Neuroscience and Biobehavioral Reviews 33 (2009) 593–600

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Epigenetic mechanisms mediating the long-term effects of maternal care on development

Frances A. Champagne [a,*], James P. Curley [b]

[a] Department of Psychology, Columbia University, 406 Schermerhorn, 1190 Amsterdam Avenue, New York, NY 10025, United States
[b] Sub-Department of Animal Behaviour, University of Cambridge, UK

ARTICLE INFO

Keywords:
Mother–infant
Stress responsivity
Maternal behavior
Epigenetic
DNA methylation
Psychiatry

ABSTRACT

The long-term consequences of early environmental experiences for development have been explored extensively in animal models to better understand the mechanisms mediating risk of psychopathology in individuals exposed to childhood adversity. One common feature of these models is disruption of the mother–infant relationship which is associated with impairments in stress responsivity and maternal behavior in adult offspring. These behavioral and physiological characteristics are associated with stable changes in gene expression which emerge in infancy and are sustained into adulthood. Recent evidence suggests that these long-term effects may be mediated by epigenetic modification to the promoter regions of steroid receptor genes. In particular, DNA methylation may be critical to maternal effects on gene expression and thus generate phenotypic differentiation of offspring and, through effects on maternal behavior of offspring, mediate the transmission of these effects across generations. In this review we explore evidence for the influence of mother–infant interactions on the epigenome and consider evidence for and the implications of such epigenetic effects for human mental health.

Contents

In humans, environmental adversity occurring early in development is associated with an increased risk of both physical and psychiatric disorder in adulthood. Thus, the experience of childhood abuse and neglect has been demonstrated to increase rates of diabetes and cardiovascular disease (Baten et al., 2004; Goodwin and Stein, 2004) as well as increasing susceptibility to drug abuse (Dube et al., 2003; Anda et al., 2006), depression (Baten et al., 2004), schizophrenia (Read et al., 2005; Rutter et al., 2006) and anxiety-related disorders (Phillips et al., 2005). Though there has been progress in determining the neurobiological consequences of these experiences in humans (Teicher et al., 2006; Tarullo and Gunnar, 2006; Gunnar and Fisher, 2006), most of our understanding of these effects comes from animal models in which the relationship between variation in gene expression within the central nervous system and behavioral patterns can be explored in response to discrete environmental events. These studies provide evidence for the long-term impact of disruptions of the early environment, particularly of the mother–infant relationship or of peer–peer interactions during the juvenile period, on the neuroendocrine systems regulating stress responsivity and social behavior. Moreover, by altering social and reproductive behavior of offspring, these experiences have significant consequences for the development and behavior of subsequent generations (Champagne and Curley, 2005). One of the most intriguing questions to emerge from this research involves the mechanism mediating these effects: How are early environmental effects sustained into

* Corresponding author. Tel.: +1 212 854 2589; fax: +1 212 854 3609.
E-mail address: fac2105@columbia.edu (F.A. Champagne).

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2007.10.009

adulthood? Recent work suggests that the answer to this question involves understanding of epigenetic modifications of gene expression in response to environmental cues. In this review, we will explore evidence from animal models for the long-term consequences of mother–infant interactions both within and across generations, the emerging evidence for the role of epigenetics in mediating these effects, and discuss the potential relevance of these mechanisms to the pathophysiology of psychiatric disorders in humans.

1. Deprivation, separation and variation: studying maternal influence on offspring development

The profound effect of maternal deprivation on infant development that has been implied by longitudinal studies of orphans reared in institutional settings (Kaler and Freeman, 1994; Gunnar et al., 2001; Chugani et al., 2001; Roy et al., 2004) has been investigated experimentally in both primates and rodents. Harlow's artificial rearing paradigm in which infant rhesus macaques were socially isolated for periods of 3–12 months (Harlow and Suomi, 1971, 1974) illustrated that normal development requires more than simply access to adequate nutrition. Juveniles reared in this environment display marked deficits in play behavior, exhibit high levels of aggression with peers, perform poorly on learning and cognitive discrimination tasks and are behaviorally inhibited associated with a heightened fear-response to novelty (Suomi et al., 1971; Seay et al., 1964; Seay and Harlow, 1965). These behavioral patterns continue into adulthood and thus alter reproductive success, particularly of artificially reared females, who display high rates of infant abuse, neglect and infanticide (Arling and Harlow, 1967; Harlow and Suomi, 1971; Seay et al., 1964). Maternally deprived macaques that are permitted to interact with same-age same-sex peers also have an elevated hypothalamic–pituitary–adrenal (HPA) response to stress, impairments in learning and social behavior (Shannon et al., 1998; Fahlke et al., 2000) and altered serotonergic systems (Ichise et al., 2006; Shannon et al., 2005) suggesting that it is disruption of the mother–infant relationship rather than the general consequences of social isolation that contribute to these effects. Likewise, complete maternal deprivation of rodent pups during the postpartum period leads to increased HPA activity, reduces exploratory behavior in adulthood and is associated with locomotor hyperactivity, cognitive impairments and reductions in maternal care (Gonzalez and Fleming, 2002; Gonzalez et al., 2001; Lovic and Fleming, 2004) with females displaying deficits in hormonal priming of maternal behavior (Novakov and Fleming, 2005) and engaging in less maternal licking/grooming and contact toward their pups.

Investigation of the consequence of prolonged periods of separation between mother and infant has also demonstrated the long-term impact of disruptions of the maternal environment on offspring development. In primates, this has been accomplished by increasing the variability of foraging demand placed on mothers such that the time required to acquire food fluctuates randomly across days (Rosenblum and Paully, 1984). Offspring reared under these conditions exhibit behavioral inhibition, reduced social behavior associated with increased HPA activity, reduced levels of growth factors, a compromised immune response, and altered neurotransmitter metabolite levels in the anterior cingulate and medial temporal lobes (Andrews and Rosenblum, 1991, 1994; Coplan et al., 2005, 2001, 1998, 2000; Rosenblum et al., 2001). In addition to creating prolonged maternal separation, variable foraging demand has been show to reduce the maternal responsivity of mothers when they are in contact with offspring (Rosenblum and Paully, 1984) suggesting that these effects may be mediated by changes in the quality rather than the simply the quantity of care received. Similar effects have been demonstrated in rodents, either by imposing variable foraging demand (Bredy et al., 2007) or by inducing forced periods of physical separation between mother and pups (Lehmann and Feldon, 2000). The maternal separation paradigm, involving hours of daily mother–infant separation has both short-and long-term effects on the responsivity of the HPA axis (Lehmann and Feldon, 2000; Plotsky and Meaney, 1993; Plotsky et al., 2005; Rosenfeld et al., 1992) and leads to a cascade of behavioral and neurobiological changes though the consistency and direction of these changes has been debated (Pryce and Feldon, 2003; Macri and Wurbel, 2006). These manipulations are typically associated with decreased exploration, behavioral inhibition, increased corticosterone releasing hormone (CRH) mRNA in the paraventricular nucleus (PVN), increased corticosterone response to stress and decreased levels of hippocampal glucocorticoid receptor (GR) mRNA (Plotsky and Meaney, 1993; Meaney et al., 1996; Lehmann et al., 1999). Cognitive ability is also modified by this experience as indicated by increased performance latencies on the Morris Water Maze, decreased hippocampal synaptophysin levels and increased apoptosis (Lehmann et al., 2002). Females separated from their mothers for 5 h per day during the pre-weaning period show reduced levels of maternal licking/grooming toward their offspring (Fleming et al., 2002) suggesting reproductive consequences of this disruption to the early environment.

