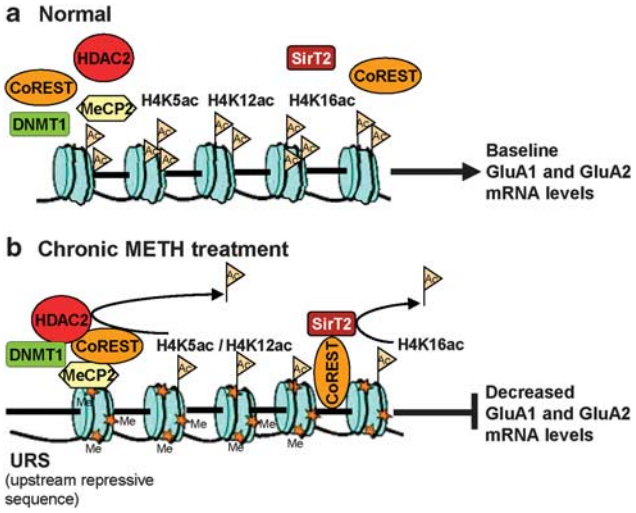

Figure 1. Models illustrating METH-induced epigenetic modifications in the dorsal striatum. Under normal conditions, a balance exists between histone acetyltransferases (HATs) and histone deacetylases (HDACs) that regulate the histone acetylation/deacetylation status that control the mRNA expression of AMPA receptor subunits (a). Chronic METH exposure (b) increases the expression of HDAC2, SIRT2, CoREST, and MeCP2. This is followed by the formation of protein repressor complexes that cause histone H4 hypoacetylation. Histone H4 hypoacetylation then produces decreased expression of GluA1 and GuA2 in the dorsal striatum of chronically METH-exposed rats.

Gene transcription is regulated by complex epigenetic changes that include post-translational histone modifications and DNA methylation (Mehler, 2008). There is evidence that epigenetic phenomena are intimately involved in the development and the clinical course of complex neuropsychiatric diseases including addiction (Robison and Nestler, 2011). Therefore, we thought it likely that METH might engender transcriptional and epigenetic alterations that are unique to this clinically devastating drug.

As a first step toward clarifying the effects of METH on glutamatergic function, we treated rats with an escalating METH dose paradigm that started at METH (0.5 mg/kg twice/day) and ended with METH (3 mg/kg four times per day) over a period of 2 weeks (McCoy *et al*, 2011). We found that chronic METH caused significant decreases in mRNA and protein levels of both GluA1 and GluA2 AMPA receptor subunits. We also found that METH caused significant decreases in acetylation of histone H4 at lysine 5 (H4K5), lysine 12 (H4K12), and lysine 16 (H4K16). Using chromatin immunoprecipitation-PCR assay, we found that repeated METH injections produced decreased binding of acetylated H4K5, H4K12, and H4K16 on GluA1 and GluA2 DNA sequences. In addition, chronic METH administration enhanced the recruitment of corepressor of RE1 silencing transcription (CoREST) factor onto GluA1 and GluA2 DNA sequences. METH also caused CoREST co-immunoprecipitation with histone deacetylase 2 (HDAC2) and sirtuin 2 (SIRT2). Moreover, METH increased enrichment of methyl CpG binding protein 2 (MeCP2) on the promoters of both GluA1 and GluA2, with co-immunoprecipitation studies revealing METH-induced MeCP2 interactions with HDAC2. Finally, we demonstrated that the FDA-approved HDAC inhibitor, valproic acid, prevented METH-induced downregulation of GluA1 and GluA2 mRNA levels.

In summary, the present study provides direct evidence for epigenetic regulation of chronic transcriptional effects of METH in the dorsal striatum. Figure 1 provides a scheme that describes a potential role of CoREST, HDAC2, MeCP2, and SIRT2 in the mediation of METH-induced downregulation of GluA1 and GluA2 mRNA levels. Specifically, CoREST might recruit SIRT2 onto the chromatin, with resulting H4K16ac hypoacetylation and decreased H4K16ac binding onto GluA1 and GluA2 DNA sequences. In addition, a METH-induced MeCP2-CoREST-HDAC2 complex might preferentially be involved in the hypoacetylation of histone H4 at lysines 5 and 12. The present observations add to the accumulating evidence that psychostimulants can cause substantial transcriptional and epigenetic changes in the brain. These results also suggest that therapeutic approaches that involved the use of epigenetic agents might be important areas for future investigations.

