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Epigenetics of Neurobiology and Behavior during Development and Adulthood

ABSTRACT: *Gene–environment interactions have long been recognized for their important role in mediating the development and functions of the central nervous system (CNS). The study of DNA methylation and histone modifications, biochemical processes collectively referred to as epigenetic mechanisms, is helping to elucidate how gene–environmental interactions alter neurobiology and behavior over the course of the lifespan. In this review, landmark and recent studies that highlight the role of epigenetic mechanisms in the sustained effects of early-life experiences on gene activity and behavioral outcome will be discussed. Likewise, studies that implicate epigenetics in CNS and behavioral plasticity in the adult animal will be discussed. As our current understanding of epigenetics in these capacities is still evolving, epigenetic research will continue to be of considerable interest for understanding the molecular mechanisms mediating neurobiology and behavior both within and outside of sensitive periods of development.* © *2012 Wiley Periodicals, Inc.* Dev Psychobiol

Keywords: *early-life experience; stress; memory; epigenetic; DNA methylation; histone modification*

INTRODUCTION

Recent advances in the field of epigenetics indicate that early-life environmental influences, particularly those occurring during sensitive periods of development, can trigger functional changes in genes without altering the DNA sequence itself. Data demonstrate that through DNA methylation and histone acetylation, biochemical processes collectively referred to as epigenetic mechanisms, factors including infant stress and quality of parental care can stably mark an infant's genome and dictate gene expression patterns throughout the lifespan to promote specific behavioral outcomes (Champagne, 2010; McGowan & Szyf, 2010; Murgatroyd, Wu, Bockmuhl, & Spengler, 2010; Zhang & Meaney, 2010). Thus, epigenetic mechanisms are increasingly being recognized as one class of mechanisms by which early-life environmental influences can have long-lasting and even permanent effects on neurobiology and behavior.

At the same time studies in older animals indicate that epigenetic marking of the genome is a phenomenon not exclusive to development, but is a process that continues throughout the lifespan. For example, DNA methylation and histone acetylation have now been linked to adulthood learning and memory, drug addiction, and several psychiatric and neurological illnesses (Franklin & Mansuy, 2010; Hsieh & Eisch, 2010; LaPlant & Nestler, 2010; Liu, van Groen, Kadish, & Tollefsbol, 2009; Roth, Lubin, Sodhi, & Kleinman, 2009). Thus, epigenetic mechanisms not only play a role in mediating developmental changes in neurobiology and behavior, but changes in neurobiology and behavior over the course of the lifespan. This is the central theme explored in this review.

EPIGENETIC GENE REGULATION

There are two basic molecular epigenetic mechanisms that are currently studied in regard to neurobiology and behavior within and outside of sensitive periods of

Received 1 August 2010; Accepted 24 March 2011
Correspondence to: T. L. Roth
Contract grant sponsor: National Alliance for Research on Schizophrenia and Depression
Contract grant sponsor: The University of Delaware
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/dev.20550

development—posttranslational histone modifications and DNA methylation. In the cell nucleus, DNA is wrapped around a core of histone proteins much like thread is on a spool. Posttranslational modifications of histones, including acetylation, phosphorylation, and methylation, mediate the interactions between histones and DNA, and help determine whether DNA is accessible for gene transcription (Strahl & Allis, 2000). For example, acetylation of lysine residues of histones, a reaction catalyzed by enzymes known as histone acetyltransferases (HATs), decreases the affinity between histones and DNA. In addition to relaxing chromatin structure, histone acetylation also enhances recruitment, stabilization, and activation of transcriptional machinery (Marmorstein & Trievel, 2009). Histone acetylation is therefore an epigenetic mark generally associated with active gene transcription (Fig. 1A).

Transcriptionally active genes are also characterized by mostly unmethylated cytosines of CG dinucleotides, whereas transcriptionally inactive genes are characterized by methylated CG dinucleotides and deacetylated histones (Fig. 1B). Histone methylation can be associated with either repression or activation, dependent upon the specific location of the modification. The addition of methyl groups to cytosines is a process referred to as DNA methylation, and is catalyzed by DNA methyltransferases (DNMTs). Methylated cytosines in turn bind repressor proteins, including the methyl-binding domain protein MeCP2 and histone deacetylases (HDACs) (Jaenisch & Bird, 2003; Miranda & Jones, 2007). DNA methylation promotes a higher-affinity interaction between DNA and the histone core, ultimately blocking access for transcriptional machinery and thus suppressing gene transcription. DNA methylation is recognized as one of the most stable epigenetic processes affecting gene expression.

