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Epigenetic mechanisms in the development of behavior: advances, challenges, and future promises of a new field

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Abstract

In the past decade, there have been exciting advances in the field of behavioral epigenetics that have provided new insights into a biological basis of neural and behavioral effects of gene-environment interactions. We now understand that changes in the activity of genes established through epigenetic alterations occur as a consequence of exposure to environmental adversity, social stress, and traumatic experiences. DNA methylation in particular has thus emerged as a leading candidate biological pathway linking gene-environment interactions to long-term and even multi-generational trajectories in behavioral development, including the vulnerability and resilience to psychopathology. To highlight advances concerning this theme I will first discuss what we have learned from studies using animal models with relevance to developmental psychopathology and from studies in which the translation of these findings has been made to humans. Second, I will highlight studies concerning the significance of DNA methylation alterations in outcomes associated with stress exposure later in life and dysfunction in the form of neuropsychiatric disorders. Finally, I will discuss several unanswered questions that once addressed, hold promise to advance our understanding of epigenetics both as a mechanism by which the environment can contribute to the development of psychiatric disorders and as an avenue for more effective intervention and treatment strategies.

Keywords

epigenetics; DNA methylation; psychopathology; early-life stress; trauma

Psychological and social-contextual factors are recognized for their ability to produce profound effects on brain development and plasticity, and in turn, their influence on the development of behavior. Mechanisms underlying these environmentally-driven phenomena are not fully understood, but over the past decade the birth of epigenetics research has caused a paradigm shift to occur with respect to our understanding of gene-environment interactions in this capacity. It has become clear that epigenetic processes such as DNA methylation (Figure 1) actively regulate our genomes in response to environmental input, and are poised to do so not just during early-life development but as we develop throughout the lifespan. One alluring aspect of epigenetic regulation of gene expression that has emerged too is its capability to drive long-term and even multi-generational trajectories in

behavioral development. The birth of epigenetics research has thus provided an exciting new level of analysis for understanding tenets central to the discipline of developmental psychopathology.

Central to a developmental psychopathology perspective is examining the biological, psychological, and social-contextual factors that facilitate adaptation and maladaptation across the lifespan (Cicchetti, 1993; Cicchetti, 2006; Sroufe & Rutter, 1984). As will be reviewed here, studies have demonstrated that DNA methylation alterations are biological responses to psychological and social-contextual factors. This has afforded a new framework to understand how psychological and social-contextual factors can interact with our biology, and in turn, a route through which behavior could arise. Indeed the dynamic nature of DNA methylation renders it an ideal substrate that is responsive to environmental factors, while its stable nature renders it capable of maintaining sustained changes in brain function and behavior that are a consequence of environmentally-driven changes in gene regulation and activity. Also central to a developmental psychopathology perspective is the examination of risk and protective processes and mechanisms in typical and atypical development (Cicchetti, 1993; Cicchetti, 2006; Sroufe & Rutter, 1984). To this end, evidence is emerging that DNA methylation alterations could serve as mechanisms through which risk and protective factors may operate to yield a phenotype. DNA methylation too is increasingly being recognized as a biological process that can influence our psychological functioning, from infancy to senescence. Finally, as a focus on the boundary between normal and abnormal development is central to a developmental psychopathology perspective (Cicchetti, 1993; Cicchetti, 2006; Sroufe & Rutter, 1984), DNA methylation is highlighted as a valuable measure informative of norms and aberrations present at the molecular level.

