

Target Article

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Epigenetic Influence of Social Experiences Across the Lifespan

ABSTRACT: *The critical role of social interactions in driving phenotypic variation has long been inferred from the association between early social deprivation and adverse neurodevelopmental outcomes. Recent evidence has implicated molecular pathways involved in the regulation of gene expression as one possible route through which these long-term outcomes are achieved. These epigenetic effects, though not exclusive to social experiences, may be a mechanism through which the quality of the social environment becomes embedded at a biological level. Moreover, there is increasing evidence for the transgenerational impact of these early experiences mediated through changes in social and reproductive behavior exhibited in adulthood. In this review, recent studies which highlight the epigenetic effects of parent–offspring, peer and adult social interactions both with and across generations will be discussed and the implications of this research for understanding the developmental origins of individual differences in brain and behavior will be explored. © 2010 Wiley Periodicals, Inc. Dev Psychobiol*

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INTRODUCTION

Development typically occurs within a social context. The relationship between the quality of the early social environment and risk or resilience to subsequent physiological, neurobiological, and behavioral outcomes has been explored in longitudinal studies in humans and in experimental settings within the laboratory using a variety of animal models. Both of these approaches have provided evidence for the profound effects of social-interactions on the developing brain. Classic examples of these associations can be found in the mother–infant attachment literature, with a secure attachment relationship predicting long-term resilience to physical and psychological distress and insecure relationships predicting increased risk of anxiety and depression (Sroufe, 2005). Maternal

sensitivity to infant behavioral cues is critical in the formation of a secure attachment and low levels of sensitivity are associated with increased fearfulness, negative affect, and EEG asymmetry amongst 9-month-old infants (Hane & Fox, 2006). The effects of variations in parental care persist into adulthood with high parental bonding associated with elevated self-esteem, reduced trait anxiety, decreased salivary cortisol, and reduced activation within the ventral striatum in response to stress (Lee, Gollan, Kasckow, Geraciotti, & Coccaro, 2006; Pruessner, Champagne, Meaney, & Dagher, 2004). These findings complement work in primates and humans on the consequences of early-life social deprivation (Fries, Shirtcliff, & Pollak, 2008, 2005; Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005; Harlow, Dodsworth, & Harlow, 1965; Seay & Harlow, 1965; Suomi, Harlow, & Kimball, 1971) and suggest that the social environment can lead to divergent developmental pathways with implications for the adult brain and behavior.

Study of the biological basis of these effects has relied primarily on rodent models in which the quality of the early social environment is characterized or manipulated and then associated with specific neuroendocrine and behavioral changes. A common theme that emerges from these studies is the finding that environmentally induced

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variations in gene expression both within the brain and the periphery can persist beyond infancy and be observed in adulthood suggesting that there is an interplay between genes and the environment that may be critical in mediating the long-term effects of social experiences. Exploration of the molecular mechanisms through which these effects are achieved has provided exciting new insights into dynamic nature of gene regulation and the potential of these mechanisms to serve as an underlying biological link between experiences of an organism and individual differences in neurodevelopment, physiology, and behavior. Importantly, there appears to be plasticity in gene regulation in response to experiences across the lifespan. Thus, the quality of the social environment beyond infancy is capable of shifting patterns of gene expression with consequences for the functioning of the individual within their social context. These epigenetic effects may play a critical role in developmental plasticity and in mediating adaptive responses to environmental conditions both within and across generations. In this review, evidence for the influence of parent–offspring, juvenile, and adult social interactions on epigenetic mechanisms (see Fig. 1) will be explored and the implications of these effects for transgenerational inheritance of environmentally induced changes in phenotype will be discussed.

