Neurotherapeutics (2013) 10:734–741
DOI 10.1007/s13311-013-0213-6

REVIEW

Epigenetics and Psychiatry

Melissa Mahgoub · Lisa M. Monteggia

Published online: 4 October 2013

Abstract Psychiatric disorders including major depressive disorder, drug addiction, and schizophrenia are debilitating illnesses with a multitude of complex symptoms underlying each of these disorders. In recent years, it has become appreciated that the onset and development of these disorders goes beyond the one gene–one disease approach. Rather, the involvement of many genes is likely linked to these illnesses, and regulating the activation or silencing of gene function may play a crucial role in contributing to their pathophysiology. Epigenetic modifications such as histone acetylation and deacetylation, as well as DNA methylation can induce lasting and stable changes in gene expression, and have therefore been implicated in promoting the adaptive behavioral and neuronal changes that accompany each of these illnesses. In this review we will discuss some of the latest work implicating a potential role for epigenetics in psychiatric disorders, namely, depression, addiction, and schizophrenia as well as a possible role in treatment.

Keywords Epigenetics · Depression · Addiction · Schizophrenia · Histone

Introduction

Psychiatric disorders such as depression, drug addiction, and schizophrenia are complex and heterogeneous diseases with a multitude of factors that contribute to their pathophysiology, making it difficult to link any one specific gene to the underlying cause of the disorder or the treatment. While data from twin studies have provided compelling evidence for the contribution of genetics as a predisposition to the development of these psychiatric diseases [1], environmental factors such as stress are also known to play significant roles in the manifestation of mental illness [2–4]. These external stimuli are often chronic in nature and extend over significant periods of time, leading to long-term behavioral changes as those observed in patients suffering from psychiatric disorders. Mounting evidence suggests that epigenetic mechanisms, which induce stable and lasting changes in gene expression in response to environmental events and behavioral experiences, may play a role in processes that contribute to the pathophysiology of psychiatric disorders.

Epigenetics is a dynamic process that can change gene expression without alterations in the DNA sequence, and promote stable changes in the chromatin structure allowing for regulation of gene transcriptional states [5–7]. Chromatin is comprised of DNA that is wrapped around the histone octamer to make up the core nucleosome that contains two copies each of the core histones H2A, H2B, H3, and H4 [8, 9]. A variety of chromatin remodeling enzymes, including histone acetyltransferases (HATs) and histone deacetylases (HDACs), can influence gene activity by inducing either an active or inactive chromatin state, respectively. Histone acetyltransferases add acetyl groups to lysine residues of the histone tail, causing the chromatin to be in a relaxed state and therefore favoring gene transcription. Histone deacetylases work by promoting transcriptional repression through the removal of acetyl groups from histone tails. Together, HDACs and HATs function to tightly regulate the chromatin state by regulating histone acetylation and impacting gene expression. There are many other posttranslational modifications that can occur on histone residues to impact gene expression including but not limited to phosphorylation, sumoylation, methylation and ubiquitination. These epigenetic mechanisms occur in postmitotic neurons, suggesting alterations in these processes may impact adult brain function. Another epigenetic mechanism targets DNA directly. DNA can be methylated via DNA methyltransferases (DNMTs), typically occuring at CpG sites and repressing gene activity [10–12]. While the importance of DNA methylation during development is well established, the role of DNA methylation-demethylation in the adult brain has only recently become an active area of

M. Mahgoub · L. M. Monteggia (✉)
Department of Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9111, USA
e-mail: lisa.monteggia@utsouthwestern.edu

investigation. Currently there is little known about DNA demethylation in postmitotic neurons and there remains much speculation about how this process may occur. Nevertheless, epigenetic mechanisms, through their impact on gene expression, can contribute to functional changes within cells that impact circuit level changes in brain and ultimately behavior. Studies of epigenetic mechanisms in psychiatric disorders have primarily focused on acetylation on specific histone residues and DNA methylation, thus this review will provide an overview of these processes in the field.

Epigenetic Mechanisms of Antidepressant Action and Depression

Major depressive disorder (MDD) is the second leading cause of disability worldwide, and current estimates reported by the National Institute of Mental Health (NIMH) show the 12-month prevalence of MDD is approximately 6.7 % of the U.S. adult population with 30.4 % of these affected individuals classified as severe cases [13]. Persons suffering from MDD can experience a wide range of symptoms including anhedonia, sleep disturbances, anxiety, and loss of appetite, and these symptoms are often of such severity that it interferes with the patient's daily activities [14, 15].