EPIGENETIC MARKING OF THE GENOME BY EARLY-LIFE EXPERIENCES

Historically, epigenetic marking of the genome, and particularly DNA methylation, has been associated with events exclusive to cellular development and differentiation or cancer. In 2004, a landmark study challenged this view, arguing that the epigenome is responsive to environmental influences beyond embryonic development (Weaver et al., 2004). In that study, researchers determined that DNA methylation and histone acetylation patterns of the glucocorticoid receptor (GR) gene in the hippocampus of adult male rats were a direct product of the type of maternal care that they had received during infancy. GRs are intimately associated with HPA stress responses, and receptor activation inhibits HPA activity. They showed that adults that had been raised by mothers who displayed high levels of licking/grooming and an arched-back nursing position (high LG-ABN) exhibited low levels of DNA methylation of the GR gene, as well as high levels of hippocampal histone acetylation. On the other hand, adults who had been raised by mothers displaying low levels of licking/grooming exhibited hypermethylation of GR DNA and less histone acetylation. Importantly, the

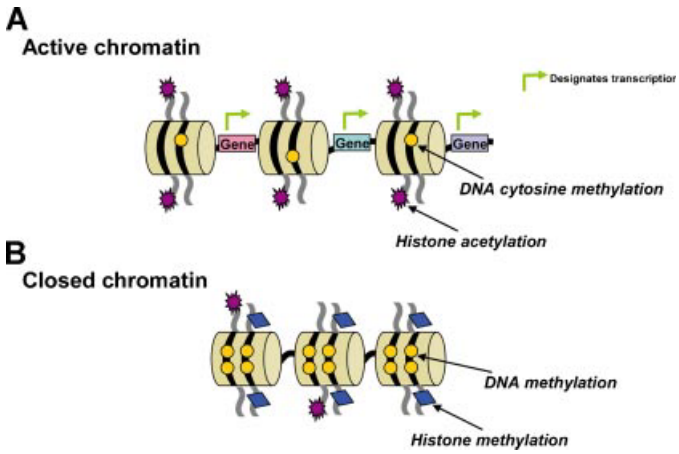

FIGURE 1 Schematic of epigenetic modifications. Site-specific histone modifications (acetylation, methylation, phosphorylation, sumoylation) occur at amino-acid residues of histone tails, some of which are depicted here. DNA methylation occurs at cytosine residues of cytosine–guanine dinucleotides typically clustered within gene regulatory regions. Together, these modifications provide a unique epigenetic signature that governs either (A) active chromatin structure or (B) closed chromatin structure.

authors also showed that these methylation changes were occurring at a functionally relevant site of the gene that would affect transcription. Specifically, within the NGFI-A binding region (NGFI-A is a transcription factor), the 5′ CG dinucleotide (site 16) was always methylated in adult offspring of low compared to high LG-ABN mothers. In these same offspring, there was reduced interaction between NGFI-A and the GR promoter sequence. Epigenetic alterations in NGFI-A binding to the promoter thus demonstrate a mechanism of how maternal care is able to directly influence hippocampal GR expression.

Through a series of drug manipulations and cross-fostering experiments it was also demonstrated that these epigenetic changes emerged during the first postnatal week, and were directly responsible for programming the expression of that gene over the course of the lifespan as well as the animal's behavioral outcome. Adults with lower levels of GR DNA methylation and higher levels of histone acetylation had increased expression of the GR gene, displayed a more moderate stress response (decreased HPA activation), and exhibited less fear-like behavior. The opposite held true for gene expression and behavior in animals with higher levels of DNA methylation and lower levels of acetylation.

