Development and Psychopathology **28** (2016), 1229–1243

doi:10.1017/S095457941600081X

Insight from animal models of environmentally driven epigenetic changes in the developing and adult brain

TIFFANY S. DOHERTY AND TANIA L. ROTH
University of Delaware, Newark

Abstract

The efforts of many neuroscientists are directed toward understanding the appreciable plasticity of the brain and behavior. In recent years, epigenetics has become a core of this focus as a prime mechanistic candidate for behavioral modifications. Animal models have been instrumental in advancing our understanding of environmentally driven changes to the epigenome in the developing and adult brain. This review focuses mainly on such discoveries driven by adverse environments along with their associated behavioral outcomes. While much of the evidence discussed focuses on epigenetics within the central nervous system, several peripheral studies in humans who have experienced significant adversity are also highlighted. As we continue to unravel the link between epigenetics and phenotype, discerning the complexity and specificity of epigenetic changes induced by environments is an important step toward understanding optimal development and how to prevent or ameliorate behavioral deficits bred by disruptive environments.

One of the most astonishing things about the central nervous system is its ability to adjust to the demands of an ever-changing environment. This plasticity allows for behavioral adaptations critical to survival, and the mechanisms behind it are of great interest to many in the fields of neuroscience, psychology, and psychiatry. These adaptations require environmentally driven changes in gene expression from gestation through senescence, a feat we now know is made possible by dynamic modifications of DNA and its associated proteins, or chromatin. The idea that DNA codes for RNA, which codes for proteins, is a central dogma of molecular biology. Because proteins are essential to cell function, tight regulation of their synthesis is critical to homeostasis and adaptation. Epigenetics (literally "on top of" genetics), a term first coined by Conrad Waddington (1957), allows this regulation via changes that bidirectionally control transcription and translation without changing the underlying DNA sequence. These mechanisms are highly responsive to our experiences and thus are considered one major route by which environmental factors can catalyze changes in the nervous system, thereby altering behavior.

In this review, after a brief introduction to several epigenetic modifications, we examine evidence obtained from animal models on the nature of these modifications in response to environmental adversity, though a few other experiences (both within and outside of early development) are discussed as well. In addition, each section will briefly review evidence supporting the existence of these epigenetic modifications in humans. Finally, we will discuss pharmacological and behavioral treatments and interventions known to affect the epigenome and behavior.

Work on this article was supported by a grant from the National Institute of General Medical Sciences (1P20GM103653).

Address correspondence and reprint requests to: Tania L. Roth, Department of Psychological and Brain Sciences, University of Delaware, 108 Wolf Hall, Newark, DE 19716; E-mail troth@psych.udel.edu.

Epigenetics: The Fundamentals

DNA methylation (5mC)

Methylation of DNA involves the addition of methyl groups to cytosines, typically at cytosine–guanine dinucleotides, and this modification generally results in a suppression of transcription due to impedance of transcription factors and the recruitment of repressor proteins (Moore, Le, & Fan, 2013). Methylation has also been found to occur in non-CG contexts (Lister et al., 2009; Ramsahoye et al., 2000). While the biological significance of non-CG methylation is not yet entirely clear, it has been associated with transcriptional suppression in vitro (Guo et al., 2014). DNA methyltransferases (DNMTs), the enzymes that catalyze DNA methylation, are responsible for transferring methyl groups from *S*-adenosylmethionine to the 5-carbon position of the pyrimidine ring of cytosines (Moore et al., 2013). Activity of demethylases such as GADD45β (Ma et al., 2009) and MBD2 (Detich, Theberge, & Szyf, 2002) appear responsible for removing methyl groups in an active fashion. DNMT1 mainly functions to maintain methylation patterns by targeting hemimethylated DNA during replication, whereas DNMT3a and DNMT3b are de novo methyltransferases responsible for establishing new patterns of methylation (Bestor, 2000).

DNA hydroxymethylation (5hmC)

Hydroxymethylation of DNA involves the oxidation of methylated cytosines by the ten–eleven translocation (TET) fam-

ily of proteins. The relationship between this modification and gene expression is not as clear as that of DNA methylation; the direction of transcriptional regulation associated with 5hmC appears to be much more dynamic (Robertson, Robertson, & Klungland, 2011; Szulwach et al., 2011; Valinluck et al., 2004). While it was originally thought to only be an intermediary step in active DNA demethylation, evidence now suggests it could play a more stable role in gene expression. Evidence for the stability and behavioral relevance of this modification include its responsiveness to neuronal activity (Guo, Su, Zhong, Ming, & Song, 2011), its increase in neuronal cells with age (Szulwach et al., 2011), and its overall enrichment in the brain (Kato & Iwamoto, 2014).

Methyl-CpG binding protein 2 (MeCP2)

MeCP2 is a protein that binds to DNA in a methyl-dependent manner, recruiting either corepressors such as HDACs and mSin3 (Nan et al., 1998) or coactivators such as CREB1 (Chahrour et al., 2008), thereby contributing to the silencing or enhancement of gene expression in a context-dependent manner.

Histone acetylation

Histone acetylation involves the addition of acetyl groups at lysine residues on the N-terminal tail of histone proteins, decreasing the affinity between the histone and DNA and thereby allowing a more permissive transcriptional state (Grunstein, 1997). This process is accomplished by histone acetyltransferases, which transfer the acetyl group from acetyl coenzyme A, and is reversed (i.e., the acetyl group removed) by histone deacetylases (HDACs; De Ruijter, Van Gennip, Caron, Kemp, & van Kuilenburg, 2003).

Histone methylation

Histone methylation involves the addition of methyl groups at arginine and lysine residues on the N-terminal tail of histone proteins. Mono-, di-, or trimethylation can occur at lysine residues while only mono- or dimethylation can occur at arginine residues (Zhang & Reinberg, 2001). This process is accomplished by histone methyltransferases and is reversed (i.e., the methyl group removed) by histone demethylases. The direction of transcriptional regulation depends on the location and number of methyl groups. For example, monomethylation of histone 3 at lysine 36 (H3K36me) and trimethylation of H3K4 (H3K4me3) are activational marks. Examples of repressive histone methylation marks are H3K9me3, H4K20me3, and H3K27me3.

Epigenetic Changes Driven by Stress During the Postnatal Period

One of the most widely studied environmental effectors of epigenetic change in rodents has been early-life stress (ELS) occurring during the postnatal period. Stress is studied in the rodent postnatal period commonly through examination of natural variations in (or manipulation of) the caregiving environment. Considering the programming effects of maternal behavior on hypothalamus–pituitary–adrenal (HPA) axis function and stress responsivity in offspring (Levine, 1994; Liu et al., 1997; Maccari et al., 2003), it is no surprise that this system has been a focal point in the search for mechanisms by which the early environment is able to shape biological and behavioral outcomes.

The HPA axis is a set of three structures (the hypothalamus, the anterior pituitary gland, and the adrenal glands) that plays a central role in stress responsivity (as reviewed in Frodl & O'Keane, 2013; Herman & Cullinan, 1997; Leonard, 2005). Briefly, corticotropin-releasing hormone (also referred to as corticotropin-releasing factor) and arginine vasopressin are released from the paraventricular nucleus (PVN) of the hypothalamus in response to stress. These hormones then trigger the production and release of adrenocorticotrophic hormone from the anterior pituitary, which then goes on to trigger the production and release of corticosterone (cortisol in humans) from the adrenal glands (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998).

Consistent with this focal point is one of the most well-known studies of environmentally driven epigenetic changes, conducted in 2004 by Weaver et al. Briefly, this study investigated natural variations in maternal care and found that adult male offspring of female rats that exhibited high levels of licking and grooming showed different epigenetic patterns at the glucocorticoid receptor (*GR*) gene than the male offspring of low licking and grooming females (Weaver et al., 2004). Offspring of mothers that exhibited lower levels of care were found to have high levels of DNA methylation and less histone acetylation of hippocampal *GR* DNA, leading to less *GR* expression. This epigenetic, maternal care-induced reduction in GRs resulted in a lack of negative feedback in the HPA system and therefore to an exaggerated stress response in the offspring (when assessed in adulthood). Further demonstrated by this study was the reversibility of these outcomes either by moving pups to a positive caregiving environment (cross-fostering of pups to high-care mothers) or by altering epigenetic patterns via drug administration. These results demonstrated the capability of the early environment to shape the nervous system in such a way that behavior was altered throughout the life of the organism and, more importantly, pinpointed epigenetics as a mechanism by which this incredible interaction was likely to occur.

A 2009 study by Murgatroyd et al. also focused on the HPA axis and found sustained epigenetic changes of the mouse *Avp* gene in response to maternal separation, another common inducer of ELS in rodents. Specifically, the authors discovered hypomethylated *Avp* DNA accompanied by less MeCP2 in the enhancer region and greater *Avp* mRNA in the PVN of offspring that had experienced maternal separation. These changes led to increased activity of the HPA axis as well as deficits in memory (as assessed by an inhibi-

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

tory avoidance task) and stress coping (as assessed by a forced swim task). Further, administration of an arginine vasopressin receptor antagonist proved able to partially or fully attenuate, respectively, these deficits. In addition, higher mRNA levels of the precursor hormone for adrenocorticotropic hormone (proopiomelanocortin [*Pomc*]) were seen in maternally separated animals, a change attributed to less methylation of the *Pomc* promoter region (Wu, Patchev, Daniel, Almeida, & Spengler, 2014).

A more recent study along these lines demonstrated that while ELS resulted in hypermethylation of a region located a short distance from the *GR* promoter region in the PVN, an increase in *GR* mRNA was also seen (Bockmühl et al., 2015). It is interesting that ELS animals exposed to chronic stress in adulthood did not exhibit an increase in *Crh* when compared to controls, likely because of this GR upregulation. Considering here that higher methylation was not correlated with a decrease in gene expression, these data highlight that DNA methylation is not always synonymous with less gene expression and suggest that other factors (e.g., other epigenetic marks such as 5hmC) may be involved, interacting with 5mC to produce different outcomes. However, data from these studies demonstrate long-term shaping of the HPA axis by the early environment that affects behavioral outcomes (whether adaptive or not) and pinpoint epigenetic changes as a mechanism of action.

Other studies have ventured outside of this stress response system to investigate whether there are ELS-induced epigenetic changes within other brain regions and genes of interest. Following maternal separation for 3 hr on each of the first 13 days of life, the neurotensin receptor 1 gene (*Nt-r1*; a receptor for the neuropeptide neurotensin thought to play an important role in fear and anxiety) was found to be hypermethylated in the adult rodent amygdala (Toda et al., 2014). These rodents also displayed enhanced freezing behavior in a fear conditioning task. Given these results and the potential anxiolytic role of neurotensin (Saiz, Carrasco, & Hernanz, 1991; Shilling & Feifel, 2008), epigenetic changes at this gene may be a source of some of the behavioral outcomes associated with ELS.