A major obstacle in the treatment of MDD is the lack of fast acting efficacious drugs. Traditional antidepressants such as serotonin selective reuptake inhibitors (SSRIs) typically take several weeks to exert a therapeutic effect with a significant number of patients failing to respond, making it critical to better delineate the mechanisms of antidepressant action. Several lines of evidence have linked brain-derived-neurotrophic factor (BDNF) as a potential therapeutic target in antidepressant action as well as in mediating depressive-like behaviors (for review [16]). Chronic antidepressant treatment that mirrors the time necessary to elicit an antidepressant response increases BDNF expression in the hippocampus [17, 18]; an infusion of BDNF into the midbrain [19] and hippocampus [20] is sufficient to trigger an antidepressant response in rodents, and the loss of BDNF in the hippocampus attenuates antidepressant efficacy in animal models [21–23], providing evidence of a role for BDNF in antidepressant efficacy. Conversely, it is known that there is a high degree of comorbidity between stress and depression, and decreased BDNF expression is observed in the hippocampus in response to different forms of stress [24] that correlate with depression-related behavior. Previous studies have indicated that stress can alter circuitry in limbic brain regions, specifically in the hippocampus where neurotrophic factors are known to exert effects [25]. Interestingly, BDNF, which is highly expressed in limbic structures, is indeed decreased in the hippocampus of rodents following exposure to chronic stress paradigms such as immobilization [26], unpredictable stress [27], and swim stress [28]. In many of these studies the changes in BDNF expression were sustained, indicating that stress can leave lasting marks on the genome, which has led to the suggestion that epigenetic mechanisms may be involved in mediating these effects.

Recent work has started to investigate whether alterations in BDNF related to depression and antidepressant responses are driven by epigenetics. A role for chromatin remodeling in mediating long-lasting adaptations in the brain and contributing to the development of depressive-like behaviors was recently investigated in rodents [29]. Chronic social defeat stress (CSDS), which induces depression-like behavior in mice, resulted in decreased mRNA levels of two *Bdnf* splice variants with increased histone methylation at their respective promoters in the hippocampus. This downregulation of *Bdnf* was reversed with chronic administration of the tricylic antidepressant imipramine, which also increased histone acetylation at the respective promoters. A later study used perinatal exposure to methylmercury in mice to induce a depressive-like phenotype and found a similar decrease in *Bdnf* expression in the hippocampus; it was shown to be mediated through hypermethylation on histone 3 lysine 27 (H3K27), a site correlated with transcriptional repression, thus providing a link between chromatin modifications and depressive-like behavior [30]. A separate study established that decreased BDNF expression observed in the mesolimbic pathway following CSDS (which persisted for 4 weeks after the paradigm) is required for the avoidance behavior seen in mice following CSDS, and that deletion of BDNF in the ventral tegmental area (VTA) exerted an antidepressant like effect and rescued the avoidance behavior [31]. In all these studies, the changes in BDNF expression were reversed by chronic, but not acute administration of imipramine or fluoxetine respectively, suggesting that sustained changes in gene expression may underlie the chronic changes in behaviors related to depression and stress. These putative links between depressive-like behaviors, antidepressant efficacy, and BDNF expression in rodent models have put forth the hypothesis that epigenetic mechanisms may underlie the involvement of BDNF in the etiology of MDD, specifically in cases of chronic stress, as well as in its treatment.

Epigenetic regulation of additional genes have started to be examined in the context of depression-like behavior or antidepressant responses. A recent study investigated the epigenetic regulation of the small Rho-GTPase, RAS-related C3 botulinum toxin substrate 1 (Rac1) in relation to depressive like behaviors [32]. Rac1 has previously been characterized as a crucial regulator of synaptic stability, and postmortem studies from patients with MDD have identified decreases in synapse number in cortical regions of the brain [33] although the precise mechanism behind these changes is unknown. To further explore this in rodents, mice were subjected to CSDS and showed social avoidance behavior suggestive of depression-related behavior. Moreover, there was a significant reduction in Rac1 expression

selectively in a subcortical reward region, the nucleus accumbens (NAc), for 35 days following CSDS with these effects partially reversed following chronic administration of the tricyclic antidepressant imipramine. Such long-lasting decreases in gene expression led the authors to examine whether this was the result of epigenetic regulation of Rac1. Quantitative ChIP (qChIP) analysis revealed a reduction in histone H3 acetylation (pan-acH3) as well as enhanced methylation at the lysine 27 residue of H3 (H3K27) site of the Rac1 promoter region in CSDS mice, which helped bring about a repressive chromatin state and the subsequent decrease in Rac1 gene expression. Interestingly, overexpression of Rac1 in the NAc was sufficient to rescue the social deficits observed following CSDS, suggesting an important role for Rac1 in modulating depressive-like behaviors. Postmortem tissue from patients diagnosed with MDD yielded similar results as the animal studies. In MDD subjects who were not on antidepressant treatment at the time of death, Rac1 levels in the NAc were significantly decreased. In MDD patients on antidepressant treatment at their time of death, the results were less conclusive with ~50 % of the subjects having normalized Rac1 levels compared to control patients. Future studies are needed to more closely examine the potential involvement of epigenetic mechanisms contributing to the alterations in Rac1 expression in MDD patients as suggested by the animal studies.