A third approach to studying the influence mother–infant interactions on neurobiology and behavior comes from the study of individual differences in maternal care. Amongst humans, primates and rodents, females display considerable variation in the quantity and quality of care they provide for offspring (Fairbanks, 1989; Berman, 1990; Fleming et al., 1997; Champagne et al., 2003a) and this variability can be used in a longitudinal design to predict phenotype in adulthood. Maternal behavior of vervet monkeys living in undisturbed social groups has been found to vary along two-dimensions; (1) protectiveness, which consists of high levels of "contact-seeking" by the mother and (2) rejection, which is associated with frequent attempts to break contact or to leave the infant (Fairbanks and McGuire, 1988). Behavioral response to novelty in 1- and 2-year-old infants is associated with variation in maternal protectiveness, with increased latency to enter a novel environment associated with having a more protective mother (Fairbanks and McGuire, 1988). Individual differences in abusive behavior amongst postpartum rhesus and pigtail macaques are also associated with behavioral and neurobiological characteristics of offspring (Maestripieri et al., 1999, 2005, 1997). Infant abuse occurring during the first 3 months is associated with an increased frequency of screaming, yawning, and other indices of infant distress at 4–6 months (Maestripieri et al., 2005). The high levels of maternal rejection exhibited by these females is correlated with increased solitary play and decreased CSF levels of 5-HIAA of their offspring, implicating the role of serotonergic activity in mediating these effects (Maestripieri et al., 2005, 2006). Cross-fostering of infants from abusive to non-abusive mothers indicates that these effects are indeed mediated by the quality of care received rather than a genetic transmission (Maestripieri, 2005).

Postpartum maternal care exhibited by rodents has been found to vary significantly between individuals and display the same level of stability over time illustrated by human and primate females. During the first week postpartum, lactating female rats and mice display high levels of nursing/contact with pups accompanied by bouts of licking/grooming with the frequency of these behaviors varying both within and between strains (Shoji and Kato, 2006; Champagne et al., 2003a). Strain differences in adult blood pressure between offspring of spontaneously hypertensive (SHR) and Wistar Kyoto (WKY) rats have been correlated to

differences in the frequency of maternal licking/grooming, retrieval of pups, and nursing posture exhibited by these two strains (Myers et al., 1989b). Cross-fostering pups from a WKY mother to a SHR mother shifts the WKY phenotype to that of the biological offspring of a SHR mother, suggesting the importance of variation of the maternal environment in mediating these strain differences (Myers et al., 1989a). Strain differences in maternal care of Balb/c and C57BL/6 mice have also been implicated as an influence on offspring stress reactivity (Francis et al., 2003; Priebe et al., 2005). C57BL/6 embryos that are transferred prenatally to Balb/c dams and reared by a Balb/c female develop characteristics similar to Balb/c mice including decreased exploration of a novel environment indicating increased anxiety (Francis et al., 2003). Though the characteristics that differentiate the prenatal environment of these strains is unknown, Balc/c females display decreased levels of postpartum licking/grooming compared to C57BL/6 dams which may contribute to the rearing effects observed (Francis et al., 2003).

The role of individual differences in maternal licking/grooming in modulating offspring gene expression, physiology and behavior has been explored extensively in Long Evans rats (Meaney, 2001). Amongst Long Evans lactating female rats there are considerable variations in the frequency with which dams engage in maternal licking/grooming of pups during the first week postpartum and licking/grooming behavior has been found to be a normally distributed behavior (Champagne et al., 2003a,b). Thus by selecting females that engage in a frequency of licking/grooming that is either 1 standard deviation below (Low LG) or above (High LG) the cohort mean it is possible to compare two groups of offspring that experience a 2–3-fold difference in maternal care. Initial studies demonstrated an association between levels of LG and stress responsivity, with the adult male offspring of High LG females being more exploratory in a novel environment, having reduced plasma adrenocorticotropin and corticosterone in response to stress, elevated hippocampal glucocorticoid receptor mRNA, elevated hypothalamic CRH mRNA, and increased density of benzodiazepine receptors in the amygdala compared to the offspring of Low LG dams (Caldji et al., 2000a; D.D. Francis et al., 1999; Liu et al., 2000, 1997). Offspring of High LG dams also exhibit enhanced performance on tests of spatial leaning and memory, elevated hippocampal brain derived neurotrophic factor (BDNF) mRNA, and increased hippocampal choline acetyltransferase and synaptophysin (Liu et al., 2000). GABA subunit expression is altered by maternal LG with implications for benzodiazepine binding (Caldji et al., 2000b). Neuronal survival in the hippocampus is increased and apoptosis decreased amongst the offspring of High LG dams associated with elevated levels of fibroblast growth factor (Bredy et al., 2003; Weaver et al., 2002). Dopaminergic release associated with stress responsivity in males and reward in females is also altered as a function of LG (Zhang et al., 2005; Champagne et al., 2004). Natural variations in maternal care are also transmitted across generations. The offspring of High LG rat dams exhibit high levels of maternal LG toward their own offspring whereas the offspring of Low LG dams are themselves low in LG (Champagne et al., 2003a; D. Francis et al., 1999; Fleming et al., 2002). Female offspring of Low LG dams exhibit decreased estrogen-mediated upregulation of oxytocin receptor binding and c-fos immunoreactivity in hypothalamic regions implicated in maternal care such as the medial preoptic area (MPOA; Champagne et al., 2001, 2003b; Francis et al., 2000). This sensitivity may be mediated by decreased levels of estrogen receptor (ER) α mRNA in the MPOA that are found in offspring of Low compared to High LG (Champagne et al., 2003b). Importantly, cross-fostering studies have demonstrated that these changes in offspring phenotype are related to the level of postpartum care received rather that genetic or prenatal factors (Champagne et al., 2003a; D. Francis et al., 1999). Thus, the offspring of High LG dams cross-fostered to Low LG dams are indistinguishable in phenotype from the biological offspring of Low LG dams. Conversely, the offspring of Low LG dams when reared by High LG dams resemble the biological offspring of High LG dams on measures of both gene expression and behavior.

2. Maternal influence on the epigenome

Converging evidence from primate and rodent studies support the hypothesis that maternal environment has a profound influence on offspring phenotype and that this influence is mediated by changes in gene expression. Consequently, understanding the mechanisms governing these effects requires an investigation of the molecular mechanisms which regulate gene transcription and thus exploration of the epigenetics of gene expression. The molecular mechanisms involved in the epigenetics of the genome are numerous and complex including RNA interference, chromatin remodelling, histone modification and DNA methylation (Turner, 2001) however, in this review we shall limit our focus to the modification of histone proteins and DNA methylation. In order to fit within the nucleus of the cell, DNA must be very tightly coiled. This condensed structure is maintained by complexes composed of four histone proteins: H1, H2, H3 and H4 (Turner, 2001). The structure of these proteins includes a highly positively charged region known as a histone "tail". It is this positively charged histone tail that wraps around the negatively charged DNA maintaining a very dense complex. In this state, DNA will not be transcribed and gene expression will be inhibited. However, histone tails can undergo several post-translational modifications that will alter this DNA–protein interaction. In particular, acetylation can occur, where through an enzymatic reaction, an acetyl group is attached to the histone tail. When this occurs, the histone tail and DNA become more similar in electrical change and hence repel each other allowing exposure of the DNA to transcription factors. Thus, increases in acetylation of histone tails promote gene expression whereas inhibition of this modification will decrease gene expression (Verdone et al., 2005).