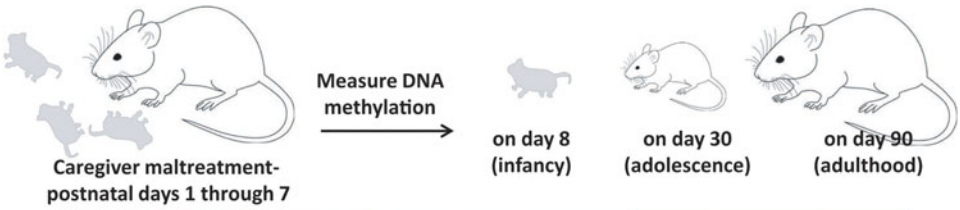
Plasticity-related genes have also been a focus in behavioral epigenetics and have proven to be quite sensitive to early postnatal events. Using a rodent model wherein rat pups are briefly exposed (30 min) daily during the first week of life to an aversive form of caregiving (i.e., stepping on, dragging, roughly handling, and actively avoiding), our lab has found changes in DNA methylation of plasticity-related genes in several different brain regions (Blaze, Scheuing, & Roth, 2013; Roth, Matt, Chen, & Blaze, 2014). Several of these studies have focused on DNA associated with various exons of brain-derived neurotrophic factor (*Bdnf*), a gene critical to the processes of neural development and synaptic plasticity (Greenberg, Xu, Lu, & Hempstead, 2009). These studies underscore the complex nature of DNA methylation, finding ELS-induced changes in methylation that vary by exon examined, as well as by age, sex, and brain region (Figure 1). Following this type of ELS, rats of both sexes in adulthood, adolescence, and infancy exhibit specific changes in *Bdnf* DNA methylation in the whole prefrontal cortex (PFC; Roth et al., 2009) and medial PFC (mPFC; Blaze et al., 2013) and in the hippocampus (dorsal vs. ventral) and amygdala (Doherty, Forster, & Roth, 2015; Roth et al., 2014). Further, altered patterns of histone acetylation at *Bdnf* exon IV were found in the mPFC of maltreated females (Blaze, Asok, & Roth, 2015). These latter results are especially interesting in light of recent findings describing downregulation of histone modifiers in the mPFC of maternally separated rats (Pusalkar et al., 2016).

In addition, using our ELS paradigm, we have also examined methylation of *Reelin*, another gene critical to brain development and synaptic plasticity (Curran & D'Arcangelo, 1998; Weeber et al., 2002), finding transiently low levels of mPFC methylation in maltreated females (i.e., this difference did not persist into adulthood) and a trend toward high methylation in maltreated males when adult (Blaze et al., 2013). Finally, we have measured the expression of various epigenetic regulators occurring in response to this ELS model and found significant differences varying by sex and age in the mPFC of maltreated animals, with the strongest differences present in adulthood (Blaze & Roth, 2013). Altogether, our data indicate that amazingly brief environmental manipulations during the first postnatal week are sufficient to epigenetically modify genes, an effect that at some *Bdnf* loci (i.e., exon IX in the PFC) can be remarkably maintained throughout development and into adulthood. These data also help illustrate the importance of incorporating a longitudinal approach in epigenetic studies because our results for other *Bdnf* loci (e.g., exon IV in the female PFC and male ventral hippocampus) indicate that maltreatment does not always translate into immediate epigenetic changes but results in changes that can evolve after an appreciable delay.

All of the data reviewed thus far tell us that ELS can alter the epigenome, suggesting that epigenetic changes may be partly responsible for the adverse outcomes associated with ELS such as changes in mood, cognition, and stress responsivity (Cicchetti & Toth, 2005; Ivy et al., 2010; Lee & Hoaken, 2007), increased drug-seeking behavior (Dembo et al., 1989; Deminière et al., 1992; Huang et al., 2011), and psychiatric disorders (Cicchetti & Toth, 2005; Heim & Nemeroff, 2001; Kaffman & Meaney, 2007). Epigenetic changes may also be responsible for altered patterns of parenting, another realm of behavior significantly affected by ELS. It has been well established in humans that patterns of abuse are often perpetuated from one generation to the next (Haapasalo & Aaltonen, 1999; Ney, 1988; Zaidi, Knutson, & Mehm, 1989), and animal models have allowed for investigation of the molecular substrates of this perpetuation.

Female rodents receiving low levels of maternal care in infancy will in turn exhibit low levels of care toward their own pups (Francis, Diorio, Liu, & Meaney, 1999). From the early to mid-2000s, Michael Meaney's laboratory made a series of discoveries that have greatly contributed to our understanding of this phenomenon. Initially, this group reported low levels of oxytocin receptor binding in rodent mothers displaying

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press



Brain Region		DNA methylation patterns when adult		Were same patterns detected earlier in development?	
		bdnf IV	*bdnf* IX	*bdnf* IV	*bdnf* IX
PFC (whole)		higher	higher	no	yes
Brain Region	**Sex**	***bdnf* I**	***bdnf* IV**	***bdnf* I**	***bdnf* IV**
Medial PFC	male	lower	no change	no	yes
	female	lower	higher	no	no
Amygdala	male	lower	lower	no	no
	female	no change	lower	no	no
Dorsal Hippocampus	male	lower	lower	no	no
	female	no change	no change	no	no
Ventral Hippocampus	male	no change	higher	yes	no
	female	higher	no change	no	no

Figure 1. (Color online) Schematic of brain-derived neurotrophic factor (*Bdnf*) DNA methylation changes we have observed in the brain of infant (8 days old), adolescent (30 days old), and adult (90 days old) male and female rats exposed to our maltreatment regimen. Higher, lower, or no change refers to methylation levels in maltreated rats in comparison to normal (nurturing) care controls. Changes in methylation are for DNA associated with important regulatory or coding regions of the *Bdnf* gene (*Bdnf* I, IV, IX). Note we did not examine DNA associated with exon I for the prefrontal cortex (PFC) as a whole, nor did we examine DNA associated with exon IX in the medial PFC, amygdala, or hippocampus. For the whole PFC study, male and female data were combined and sexes were not examined individually (cf. data in Blaze et al., 2013; Doherty et al., 2015; and Roth et al., 2009, 2014).

low levels of care toward pups (Francis, Champagne, & Meaney, 2000), and then that sensitivity to estrogen, which increased binding at these receptors in brain regions relevant to maternal behavior, was lower in the offspring of low-care mothers (Champagne, Diorio, Sharma, & Meaney, 2001). Further, they found lower levels of estrogen receptor-α mRNA in the medial preoptic area of low- versus high-care females (Champagne, Weaver, Diorio, Sharma, & Meaney, 2003). In addition, they reported differential methylation of the estrogen receptor-α promoter region in the medial preoptic area of low- and high-care females (Champagne et al., 2006). Cross-fostering the offspring in these studies led to biological and behavioral outcomes resembling those of the caretaker, not the biological mother, suggesting that transmission of these patterns is nongenomic. Taken as a whole, these studies suggest that estrogen-related oxytocin binding is a critical component of rodent maternal behavior and that DNA methylation may be the mechanism by which differences in this biological state, and therefore differences in maternal behavior, are passed from one generation to the next.

A recurring theme in many of the studies discussed above is sex differences in the epigenetic state and their associated behavioral outcomes. Perhaps maternal behavior may play a significant role in these differences. Rodent mothers exhibit a different pattern of behavior toward infant male offspring than they do toward infant female offspring, with male pups receiving higher levels of maternal attention through behaviors such as licking and grooming (Moore & Morelli, 1979; Richmond & Sachs, 1984). When compared to mothers of all-female or mixed-sex litters, higher nurturing behavior (e.g., licking, active nursing, and nest building) has been observed in mothers of all-male litters (Alleva, Caprioli, & Laviola, 1989; Cirulli, Adriani, & Laviola, 1997). These differences affect offspring outcomes, likely via epigenetic pathways. For example, in male- or female-only (single-sex) litters the mu-opioid receptor-encoding gene (*Oprm1*) exhibits site-specific hypermethylation in the hippocampus (males and females) and nucleus accumbens (males only; Hao, Huang, Nielsen, & Kosten, 2011). This receptor is thought to be involved in both attachment and reward (Kieffer & Gavériaux-Ruff, 2002; Matthes et al., 1996; Moles, Kieffer, & D'Amato, 2004; Nelson & Panksepp, 1998), making it an interesting target considering that reward-based behaviors such as drug use may be intimately related to disruptions in caregiver attachment (Kosten, Miserendino, & Kehoe, 2000). Endogenous opioids are released by the infant during caregiver interactions (Nelson & Panksepp, 1998; Roth & Sullivan, 2006; Weller & Feldman, 2003). Thus, it appears that the caregiving environment plays a programming role in the development of this system.

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

Using the same litter composition model (mixed-sex vs. single-sex), methylation levels of *GR*, early growth response protein 1 (*Egr1*, a transcription factor that may be involved in neuronal plasticity; Knapska & Kaczmarek, 2004); and *Bdnf* were measured in the nucleus accumbens and hippocampus of offspring (Kosten, Huang, & Nielsen, 2014). In the nucleus accumbens, a number of cytosine sites in the *GR* promoter region exhibited higher methylation in female pups reared in single-sex litters. In male pups reared in single-sex litters, *Egr1* methylation was lower in this same brain region. *Bdnf* methylation was not significantly different between groups in either brain region. Given that we know *GR* gene methylation is higher when maternal (nurturing) interactions are lacking, and that female pups receive less of this nurturing behavior when compared to male pups, these *GR* data appear consistent with one another. This study also assessed fear and anxiety behaviors on postnatal day 35 but found no significant effect of litter composition, making the results difficult to interpret at a phenotypic level. Given that many studies find changes in adult behavior following disruption of the early environment, it is reasonable to suggest that litter composition could affect these behaviors at a later time point. Overall, differences in the sex composition of a litter affect maternal behavior, behavior that is already differentially exhibited toward male and female pups. Through animal models, we have come to understand that these factors alone (i.e., litter composition and male-directed maternal behavior) are environmental drivers of epigenetic change. Understanding their combined effect will help further elucidate the relationship between the early environment and epigenetically mediated behavioral outcomes, specifically those of a sex-specific nature.

Although the majority of studies we have discussed thus far have focused on specific genes, several have also zoomed out to investigate global activity of the epigenome. While there are some challenges in this approach (including costs and burdensome data sets), increasing evidence suggests that changes in genome-wide levels of methylation are associated with maladaptive behavioral outcomes (Anier et al., 2014; Kinnally et al., 2011). Understanding epigenetic activity on a broad scale is of course instrumental in understanding larger behavioral domains (i.e., a psychiatric disorder) and particularly for treatment considering that current drug and behavior therapies will act on a global level.

Differential promoter methylation on a broad scale has been seen in the brain (PFC) and in T cells (a component of the immune system) of maternal- versus peer-reared rhesus macaques (Provençal et al., 2012). In addition, these groups showed differential levels of hydroxymethylation in the promoter region of numerous neurologically and psychologically relevant genes (Massart et al., 2014). While there is little research thus far on epigenetic regulation of the immune system following ELS, it is a promising regulatory candidate for the ELS-induced immune changes seen in both animals and humans (Miller et al., 2009; O'Mahony et al., 2009). Though no global effects were seen in the hippocampus in an earlier study by Brown, Weaver, Meaney, and Szyf (2008) focusing on natural variations in maternal care, our lab recently found changes in global levels of methylation and hydroxymethylation in adolescent rats exposed to caregiver maltreatment. Specifically, maltreated males exhibited high 5-mC levels in the dorsal hippocampus and low 5-hmC levels in the amygdala (Doherty et al., 2015). This change in global 5-hmC may be of interest in particular because evidence suggests that this cytosine modification plays a pivotal role in behavioral adaptation (Li et al., 2014).

Many of the animal findings of epigenetic consequences associated with ELS have been translated to humans. Some of the most compelling results in this regard are those of a 2009 study from Patrick McGowan and colleagues. An investigation of postmortem hippocampal tissue revealed that in suicide victims with a history of child abuse, *NR3C1* (*GR*) promoter methylation and gene expression were significantly increased and decreased, respectively. These results mirror those found in the low-care rodent offspring discussed previously. Infants of mothers with postpartum depression have been found to exhibit significant methylation of the *NR3C1* gene as well, an effect that is attenuated with tactile stimulation (i.e., stroking) of the infant by its mother (Murgatroyd, Quinn, Sharp, Pickles, & Hill, 2015). Higher *NR3C1* methylation is also seen in adolescents following acute social stress, a change accompanied by aberrant cortisol recovery (Van Der Knaap, Oldehinkel, Verhulst, Van Oort, & Riese, 2015). One line of work is even showing far-reaching *NR3C1* methylation changes (and stress responsivity) in Holocaust survivor offspring (Yehuda et al., 2014).