Epigenetic regulation of type-2 metabotropic glutamate (mGluR2) receptors have recently been linked to antidepressant efficacy [34]. Previous work has demonstrated that L-acetylcarnitine (LAC), a pharmacological compound which promotes acetylation of histones as well as non-histone proteins, can induce mGlu2 receptor expression by increasing acetylation of the p65 subunit of NF-kappaB (NF-κB) in dorsal root ganglion (DSR) neurons, thus controlling its transcriptional activity and providing an analgesic effect [35]. Following 3 days of intraperitoneal injections, LAC was found to have a rapid and enduring antidepressant effect (up to 2 weeks) in Flinders Sensitive Line (FSL) rats, which have been previously characterized as an animal model of depressive-like behaviors and have reduced expression and function of mGlu2/3receptors in the hippocampus [36, 37]. The 3 days of LAC injections also rescued the decrease in mGlu2 receptor levels in the prefrontal cortex and hippocampus observed in rats treated with saline via increased levels of acetylated H3K27 at the Grm2 promoter. Furthermore, LAC treatment increased acetylation of the p65 subunit of NF-κB thereby promoting transcription of the mGlu2 receptor (*Grm2*) gene in the hippocampus and prefrontal cortex of the FSL rats. Taken together, these data suggest a link between epigenetic regulation of mGlu2 receptors and antidepressant action. Rather intriguingly, clinical studies have shown LAC to be well tolerated in humans leaving open the possibility of examining whether LAC is effective in producing an antidepressant response in depressed patients.

In addition to the histone modifications detailed above, there are other forms of epigenetic processes, including DNA methylation, that have been implicated in depressive-like behaviors. DNMTs are believed to play important roles in regulating learning and memory [38–40], and recent work has explored a possible link to depressive-like behaviors. Following CSDS, the expression of the de novo DNMT enzyme, DNMT3a, was significantly increased in the NAc of mice, and this change persisted for 10 days [41]. This same study also showed that overexpression of DNMT3a in rat in the NAc resulted in social avoidance behavior and less latency to immobility time in the Forced Swim Test paradigms, both indicative of depressive-like phenotypes. This effect was specific to DNMT3a and no changes in expression of the other DNMT family members, DNMT1 or DNMT3b, were detected following CSDS, suggesting a possible role for DNMT3a in behaviors related to depression (Table 1).

MDD is a disease encompassed by the development of multiple symptoms that often manifest slowly over time and cause long-term changes in behavior. Recent data from rodent studies as well as postmortem tissue has suggested that epigenetic processes, known to cause stable and enduring changes in gene function, may be involved in the disease process. Future studies will be necessary to extend these findings into human depression as well as investigate whether specific epigenetic mechanisms can be targeted as more effective treatments for depression.

Epigenetics and Addiction

Drug addiction is a chronic and debilitating psychiatric illness characterized by uncontrollable and compulsive drug seeking behavior despite the mental and physical consequences

Table 1 Epigenetic modifications and MDD

Treatment	Modification	Effect	Reference
CSDS	↑ Histone methylation at *Bdnf* promoter	↓ *Bdnf* mRNA in HC	Tsankova et al., 2006 [19]
Perinatal methylmecury exposure	↑ Histone methylation at H3K27	↓ *Bdnf* mRNA in HC	Onischenko et al. 2008 [30]
CSDS	↓ pan-acH3 acetylation and ↑ methylation at H3K27 site of Rac1 promoter	↓ Rac 1 in NAc	Golden et al., 2013 [32]
LAC	↑ Acetylation of NF-κB	↑ mGlu2 receptor in PFC and HC	Nasca et al. 2013 [34]
CSDS	↑ DNA methylation	↑ DNMT3a mRNA in NAc	LaPlant et al. 2010 [41]

associated with being addicted to drugs of abuse [42]. The path to addiction can begin with an individual's voluntary use of drugs, however, repeated exposure can induce lasting changes in brain reward areas, causing individuals to compulsively use and seek drugs. It has previously been shown that chronic exposure to drugs of abuse can alter gene expression in key brain reward areas including the ventral tegmental area (VTA), NAc, and PFC [43]. Acute or chronic cocaine administration has been shown to increase overall histone H3 and H4 acetylation in the NAc suggesting that stimulants can influence epigenetic processes [48]. An active area of research is whether epigenetic mechanisms may be involved in the long-term changes in brain circuitry induced by drug exposure.