Changes in DNA methylation as a function of caregiving environments

Though over the past decade it has become clear that epigenetic processes operate throughout the lifespan, the evidence we have at present indicates that environmentally-driven DNA methylation changes appear especially robust and long-lived when they occur during sensitive periods (i.e. prenatal or early postnatal development). Cross-disciplinary studies have long indicated that sensitive periods during development are heightened epochs of brain plasticity where environmental factors are able to shape (i.e. program) neural circuits to direct structural and functional aspects of brain and behavior for the lifespan. Though it has been appreciated for some time that the long-term consequences of early-life experiences represent so-called epigenetic influences, it has only been within the past decade where empirical evidence that directly supports this notion has been presented. Indeed such paradigm-shifting studies have forced us to recognize the incredible sensitivity of DNA methylation at specific gene loci within the brain to the quality of early-life experiences. Furthermore, they have illustrated the ability of parental care (including the lack thereof) to canalize DNA methylation patterns with multi-generational consequences for the genome and behavior. To this extent, I begin by discussing developmental studies with rodent models that have made it clear that DNA methylation is a molecular process sensitive to early-life environmental input. These studies have also illustrated that experience-induced

changes in DNA methylation occur in brain circuitry with functional relevance to behavioral trajectories and psychopathology.

Evidence from rodent studies

In 2004, investigators brought forth evidence that challenged the previously held view that epigenetic mechanisms are static and unresponsive to the environment outside of embryonic development and periods of cellular differentiation. Data they presented indicated that methylation of DNA associated with the *glucocorticoid receptor (GR)* gene, a gene underlying stress-responsivity through its regulation of hypothalamic-pituitary-adrenal (HPA) activity, was directly associated with the type of caregiving experienced during the first postnatal week (Weaver et al., 2004). Specifically, they showed that adult male rats that had been reared by nurturing mothers that exhibited high levels of pup licking and grooming (LG) had low levels of methylation of DNA associated with the *GR* gene within their hippocampus, while adults who had been raised by low LG mothers exhibited hypermethylation of *GR* DNA. These observations were consistent with *GR* gene expression patterns and anxiety-related behavior of the animals. Animals with low methylation had higher expression of the *GR* gene and exhibited stress resilience, while animals with higher methylation had lower gene expression and increased anxiety-like behavior. Through a series of cross-fostering studies, they were able to demonstrate that the levels of *GR* promoter methylation were determined by the mother's behavior during the postnatal period and were not a product of the biological mother's behavioral predilection. These data were key in providing an association between the levels of caregiving behavior and DNA methylation of the *GR* gene promoter. Finally, in an effort to help establish a causal link between the observed epigenetic modifications, gene expression patterns, and adult behavior, they demonstrated that pharmacologically manipulating methylation patterns removed group differences in DNA methylation, histone acetylation (another epigenetic mark), gene expression, and behavior.

Since this landmark study, laboratories have continued to link caregiver experiences with DNA methylation patterns. We have also learned that the effects of the caregiving environment on DNA methylation are not exclusive to the *GR* gene, as other genes within the hippocampus (and other brain regions as we will learn below) show similar sensitivity to the quality of the caregiving environment. For example, maternal LG behavior affects γ -aminobutyric acid (GABA) inhibitory circuits, as males reared by low LG mothers show reduced hippocampal levels of the rate-limiting enzyme in GABA synthesis (glutamic acid decarboxylase, *GAD1*), an effect shown to be associated with increased methylation of *GAD1* promoter DNA (Zhang et al., 2010). Other studies have shown that infant male rats experiencing repeated separation from their mother and nest environment show altered methylation and expression of *estrogen receptor (ER β)* DNA (a gene that encodes a receptor responsive to estrogen) (Wang, Meyer & Korz, 2012) and increased methylation (and therefore reduced expression) of the synaptic plasticity gene *reelin* within the hippocampus (Qin et al., 2011). Furthermore, it has been demonstrated that epigenetic changes can occur on a much broader genome-wide scale within the hippocampus in response to maternal LG behaviors (McGowan et al., 2011).