In addition, methylation of *Bdnf* (Perroud et al., 2013; Unternaehrer et al., 2015; Weder et al., 2016), the oxytocin receptor gene (*OXTR*; Unternaehrer et al., 2015), the serotonin transporter gene (solute carrier family C6, member 4 [*SLC6A4*]; Beach, Brody, Todorov, Gunter, & Philibert, 2011; Vijayendran, Beach, Plume, Brody, & Philibert, 2012), and *FKBP5* (Mehta et al., 2011; Weder et al., 2016) are associated with the type of parental care experienced in childhood. Of note, high levels of methylation in individuals who report experiencing child abuse and neglect mirror many of the brain observations we have found in our maltreated rats. In summary, data are consistent between animal models and humans, arguing that epigenetic changes are one route through which early postnatal environments could be yielding their behavioral effects.

Epigenetic Changes Driven by Stress During Gestation

Though epigenetic changes are a consequence of environmental adversity experienced during the early postnatal period, it is clearly not the earliest time point at which the nervous system can be altered by the environment. Several groups have found that the epigenome is also highly responsive to prenatal experiences and that this interaction, again, frequently occurs within the HPA axis. For example, prenatally stressed male rats exhibit altered methylation with corresponding changes in gene expression of *Crf* (low methylation and high gene expression) and *GR* (high methylation and low gene expression).

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

These changes were accompanied by aberrant stress responses in adulthood (Mueller & Bale, 2008). Beyond reinforcing our understanding of the programming effect of the prenatal environment, this study also underscored sex differences inherent in epigenetic factors even at basal levels, with higher *Dnmt1* levels in control male placentas.

Related to the function of glucocorticoids during gestation is 11ß-hydroxysteroid dehydrogenase type 2 (*Hsd11B2*). This enzyme, which aids in protecting the fetus from maternal glucocorticoids (via oxidation of corticosterone to an inactive metabolite), may decrease in response to maternal stress (Mairesse et al., 2007). This decrease was investigated in rodents using restraint stress during pregnancy, and results revealed epigenetic responses to be a likely cause of the stress-induced downregulation of this gene. Specifically, low placental levels of *Hsd11B2* mRNA were accompanied by high methylation at the promoter region as well as an increase in *Dnmt* mRNA, patterns that differed from those found in the fetal cortex and hypothalamus (Peña, Monk, & Champagne, 2012). These results are consistent with the hypothesis that developmental epigenetic changes serve to adapt an organism to the environment it will encounter throughout its lifetime. In this case, while a mechanism exists to protect the fetus from stress, perhaps there is a threshold (of maternal glucocorticoid exposure) above which the nervous system will react to prepare the organism for an environment that is signaling higher than "normal" adversity levels. The pattern differences between tissue types examined in this study also demonstrate the regional specificity of epigenetic mechanisms, lending support to the idea that these changes occur in a meaningful fashion.

Like postnatal stressors, prenatal stress has also been found to impact the epigenome outside of the HPA axis. For example, Boersma et al. (2014) discovered higher *Bdnf* methylation (accompanied by lower gene expression) and increased expression of *Dnmt1* and *3a* in the amygdala and hippocampus of adult rats that had been exposed to variable stress during gestation in comparison to controls. Chronic, unpredictable stress during gestation led to impaired spatial memory in male and female adult offspring, with females exhibiting high levels of *Dnmt1* and low levels of acetylation of histone 3 (Benoit, Rakic, & Frick, 2015). In addition, St.-Cyr and McGowan (2015) found that adult female offspring of mothers exposed to predator odor during pregnancy exhibited less *Bdnf IV* methylation in the hippocampus along with an increase in antipredator behavior in both female and male offspring. The results from these two studies strongly support the sex-specific nature of epigenetic modifications.

Using restraint stress, studies by Matrisciano et al. (2013) and Matrisciano, Tueting, Maccari, Nicoletti, and Guidotti (2012) found differences in *Bdnf* and *Dnmt1* expression similar to those of Boersma et al. (2014) as well as numerous other epigenetic changes in mice coupled with behavioral abnormalities representing a schizophrenia-like phenotype. More specifically, mice exposed to gestational stress exhibited low levels of the schizophrenia-related genes *Bdnf* (consistent with previously discussed postnatal stress reports, suggesting epigenetic involvement) and glutamic acid decarboxylase 67 (*Gad67*). They also exhibited more *Dnmt1* expression, including greater DNMT1 binding in the promoter region of the genes coding for metabotropic glutamate 2 and 3 (*mGlu2* and *mGlu3*) receptors, and greater MeCP2 binding at the *mGlu2* promoter region (Matrisciano et al., 2012). Given that mGlu2/3 receptor activity is implicated in an antipsychotic state (Patil et al., 2007), stress-induced methylation of these promoters is particularly relevant when examining epigenetics in the context of early adversity and later mental health outcomes. In another study, prenatally stressed mice exhibited higher *Dnmt* levels throughout the lifespan associated with less expression of genes with known roles in schizophrenia (i.e., *reelin* and *Gad67*). These mice also exhibited more methylated and hydroxymethylated cytosines in the promoter region of these genes as well as an increase in MeCP2 binding (Matrisciano et al., 2013). In addition, mice in both studies exhibited behaviors typical in schizophrenia-like phenotypes such as abnormal social behavior, deficits in prepulse inhibition and fear conditioning, and hyperactivity. These behavioral effects were reversible by mGlu2/3 receptor agonists or drugs with epigenetic targets (i.e., histone deacetylase inhibition and DNA-demethylation), respectively (Matrisciano et al., 2012, 2013). These studies provide further information on the link between prenatal adversity and later psychiatric disorders and provide evidence for the mechanistic role of epigenetics in these outcomes. Evidence suggests that *Bdnf* and *Dnmt1* in particular play critical roles in this relationship and may therefore be fruitful targets in strategies of intervention.

Prenatal susceptibility of the epigenome translates to humans as well. Human offspring of mothers who reported anxiety during gestation exhibited higher methylation of *11BHSD2* while offspring of mothers who reported depression during gestation exhibited higher *NR3C1* methylation (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013). In addition, maternal depression during gestation in conjunction with a specific variant of the *MTHFR* gene (responsible for encoding methylenetetrahydrofolate reductase, a critical enzyme in the production of methionine) leads to less methylation of *SLC6A4* in both mother and offspring (Devlin, Brain, Austin, & Oberlander, 2010). Considering that serotonin dysfunction has been implicated in depression risk (Jans, Riedel, Markus, & Blokland, 2007), methylation of this gene so early in development will undoubtedly have great implications for later mental health.

In addition to psychosocial factors, several physical factors are at play in determining the epigenetic state, including maternal diet and exposure to toxins. The epigenome is inextricably related to diet due to the dependence of the methyl donor *S*-adenosylmethionine on diet-derived folates (Cooney, 1992). This relationship encompasses the interplay between maternal diet and offspring outcomes, an effect illustrated in the offspring of low- and high-care mothers following methionine infusion (Weaver et al., 2005). Offspring of high-care mothers, which generally exhibit less *GR* methylation and lower anxiety responses in adulthood (as previously discussed), exhibit the

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

opposite pattern of methylation and behavior following methionine infusion. In addition, methionine infusion was found to have an effect on only a subset of genes (Weaver, Meaney, & Szyf, 2006), suggesting specificity in a nonspecific type of treatment. Male offspring of female mice consuming a high-fat diet during pregnancy exhibited significant decreases in both global methylation and dopamine- and opioid-related genes accompanied by higher gene expression and behavioral preferences for sucrose and fat (Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010). Given that these genes are associated with reward and that their expression varied in both reward circuitry and the hypothalamus (known to regulate feeding behavior), these data suggest an epigenetic basis for the transmission of obesity from parent to offspring. A second related study looking at both male and female offspring found that maternal methyl supplementation reversed some but not all of the diet-induced epigenetic changes in both males and females. This intervention was also able to attenuate the fat preference found in males (Carlin, George, & Reyes, 2013).

The agouti mouse provides another example of the epigenetic interaction between diet and phenotype. *Agouti* gene expression in the mouse varies based on early epigenetic marks, leading to very distinct phenotypes in offspring: hypermethylation of a retrotransposon upstream of the *Agouti* gene results in brown, normal weight mice whereas hypomethylation is associated with yellow, obese mice (Dolinoy, 2008). The latter phenotype can be prevented via epigenetic changes following methyl supplementation of the maternal diet during pregnancy (Waterland & Jirtle, 2003; Wolff, Kodell, Moore, & Cooney, 1998). Other dietary components are also known to regulate the epigenome (e.g., turmeric; for a review of epigenetics and natural compounds, see Reuter, Gupta, Park, Goel, & Aggarwal, 2011). Thus, dietary interventions may prove to be a useful tool in epigenome management. It appears that nutrition, stress, and maternal behavior interact to contribute to the development of the adult brain (Hoeijmakers, Lucassen, & Korosi, 2015; Lucassen et al., 2013). While not discussed here, epigenetic responses to dietary factors also occur outside of developmental periods (Milagro et al., 2009).

Developmental exposure to endocrine disruptors found in plastic (bisphenol A [BPA], the most dominant substance in this category), certain pesticides, and even in some pharmaceuticals can have drastic consequences for an organism, and emerging evidence suggests that changes in epigenetic pathways are responsible for these outcomes (Kundakovic & Champagne, 2011). For example, in a mouse model of prenatal BPA exposure, *Bdnf* methylation is altered after exposure in both brain (hippocampus) and blood (Kundakovic et al., 2015). It is interesting that prenatal BPA exposure also results in epigenetic changes affecting the *Agouti* gene in mice such that offspring coat color is shifted toward yellow, a nonadvantageous mark that can be nullified by coadministration of methyl supplements to the pregnant dam (Dolinoy, Huang, & Jirtle, 2007).

The effects of toxin exposure and dietary factors have been demonstrated in human studies, lending support to the translational implications of these rodent data. For example, altered *BDNF* methylation is seen in human cord blood following high maternal BPA levels during pregnancy (Kundakovic et al., 2015), a result that is consistent with the previously discussed *Bdnf* methylation findings in mice prenatally exposed to BPA. In a study of individuals whose early gestational period occurred during a time of famine (i.e., during the Dutch Hunger Winter, 1944–1945) it was discovered that the maternally imprinted *IGF2* (insulin-like growth factor 2) gene is less methylated in comparison to sibling controls (Heijmans et al., 2008). Altogether, these data demonstrate the extreme responsiveness of the fetal epigenome and serve as a reminder of the many considerations to be made when attempting to study the role of epigenetics in the development of behavior.

Epigenetic Changes Driven by Adult Environments and Experiences

While the early environment has been a major focus in behavioral epigenetics, it is not the only time point during which changes in the epigenetic state can be catalyzed by external stimuli; animal studies have also shed light on the incredible plasticity of the adult epigenome. For example, an acute stressful experience in adulthood has been shown to alter epigenetic patterns in rodents. Specifically, adult rats exhibit a short-term decrease in histone H3 acetylation at *Bdnf* I, IV, and VI promoters following a single bout of immobilization stress (Fuchikami, Morinobu, Kurata, Yamamoto, & Yamawaki, 2009). Though no long-term (i.e., 24 hr post-single bout of immobilization stress) changes in acetylation or gene expression were found, lower gene expression and protein levels accompanied the initial decrease in histone acetylation. While the implications of these transient changes are difficult to surmise, they may be an inherent component of the organism's ability to respond to sudden but short-term stressors.

