Epigenetics and the Environmental Regulation of the Genome and Its Function

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Abstract

There are numerous examples in psychology and other disciplines of the enduring effects of early experience on neural function. In this article, we review the emerging evidence for epigenetics as a candidate mechanism for these effects. Epigenetics refers to functionally relevant modifications to the genome that do not involve a change in nucleotide sequence. Such modifications include chemical marks that regulate the transcription of the genome. There is now evidence that environmental events can directly modify the epigenetic state of the genome. Thus studies with rodent models suggest that during both early development and in adult life, environmental signals can activate intracellular pathways that directly remodel the "epigenome," leading to changes in gene expression and neural function. These studies define a biological basis for the interplay between environmental signals and the genome in the regulation of individual differences in behavior, cognition, and physiology.

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INTRODUCTION

Psychology has seen a major transition in personality theory. Personality traits were once thought to emerge under the dominion of influences associated with "nurture." The postnatal family environment was considered as the primary candidate force in the development of individual differences in personality. This perspective changed dramatically in response to integration of the biological sciences into personality psychology. First, evolutionary approaches established the idea that the brain and its development, like any other organ, are subject to evolutionary forces. Second, behavioral genetics (Ebstein 2006, Kendler 2001, Plomin & Rutter 1998) provided evidence for a relation between variation at the level of the genome and that in personality and mental health. Although efforts to quantify the independent contribution of genetic and environmental influences are fraught with complications (e.g., gene–environment interactions, nongenomic mechanisms of inheritance), measures of concordance in specific traits between monozygotic and dizygotic twins, among other approaches, suggest a pervasive influence of genetic variation. Indeed, it is impossible to imagine that the function of brain cells could occur independent of variations in the genes that encode for proteins that regulate neuronal functions.

Genomic variation at the level of nucleotide sequence is associated with individual differences in personality and thus with vulnerability and resistance to a wide range of chronic illness (Ebstein 2006, Meyer-Lindenberg & Weinberger 2006, Rutter 2007). Such variations can take multiple forms, including variation at the level of (*a*) a single nucleotide (i.e., single-nucleotide polymorphisms or SNPs), (*b*) variation in the number of nucleotide repeats (i.e., variable number of tandem repeats or VNTRs), or (*c*) chromosomal reorganization. Each form of variation can potentially alter genomic function and thus phenotype. The challenge for psychology is that of conceptually integrating findings from genetics into the study of personality and our understanding of the pathophysiology of mental illness. How and under what conditions does genomic variation influence brain development and function? How might relevant findings from the field of genetics influence the design of public policy and therapies in psychology?

It is important to note the simple fact that genes encode for protein, not function. Thus, as described below, the effects of genetic variation are contextually determined and best considered as probabilistic. Cellular function can only be understood in terms of the constant dialogue that occurs between the genome and its environment. The environment regulates the cellular signals that control the operation of the genome. The objective of this review is to describe recent advances in molecular biology, notably in the field of epigenetics, and to suggest that epigenetic mechanisms are an ideal candidate mechanism for the effects of environmental signals, including events such

Phenotype: any observable characteristic or trait of an organism, such as its morphology, development, biochemical or physiological properties, or behavior

as social interactions, on the structure and function of the genome (Harper 2005). The intent is to first consider the processes by which cellular signals, referred to as transcription factors, regulate the activity (or expression) of a gene. The biological primacy of gene–environment interactions is apparent from the simple realization that the levels and the activity of these transcription factors is controlled by environmental signals. Thus the operation of the genome is dependent upon context. The question concerns the mechanisms responsible for such contextual influences. We suggest that epigenetics is one such process and can account, in part, for instances in which environmental events occurring at any time over the lifespan exert a sustained effect on genomic function and phenotype.

Epigenetics signals refer to a series of chemical modifications to the DNA or to regions surrounding the DNA. The transcriptional activity of the genome is regulated by signals, transcription factors, that physically bind to specific DNA sites. The importance of epigenetics mechanisms lies in the ability to regulate the ease with which transcription factors can access the DNA. Epigenetic signals can thus determine the capacity for environmental regulation of the genome. There is emerging evidence for the idea that epigenetic marks are directly altered in early life by environmental events and thus influence the development of individual differences in specific neural functions that underlie cognition and emotion. More recent studies suggest that dynamic alterations in these same epigenetic signals are crucial for the synaptic remodeling that mediates learning and memory. Thus, epigenetics provides a remarkable insight into the biology that governs the function of the genome in response to environmental signals.

GENE TRANSCRIPTION

The most compelling evidence for the predominance of gene–environment interactions in cellular function emerges from the study of gene transcription [Gilbert (2006) provides a very clear and well-illustrated description]. The transcription of the genome is a highly regulated event. At the heart of this process lies a class of proteins referred to as transcription factors. As the name implies, these proteins have the ability to bind to regulatory elements of the gene and to activate or repress gene transcription. Importantly, the expression and activation of the transcription factors themselves are dynamically regulated by environmental signals. Many of the earliest cellular responses to environmental stimuli involve either the activation of pre-existing transcriptional signals through chemical modifications such as phosphorylation (i.e., the addition of a phosphate) of specific amino acids of the protein, or an increase in gene expression that results in the rapid synthesis of proteins (e.g., immediate early gene products) that then serve to regulate the activity of other genes. This includes genes that are involved in synaptic plasticity. The binding of transcription factors to DNA sites is the biological machinery for the dynamic gene–environment interactions that result in altered rates of gene transcription.

Figure 1 portrays the organization of the glucocorticoid receptor gene as an example of genomic organization and a target for discussion below. The schema is actually somewhat misleading. For reasons of graphic simplicity, we often describe the organization of a gene or the interactions between transcription factors and DNA as if the DNA were a linear molecule to which transcription factors gain unimpeded access. The reality of protein–DNA interactions is very different. **Figure 2** presents the classic crystallographic analysis of the organization of DNA (Luger et al. 1997). DNA is organized into units referred to as nucleosomes, each of which contains about 145–150 base pairs wrapped around a core region of histone proteins (Turner 2001). The histones and DNA together are referred to as chromatin; the nucleosome is the organization of chromatin. Under normal conditions there is a tight physical relation between the histone proteins and its accompanying DNA, resulting in a rather closed nucleosome configuration.

Gene transcription: the synthesis of RNA under the direction of DNA. RNA synthesis is the process of transcribing DNA nucleotide sequence information into RNA sequence information

Receptor: a protein embedded in either the plasma membrane or cytoplasm of a cell to which a mobile signaling molecule (ligand) may bind. The signaling molecule can be a peptide, a hormone, a pharmaceutical drug, or a toxin, and when such binding occurs, the receptor goes into a conformational change that ordinarily initiates a cellular response

Chromatin: the combination of DNA, RNA, and protein that makes up chromosomes. The major components of chromatin are DNA and histone proteins

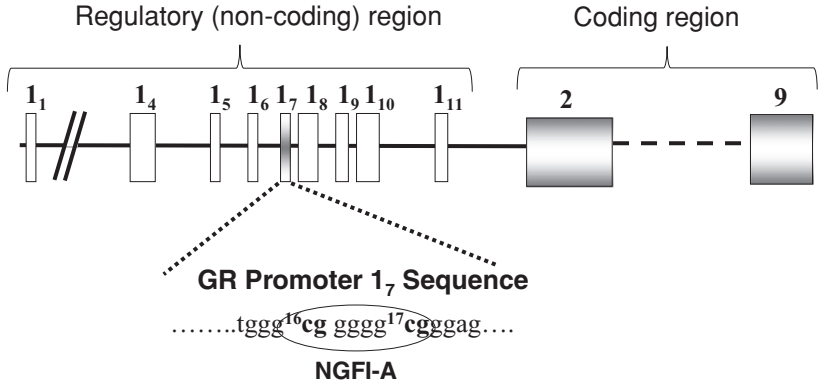

Figure 1

A schema describing the organization of the rat glucocorticoid receptor gene including 9 exon regions. Exons 2–9 participate in the coding for the glucocorticoid receptor protein. Exon 1 is composed of multiple regulatory regions, each of which is capable of activating gene transcription (i.e., promoter sequences). The activity of the various exon 1 promoters is tissue-specific, with evidence suggesting that certain promoters are more active in areas such as liver or thymus, and others are more active in brain (e.g., exon 1_7; based on McCormick et al. 2000; see Turner & Muller 2005 for comparable data in humans). The use of multiple promoters permits regulation in one tissue independently from other regions (i.e., increased glucocorticoid receptor in pulmonary tissues prior to birth that is necessary for respiratory competency at parturition, while maintaining reduced glucocorticoid receptor levels in brain, where glucocorticoid effects might inhibit neurogenesis). The consensus binding site for nerve growth factor–inducible factor A (NGFI-A) lying within the exon 1_7 promoter is highlighted. The reader should note that this organization is not necessarily typical. Regulatory elements (promoters or enhancers) can exist between exons (i.e., within introns) or at sites that are either 5′ or 3′ to the coding region, sometimes at considerable distances.

This restrictive configuration is maintained, in part, by electrostatic bonds between the positively charged histones and the negatively charged DNA. The closed configuration impedes transcription factor binding and is associated with a reduced level of gene expression. An increase in transcription factor binding to DNA and the subsequent activation of gene expression commonly requires chemical modification of the chromatin that occurs on the histone proteins. The primary targets for such events are the amino acids that form the histone tails extending from the nucleosome (**Figure 2**). These modifications alter chromatin in a manner that either increases or decreases the ability of transcription factors to access regulatory sites on the DNA that control gene transcription.