Experience-induced changes in DNA methylation are a mechanism by which early-life caregiving experiences can also produce long-lasting alterations in function of the hypothalamic-pituitary-adrenal (HPA) axis, particularly at the level of the hypothalamus. Increased LG behavior of male infant rats, which improves learning and memory capacity in adulthood, has been shown to reduce expression of and methylation of the *corticotropin releasing hormone* (*Crh*) gene in the paraventricular nucleus (PVN) of the hypothalamus (Korosi et al., 2010; McClelland et al., 2011). The impact of infant (male and female) separation on depressive-like behaviors and *Crh* and *GR* gene expression in the hypothalamus have been linked to DNA methylation profiles (Chen et al., 2012a; Franklin et al., 2010). Furthermore, male mice show hypomethylation of *arginine vasopressin* (*AVP*) DNA and increased *AVP* gene expression in the PVN, effects that coincide with increased corticosterone secretion both at basal conditions and in response to stress, as well as an attenuated memory capacity a year after experiencing repeated separations from their mother (Murgatroyd et al., 2009).

Maternal care also promotes epigenetic changes of additional genes and epicenters of stress regulation, cognitive control, addiction, and maternal behavior. For example, some of our work has shown that infant rats repeatedly exposed to an adverse caregiving environment exhibit significant methylation of *Brain-derived neurotrophic factor* (*Bdnf*) DNA in their prefrontal cortex that either persists throughout (DNA associated with exon IX) or evolves (exon IV) during development (Roth et al., 2009). Aberrant caregiving behaviors were elicited by the combination of environmental novelty and resource deprivation (lack of nesting material), factors in our hands and those of others capable of producing abnormal caregiving behaviors that include a high proportion of rough handling, pup stepping on and dragging, active avoidance (neglect), and decreased LG of pups (Ivy et al., 2008; Rainekei et al., 2012; Roth et al., 2009; Roth & Sullivan, 2005). Adult DNA methylation profiles in our study were also found to coincide with reduced *Bdnf* gene expression and aberrant maternal behavior. Helping to establish a link between the methylation and gene changes, we also demonstrated that the gene deficits could be reversed through pharmacological manipulation of the methylation patterns.

In the hippocampus and nucleus accumbens of adolescent rats (age 35 days), methylation of *mu-opioid receptor* (*Oprm1*) DNA has been linked to the quantity of pup LG behavior (Hao et al., 2011). Additionally, low LG mothers are known to yield female offspring that exhibit decreased *ER-α* expression and a corresponding increase in methylation associated with the *ER-α* promoter in the medial preoptic area (MPOA) of the hypothalamus, whereas the opposite is true of high LG mothers (Champagne et al., 2006). Finally, work has shown that increased maternal care of male rats increases adulthood expression of anti-inflammatory cytokine *IL-10* mRNA within microglia of the nucleus accumbens, an effect established during the first postnatal week and maintained via decreased methylation of DNA associated with *IL-10* gene (Schwarz, Hutchinson & Bilbo, 2011). Increased maternal care in this study also produced animals that were more resilient to reinstatement of morphine conditioned place preference.

Evidence from human studies

In human epigenetic studies (which to date have mostly focused on adults) it is difficult to distinguish methylation patterns that may have developed as a response to the caregiving environment from those that occurred as a consequence of additional experiences throughout life. Of course functional polymorphisms are predicted to add an extra layer of complexity to understanding how behavioral outcome is moderated by early-life experiences. Furthermore, there is the question of the validity of peripheral measures of DNA methylation (obtained from blood samples or cheek swabs) in accurately reflecting the complexity of DNA methylation patterns within the brain (i.e. gene-specific and region-specific responses). Nonetheless, studies have reported associations between DNA methylation changes and early-life caregiving experiences.

Akin to the rodent literature, the human *GR* gene (*Nr3c1*) appears equally susceptible to experience-induced and long-lasting changes in DNA methylation. For example, increased DNA methylation of *Nr3c1* and *ribosomal RNA* genes (and a corresponding decrease in transcript levels) were found in hippocampal samples derived from adult males with a history of childhood abuse (Labonté et al., 2012b; McGowan et al., 2009; McGowan et al., 2008). In another study linking the effects of early-life adversity with epigenetic modification of the human *GR* gene, parental loss, childhood maltreatment, and disruptions in parental care were found to be associated with increased *NR3C1* promoter DNA methylation (as determined from leukocyte DNA) and attenuated cortisol responses to a stress challenge (Tyrka et al., 2012). Epigenetic changes in response to early-life experiences also appear to occur on a much broader genome-wide scale within the hippocampus. Male individuals with severe abuse during childhood have been shown to exhibit genome-wide changes in hippocampal DNA methylation, including hypermethylation of over 200 gene promoters and hypomethylation of around 100 gene promoters, many of which are involved in neural plasticity (Labonté et al., 2012a).