As further evidence for epigenetic plasticity in adulthood, a growing body of research suggests that altered epigenetic patterns at various genes have a functional role in posttraumatic stress disorder (PTSD). For example, researchers found that the disks large-associated protein 2 (*Dlgap2*), a gene involved in neuronal synaptic organization and transmission (Ranta et al., 2000), exhibited higher methylation levels in the hippocampus of rats with a PTSD-like phenotype (induced by predator scent exposure) when compared to controls (Chertkow-Deutsher, Cohen, Klein, & Ben-Shachar, 2010). This increase was accompanied by less gene expression and enhanced stress reactivity in behavioral tests. In a rodent model of PTSD pairing acute cat exposure and social instability, Roth, Zoladz, Sweatt, and Diamond (2011) found higher methylation of *Bdnf* DNA at exon IV in the dorsal dentate gyrus and dorsal CA1, whereas less methylation of this exon was found in the ventral CA3. Results such as these may hold therapeutic promise because they provide potential mechanisms for dysregulation, especially considering that downregulation of *Bdnf* in the hippocampus has been implicated in PTSD (Andero & Ressler, 2012; Deppermann, Storchak, Fallgatter, & Ehlis, 2014;

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

Kozlovsky et al., 2007). Gene expression analysis by Roth et al. (2011) in CA1 revealed less *Bdnf* mRNA in both dorsal and ventral regions. That they did not find corresponding methylation changes in ventral CA1 (i.e., higher gene expression was not accompanied by a change in methylation in this area) is not particularly worrisome because many different types of epigenetic modifications exist that are equally responsive to the environment and equally capable of/likely to be regulating gene expression in these cases (many of which are cited throughout this review). Further research is required to assess this possibility. In addition, epigenetic mechanisms appear to be highly regulated in animal models of fear conditioning (Li et al., 2014; Lubin, Roth, & Sweatt, 2008; Mahan et al., 2012; Monsey, Ota, Akingbade, Hong, & Schafe, 2011). This paradigm is useful when exploring PTSD symptomology in rodents because it allows investigation of the neural circuitry of fear as well as memory formation and reformation, both critical components of this disorder (Amstadter, Nugent, & Koenen, 2009; Mahan & Ressler, 2012).

Adult animal models have also provided insight into the epigenetics of depression. Social defeat stress is a common paradigm used to study depressive-like behavior in rodent models. In one such study, Tsankova et al. (2006) found exon-specific decreases in *Bdnf* expression following social defeat. Lower gene expression was associated with repressive histone methylation at promoter regions and was reversible with chronic administration of imipramine (a tricyclic antidepressant), which increased histone acetylation and lowered expression of histone deacetylase 5 (*Hdac5*). These results are particularly intriguing from a treatment perspective as a later study demonstrated that mice who prove to be resilient to the effects of social defeat possess epigenetic patterns in the nucleus accumbens very similar to those that are induced by imipramine in nonresilient animals (Wilkinson et al., 2009). It is important to note that histone methylation in the former study was not reversed with imipramine administration. Rather, a more open chromatin state was achieved through the increase in acetylation. Chromatin remodeling is a complex process; this study is an excellent example of how animal models aid our understanding of the many layers involved in chromatin configuration, thereby leading to greater understanding of disorder and the pathways through which it can be treated.

This complexity, as well as the intensity-responsive nature of epigenetic activity, was underscored by a 2009 study by Hunter, McCarthy, Milne, Pfaff, and McEwen, which investigated hippocampal H3 methylation following stress of various intensities. Following acute restraint stress (30 min, one time), the dentate gyrus and CA1 exhibited higher H3K9 trimethylation as well as less H3K9 monomethylation and H3K27 trimethylation (refer to the Epigenetics: The Fundamentals section for a review on the transcriptional consequences of these marks). Following subchronic restraint stress (30 min/day for 7 days), these areas again exhibited lower levels of H3K27 trimethylation as well as reduced levels of H3K4 trimethylation in the CA1. Finally, following chronic stress (6 hr/day for 21 days), the dentate gyrus exhibited higher H3K4 trimethylation and less H3K9 trimethylation. Treatment with the antidepressant fluoxetine was able to attenuate the decrease in H3K9 methylation when administered with chronic stress, though it did not attenuate the increase in H3K4 methylation, again demonstrating that a relationship exists between antidepressants and stress-induced histone modifications that is highly variable and not yet fully understood. The behavioral response to antidepressants in adolescent mice with ELS-induced histone modifications differs from that of nonstressed mice (Levine, Worrell, Zimnisky, & Schmauss, 2012). It is interesting that the antidepressant's behavioral rescue was associated with potentiation of the histone modifications found in the ELS group, whereas reversing ELS-induced histone marks worsened behavioral outcomes. Thus, epigenetic modifications following stress do not always lead to dysfunctional behavior, suggesting that it would be wise in some cases to work with, rather than against, these modifications. Other studies using animal models to investigate epigenetic mechanisms in this disorder have found less *Crf* methylation in mice exhibiting social avoidance after chronic social stress (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010), higher levels of *Dnmt3a* in the nucleus accumbens following chronic social defeat (as well as induction of a prodepressive state via overexpression of *Dnmt3a*; LaPlant et al., 2010), and changes in nucleosome positioning associated with the increase of a specific chromatin-remodeling complex (Sun et al., 2015).

Consistent with the animal literature, the human epigenome is responsive to stress outside of critical developmental periods, and aberrant methylation continues to be linked to several psychiatric disorders. For example, methylation of the *OXTR* gene changes in response to the Trier Social Stress Test (Unternaehrer et al., 2012), and low methylation of the *SLC6A4* gene is correlated with an increased risk for PTSD following a high number of exposures to traumatic stress (Koenen et al., 2011). Also seen in relation to PTSD are rises in global methylation as well as altered methylation patterns of immune-related genes (Smith et al., 2011) and of *FKBP5*, an important component of the stress response (Klengel et al., 2013). It is interesting that epigenetic effects have been seen in this gene in the offspring of Holocaust survivors, with survivors exhibiting higher *FKBP5* methylation and their adult offspring exhibiting lower levels (Yehuda et al., 2015). In addition, methylation patterns of repetitive elements (highly repeated, functionally important stretches of DNA) in the genome may aid in the prediction of PTSD resiliency or vulnerability (Rusiecki et al., 2012).

In regard to other psychiatric disorders, analysis of postmortem cortical tissue in schizophrenia patients has revealed higher methylation within critical regulatory positions of the *REELIN* promoter region (Grayson et al., 2005). An upregulation of TET1 (one of the enzymes involved in hydroxymethylation) is seen in the parietal cortex of psychotic patients (Dong Gavin, Chen, & Davis, 2012). Studies in humans have shown changes in *BDNF* methylation levels dif-

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

fering with depression status and job strain (Song et al., 2014). In human subjects diagnosed with major depressive disorder, antidepressants appear to regulate *BDNF* expression through epigenetic mechanisms (Lopez et al., 2013). In addition, in subjects diagnosed with borderline personality disorder, *BDNF* was found to be hypermethylated compared to controls, an increase that correlated with child maltreatment (Perroud et al., 2013). It is important to note that these methylation patterns were altered in response to behavioral therapy, suggesting that the epigenome's responsiveness can be taken advantage of in a clinically relevant manner.

Epigenetic Changes Subserving Behavioral Change Outside of Adversity

The discussion thus far might lead one to conclude that the epigenome's plasticity serves only as a mechanism for adaptation to adverse circumstances. This, however, is not a full characterization of the role of epigenetics in behavior. Epigenetic mechanisms may underlie learning and memory processes as well as the positive effects that follow experiences such as social interaction or other forms of environmental enrichment throughout the life span.

DNA methylation in particular has been implicated in learning and memory processes. In a recent paper, Roth et al. (2015) demonstrated that *Bdnf* methylation patterns in the hippocampus were altered following a task requiring remapping of place cells (neurons that provide a "map" by firing when the animal occupies a specific location), a change that did not endure in rats given the DNMT inhibitor zebularine. Data also demonstrate an important role for methylation in other learning tasks including context fear conditioning (Lubin et al., 2008) and associative reward learning (Day et al., 2013) as well as a demonstrable role in long-term potentiation (Levenson et al., 2006).

Developmental studies in this field have found lower global methylation levels in the hippocampus and frontal cortex of 21-day-old offspring whose mothers had experienced an enriched environment during pregnancy, an effect also seen in offspring of environmentally enriched fathers (Mychasiuk et al., 2012). This latter effect may have important implications for the currently controversial topic of intergenerational/transgenerational epigenetics (for a recent review, see Blaze & Roth, 2015). In adolescence, genome-wide levels of histone 3 acetylation were higher in the male hippocampus and cerebellum following 1 week of voluntary wheel running (Abel & Rissman, 2013). Both DNMTS and HDACS were downregulated in these regions as well, accompanied by changes in gene transcription associated with synaptic plasticity and signaling pathways. This suggests a widespread, functionally relevant epigenetic response to exercise.

Environmental enrichment in adulthood has also led to restructured epigenetic patterns followed by positive behavioral outcomes. Kuzumaki et al. (2011) found that environmental enrichment in mice led to an increase in hippocampal histone methylation patterns associated with open chromatin and a decrease in those associated with closed chromatin, both at specific promoters of *Bdnf*. These changes were accompanied by an increase in *Bdnf* mRNA, a step known to be required for environmentally driven neurogenesis in the rodent hippocampus (Rossi et al., 2006), suggesting that epigenetic regulation is critical to such an outcome. In addition, adult rats exposed to a voluntary exercise paradigm displayed an increase in adaptive behavior (i.e., improved coping response to stress) accompanied by chromatin reconfiguration in dentate granule neurons (Collins et al., 2009). Exercise also induces lowered methylation of *Bdnf* exon IV accompanied by increased MeCP2 levels in the hippocampus (Gomez-Pinilla, Zhuang, Feng, Ying, & Fan, 2011). Thus, it appears that epigenetic mechanisms underlie exercise-induced plasticity in the adult hippocampus. In humans, muscle methylation profiles and the related transcripts change in response to exercise (Lindholm et al., 2014).

The epigenetics of environmental enrichment are also highly relevant in the aging process. Impairment of processes such as learning and memory are inherent in aging, and evidence suggests that the interaction between enrichment and epigenetics may be a fruitful path in the journey to attenuate such age-related impairments. For example, in a mouse model of neurodegeneration resulting in impaired learning, mice were found to exhibit improvements in learning and memory following environmental enrichment, changes that were correlated with more histone acetylation (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). Furthermore, pharmacologically increasing histone acetylation increased dendritic sprouts and synapse number in these mice while also rescuing learning and memory deficits.

Other epigenetic modifications are responsive to enrichment as well. Lower hydroxymethylcytosine levels in aged rats, coupled with improved learning and memory propensities, were found to resemble those of young rats following exposure to an environmental enrichment paradigm (Irier et al., 2014). Considering that hydroxymethylation has often been implicated in demethylation (Guo et al., 2011; He et al., 2011; Kohli & Zhang, 2013; Maiti & Drohat, 2011; Shen, Song, He, & Zhang, 2014), the discovery of an association between lower levels of 5-hmC and improvements in learning and memory may seem counterintuitive. However, ample evidence is now available to suggest that the role of 5-hmC is quite diverse, including evidence associating this modification with bidirectional changes in gene expression that may depend on several factors such as promoter CG content, 5-mC levels, and the specific gene promoters at which it is found (Massart et al., 2014).

Given that early adversity has proven to be impactful at the level of the epigenome, and that this impact correlates with deleterious behavioral outcomes, it is especially encouraging that the epigenome also responds to positive, therapeutic-like experience. Environmental restructuring throughout the life span may lead to restructuring of the nervous system, thereby leading to behaviors that are more constructive in the current, ongoing context. Environmental enrichment has reversed biological and behavioral outcomes associated with early stress exposure (Bredy, Zhang, Grant, Diorio, & Meaney, 2004;

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

Francis, Diorio, Plotsky, & Meaney, 2002; Morley-Fletcher, Rea, Maccari, & Laviola, 2003), though whether this reversal is solely an epigenetic phenomenon is not yet known.