A second epigenetic process that has particular implications for long-term changes in phenotype is DNA methylation (Turner, 2001; Razin, 1998). Within the DNA sequence, there are specific sites where a methyl group can attach to a cytosine nucleotide through an enzymatic reaction. The sites where this can occur reside primarily within the regulatory regions of a gene, in the promoter area upstream from the transcription start site. At a functional level, methylation prevents access of transcription factors and RNA polymerase to DNA resulting in silencing of the gene. In addition to the gene silencing that occurs in the presence of DNA methylation, these methyl groups attract other protein complexes which promote histone deacetylation, further inhibiting the likelihood of gene expression (Strathdee and Brown, 2002; Turner, 2001). Unlike histone acetylation, which is a relatively dynamic modification, the bond between the cytosine nucleotide and methyl group is very strong, resulting in a stable yet potentially reversible change in gene expression. DNA methylation patterns are maintained after cell division and thus passed from parent to daughter cells and it is through this form of epigenetic modification that cellular differentiation occurs (Turner, 2001; Taylor and Jones, 1985; Razin, 1998).

Previous studies have demonstrated that changes in DNA methylation can be environmentally induced (Waterland, 2006; Jaenisch and Bird, 2003; Anway et al., 2005), however the question we would like to address is whether the changes in gene expression that have been associated with postnatal mother–infant interactions are likewise associated with these epigenetic modifications. To address this question, initial research focused on

the differences in hippocampal glucocorticoid receptor mRNA observed in the offspring of High and Low LG dams (Weaver et al., 2004). Levels of hippocampal GR regulate the HPA response to stress though a negative feedback relationship with higher levels of GR mRNA associated with attenuated stress responsivity (Sapolsky et al., 1985; Jacobson and Sapolsky, 1991). Analysis of the level of DNA methylation within the GR 1_7 promoter region suggests that elevated levels of maternal LG are associated with decreased GR 1_7 methylation corresponding to the elevated levels of receptor expression observed in the hippocampus (Weaver et al., 2004). Site-specific analysis of the methylation pattern in this region indicates that the binding site for NGFI-A, a transcription factor induced by nerve growth factor, is differentially methylated in the offspring of High and Low LG dams and subsequent analysis indicated that the binding of NGFI-A to this region is reduced in hippocampal tissue taken from the offspring of Low LG dams (Weaver et al., 2004). A temporal analysis of the methylation of the GR 1_7 promoter indicates that differences between the offspring of High and Low emerge during the postpartum period and are sustained at weaning and into adulthood. Thus, the differences in gene expression and behavior that are observed in the adult offspring associated with the quality of maternal care received during the first week postpartum may be mediated by the long-term silencing of gene expression achieved through differential DNA methylation.

In addition to altering stress responsivity, maternal licking/grooming has consequences for the postpartum behavior of female offspring associated with levels of ERα gene expression in the MPOA (D. Francis et al., 1999; Champagne et al., 2003a,b). Temporal analysis of ERα in the MPOA indicates that differential levels of ERα mRNA are observed in infancy and maintained into adulthood suggesting a long-term suppression of gene expression in response to low levels of LG (Champagne et al., 2006). Analysis of MPOA levels of DNA methylation within the ERα promoter indicate that low levels of maternal LG are associated with high levels of ERα methylation whereas high levels of LG are associated with low levels of ERα methylation amongst female offspring (Champagne et al., 2006). This differential methylation occurs at multiple regions within the ERα promoter including a binding site for signal transducer and activator of transcription (STAT) protein Stat-5. Chromatin immunoprecipitation assay with Stat-5 antibody indicates that the high levels of ERα promoter methylation observed in the female offspring of Low LG dams results in less Stat-5 immunoreactivity indicating that differential methylation of the ERα has functional consequences for the binding of factors that normally enhance gene expression (Champagne et al., 2006; Frasor et al., 2001). Thus licking/grooming is associated with epigenetic effects in female offspring that mediate long-term changes in the expression of a gene involved in maternal behavior and as such mediates the transmission of maternal care across generations.

3. Pharmacological manipulations of the epigenome

The mediating role of epigenetic modifications in sustaining the differences in gene expression and behavior of High and Low LG offspring is supported by findings that these phenotypes can be altered through pharmacological manipulation of DNA methylation. ICV infusion of trichostatin-A (TSA), a histone deacetylase inhibitor that promotes demethylation, has been demonstrated to reverse the effects of low levels of maternal LG when administered to adult offspring (Weaver et al., 2006, 2004). Thus, the TSA-treated offspring of Low LG dams exhibit increased behavioral exploration, decreased levels of stress-induced corticosterone, and decreased hippocampal GR mRNA expression compared to vehicle-treated offspring of Low LG dams and are indistinguishable from that of the offspring of High LG dams (Weaver et al., 2006, 2004). This treatment has been found to specifically target the GR 1_7 promotor and decrease DNA methylation of this region. Conversely, central administration of methionine, a methyl donor that promotes methylation, to the adult offspring of High LG dams results in increased anxiety, increased corticosterone response to stress, decreased GR mRNA and decreased binding of NGFI-A to the hippocampal GR 1_7 promotor region (Weaver et al., 2005). Thus, by pharmacologically targetting low levels of GR 1_7 promotor methylation it is possible to shift the phenotype of the offspring of a High LG dam to resemble that of the offspring of a Low LG dam.

Evidence for the plasticity of the adult epigenome and phenotype in response to pharmacological intervention is certainly not limited to studies of mother–infant interactions. In rats, acute and chronic cocaine administration induces distinct patterns of histone modification at specific gene promoters within the striatum. Acute administration is associated with H4 acetylation and repeated administration associated with H3 acetylation (Kumar et al., 2005). Similar chromatin remodelling effects are observed in rat striatal neurons following dopamine-2-like-antagonist administration (Li et al., 2004). It has been proposed that such epigenetic modifications could therefore be underlying some of the long-term stable gene expression and behavioral changes observed in drug abusers (Colvis et al., 2005). Moreover, DNA methylation can be altered through increasing dietary intake of the methyl donor S-adenosyl methionine. Examination of the reelin gene, which produces a protein required for normal neuronal migration, axonal branching, synaptogenesis and cell signaling (Forster et al., 2006) in rats placed on a high-methionine diet indicates that this treatment results in hypermethylation at the reelin gene promoter, decreased reelin mRNA in the frontal cortex and deficits in social recognition and prepulse inhibition (Tremolizzo et al., 2002, 2005). Significantly, this hypermethylation can be prevented when rats were also treated with valproate which, like TSA enhances H3 acetylation and promotes demethylation (Tremolizzo et al., 2005). Finally, in mice with the 'viable yellow' A^{vy} agouti allele, increasing the levels of methionine in the maternal diet causes an increase in the methylation of the A^{vy} allele in the offspring leading to a shift from yellow to brown coat color (Wolff et al., 1998; Waterland, 2006; Waterland and Jirtle, 2003). Maternal gestational dietary intake of genistein, the major phytoestrogen in soy, also leads to an increase in the methylation of a retrotransposon upstream of the Agouti gene, causing the same shift in coat color (Dolinoy et al., 2006). Thus, changes in gene expression and phenotype can be induced in adulthood with pharmacological and dietary interventions that directly target the epigenome.