Epigenetic regulation of other gene loci has been linked to childhood experiences. For example, antisocial behavior in females with a history of childhood sexual abuse coincides with both genotype and hypermethylation of DNA associated with the promoter region of the gene encoding the serotonin transporter (Beach et al., 2011; Vijayendran et al., 2012). As an aside, increased stress responsivity in maternally and socially isolated infant macaques has likewise been linked to genotype and hypermethylation of the gene encoding the serotonin transporter (Kinnally et al., 2010; Kinnally et al., 2011). Children (male and female) aged 7-10 years and raised in institutional care, in comparison to children of the same age but raised by their biological parents, show greater methylation of DNA associated with a number of genes involved in controlling serotonin and glucocorticoid biosynthesis, immune responses, and cell-signaling pathways involved in memory formation (Naumova et al., 2012). Finally, adolescent and adult DNA methylation levels, including those of genes known to play an important role in cell-signaling pathways within the brain, have been linked to maternal and paternal stress levels during early childhood years (Borghol et al., 2012; Essex et al., 2011).

Changes in DNA methylation as a function of the prenatal environment

The intrauterine environment too is recognized as a major contributor to normal growth and development of an individual, and disturbances at this critical time are recognized for their ability to adversely affect behavioral development and the long-term mental health of offspring. Across-species studies have shown that one way prenatal stress and environmental factors can alter developmental trajectories is through changes in DNA methylation.

Evidence from rodent studies

In one of the earliest studies of gestational stress (using a regimen that included restraint stress, and exposure to predator odor or loud noises), prenatally-stressed male (but interestingly not female) offspring when adult were found to exhibit marked changes in expression of the *Crh* and *GR* genes, reduced methylation of *Crh* DNA in both the hypothalamus and amygdala, and increased HPA-axis responsivity and a depressive-like phenotype (Mueller & Bale, 2008). Data since have been consistent in showing the ability of stress experienced directly by the mother to render epigenetic consequences on offspring. Restraint stress has been shown to produce high levels of *Dnmt1* and *3a* (genes encoding enzymes that are responsible for adding methyl groups to DNA) mRNA in the frontal cortex and hippocampus of male offspring (Matrisciano et al., 2012). This same study showed that prenatally-stressed mice also displayed increased methylation of DNA associated with synaptic plasticity genes (including *reelin*) and several schizophrenic-like behaviors, including hyperactivity, deficits in social interaction, altered prepulse inhibition, and memory capacity. Restraint stress of pregnant rats has also recently been associated with changes in placental and fetal *HSD11B2* mRNA and methylation, a gene whose product helps protect the fetus against the damaging effects of stress hormones (Jensen Peña, Monk & Champagne, 2012).

In utero experiences also affect epigenetic regulation of genes and circuitry associated with addiction and motivation. Altered DNA methylation of the *dopamine receptor 2* gene has been found in the nucleus accumbens of adult rats that were exposed to *in utero* glucocorticoids (Rodrigues et al., 2011). Consumption of a high fat diet during pregnancy has been shown to produce offspring that prefer sucrose and fat in adulthood, a phenotype that is accompanied by DNA hypomethylation and increased expression of several reward-related genes (including the mu-opioid receptor and dopamine reuptake transporter) within the nucleus accumbens or prefrontal cortex (Vucetic et al., 2010). Finally, studies are beginning to indicate that the epigenetic consequences of prenatal stress likely occur on a broad genome-wide scale (Mychasiuk et al., 2011a), and strikingly, that stress does not have to be experienced directly by the mother in order for it to affect her offspring. Specifically, one report has shown global DNA methylation (frontal cortex and hippocampus), gene expression, and behavioral alterations in offspring of pregnant rats that were simply housed with another female who was repeatedly subjected to stress outside of the homecage (Mychasiuk et al., 2011b).