Chromatin Modifications

The dynamic alteration of chromatin structure is achieved through modifications to the histone proteins at the amino acids that form the histone protein tails that extend out from the nucleosome (**Figure 2**). These modifications are achieved through a series of enzymes that bind to the histone tails and modify the local chemical properties of specific amino acids (Grunstein 1997, Hake & Allis 2006, Jenuwein & Allis 2001). For example, the enzyme histone acetyltransferase transfers an acetyl group onto specific lysines on the histone tails. The addition of the acetyl group diminishes the positive charge, loosening the relation between the histones and DNA, opening the chromatin and improving the ability of transcription factors to access DNA sites. Thus, histone acetylation at specific lysine sites is commonly associated with active gene transcription.

The functional antagonists of the histone acetyltransferases are a class of enzymes known as histone deacetylases (HDACs). These enzymes remove acetyl groups and prevent further acetylation, thus maintaining a closed

Enzyme: a molecule, usually protein, that catalyzes (i.e., increases the rate of) a specific chemical reaction

Histone deacetylases (HDACs): a class of enzymes that remove acetyl groups from an ε-N-acetyl lysine amino acid on a histone. The action of HDACs is thus the opposite to that of histone acetyltransferases, and HDACs are associated with transcriptional silencing

chromatin structure, decreasing transcription factor and gene expression. Both the acetylation and deacetylation of histones are dynamic processes that are regulated by environmental signals. Indeed, a number of proteins that were known to be associated with transcriptional activation (e.g., transcriptional cofactors) have been identified as histone acetyltransferases. These factors enhance the efficacy of transcription factors by opening chromatin and thus increasing the binding of the factor to the regulatory regions of the gene.

The reader should note that there are actually multiple modifications to histone tails, including methylation (in this case on the histones), phosphorylation, and ubiquitination. For the sake of simplicity, the discussion is limited to histone acetylation/deacetylation.

Regulation of Glucocorticoid Receptor Expression

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) regulates glucocorticoid receptor gene transcription in hippocampal neurons (**Figure 3**; Mitchell et al. 1990, 1992; Weaver et al. 2007). This effect is dependent upon the binding of the transcription factor nerve growth factor–inducible factor A (NGFI-A) to a specific binding site on the exon 1_7 glucocorticoid (GR) promoter (**Figure 1**). The importance of this interaction can be precisely defined. For example, mutating a single nucleotide, in this case simply exchanging a cytosine for an adenine, in the region of the promoter that normally binds NGFI-A abolishes the ability of NGFI-A to associate with the exon 1_7 promoter and eliminates the effect of NGFI-A on gene transcription (Weaver et al. 2007). However, the ability of NGFI-A to bind to the exon 1_7 promoter is regulated by another protein, a transcriptional cofactor, the CREB-binding protein, that is activated by the same 5-HT-cyclic adenosine monophosphate (cAMP)/cyclic nucleotide–dependent kinases (PKA)-signaling cascade that results in the increased levels of NGFI-A (**Figure 3**). The CREB-binding protein is a histone acetyltransferase. The association of the CREB-binding protein with the exon 1_7 promoter is accompanied by an increase in the acetylation of a specific lysine on the tail of histone 3 of the exon 1_7 promoter (Weaver et al. 2004, 2007). Thus, 5-HT activates both NGFI-A and the CREB-binding protein. Interestingly, NGFI-A and the CREB–binding protein physically associate with one another prior to DNA binding. The CREB–binding protein acetylates histones associated with the exon 1_7 promoter, enhancing the ability of NGFI-A to bind and activate gene transcription.

Environmental signals alter 5-HT activity. Indeed, the effect of 5-HT on glucocorticoid receptor expression reflects the dependency of gene transcription on signals that derive from environmental events (note that the relevant environmental event may be internal or external to the organism; e.g., a change in the availability of glucose, an electrical impulse, or a social interaction). Such effects underlie the dynamic interdependence of gene and environment. However, psychologists, and in particular developmental psychologists, are familiar with more enduring environmental influences; instances where experience in early life has shaped neural development and function in a manner that is sustained into adulthood. Such effects are considered as the basis for environmental influences over the development of individual differences. In certain cases, the sustained effects of early experience have been associated with structural alterations in neural circuits that mediate specific functions. The process of sexual differentiation among vertebrates provides excellent examples where environmental signals lead to differences in morphology and thus to gender. However, more recent studies suggest another form of environmentally regulated plasticity that exists at the level of genome itself. Such effects appear to involve the modification of epigenetic marks on the DNA. These studies suggest that environmental events alter the activity of specific intracellular signals that modify the nature of the epigenetic marks at specific sites

Histone acetyltransferases: enzymes that acetylate lysine amino acids on histone proteins by transferring an acetyl group from acetyl CoA to form ε-N-acetyl lysine. Histone acetylation is associated with the activation of gene transcription

Promoter: a region of DNA that facilitates the transcription of a particular gene. Promoters are typically located near the genes they regulate, on the same strand and upstream from the coding region

in the genome, leading to sustained effects on gene expression and thus neural function.

ENVIRONMENTAL PROGRAMMING OF GENE EXPRESSION

Studies in developmental psychobiology and physiology are replete with examples of the environmental programming of gene expression. Such studies commonly report that a variation in the early environment associates with changes in gene expression and biological function that persists into adulthood and thus well beyond the duration of the relevant environmental event. In the rat, for example, prenatal nutrient deprivation or enhanced exposure to hormonal signals associated with stress stably alter, or program, the activity of genes in the liver and other sites that are associated with glucose and fat metabolism, including the gene for the glucocorticoid receptor (Bateson et al. 2004; Gluckman & Hanson 2004, 2007; Jirtle & Skinner 2007; Meaney et al. 2007; Seckl & Holmes 2007). These findings are assumed to represent instances in which the operation of a genomic region in adulthood varies as a function of early environmental influences. The results of recent studies suggest that such "programming" effects can derive from gene–environment interactions in early life that lead to a structural alteration of the DNA, which in turn mediates the effects on gene expression as well as more complex levels of phenotype (Jirtle & Skinner 2007, Meaney 2007, Meaney & Szyf 2005). These studies were performed in rodents but were inspired by the vast literature reporting the pervasive effects of family environment on health outcomes in humans (Repetti et al. 2002). No less compelling are the results of studies on "maternal effects" in plants, insects, reptiles, and birds showing that variations in nongenomic signals of maternal origin associate with sustained effects on the phenotype of the offspring (Cameron et al. 2005, Mousseau & Fox 1998, Rossiter 1998).

The objective of these studies is to examine the biological mechanisms whereby variations in mother–infant interactions might directly influence gene expression and behavior (Meaney 2001). Such studies focus on variations in maternal behavior that lie within the normal range for the species, in this case the Norway rat, and that occur in the absence of any experimental manipulations (i.e., naturally occurring variations in mother–pup interactions). Variations on maternal care in the rat are studied with simple, albeit very time-consuming, observations on animals in their home cages (Champagne 2008, Champagne et al. 2003). One behavior, pup licking/grooming (LG), emerges as highly variable across mothers. Pup LG is a major source of tactile stimulation for the neonatal rat that regulates endocrine and cardiovascular function in the pup (Hofer 2005, Levine 1994, Schanberg et al. 1984). The question then was whether such variations in pup LG might directly alter the development of individual differences in behavior and physiology. For the studies reviewed here, the focus is on the development of individual differences in defensive responses.

Subsequent findings revealed considerable evidence for the effect of maternal care on the behavioral and endocrine responses to stress in the offspring. The male or female adult offspring of mothers that naturally exhibit increased levels of pup LG (i.e., the offspring of high-LG mothers) show more modest behavioral and endocrine responses to stress compared to animals reared by low-LG mothers (Caldji et al. 1998, Francis et al. 1999, Liu et al. 1997, Menard et al. 2004, Toki et al. 2007, Weaver et al. 2004). Specifically, the offspring of high-LG mothers show reduced fearfulness and more modest hypothalamic-pituitary-adrenal (HPA) responses to stress. Cross-fostering studies, where pups born to high-LG mothers are fostered at birth to low-LG mothers (and vice versa), reveal a direct relationship between maternal care and the postnatal development of individual differences in behavioral and HPA responses to stress (Caldji et al. 2000, 2003; Francis et al. 1999; Weaver et al. 2004). In these studies, the rearing mother determined the phenotype of

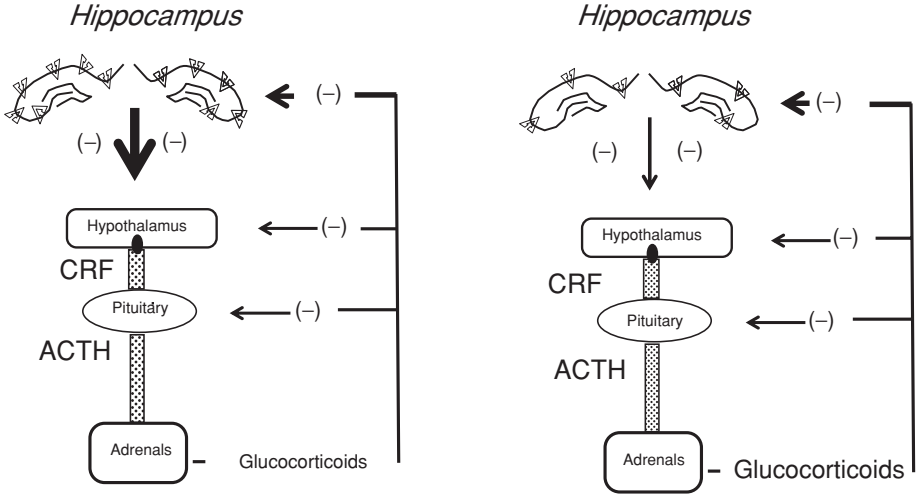

Figure 4

A schema outlining the function of the hypothalamic-pituitary-adrenal axis, the nexus of which are the corticotropin-releasing factor (CRF) neurons of the paraventricular nucleus of the hypothalamus. CRF is released into the portal system of the anterior pituitary, stimulating the synthesis and release of adrenocorticotropin (ACTH), which then stimulates adrenal glucocorticoid release. Glucocorticoids act on glucocorticoid receptors in multiple brain regions, including the hippocampus, to inhibit the synthesis and release of CRF (i.e., glucocorticoid negative feedback). The adult offspring of high-LG mothers, by comparison to those of low-LG dams, show (*a*) increased glucocorticoid receptor expression, (*b*) enhanced negative-feedback sensitivity to glucocorticoids, (*c*) reduced CRF expression in the hypothalamus, and (*d*) more modest pituitary-adrenal responses to stress.

the offspring. Thus variations within a normal range of parental care can dramatically alter phenotypic development in the rat.