4. Signalling pathways from maternal care to DNA methylation

In the maternal rat, licking/grooming may serve as a critical source of tactile stimulation for the developing pup. The question is how this physical stimulation leads to epigenetic changes to specific genes within hippocampal and medial preoptic area cells that have been observed in offspring of High compared to Low LG dams. Pups provided with tactile stimulation in the form of stroking with a paintbrush or maternal LG both exhibit increases in hippocampal GR expression (Jutapakdeegul et al., 2003; Liu et al., 1997). *In vitro* studies suggest that these effects are mediated by increases in NGFI-A which is dependent on serotonergic activation of cAMP-coupled 5-HT_7 receptors (Meaney et al., 2000; Mitchell et al., 1992, 1990). Thus, the effects on GR expression of tactile stimulation provided by mothers can be mimicked by administration of a cAMP analogue and blocked by a 5-HT_7 receptor antagonist (Laplante et al., 2002). Recent evidence highlights the importance of NGFI-A as a downstream target of this pharmacological or behavioral treatment (Weaver et al., 2007). Hippocampal GR expression is not enhanced by 5-HT when an NGFI-A antisense

is co-administered and both cAMP and 5-HT have been found to alter the methylation status of the NGFI-A binding site within the GR 1_7 promoter region. Furthermore, though increasing levels of NGFI-A are associated with decreased methylation of the GR 1_7 promoter and thus increased GR expression, if the NGFI-A binding site within the GR 1_7 promoter is mutated, effects of NGFI-A are blocked. Though the exact role NGFI-A plays in the demethylation of the GR 1_7 promoter is not known, these findings suggest that through the stimulation of specific factors that bind within steroid receptor promoter regions, maternal care can lead to a cascade of events that alter offspring development and result in stable patterns of adult gene expression and behavior. This same principle of activation may be applicable to the relationship between Stat-5 interactions with the ERα promoter and estrogen receptor gene expression, however this particular cascade has not yet been investigated.

5. Implications of the study of epigenetics for psychiatry

Epigenetic modification in response to early environmental conditions provides an elegant mechanism to explain the effects of childhood adversity on increasing risk of psychopathology in adulthood. However, studying the role of epigenetic modifications in mediating these effects in humans is limited by several methodological constraints. Nevertheless, recent studies in humans suggest that similar epigenetic processes to those observed experimentally in the rat may play a significant role in shaping human behavioral plasticity.

One approach to studying environmentally induced epigenetic effects in humans is to compare monozygotic (MZ) twins. A recent study compared the gene expression of 3-year-old and 50-year-old MZ twins and found a 4-fold discordance amongst older twins which was associated with increasing differences in DNA methylation and histone H3 and H4 acetylation of genes in peripheral blood lymphocyte and other non-neural tissues (Fraga et al., 2005). One potential explanation of these findings is that epigenetic modification of the genome is induced through random stochastic accumulation or "epigenetic drift" (Martin, 2005). Epigenetic marks are inherited mitotically from mother to daughter cells (Zhou et al., 2005). Though these marks are stable over the long-term, studies *in vitro* using mammalian cells in tissue culture reveal that *de novo* methylation occurs in about 3–5% daughter cells per mitosis and methylation loss occurs in 0.1–3% daughter cells per mitosis (Pfeifer et al., 1990; Riggs et al., 1998). However, it is unlikely that the magnitude of difference in gene expression between 50-year-old MZ twins compared to 3-year-old MZ twins is entirely accounted for by random stochastic effects and thus may also be related to the degree of discordance in environmental variables between the twins. The significance of such epigenetic divergence has been investigated in other studies of MZ twins. Using restriction landmark genome scanning, genomic DNA extracted from leukocytes of male MZ twins discordant for schizophrenia was found to have significant differences between twins at NotI methylation sites (Tsujita et al., 1998). Using bisulfite mapping, differential methylation in the 5'-regulatory region of the dopamine D2 receptor gene (DRD2) in lymphocytes of MZ twins discordant for schizophrenia has also been reported (Petronis et al., 2003). Using fine detail methylation mapping technology on buccal cell samples, 5-year-old MZ twins have been shown to vary in the degree of discordance in methylation status at two CpG islands of the promoter region of the catechol-*O*-methyltransferase (COMT) gene. Some MZ twin pairs showed a high degree of discordance whereas others were very similar in their epigenetic status (Mill et al., 2006). This finding is intriguing given the implications of COMT and DRD2 in the risk of psychopathology due to their role in dopamine catabolism (Shifman et al., 2004), a risk that is enhanced when interacting with environmental variables such as drug use (Thapar et al., 2005; Caspi et al., 2005). Indeed, though most previous work has focused upon how different genetic polymorphisms of genes such as COMT and DRD2 may be associated with gene expression and psychopathology (Kukreti et al., 2006; Shifman et al., 2004; Bray et al., 2003), these recent epigenetic studies suggest that the accumulation of epigenetic variation in gene promoters through environmental or stochastic means may account for changes in brain development and risk of mental illness.

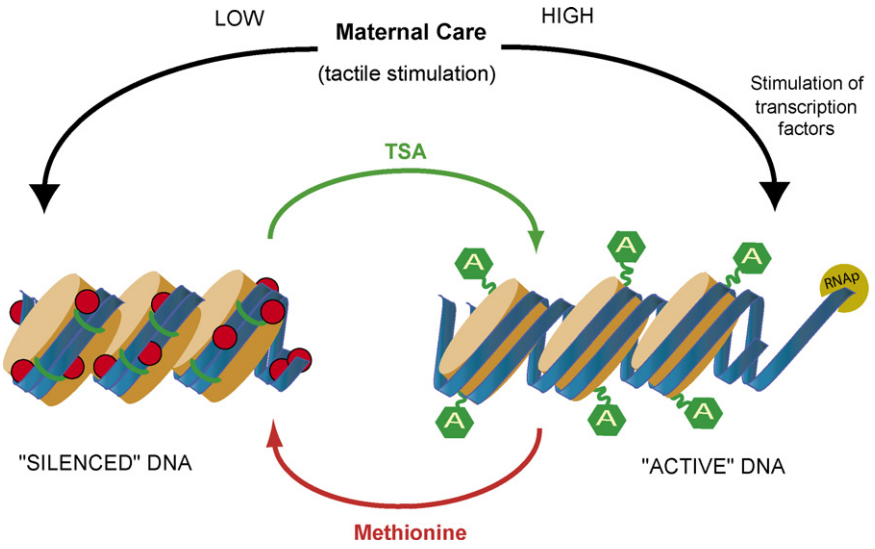

Fig. 1. *The epigenetic modification of DNA.* "Silenced" DNA is heavily methylated (red circles) with deacetylated histone tails (green bands). Thus the DNA (blue bands) is tightly bound to the histone proteins (brown cylinders) preventing transcription by RNA polymerase (RNAp). "Active" DNA is demethylated with acetylated histone tails (green 'A's) allowing transcription by RNA polymerase. The expression of genes can be adjusted by stochastic variation and environmental triggers such as maternal care, drugs, dietary factors and pharmacological agents. In the rat, high levels of tactile stimulation by dams leads to the long-term stable reduction in methylation of both GR and ERα gene promoters in the hippocampus and MPOA, respectively. This is believed to occur through the stimulation of transcription factors such as NGFI-A and Stat-5. Low levels of tactile stimulation by rat dams leads to the methylation and deacetylation of the same gene promoters. These environmentally induced epigenetic modifications can be partially reversed in adult animals through central administration of pharmacological agents such as the histone deacetylase inhibitor trichostatin A (TSA) and methyl donor methionine.