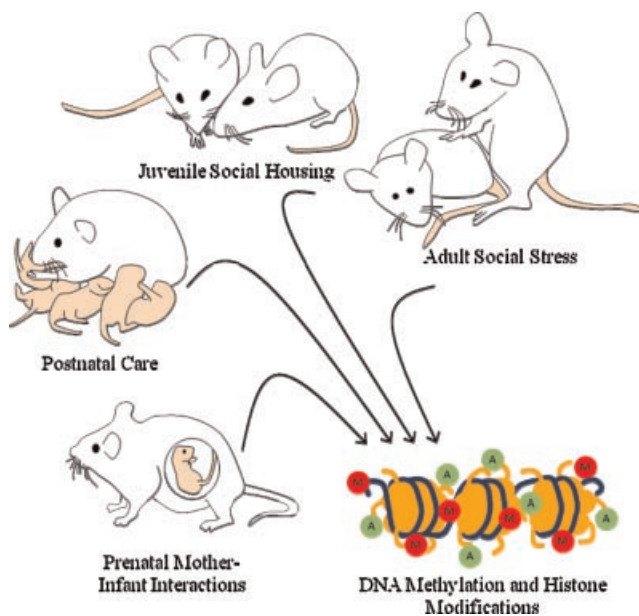


FIGURE 1 Epigenetic consequences of social experiences across the lifespan. Emerging evidence suggests that prenatal environmental exposures, postnatal mother–infant interactions, juvenile social rearing, and adult social stress can alter epigenetic processes such as DNA methylation (red circles) and histone acetylation (green circles)/methylation with long-term consequences for gene expression, physiology, and behavior.

EPIGENETICS: LINKING GENES AND ENVIRONMENT TO DEVELOPMENT

Historically, the term “epigenetic” was used to describe the dynamic interplay between genes and the environment which leads to variations in phenotype (Jablonka & Lamb, 2002). Broadly, this term is currently used to describe phenotypic variation that is not attributable to genetic variation with more specific definitions referring to the molecular mechanisms that achieve these non-genomic effects. Variation in gene expression rather than gene sequence is the key concept within the study of epigenetics. The molecular mechanisms through which this regulation occurs are many and varied (Feng, Fouse, & Fan, 2007; Razin, 1998; Turner, 2001). Ultimately, the transcriptional activity of a gene is dependent on the accessibility of the DNA to RNA polymerase and other gene-specific transcription factors. In densely packed chromatin, this accessibility is reduced and gene expression is repressed. Within the cell nucleus, DNA is wrapped around a core of histone proteins which can undergo multiple post-translational modifications including methylation, acetylation, and ubiquitination (Peterson & Laniel, 2004; Zhang & Reinberg, 2001). These modifications alter the dynamic interactions between the histones and DNA which either reduce or enhance the accessibility of DNA. In particular, histone acetylation is associated with increased transcriptional activity whereas histone deacetylation or methylation is associated with transcriptional repression. Acetylation of histones is mediated by the enzyme histone acetyltransferase (HAT), whereas histone deacetylase (HDAC) promotes removal of the acetyl group from the histone tails. Thus, through alterations in the conformation of histones, the accessibility of DNA can be rapidly and reversibly altered.

The epigenetic process of DNA methylation represents what is generally considered a more stable and enduring modification to the activity of genes. DNA methylation occurs when cytosine nucleotides within DNA become converted to 5-methylcytosine. This process is mediated by methyltransferases which either promote maintenance (i.e., DNMT1) or de novo DNA methylation (i.e., DNMT3) (Feng et al., 2007; Razin, 1998; Turner, 2001). The conversion to 5-methylcytosine does not alter the DNA sequence but does reduce the likelihood that that sequence of DNA will be transcribed. Methylated DNA attracts methyl-binding proteins, such as MeCP2, which further reduce the accessibility of the gene and is associated with transcriptional repression (Fan & Hutnick, 2005). The stability of DNA methylation patterns within the genome permits the stable regulation of gene expression associated with cellular differentiation. Importantly, during cell division, both DNA and

DNA methylation patterns are inherited by daughter cells, thus allowing differentiated cells to transmit their phenotype to the next generation of cells (Fukuda & Taga, 2005).

Epigenetic regulation of gene expression is particularly important during the early stages of development. The reorganization of maternal and paternal genetic material immediately post-fertilization is associated with decreased levels of 5-methylcytosine of the male pronucleus with species-specific differences in the degree of demethylation (McLay & Clarke, 2003; Santos, Hendrich, Reik, & Dean, 2002; Young & Beaujean, 2004). The male pronucleus is also subject to further epigenetic modification through the replacement of protamines with acetylated histone proteins in the chromatin structure following fertilization (Nonchev & Tsanev, 1990). Oocyte factors seem to be critical in the chromatin remodeling that occurs during this phase and there is evidence for species differences in the capacity of oocytes to induce epigenetic change (Beaujean et al., 2004). Zygotic genes are silenced through chromatin-mediated suppression of transcription during the post-fertilization phase and thus all protein synthesis is mediated by maternal mRNAs and enzymes alone until zygotic gene activation during the 2-cell embryo stage (De Sousa, Caveney, Westhusin, & Watson, 1998; Nothias, Majumder, Kaneko, & DePamphilis, 1995). The importance of DNA methylation and histone acetylation for embryonic survival is further illustrated by gene-knockout studies in mice. Targeted deletion of the histone acetyltransferase *Gcn5* gene is lethal and even when apoptosis is suppressed in *Gcn5*^{-/-} embryos, mortality is only delayed and associated with deficits in neural tube closing (Bu, Evrard, Lozano, & Dent, 2007). Deletion of *DNMT1* is associated with genome wide hypomethylation whereas over-expression of this gene leads to DNA hypermethylation and both of these genetic manipulations induce embryonic lethality (Biniszkiwicz et al., 2002; Jackson-Grusby et al., 2001). Levels of DNMT1 may be of particular importance in maintaining the mono-allelic expression of imprinted genes. Maternally and paternally imprinted genes exhibit parent-of-origin expression patterns that are maintained through epigenetic mechanisms such as DNA methylation. These genes have a variety of functions and the appropriate silencing of either the maternal or paternal allele is essential to establishing normal patterns of growth and development (Reik, Davies, Dean, Kelsey, & Constancia, 2001). Disruption to the expression of *DNMT1* or the de novo methyltransferases *DNMT3a/3b* can lead to altered genomic imprinting (Biniszkiwicz et al., 2002; Okano, Bell, Haber, & Li, 1999). Overall, it is evident that the fine control of gene expression mediated through epigenetic mechanisms determines the successful transition from