The effects of maternal care on the development of defensive responses to stress in the rat involve alterations in the function of the corticotrophin-releasing factor (CRF) systems in selected brain regions (**Figure 4**). The CRF system furnishes the critical signal for the activation of behavioral, emotional, autonomic, and endocrine responses to stressors (Bale & Vale 2004, Koob et al. 1994, Plotsky et al. 1989). As adults, the offspring of high-LG mothers show decreased CRF expression in the hypothalamus as well as reduced plasma ACTH and glucocorticoid responses to acute stress by comparison to the adult offspring of low-LG mothers (Francis et al. 1999; Liu et al. 1997; Weaver et al. 2004, 2005). Circulating glucocorticoids act at glucocorticoid receptor sites in corticolimbic structures, such as the hippocampus, to regulate HPA activity (**Figure 4**). Such feedback effects commonly inhibit hypothalamic CRF expression. The high-LG offspring showed significantly increased hippocampal glucocorticoid receptor expression, enhanced glucocorticoid negative feedback sensitivity, and decreased hypothalamic CRF levels. Indeed, the magnitude of the glucocorticoid response to acute stress is significantly correlated with the frequency of pup LG during the first week of life, as is the level of both hippocampal glucocorticoid receptor and hypothalamic CRF expression (all r's >0.70; Liu et al. 1997). Importantly, pharmacological manipulations that block the effect of the glucocorticoid receptor eliminate the maternal effect on the HPA response to stress, suggesting that the differences in hippocampal glucocorticoid receptor expression are directly related to those at the level of HPA function.

Pup LG is a major source of tactile stimulation for the neonate. Experimental models that directly apply tactile stimulation, through the stroking of the pup with a brush, provide direct

evidence for the importance of tactile stimulation derived from pup LG. Thus, stroking pups over the first week of life increases hippocampal glucocorticoid receptor expression (Jutapakdeegul et al. 2003) and dampens behavioral and HPA responses to stress (Burton et al. 2007, Gonzalez et al. 2001). Likewise, manipulations of lactating mothers that directly increase the frequency of pup LG also increase hippocampal glucocorticoid receptor expression and decrease HPA responses to stress (Francis et al. 1999, Toki et al. 2007). Manipulations, notably stressors imposed on the mother, that decrease pup LG are associated with increased behavioral and HPA responses to stress and are associated with decreased hippocampal glucocorticoid receptor expression and increased hypothalamic expression of CRF (Champagne & Meaney 2006, Fenoglio et al. 2005).

The offspring of the high-LG and low-LG mothers also differ in behavioral responses to novelty (Caldji et al. 1998, Francis et al. 1999, Zhang et al. 2004). As adults, the offspring of the high-LG mothers show decreased startle responses, increased open-field exploration, and shorter latencies to eat food provided in a novel environment. There are also behavioral differences in response to more precise forms of threat. Thus, the offspring of low-LG mothers show greater burying of an electrified probe in the defensive burying paradigm (Menard et al. 2004), which involves an active response to a threat. These differences in behavioral responses to stress are associated with altered activity in the CRF system that links the amygdala (and bed nucleus of the stria terminalis) to the noradrenergic cells of the locus coeruleus (Caldji et al. 1998, Zhang et al. 2004).

The results of these studies suggest that the behavior of the mother toward her offspring can "program" stable changes in gene expression that then serve as the basis for individual differences in behavioral and neuroendocrine responses to stress in adulthood. The maternal effects on phenotype are associated with sustained changes in the expression of genes in brain regions that mediate responses to stress and form the basis for stable individual differences in stress reactivity. These findings provide a potential mechanism for the influence of parental care on vulnerability/resistance to stress-induced illness over the lifespan. But the critical issue is simply that of how maternal care might stably affect gene expression. How are variations in the social interactions between the mother and her offspring biologically embedded so as to stably alter the activity of specific regions of the genome? The answers to these questions appear to involve the ability of social interactions in early development to structurally modify relevant genomic regions. For the sake of this review, we focus on the maternal effect on the regulation of hippocampal glucocorticoid receptor expression.

EPIGENETIC REGULATION OF THE GENOME

The molecular processes that lead to the initiation of gene transcription involve modifications to the histone proteins that form the core of the nucleosome (**Figure 2**). Such modifications open chromatin, permitting transcription factor binding and the activation of gene transcription. A second level of regulation occurs not on the histone proteins, but rather directly on the DNA. Indeed, the classic epigenetic alteration is that of DNA methylation, which involves the addition of a methyl group (CH_3) onto cytosines in the DNA (Bird 1986, Holliday 1989, Razin & Riggs 1980). DNA methylation is associated with the silencing of gene transcription. This effect appears to be mediated in one of two ways (Bird 2002). First, wide swaths of densely methylated DNA preclude transcription factor binding to DNA sites, thus silencing gene expression. The second manner is subtler and probably far more prevalent in regions with more dynamic variations in gene transcription, such as the brain. In this case, selected cytosines are methylated, and the presence of the methyl group attracts a class of proteins know as methylated-DNA binding proteins (Klose & Bird 2007). These proteins, in turn, attract an entire cluster of

proteins that form a repressor complex, which includes active mediators of gene silencing. The HDACs are a critical component of the repressor complex. HDACs prevent histone acetylation and favor a closed chromatin state that constrains transcription factor binding and gene expression (**Figure 2** and see above). Compounds that inhibit HDACs can thus increase transcription from methylated DNA.

When we think of genomic influences, we most commonly imagine effects associated with variation in nucleotide sequence. Yet this is only one form of information contained within the genome. Despite the reverence afforded DNA, a gene is basically like any other molecule in the cell; it is subject to physical modifications. As described above, these modifications alter the structure and chemical properties of the DNA and thus gene expression. Collectively, the modifications to the DNA and its chromatin environment can be considered as an additional layer of information that is contained within the genome. This information is thus epigenetic in nature (the name derives from the Greek *epi* meaning "upon" and *genetics*). The acetylation of histone proteins or the methylation of DNA are examples of epigenetic modifications. Epigenetic modifications do not alter the sequence composition of the genome. Instead, these epigenetic marks on the DNA and the histone proteins of the chromatin regulate the operation of the genome. Thus, "epigenetics" has been defined as a functional modification to the DNA that does not involve an alteration of sequence (Waddington 1957). Although this definition has been subjected to revision (Bird 2007, Hake & Allis 2006), the essential features of epigenetic mechanisms are (*a*) structural modifications to chromatin either at the level of the histone proteins (**Figure 2**) or the DNA, (*b*) the associated regulation of the structure and function of chromatin, (*c*) the downstream effects on gene expression, and (*d*) the fact that these effects occur in the absence of any change in nucleotide sequence.

The methylation of DNA in mammals is an active biochemical modification that selectively targets cytosines and is achieved through the actions of enzymes, DNA methyltransferases, that transfer the methyl groups from methyl donors. There are two critical features to DNA methylation: First, it is a stable chemical modification, and second, it is associated with the silencing of gene transcription (Bestor 1998, Bird 2002, Bird & Wolffe 1999, Razin 1998).

Until very recently, it was thought that DNA methylation patterns on the genome were overlaid upon the genome only during early periods in embryonic development. Indeed, DNA methylation is considered as a fundamental feature of cell differentiation. It is important to consider a simple feature of cell biology: All cells in the body generally share the same DNA. Thus, the processes of cell specialization, whereby liver cells specialize in functions related to energy metabolism and brain cells establish the capacity for learning and memory, involve silencing certain regions of the genome in a manner that is specific for each cell type. Genes associated with gluconeogenesis are silenced in brain cells but remain active in liver cells. Such processes define the function of the cell type (e.g., Fan et al. 2005). DNA methylation is considered as a mechanism for the genomic silencing that underlies cell specialization. Such events occur early in development and are considered to be highly stable, such that dedifferentiation (whereby a cell loses its specialization) is rare and often is associated with organ dysfunction.