BDNF, aside from its putative involvement in MDD, has been implicated to play a role in addiction. Acute self-administration of cocaine causes an increase in BDNF protein in the NAc [44], and infusions of BDNF into the NAc [44] and VTA [45] cause an increase in cocaine self-administration in rats, suggesting a role for BDNF in the facilitation of reward related behaviors such as that seen in drug abuse and drug seeking. Following cocaine exposure, there is a persistent release of BDNF in the VTA and NAc [46] as well as the striatum [47] during withdrawal. In 2005, Kumar et al. reported that histone modifications play a role in cocaine's effect on BDNF in an animal model of addiction. Chronic cocaine exposure induced acetylation of histone H3 at the BDNF promoter region in the striatum, an effect that lasted for 24 hours after the last cocaine injection [48], suggesting that epigenetic mechanisms may play a role in cocaine's regulation of BDNF.

In yet another study, it was established that an acute injection of cocaine increases expression of the immediate early genes *c-fos* and *fosB* in the NAc by inducing histone H4 acetylation on their respective proximal promoter sites [48, 49]. A similar study followed up on this work and demonstrated that the mechanism through which this induction of *fosB* occurs is via the histone acetyltransferase CREB-binding protein (CBP) [50]. Following acute exposure to cocaine, CBP is recruited to the *fosB* promoter region and acetylates histone H4 resulting in an overall increase in *fosB* expression. The results of this study demonstrate a role for histone acetylation in regulating changes in gene expression that underlie addiction behaviors.

As previously mentioned, histone deacetylases play a crucial role in regulating gene activity by inducing modifications of the chromatin structure. There are 11 mammalian HDACs classified into four distinct HDAC families, class I, IIa, IIb, and IV, which are grouped according to sequence homology, subcellular localization, and expression patterns [51]. In a recent study, it was shown that the loss of the class II HDAC, HDAC5, results in an increased response to cocaine reward following conditioned place preference (CPP), and this effect was specific to HDAC5 with no changes seen in HDAC9 knockout mice [52]. Interestingly, this effect was normalized with a partial rescue of HDAC5, specifically in the NAc. The authors concluded that HDAC5 regulates the cocaine response via acetylation of target genes within the NAc, including RapGEF6, Gnb4, Suv39H1, and the NK1 receptor, highlighting an important example of how histone decacetylases can function to regulate gene activity in response to drugs of abuse.

HDAC inhibitors have received notable attention in recent literature as regulators of cocaine-induced addiction behaviors in rodents [53–55]. Interestingly, in the study from Kumar et al. described above, the authors were able to demonstrate that histone acetylation is an important process in the regulation of addiction behaviors through the use of a pan-HDAC inhibitor, sodium butyrate, which has been previously shown to provide therapeutic effects in neurodegenerative disease [56]. Co-administration of sodium butyrate and cocaine resulted in a synergistic effect, leading to increased cFos expression as well as increased histone H3 acetylation at the cFos promoter [48]. Additional data from a more recent publication demonstrated that the chronic infusion of a more specific class I HDAC inhibitor, *N*-(2-aminophenyl)-4-[*N*-(pyridin-3-yl-methoxycarbonyl)aminomethyl]benzamide (MS-275), into the NAc blocks cocaine-induced locomotor sensitization, and this occurs through an induction in global histone H3 acetylation [57]. This work suggests a role for class I HDACs in epigenetic mechanisms that contribute to addiction behaviors. Further work will be necessary to delineate which specific HDAC may be involved in this process (Table 2).

Chronic exposure to drugs of abuse leads to long-term changes in brain function suggesting that alterations in gene activity may contribute to the phenotypes seen in addicted individuals. There has been much work over the past several years outlining the important role of transcription and

Table 2 Epigenetic modifications and addiction

Treatment	Modification	Effect	Reference
Chronic cocaine exposure	↑ H3 acetylation	↑ Induction of BDNF at promoter region	Kumar et al. 2005 [48]
Acute cocaine exposure	↑ H4 acetyation	↓ *fosB*	Levine et al. 2005 [50]
Co-administration of sodium butyrate and cocaine	↑ H3 acetylation	↑ cFos mRNA in striatum	Kumar et al. 2005 [48]
Chronic infusion of MS-275	↑ global H3 acetylation	Blocks cocaine induced locomotor sensitization	Kennedy et al. 2013 [57]

downstream targets in the action of drugs of abuse. More recent work has started to examine whether epigenetic modifications in response to administration of drugs of abuse contribute to the development and maintenance of addiction. The studies outlined above illustrate a few examples of how epigenetic regulation of genes related to drug addiction may underlie the lasting changes in neuronal and behavioral adaptations that result from the addicted state. However, more work is needed to better delineate how epigenetic changes may influence specific downstream targets implicated in mediating long-term aspects of addiction following drug exposure.