zygote to embryo to fetus and sets the stage for the regulation of prenatal and postnatal developmental influences.

MATERNAL EFFECTS DURING FETAL DEVELOPMENT

Though consideration of the social influences on development does not typically include the prenatal period, there is increasing evidence for the epigenetic influence of maternal nutrition, physiology, and psychological state on the developing fetus that are relevant to our understanding of how the social and environmental experiences of the mother can lead to divergent developmental pathways of offspring. The quality of the maternal nutritional environment during pregnancy can have a significant impact on the growth and development of the fetus, with long-term consequences for brain development and metabolism (Godfrey & Barker, 2001; Symonds, Stephenson, Gardner, & Budge, 2007; Zeisel, 2009). Epidemiological studies of cohorts exposed prenatally to conditions of famine, suggest a heightened risk of schizophrenia, affective disorders, antisocial personality, and other neurodevelopmental abnormalities. Analysis of blood samples from famine exposed versus non-exposed siblings indicates that there is decreased DNA methylation of the insulin-like growth factor II (*IGF2*) gene as a consequence of maternal periconceptual exposure to famine (Heijmans et al., 2008). Laboratory studies in rodents have subsequently identified specific nutritional deficits, such as prenatal protein restriction or folic acid/choline deficiency as having similar epigenetic consequences. Offspring of female rats placed on a protein deficient diet throughout gestation were found to have elevated hepatic glucocorticoid receptor (*GR*) and peroxisomal proliferator-activated receptor (*PPAR*) gene expression associated with decreased DNA methylation of these genes (Lillycrop, Phillips, Jackson, Hanson, & Burdge, 2005; Lillycrop et al., 2008). Moreover, these epigenetic effects are not observed when gestational protein restriction is accompanied by folic acid supplementation (Lillycrop et al., 2005). Dietary effects on levels of DNMT1 may account for these observed modifications in global and gene-specific methylation, as *DNMT1* expression is increased in hepatic (Lillycrop et al., 2007) and brain tissue (Kovacheva et al., 2007) as a function of protein/choline restriction. The impact of dietary supplementation with methyl-donors during fetal development is also clearly demonstrated by the consequences for phenotype amongst mice with the *A^{vy}* or *Axin^{Fu}* epialleles. The expression of these alleles is epigenetically regulated through levels of DNA methylation, with decreased methylation associated with yellow

coat color and obesity amongst A^{vy} mice or a “kinky” tail phenotype amongst $Axin^{Ftu}$ mice (Morgan, Sutherland, Martin, & Whitelaw, 1999; Rakan et al., 2003). Though there is typically an epigenetic inheritance of these phenotypes, gestational exposure to methyl donors through dietary supplementation of the mother can effectively silence the expression of these alleles with the consequence of inducing a pseudo wild-type phenotype (Waterland et al., 2006; Wolff, Kodell, Moore, & Cooney, 1998). Thus, the maternal nutritional environment can have a sustained impact on development through alterations in gene expression that are maintained through DNA methylation.