Prevention and Intervention Research Regarding the Epigenome

Much interest has been generated recently around epigenetic therapy. Drugs such as 5-aza-2′-deoxycytidine and zebularine (DNA methyltransferase inhibitors [DNMTi]) primarily inhibit DNA methylation while others, such as sodium butyrate or valproic acid (histone deacetylase inhibitors; HDACi), primarily inhibit histone deacetylation. It is important to note that these drugs and their primary epigenetic modifications are not mutually exclusive. Rather, there is much cross talk between them. For example, DNA methylation alters histone marks through the recruitment of HDACs via MeCP2 (Rountree, Bachman, Herman, & Baylin, 2001), and histone deacetylase inhibitors reduce methylation, likely via downregulation of DNMT1 (Sarkar et al., 2011) and upregulation of DNA demethylase (Detich, Bovenzis, & Szyf, 2003).

Epigenetic drugs in various animal models have proven to be effective in ameliorating behavioral deficits by reversing or preventing deleterious epigenetic marks. For example, in the well-known and previously discussed study conducted by Weaver et al. (2004), central administration of a HDACi ameliorated both the epigenetic changes and behavioral deficits found in low-care offspring. Similarly, Roth, Lubin, Funk, and Sweatt (2009) found that administration of a DNMTi successfully reversed *Bdnf* methylation and gene expression changes found in adult rats that had experienced maltreatment in infancy. In 2012, Kao et al. reported that administration of a HDACi prior to maternal separation prevented separation-induced histone methylation. These histone marks were associated with a decrease in fear-potentiated startle in female offspring in adulthood, a behavioral alteration that was prevented with HDACi administration.

Given that chromatin modifications are often seen in psychiatric disorders (Klengel et al., 2013; Matrisciano et al., 2013) and specific HDACs have been implicated in disorders such as depression (Tsankova et al., 2006) and schizophrenia (Sharma, Grayson, & Gavin, 2008), drugs that can target these modifications hold promise for psychiatric intervention. Coadministration of the HDACi sodium butyrate with the antidepressant fluoxetine (which also affects histone modifications; Cassel et al., 2006; Hunter et al., 2009) reduced depressive-like behavior in mice (Schroeder, Lin, Crusio, & Akbarian, 2007). Administration of DNMT inhibitors shows similar effects in rats (Sales et al., 2011). The HDACi valproic acid is able to attenuate schizophrenic-like behaviors induced by methionine in mice (Tremolizzo et al., 2005). Data such as these are particularly relevant to the focus of this review as ELS is often a precipitating factor for many psychiatric disorders (Cicchetti & Toth, 2005; Jovanovic et al., 2009).

Finally, while many of the epigenetic drugs used in animal models are not yet approved for humans (outside of cancer treatment), many psychotropic drugs prescribed to humans affect epigenetic activity (some of which are also used in animal models, discussed in previous sections). For example, the antipsychotic drug haloperidol affects DNA methylation (Shimabukuro, Jinno, Fuke, & Okazaki, 2006) and some histone modifications (Bertran-Gonzalez et al., 2008), whereas monoamine oxidase inhibitors affect both mono- and dimethylation of histones (Lee, Wynder, Schmidt, McCafferty, & Shiekhattar, 2006). Behavioral therapies are also proving to be very effective at reshaping the epigenome. Children diagnosed with anxiety disorders who respond well to cognitive behavioral therapy exhibit higher methylation of the stress- and depression-related *SLC6A4* gene (Roberts et al., 2014). In addition, as previously discussed, the epigenome of subjects diagnosed with borderline personality disorder who exhibited a positive response to behavioral therapy exhibited changes to previously hypermethylated regions of DNA as well (Perroud et al., 2013).

Other environmental alterations that have been found to interact with the human epigenome include exercise (mentioned previously) and practices such as tai chi. Regarding the former, genome-wide methylation patterns in adipose tissue of low-activity individuals exhibited significant changes in response to a 6-month exercise intervention (Rönn et al., 2013). In regard to the latter, females who had practiced tai chi for at least 3 years exhibited differential methylation patterns when compared to age-matched controls, with methylation patterns opposing those generally associated with increased age (Ren et al., 2012). Altogether, data reviewed in these two sections demonstrate the malleability of the epigenome to not only adversity but also positive experiences and therapeutic interventions.

Conclusions and Perspectives

The ability of the central nervous system to mold itself in such a way that an organism's behavior will match the environment in which it will likely be required to survive is an incredible and highly adaptive characteristic. Evidence from animal models suggests that epigenetic mechanisms possess the responsiveness and plasticity necessary to make this adaptation possible. The tissue specificity and sexual dimorphism of environmentally induced epigenetic modifications suggest that they are functionally significant, and behavioral data continue to support this notion. Equally incredible is that this mechanism appears to be active throughout the lifetime, aiding in behavioral adaptation long after developmental windows have closed. In addition, data thus far demonstrate that the epigenome is responsive to behavioral therapies, pharmacological manipulations, and lifestyle factors such as diet and enrichment, making it a promising target for intervention. Most promising, perhaps, is that we are beginning to see these data replicated in humans.

Epigenetic modifications mark experiences such that transcriptional regimes are altered in a cascade that begins in the nucleus and expands to shape behavioral outcomes (Figure 2). Some of these marks and their associated outcomes are favor-

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

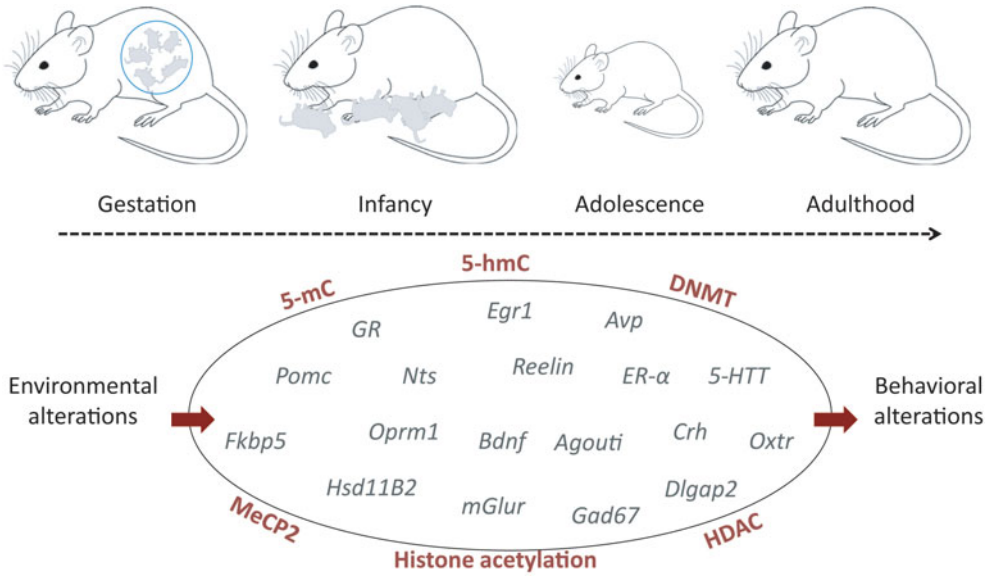


Figure 2. (Color online) Schematic of environmentally driven epigenetic modifications to DNA across the life span with many of the genes (gray) discussed in this review. 5-mC, methylated cytosine; 5-hmC, hydroxymethylated cytosine; DNMT, DNA methyltransferase; MeCP2, methyl-CpG binding protein 2; HDAC, histone deacetylase. See text for gene definitions.

able to the organism while others are not. One very important task for our field is to parse apart these differences in enough detail that we can use epigenetic information to inform diagnoses as well as targeted treatments to produce the most favorable outcomes. Inherent in this process will be the need for carefully designed longitudinal studies, which will allow the elucidation of the developmental trajectories of epigenetic changes and behavior. Further, to better inform diagnoses, studies will need to incorporate the use of multiple biospecimens, an approach easily achieved in rodent models but to date has been rarely employed. Finally, in terms of treatment, one of the major challenges for epigenetic therapy is target specificity of drugs (an issue that is true of most drugs used in psychiatry). Animal model and in vitro work is already pioneering the way for this, using targeted epigenetic editing such as transcription activator-like effectors fused with chromatin modifying enzymes (Bernstein, Le Lay, Ruano, & Kaestner, 2015; Heller et al., 2014; Konermann et al., 2013; Maeder et al., 2013; Sanjana et al., 2012) to alter cytosine methylation and chromatin configuration at specific gene loci. Strategies to target specific epigenetic changes in humans may be coming over the horizon.

References

Abel, J. L., & Rissman, E. F. (2013). Running-induced epigenetic and gene expression changes in the adolescent brain. *International Journal of Developmental Neuroscience*, *31*, 382–390.

Alleva, E., Caprioli, A., & Laviola, G. (1989). Litter gender composition affects maternal behavior of the primiparous mouse dam (*Mus musculus*). *Journal of Comparative Psychology*, *103*, 83–87.

Amstadter, A. B., Nugent, N. R., & Koenen, K. C. (2009). Genetics of PTSD: Fear conditioning as a model for future research. *Psychiatric Annals*, *39*, 358.

Andero, R., & Ressler, K. J. (2012). Fear extinction and BDNF: Translating animal models of PTSD to the clinic. *Genes, Brain and Behavior*, *11*, 503–512.

Anier, K., Malinovskaja, K., Pruus, K., Aonurm-Helm, A., Zharkovsky, A., & Kalda, A. (2014). Maternal separation is associated with DNA methylation and behavioural changes in adult rats. *European Neuropsychopharmacology*, *24*, 459–468.

Beach, S. R., Brody, G. H., Todorov, A. A., Gunter, T. D., & Philibert, R. A. (2011). Methylation at 5HTT mediates the impact of child sex abuse on women's antisocial behavior: An examination of the Iowa adoptee sample. *Psychosomatic Medicine*, *73*, 83–87.

Benoit, J. D., Rakic, P., & Frick, K. M. (2015). Prenatal stress induces spatial memory deficits and epigenetic changes in the hippocampus indicative of heterochromatin formation and reduced gene expression. *Behavioural Brain Research*, *281*, 1–8.

Bernstein, D. L., Le Lay, J. E., Ruano, E. G., & Kaestner, K. H. (2015). Tale-mediated epigenetic suppression of CDKN2A increases replication in human fibroblasts. *Journal of Clinical Investigation*, *125*, 1998–2006.

Bertran-Gonzalez, J., Bosch, C., Maroteaux, M., Matamales, M., Hervé, D., Valjent, E., et al. (2008). Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. *Journal of Neuroscience*, *28*, 5671–5685.

Bestor, T. H. (2000). The DNA methyltransferases of mammals. *Human Molecular Genetics*, *9*, 2395–2402.

Blaze, J., Asok, A., & Roth, T. L. (2015). Long-term effects of early-life caregiving experiences on brain-derived neurotrophic factor histone acetylation in the adult rat mpfc. *Stress*. Advance online publication.

Blaze, J., & Roth, T. L. (2013). Exposure to caregiver maltreatment alters expression levels of epigenetic regulators in the medial prefrontal cortex. *International Journal of Developmental Neuroscience*, *31*, 804–810.

Blaze, J., & Roth, T. L. (2015). Evidence from clinical and animal model studies of the long-term and transgenerational impact of stress on DNA methylation. *Seminars in Cell and Developmental Biology*, *43*, 76–84.

Blaze, J., Scheuing, L., & Roth, T. L. (2013). Differential methylation of genes in the medial prefrontal cortex of developing and adult rats following exposure to maltreatment or nurturing care during infancy. *Developmental Neuroscience*, *35*, 306–316.