Evidence from human studies

Methylation status of the human genome appears equally sensitive to a variant of prenatal factors. For example, infants born to mothers that reported high levels of depression and anxiety during their third trimester of pregnancy exhibit increased methylation of the *Nr3c1* promoter in cord blood cells (Oberlander et al., 2008). Methylation status of the gene encoding the serotonin transporter (*SLC6A4*) is likewise affected by maternal depression, as increased maternal depressed mood scores have been associated with decreased maternal (peripheral leukocytes) and infant (umbilical cord) *SLC6A4* promoter methylation (Devlin et al., 2010). An unbalanced diet consumed during pregnancy (one that is linked to elevated blood pressure and cortisol in adult offspring) produces methylation of the *GR* gene (Drake et al., 2012). In addition, maternal alcohol and tobacco use are factors known to alter methylation of DNA associated with genes important in placental growth and development (Suter et al., 2011; Wilhelm-Benartzi et al., 2011).

Changes in DNA methylation as a function of later-life events

The studies highlighted in the previous sections are consistent with the notion that epigenetic alterations caused by adversity within the intrauterine or caregiving environments may provide a basis for the concept of developmental origins of health and disease. Adversity experienced later in life is likewise recognized for its ability to render lasting psychological and health costs, and emerging evidence suggests that changes in gene expression mediated by DNA methylation have significance in these outcomes as well.

Evidence from rodent studies

In parallel to developmental studies, research efforts aimed at understanding molecular mechanisms underlying memory processes and stress outcomes have illustrated the sensitivity of the adult rodent brain to environmentally-driven epigenetic alterations. Interestingly, these experience-driven changes appear to occur with similar selectivity for gene networks and circuitry as that affected by early-life adversity. Much of the pioneering work in regards to DNA methylation alterations in memory formation has utilized contextual fear conditioning, a behavioral paradigm that produces robust and long-lasting fear memories in rodents. Data illustrate that hours following fear conditioning when the fear memory is being formed (consolidated) there are changes in hippocampal DNA methylation that include demethylation and transcriptional activation of the memory enhancing gene *reelin* (Miller & Sweatt, 2007) and both DNA methylation and demethylation of DNA associated with the *Bdnf* gene within the hippocampus (Lubin, Roth & Sweatt, 2008). There are also changes in methylation of DNA associated with *calcineurin* within the prefrontal cortex, an effect that is sustained for at least several weeks (Miller et al., 2010).

Alterations in hippocampal DNA methylation not only appear to serve as markers of memory, but of exposure to chronic stress (Chertkow-Deutsher et al., 2010; Roth et al., 2011). For example, repeated exposure to predatory and social instability stress produces rodents that show learning and memory deficits, increased anxiety-like behavior, and glucocorticoid abnormalities weeks to months following the initiation of the stress regimen

(Zoladz et al., 2008; Zoladz, Fleshner & Diamond, 2012). We have recently shown that these behavioral abnormalities coincide with robust alterations in hippocampal *Bdnf* DNA methylation (that vary by subregion) and gene expression (Roth et al., 2011).