The rapid period of cellular proliferation and differentiation that occurs during fetal development provides a critical window during which maternal gestational exposure to toxins may lead to long-term disruptions in offspring and there is increasing evidence for the epigenetic basis of these effects. In utero methyl mercury exposure in mice has been shown to lead to DNA hypermethylation, increased histone tri-methylation, and decreased histone acetylation within the IV promoter of the brain-derived neurotrophic factor (*BDNF*) gene in the hippocampus of offspring and is associated with depressive-like behaviors (Onishchenko, Karpova, Sabri, Castren, & Ceccatelli, 2008). Prenatal exposure of pregnant mice to inhaled diesel exhaust particles combined with an allergen results in altered immunoglobulin (IgE) levels associated with hypermethylation of the interferon (*IFN*)-gamma promoter and hypomethylation of the interleukin (*IL*)-4 promoter (Liu et al., 2008). Altered DNA methylation within these immune pathways may account for observed maternal effects of prenatal smoking on offspring asthma risk (Li, Langholz, Salam, & Gilliland, 2005). In rats, prenatal exposure to the anti-androgenic fungicide vinclozolin or the estrogenic pesticide methoxychlor results in increased rates of prostate disease, kidney disease, immune system abnormalities, testis abnormalities, and tumor development (Anway, Leathers, & Skinner, 2006). This exposure is associated with altered DNA methylation patterns in sperm and impairments in reproduction in male offspring (Anway, Cupp, Uzumcu, & Skinner, 2005). In utero exposure to the endocrine disruptor bisphenol-A (BPA) has been demonstrated to induce widespread changes in promoter methylation in the fetal mouse brain, with consequences for neural development (Yaoi et al., 2008). BPA-induced hypomethylation of the A^{vy} allele in mice leads to metabolic abnormality and obesity in adulthood. Interestingly, these toxin-induced effects can be reversed through folate supplementation in the mother’s diet (Dolinoy, Huang, & Jirtle, 2007), suggesting that abnormalities in DNA methylation can be ameliorated through exposure to increased levels of methyl-donors.

The timing of dietary supplementation may be critical in determining the ameliorating effects of folate, as recent studies have indicated that the epigenetic effects of prenatal protein restriction are not reversed when the diet is subsequently enriched with folate during juvenile development (Burdge et al., 2009).

Evidence for the epigenetic influence of antenatal maternal mood has emerged from human cohort studies and animal models; providing further support for the role of epigenetic mechanisms in mediating developmental outcomes. Analysis of cord blood samples from infants born to mothers with elevated ratings of depression (using the Hamilton Depression Scale) during the third trimester of pregnancy indicates elevated *GR* 1F promoter DNA methylation levels associated with maternal depressed mood (Oberlander et al., 2008). Moreover, the level of methylation within the neonatal *GR* 1F promoter predicts increased salivary cortisol levels of infants at 3 months of age and these effects are independent of exposure to selective serotonin reuptake inhibitors during pregnancy. The long-term consequences of prenatal stress for brain and behavior have likewise been explored with recent evidence of altered gene expression and DNA methylation within the placenta and hypothalamus as possible mediators of these maternal effects. In mice, chronic variable stress during the first trimester is associated with decreased DNA methylation of the corticotrophin-releasing-factor (*CRF*) gene promoter and increased methylation of the *GR* exon 1₇ promoter region in hypothalamic tissue of adult male offspring (Mueller & Bale, 2008). Gestational stress within these experiments was found to exert sex-specific effects on the expression of *DNMT1* in the placenta which may induce disruption of the epigenetic status of genes within this critical interface between mother and fetus. Imprinted genes, such as *IGF2*, may be particularly sensitive to this disruption, leading to impairments in placental growth and function with subsequent consequences for offspring growth and neurodevelopment (Reik et al., 2003).

Epigenetic regulation during these early stages of development and the implications for social behavior can also be explored in insects, providing some intriguing insights into the developmental origins of reproductive behavior. Honeybees (*Apis mellifera*) have functional DNA methyltransferases and the degree of methylation of the genome varies during the course of development (Wang et al., 2006). Amongst female honeybees, social/reproductive caste is determined through early nutritional exposure to royal jelly (Laidlaw, 1992). Larvae provided with a diet composed primarily of royal jelly grow more rapidly, have well-developed ovaries and emerge as queen bees. In contrast, worker bees are not provided with high levels of this rich nutritional resource and thus are smaller with only rudimentary ovaries. These caste differences in

development are associated with differential gene expression in queen bees versus workers (Evans & Wheeler, 1999). Manipulation of the activity of *DNMT3* in honey bee larvae through use of RNA interference provides evidence that DNA methylation mediates these divergent phenotypes (Kucharski, Maleszka, Foret, & Maleszka, 2008). Under control conditions, 75% of larvae develop as worker bees whereas inhibiting *DNMT3* leads to the majority of larvae developing morphologically as queen bees. Thus, the capacity of royal jelly to induce caste differences in this eusocial insect may be linked to the presence of factors which inhibit DNA methylation.