Bockmühl, Y., Patchev, A. V., Madejska, A., Hoffmann, A., Sousa, J. C., Sousa, N., et al. (2015). Methylation at the CpG island shore region up-

https://doi.org/10.1017/S095457941600081X Published online by Cambridge University Press

regulates Nr3c1 promoter activity after early-life stress. *Epigenetics*, *10*, 247–257.
Boersma, G. J., Lee, R. S., Cordner, Z. A., Ewald, E. R., Purcell, R. H., Moghadam, A. A., et al. (2014). Prenatal stress decreases Bdnf expression and increases methylation of Bdnf exon IV in rats. *Epigenetics*, *9*, 437–447.
Bredy, T. W., Zhang, T. Y., Grant, R. J., Diorio, J., & Meaney, M. J. (2004). Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. *European Journal of Neuroscience*, *20*, 1355–1362.
Brown, S. E., Weaver, I. C., Meaney, M. J., & Szyf, M. (2008). Regional-specific global cytosine methylation and DNA methyltransferase expression in the adult rat hippocampus. *Neuroscience Letters*, *440*, 49–53.
Carlin, J., George, R., & Reyes, T. M. (2013). Methyl donor supplementation blocks the adverse effects of maternal high fat diet on offspring physiology. *PLOS ONE*, *8*, e63549.
Cassel, S., Carouge, D., Gensburger, C., Anglard, P., Burgun, C., Dietrich, J.-B., et al. (2006). Fluoxetine and cocaine induce the epigenetic factors MeCP2 and MBD1 in adult rat brain. *Molecular Pharmacology*, *70*, 487–492.
Chahrour, M., Jung, S. Y., Shaw, C., Zhou, X., Wong, S. T. C., Qin, J., et al. (2008). Mecp2, a key contributor to neurological disease, activates and represses transcription. *Science*, *320*, 1224–1229.
Champagne, F., Diorio, J., Sharma, S., & Meaney, M. (2001). Variations in maternal care in the rat are associated with differences in estrogen-related changes in oxytocin receptor levels. *Proceedings of the National Academy of Sciences*, *98*, 12736–12741.
Champagne, F. A., Weaver, I. C., Diorio, J., Dymov, S., Szyf, M., & Meaney, M. J. (2006). Maternal care associated with methylation of the estrogen receptor-α1b promoter and estrogen receptor-α expression in the medial preoptic area of female offspring. *Endocrinology*, *147*, 2909–2915.
Champagne, F. A., Weaver, I. C., Diorio, J., Sharma, S., & Meaney, M. J. (2003). Natural variations in maternal care are associated with estrogen receptor α expression and estrogen sensitivity in the medial preoptic area. *Endocrinology*, *144*, 4720–4724.
Chertkow-Deutsher, Y., Cohen, H., Klein, E., & Ben-Shachar, D. (2010). DNA methylation in vulnerability to post-traumatic stress in rats: Evidence for the role of the post-synaptic density protein Dlgap2. *International Journal of Neuropsychopharmacology*, *13*, 347–359.
Cicchetti, D., & Toth, S. L. (2005). Child maltreatment. *Annual Review of Clinical Psychology*, *1*, 409–438.
Cirulli, F., Adriani, W., & Laviola, G. (1997). Sexual segregation in infant mice: Behavioural and neuroendocrine responses to d-amphetamine administration. *Psychopharmacology*, *134*, 140–152.
Collins, A., Hill, L. E., Chandramohan, Y., Whitcomb, D., Droste, S. K., & Reul, J. (2009). Exercise improves cognitive responses to psychological stress through enhancement of epigenetic mechanisms and gene expression in the dentate gyrus. *PLOS ONE*, *4*, e4330.
Conradt, E., Lester, B. M., Appleton, A. A., Armstrong, D. A., & Marsit, C. J. (2013). The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics*, *8*, 1321–1329.
Cooney, C. (1992). Are somatic cells inherently deficient in methylation metabolism? A proposed mechanism for DNA methylation loss, senescence and aging. *Growth, Development, and Aging*, *57*, 261–273.
Curran, T., & D'Arcangelo, G. (1998). Role of reelin in the control of brain development. *Brain Research Reviews*, *26*, 285–294.
Day, J. J., Childs, D., Guzman-Karlsson, M. C., Kibe, M., Moulden, J., Song, E., et al. (2013). DNA methylation regulates associative reward learning. *Nature Neuroscience*, *16*, 1445–1452.
De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain corticosteroid receptor balance in health and disease 1. *Endocrine Reviews*, *19*, 269–301.
Dembo, R., Williams, L., La Voie, L., Berry, E., Getreu, A., Wish, E. D., et al. (1989). Physical abuse, sexual victimization, and illicit drug use: Replication of a structural analysis among a new sample of high-risk youths. *Violence and Victims*, *4*, 121–138.
Deminière, J. M., Piazza, P. V., Guegan, G., Abrous, N., Maccari, S., Le Moal, M., et al. (1992). Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. *Brain Research*, *586*, 135–139.
Deppermann, S., Storchak, H., Fallgatter, A. J., & Ehlis, A. C. (2014). Stress-induced neuroplasticity: (mal)adaptation to adverse life events in patients with PTSD—A critical overview. *Neuroscience*, *283*, 166–177.
De Ruijter, A., Van Gennip, A., Caron, H., Kemp, S., & van Kuilenburg, A. (2003). Histone deacetylases (HDACs): Characterization of the classical HDAC family. *Biochemistry Journal*, *370*, 737–749.
Detich, N., Bovenzi, V., & Szyf, M. (2003). Valproate induces replication-independent active DNA demethylation. *Journal of Biological Chemistry*, *278*, 27586–27592.
Detich, N., Theberge, J., & Szyf, M. (2002). Promoter-specific activation and demethylation by MBD2/demethylase. *Journal of Biological Chemistry*, *277*, 35791–35794.
Devlin, A. M., Brain, U., Austin, J., & Oberlander, T. F. (2010). Prenatal exposure to maternal depressed mood and the MTHFR C677t variant affect SLC6A4 methylation in infants at birth. *PLOS ONE*, *5*, e12201.
Doherty, T. S., Forster, A., & Roth, T. L. (2015). Global and gene-specific DNA methylation alterations in the adolescent amygdala and hippocampus in an animal model of caregiver maltreatment. *Behavioural Brain Research*. Advance online publication.
Dolinoy, D. C. (2008). The agouti mouse model: An epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. *Nutrition Reviews*, *66*, S7–S11.
Dolinoy, D. C., Huang, D., & Jirtle, R. L. (2007). Maternal nutrient supplementation counteracts bisphenol a-induced DNA hypomethylation in early development. *Proceedings of the National Academy of Sciences*, *104*, 13056–13061.
Dong, E., Gavin, D. P., Chen, Y., & Davis, J. (2012). Upregulation of TET1 and downregulation of APOBEC3A and APOBEC3C in the parietal cortex of psychotic patients. *Translational Psychiatry*, *2*, e159.
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*, 1351–1353.
Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M., & Tsai, L.-H. (2007). Recovery of learning and memory is associated with chromatin remodelling. *Nature*, *447*, 178–182.
Francis, D. D., Champagne, F. C., & Meaney, M. J. (2000). Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. *Journal of Neuroendocrinology*, *12*, 1145–1148.
Francis, D. D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, *286*, 1155–1158.
Francis, D. D., Diorio, J., Plotsky, P. M., & Meaney, M. J. (2002). Environmental enrichment reverses the effects of maternal separation on stress reactivity. *Journal of Neuroscience*, *22*, 7840–7843.
Frodl, T., & O'Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of Disease*, *52*, 24–37.
Fuchikami, M., Morinobu, S., Kurata, A., Yamamoto, S., & Yamawaki, S. (2009). Single immobilization stress differentially alters the expression profile of transcripts of the brain-derived neurotrophic factor (BDNF) gene and histone acetylation at its promoters in the rat hippocampus. *International Journal of Neuropsychopharmacology*, *12*, 73–82.
Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z., & Fan, G. (2011). Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *European Journal of Neuroscience*, *33*, 383–390.
Grayson, D. R., Jia, X., Chen, Y., Sharma, R. P., Mitchell, C. P., Guidotti, A., et al. (2005). Reelin promoter hypermethylation in schizophrenia. *Proceedings of the National Academy of Sciences*, *102*, 9341–9346.
Greenberg, M. E., Xu, B., Lu, B., & Hempstead, B. L. (2009). New insights in the biology of BDNF synthesis and release: Implications in CNS function. *Journal of Neuroscience*, *29*, 12764–12767.
Grunstein, M. (1997). Histone acetylation in chromatin structure and transcription. *Nature*, *389*, 349–352.
Guo, J. U., Su, Y., Shin, J. H., Shin, J., Li, H., Xie, B., et al. (2014). Distribution, recognition and regulation of non-CpG methylation in the adult mammalian brain. *Nature Neuroscience*, *17*, 215–222.
Guo, J. U., Su, Y., Zhong, C., Ming, G.-L., & Song, H. (2011). Hydroxylation of 5-methylcytosine by TET1 promotes active DNA demethylation in the adult brain. *Cell*, *145*, 423–434.
Haapasalo, J., & Aaltonen, T. (1999). Mothers' abusive childhood predicts child abuse. *Child Abuse Review*, *8*, 231–250.
Hao, Y., Huang, W., Nielsen, D. A., & Kosten, T. A. (2011). Litter gender composition and sex affect maternal behavior and DNA methylation levels of the oprm1 gene in rat offspring. *Frontiers in Psychiatry*, *2*, 21.
He, Y.-F., Li, B.-Z., Li, Z., Liu, P., Wang, Y., Tang, Q., et al. (2011). Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. *Science*, *333*, 1303–1307.

Heijmans, B. T., Tobi, E. W., Stein, A. D., Putter, H., Blauw, G. J., Susser, E. S., et al. (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences*, *105*, 17046–17049.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry*, *49*, 1023–1039.

Heller, E. A., Cates, H. M., Pena, C. J., Sun, H., Shao, N., Feng, J., et al. (2014). Locus-specific epigenetic remodeling controls addiction- and depression-related behaviors. *Nature Neuroscience*, *17*, 1720–1727.

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: Central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in Neurosciences*, *20*, 78–84.

Hoeijmakers, L., Lucassen, P., & Korosi, A. (2015). The interplay of early-life stress, nutrition and immune activation programs adult hippocampal structure and function. *Frontiers in Molecular Neuroscience*, *7*, 103.

Huang, S., Trapido, E., Fleming, L., Arheart, K., Crandall, L., French, M., et al. (2011). The long-term effects of childhood maltreatment experiences on subsequent illicit drug use and drug-related problems in young adulthood. *Addictive Behaviors*, *36*, 95–102.

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*, 20912–20917.

Irier, H., Street, R. C., Dave, R., Lin, L., Cai, C., Davis, T. H., et al. (2014). Environmental enrichment modulates 5-hydroxymethylcytosine dynamics in hippocampus. *Genomics*, *104*, 376–382.

Ivy, A. S., Rex, C. S., Chen, Y., Dubé, C., Maras, P. M., Grigoriadis, D. E., et al. (2010). Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *Journal of Neuroscience*, *30*, 13005–13015.

Jans, L., Riedel, W., Markus, C., & Blokland, A. (2007). Serotonergic vulnerability and depression: Assumptions, experimental evidence and implications. *Molecular Psychiatry*, *12*, 522–543.

Jovanovic, T., Blanding, N. Q., Norrholm, S. D., Duncan, E., Bradley, B., & Ressler, K. J. (2009). Childhood abuse is associated with increased startle reactivity in adulthood. *Depression and Anxiety*, *26*, 1018–1026.

Kaffman, A., & Meaney, M. J. (2007). Neurodevelopmental sequelae of postnatal maternal care in rodents: Clinical and research implications of molecular insights. *Journal of Child Psychology and Psychiatry*, *48*, 224–244.

Kao, G.-S., Cheng, L.-Y., Chen, L.-H., Tzeng, W.-Y., Cherng, C. G., Su, C.-C., et al. (2012). Neonatal isolation decreases cued fear conditioning and frontal cortical histone 3 lysine 9 methylation in adult female rats. *European Journal of Pharmacology*, *697*, 65–72.

Kato, T., & Iwamoto, K. (2014). Comprehensive DNA methylation and hydroxymethylation analysis in the human brain and its implication in mental disorders. *Neuropharmacology*, *80*, 133–139.

Kieffer, B. L., & Gavériaux-Ruff, C. (2002). Exploring the opioid system by gene knockout. *Progress in Neurobiology*, *66*, 285–306.