Thus DNA methylation was considered both unique to early periods in development and irreversible. Experimental models commonly used to study DNA methylation further reinforced this view. DNA methylation-induced gene silencing mediates two of the most commonly studied examples of the epigenetic silencing of genes, namely X-chromosome inactivation and gene imprinting. Mammalian females bear two copies of the X-chromosome. The inactivation of one copy of the X-chromosome occurs in all mammalian females and is essential for normal function (i.e., maintaining a constant gene dosage in males and females). The silencing of the X-chromosome is associated

with DNA methylation (Mohandas et al. 1981, Riggs & Pfieffer 1992; but also see Hellman & Chess 2007 for a more current update). The second example of epigenetic-mediated gene silencing is that of gene imprinting (da Rocha & Ferguson-Smith 2004, Reik 2001), a remarkable subject in its own right and one with considerable implications for growth and development (Charalambous et al. 2007). For humans and other mammals, the expression of specific genes is determined by the parent of origin. For certain genes, the copy derived from the mother is active while that emanating from the father is silenced—a maternally imprinted gene. In other cases, it is the reverse: The copy of the gene inherited from the father is active while that from the mother is silenced—a paternally imprinted gene. The silent copy is methylated in DNA regions that regulate gene expression and thus is inactive. Again, the epigenetic marks associated with gene imprinting are established very early in life. These marks, as well as those associated with X-chromosome inactivation, are largely stable.

Collectively, these models have left biologists with the impression that under normal conditions, DNA methylation occurs early in embryonic life and is irreversible. DNA methylation was considered to be an actively dynamic process only during periods of cell division and differentiation (see above) such that in mature postmitotic cells, further alteration of methylation patterns was improbable. Moreover, the extensive loss of cytosine methylation in the models described above is associated with pathology. This perspective was further reinforced by findings showing that an alteration of DNA methylation at critical genomic targets (i.e., tumor suppressors) is associated with cancer (Eden et al. 2003, Feinberg 2007, Laird 2005).

At this point, dynamic changes in DNA methylation were of considerable interest for developmental biologists but somewhat less so for psychologists, who study the aftermath of more subtle variations in neuronal differentiation that occur in later periods of development or even in the fully mature brain. The issue for developmental psychologists concerns less the process by which cells specialize as neurons and more the issues related to why neurons in one individual function differently from those of another, or how neurons might dynamically later alter functional properties in relation to experience (i.e., activity-dependent neuronal plasticity). The studies reviewed below provide an important revision to this perspective. There is now considerable evidence in neuroscience and other fields, including immunology and endocrinology/metabolism, that the state of DNA methylation at specific genomic sites is indeed dynamic even in adult animals (Bird 2007, Jirtle & Skinner 2007, Meaney & Szyf 2005). Moreover, alterations in DNA methylation are emerging as a candidate mechanism for the effects of early experience in individual differences in neural function as well as in learning and memory. Thus, although the assumptions concerning DNA methylation appear valid for the examples cited above, recent studies reveal that DNA methylation patterns are actively modified in mature (i.e., fully differentiated) cells including, and perhaps especially, neurons, and that such modifications can occur in animals in response to cellular signals driven by environmental events (Jirtle & Skinner 2007, Meaney & Szyf 2005, Sweatt 2009). For example, variations in the diet of mice during gestation or later in development, such as the early postweaning period, can stably alter the methylation status of the DNA (Cooney et al. 2002, Waterland & Jirtle 2003, Waterland et al. 2006, Whitelaw & Whitelaw 2006). Likewise, both mature lymphocytes (Bruniquel & Schwartz 2003, Murayama et al. 2006) and neurons (e.g., Champagne 2008, Champagne et al. 2006, Lubin et al. 2008, Martinowich et al. 2003, Sweatt 2009) show changes in the DNA methylation patterns at critical genomic regions in response to environmental stimuli that stably alter cellular function. The ability of environmental signals to actively remodel epigenetic marks that regulate gene expression is a rather radical change in our understanding of the environmental regulation of gene expression. Such epigenetic modifications are thus

a candidate mechanism for the environmental programming of gene expression.

Epigenetics and the Social Environment

The section below describes studies of the molecular basis for the effects of maternal care on the development of individual differences in gene expression and stress responses. The mechanism for this interaction is epigenetic, involving alterations in DNA methylation at specific sites in the genome. In summary, variations in mother–infant interactions in the rat alter the extra- and intracellular environment of neurons in selected brain regions. Such alterations directly modify the epigenetic marks on regions of the DNA that regulate the transcription of the glucocorticoid receptor, which in turn regulates the HPA response to stress. These epigenetic marks are stable, enduring well beyond the period of maternal care, and provide a molecular basis for a stable maternal effect on the phenotype of the offspring. Thus, the behavior of the mother directly alters cellular signals that then actively sculpt the epigenetic landscape of the offspring, influencing the activity of specific regions of the genome and the phenotype of the offspring.

The critical feature of the maternal effects described above is that of persistence. The differences in the frequency of pup LG between high- and low-LG mothers are limited to the first week of postnatal life. And yet the differences in gene expression and neural function are apparent well into adulthood. How might the effects of an essentially social interaction stably alter the expression of the genes that regulate the activity of neural systems that mediate endocrine and behavioral responses to stress? To address this question, we focused on the sustained effect of maternal care on glucocorticoid receptor gene transcription in the hippocampus as a model system for the environmental programming of gene expression.

The focus of the epigenetic studies is the NGFI-A consensus sequence in the exon 1_7 promoter (**Figure 1**) that activates glucocorticoid receptor expression in hippocampal neurons. The tactile stimulation associated with pup LG increases 5-HT activity in the hippocampus. In vitro studies with cultured hippocampal neurons show that 5-HT acts on 5-HT_7 receptors to initiate a series of intracellular signals that culminate with an increase in the expression of NGFI-A as well as in the CREB-binding protein (**Figure 3**). Comparable effects occur in vivo. Manipulations that increase pup LG by lactating rats result in an increased level of cAMP as well as NGFI-A (Meaney et al. 2000). Pups reared by high-LG mothers show increased NGFI-A expression in hippocampal neurons as well as an increased binding of NGFI-A to the exon 1_7 promoter sequence (Weaver et al. 2007, Zhang et al. 2009). Moreover, the binding of NGFI-A to the exon 1_7 promoter sequence is actively regulated by mother–pup interactions, such that there is increased NGFI-A bound to the exon 1_7 promoter immediately following a nursing bout, but not at a period that follows 25 minutes without mother–pup contact (Zhang et al. 2009).

NGFI-A and the CREB-binding protein form a complex that binds directly to the exon 1_7 promoter sequence and actively redesigns the methylation pattern at this region of the genome (Weaver et al. 2004, 2007). Thus, as adults, the offspring reared by high-LG mothers show very modest levels of methylation at the 5′ CpG of the NGFI-A consensus sequence (**Figure 5**). This effect on methylation is very precise. Located only a few nucleotides removed from this site is the 3′ CpG site (**Figures 1** and **5**), the methylation status of which is unaffected by maternal care.

A rather novel aspect of the effect of maternal care on DNA methylation was apparent in the results of a simple developmental study examining the methylation status of the 5′ and 3′ CpG sites from late in fetal life to adulthood (Weaver et al. 2004). Neither the 5′ nor the 3′ CpG sites within the NGFI-A binding region is methylated in hippocampal neurons from fetal rats, whereas both sites are heavily methylated on the day following birth, with no difference as a function of maternal care.

These findings reflect what is referred to as de novo methylation, whereby a methyl group is applied to previously unmethylated sites. However, between the day following birth and the end of the first week of life, the 5′ CpG is demethylated in pups reared by high-LG, but not low-LG, mothers. This difference then persists into adulthood. Importantly, the period over which the demethylation occurs falls precisely within that time when high- and low-LG mothers differ in the frequency of pup LG; the difference in pup LG between high- and low-LG mothers is not apparent in the second week of postnatal life (Caldji et al. 1998, Champagne 2008, Champagne et al. 2003).

The demethylation of the 5′ CpG site occurs as a function of the same 5-HT-activated signals that regulate glucocorticoid receptor gene expression in cultured hippocampal neurons (Weaver et al. 2007). Thus, when hippocampal neurons of embryonic origin are placed in culture and treated with 5-HT, which mimics the extracellular signal associated with maternal LG, the 5′ CpG site is demethylated; there is no effect at the 3′ CpG site. The binding of NGFI-A to the exon 1_7 site is critical. Hippocampal neurons that are rendered incapable of increasing NGFI-A expression through antisense or siRNA treatment show neither the demethylation of the 5′ CpG site nor the increase in glucocorticoid receptor expression (Weaver et al. 2007). Likewise, a mutation of the NGFI-A site (exchanging a C for an A at the 3′ CpG site) that completely abolishes the binding of NGFI-A to the exon 1_7 promoter also prevents the demethylation of the 5′ CpG. Finally, the infection of hippocampal neurons with a virus containing a nucleotide construct engineered to express high levels of NGFI-A produces demethylation of the 5′ CpG of the exon 1_7 promoter sequence and increases glucocorticoid receptor expression.