Epigenetics and Schizophrenia

Schizophrenia is a chronic and severe mental disorder that affects approximately 1 % of the population [58] and is characterized by deficits in thought processes and social behaviors, paranoia, hallucinations, and inappropriate emotional responses [59, 60]. Linkage and association studies suggest a contribution of genetics to the development of schizophrenia [61], however no single gene has been isolated to its etiology. Recent studies have started to examine whether epigenetic processes may underlie the pathophysiology of this disease.

An early hypothesis that emerged regarding schizophrenia was that epigenetic control of gene expression, specifically DNA methylation, at promoters within γ-aminobutyric acid (GABA) containing neurons, is a key factor in the development of this illness [62]. Studies done in postmortem tissue have reported a downregulation of several genes expressed within GABAergic neurons, including reelin and GAD1, in individuals with a history of schizophrenia, suggesting that a disruption in inhibitory neuronal circuitry contributes to the deficits observed in these patients [63, 64]. Interestingly, the reelin promoter contains a prominent CpG island suggesting it may be vulnerable to epigenetic modifications via DNA methylation [65]. Indeed, recent studies reported an increase in methylation at the promoter region of reelin in postmortem brain tissue of patients diagnosed with schizophrenia [66, 67]. Moreover, in vitro experiments utilizing human cell lines showed that treatment with the DNMT1 inhibitor aza-2′-deoxycytidine significantly increases reelin mRNA expression [65]. In a mouse model of schizophrenia, reelin mice treated with L-methionine, a compound previously shown to exacerbate the symptoms of schizophrenia in human subjects, had decreased reelin expression levels associated with hypermethylation of the reelin promoter following chronic administration of L-methionine [68]. These data suggest a possible role for alterations in DNA methylation in regulating reelin expression levels and potentially the etiology of schizophrenia; however, much work is needed to delineate which DNMTs (DNMT1, 3a, or 3b) may be involved in carrying out these modifications and how important these specific genes are in mediating the pathophysiology of schizophrenia.

Likewise, the GAD67 promoter is rich in GC cites and it is hypothesized that changes in methylation may regulate GAD67 activity in a similar fashion to reelin, which may underlie the functional deficits of these genes as seen in patients with schizophrenia. More recent work has demonstrated a correlation in vitro between increased GAD67 expression and decreases in methylation at key regions within the promoter following the administration of MS-275, an inhibitor of histone methylation, providing some evidence that GAD67 is prone to hypermethylation [69]. However, this work was done using pharmacological agents that offer less target specificity, and additional studies are necessary to understand the mechanisms that drive the changes in methylation to regulate the function of GAD67.

Several recent studies have reported changes in DNMT1 and DNMT3a in postmortem tissue of individuals with schizophrenia, further suggesting the potential involvement of aberrant DNA methylation with the disease process. In a group of patients where some individuals were on antipsychotic medication, there was a significant increase in DNMT1 mRNA expression in cortical GABAergic neurons of schizophrenic patients compared to non-psychiatric patient controls [65, 70]. Likewise, DNMT3a (but not DNMT3b) expression was significantly upregulated in GABA expressing neurons in the cortex of patients with schizophrenia, and this increase was independent of any antipsychotic medication the patients were taking at the time of death [71]. This abundant overexpression of DNMTs in postmortem brains of schizophrenia patients suggests they may be responsible for the hypermethylation of genes within GABAergic neurons including reelin and GAD67. These data provide further support for the prevailing view that changes in DNA methylation of key genes within GABA expressing neurons may have a significant role in the etiology of schizophrenia.

It is also plausible that HDACs may be involved in regulating epigenetic mechanisms that underlie schizophrenia. In the study described above, it was demonstrated that administration of valproate, a mood stabilizer with HDAC inhibition activity, normalizes the decrease in reelin expression following administration of L-methionine and promotes acetylation of global histone H3 in the mouse brain [68]. It has also been reported that valproate can facilitate demethylation at the reelin promoter following withdrawal of L-methionine treatment as well as increase acetylation levels of histone H3 at the reelin promoter by approximately 50 % [72]. Taken together, these studies suggest a crosstalk between histone acetylation and DNA methylation at key promoters of GABA containing neurons, which may underlie the pathophysiology of schizophrenia.