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Preclinical Studies Shed Light on Individual Variation in Addiction Vulnerability

Cues associated with drug use attract the attention of addicts, draw them to locations where drugs are located, and motivate drug-seeking—often leading

to relapse—even in the face of an expressed desire to remain abstinent. There is, however, considerable individual variation in the ability of reward cues to gain motivational control over behavior. Emerging evidence from preclinical studies suggests that such variation is due, at least in part, to intrinsic differences in the extent to which reward cues are attributed with incentive salience, thereby acquiring the properties of incentive stimuli. When a Pavlovian conditional stimulus (CS) reliably predicts delivery of a food reward, for some rats (sign-trackers; STs), the CS itself becomes attractive, in that these rats approach and interact with the CS, and becomes 'wanted', in that these rats will work just to obtain the CS. For other rats (goal-trackers; GTs), the CS itself is not attractive, but instead evokes conditioned approach towards the location of food delivery (rather than the CS), and GTs will not work avidly to get the CS (Meyer *et al*, 2012). Importantly, variation in the propensity to attribute incentive salience to a food cue predicts the extent to which drug cues gain motivational control over behavior. For example, a cocaine-associated cue is more effective in maintaining self-administration behavior, and instigates more robust relapse behavior, in STs than GTs (Saunders and Robinson, 2010). Additionally, STs will exert more effort to self-administer cocaine, and are more likely to relapse when 'primed' with drugs themselves (Saunders and Robinson, 2011). Therefore, it is possible to predict, *before any drug experience*, which rats will find drug cues more desirable, will exhibit greater motivation to take drugs, and will be more likely to relapse. Thus, the extent to which drugs cues acquire motivational properties may not only influence their ability to control normal behavior but to also tempt maladaptive behavior, thereby contributing to addiction vulnerability.

Several lines of evidence suggest that the propensity to attribute incentive salience to reward cues represents a complex psychological trait (Meyer *et al*, 2012). First, there are neurobiological differences between STs and GTs, including differences in dopaminergic systems (Flagel *et al*, 2011; Flagel *et al*, 2010). Second, the variation is heritable (Flagel *et al*, 2010), indicating that some unknown genetic differences contribute to variation in reward cue processing. Third, the extent to which rats become STs or GTs is influenced by early life experiences (Lomanowska *et al*, 2011), suggesting that environmental factors also contribute to how individuals process and respond to reward cues in adulthood. In conclusion, this line of research provides a novel approach to understanding the interplay between genetic, epigenetic, environmental, and neural-systems-level factors that confer susceptibility (and resilience) to impulse-control disorders, such as addiction. Implications for the development of clinical intervention strategies include: (1) greater attention to individual differences in the psychological factors that control pathological motivation for drugs, and (2) greater recognition that, in susceptible individuals, drug cues may be especially insidious in instigating and maintaining drug-seeking behavior.

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Fractionating the Impulsivity Construct in Adolescence

The teenage years are often associated with 'impulsive' behavior; that is, behavior with diminished regard to potential negative consequences. Adolescent impulsivity, while often adaptive, can manifest itself in a range of sub-optimal behaviors, including use of nicotine, alcohol, or illicit substances, symptoms associated with attention deficit hyperactivity disorder (ADHD), or poorer performance on laboratory assays of impulse control. Although these maladaptive behaviors are often co-morbid, their correlation is not perfect. It is therefore increasingly recognized that impulsivity is multi-dimensional, with some predicting that 'what is generally denoted as impulsivity will be fractionated into distinct forms that may, however, often coexist in the same individual' (Dalley *et al*, 2011, page 691).

Fractionating impulsivity is challenging, not least because of the large sample size needed to ensure an adequate number of participants in each phenotypic group, although recently the 'population neuroscience' (Paus, 2010) approach has provided these large samples. Data from the IMAGEN (Schumann *et al*, 2010) project permitted the data-driven identification of impulsivity subtypes by Whelan *et al* (2012). Nearly 1900