These findings suggest that maternal licking of pups increases NGFI-A levels in the hippocampal neurons of the offspring, thus altering DNA methylation. But there is a complication. If DNA methylation blocks transcription factor binding and the 5′ CpG site of the exon 1_7 promoter is heavily methylated in neonates, then how might maternally activated NGFI-A bind to and remodel the exon 1_7 region? And why is the effect apparent at the 5′ but not the 3′ CpG? The answer to these questions appears to involve other transcriptional signals that are affected by maternal care. Levels of the transcription factor–specific protein-1 (SP-1) and the CREB-binding protein are also increased in the hippocampus of pups reared by high-LG mothers (Weaver et al. 2007, Zhang et al. 2009). The exon 1_7 promoter contains a DNA sequence that binds SP-1, and this region overlaps with that for NGFI-A. SP-1 can actively target both methylation and demethylation of CpG sites (Brandeis et al. 1994). The 5′CpG site is the region of overlap in the binding sites. The CREB-binding protein, on the other hand, acts as a histone acetyltransferase, an enzyme capable of acetylating histone tails, including the exon 1_7 region, opening chromatin and permitting the binding of transcription factors such as NGFI-A and SP-1. Increasing histone acetylation can lead to transcription factor binding at previously methylated sites and the subsequent demethylation of these regions (Fan et al. 2005, Szyf et al. 2005). Thus, we suggest that the binding of this complex of proteins, NGFI-A, the CREB-binding protein, and SP-1 is critical in activating the process of demethylation. The results to date are certainly consistent with this model, but we should note that we have yet to firmly establish the identity of the enzyme that is responsible for the demethylation of the 5′ CpG site.

These findings suggest that maternally induced increases in hippocampal NGFI-A levels can initiate the remodeling of DNA methylation at the regions of the DNA that regulate glucocorticoid receptor expression. The NGFI-A transcription factor binds to multiple sites across the genome. If NGFI-A-related complexes target demethylation, then one might assume that other NGFI-A-sensitive regions should show a maternal effect on DNA methylation and gene expression comparable to that observed with the glucocorticoid receptor. Zhang and colleagues (2009) showed that

the hippocampal expression of the *GAD1* gene that encodes for glutamic acid decarboxylase, an enzyme in the production of the neurotransmitter GABA, is increased in the adult offspring of high-LG mothers. This effect is associated with altered DNA methylation of an NGFI-A response element in a manner comparable to that for the glucocorticoid receptor gene. Moreover, as with the effect on the glucocorticoid receptor, an in vitro increase in NGFI-A expression mimics the effects of increased pup LG. The function of GABAergic neurons in the limbic system is also regulated by maternal care (Caldji et al. 1998, 2000, 2003) and is a major target for anxiolytic agents. These findings are therefore likely relevant for the decreased fearfulness observed in the adult offspring of high-LG mothers.

In summary, the maternally induced changes in specific intracellular signals in hippocampal neurons can physically remodel the genome. The increased binding of NGFI-A that derives from pup LG appears critical for the demethylation of the exon 1_7 promoter. We suggest that this process involves accompanying increases in SP-1 and the CREB-binding protein, and that the combination of these factors results in the active demethylation of the exon 1_7 promoter. It should be noted that there are important features of this model that remain to be clearly defined, including the identification of the enzyme that is directly responsible for the demethylation. Nevertheless, the events described to date represent a model by which the biological pathways activated by a social event may become imprinted onto the genome. This imprint is then physically apparent in the adult genome, resulting in stable alterations (or programming) of gene expression.

THE FUNCTIONAL IMPORTANCE OF THE SOCIAL IMPRINT

A critical issue is that of relating the epigenetic modifications at specific DNA regions to function. The presence of a methyl group on the 5′ CpG of the NGFI-A binding site is functionally related to glucocorticoid receptor gene expression in adult animals. In vitro studies reveal that the methylation of the 5′CpG site reduces the ability of NGFI-A to bind to the exon 1_7 promoter and activate glucocorticoid receptor transcription (Weaver et al. 2007). These findings are consistent with the model described above, whereby DNA methylation impedes transcription factor binding and thus the activation of gene expression. The next question concerns the in vivo situation and function at a level beyond that of gene expression.

In contrast to the situation with neonates, there is no difference in NGFI-A expression as a function of maternal care among adult animals: Hippocampal levels of NGFI-A are comparable in the adult offspring of high- and low-LG mothers. However, the altered methylation of the exon 1_7 promoter would suggest differences in the ability of NGFI-A to access its binding site on the exon 1_7 promoter. Chromatin-immunoprecipitation assays, which permit measurement of the interaction between a specific protein and a defined region of the DNA, reveal increased NGFI-A association with the exon 1_7 promoter in hippocampi from adult offspring of high- compared to low-LG mothers (Weaver et al. 2004, 2005). This difference occurs despite the comparable levels of NGFI-A. These findings show that in the living animal, under normal conditions, there is more NGFI-A associated with the exon 1_7 promoter in hippocampal neurons of adult animals reared by high- compared with low-LG mothers.

There is also evidence that directly links the maternal effect on the epigenetic state of the exon 1_7 promoter to the changes in glucocorticoid receptor expression and HPA responses to stress. Recall that the methylation of specific CpG sites can diminish transcription factor binding through the recruitment of repressor complexes that include HDACs. The HDACs deacetylate histone tails, thus favoring a closed chromatin configuration. Indeed, the exon 1_7 promoter is more prominently acetylated in hippocampi from adult offspring of high- compared with low-LG mothers

(Weaver et al. 2004, 2005). This finding is consistent with the increased transcription of the glucocorticoid receptor gene in animals reared by high- versus low-LG mothers. A subsequent study (Weaver et al. 2004) examined the effects of directly blocking the actions of the HDACs in the adult offspring of high- and low-LG mothers by directly infusing an HDAC inhibitor into the hippocampus daily for four consecutive days. The treatment with the HDAC inhibitor produces a series of predictable results that reflect a cause-effect relation between DNA methylation and gene expression. First, as expected, HDAC blockade eliminates the differences in the acetylation of the histone tails (open chromatin) of the exon 1_7 promoter in hippocampal samples from high- and low-LG mothers. Second, the increased histone acetylation of the exon 1_7 promoter in the offspring of low-LG mothers is associated with an increase in the binding of NGFI- A to the exon 1_7 promoter in the offspring of low-LG mothers, eliminating the maternal effect on NGFI-A binding to the exon 1_7 promoter. Comparable levels of NGFI-A binding to the exon 1_7 promoter then eliminate the maternal effect on hippocampal glucocorticoid receptor expression, such that glucocorticoid receptor levels in the adult offspring of low-LG mothers treated with the HDAC inhibitor are comparable to those in animals reared by high-LG mothers. And most importantly, the infusion of the HDAC inhibitor reversed the differences in the HPA response to stress.

HDAC inhibition increases NGFI-A binding to the exon 1_7 promoter in the offspring of low-LG mothers. The studies with neonates reveal that increased NGFI-A binding results in the demethylation of the 5′ CpG. In vitro, the introduction of a viral tool that leads to the increased expression of NGFI-A is sufficient to demethylate the exon 1_7 promoter. Weaver et al. (2007) argue that the binding of NGFI-A is critical for the demethylation of the 5′CpG site. The same effect is apparent in vivo and even with the adult animals used in the studies described above. HDAC infusion into the hippocampus increases NGFI-A binding to the exon 1_7 promoter in the adult offspring of low-LG mothers and decreases the level of methylation of the 5′CpG site on the exon 1_7 promoter. Another study (Weaver et al. 2005) showed that the reverse pattern of results could be obtained in response to the infusion of methionine into the hippocampus. The methionine infusion produced greater methylation of the 5′CpG in the offspring of high-LG mothers, decreased NGFI-A binding and GR expression, and increased HPA responses to stress (Weaver et al. 2005).

Although these studies employ rather crude pharmacological manipulations, the results are critical as they suggest that fully mature neurons in an adult animal express the necessary enzymatic machinery to demethylate or remethylate DNA. The importance of this plasticity at the level of DNA methylation is revealed in subsequent studies of cognition (see below), which suggest that dynamic modification of DNA methylation in critical neuronal populations in adult animals is involved in specific forms of learning and memory.

ACTIVITY-DEPENDENT REGULATION OF THE EPIGENOME

The maternal effect on the epigenetic state of the glucocorticoid receptor exon 1_7 promoter and glucocorticoid receptor gene expression is apparent over the first week of life and occurs in response to an increased NGFI-A signal in hippocampal neurons. The increased expression of NGFI-A and its binding to the exon 1_7 GR promoter over the first week of life are activated by maternal behavior (Weaver et al. 2007, Zhang et al. 2009). An increase in the expression of NGFI-A is associated with synaptic plasticity and with learning and memory (Dragunow 1996, Jones et al. 2001, Knapska & Kaczmarek 2004, Li et al. 2005, O'Donovan et al. 1999). Thus it is not surprising that the offspring of high-LG mothers show increased synaptic density both in early life (Liu et al. 2000) and in adulthood (Bagot et al. 2009, Bredy et al. 2003, Champagne et al. 2008, Liu et al. 2000).

Such events occur as a function of a series of activity-dependent changes in neuronal activity triggered by the action of glutamate at the NMDA receptor site (Ali & Salter 2001, Bear & Malenka 1994, Malenka & Nicoll 1993, Morris & Frey 1997). Thus, it is possible that environmentally driven changes in neuronal transcriptional signals could potentially remodel the methylation state of specific regions of the DNA (Meaney & Szyf 2005, Sng & Meaney 2009). These effects could, in turn, prove essential for sustained alterations in synaptic function.