One limitation to studying the influence of epigenetic effects on human mental health is the general unavailability of brain tissue for analysis. Such material is critical when evaluating the molecular basis of long-term changes in brain development and behavior. Though there are data suggesting that the methylation status of some human gene promoters (e.g. COMT) are similar between blood and brain tissues (Murphy et al., 2005), findings from rodent studies suggest that epigenetic changes occur in a gene- and site-specific manner within the brain in response to variation in early experiences (Weaver et al., 2004, 2006; Champagne et al., 2006, 2003b). To examine epigenetic effects in the human central nervous system, researchers have been reliant on the availability of post-mortem tissue. Analysis of cortical tissue samples from bipolar and schizophrenic patients indicates a general hypermethylation compared to individuals with no history of mental illness (Veldic et al., 2005). In particular, this hypermethylation is of specific CpG islands flanking binding sites of the reelin gene promoter leading to a downregulation of reelin gene expression in various cortical regions (Abdolmaleky et al., 2005; Chen et al., 2002; Grayson et al., 2006, 2005). In contrast, hypomethylation of the COMT gene in the frontal lobe has been found in the post-mortem brain tissue from schizophrenia patients (Abdolmaleky et al., 2006). It is interesting to note that other reports suggest no evidence of altered COMT expression and methylation in the cerebellum of schizophrenia, bipolar and depressed patients compared to controls (Dempster et al., 2006), providing further evidence for the complexity and perhaps site-specificity of these differences in epigenetic regulation.

6. Concluding remarks

The long-term neurobiological consequences of early experiences have been explored extensively in animal models and suggest that epigenetic mechanisms may play a critical role in shaping stable individual differences in gene expression, physiology and behavior. In particular, these studies suggest that maternal care can have profound effects on offspring phenotype that is associated with molecular changes in the structure of DNA with consequences for the activity level of genes that are critical for regulating stress responsivity and maternal behavior (Fig. 1). Though these studies provide a framework for studying the effects of early environmental adversity in humans, there are several challenges to applying this type of approach including the ability to conduct longitudinal studies in which environmental influences can be assessed and the methodological constraints involved in analysis of epigenetic modification in human brain tissue. However, there is evidence from studies in both rodents and humans that the epigenome can be manipulated pharmacologically suggesting that the effects of early environment can be reversed in adulthood thus providing a potential therapeutic target that can be investigated in the context of human health and disease.

References

Abdolmaleky, H.M., Cheng, K.H., Faraone, S.V., Wilcox, M., Glatt, S.J., Gao, F., Smith, C.L., Shafa, R., Aeali, B., Carnevale, J., Pan, H., Papageorgis, P., Ponte, J.F., Sivaraman, V., Tsuang, M.T., Thiagalingam, S., 2006. Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Hum. Mol. Genet. 15, 3132–3145.

Abdolmaleky, H.M., Cheng, K.H., Russo, A., Smith, C.L., Faraone, S.V., Wilcox, M., Shafa, R., Glatt, S.J., Nguyen, G., Ponte, J.F., Thiagalingam, S., Tsuang, M.T., 2005. Hypermethylation of the reelin (RELN) promoter in the brain of schizophrenic patients: a preliminary report. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 134, 60–66.

Anda, R.F., Felitti, V.J., Bremner, J.D., Walker, J.D., Whitfield, C., Perry, B.D., Dube Sh, R., Giles, W.H., 2006. The enduring effects of abuse and related adverse experiences in childhood: a convergence of evidence from neurobiology and epidemiology. Eur. Arch. Psychiatry Clin. Neurosci. 256, 174–186.

Andrews, M.W., Rosenblum, L.A., 1991. Attachment in monkey infants raised in variable- and low-demand environments. Child Dev. 62, 686–693.

Andrews, M.W., Rosenblum, L.A., 1994. The development of affiliative and agonistic social patterns in differentially reared monkeys. Child Dev. 65, 1398–1404.

Anway, M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K., 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308, 1466–1469.

Arling, G.L., Harlow, H.F., 1967. Effects of social deprivation on maternal behavior of rhesus monkeys. J. Comp. Physiol. Psychol. 64, 371–377.

Batten, S.V., Aslan, M., Maciejewski, P.K., Mazure, C.M., 2004. Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. J. Clin. Psychiatry 65, 249–254.

Berman, C., 1990. Intergenerational transmission of maternal rejection rates among free-ranging rheus monkeys on Cayo Santiago. Anim. Behav. 44, 247–258.

Bray, N.J., Buckland, P.R., Williams, N.M., Williams, H.J., Norton, N., Owen, M.J., O'Donovan, M.C., 2003. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. Am. J. Hum. Genet. 73, 152–161.

Bredy, T.W., Brown, R.E., Meaney, M.J., 2007. Effect of resource availability on biparental care, and offspring neural and behavioral development in the California mouse (*Peromyscus californicus*). Eur. J. Neurosci. 25, 567–575.

Bredy, T.W., Grant, R.J., Champagne, D.L., Meaney, M.J., 2003. Maternal care influences neuronal survival in the hippocampus of the rat. Eur. J. Neurosci. 18, 2903–2909.

Caldji, C., Diorio, J., Meaney, M.J., 2000a. Variations in maternal care in infancy regulate the development of stress reactivity. Biol. Psychiatry 48, 1164–1174.

Caldji, C., Francis, D., Sharma, S., Plotsky, P.M., Meaney, M.J., 2000b. The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. Neuropsychopharmacology 22, 219–229.

Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., Craig, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol. Psychiatry 57, 1117–1127.

Champagne, F.A., Chretien, P., Stevenson, C.W., Zhang, T.Y., Gratton, A., Meaney, M.J., 2004. Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. J. Neurosci. 24, 4113–4123.

Champagne, F.A., Curley, J.P., 2005. How social experiences influence the brain. Curr. Opin. Neurobiol. 15, 704–709.

Champagne, F.A., Diorio, J., Sharma, S., Meaney, M.J., 2001. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proc. Natl. Acad. Sci. U.S.A. 98, 12736–12741.

Champagne, F.A., Francis, D.D., Mar, A., Meaney, M.J., 2003a. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. Physiol. Behav. 79, 359–371.

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-alpha1b promoter and estrogen receptor-alpha 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., 2003b. Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area. Endocrinology 144, 4720–4724.

Chen, Y., Sharma, R.P., Costa, R.H., Costa, E., Grayson, D.R., 2002. On the epigenetic regulation of the human reelin promoter. Nucleic Acids Res. 30, 2930–2939.

Chugani, H.T., Behen, M.E., Muzik, O., Juhasz, C., Nagy, F., Chugani, D.C., 2001. Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. Neuroimage 14, 1290–1301.

