neurons [6]. Mice expressing channelrhodopsin-2 in intralaminar thalamic neurons were trained in a self-paced operant lever-press task. In response to each lever press, mice received a brief train of optical stimulation delivered to thalamic terminals in the DMS. Across multiple training sessions, mice readily acquired self-stimulation behavior. Examination of temporal patterns of responding revealed a clustered response architecture. Importantly, mice acquired self-stimulation of thalamostriatal terminals without prior training for an alternative reinforcer or enhancement of motivational state. Our findings suggest that thalamostriatal transmission is sufficient to reinforce a novel action. This study expands upon a previous report that stimulation of thalamostriatal terminals sustains operant responding in food-restricted mice that were first trained to respond for a food reinforcer [3].

Extending our previous work demonstrating that the presynaptic G protein-coupled receptor (GPCR) metabotropic glutamate receptor 2 ($mGlu_2$) reduces thalamically-driven glutamate and dopamine release in the striatum [7], we predicted that $mGlu_2$ activation would diminish the reinforcing properties of thalamostriatal self-stimulation. Indeed, an $mGlu_{2/3}$ agonist or $mGlu_2$-selective positive allosteric modulator administered prior to testing reduced lever pressing [6]. Conversely, blockade of $mGlu_2$ increased self-stimulation, suggesting that endogenous $mGlu_2$ activity constrains reinforcement in this paradigm. Intriguingly, the architecture of press clusters (e.g., duration, press rates) was unaffected by manipulation of $mGlu_2$. Instead, the number of clusters per session was bidirectionally modulated. Whether endogenous modulation is caused by acute engagement of the receptor during the task or involves receptor-mediated plasticity remains uncertain.

Future studies using genetically-encoded biosensors to monitor striatal neuron activation and dopamine release will clarify the downstream anatomical and physiological substrates by which thalamostriatal activity drives reinforcement. Such studies will also shed light on how presynaptic GPCRs selectively modify specific characteristics of action control. Looking forward, it will be important to consider how thalamostriatal contributions to behavioral reinforcement are altered in pathological conditions related to action control, including after patterns of drug exposure associated with substance use disorders.

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