Learning and long-term memory commonly require changes in gene expression and protein synthesis (Alberini et al. 1995, Kandel 2001, Lynch 2004). As described above, gene transcription is associated with chromatin remodeling engineered by enzymes that modify the histone proteins within chromatin complexes. A number of the intracellular signals that are crucial for learning and memory are in fact enzymes that modify histone proteins. One example is that of the CREB-binding protein, which functions as a histone acetyltransferase and is strongly implicated in cognitive function (e.g., Alarcon et al. 2004). Thus, contextual fear conditioning, which is a hippocampus-dependent learning paradigm whereby an animal associates a novel context with an aversive stimulus, is accompanied by increased acetylation of histone H3 (Levenson et al. 2004). Likewise, there is evidence for the importance of epigenetic modifications of histones in the amygdala during fear conditioning (Yeh et al. 2004). Interestingly, extinction of the conditioned fear response is associated with increased histone acetylation in the prefrontal cortex, which mediates the inhibition of conditioned fear responses (Bredy et al. 2007). The CREB-binding protein is probably involved in the relevant histone modifications. Mice that are heterozygous for a dysfunction form of the CREB-binding protein show significant impairments in multiple forms of hippocampal-dependent, long-term memory (Bourtchouladze et al. 2003, Korzus et al. 2004, Wood et al. 2006; also see Guan et al. 2002, Vecsey et al. 2007). Importantly, the cognitive impairments are reversed with HDAC administration, suggesting that CREB-binding protein-induced histone acetylation mediates effects on learning and memory.

There is also evidence for the importance of dynamic changes in DNA methylation at specific sites during learning and memory. Fear conditioning results in the rapid methylation and transcriptional silencing of the gene for protein phosphatase 1 (PP1), which suppresses learning. The same training results in the demethylation and transcriptional activation of the synaptic plasticity gene reelin. These findings imply that both DNA methylation and demethylation might be involved in long-term memory consolidation.

BDNF has been implicated in adult neural plasticity, including learning and memory (West 2001). The genomic structure of the *Bdnf* gene contains multiple promoters that generate mRNAs containing different noncoding exons spliced upstream of a common coding exon (Timmusk et al. 1993). This organization is somewhat like that described above for the glucocorticoid receptor (**Figure 1**). In the case of BDNF, the exon IV promoter in rat is activated upon membrane depolarization in cultured cortical and hippocampal neurons by means of KCl, which leads to calcium influx, activating signaling cascades and inducing the expression of an array of genes that are involved in neural plasticity (West 2001).

Importantly, the activity-dependent *Bdnf* gene is also regulated through epigenetic modifications that involve dynamic changes in DNA methylation and the association of methylated-DNA binding proteins to the relevant sites on the *bdnf* promoter. Thus, increased DNA methylation of the exon IV promoter at sites that bind to transcriptional activators is associated with the presence of the methylated-DNA-binding protein, MeCP2, and a decreased level of *bdnf* expression. This transcriptionally quiescent state prior to depolarization is also associated with the presence of histone deacetylases (i.e., HDAC1) and mSIN3A, which form a common repressor complex. Membrane

depolarization of the neuron leads to a decrease in CpG methylation and a dissociation of MeCP2-related repressor complex from the exon IV promoter. As described above for the glucocorticoid receptor, the decrease in CpG methylation is then associated with an increase in histone acetylation and the binding of the transcription factor, CREB. CREB is known to activate *bdnf* expression. These data suggest that DNA methylation at a particular site can suppress activity-dependent transcription of *Bdnf*. These findings also indicate that DNA methylation patterns in postmitotic neurons can undergo dynamic changes in response to neuronal activation, and a lower level of DNA methylation correlates with a higher level of *Bdnf* gene transcription in neurons.

Protein phosphorylation: a modification of proteins in which a specific amino acid (serine, a threonine or a tyrosine) is phosphorylated by a protein kinase by the addition of a covalently bound phosphate group. In such cases of phosphoregulation, the protein switches between a phosphorylated and an unphosphorylated state, with one in an active form and the other inactive

Interestingly, MeCP2 levels increase as neurons mature (Zoghbi 2003). The high level of MeCP2 protein in mature neurons is consistent with a possible role for MeCP2 in synaptic remodeling associated with learning and memory (Zhou et al. 2006). Further supporting a role for MeCP2 in mature synaptic function and plasticity, Mecp2-null mice exhibit abnormalities in dendritic arborization (Chen et al. 2003, Kishi & Macklis 2004), basal synaptic transmission (Moretti et al. 2006), presynaptic function (Asaka et al. 2006, Moretti et al. 2006, Nelson et al. 2006), excitatory synaptic plasticity (Asaka et al. 2006, Moretti et al. 2006), and hippocampal and amygdalar learning (Moretti et al. 2006, Pelka et al. 2006). Zhou et al. (2006) found that neuronal activity (membrane depolarization) is associated with a phosphorylation of MeCP2 at Serine421 that led to its dissociation from the *bdnf* exon IV promoter and an increase in *bdnf* expression (also see Chen et al. 2003). Importantly, activity-dependent increases in BDNF levels are blocked in cells bearing a mutant version of MeCP2 that is unable to undergo phosphorylation. Glutamate is a primary neural signal for synaptic plasticity, and both glutamate as well as the direct activation of its NMDA receptor produced MeCP2 phosphorylation in neurons. Glutamate activates NMDA receptors, resulting in a neuronal calcium influx and the activation of calcium-modulated kinase II (CaMKII), which regulates synaptic plasticity (Lisman et al. 2002). Zhou et al. (2006) found that CaMKII actively phosphorylates MeCP2.

The protein phosphorylation occurring at MeCP2 in response to neuronal activation is a transient event. The results described above (Martinowich et al. 2003) suggest that neuronal activation can lead to changes in DNA methylation, which is a potentially more stable, epigenetic alteration that could conceivably result in a long-term change in *bdnf* expression. Thus far, this review has considered the relation between DNA methylation, histone acetylation/deacetylation, transcription factor binding, and gene expression. However, there is evidence that the chromatin alterations can alter DNA methylation. Thus, HDAC inhibitors result in an increase in histone acetylation, enhanced transcription factor binding, and decreased DNA methylation. Such effects were described above in relation to DNA methylation and glucocorticoid receptor expression (Weaver et al. 2004, 2005). Thus, it is possible that (*a*) neuronal activation leads to the transient phosphorylation of MeCP2 and its dissociation from the exon IV *bdnf* promoter and (*b*) an increase in histone acetylation and CREB binding, producing increased *bdnf* expression; and that (*c*) the histone acetylation and CREB binding are also associated with DNA demethylation, as described above in the case of the glucocorticoid receptor for histone acetylation and NGFI-A binding. Such events could underlie a common process of activity-dependent modification of DNA methylation (Meaney & Szyf 2005).

Studies by Sweatt and colleagues suggest that the changes in DNA methylation at the exon IV *bdnf* promoter are involved in specific forms of learning and memory (Sweatt 2009). *Bdnf* gene expression increases in the hippocampus with contextual and spatial learning and appears essential for the synaptic remodeling that accompanies such forms of learning and memory (Hall et al. 2000, Linnarsson et al. 1997). NMDA receptor activation is critical for both contextual (Maren & Quirk 2000) and spatial (Morris et al. 2003) learning as

well as for the increase in *bdnf expression* that accompanies such events. Lubin et al. (2008) found that contextual fear conditioning was associated with a demethylation of the exon IV *bdnf* promoter and an increase in *bdnf* expression: Both effects were blocked with a glutamate receptor antagonist. Taken together, these findings suggest that the activity-dependent changes in neuronal activity that associate with learning and memory induce a dynamic alteration in DNA methylation that, in turn, subserves the sustained changes in gene expression critical for long-term memory. Although this remains a working hypothesis, the findings discussed above further emphasize the degree to which neuronal activation can structurally remodel the genome and alters its operation.

Interestingly, there is also evidence that environmental influences prevailing during early development may determine the capacity for such activity-driven, epigenetic modifications. Disruptions to mother–infant interactions during early development are associated with alterations in hippocampal *bdnf* expression (Branchi et al. 2006; Lippman et al. 2007; Roceri et al. 2002, 2004; but also see Griesen et al. 2005) and increased DNA methylation at the exon IV *bdnf* promoter (Roth et al. 2009). Rearing mice in a communal nest, with three mothers and their litters, increases maternal care toward the offspring, which in turn is associated with increased BDNF expression (Branchi et al. 2006). And in the rat, the offspring of high-LG mothers show decreased MeCP2 association with the exon IV *bdnf* promoter (Weaver et al. 2007) and increased *bdnf* expression (Liu et al. 2000). Such maternal effects might bias in favor of reduced capacity for epigenetic remodeling at this critical site and restrain synaptic plasticity associated with learning and memory.

Summary (and Perhaps Some Constraints)

Studies over the past five years have created considerable enthusiasm for epigenetic models of the effects of early experience, synaptic plasticity, and neural function. The hypothesis underlying this approach considers epigenetic effects on gene expression as a candidate mechanism for the effects of environmental signals on the future behavior of the organism. This hypothesis is particularly attractive for those examining the sustained effects of early experience or of chronic, biologically relevant events in adulthood (e.g., environmental enrichment, chronic stress) on gene expression and neural function. Mature neurons undergo considerable changes in phenotype and are therefore an ideal cell population for epigenetic regulation. Nevertheless, there are constraints on the influence of epigenetic marks. For example, the effects of DNA methylation on gene expression are influenced by the organization of the relevant genomic region. DNA methylation appears to have a reduced effect on gene expression in regions that have a very high density of cytosine-guanine paired sites (Weber et al. 2007). Moreover, much of the DNA within a cell is packed tightly in heterochromatin (Fraser & Bickmore 2007) and is probably inaccessible to environmentally induced chromatin remodeling signals. Thus, the infusion of an HDAC inhibitor directly into the adult hippocampus alters the expression of only about 2% of all the genes normally expressed in the rat hippocampus (Weaver et al. 2006). Were the entire genome subject to dynamic epigenetic regulation such as described above for the *bdnf* gene, then we could expect this percentage to be substantially higher. It is likely that there is a pool of genes that retains the capacity for dynamic environmental regulation through epigenetic mechanisms. Of course this begs questions concerning the factors that determine the nature and contents of such pools. These considerations notwithstanding, it appears that with neurons, a number of genes are closely related to synaptic plasticity and neural function and are subject to dynamic regulation through epigenetic mechanisms, including DNA methylation.