Kinnally, E. L., Feinberg, C., Kim, D., Ferguson, K., Leibel, R., Coplan, J. D., et al. (2011). DNA methylation as a risk factor in the effects of early life stress. *Brain, Behavior, and Immunity*, *25*, 1548–1553.

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., et al. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nature Neuroscience*, *16*, 33–41.

Knapska, E., & Kaczmarek, L. (2004). A gene for neuronal plasticity in the mammalian brain: Zif268/Egr-1/NGFI-A/Krox-24/TIS8/ZENK? *Progress in Neurobiology*, *74*, 183–211.

Koenen, K. C., Uddin, M., Chang, S.-C., Aiello, A. E., Wildman, D. E., Goldmann, E., et al. (2011). SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. *Depression and Anxiety*, *28*, 639–647.

Kohli, R. M., & Zhang, Y. (2013). TET enzymes, TDG and the dynamics of DNA demethylation. *Nature*, *502*, 472–479.

Konermann, S., Brigham, M. D., Trevino, A., Hsu, P. D., Heidenreich, M., Le, C., et al. (2013). Optical control of mammalian endogenous transcription and epigenetic states. *Nature*, *500*, 472–476.

Kosten, T. A., Huang, W., & Nielsen, D. A. (2014). Sex and litter effects on anxiety and DNA methylation levels of stress and neurotrophin genes in adolescent rats. *Developmental Psychobiology*, *56*, 392–406.

Kosten, T. A., Miserendino, M. J., & Kehoe, P. (2000). Enhanced acquisition of cocaine self-administration in adult rats with neonatal isolation stress experience. *Brain Research*, *875*, 44–50.

Kozlovsky, N., Matar, M. A., Kaplan, Z., Kotler, M., Zohar, J., & Cohen, H. (2007). Long-term down-regulation of BDNF mRNA in rat hippocampal CA1 subregion correlates with PTSD-like behavioural stress response. *International Journal of Neuropsychopharmacology*, *10*, 741–758.

Kundakovic, M., & Champagne, F. A. (2011). Epigenetic perspective on the developmental effects of bisphenol A. *Brain, Behavior, and Immunity*, *25*, 1084–1093.

Kundakovic, M., Gudsnuk, K., Herbstman, J. B., Tang, D., Perera, F. P., & Champagne, F. A. (2015). DNA methylation of BDNF as a biomarker of early-life adversity. *Proceedings of the National Academy of Sciences*, *112*, 6807–6813.

Kuzumaki, N., Ikegami, D., Tamura, R., Hareyama, N., Imai, S., Narita, M., et al. (2011). Hippocampal epigenetic modification at the brain-derived neurotrophic factor gene induced by an enriched environment. *Hippocampus*, *21*, 127–132.

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*, 1137–1143.

Lee, M. G., Wynder, C., Schmidt, D. M., McCafferty, D. G., & Shiekhattar, R. (2006). Histone H3 lysine 4 demethylation is a target of nonselective antidepressive medications. *Chemistry and Biology*, *13*, 563–567.

Lee, V., & Hoaken, P. N. (2007). Cognition, emotion, and neurobiological development: Mediating the relation between maltreatment and aggression. *Child Maltreatment*, *12*, 281–298.

Leonard, B. (2005). The HPA and immune axes in stress: The involvement of the serotonergic system. *European Psychiatry*, *20*, S302–S306.

Levenson, J. M., Roth, T. L., Lubin, F. D., Miller, C. A., Huang, I.-C., Desai, P., et al. (2006). Evidence that DNA (cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. *Journal of Biological Chemistry*, *281*, 15763–15773.

Levine, A., Worrell, T. R., Zimnisky, R., & Schmauss, C. (2012). Early life stress triggers sustained changes in histone deacetylase expression and histone H4 modifications that alter responsiveness to adolescent antidepressant treatment. *Neurobiology of Disease*, *45*, 488–498.

Levine, S. (1994). The ontogeny of the hypothalamic–pituitary–adrenal axis: The influence of maternal factors. *Annals of the New York Academy of Sciences*, *746*, 275–288.

Li, X., Wei, W., Zhao, Q.-Y., Widagdo, J., Baker-Andresen, D., Flavell, C. R., et al. (2014). Neocortical Tet3-mediated accumulation of 5-hydroxymethylcytosine promotes rapid behavioral adaptation. *Proceedings of the National Academy of Sciences*, *111*, 7120–7125.

Lindholm, M. E., Marabita, F., Gomez-Cabrero, D., Rundqvist, H., Ekström, T. J., Tegnér, J., et al. (2014). An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. *Epigenetics*, *9*, 1557–1569.

Lister, R., Pelizzola, M., Dowen, R. H., Hawkins, R. D., Hon, G., Tonti-Filippini, J., et al. (2009). Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature*, *462*, 315–322.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., et al. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science*, *277*, 1659–1662.

Lopez, J., Mamdani, F., Labonte, B., Beaulieu, M., Yang, J., Berlim, M., et al. (2013). Epigenetic regulation of BDNF expression according to antidepressant response. *Molecular Psychiatry*, *18*, 398–399.

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*, 10576–10586.

Lucassen, P. J., Naninck, E. F., van Goudoever, J. B., Fitzsimons, C., Joels, M., & Korosi, A. (2013). Perinatal programming of adult hippocampal structure and function: Emerging roles of stress, nutrition and epigenetics. *Trends in Neurosciences*, *36*, 621–631.

Ma, D. K., Jang, M.-H., Guo, J. U., Kitabatake, Y., Chang, M.-L., Pow-Anpongkul, N., et al. (2009). Neuronal activity–induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. *Science*, *323*, 1074–1077.

Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A., Cinque, C., & Van Reeth, O. (2003). Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. *Neuroscience & Biobehavioral Reviews*, *27*, 119–127.

Maeder, M. L., Angstman, J. F., Richardson, M. E., Linder, S. J., Cascio, V. M., Tsai, S. Q., et al. (2013). Targeted DNA demethylation and activation of endogenous genes using programmable TALE-TET1 fusion proteins. *Nature Biotechnology*, *31*, 1137–1142.

Mahan, A. L., Mou, L., Shah, N., Hu, J.-H., Worley, P. F., & Ressler, K. J. (2012). Epigenetic modulation of Homer1a transcription regulation in amygdala and hippocampus with Pavlovian fear conditioning. *Journal of Neuroscience*, *32*, 4651–4659.

Mahan, A. L., & Ressler, K. J. (2012). Fear conditioning, synaptic plasticity and the amygdala: Implications for posttraumatic stress disorder. *Trends in Neurosciences*, *35*, 24–35.

Mairesse, J., Lesage, J., Breton, C., Bréant, B., Hahn, T., Darnaudéry, M., et al. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. *American Journal of Physiology—Endocrinology and Metabolism*, *292*, E1526–E1533.

Maiti, A., & Drohat, A. C. (2011). Thymine DNA glycosylase can rapidly excise 5-formylcytosine and 5-carboxylcytosine: Potential implications for active demethylation of CpG sites. *Journal of Biological Chemistry*, *286*, 35334–35338.

Massart, R., Suderman, M., Provencal, N., Yi, C., Bennett, A., Suomi, S., et al. (2014). Hydroxymethylation and DNA methylation profiles in the prefrontal cortex of the non-human primate rhesus macaque and the impact of maternal deprivation on hydroxymethylation. *Neuroscience*, *268*, 139–148.

Matrisciano, F., Tueting, P., Dalal, I., Kadriu, B., Grayson, D. R., Davis, J. M., et al. (2013). Epigenetic modifications of gabaergic interneurons are associated with the schizophrenia-like phenotype induced by prenatal stress in mice. *Neuropharmacology*, *68*, 184–194.

Matrisciano, F., Tueting, P., Maccari, S., Nicoletti, F., & Guidotti, A. (2012). Pharmacological activation of group-II metabotropic glutamate receptors corrects a schizophrenia-like phenotype induced by prenatal stress in mice. *Neuropsychopharmacology*, *37*, 929–938.

Matthes, H. W. D., Maldonado, R., Simonin, F., Valverde, O., Slowe, S., Kitchen, I., et al. (1996). Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature*, *383*, 819–823.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, *12*, 342–348.

Mehta, D., Gonik, M., Klengel, T., Rex-Haffner, M., Menke, A., Rubel, J., et al. (2011). Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: Evidence from endocrine and gene expression studies. *Archives of General Psychiatry*, *68*, 901–910.

Milagro, F., Campion, J., Garcia-Diaz, D., Goyenechea, E., Paternain, L., & Martinez, J. (2009). High fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. *Journal of Physiology and Biochemistry*, *65*, 1–9.

Miller, G. E., Chen, E., Fok, A. K., Walker, H., Lim, A., Nicholls, E. F., et al. (2009). Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proceedings of the National Academy of Sciences*, *106*, 14716–14721.

Moles, A., Kieffer, B. L., & D'Amato, F. R. (2004). Deficit in attachment behavior in mice lacking the μ-opioid receptor gene. *Science*, *304*, 1983–1986.

Monsey, M. S., Ota, K. T., Akingbade, I. F., Hong, E. S., & Schafe, G. E. (2011). Epigenetic alterations are critical for fear memory consolidation and synaptic plasticity in the lateral amygdala. *PLOS ONE*, *6*, e19958.

Moore, C. L., & Morelli, G. A. (1979). Mother rats interact differently with male and female offspring. *Journal of Comparative and Physiological Psychology*, *93*, 677.

Moore, L. D., Le, T., & Fan, G. (2013). DNA methylation and its basic function. *Neuropsychopharmacology*, *38*, 23–38.

Morley-Fletcher, S., Rea, M., Maccari, S., & Laviola, G. (2003). Environmental enrichment during adolescence reverses the effects of prenatal stress on play behaviour and hpa axis reactivity in rats. *European Journal of Neuroscience*, *18*, 3367–3374.

Mueller, B. R., & Bale, T. L. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience*, *28*, 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*, 1559–1566.

Murgatroyd, C., Quinn, J. P., Sharp, H. M., Pickles, A., & Hill, J. (2015). Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene. *Translational Psychiatry*, *5*, e560.

Mychasiuk, R., Zahir, S., Schmold, N., Ilnytskyy, S., Kovalchuk, O., & Gibb, R. (2012). Parental enrichment and offspring development: Modifications to brain, behavior and the epigenome. *Behavioural Brain Research*, *228*, 294–298.

Nan, X., Ng, H.-H., Johnson, C. A., Laherty, C. D., Turner, B. M., Eisenman, R. N., et al. (1998). Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature*, *393*, 386–389.

Nelson, E. E., & Panksepp, J. (1998). Brain substrates of infant–mother attachment: Contributions of opioids, oxytocin, and norepinephrine. *Neuroscience & Biobehavioral Reviews*, *22*, 437–452.

Ney, P. G. (1988). Transgenerational child abuse. *Child Psychiatry and Human Development*, *18*, 151–168.

O'Mahony, S. M., Marchesi, J. R., Scully, P., Codling, C., Ceolho, A.-M., Quigley, E. M. M., et al. (2009). Early life stress alters behavior, immunity, and microbiota in rats: Implications for irritable bowel syndrome and psychiatric illnesses. *Biological Psychiatry*, *65*, 263–267.

Patil, S. T., Zhang, L., Martenyi, F., Lowe, S. L., Jackson, K. A., Andreev, B. V., et al. (2007). Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized phase 2 clinical trial. *Nature Medicine*, *13*, 1102–1107.

Peña, C. J., Monk, C., & Champagne, F. A. (2012). Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. *PLOS ONE*, *7*, e39791.

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M., Furrer, S., et al. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the bdnf gene. *Translational Psychiatry*, *3*, e207.

Provençal, N., Suderman, M. J., Guillemin, C., Massart, R., Ruggiero, A., Wang, D., et al. (2012). The signature of maternal rearing in the methylome in rhesus macaque prefrontal cortex and T cells. *Journal of Neuroscience*, *32*, 15626–15642.