In accordance with a possible role in the development of schizophrenia, histone acetylation/deacetylation may be involved in mediating antipsychotic treatment. A recent paper showed that chronic treatment with the atypical antipsychotic, clozapine, in mice and humans leads to a downregulation of mGlu2 receptor expression via a decrease in acetylation at its promoter site, and that it is specifically an increase of HDAC2 binding to the mGlu2 promoter that mediates this effect [73]. Additionally, chronic infusion of the class I and II HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) in mice blocked the repressive histone modifications and augmented the beneficial behavioral effects induced by clozapine treatment. These findings suggest a novel role for HDAC2 as a therapeutic target in the treatment of schizophrenia, and encourage a need for the development of selective inhibitors that can distinguish between the individual HDACs (Table 3).

Altogether, the studies in this section detail the strong correlation between epigenetic modifications of genes implicated in schizophrenia and the disorder. While much of this evidence comes from postmortem studies, complementary approaches with mouse models have also tried to implicate epigenetic mechanisms with the disease process as well as the mechanism for antipsychotic action. An active area of investigation is whether these epigenetic alterations that have been identified contribute to the development of schizophrenia or whether they occur as part of the disease process. The generation of better animal models for schizophrenia will hopefully provide a better understanding of critical factors that are involved in this disorder and treatment options. In the meantime, further investigation of epigenetic mechanisms that may contribute to alterations of specific genes implicated in schizophrenia remains an active area of research.

Conclusions and Future Studies

A growing body of work suggests that epigenetics may play a role in the pathophysiologies that contribute to psychiatric illness such as major depressive disorder, drug addiction, and schizophrenia. These modifications, which often occur in response to environmental stimuli such as chronic stress and drugs of abuse, can drive changes in epigenetic mechanisms such as histone modifications and DNA methylation at global levels as well as at promoter regions of key target proteins to produce long-lasting and stable changes in gene expression. With a better understanding of how epigenetic mechanisms underlie psychiatric disorders, the hope is to better characterize how these modifications impact specific genes that may contribute to these disorders.

Much emphasis has been placed on histone modifications and DNA methylation and there has been data in support of using pharmacological HDAC and DNMT inhibitors as therapeutic tools in treating the psychiatric disorders mentioned in this review. However, most of these drugs are pan inhibitors with multiple targets, offering little specificity towards an individual gene or specific drug target. This could prove to be problematic in treating psychiatric illnesses as chronic administration of these drugs may cause deleterious effects that are not yet clearly understood. Furthermore, different HDAC and DNMT subtypes have distinct roles in psychiatric disorders and there is little known about how they impact specific downstream genes. These concerns could potentially be addressed in the future through more extensive delineation of the distinct mechanisms that underlie the epigenetic action of the different subtypes within the HDAC and DNMT family. Overall, through a better understanding of how epigenetic mechanisms carry out long-lasting and adaptive changes in gene function and expression, researchers will uncover new avenues of treatment

Table 3 Epigenetic modifications and schizophrenia

Tissue/Species	Treatment	Effect	Reference
Postmortem brain tissue	Patients diagnosed with SZ	↑ Methylation at reelin promoter	Abdolmaleky et al. 2005 [66] Grayson et al. 2005 [67]
Human cell line	aza-2′-deoxycytidine	↑ Reelin MRNA	Chen et al. 2002 [65]
Reelin mice	Chronic L-methionine administration	↓ Reelin via hypermethylation of reelin promoter	Tremolizzo et al. 2002 [68]
N2T cells	MS-275	↓ Methylation at GAD67 promoter and ↑ GAD67 expression	Chen et al. 2011 [69]
Postmortem brain tissue	Patients diagnosed with SZ (some on antipsychotics)	↑ DNMT1, 3a mRNA in cortical GABA neurons	Chen et al. 2002 [65] Veldic et al. 2005 [70] Zhubi et al. 2009 [71]
Mice	Chronic treatment with clozapine	↓ mGlu2 receptor expression via acetylation at the promoter site	Kurita et al. 2012 [73]
Mice	Chronic treatment with SAHA in PFC	↑ mGlu2, mGlu3 mRNA in PFC via H3 acetylation at respective promoters	Kurita et al. 2012 [73]

therapies to address the needs of individuals suffering from psychiatric illness.