Epigenetics refers to a collection of chemical modifications that occur to histones or directly on the DNA. These modifications, in turn, alter gene transcription. One might argue

that in defining such mechanisms we have, in effect, simply better defined the processes that regulate gene transcription. Although the value of such findings is obvious for molecular biology, how might such processes revise our thinking at the level of the systems sciences? We suggest that these findings provide researchers with a renewed appreciation of the environmental regulation of cellular activity. We now understand the physical basis for the Hebbian synapse (Hebb 1958), whereby environmental signals activate intracellular pathways that result in the remodeling of synaptic connections in a manner that influences subsequent activity at relevant sites. There is a physical reference for the process of neuroplasticity. Epigenetic modifications provide the mechanism for a comparable level of plasticity at the level of the genome. We once thought of synaptic connections as being fixed, immutable to further changes beyond some critical period in development. Studies of synaptic plasticity revised our appreciation of the brain, revealing instead a dynamic tissue, subject to constant remodeling through the environmental activation of activity-dependent synaptic plasticity. The study of epigenetics suggests a comparable process at the level of the genome, also once considered a constant, static source of influence. Indeed, we must emphasize that epigenetic modifications do not alter DNA sequence. The product of the glucocorticoid receptor gene is unaffected by epigenetic marks. However, it appears that the operation of the genome is indeed subject to environmental regulation in a manner that may be no less dynamic than that of synaptic connections.

Recent studies from Nestler and colleagues reveal considerable epigenetic modification at specific genomic sites associated with chronic stress or repeated exposure to psychostimulant drugs, both of which produce sustained influences on behavior (Nestler 2009, Renthal et al. 2009). Although such effects have yet to be reported for DNA methylation, modifications of histone proteins are associated with exposure to drugs of abuse and stressors in rodent models (Renthal et al. 2009, Renthal & Nestler 2008). These findings suggest that epigenetic states, including DNA methylation, are altered by a wide range of biologically relevant events (Meaney & Szyf 2005, Renthal & Nestler 2008, Szyf et al. 2005). Such epigenetic modifications might therefore underlie a wide range of stable changes in neural function following exposure to highly salient events (e.g., chronic stress, drugs of abuse, reproductive phases such as parenting) and are thus logical mechanisms for environmentally induced alterations in mental health (Akbarian & Huang 2009, Jiang et al. 2008, Tsankova et al. 2007).

EPIGENETICS AND MENTAL HEALTH

Emerging evidence links the alterations in gene expression associated with DNA methylation to psychiatric illness. Cortical dysfunction in schizophrenia is associated with changes in GABAergic circuitry (Benes & Berretta 2001). This effect is associated with a decrease in the expression of the *GAD1* gene that encodes for a specific form of glutamic acid decarboxylase (GAD_{67}), one to two key enzymes for GABA synthesis in cortical interneurons. There is compelling evidence for the decreased expression of GAD_{67} in cortical tissues from schizophrenic patients (Akbarian & Huang 2006, Costa et al. 2004). The dysregulated GAD_{67} expression in the chandelier GABA neurons is thought to result in disruption of synchronized cortical activity and impairment of executive functions in schizophrenia subjects (Lewis et al. 2005). Likewise, allelic variation in *GAD1* is associated with schizophrenia (Straub et al. 2007).

In addition to GAD_{67}, there is also a decrease in cortical expression of reelin in schizophrenic brains (Eastwood & Harrison 2003); reelin is closely associated with synaptic plasticity. The same GABAergic neurons in the schizophrenic brain that express reelin and GAD_{67} exhibit an increase in DNA methyltransferases 1 (DNMT1; Veldic et al. 2004). DNMT1 is a member of a family of enzymes that transfers a methyl group from the

methyl donor *S*-adenosyl-methionine (SAM) onto cytosines, thus producing DNA methylation. The promoter for the *reelin* gene shows increased methylation in the brains of patients with schizophrenia compared with control subjects (Abdolmaleky et al. 2005, Grayson et al. 2005). Kundakovic et al. (2007) showed that the inhibition of DNMT1 in neuronal cell lines resulted in the increased expression of both reelin and GAD_{67}. The increase in gene expression was associated with a decreased association of MeCP2, further suggesting that these differences are associated with alteration in DNA methylation. Recall that maternal care directly alters DNA methylation of the GAD_{67} promoter in the rat (Zhang et al. 2009). This effect is associated with a decrease in DNMT1 expression and reduced MeCP2 association with the *GAD1* promoter.

An important question is that of the developmental origins of such differences in DNA methylation. A set of recent studies (McGowan et al. 2009) suggests that epigenetic modifications might occur in humans in response to variations in parent–offspring interactions. DNA was extracted from hippocampal samples obtained from victims of suicide or from individuals who had died suddenly from other causes (auto accidents, heart attacks, etc.). The samples were obtained from the Québec Suicide Brain Bank, which conducts forensic phenotyping that includes a validated assessment of psychiatric status and developmental history (e.g., McGirr et al. 2008). The studies examined the methylation status of the exon 1_F promoter of the glucocorticoid receptor, which corresponds to the exon 1_7 promoter in the rat (Turner & Muller 2005). The results showed increased DNA methylation of the exon 1_F promoter in hippocampal samples from suicide victims compared with controls, but only if suicide was accompanied with a developmental history of child maltreatment. Child maltreatment, independent of psychiatric state, predicted the DNA methylation status of the exon 1_F promoter. As in the previous rodent studies, the methylation state of the exon 1_F promoter also determined the ability of NGFI-A to bind to the promoter and activate gene transcription. Although such studies are obviously correlational and limited by postmortem approaches, the results are nevertheless consistent with the hypothesis that variations in parental care can modify the epigenetic state of selected sites of the human genome. Moreover, the findings are also consistent with studies that link childhood abuse to individual differences in stress responses (Heim et al. 2000). Childhood abuse is associated with an increase in pituitary ACTH responses to stress among individuals with or without concurrent major depression. These findings are particularly relevant, since pituitary ACTH directly reflects central activation of the HPA stress response, and hippocampal glucocorticoid receptor activation dampens HPA activity. The findings in humans are consistent with the rodent studies cited above investigating epigenetic regulation of the glucocorticoid receptor gene and with the hypothesis that early life events can alter the epigenetic state of relevant genomic regions, the expression of which may contribute to individual differences in the risk for psychopathology (Holsboer 2000, Neigh & Nemeroff 2006, Schatzberg et al. 1985).

Certain limitations need to be considered as we integrate epigenetics into the study of psychopathology. The study of epigenetic mechanisms in humans is complicated by the fact that epigenetic marks are often tissue-specific. For example, the brain contains some neurons that synthesize and release dopamine as a neurotransmitter and others that rely on acetylcholine. We might assume that among dopaminergic neurons, the genes associated with the capacity for acetylcholine production are silenced, likely through some level of epigenetic regulation. Such processes are inherent in the specialization of brain cells, as with all other differentiated cells in the body. This process of specialization involves epigenetic regulation and implies that the epigenetic marks vary from cell type to cell type. Indeed, there is considerable variation in epigenetic marks from one brain region to another, perhaps even more so than variation within the same brain region

across individuals (Ladd-Acosta et al. 2007). Brain samples are for the most part beyond direct examination in the living individual at the level of molecular analysis. This often leaves us with measures of DNA extracted from blood or saliva and with the question of whether the epigenetic marks within such samples actually reflect those within the relevant neuronal population. Thus, for the time being advances in the study of "neuroepigenetics" will rely heavily on relevant models with nonhuman species as well as complementary studies of samples from postmortem human brains.

CONCLUSIONS

It is now evident that genomic variation at the level of nucleotide sequence is associated with individual differences in personality and thus with vulnerability and resistance to a wide range of chronic illness (Ebstein 2006, Meyer-Lindenberg & Weinberger 2006, Rutter 2007). The challenge is how to conceptually integrate the findings from genetics into psychology. The operation of the genome is regulated by cellular signals that are responsive to environmental conditions. Thus, the effects of genetic variation are contextually determined and therefore best considered as probabilistic. Genetic variations influence cellular activity and, depending upon current and past environmental conditions, will bias toward particular functional outcomes. The molecular events that mediate gene transcription reveal the interdependence of gene and environment (Sokolowski 2001, Sokolowski & Wahlsten 2001). Oddly, what is perhaps the most profound comment on this issue dates back several years. In response to a question from a journalist considering the relative importance of nature versus nurture in defining individual differences in personality, Hebb responded that such comparisons are akin to asking what contributes more to the area of rectangle, the length or the width? The recent flush of studies examining gene x environment effects on personality and vulnerability/resistance to mental illness (Caspi et al. 2003, Meaney 2009, Rutter 2007, Suomi 2006) reflects the interdependence of genetic and environmental influences, such that the effects at one level can only be understood within the context of the other. Indeed, developmental processes are best considered as the outcome of a constant dialog between the genome and its environment (Bateson 1994; Gottelieb 1997, 1998; Lewontin 1974).

