changes in DNA methylation and histone acetylation (Heyward and Sweatt, 2015). The involvement of DNA methylation and histone acetylation/deacetylation enzymes in learning and memory raises the possibility that they might be targeted to attenuate remote memories for treatment of PTSD(Graff *et al*, 2014). HDAC inhibition enhances cognitive performance in a mouse model of impaired cognition, and CREB pathway-specific selected HDAC inhibitor crebinostat was shown to significantly improve memory (Fass *et al*, 2013). It is unclear, however, whether this approach works in humans. If indeed the clinical data replicates animal studies, isotype-specific HDAC inhibitors should have a large impact on the treatment of cognitive decline and dementia, and perhaps PTSD.

Evidence suggests that addiction is mediated by epigenetic reprogramming in response to drug exposure (Massart *et al*, 2015). Epigenetic therapy might potentially 'reprogram' the addicted state and revert the phenotype to a non-addictive phenotype. Treatment of rats that crave cocaine with the DNA methylation inhibitor RG108 inhibited cocaine craving. Importantly, although the treatment was acute, the effects on blocking addiction persisted up to 60 days, suggesting stable epigenetic reprogramming by the treatment (Massart *et al*, 2015). Epigenetic therapy could potentially erase the epigenetic marks of exposure and exert a long-lasting effect that should persist unless a similar exposure is encountered, in difference from symptomatic therapy, which provides a transient relief.

However, there are critical caveats that need to be addressed. First, epigenetic drugs target general epigenetic processes, how could we guarantee specificity to particular genes? Nevertheless, since epigenetic reprogramming probably involves gene networks (for example, see (Massart *et al*, 2015), perhaps multi-targeted epigenetic drugs might be more potent than other approaches. Second, neurodevelopmental programs involve an organized sequence of epigenetic alterations, how could they be reversed once the neurodevelopmental processes have taken shape? There is genetic evidence that this might be possible; a RETT syndrome phenotype caused by transgenic *mecp2* mutation in mice could be rescued by restoring *MeCP2* gene expression in adult mutant animals (Guy *et al*, 2007). Animal studies have shown that general HDAC inhibitors could reverse learning deficiencies in a neurodegenerative mouse model (Fischer *et al*, 2007), but clinical studies have been limited, used nonspecific HDAC inhibitors, and examined a small number of patients (Sajatovic *et al*, 2008). The main epigenetic drug that is currently in use in psychiatry is valproic acid, a nonspecific HDAC inhibitor. A recent meta-analysis suggests that Valproic acid augmentation might improve treatment of schizophrenia patients (Tseng *et al*, 2016). The question remains, however, whether HDAC inhibitors could reverse behavioral and neuropsychiatric disorders, whether isotype-specific inhibitors would exhibit a more potent reprogramming activity, or whether multi-targeted drugs acting on gene networks rather than single selective agents would exert a more potent clinical benefit, and whether other epigenetic modulators such as DNA methylation inhibitors might elicit stronger responses?

The preclinical evidence for a potential paradigm shift in treatment of mental health conditions using epigenetic modulators has been surprisingly slow in translation to the clinical arena. The clinical studies are sparse, and the selection of epigenetic modulators that cross the blood–brain barrier that are appropriate for clinical studies is limited. Though more work needs to be done, there is vast potential for epigenetic approaches to change the way mental health disorders are treated.

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Ketamine Mechanism of Action: Separating the Wheat from the Chaff

(*R,S*)-ketamine (ketamine) exerts rapid (within hours) and robust (>60% response) antidepressant effects in severely ill-depressed patients who have failed conventional treatments (Zarate *et al*, 2006). This clinical finding has been paradigm-shifting as there is now tremendous hope that very ill-depressed patients can be treated in a matter of hours, rather than many weeks or months required for standard therapies to take effect (if they do at all). However, although the therapeutic potential of ketamine has elicited tremendous excitement in the field, ketamine's use outside of a monitored clinic setting is

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