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Positive reinforcement produced by stimulation of dopaminergic neurons in *C. elegans.*

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Substance use disorders (SUD) manifest in persistent substance engagement despite awareness of negative consequences. Yet, the precise molecular mechanisms underlying this behavior remain elusive. To unravel the neurobehavioral aspects and conserved functions of molecular pathways within neural circuits associated with preference and seeking, we scrutinize these intricate behavioral paradigms within a simplified system, leveraging *Caenorhabditis elegans* providing a high-throughput (HTP) model endowed with a well-defined neuroconnectome. This offers the advantage of simultaneously manipulating multiple neuromodulators, monitoring complex neural activity, and measuring subsequent behavioral outcomes, particularly in the context of preference and seeking.

Since Olds and Milner's pioneering discovery of positive reinforcement circuits in rats in the 1950s, characterized by robust lever-pressing behavior upon electrical stimulation, dopamine's pivotal role in these circuits, driven by substances-induced elevation in the ventral tegmental area (VTA) and nucleus accumbens (NAc), has been evident. Utilizing the Conditioned Cue Preference (CCP) paradigm, we recently demonstrated *C. elegans*' faithful recapitulation of mammalian Conditioned Place Preference (CPP) properties mediated by nicotinic acetylcholine receptors (nAChRs) and dopamine signaling. Accordingly, we comprehensively explore positive reinforcement circuits in this simplified system. For enhanced precision, we employed optogenetics to stimulate neural circuits resembling the mammalian mesolimbic dopaminergic system, eliciting positive reinforcement and enabling analysis at a cellular level. Our investigation delves into reinforcing circuits linked with preference and elucidates the molecular components shaping this behavior. Through employing optogenetic manipulation, we elucidated the positive reinforcement elicited by optogenetic stimulation of dopaminergic neurons, affording a reliable platform identifying the neurons and molecules influencing positive reinforcement.