The gene x environment perspective is critical in the establishment of an understanding of the development of individual differences in neural function and personality. Until recently, most experimental approaches were limited to identifying factors that could influence neural development. Our own studies of maternal care in the rat are a case in point. This research examines the effects of variation in maternal care in animals that are housed from weaning onward under identical conditions. We systematically minimize variation from weaning onward. This approach permits conclusions as to the potential effects of variations in maternal care but cannot estimate the importance of such effects for individual differences in adult function under natural conditions. Indeed, environmental enrichment in the postweaning period can reverse effects associated with the variations in maternal care (Bredy et al. 2004, Champagne & Meaney 2006, Zhang et al. 2006). Likewise, studies of monozygotic-dizygotic twins examine what are, in effect, differences in parental gene dosage while minimizing variation in the early environment. Such approaches have provided convincing evidence that genetic factors can influence the development of individual differences, but do not identify how. Indeed, the challenge is to define how, when, and under which conditions specific genetic or environment factors operate to regulate development. Herein lies the enormous contribution of the gene x environment perspective, particularly when integrated into longitudinal studies of development.

The excitement concerning the findings in the area of epigenetics derives from the realization that such mechanisms could form the biological basis for the interplay between environmental signals and the genome. The

studies reviewed here suggest that (*a*) epigenetic remodeling occurs in response to the environmental activation of the classic "activity-dependent" cellular signaling pathways that are associated with synaptic plasticity, (*b*) epigenetic marks, particularly DNA methylation, are actively remodeled over early development in response to environmental events that regulate neural development and function, and (*c*) epigenetic marks at histone proteins and the DNA are subject to remodeling in response to environmental influences even at later stages in development. We have highlighted examples of environmental influences that are of obvious relevance for psychologists. However, increasing evidence from animal studies indicates that prenatal and early postnatal environmental factors, including nutritional supplements, xenobiotic chemicals, and reproductive technologies, can alter the epigenetic state of specific genomic regions (Jirtle & Skinner 2007).

These findings suggest that epigenetic remodeling might serve as an ideal mechanism for phenotypic plasticity—the process whereby the environment interacts with the genome to produce individual differences in the expression of specific traits. One could easily imagine that such processes mediate observed discordances between monozygotic twins (Petronis 2006, Weksberg et al. 2002). Thus, differences at the level of experience might lead to discordance in the nature of the epigenetic marks at specific sites in the genome, leading to differences in phenotype despite a common genotype. If this is the case, then one might expect an increasing degree of discordance in epigenetic marks over time among monozygotic twins, and there is indeed evidence for such an effect (Fraga et al. 2005). The same processes are likely to account for instances of statistical gene–environment interactions, whereby the genotype–phenotype relation is apparent in one environmental context but not in another (Sokolowski & Wahlsten 2000). In such cases, we could imagine an environmentally regulated epigenetic mark that alters the functional consequences of a genomic variation in sequence. Because the operation of the genome is determined by both sequence-based variation as well as epigenetic state, the process of environmentally regulated plasticity of the epigenome emerges as an exciting context for the integration of genetics and psychology.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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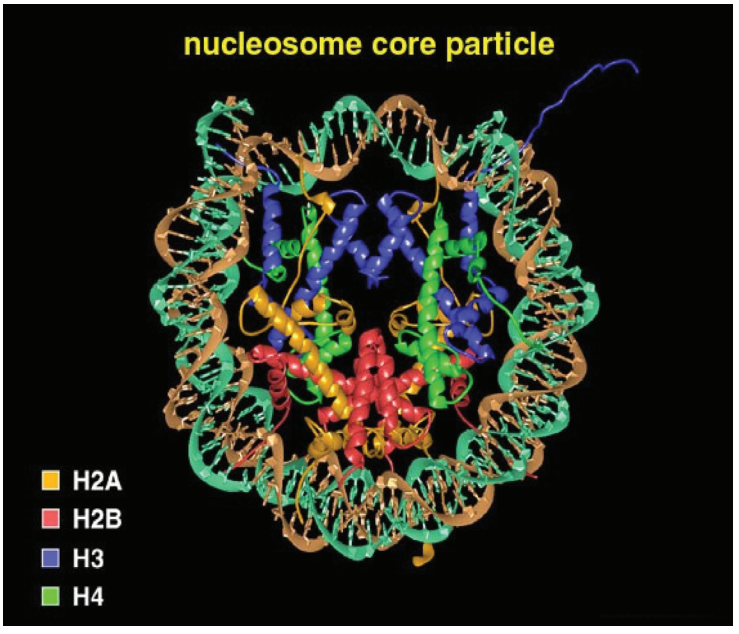

Figure 2

Crystallographic image of the nucleosome showing 145–150 base pairs wrapped around a histone complex that is composed of histone 2A, 2B, 3, and 4 proteins. The tight configuration is maintained, in part, by electrostatic bonds. Modifications, such as acetylation, to the histone regulate transcription factor binding and occur primarily at the histone tails protruding out of the nucleosome (pictured is the blue tail of histone 3).

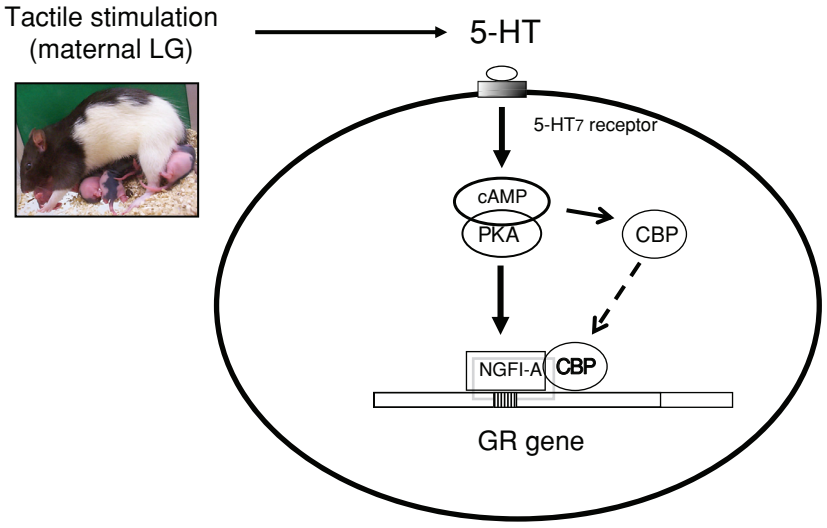

Figure 3

A summary of in vivo studies with hippocampal tissue samples from neonates and in vitro studies using primary hippocampal cell cultures. In vivo, an increased frequency of pup licking/grooming (LG) from the mother associates with hippocampal 5-hydroxytryptamine (5-HT) turnover, activation of a 5-HT7 receptor positively coupled to cyclic adenosine monophosphate (cAMP) and cyclic nucleotide dependent kinases (PKA) and the induction of nerve growth factor–inducible factor A (NGFI-A) expression. In vivo, increased pup LG or artificial tactile stimulation induces NGFI-A expression as well as that of the cAMP-response element-binding protein (CREB)-binding protein, both of which show greater binding to the exon 1_7 promoter in the neonatal offspring high-LG compared with low-LG mothers. Results of in vitro studies show that blockade of cAMP, PKA, or NGFI-A abolish the effect of 5-HT of glucocorticoid receptor expression. GR, glucocorticoid.

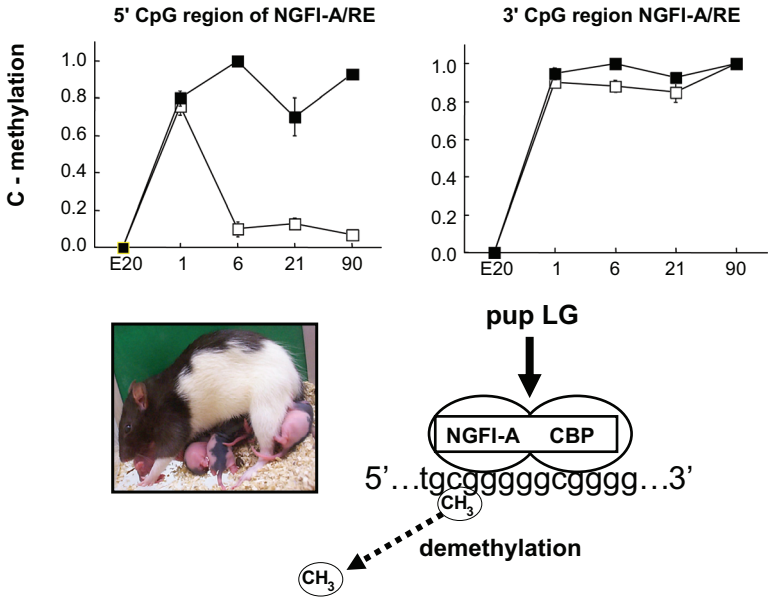

Figure 5

(*Top panels*) A summary of the developmental changes in the methylation status of the 5′ and 3′ CpG (see **Figure 1**) of the nerve growth factor–inducible factor A (NGFI-A) consensus sequence lying within the exon 1_7 glucocorticoid receptor promoter. Note that neither CpG site is methylated in late fetal life, followed by a period of de novo methylation following birth. The critical alteration at the 5′ CpG site involves an apparent demethylation of the site. (*Bottom panels*) A working hypothesis for the experience (maternal care)-driven remodeling of the epigenetic state of the NGFI-A consensus-binding sequence over the first week of postnatal life in the offspring of high-LG mothers. The binding of a NGFI-A/CREB-binding protein (CBP) complex actively targets the as yet unidentified demethylase process resulting in the removal of the methyl group from the 5′ CpG site of the NGFI-A-binding site (Meaney & Szyf 2005). (Top panel adapted from Weaver et al. 2004.)

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Errata

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