Acknowledgments The authors would like to thank members of the Monteggia laboratory, especially Dr. Megumi Adachi, as well as Dr. Ege Kavalali for helpful discussions and comments on the manuscript. This work was supported by MH081060 (LMM). The authors report no conflicts of interest.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Kendler KS. Twin studies of psychiatric illness: an update. Arch Gen Psychiatry 2001;58:1005–14.
2. Sapolsky RM. Depression, antidepressants, and the shrinking hippocampus. Proc Natl Acad Sci USA 2001;98:12320–2.
3. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34:13–25.
4. McEwen BS. Effects of adverse experiences for brain structure and function. Biol Psychiatry 2000;48:721–31.
5. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. Science 1975;187:226–32.
6. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245–54.
7. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell 2007;128:635–8.
8. Felsenfeld G, Groudine M. Controlling the double helix. Nature 2003;421:448–53.
9. Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P. Decoding the epigenetic language of neuronal plasticity. Neuron 2008;60:961–74.
10. Bird AP. CpG-rich islands and the function of DNA methylation. Nature 1986;321:209–13.
11. Bird AP, Wolffe AP. Methylation-induced repression–belts, braces, and chromatin. Cell 1999;99:451–4.
12. Goll MG, Bestor TH. Eukaryotic cytosine methyltransferases. Annu Rev Biochem 2005;74:481–514.
13. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–27.
14. Fava M, Kendler KS. Major depressive disorder. Neuron 2000;28:335–41.
15. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008;358:55–68.
16. Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev Neurobiol 2010;70:289–97.
17. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997;54:597–606.
18. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001;50:260–5.
19. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997;56:131–7.
20. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;22:3251–61.
21. Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T et al. Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA 2004;101:10827–32.
22. Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S et al. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biol Psychiatry 2007;61:187–97.
23. Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry 2008;63:642–9.
24. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006;59:1116–27.
25. Sapolsky RM. Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. Stress 1996;1:1–19.
26. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 1995;15:1768–77.
27. Nibuya M, Takahashi M, Russell DS, Duman RS. Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci Lett 1999;267:81–4.
28. Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, Riva MA. Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. Biol Psychiatry 2004;55:708–14.
29. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci 2006;9:519–25.
30. Onishchenko N, Karpova N, Sabri F, Castren E, Ceccatelli S. Long-lasting depression-like behavior and epigenetic changes of BDNF gene expression induced by perinatal exposure to methylmercury. J Neurochem 2008;106:1378–87.
31. Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, Russo SJ et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 2006;311:864–8.
32. Golden SA, Christoffel DJ, Heshmati M, Hodes GE, Magida J, Davis K et al. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. Nat Med 2013;19:337–44.
33. Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznerski P et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat Med 2012;18:1413–7.
34. Nasca C, Xenos D, Barone Y, Caruso A, Scaccianoce S, Matrisciano F et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci USA 2013;110:4804–9.
35. Chiechio S, Copani A, Zammataro M, Battaglia G, Gereau RWt, Nicoletti F. Transcriptional regulation of type-2 metabotropic glutamate receptors: an epigenetic path to novel treatments for chronic pain. Trends Pharmacol Sci 2010;31:153–60.
36. Overstreet DH, Friedman E, Mathe AA, Yadid G. The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev 2005;29:739–59.
37. Matrisciano F, Caruso A, Orlando R, Marchiafava M, Bruno V, Battaglia G et al. Defective group-II metaboropic glutamate receptors in the hippocampus of spontaneously depressed rats. Neuropharmacology 2008;55:525–31.
38. Feng J, Zhou Y, Campbell SL, Le T, Li E, Sweatt JD et al. Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. Nat Neurosci 2010;13:423–30.
39. Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. Neuron 2007;53:857–69.
40. Levenson JM, Roth TL, Lubin FD, Miller CA, Huang IC, Desai P et al. Evidence that DNA (cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. J Biol Chem 2006;281:15763–73.