Such exciting observations provided the impetus for several laboratories to begin to investigate the capacity of changes in DNA methylation to mediate other developmental changes in neurobiology and behavior. For example, levels of cytosine methylation of the estrogen receptor alpha (ER-alpha) gene promoter have since been shown to be influenced by the mother's care (Champagne et al., 2006). ER-alpha is a gene whose activation supports the expression of maternal behavior, and ER-alpha expression is regulated by the Janus kinase-Stab5b pathway. In this study, adult female offspring of high LG-ABN mothers were found to have lower levels of ER-alpha gene DNA methylation, increased binding of a particular transcription factor (Stat5b) within the gene regulatory region, and increased expression of the ER-alpha gene. These animals ultimately displayed high levels of licking/grooming and the arched-backed nursing position toward their own offspring (Champagne, Diorio, Sharma, & Meaney, 2001). The opposite was found true for adult offspring of low LG-ABN mothers: they had increased DNA methylation, including methylation of the CG site within the Stat5b binding site, decreased binding of Stat5b (thus inhibiting ER-alpha transcription), and decreased gene expression. Reminiscent of the outcome regarding fear-like behavior, variations in maternal care confers differences in future mothering behavior via epigenetic mechanisms.

While the studies reviewed above were the first to definitively demonstrate epigenetic programming of neurobiology and behavior by infant-caregiver experiences, studies have since also linked epigenetic mechanisms to the maladaptive outcomes of an adverse early-life environment. In 2008, an investigation highlighted the role of epigenetic mechanisms in the maladaptive effects of prenatal stress on adult HPA responsivity and behavior (Mueller & Bale, 2008). Researchers found that adult males born to mothers who had been subjected to gestational stress exhibited marked changes in expression of the corticotropin-releasing factor (CRF) and GR genes, increased HPA-axis responsivity, and a depressive-like phenotype (anhedonia for example). CRF is secreted by the hypothalamus in response to stress, with consequent secretion of adrenocorticotropin from the anterior pituitary and glucocorticoids from the adrenal gland. Examination of the CRF gene in these adults indicated that the prenatal stress regimen had significantly reduced methylation of specific cytosines within the regulatory region of the CRF gene in both the hypothalamus and amygdala. Reduced methylation is consistent with their observation of increased CRF gene expression, which together might contribute to the depressive-like phenotype present in the offspring. Importantly, these results suggest a mechanism whereby stressors in the womb could give rise to adult onset diseases associated with stress responsivity and depression.

Adverse social experiences and environmental conditions during early postnatal development have too been shown to their leave their lasting marks on the epigenome. In the first of two studies published in 2009, researchers showed that rats at least 3 months out following their last experience with an abusive caregiver/adverse nest environment had significantly less expression of the brain-derived neurotrophic factor (BDNF) gene in their prefrontal cortex, an effect that was attributed to sustained hypermethylation of the gene's DNA (Roth, Lubin, Funk, & Sweatt, 2009). Specifically, within an important regulatory region of the BDNF gene (exon IV, which contributes to activity-dependent gene transcription and is epigenetically modulated), it was shown that normal adults (i.e., adults with a history of normal infancy) had either no or very little CG dinucleotide methylation. This was in sharp contrast to the adults who had experienced maltreatment during infancy, where sequencing of that same regulatory region revealed that the same CG dinucleotides were all highly methylated.

Intriguingly, it was also found that females with a history of maltreatment (maltreated-females) showed the same types of abusive behaviors toward their own offspring that they had experienced themselves as

infants, and that the epigenetic modifications acquired in one generation were even transmitted to the next generation of infants. Specifically, 8-day-old offspring (both males and females) derived from the maltreated-females had significant methylation of BDNF DNA in both their prefrontal cortex and hippocampus in comparison to offspring derived from normal-treated females (females who had experienced a normal infancy). Surprisingly, cross-fostering experiments (where offspring born to maltreated-females were cross-fostered to normal females and vice versa) suggested that the transgenerational inheritance was not simply a reflection of the postnatal experience, but likely reflected some unidentified prenatal component.

As BDNF strongly modulates the establishment of neuronal connectivity, and suppression of BDNF expression has been linked to anxiety and depressive-like symptoms in early-life stress models, these results provide new mechanisms through which neurotrophin expression may be regulated by environmental insults (such as early-life stress) with profound consequences for subsequent behavior. Of future interest, will be to assess the impact of interventional pharmacological (HDACS or antidepressants) and behavioral therapies to counteract these early-life experiences and asses the consequences of such treatments on the epigenome and behavior.