Colvis, C.M., Pollock, J.D., Goodman, R.H., Impey, S., Dunn, J., Mandel, G., Champagne, F.A., Mayford, M., Korzus, E., Kumar, A., Renthal, W., Theobald, D.E., Nestler, E.J., 2005. Epigenetic mechanisms and gene networks in the nervous system. J. Neurosci. 25, 10379–10389.

Coplan, J.D., Altemus, M., Mathew, S.J., Smith, E.L., Sharf, B., Coplan, P.M., Kral, J.G., Gorman, J.M., Owens, M.J., Nemeroff, C.B., Rosenblum, L.A., 2005. Synchronized maternal-infant elevations of primate CSF CRF concentrations in response to variable foraging demand. CNS Spectr. 10, 530–536.

Coplan, J.D., Smith, E.L., Altemus, M., Scharf, B.A., Owens, M.J., Nemeroff, C.B., Gorman, J.M., Rosenblum, L.A., 2001. Variable foraging demand rearing: sustained elevations in cisternal cerebrospinal fluid corticotropin-releasing factor concentrations in adult primates. Biol. Psychiatry 50, 200–204.

Coplan, J.D., Smith, E.L., Trost, R.C., Scharf, B.A., Altemus, M., Bjornson, L., Owens, M.J., Gorman, J.M., Nemeroff, C.B., Rosenblum, L.A., 2000. Growth hormone response to clonidine in adversely reared young adult primates: relationship to serial cerebrospinal fluid corticotropin-releasing factor concentrations. Psychiatry Res. 95, 93–102.

Coplan, J.D., Trost, R.C., Owens, M.J., Cooper, T.B., Gorman, J.M., Nemeroff, C.B., Rosenblum, L.A., 1998. Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. Arch. Gen. Psychiatry 55, 473–477.

Dempster, E.L., Mill, J., Craig, I.W., Collier, D.A., 2006. The quantification of COMT mRNA in post mortem cerebellum tissue: diagnosis, genotype, methylation and expression. BMC Med. Genet. 7, 10.