41. LaPlant Q, Vialou V, Covington HE, 3rd, Dumitriu D, Feng J, Warren BL et al. Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. Nat Neurosci 2010;13:1137–43.
42. Nestler EJ. Molecular mechanisms of drug addiction. Neuropharmacology 2004;47 Suppl 1:24–32.
43. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001;2:119–28.
44. Graham DL, Edwards S, Bachtell RK, DiLeone RJ, Rios M, Self DW. Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse. Nat Neurosci 2007;10:1029–37.
45. Lu L, Dempsey J, Liu SY, Bossert JM, Shaham Y. A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal. J Neurosci 2004;24:1604–11.
46. Grimm JW, Lu L, Hayashi T, Hope BT, Su TP, Shaham Y. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. J Neurosci 2003;23:742–7.
47. Im HI, Hollander JA, Bali P, Kenny PJ. MeCP2 controls BDNF expression and cocaine intake through homeostatic interactions with microRNA-212. Nat Neurosci 2010;13:1120–7.
48. Kumar A, Choi KH, Renthal W, Tsankova NM, Theobald DE, Truong HT et al. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron 2005;48:303–14.
49. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. Nat Rev Neurosci 2011;12:623–37.
50. Levine AA, Guan Z, Barco A, Xu S, Kandel ER, Schwartz JH. CREB-binding protein controls response to cocaine by acetylating histones at the fosB promoter in the mouse striatum. Proc Natl Acad Sci USA 2005;102:19186–91.
51. Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 2009;10:32–42.
52. Renthal W, Maze I, Krishnan V, Covington HE, 3rd, Xiao G, Kumar A et al. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. Neuron 2007;56:517–29.
53. Romieu P, Host L, Gobaille S, Sandner G, Aunis D, Zwiller J. Histone deacetylase inhibitors decrease cocaine but not sucrose self-administration in rats. J Neurosci 2008;28:9342–8.
54. Sun J, Wang L, Jiang B, Hui B, Lv Z, Ma L. The effects of sodium butyrate, an inhibitor of histone deacetylase, on the cocaine- and sucrose-maintained self-administration in rats. Neurosci Lett 2008;441:72–6.
55. Wang L, Lv Z, Hu Z, Sheng J, Hui B, Sun J et al. Chronic cocaine-induced H3 acetylation and transcriptional activation of CaMKIIalpha in the nucleus accumbens is critical for motivation for drug reinforcement. Neuropsychopharmacology 2010;35:913–28.
56. Ferrante RJ, Kubilus JK, Lee J, Ryu H, Beesen A, Zucker B et al. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 2003;23:9418–27.
57. Kennedy PJ, Feng J, Robison AJ, Maze I, Badimon A, Mouzon E et al. Class I HDAC inhibition blocks cocaine-induced plasticity by targeted changes in histone methylation. Nat Neurosci 2013;16:434–40.
58. Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94.
59. Carpenter WT, Jr., Buchanan RW. Schizophrenia. N Engl J Med 1994;330:681–90.
60. Tamminga CA, Holcomb HH. Phenotype of schizophrenia: a review and formulation. Mol Psychiatry 2005;10:27–39.
61. Owen MJ, Williams NM, O'Donovan MC. The molecular genetics of schizophrenia: new findings promise new insights. Mol Psychiatry 2004;9:14–27.
62. Costa E, Chen Y, Davis J, Dong E, Noh JS, Tremolizzo L et al. REELIN and schizophrenia: a disease at the interface of the genome and the epigenome. Mol Interv 2002;2:47–57.
63. Huang HS, Akbarian S. GAD1 mRNA expression and DNA methylation in prefrontal cortex of subjects with schizophrenia. PLoS One 2007;2:e809.
64. Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Arch Gen Psychiatry 2000;57:1061–9.
65. Chen Y, Sharma RP, Costa RH, Costa E, Grayson DR. On the epigenetic regulation of the human reelin promoter. Nucleic Acids Res 2002;30:2930–9.
66. Abdolmaleky HM, Cheng KH, Russo A, Smith CL, Faraone SV, Wilcox M et al. Hypermethylation of the reelin (RELN) promoter in the brain of schizophrenic patients: a preliminary report. Am J Med Genet B Neuropsychiatr Genet 2005;134B:60–6.
67. Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A et al. Reelin promoter hypermethylation in schizophrenia. Proc Natl Acad Sci USA 2005;102:9341–6.
68. Tremolizzo L, Carboni G, Ruzicka WB, Mitchell CP, Sugaya I, Tueting P et al. An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability. Proc Natl Acad Sci USA 2002;99:17095–100.
69. Chen Y, Dong E, Grayson DR. Analysis of the GAD1 promoter: trans-acting factors and DNA methylation converge on the 5' untranslated region. Neuropharmacology 2011;60:1075–87.
70. Veldic M, Guidotti A, Maloku E, Davis JM, Costa E. In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. Proc Natl Acad Sci USA 2005;102:2152–7.
71. Zhubi A, Veldic M, Puri NV, Kadriu B, Caruncho H, Loza I et al. An upregulation of DNA-methyltransferase 1 and 3a expressed in telencephalic GABAergic neurons of schizophrenia patients is also detected in peripheral blood lymphocytes. Schizophr Res 2009;111:115–22.
72. Dong E, Guidotti A, Grayson DR, Costa E. Histone hyperacetylation induces demethylation of reelin and 67-kDa glutamic acid decarboxylase promoters. Proc Natl Acad Sci USA 2007;104:4676–81.
73. Kurita M, Holloway T, Garcia-Bea A, Kozlenkov A, Friedman AK, Moreno JL et al. HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity. Nat Neurosci 2012;15:1245–54.