EPIGENETIC MODIFICATION DURING EARLY INFANCY

Though dynamic epigenetic modifications were once thought to be limited to the very early stages of development, evidence for continued parental influence on DNA methylation beyond the prenatal period has challenged this view. Studies of the effects of natural variations in postnatal care in rodents have established the mediating role of epigenetic factors in shaping individual differences in brain and behavior (Meaney, 2001; Szyf, Weaver, Champagne, Diorio, & Meaney, 2005). Postnatal maternal licking/grooming (LG) behavior, in particular, has been found to induce increased hippocampal *GR* expression leading to more efficient negative feedback of the stress response with consequences for behavioral response to novelty and cross-fostering studies have confirmed that these effects are mediated by the level of maternal care received during postnatal development (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997). Analysis of the *GR* 1₇ promoter region suggests that variations in *GR* expression associated with differential levels of maternal care are maintained though altered DNA methylation (Weaver et al., 2004). Thus, offspring who receive high levels of maternal LG during the early postnatal period have decreased hippocampal *GR* 1₇ promoter methylation, increased *GR* expression, and decreased stress responsivity. In contrast, low levels of LG are associated with increased *GR* 1₇ methylation, decreased *GR* expression and an increased hypothalamic–pituitary–adrenal (HPA) response to stress. Time course analysis has indicated that these maternally induced epigenetic profiles emerge during the postnatal period and are sustained into adulthood (Weaver et al., 2004). The pathways through which these effects are achieved are currently being elucidated and it appears likely that maternal LG mediated up-regulation of nerve growth factor inducible protein A (NGFI-A) in infancy may be critical to activating *GR* transcription and

maintaining low levels of DNA methylation within the *GR* 1₇ promoter (Weaver et al., 2007). Though these epigenetic effects can be stably maintained into adulthood, pharmacological targeting of the epigenome through exposure to the HDAC inhibitor trichostatin-A or to methionine (a methyl donor) can reverse the effects of early maternal care on *GR* methylation and expression (Weaver et al., 2004, 2005).

Though the exploration of these brain region-specific maternal effects in humans is limited by the inaccessibility of brain tissue, recent studies have illustrated the long-term effects of childhood abuse on hippocampal DNA methylation patterns of suicide victims (McGowan et al., 2008, 2009). Analysis of hippocampal tissue from suicide victims with a history of childhood abuse indicates decreased *GR* expression and elevated *GR* 1F promoter methylation associated with disruptions of the early environment. These studies also confirm the potential role of NGFI-A as a mediator of differential *GR* promoter methylation (McGowan et al., 2009). Early life effects on *GR* signaling pathways in humans are further illustrated by a recent genome wide analysis of gene expression of peripheral blood mononuclear cells from healthy adults who had experienced conditions of low versus high socioeconomic (SES) status during childhood, with low childhood SES associated with a down-regulation of genes containing *GR* response elements (Miller et al., 2009).

The influence of maternal care during early postnatal development is not limited to effects on stress responsivity/*GR* negative feedback. In rodents, exposure of female neonates to low levels of LG leads to reduced expression of estrogen receptor alpha (*ER*α) in the medial preoptic area (MPOA) of the hypothalamus (Champagne, Weaver, Diorio, Sharma, & Meaney, 2003). These effects on *ER*α expression are sustained into adulthood with consequences for the estrogen sensitivity of these females. During late gestation, there is typically increased levels of circulating estrogen which serve to “prime” the mother for the behavioral and physiological demands of parturition and lactation. Within the MPOA of female offspring who received low levels of LG in infancy, there is reduced neural activation in response to estrogen and reduced estrogen-mediated increases in levels of oxytocin receptors (Champagne, Diorio, Sharma, & Meaney, 2001; Champagne, Weaver, et al., 2003). As a consequence of this reduced priming, female offspring who received low levels of LG also provide low levels of this form of maternal care to their own offspring. Analysis of the 1B promoter region of the *ER*α gene in MPOA tissue implicates DNA methylation as a potential mediator of these maternal effects. At several sites within the *ER*α promoter there is elevated DNA methylation associated with exposure to low levels of LG (Champagne et al.,

2006). Chromatin immunoprecipitation assays demonstrate that this differential DNA methylation has consequences for the binding of transcription factors such as STAT5a to the 1B promoter. Maternal LG is associated with increased levels of STAT5a during the postnatal period and the increased levels of this factor may lead to sustained activation of transcription and reduced DNA methylation.