Dolinoy, D.C., Weidman, J.R., Waterland, R.A., Jirtle, R.L., 2006. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environ. Health Perspect. 114, 567–572.
Dube, S.R., Felitti, V.J., Dong, M., Chapman, D.P., Giles, W.H., Anda, R.F., 2003. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. Pediatrics 111, 564–572.
Fahlke, C., Lorenz, J.G., Long, J., Champoux, M., Suomi, S.J., Higley, J.D., 2000. Rearing experiences and stress-induced plasma cortisol as early risk factors for excessive alcohol consumption in nonhuman primates. Alcohol. Clin. Exp. Res. 24, 644–650.
Fairbanks, L.A., 1989. Early experience and cross-generational continuity of mother–infant contact in vervet monkeys. Dev. Psychobiol. 22, 669–681.
Fairbanks, L.A., McGuire, M.T., 1988. Long-term effects of early mothering behavior on responsiveness to the environment in vervet monkeys. Dev. Psychobiol. 21, 711–724.
Fleming, A.S., Kraemer, G.W., Gonzalez, A., Lovic, V., Rees, S., Melo, A., 2002. Mothering begets mothering: the transmission of behavior and its neurobiology across generations. Pharmacol. Biochem. Behav. 73, 61–75.
Fleming, A.S., Steiner, M., Corter, C., 1997. Cortisol, hedonics, and maternal responsiveness in human mothers. Horm. Behav. 32, 85–98.
Forster, E., Jossin, Y., Zhao, S., Chai, X., Frotscher, M., Goffinet, A.M., 2006. Recent progress in understanding the role of Reelin in radial neuronal migration, with specific emphasis on the dentate gyrus. Eur. J. Neurosci. 23, 901–909.
Fraga, M.F., Ballestar, E., Paz, M.F., Ropero, S., Setien, F., Ballestar, M.L., Heine-Suner, D., Cigudosa, J.C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aguilera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T.D., Wu, Y.Z., Plass, C., Esteller, M., 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proc. Natl. Acad. Sci. U.S.A. 102, 10604–10609.
Francis, 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., Caldji, C., Champagne, F., Plotsky, P.M., Meaney, M.J., 1999. The role of corticotropin-releasing factor–norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol. Psychiatry 46, 1153–1166.
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. J. Neuroendocrinol. 12, 1145–1148.
Francis, D.D., Szegda, K., Campbell, G., Martin, W.D., Insel, T.R., 2003. Epigenetic sources of behavioral differences in mice. Nat. Neurosci. 6, 445–446.
Frasor, J., Park, K., Byers, M., Telleria, C., Kitamura, T., Yu-Lee, L.Y., Djiane, J., Park-Sarge, O.K., Gibori, G., 2001. Differential roles for signal transducers and activators of transcription 5a and 5b in PRL stimulation of ERalpha and ERbeta transcription. Mol. Endocrinol. 15, 2172–2181.
Gonzalez, A., Fleming, A.S., 2002. Artificial rearing causes changes in maternal behavior and c-fos expression in juvenile female rats. Behav. Neurosci. 116, 999–1013.
Gonzalez, A., Lovic, V., Ward, G.R., Wainwright, P.E., Fleming, A.S., 2001. Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats. Dev. Psychobiol. 38, 11–32.
Goodwin, R.D., Stein, M.B., 2004. Association between childhood trauma and physical disorders among adults in the United States. Psychol. Med. 34, 509–520.
Grayson, D.R., Chen, Y., Costa, E., Dong, E., Guidotti, A., Kundakovic, M., Sharma, R.P., 2006. The human reelin gene: transcription factors (+), repressors (−) and the methylation switch (+/−) in schizophrenia. Pharmacol. Ther..
Grayson, D.R., Jia, X., Chen, Y., Sharma, R.P., Mitchell, C.P., Guidotti, A., Costa, E., 2005. Reelin promoter hypermethylation in schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 102, 9341–9346.
Gunnar, M.R., Fisher, P.A., 2006. Bringing basic research on early experience and stress neurobiology to bear on preventive interventions for neglected and maltreated children. Dev. Psychopathol. 18, 651–677.
Gunnar, M.R., Morison, S.J., Chisholm, K., Schuder, M., 2001. Salivary cortisol levels in children adopted from romanian orphanages. Dev. Psychopathol. 13, 611–628.
Harlow, H.F., Suomi, S.J., 1971. Social recovery by isolation-reared monkeys. Proc. Natl. Acad. Sci. U.S.A. 68, 1534–1538.
Harlow, H.F., Suomi, S.J., 1974. Induced depression in monkeys. Behav. Biol. 12, 273–296.
Ichise, M., Vines, D.C., Gura, T., Anderson, G.M., Suomi, S.J., Higley, J.D., Innis, R.B., 2006. Effects of early life stress on [11C]DASB positron emission tomography imaging of serotonin transporters in adolescent peer- and mother-reared rhesus monkeys. J. Neurosci. 26, 4638–4643.
Jacobson, L., Sapolsky, R., 1991. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr. Rev. 12, 118–134.
Jaenisch, R., Bird, A., 2003. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat. Genet. 33 (Suppl.), 245–254.
Jutapakdeegul, N., Casalotti, S.O., Govitrapong, P., Kotchabhakdi, N., 2003. Postnatal touch stimulation acutely alters corticosterone levels and glucocorticoid receptor gene expression in the neonatal rat. Dev. Neurosci. 25, 26–33.
Kaler, S.R., Freeman, B.J., 1994. Analysis of environmental deprivation: cognitive and social development in Romanian orphans. J. Child Psychol. Psychiatry 35, 769–781.
Kukreti, R., Tripathi, S., Bhatnagar, P., Gupta, S., Chauhan, C., Kubendran, S., Janardhan Reddy, Y.C., Jain, S., Brahmachari, S.K., 2006. Association of DRD2 gene variant with schizophrenia. Neurosci. Lett. 392, 68–71.
Kumar, A., Choi, K.H., Renthal, W., Tsankova, N.M., Theobald, D.E., Truong, H.T., Russo, S.J., Laplant, Q., Sasaki, T.S., Whistler, K.N., Neve, R.L., Self, D.W., Nestler, E.J., 2005. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron 48, 303–314.
Laplante, P., Diorio, J., Meaney, M.J., 2002. Serotonin regulates hippocampal glucocorticoid receptor expression via a 5-HT7 receptor. Brain Res. Dev. Brain Res. 139, 199–203.
Lehmann, J., Feldon, J., 2000. Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing? Rev. Neurosci. 11, 383–408.
Lehmann, J., Pryce, C.R., Bettschen, D., Feldon, J., 1999. The maternal separation paradigm and adult emotionality and cognition in male and female Wistar rats. Pharmacol. Biochem. Behav. 64, 705–715.
Lehmann, J., Pryce, C.R., Jongen-Relo, A.L., Stohr, T., Pothuizen, H.H., Feldon, J., 2002. Comparison of maternal separation and early handling in terms of their neurobehavioral effects in aged rats. Neurobiol. Aging 23, 457–466.
Li, J., Guo, Y., Schroeder, F.A., Youngs, R.M., Schmidt, T.W., Ferris, C., Konradi, C., Akbarian, S., 2004. Dopamine D2-like antagonists induce chromatin remodeling in striatal neurons through cyclic AMP-protein kinase A and NMDA receptor signaling. J. Neurochem. 90, 1117–1131.
Liu, D., Diorio, J., Day, J.C., Francis, D.D., Meaney, M.J., 2000. Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat. Neurosci. 3, 799–806.
Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., Pearson, D., Plotsky, P.M., Meaney, M.J., 1997. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 277, 1659–1662.
Lovic, V., Fleming, A.S., 2004. Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional set shifting task–reversal of effects with maternal-like licking stimulation. Behav. Brain Res. 148, 209–219.
Macri, S., Wurbel, H., 2006. Developmental plasticity of HPA and fear responses in rats: a critical review of the maternal mediation hypothesis. Horm. Behav. 50, 667–680.
Maestripieri, D., 2005. Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. Proc. Natl. Acad. Sci. U.S.A. 102, 9726–9729.
Maestripieri, D., Lindell, S.G., Ayala, A., Gold, P.W., Higley, J.D., 2005. Neurobiological characteristics of rhesus macaque abusive mothers and their relation to social and maternal behavior. Neurosci. Biobehav. Rev. 29, 51–57.
Maestripieri, D., McCormack, K., Lindell, S.G., Higley, J.D., Sanchez, M.M., 2006. Influence of parenting style on the offspring's behaviour and CSF monoamine metabolite levels in crossfostered and noncrossfostered female rhesus macaques. Behav. Brain Res. 175, 90–95.
Maestripieri, D., Tomaszycki, M., Carroll, K.A., 1999. Consistency and change in the behavior of rhesus macaque abusive mothers with successive infants. Dev. Psychobiol. 34, 29–35.
Maestripieri, D., Wallen, K., Carroll, K.A., 1997. Infant abuse runs in families of group-living pigtail macaques. Child Abuse Negl. 21, 465–471.
Martin, G.M., 2005. Epigenetic drift in aging identical twins. Proc. Natl. Acad. Sci. U.S.A. 102, 10413–10414.
Meaney, M.J., 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu. Rev. Neurosci. 24, 1161–1192.
Meaney, M.J., Diorio, J., Francis, D., Weaver, S., Yau, J., Chapman, K., Seckl, J.R., 2000. Postnatal handling increases the expression of cAMP-inducible transcription factors in the rat hippocampus: the effects of thyroid hormones and serotonin. J. Neurosci. 20, 3926–3935.
Meaney, M.J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., Sharma, S., Seckl, J.R., Plotsky, P.M., 1996. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. Dev. Neurosci. 18, 49–72.
Mill, J., Dempster, E., Caspi, A., Williams, B., Moffitt, T., Craig, I., 2006. Evidence for monozygotic twin (MZ) discordance in methylation level at two CpG sites in the promoter region of the catechol-O-methyltransferase (COMT) gene. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 141, 421–425.
Mitchell, J.B., Betito, K., Rowe, W., Boksa, P., Meaney, M.J., 1992. Serotonergic regulation of type II corticosteroid receptor binding in hippocampal cell cultures: evidence for the importance of serotonin-induced changes in cAMP levels. Neuroscience 48, 631–639.
Mitchell, J.B., Rowe, W., Boksa, P., Meaney, M.J., 1990. Serotonin regulates type II corticosteroid receptor binding in hippocampal cell cultures. J. Neurosci. 10, 1745–1752.
Murphy, B.C., O'Reilly, R.L., Singh, S.M., 2005. Site-specific cytosine methylation in S-COMT promoter in 31 brain regions with implications for studies involving schizophrenia. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 133, 37–42.
Myers, M.M., Brunelli, S.A., Shair, H.N., Squire, J.M., Hofer, M.A., 1989a. Relationships between maternal behavior of SHR and WKY dams and adult blood pressures of cross-fostered F1 pups. Dev. Psychobiol. 22, 55–67.
Myers, M.M., Brunelli, S.A., Squire, J.M., Shindeldecker, R.D., Hofer, M.A., 1989b. Maternal behavior of SHR rats and its relationship to offspring blood pressures. Dev. Psychobiol. 22, 29–53.
Novakov, M., Fleming, A.S., 2005. The effects of early rearing environment on the hormonal induction of maternal behavior in virgin rats. Horm. Behav. 48, 528–536.