In the second study published in 2009, separation from the caregiver was likewise shown to evoke lasting epigenetic modifications (Murgatroyd et al., 2009). In this study, mice as far as 1 year out from the last infant separation experience were shown to have hypomethylation of arginine vasopressin (AVP) DNA in their paraventricular nucleus (PVN). The product of the AVP gene is a hypothalamic secretagogue that induces the synthesis and release of adrenocorticotropin from the pituitary. The lower levels of DNA methylation inversely correlated with AVP expression, as well as reduced binding of MeCP2, a DNA methyl-binding protein typically associated with gene suppression. Together, these effects coincided with increased corticosterone secretion both at basal conditions and in response to stress, as well as an attenuated memory capacity. The abnormal stress responses in adults could be partially reversed by AVP antagonism (via the AVP V1b receptor antagonist SSR149415). Overall, these results indicate that an early-life stressor activates a key group of stress regulating neurons within the PVN, leads to stables changes in MeCP2 function, which in turn epigenetically reprograms AVP, a key gene involved in the stress regulatory pathway.

Finally, in more recent examples of the ability of early-life adversity to epigenetically mark genes, increased stress responsivity in maternally and socially isolated infant macaques has been linked to hypermethylation of the serotonin transporter gene (Kinnally et al., 2010), and the impact of chronic and unpredictable infant separation on depressive-like behaviors in mice that experienced the stress and in their subsequent offspring has been linked to the DNA methylation profile of several stress-related and behaviorally relevant genes (Franklin et al., 2010). In this latter study, depressive-like behaviors were not just present in the male mice that experienced the early-life stress regimen, but in their offspring that were never subjected to any stress and had been raised normally. In parallel, DNA methylation patterns that were present in the germline (sperm) and brains of the male mice that had experienced the early-life stress (i.e., the fathers) were present in the brains of the offspring. By demonstrating that there were epigenetic changes in the germline, this study elegantly demonstrates a mechanism by which stress effects may be passed across generations independent of maternal care or other environmental factors.

Together, the studies reviewed above highlight the remarkable susceptibility of the genome of a developing infant to epigenetic modifications by experiential and environmental factors (Fig. 2). Most provocatively, these studies provide compelling data that epigenetic marking of the genome, particularly sustained changes in DNA methylation, is a molecular basis by which early-life experiences can have lifelong and even transgenerational effects on neurobiology and behavior.

EPIGENETIC MARKING OF THE GENOME OUTSIDE OF SENSITIVE PERIODS OF DEVELOPMENT

Within the field of behavioral neuroscience, there is growing evidence that epigenetic mechanisms not only have a prominent role in programming neurobiology and behavior within sensitive periods of development, but support neural and behavioral plasticity in adulthood. Below several studies are briefly reviewed to make the point that epigenetic regulation of genes continues to play an active process in regulating an adult animal's ability to respond to and even form memories of its environment and experiences.

Epigenetics of Learning and Memory

For example, several studies in the last few years have linked the ability of an adult animal to learn and form a memory of some experience with rapid and transient changes in hippocampal DNA methylation. Specifically, associative learning and fear memory formation in a