Variations in mother–infant interactions can also be induced in laboratory rodents with consequences for the epigenetic regulation of genes involved in developmental plasticity. Disruption to the nesting materials within a female’s home cage can lead to abusive caregiving characterized by increased frequency of rough handling, dragging, dropping, and stepping on pups (Roth & Sullivan, 2005). Daily exposure to this form of abusive social interaction leads to reduced expression of *BDNF* in the prefrontal cortex in adulthood associated with increased DNA methylation within the IV *BDNF* promoter region (Roth, Lubin, Funk, & Sweatt, 2009). The functional importance of DNA methylation in mediating the long-term effects of abuse is further supported by findings that central administration of zebularine, a compound that reduces DNA methylation, leads to increased *BDNF* expression in maltreated rats such that *BDNF* levels are equivalent amongst abused and non-abused offspring. Thus, as is the case for natural variations in LG, there are persistent epigenetic consequences of early-life experience that have consequences for gene expression and the adult brain.

BEYOND INFANCY: PLASTICITY DURING JUVENILE DEVELOPMENT

Illustrations of the importance of the social environment beyond early infancy in promoting species-specific patterns of social behavior suggest the occurrence of plasticity during later periods of development. Social isolation of juvenile rhesus macaques leads to increased cortisol and reduced immune responsiveness (Gordon et al., 1992). Juvenile social isolation in rodents induces what has been referred to as an “isolation syndrome” characterized by multiple behavioral and neuroendocrine changes which can be attenuated by treatment with antidepressants (Heritch, Henderson, & Westfall, 1990). In contrast, social and physical enrichment during the post-weaning period leads to increased synaptic plasticity, improved cognition, and reduced anxiety-like behavior (Nithianantharajah & Hannan, 2006). Increasing environmental complexity during the juvenile period has also been demonstrated to compensate for deficits in brain and behavior induced by exposures occurring during prenatal

and postnatal development. Prenatal stress-induced reductions in social play behavior and increases in corticosterone response to stress in rat offspring can be reversed through post-weaning environmental enrichment (Morley-Fletcher, Rea, Maccari, & Laviola, 2003). Amongst offspring who experienced low levels of maternal LG, social and physical environmental enrichment can reduce deficits in maze learning ability, increase exploratory behavior, and increase maternal care (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Bredy, Zhang, Grant, Diorio, & Meaney, 2004; Champagne & Meaney, 2007).

Post-weaning environmental manipulations have been demonstrated to delay onset of symptomatology in genetic mouse models of Huntington’s and Alzheimer’s disease (Jankowsky et al., 2005; van Dellen, Blakemore, Deacon, York, & Hannan, 2000) and to promote recovery following stroke (Buchhold et al., 2007) or CNS damage (Kim, Dai, McAtee, & Bregman, 2008). The mechanism through which these effects are achieved may be dependent on the underlying neurobiological or physiological deficit. For example, mutation of the *Huntingtin* gene leads to reductions in *BDNF* transcriptional activity leading to the neurodegeneration associated with Huntington’s disease (Zuccato et al., 2005) and environmental enrichment has been demonstrated to delay the onset of motor deficits and decreases in brain volume in mice with the Huntington’s transgene (Hockly et al., 2002; van Dellen et al., 2000). This environmental manipulation has been found to up-regulate *BDNF* levels amongst *Huntingtin*-deficient mice, though these effects may not be due to changes in *BDNF* promoter methylation (Zajac et al., 2009). Recovery of memory deficits induced through p25-mediated neuronal loss can be achieved through exposure to complex housing environments and this enrichment is associated with increased histone (H3 and H4) acetylation in hippocampus and cortex (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). Moreover, treatment with histone deacetylase inhibitors can mimic the effects of environmental enrichment on learning and synaptic plasticity. Though these studies do not differentiate between aspects of the social versus physical environment, it is clear that the quality of environmental conditions beyond the postnatal period can have significant implications for adult behavior.