Petronis, A., Gottesman, I.I., Kan, P., Kennedy, J.L., Basile, V.S., Paterson, A.D., Popendikyte, V., 2003. Monozygotic twins exhibit numerous epigenetic differences: clues to twin discordance? Schizophr. Bull. 29, 169–178.
Pfeifer, G.P., Steigerwald, S.D., Hansen, R.S., Gartler, S.M., Riggs, A.D., 1990. Polymerase chain reaction-aided genomic sequencing of an X chromosome-linked CpG island: methylation patterns suggest clonal inheritance, CpG site autonomy, and an explanation of activity state stability. Proc. Natl. Acad. Sci. U.S.A. 87, 8252–8256.
Phillips, N.K., Hammen, C.L., Brennan, P.A., Najman, J.M., Bor, W., 2005. Early adversity and the prospective prediction of depressive and anxiety disorders in adolescents. J. Abnorm. Child Psychol. 33, 13–24.
Plotsky, P.M., Meaney, M.J., 1993. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain Res. Mol. Brain Res. 18, 195–200.
Plotsky, P.M., Thrivikraman, K.V., Nemeroff, C.B., Caldji, C., Sharma, S., Meaney, M.J., 2005. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology 30, 2192–2204.
Priebe, K., Romeo, R.D., Francis, D.D., Sisti, H.M., Mueller, A., McEwen, B.S., Brake, W.G., 2005. Maternal influences on adult stress and anxiety-like behavior in C57BL/6J and BALB/cJ mice: a cross-fostering study. Dev. Psychobiol. 47, 398–407.
Pryce, C.R., Feldon, J., 2003. Long-term neurobehavioural impact of the postnatal environment in rats: manipulations, effects and mediating mechanisms. Neurosci. Biobehav. Rev. 27, 57–71.
Razin, A., 1998. CpG methylation, chromatin structure and gene silencing-a three-way connection. EMBO. J. 17, 4905–4908.
Read, J., van Os, J., Morrison, A.P., Ross, C.A., 2005. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr. Scand. 112, 330–350.
Riggs, A.D., Xiong, Z., Wang, L., LeBon, J.M., 1998. Methylation dynamics, epigenetic fidelity and X chromosome structure. Novartis. Found Symp. 214, 214–225 (discussion 225–232).
Rosenblum, L.A., Forger, C., Noland, S., Trost, R.C., Coplan, J.D., 2001. Response of adolescent bonnet macaques to an acute fear stimulus as a function of early rearing conditions. Dev. Psychobiol. 39, 40–45.
Rosenblum, L.A., Paully, G.S., 1984. The effects of varying environmental demands on maternal and infant behavior. Child Dev. 55, 305–314.
Rosenfeld, P., Wetmore, J.B., Levine, S., 1992. Effects of repeated maternal separations on the adrenocortical response to stress of preweanling rats. Physiol. Behav. 52, 787–791.
Roy, P., Rutter, M., Pickles, A., 2004. Institutional care: associations between overactivity and lack of selectivity in social relationships. J. Child Psychol. Psychiatry 45, 866–873.
Rutter, M., Kim-Cohen, J., Maughan, B., 2006. Continuities and discontinuities in psychopathology between childhood and adult life. J. Child Psychol. Psychiatry 47, 276–295.
Sapolsky, R.M., Meaney, M.J., McEwen, B.S., 1985. The development of the glucocorticoid receptor system in the rat limbic brain. III. Negative-feedback regulation. Brain Res. 350, 169–173.
Seay, B., Alexander, B.K., Harlow, H.F., 1964. Maternal behavior of socially deprived Rhesus monkeys. J. Abnorm. Psychol. 69, 345–354.
Seay, B., Harlow, H.F., 1965. Maternal separation in the rhesus monkey. J. Nerv. Ment. Dis. 140, 434–441.
Shannon, C., Champoux, M., Suomi, S.J., 1998. Rearing condition and plasma cortisol in rhesus monkey infants. Am. J. Primatol. 46, 311–321.
Shannon, C., Schwandt, M.L., Champoux, M., Shoaf, S.E., Suomi, S.J., Linnoila, M., Higley, J.D., 2005. Maternal absence and stability of individual differences in CSF 5-HIAA concentrations in rhesus monkey infants. Am. J. Psychiatry 162, 1658–1664.
Shifman, S., Bronstein, M., Sternfeld, M., Pisante, A., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R.D., Swartz-Vanetik, M., Knobler, H.Y., Shinar, E., Yakir, B., Zak, N.B., Darvasi, A., 2004. COMT: a common susceptibility gene in bipolar disorder and schizophrenia. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 128, 61–64.
Shoji, H., Kato, K., 2006. Maternal behavior of primiparous females in inbred strains of mice: a detailed descriptive analysis. Physiol. Behav. 89, 320–328.
Strathdee, G., Brown, R., 2002. Aberrant DNA methylation in cancer: potential clinical interventions. Expert. Rev. Mol. Med. 2002, 1–17.
Suomi, S.J., Harlow, H.F., Kimball, S.D., 1971. Behavioral effects of prolonged partial social isolation in the rhesus monkey. Psychol. Rep. 29, 1171–1177.
Tarullo, A.R., Gunnar, M.R., 2006. Child maltreatment and the developing HPA axis. Horm. Behav. 50, 632–639.
Taylor, S.M., Jones, P.A., 1985. Cellular differentiation. Int. J. Obes. 9 (Suppl. 1), 15–21.
Teicher, M.H., Tomoda, A., Andersen, S.L., 2006. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Ann. NY Acad. Sci. 1071, 313–323.
Thapar, A., Langley, K., Fowler, T., Rice, F., Turic, D., Whittinger, N., Aggleton, J., Van den Bree, M., Owen, M., O'Donovan, M., 2005. Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. Arch. Gen. Psychiatry 62, 1275–1278.
Tremolizzo, L., Carboni, G., Ruzicka, W.B., Mitchell, C.P., Sugaya, I., Tueting, P., Sharma, R., Grayson, D.R., Costa, E., Guidotti, A., 2002. An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability. Proc. Natl. Acad. Sci. U.S.A. 99, 17095–17100.
Tremolizzo, L., Doueiri, M.S., Dong, E., Grayson, D.R., Davis, J., Pinna, G., Tueting, P., Rodriguez-Menendez, V., Costa, E., Guidotti, A., 2005. Valproate corrects the schizophrenia-like epigenetic behavioral modifications induced by methionine in mice. Biol. Psychiatry 57, 500–509.
Tsujita, T., Niikawa, N., Yamashita, H., Imamura, A., Hamada, A., Nakane, Y., Okazaki, Y., 1998. Genomic discordance between monozygotic twins discordant for schizophrenia. Am. J. Psychiatry 155, 422–424.
Turner, B., 2001. Chromatin and Gene Regulation. Blackwell Science Ltd., Oxford.
Veldic, M., Guidotti, A., Maloku, E., Davis, J.M., Costa, E., 2005. In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. Proc. Natl. Acad. Sci. U.S.A. 102, 2152–2157.
Verdone, L., Caserta, M., Di Mauro, E., 2005. Role of histone acetylation in the control of gene expression. Biochem. Cell Biol. 83, 344–353.
Waterland, R.A., 2006. Assessing the effects of high methionine intake on DNA methylation. J. Nutr. 136, 1706S–1710S.
Waterland, R.A., Jirtle, R.L., 2003. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol. Cell Biol. 23, 5293–5300.
Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854.
Weaver, I.C., Champagne, F.A., Brown, S.E., Dymov, S., Sharma, S., Meaney, M.J., Szyf, M., 2005. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J. Neurosci. 25, 11045–11054.
Weaver, I.C., D'Alessio, A.C., Brown, S.E., Hellstrom, I.C., Dymov, S., Sharma, S., Szyf, M., Meaney, M.J., 2007. The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. J. Neurosci. 27, 1756–1768.
Weaver, I.C., Grant, R.J., Meaney, M.J., 2002. Maternal behavior regulates long-term hippocampal expression of BAX and apoptosis in the offspring. J. Neurochem. 82, 998–1002.
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. Proc. Natl. Acad. Sci. U.S.A. 103, 3480–3485.
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. J. 12, 949–957.
Zhang, T.Y., Chretien, P., Meaney, M.J., Gratton, A., 2005. Influence of naturally occurring variations in maternal care on prepulse inhibition of acoustic startle and the medial prefrontal cortical dopamine response to stress in adult rats. J. Neurosci. 25, 1493–1502.
Zhou, G.L., Xin, L., Liu, D.P., Liang, C.C., 2005. Remembering the cell fate during cellular differentiation. J. Cell Biochem. 96, 962–970.