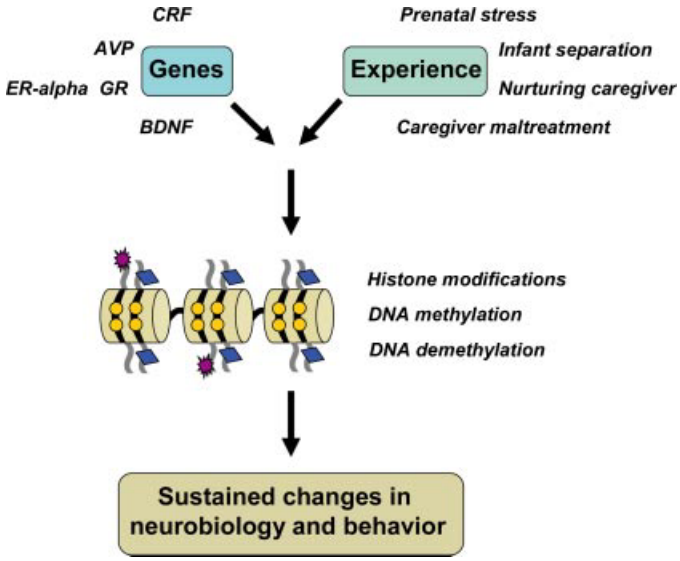

FIGURE 2 The susceptibility of the genome in infancy to sustained epigenetic modifications. Data indicate that both nurturing and stressful experiences early in development epigenetically mark genes in the CNS. Epigenetic CNS changes have been documented for several genes, including the corticotropin-releasing factor (CRF), arginine vasopressin (AVP), estrogen receptor alpha (ER-alpha), glucocorticoid receptor (GR), and brain-derived neurotrophic factor (BDNF) genes. These changes represent at least one class of mechanisms responsible for the lasting changes in neurobiology and behavior brought about by early-life experiences.

contextual fear conditioning paradigm have been shown to elicit DNA methylation and transcriptional silencing of the memory suppressor gene protein phosphatase 1, and DNA demethylation and transcriptional activation of the synaptic plasticity genes reelin and BDNF (Lubin, Roth, & Sweatt, 2008; Miller & Sweatt, 2007). A more recent study has demonstrated longer-lived (30 days) experience-induced changes in cortical DNA methylation following the contextual fear conditioning paradigm (Miller et al., 2010). Furthermore, disruption of the function of MeCP2 (Adachi, Autry, Covington, & Monteggia, 2009) or DNMTs (Feng et al., 2010) hinders memory.

Modification of histones also appears equally important in mediating adult neurobiology and behavior. During associative fear memory formation, it has been shown that there are increases in hippocampal histone acetylation as well as complex patterns of histone methylation (Gupta et al., 2010; Lubin et al., 2008). The extinction of conditioned fear has also been linked with histone acetylation in the prefrontal cortex (Bredy et al., 2007; Lubin et al., 2008). The beneficial effects of environmental enrichment on restoring learning and memory capacity in cognitively impaired mice have been shown to involve increased hippocampal and cortical histone acetylation (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). In addition, the systemic delivery of one of various HDAC inhibitors has been shown sufficient to rescue the cognitive deficits present in a mouse model of Alzheimer's disease (Kilgore et al., 2009).

Epigenetics of Addiction/Cocaine-Related Behaviors

In a 2005 study, administration of cocaine was shown to rapidly increase striatal histone acetylation on two genes known to play a critical role in cocaine-related behaviors, c-fos and fosB (Kumar et al., 2005). Gene promoters have even been found to be hyperacetylated for several days to weeks following chronic cocaine exposure (Freeman et al., 2008). Use of a chromatin immunoprecipitation coupled to microarrays (ChIP–Chip) has also identified repressive histone H3 lysine 9 (H3K9) and 27 (H3K27) methylation at several gene promoters in the nucleus accumbens after chronic cocaine exposure (Renthal et al., 2009). More recent work has elegantly dissected the role of the lysine dimethyltransferase G9a (Maze et al., 2010) and DNA methyltransferase Dnmt3a (LaPlant et al., 2010) in the morphological (dendritic spine plasticity in the nucleus accumbens) and behavioral outcomes (cocaine preference) that may underlie cocaine addiction.

Epigenetics of Stress

Epigenetics may also help explain how adulthood stressors can alter the brain and behavior. It has recently

been shown that acute or chronic restraint stress evokes patterns of hippocampal histone methylation that vary by hippocampal subregion (Hunter, McCarthy, Milne, Pfaff, & McEwen, 2009). Chronic social defeat stress also affects histones, and the downregulation of hippocampal BDNF mRNA induced by social defeat stress has been associated with an increase in suppressive histone methylation (Tsankova et al., 2006). Finally in regards to histones, a forced-swimming task has been shown to induce histone modifications within the hippocampus (Chandramohan, Droste, Arthur, & Reul, 2008). A few recent studies have documented that psychosocial stress in adulthood evokes significant changes in DNA methylation. A psychosocial stress regimen composed of two acute cat exposures in conjunction with 31 days of social instability, which produces PTSD-like behavioral stress responses, also produces robust hypermethylation of BDNF DNA in the dorsal hippocampus of adult male rats (Roth, Zoladz, Sweatt, & Diamond, 2011). Of course stress effects are not exclusive to the hippocampus, and a recent study has established a link between DNA methylation and stress-induced effects on CRF gene expression in the PVN and subsequent social avoidance behavior (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010).