Other types of stress exposure have been shown to engage DNA methylation as determined from central (Elliott et al., 2010; LaPlant et al., 2010; Sterrenburg et al., 2011; Uchida et al., 2011) or peripheral (Tung et al., 2012) measures. Social defeat stress is associated with a lasting decrease in methylation of *Crh* DNA in the hypothalamus of animals that develop social avoidance behavior (Elliott et al., 2010). Interestingly, mice in this study that did not show these epigenetic modifications also did not develop social avoidance behavior following defeat stress. Stress-susceptible (inbred BALB/c) and stress-resilient (C57BL/6) male mice are known to show behavioral differences following chronic exposure to mild stressors, and a study recently attributed these phenotypes to differential patterns of *glial cell-derived neurotrophic factor* (*Gdnf*) DNA methylation within the nucleus accumbens (Uchida et al., 2011). Specifically, while both strains of mice were shown to display increased methylation of the *Gdnf* promoter following chronic stress, stress-susceptible mice (BALB) showed additional epigenetic changes that lead to repression of *Gdnf* transcription, including gene promoter interactions with histone deacetylases (HDACs). Mice that adapted to chronic stress (B6) on the other hand showed additional epigenetic changes permissive for *Gdnf* transcription. These studies are beginning to provide a glimpse of the epigenetic attributes of stress resilience vs. stress susceptibility.

Evidence from human studies

To date, there has only been one study which investigated changes in DNA methylation immediately following a specific stressful event in humans (Unternaehrer et al., 2012). Here study participants were adults who had been exposed to war adversities in early childhood and subjected to the Trier Social Stress Test (TSST). Each participant had blood samples drawn at a time point prior to the TSST, 10 min following completion of the TSST, and 90 minutes after the TSST. Examination of DNA methylation patterns of two stress-related genes, *oxytocin receptor* (*OXTR*) and *Bdnf*, revealed stress-evoked DNA methylation changes across targeted sequences of *OXTR*, with very little change detected in *Bdnf* DNA (though change was detected at one *Bdnf* CG site). Though their study population was based on individuals who might have increased susceptibility to DNA methylation changes (due to early-life stress and/or aging), their within-subject design provides seminal evidence in regards to the ability of acute psychosocial stress in humans to have immediate epigenetic consequences. Other work that I will highlight in the next section demonstrates DNA methylation alterations with reference to experiencing a number of lifetime stressful events or trauma exposure in PTSD.

Psychiatric disorders with aberrant DNA methylation

Studies in the previous sections were chosen to demonstrate the remarkable ability of environmental input both during and outside of periods of early-life development to alter DNA methylation. These studies make it clear that DNA methylation alterations (both short- and long-lived) are biological responses to psychological and social-contextual factors. Furthermore, these observations are consistent with the hypothesis that epigenetic marking

of genes could underlie aspects of psychopathology, especially in regard to neuropsychiatric disorders that can be associated with early-life stress and abnormal brain development and function. To this end, in this section I summarize evidence linking the presence of DNA methylation alterations with Schizophrenia (SZ), PTSD, and mood disorders.

Schizophrenia

Increased *Dnmt1* expression and decreased expression of *reelin* and *GAD1* are common findings in the cortex of individuals with SZ (Guidotti et al., 2007; Ruzicka et al., 2007; Veldic et al., 2004; Veldic et al., 2005; Veldic et al., 2007). Deficits in *reelin* and *GAD1* levels have been linked to altered methylation levels (Abdolmaleky et al., 2005; Connor & Akbarian, 2008; Grayson et al., 2005; Huang & Akbarian, 2007), and genome-wide epigenetic approaches on cortical tissue suggest there are many additional gene loci with altered DNA methylation in SZ, including other gene families related to GABAergic and neurotrophic (*Bdnf*) function (Connor & Akbarian, 2008; Mill et al., 2008). Peripheral measures of DNA methylation implicate epigenetic marking of the *monoamine oxidase A* (*MAOA*) gene promoter (Chen et al., 2012b), DNA associated with several serotonin receptors (Abdolmaleky et al., 2011; Carrard et al., 2011; Ghadirivasfi et al., 2011), and the *catechol-o-methyltransferase* (*COMT*) gene (Abdolmaleky et al., 2006; Lott et al., 2012; Melas et al., 2012; Nohesara et al., 2011). Finally, a genome-wide analysis of DNA methylation on peripheral blood DNA samples obtained from MZ twin pairs discordant for major psychosis showed numerous loci with DNA methylation differences between twins discordant for SZ and Bipolar Disorder (BD) (Dempster et al., 2011).