Pusalkar, M., Suri, D., Kelkar, A., Bhattacharya, A., Galande, S., & Vaidya, V. A. (2016). Early stress evokes dysregulation of histone modifiers in the medial prefrontal cortex across the life span. *Developmental Psychobiology*, *58*, 198–210.

Ramsahoye, B. H., Biniszkiewicz, D., Lyko, F., Clark, V., Bird, A. P., & Jaenisch, R. (2000). Non-CpG methylation is prevalent in embryonic stem cells and may be mediated by DNA methyltransferase 3a. *Proceedings of the National Academy of Sciences*, *97*, 5237–5242.

Ranta, S., Zhang, Y., Ross, B., Takkunen, E., Hirvasniemi, A., de la Chapelle, A., et al. (2000). Positional cloning and characterisation of the human DLGAP2 gene and its exclusion in progressive epilepsy with mental retardation. *European Journal of Human Genetics*, *8*, 381–384.

Ren, H., Collins, V., Clarke, S. J., Han, J.-S., Lam, P., Clay, F., et al. (2012). Epigenetic changes in response to Tai Chi practice: A pilot investigation of DNA methylation marks. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 841810.

Reuter, S., Gupta, S., Park, B., Goel, A., & Aggarwal, B. (2011). Epigenetic changes induced by curcumin and other natural compounds. *Genes and Nutrition*, *6*, 93–108.

Richmond, G., & Sachs, B. D. (1984). Maternal discrimination of pup sex in rats. *Developmental Psychobiology*, *17*, 87–89.

Roberts, S., Lester, K., Hudson, J., Rapee, R., Creswell, C., Cooper, P., et al. (2014). Serotonin tranporter methylation and response to cognitive behaviour therapy in children with anxiety disorders. *Translational Psychiatry*, *4*, e444.

Robertson, J., Robertson, A. B., & Klungland, A. (2011). The presence of 5-hydroxymethylcytosine at the gene promoter and not in the gene body negatively regulates gene expression. *Biochemical and Biophysical Research Communications*, *411*, 40–43.

Rönn, T., Volkov, P., Davegårdh, C., Dayeh, T., Hall, E., Olsson, A. H., et al. (2013). A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLOS Genetics*, *9*, e1003572.

Rossi, C., Angelucci, A., Costantin, L., Braschi, C., Mazzantini, M., Babbini, F., et al. (2006). Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *European Journal of Neuroscience*, *24*, 1850–1856.

Roth, E. D., Roth, T. L., Money, K. M., SenGupta, S., Eason, D. E., & Sweatt, J. D. (2015). DNA methylation regulates neurophysiological spatial representation in memory formation. *Neuroepigenetics*, *2*, 1–8.

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

Roth, T., Matt, S., Chen, K., & Blaze, J. (2014). Bdnf DNA methylation modifications in the hippocampus and amygdala of male and female

rats exposed to different caregiving environments outside the homecage. *Developmental Psychobiology*, *56*, 1755–1763.
Roth, T., Zoladz, P., Sweatt, J., & Diamond, D. (2011). Epigenetic modification of hippocampal *Bdnf* DNA in adult rats in an animal model of post-traumatic stress disorder. *Journal of Psychiatric Research*, *45*, 919–926.
Roth, T. L., & Sullivan, R. M. (2006). Examining the role of endogenous opioids in learned odor–stroke associations in infant rats. *Developmental Psychobiology*, *48*, 71–78.
3Rountree, M. R., Bachman, K. E., Herman, J. G., & Baylin, S. B. (2001). DNA methylation, chromatin inheritance, and cancer. *Oncogene*, *20*, 3156–3165.
Rusiecki, J. A., Chen, L., Srikantan, V., Zhang, L., Yan, L., Polin, M. L., et al. (2012). DNA methylation in repetitive elements and post-traumatic stress disorder: A case-control study of us military service members. *Epigenomics*, *4*, 29–40.
Saiz, R. J., Carrasco, P. J., & Hernanz, A. (1991). Plasma neuropeptides in affective and anxiety disorders. *Archivos de neurobiologia*, *55*, 1–5.
Sales, A. J., Biojone, C., Terceti, M. S., Guimarães, F. S., Gomes, M. V., & Joca, S. R. (2011). Antidepressant-like effect induced by systemic and intra-hippocampal administration of DNA methylation inhibitors. *British Journal of Pharmacology*, *164*, 1711–1721.
Sanjana, N. E., Cong, L., Zhou, Y., Cunniff, M. M., Feng, G., & Zhang, F. (2012). A transcription activator-like effector toolbox for genome engineering. *Nature Protocols*, *7*, 171–192.
Sarkar, S., Abujamra, A. L., Loew, J. E., Forman, L. W., Perrine, S. P., & Faller, D. V. (2011). Histone deacetylase inhibitors reverse CpG methylation by regulating DNMT1 through ERK signaling. *Anticancer Research*, *31*, 2723–2732.
Schroeder, F. A., Lin, C. L., Crusio, W. E., & Akbarian, S. (2007). Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. *Biological Psychiatry*, *62*, 55–64.
Sharma, R. P., Grayson, D. R., & Gavin, D. P. (2008). Histone deactylase 1 expression is increased in the prefrontal cortex of schizophrenia subjects: Analysis of the national brain databank microarray collection. *Schizophrenia Research*, *98*, 111–117.
Shen, L., Song, C.-X., He, C., & Zhang, Y. (2014). Mechanism and function of oxidative reversal of DNA and RNA methylation. *Annual Review of Biochemistry*, *83*, 585–614.
Shilling, P. D., & Feifel, D. (2008). The neurotensin-1 receptor agonist PD149163 blocks fear-potentiated startle. *Pharmacology Biochemistry and Behavior*, *90*, 748–752.
Shimabukuro, M., Jinno, Y., Fuke, C., & Okazaki, Y. (2006). Haloperidol treatment induces tissue- and sex-specific changes in DNA methylation: A control study using rats. *Behavioral and Brain Functions*, *2*, 1–5.
Smith, A. K., Conneely, K. N., Kilaru, V., Mercer, K. B., Weiss, T. E., Bradley, B., et al. (2011). Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *156*, 700–708.
Song, Y., Miyaki, K., Suzuki, T., Sasaki, Y., Tsutsumi, A., Kawakami, N., et al. (2014). Altered DNA methylation status of human brain derived neurotrophic factor gene could be useful as biomarker of depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *165*, 357–364.
St.-Cyr, S., & McGowan, P. (2015). Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor. *Frontiers in Behavioral Neuroscience*, *9*, 145.
Sun, H., Damez-Werno, D. M., Scobie, K. N., Shao, N.-Y., Dias, C., Rabkin, J., et al. (2015). ACF chromatin-remodeling complex mediates stress-induced depressive-like behavior. *Nature Medicine*, *21*, 1146–1153.
Szulwach, K. E., Li, X., Li, Y., Song, C.-X., Wu, H., Dai, Q., et al. (2011). 5-HMC-mediated epigenetic dynamics during postnatal neurodevelopment and aging. *Nature Neuroscience*, *14*, 1607–1616.
Toda, H., Boku, S., Nakagawa, S., Inoue, T., Kato, A., Takamura, N., et al. (2014). Maternal separation enhances conditioned fear and decreases the mrna levels of the neurotensin receptor 1 gene with hypermethylation of this gene in the rat amygdala. *PLOS ONE*, *9*, e97421.
Tremolizzo, L., Doueiri, M.-S., Dong, E., Grayson, D. R., Davis, J., Pinna, G., et al. (2005). Valproate corrects the schizophrenia-like epigenetic behavioral modifications induced by methionine in mice. *Biological Psychiatry*, *57*, 500–509.
Tsankova, N. M., Berton, O., Renthal, W., Kumar, A., Neve, R. L., & Nestler, E. J. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nature Neuroscience*, *9*, 519–525.
Unternaehrer, E., Luers, P., Mill, J., Dempster, E., Meyer, A. H., Staehli, S., et al. (2012). Dynamic changes in DNA methylation of stress-associated genes (OXTR, BDNF) after acute psychosocial stress. *Translational Psychiatry*, *2*, e150.
Unternaehrer, E., Meyer, A. H., Burkhardt, S. C., Dempster, E., Staehli, S., Theill, N., et al. (2015). Childhood maternal care is associated with DNA methylation of the genes for brain-derived neurotrophic factor (BDNF) and oxytocin receptor (OXTR) in peripheral blood cells in adult men and women. *Stress*, *18*, 451–461.
Valinluck, V., Tsai, H.-H., Rogstad, D. K., Burdzy, A., Bird, A., & Sowers, L. C. (2004). Oxidative damage to methyl-CpG sequences inhibits the binding of the methyl-CpG binding domain (MBD) of methyl-CpG binding protein 2 (MeCP2). *Nucleic Acids Research*, *32*, 4100–4108.
Van Der Knaap, L. J., Oldehinkel, A. J., Verhulst, F. C., Van Oort, F. V., & Riese, H. (2015). Glucocorticoid receptor gene methylation and HPA-axis regulation in adolescents: The trails study. *Psychoneuroendocrinology*, *58*, 46–50.
Vijayendran, M., Beach, S., Plume, J. M., Brody, G., & Philibert, R. (2012). Effects of genotype and child abuse on DNA methylation and gene expression at the serotonin transporter. *Frontiers in Psychiatry*, *3*, 55.
Vucetic, Z., Kimmel, J., Totoki, K., Hollenbeck, E., & Reyes, T. M. (2010). Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology*, *151*, 4756–4764.
Waddington, C. H. (1957). *The strategy of the genes: A discussion of some aspects of theoretical biology*. London: Allen & Unwin.
Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: Targets for early nutritional effects on epigenetic gene regulation. *Molecular and Cellular Biology*, *23*, 5293–5300.
Weaver, I. C., 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*, 847–854.
Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *Journal of Neuroscience*, *25*, 11045–11054.
Weaver, I. C., Meaney, M. J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences*, *103*, 3480–3485.
Weder, N., Zhang, H., Jensen, K., Yang, B. Z., Simen, A., Jackowski, A., et al. (2016). Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *Journal of the American Academy of Child & Adolescent Psychiatry*, *53*, 417–424.
Weeber, E. J., Beffert, U., Jones, C., Christian, J. M., Förster, E., Sweatt, J. D., et al. (2002). Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. *Journal of Biological Chemistry*, *277*, 39944–39952.
Weller, A., & Feldman, R. (2003). Emotion regulation and touch in infants: The role of cholecystokinin and opioids. *Peptides*, *24*, 779–788.
Wilkinson, M. B., Xiao, G., Kumar, A., LaPlant, Q., Renthal, W., Sikder, D., et al. (2009). Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. *Journal of Neuroscience*, *29*, 7820–7832.
Wolff, G. L., Kodell, R. L., Moore, S. R., & Cooney, C. A. (1998). Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. *FASEB Journal*, *12*, 949–957.
Wu, Y., Patchev, A. V., Daniel, G., Almeida, O. F. X., & Spengler, D. (2014). Early-life stress reduces DNA methylation of the Pomc gene in male mice. *Endocrinology*, *155*, 1751–1762.
Yehuda, R., Daskalakis, N. P., Bierer, L. M., Bader, H. N., Klengel, T., Holsboer, F., et al. (2015). Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biological Psychiatry*. Advance online publication.
Yehuda, R., Daskalakis, N. P., Lehrner, A., Desarnaud, F., Bader, H. N., Makotkine, I., et al. (2014). Influences of maternal and paternal ptsd on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *American Journal of Psychiatry*, *171*, 872–880.
Zaidi, L. Y., Knutson, J. F., & Mehm, J. G. (1989). Transgenerational patterns of abusive parenting: Analog and clinical tests. *Aggressive Behavior*, *15*, 137–152.
Zhang, Y., & Reinberg, D. (2001). Transcription regulation by histone methylation: Interplay between different covalent modifications of the core histone tails. *Genes and Development*, *15*, 2343–23s60.