limited due to its anesthetic actions at higher doses, abuse liability, ataxic effects, and capacity to produce changes in sensation and dissociation even when administered at sub-anesthetic antidepressant-effective doses. Ketamine's antidepressant action had been presumed to be via its anesthetic target, which is the inhibition of the NMDA glutamate receptor (Singh *et al*, 2014). In contrast, although published clinical studies to date have suggested modest antidepressant efficacy of some alternative NMDA receptor antagonists, thus far these drugs lack the robust rapid or sustained efficacy of ketamine, and in some cases (eg, memantine) they have been proven clinically ineffective (Newport *et al*, 2015). This suggests that it is unlikely ketamine exerts its antidepressant actions solely via inhibition of the NMDA receptor.

Ketamine is rapidly metabolized in the liver via multiple cytochrome P450 isoforms to norketamine, dehydronorketamine, hydroxyketamines, and a number of hydroxynorketamines (HNKs) in a stereoselective manner (Adams *et al*, 1981; Desta *et al*, 2012). This presents the possibility that ketamine acts as a prodrug, whereby *in vivo* metabolic conversions result in the biologically active drug. We recently reported that the metabolism of ketamine is essential for its antidepressant actions in mice (Zanos *et al*, 2016). Specific HNK metabolites of ketamine, (*2S,6S*)-HNK and (*2R,6R*)-HNK, produced from (*S*)-ketamine or (*R*)-ketamine, respectively, do not bind to or functionally inhibit the NMDA receptor at antidepressant-relevant concentrations, but do exert antidepressant behavioral effects similar to that observed following administration of ketamine itself. Administration of the (*2R,6R*)-HNK enantiomer to mice fully reproduces the antidepressant (and anti-anhedonic) behavioral and biochemical actions of ketamine. (*2R,6R*)-HNK exerts unique electrophysiological actions that provide an explanation for ketamine's antidepressant efficacy (Zanos *et al*, 2016). Although the pharmacological target of these HNKs have not been identified yet, our data support a critical role of an acute increase in glutamatergic AMPA receptor activity, followed by a long-term upregulation of synaptic AMPA receptors, likely resulting in potentiation of excitatory synapses in mood-relevant brain regions. (*2R,6R*)-HNK exerts these effects without the sensory-dissociation, ataxia, and abuse liability of ketamine in animal tests. Overall, our findings, supported by pharmacokinetic and chemical validation, reveal that production of distinct metabolites of ketamine is necessary and sufficient to produce ketamine's antidepressant actions (Zanos *et al*, 2016).

Based on these data, we propose that ketamine, and individually (*S*)-ketamine and (*R*)-ketamine enantiomers, exert NMDA receptor inhibition-independent antidepressant actions via metabolism to their respective HNKs. Validation of the relevance of HNK metabolites to the clinical antidepressant actions of ketamine in humans will require human clinical trials, which are currently in preparation.

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The Direct and Indirect Pathways of the Nucleus Accumbens are not What You Think

According to current concepts, motivated and addictive behaviors across species depend on the activity of the nucleus accumbens (NAc), and specifically on two groups of projection medium spiny neurons (MSNs). Those that directly inhibit the dopaminergic ventral mesencephalon (VM) (the 'direct pathway') express the D1

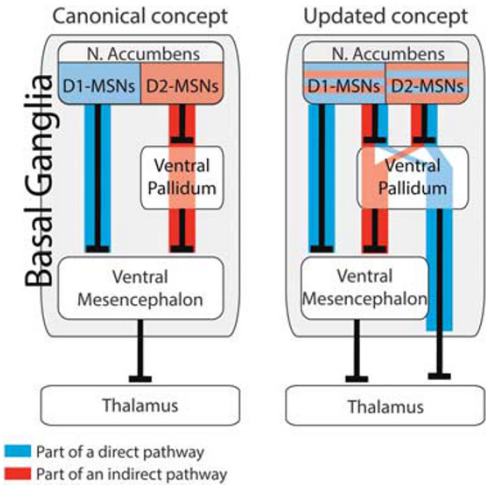

Figure 1. Past and novel concepts of the direct and indirect pathways of the nucleus accumbens. Left—canonical concept. D1-MSNs and D2-MSNs are completely segregated to direct and indirect pathways. Right—updated concept. Both D1-MSNs and D2-MSNs participate in direct and indirect pathways. Note that MSNs projecting to the VP may be part of a direct or indirect pathway, depending on the target of their downstream VP neuron.

dopamine receptor (D1-MSNs), disinhibit the thalamus and promote motivated behavior. The others, considered to be solely D2-MSNs, inhibit the ventral pallidum (VP), which inhibits the VM (the 'indirect pathway'), this results in the inhibition of the thalamus and motivated behavior (Figure 1). Importantly, these pathways were originally described for the *dorsal* striatum in times of relatively limited technology (Albin *et al*, 1989), and were assumed to be true also for the NAc.

Recent developments in cell-type-specific tools to investigate neural circuits have allowed researchers to evaluate the role of D1-MSNs and D2-MSNs in the expression of motivated and addictive behavior. As expected from the canonical circuitry, NAc D1-MSN activation promotes drug-seeking behavior while D2-MSNs had an inhibitory effect. However, other studies have shown that it is the input to the VP, rather than to the VM, which promotes reinstatement of drug-seeking behavior after withdrawal and that the VP itself, unlike its dorsal counterpart the globus pallidus, directly inhibits the thalamus (Root *et al*, 2015). Thus, the classic circuitry of the reward system was questioned.

In a recent study (Kupchik *et al*, 2015), we provided the first definitive evidence that the direct and indirect pathways of the NAc are not coded by MSN cell types (Figure 1). Using optogenetics in transgenic mice combined with neural tracing tools we showed that D1-MSNs comprise a significant portion of the classical indirect pathway by synapsing on VP neurons that project to the VM. Conversely, we showed that NAc D2-MSNs target VP neurons that innervate the thalamus directly. Thus, these D2-MSNs make a direct pathway through the VP that disinhibits the thalamus. These findings are not restricted to the ventral striatum as other emerging studies have observed similar results in the dorsal striatum (Cazorla *et al*, 2014; Saunders *et al*, 2015).

These novel findings in the ventral basal ganglia highlight the VP as a central node of the reward system. Other than the classical D1-MSN-to-VM pathway, whether a neuron is part of a direct or indirect pathway is determined in the VP. Curiously, some 15% of VP cells project to both the VM and the thalamus (Tripathi *et al*, 2013), converging the direct and indirect pathway on the same neuron. Thus, our perspective of the reward system needs to be more nuanced than simply through the prism of the direct and indirect pathways. Understanding this complexity requires deeper analysis of the reward system, and particularly of the understudied VP.

In conclusion, the traditional view of the reward system as being comprised of two distinct cell-type-specific pathways is an oversimplification. Emerging data requires developing a new perspective of the circuitry of the reward system that will guide future treatment strategies for addiction and other related mental health disorders.

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The authors declare no conflict of interest.

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