Epigenetics of Psychiatric Disorder

Evidence gathered to date also supports the hypothesis that the dysregulation of epigenetic mechanisms is associated with cognitive dysfunction in several psychiatric and brain disorders. For example, studies suggests that aberrant DNA methylation of the reelin and Gad1 genes may underlie dysfunction of GABAergic neurons in schizophrenia, and altered GABA activity appears responsible for at least some of the clinical features of schizophrenia (Grayson, Chen, Dong, Kundakovic, & Guidotti, 2009). Several studies have also reported aberrant DNA methylation and histone acetylation in Alzheimer's patients (Mastroeni, McKee, Grover, Rogers, & Coleman, 2009; Siegmund & Connor, 2007). Finally, altered DNA methylation may be involved in the dysregulation of the BDNF gene associated with suicidal behavior (Keller et al., 2010), as well as the dysregulation of immune-related genes associated with posttraumatic stress disorder (Uddin et al., 2010).

CONCLUSIONS

A prevailing tenet in the field of epigenetics has been that the epigenome is static past embryonic development. The data reviewed here indicate that this is not the case for the central nervous system (CNS). Overall, there is a growing body of work from the developmental neuroscience field that supports the view that sustained epigenetic changes underlie the long-term impact of early-life experiences. At the same time, there is swelling evidence that the CNS retains its sensitivity to epigenetic factors beyond development, and that epigenetic regulation of gene transcription is an important component of adulthood cognitive processes.

In conclusion, drawing on data from both developmental and adult studies, it is becoming increasingly clear that the susceptibility of the genome to epigenetic modifications provides a layer of genetic regulation that is sensitive to a lifetime of experiential and environmental factors. The question of whether there is increased susceptibility during particular stages of the lifespan has not been addressed. It is clear, however, that experiences during sensitive periods of development evoke epigenetic modifications that are particularly robust and long-lasting. To date, later-life experiences have not been shown to produce the type of sustained (i.e., over the course of several months to a year, or across generations) epigenetic modifications as those documented in developmental studies. Furthermore, whether epigenetic mechanisms subserve associative learning and memory during development as they do in the adult remains unknown, though there is emerging evidence that suggests this could be the case (Kisliouk, Ziv, & Meiri, 2010; Yossifoff, Kisliouk, & Meiri, 2008).

While the data discussed in this review are certainly intriguing, much more study is needed to fully appreciate and understand the discovered epigenetic phenomena. Continued investigation of epigenetics promises to revolutionize our understanding of the factors mediating developmental changes in neurobiology and behavior. How they compare to and differ from those mediating changes in neurobiology and behavior at other time points (i.e., outside of sensitive periods of development) remains an important question for future research.

NOTES

This work was funded by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression and start-up funds provided by The University of Delaware.

REFERENCES

Adachi, M., Autry, A. E., Covington, H. E., III, & Monteggia, L. M. (2009). MeCP2-mediated transcription repression in the basolateral amygdala may underlie heightened anxiety

in a mouse model of Rett Syndrome. Journal of Neuroscience, 29(13), 4218–4227.

Bredy, T. W., Wu, H., Crego, C., Zellhoefer, J., Sun, Y. E., & Barad, M. (2007). Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear. Learning and Memory, 14(4), 268–276.

Champagne, F., Diorio, J., Sharma, S., & Meaney, M. J. (2001). Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proceedings of the National Academy of Sciences of the United States of America, 98(22), 12736–12741.

Champagne, F., Weaver, I., Diorio, J., Dymov, S., Szyf, M., & Meaney, M. J. (2006). Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology, 147(6), 2909–2915.

Champagne, F. A. (2010). Epigenetic influence of social experiences across the lifespan. Developmental Psychobiology, 52(4), 299–311.