SOCIAL INTERACTIONS IN ADULTHOOD: EPIGENETIC CONSEQUENCES OF SOCIAL DEFEAT

The influence of adult social interactions on physiology and behavior has been observed in humans, primates, and

rodents, suggesting continued plasticity in developmentally mature organisms. The quality of the social stimuli and the relationship of the subject to those stimuli are particularly important in predicting the nature of the effect of adult social interactions. One experimental model that has been used to study the long-term consequences of adult social experience involves exposure of individuals to social defeat (Martinez, Calvo-Torrent, & Herbert, 2002; Tamashiro, Nguyen, & Sakai, 2005). In rodents, territorial aggression can be established such that when an "intruder" is introduced into a new territory, high levels of agonistic behaviors (fighting and submissive postures) will be observed, with the intruder typically being exposed to repeated defeats during social encounters. Socially defeated males manifest numerous behavioral and neuroendocrine changes, including reduced locomotion (Meerlo, Overkamp, Benning, Koolhaas, & Van den Hoofdakker, 1996; Raab et al., 1986), decreased social behavior (Meerlo, Overkamp, Daan, Van Den Hoofdakker, & Koolhaas, 1996), increased drug self-administration (Haney, Maccari, Le Moal, Simon, & Piazza, 1995), and increased HPA activity (Blanchard, Sakai, McEwen, Weiss, & Blanchard, 1993; Keeney et al., 2006). This cascade of neurobehavioral change induces a depression-like state that can be effectively treated with antidepressants (Keeney & Hogg, 1999; Rygula, Abumaria, Domenici, Hiemke, & Fuchs, 2006). These data are consistent with clinical and epidemiological studies suggesting that chronic social stress plays a significant role in the development of psychopathology.

The epigenetic basis of the effects of social defeat has been explored and suggests that transcriptional activity of *BDNF* may be a target of this environmental exposure. *BDNF* gene expression is significantly decreased in the hippocampus of socially defeated male mice and this effect appears to be mediated by specific decreases in the *BDNF* III and IV transcripts (Tsankova et al., 2006). These effects are observed a month following exposure to the social stress, indicating a persistent effect on gene expression. Chromatin immunoprecipitation assay analysis indicates increased histone H3-K27 dimethylation at the *BDNF* III and IV promoters amongst socially defeated males which may account for the reduced *BDNF* expression. Histone deacetylase (*HDAC5*) mRNA levels are also found to be decreased in socially defeated males (Tsankova et al., 2006). *HDAC5* appears to be important in mediating the effects of anti-depressant treatment in males exposed to chronic social stress (Renthal et al., 2007). The differential levels histone H3-K27 dimethylation observed in the hippocampus is also found across the genome in the nucleus accumbens, both in response to chronic social defeat and prolonged adult social isolation (Wilkinson et al., 2009). Analysis of histone acetylation in

the nucleus accumbens indicates that H3-K14 acetylation is initially decreased and then increased following chronic social defeat associated with decreases in *HDAC2* levels. The behavioral consequences of social defeat, such as decreased social behavior, can be reversed with an *HDAC* inhibitor infused into the nucleus accumbens (Covington et al., 2009). The effects on gene expression of this pharmacological targeting of the histones is very similar to that achieved using fluoxetine. Interestingly, post-mortem analysis of brain tissue from depressed patients indicates increases in H3-K14 acetylation and decreased *HDAC2* levels similar to those observed in socially defeated mice (Covington et al., 2009), suggesting that there may be an environmentally induced-epigenetic substrate associated with human mental illness.

TRANSGENERATIONAL EFFECTS OF THE SOCIAL ENVIRONMENT

There is increasing evidence for the transgenerational impact of early life experiences mediated either through germline epigenetic inheritance or experience-dependent epigenetic modifications. Laboratory studies in rodents have demonstrated the transgenerational impact of nutrition and indicate that prenatal protein restriction can exert effects on growth and metabolism of offspring and grand-offspring through changes in methylation status of *GR* (Zambrano et al., 2005). When F0 female mice are exposed to caloric restriction during late gestation, F2 grand-offspring are found to have impaired glucose tolerance and this effect is maintained even when the F1 generation is provided with ad libitum food throughout their lifetime. The consequences of in utero exposure to endocrine disrupting compounds has also been explored within a transgenerational model and provides evidence for the pervasive effects on epigenetic profiles of these early life exposures. In humans, matrilineal transmission of the effects of diethylstilbestrol (DES)-induced hypomethylation and increased cancer risk has been observed in daughters and granddaughters (Newbold, Padilla-Banks, & Jefferson, 2006). In utero exposure to vinclozolin in rats has been demonstrated to disrupt DNA methylation in sperm and increase rates of infertility and risk of prostate and kidney disease in F1, F2, and F3 offspring with the transmission through the patriline (Anway et al., 2005). Vinclozolin-induced alterations in gene expression within the hippocampus and amygdala have also been observed for up to three generations post-exposure with sex-specific effects on anxiety-like behavior (Skinner, Anway, Savenkova, Gore, & Crews, 2008). Mate-choice studies suggest that females

presented with F3 vinclozolin-exposed or non-exposed males show a significant partner preference for non-exposed males, indicating an additional measure of decreased reproductive success as a consequence of treatment with endocrine disruptors (Crews et al., 2007). The persistence of these disruptions beyond the F2 generation suggests that the effects of these exposures have become incorporated into the germline and there is incomplete erasure of the associated epigenetic marks during the process of gametogenesis, fertilization, and embryogenesis (Skinner, 2008).