Chandramohan, Y., Droste, S. K., Arthur, J. S. C., & Reul, J. M. H. M. (2008). The forced swimming-induced behavioural immobility response involves histone H3 phosphoacetylation and c-Fos induction in dentate gyrus granule neurons via activation of the N-methyl-d-aspartate/extracellular signal-regulated kinase/mitogen- and stress-activated kinase signaling pathway. European Journal of Neuroscience, 27(10), 2701–2713.

Elliott, E., Ezra-Nevo, G., Regev, L., Neufeld-Cohen, A., & Chen, A. (2010). Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. Nature Neuroscience, 13(11), 1351–1353.

Feng, J., Zhou, Y., Campbell, S. L., Le, T., Li, E., Sweatt, J. D., et al. (2010). Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. Nature Neuroscience, 13(4), 423–430.

Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M., & Tsai, L.-H. (2007). Recovery of learning and memory is associated with chromatin remodeling. Nature, 447(7141), 178–182.

Franklin, T. B., & Mansuy, I. M. (2010). The prevalence of epigenetic mechanisms in the regulation of cognitive functions and behaviour. Current Opinion in Neurobiology, 20(4), 441–449.

Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., et al. (2010). Epigenetic transmission of the impact of early stress across generations. Biological Psychiatry, 68(5), 408–415.

Freeman, W. M., Patel, K. M., Brucklacher, R. M., Lull, M. E., Erwin, M., Morgan, D., et al. (2008). Persistent alterations in mesolimbic gene expression with abstinence from cocaine self-administration. Neuropsychopharmacology, 33(8), 1807–1817.

Grayson, D., Chen, Y., Dong, E., Kundakovic, M., & Guidotti, A. (2009). From trans-methylation to cytosine methylation: Evolution of the methylation hypothesis of schizophrenia. Epigenetics, 4(3), 144–149.

Gupta, S., Kim, S. Y., Artis, S., Molfese, D. L., Schumacher, A., Sweatt, J. D., et al. (2010). Histone methylation regulates memory formation. Journal of Neuroscience, 30(10), 3589–3599.

Hsieh, J., & Eisch, A. J. (2010). Epigenetics, hippocampal neurogenesis, and neuropsychiatric disorders: Unraveling the genome to understand the mind. Neurobiology of Disease, 39(1), 73–84.

Hunter, R. G., McCarthy, K. J., Milne, T. A., Pfaff, D. W., & McEwen, B. S. (2009). Regulation of hippocampal H3 histone methylation by acute and chronic stress. Proceedings of the National Academy of Sciences, 106(49), 20912–20917.

Jaenisch, R., & Bird, A. (2003). Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. Nature Genetics, 33, 245–254.

Keller, S., Sarchiapone, M., Zarrilli, F., Videtic, A., Ferraro, A., Carli, V., et al. (2010). Increased BDNF promoter methylation in the Wernicke Area of suicide subjects. Archive of General Psychiatry, 67(3), 258–267.

Kilgore, M., Miller, C. A., Fass, D. M., Hennig, K. M., Haggarty, S. J., Sweatt, J. D., et al. (2009). Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology, 35(4), 870–880.

Kinnally, E. L., Capitanio, J. P., Leibel, R., Deng, L., LeDuc, C., Haghighi, F., et al. (2010). Epigenetic regulation of serotonin transporter expression and behavior in infant rhesus macaques. Genes, Brain and Behavior, 9(6), 575–582.

Kisliouk, T., Ziv, M., & Meiri, N. (2010). Epigenetic control of translation regulation: Alterations in histone H3 lysine 9 post-translation modifications are correlated with the expression of the translation initiation factor 2B (Eif2b5) during thermal control establishment. Developmental Neurobiology, 70(2), 100–113.

Kumar, A., Choi, K.-H., Renthal, W., Tsankova, N. M., Theobald, D. E. H., Truong, H.-T., et al. (2005). Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron, 48(2), 303–314.

LaPlant, Q., & Nestler, E. J. (2011). CRACKing the histone code: Cocaine's effects on chromatin structure and function. Hormones and Behavior, 59(3), 321–330.

LaPlant, Q., Vialou, V., Covington, H. E., Dumitriu, D., Feng, J., Warren, B. L., et al. (2010). Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. Nature Neuroscience, 13(9), 1137–1143.