Across species, there is evidence for the transmission of individual differences in maternal behavior from mother to offspring and grand-offspring (Benoit & Parker, 1994; Berman, 1990; Champagne & Meaney, 2001; Maestripieri, 2005; Miller, Kramer, Warner, Wickramaratne, & Weissman, 1997). The epigenetic mechanisms involved in this transmission has been explored in laboratory rodents. Natural variations in maternal LG observed in the F0 generation in rats are associated with similar levels of LG in F1 and F2 generation females (Champagne, Francis, Mar, & Meaney, 2003; Champagne & Meaney, 2007). As such, under stable environmental conditions, offspring and grand-offspring of Low LG females display low levels of LG whereas offspring and grand-offspring of High LG females display high levels of LG. Similar to the transgenerational effects of abuse in macaques, cross-fostering studies have demonstrated that the transmission of maternal LG from mother to female offspring is dependent on the level of maternal LG received in infancy (Champagne, Francis, et al., 2003; Francis et al., 1999; Maestripieri, 2005). Further evidence for the experience-dependent nature of these effects comes from studies in which maternal LG is altered, through chronic exposure to stress (Champagne & Meaney, 2006) or manipulation of the juvenile environment (Champagne & Meaney, 2007), leading to a disruption of the inheritance of the predicted maternal phenotype. Studies of the effect of maternal LG on DNA methylation within the *ER α* promotor (Champagne et al., 2006) suggest that epigenetic modifications to a gene that regulates several aspects of reproduction, including postpartum maternal behavior, results in differential levels of expression of *ER α* in adulthood. Consequently, estrogen sensitivity is altered leading to variations in the level of maternal care that these females provide to their own offspring (Champagne et al., 2001; Champagne, Weaver, et al., 2003). The transmission from mother to daughter of variations in maternal LG within this transgenerational framework is mediated by the stability of brain region-specific epigenetic modifications that occur in infancy and influence behavior in adulthood (Champagne, 2008). A similar experience-dependent transmission of behavior is observed in

response to exposure to abuse. Female rat pups exposed to abusive caregiving in infancy engage in abusive caregiving toward their own offspring and F2 offspring of these F1 females had elevated levels of methylation within the *BDNF* promotor in the PFC and hippocampus (Roth et al., 2009). Interestingly, postnatal cross-fostering of F2 females to non-abusive dams did not reverse these epigenetic effects, suggesting that there may be prenatal factors that contribute to the generational transmission of altered DNA methylation patterns.

CONCLUSIONS

Development is a dynamic process during which there is constant and reciprocal interaction between and organism and its environment. Emerging evidence suggests that epigenetic modifications may serve as a critical mechanism through which experiences occurring during the lifespan of an organism can have sustained effects on behavior. Though this may be true of numerous types of experiences, including nutritional intake or exposure to drugs/toxins, these mechanisms also appear to mediate the effects of social experiences. The biologically embedding of the quality of the social environment may have adaptive versus maladaptive consequences dependent on the context of the individual. For example, the effects of low childhood SES on gene expression profiles suggests the induction of a defensive phenotype, characterized by heightened immune and HPA reactivity which may better prepare an organism for conditions of threat (Miller et al., 2009). However, long-term exposure to these defensive responses may increase the likelihood of physical and psychiatric illness. The converging evidence for the role of DNA methylation and histone modifications in mediating the effects of social experiences may also provide insights into therapeutic approaches which can be used to reverse the consequences of early or later-life exposures. Though the appropriateness and feasibility of such an approach in clinical populations has yet to be determined, the data derived from rodent studies certainly provides support for the value of epigenetic therapy. Finally, the notion that the quality of the social environment can have a transgenerational impact is gaining considerable empirical support (Arai, Li, Hartley, & Feig, 2009; Curley, Champagne, Bateson, & Keverne, 2008). Though our current understanding of the specific role of epigenetic modifications in mediating this transmission is still evolving, there is clear evidence that environmentally induced changes in brain and behavior can influence offspring and grand-offspring with implications for research perspectives on the inheritance of risk and resilience in response to social interactions.

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