Liu, L., van Groen, T., Kadish, I., & Tollefsbol, T. O. (2009). DNA methylation impacts on learning and memory in aging. Neurobiology of Aging, 30(4), 549–560.

Lubin, F. D., Roth, T. L., & Sweatt, J. D. (2008). Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. Journal of Neuroscience, 28(42), 10576–10586.

Marmorstein, R., & Trievel, R. C. (2009). Histone modifying enzymes: Structures, mechanisms, and specificities.

Biochimica et Biophysica Acta (BBA)—Gene Regulatory Mechanisms, 1789(1), 58–68.

Mastroeni, D., McKee, A., Grover, A., Rogers, J., & Coleman, P. D. (2009). Epigenetic differences in cortical neurons from a pair of monozygotic twins discordant for Alzheimer's Disease. PLoS ONE, 4(8), e6617.

Maze, I., Covington, H. E., Dietz, D. M., LaPlant, Q., Renthal, W., Russo, S. J., et al. (2010). Essential role of the histone methyltransferase G9a in cocaine-induced plasticity. Science, 327(5962), 213–216.

McGowan, P. O., & Szyf, M. (2010). The epigenetics of social adversity in early life: Implications for mental health outcomes. Neurobiology of Disease, 39(1), 66–72.

Miller, C. A., Gavin, C. F., White, J. A., Parrish, R. R., Honasoge, A., Yancey, C. R., et al. (2010). Cortical DNA methylation maintains remote memory. Nature Neuroscience, 13(6), 664–666.

Miller, C. A., & Sweatt, J. D. (2007). Covalent modification of DNA regulates memory formation. Neuron, 53(6), 857–869.

Miranda, T. B., & Jones, P. A. (2007). DNA methylation: The nuts and bolts of repression. Journal of Cellular Physiology, 213(2), 384–390.

Mueller, B. R., & Bale, T. L. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. Journal of Neuroscience, 28(36), 9055–9065.

Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmuhl, Y., Fischer, D., et al. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nature Neuroscience, 12(12), 1559–1566.

Murgatroyd, C., Wu, Y., Bockmuhl, Y., & Spengler, D. (2010). Genes learn from stress: How infantile trauma programs us for depression. Epigenetics, 5(3), 194–199.

Renthal, W., Kumar, A., Xiao, G., Wilkinson, M., Covington, H. E., Maze, I., et al. (2009). Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. Neuron, 62(3), 335–348.

Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. Biological Psychiatry, 65(9), 760–769.

Roth, T. L., Lubin, F. D., Sodhi, M., & Kleinman, J. E. (2009). Epigenetic mechanisms in schizophrenia. Biochimica et Biophysica Acta (BBA)—General Subjects, 1790(9), 869–877.

Roth, T. L., Zoladz, P. R., Sweatt, J. D., & Diamond, D. M. (2011). Epigenetic modification of hippocampal Bdnf DNA in adult rats in an animal model of post-traumatic stress disorder. Journal of Psychiatric Research, Epub ahead of print Feb 8 2011.

Siegmund, K. D., & Connor, C. M. (2007). DNA methylation in the human cerebral cortex is dynamically regulated throughout the life span and involves differentiated neurons. PLoS ONE, 2(9), e895.

Strahl, B. D., & Allis, C. D. (2000). The language of covalent histone modifications. Nature, 403(6765), 41–45.

Tsankova, N., Berton, O., Renthal, W., Kumar, A., Neve, R., & Nestler, E. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nature Neuroscience, 9(4), 519–525.

Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., de los Santos, R., et al. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proceedings of the National Academy of Sciences, 107(20), 9470–9475.

Weaver, I. C. G., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., et al. (2004). Epigenetic programming by maternal behavior. Nature Neuroscience, 7(8), 847–854.

Yossifoff, M., Kisliouk, T., & Meiri, N. (2008). Dynamic changes in DNA methylation during thermal control establishment affect CREB binding to the brain-derived neurotrophic factor promoter. European Journal of Neuroscience, 28(11), 2267–2277.

Zhang, T.-Y., & Meaney, M. J. (2010). Epigenetics and the environmental regulation of the genome and its function. Annual Review of Psychology, 61(1), 439–466.