Post-traumatic stress disorder

Peripheral measures of methylation show strong associations between child abuse, total life stress, methylation of DNA associated with genes related to immune function and inflammation, and the diagnosis of PTSD (Smith et al., 2011; Uddin et al., 2010). An interaction between methylation status of the *SLC6A4* (Koenen et al., 2011) or *MAN2C1* (Uddin et al., 2011a) genes and the number of traumatic events experienced has been reported in PTSD. Assessment of serum DNA methylation patterns in genomic repetitive elements (LINE-1 and Alu) of US military service members pre- and post-deployment and with or without PTSD diagnosis suggest DNA methylation operative as a resilience or vulnerability factor (Rusiecki et al., 2012).

There is also emerging evidence of a so-called “double hit” model, in which having a risk allele and promoter DNA methylation may more accurately capture molecular risk of PTSD. For example, 9-repeat allele carriers of the dopamine transporter (*SLC6A3*) gene show an increased risk of lifetime PTSD when in conjunction with high methylation present in the *SLC6A3* promoter (Chang et al., 2012). Methylation of genes within the pituitary adenylate cyclase-activating polypeptide (PACAP) system, a system responsive to cellular stress and implicated in neurotrophic function, also appears to predict PTSD diagnosis. Females with high plasma PACAP levels and greater methylation of the PACAP receptor gene (*ADCYAP1R1*) containing a polymorphism show strongest PTSD symptoms and physiological fear responses (Ressler et al., 2011).

Suicide and Mood disorders

Epigenetic phenomena have similarly been associated with suicide and depression. *Dnmt* mRNA alterations (Poulter et al., 2008), increased *Bdnf* DNA methylation (Keller et al., 2010), and altered methylation patterns of numerous genes that play a role in neuronal growth, development, and cholinergic transmission (Sabunciyan et al., 2012) have been found in the brains (within the frontal cortex, amygdala, and PVN) of individuals who committed suicide and/or had been diagnosed with major depression. Altered levels of *Dnmt* mRNA (Higuchi et al., 2011) and *Bdnf* DNA methylation (Fuchikami et al., 2011) have likewise been found in peripheral measures in patients with major depression. Other findings in depressed patients include increased methylation of genes involved in brain development and metabolic processes (Uddin et al., 2011b), decreased methylation of genes such as the inflammatory gene *IL-6* (Uddin et al., 2011b), and high methylation of the angiotensin converting enzyme (ACE) gene (Zill et al., 2012).

Evidence for the heritable nature of acquired DNA methylation changes

Data from the previous sections are also consistent with the notion that if DNA methylation is an operational mechanism subserving an organism the ability to adapt to environmental factors, then the heritable nature of epigenetic changes could allow information acquired during one's lifetime to be passed on to offspring. Intriguing data from animal studies provide support that this does indeed occur. As pointed out in an earlier section, infant experiences with nurturing mothers (high LG behavior) decreases methylation of DNA associated with *ERα* gene in the MPOA, producing increased gene expression and responsivity to hormonally-primed maternal behavior (Champagne et al., 2006). As a consequence of these epigenetic modifications, offspring and grand-offspring from high LG mothers become high LG mothers themselves (Champagne, 2008; Champagne & Meaney, 2007). In this model, transmission of behavior and DNA methylation patterns represent experience-dependent inheritance mediated by maternal care itself.

As evidence of the ability of early-life adversity to produce multigenerational effects on DNA methylation, we have shown that offspring born to females that were maltreated (in their infancy) likewise showed altered *Bdnf* DNA methylation patterns (Roth et al., 2009). We used cross-fostering studies to address whether the appearance of DNA methylation alterations in this generation of infants was due to the mother's caregiving behaviors. Our results revealed that the changes in DNA methylation were not simply a product of the postnatal experience, as they were not easily reversed by altering the caregiving environment. One intriguing explanation for our results is the phenomenon of germ-line inheritance, and though we have yet to address this notion in our model, other studies have directly demonstrated heritable epigenetic and behavior changes via the germ-line that are independent of maternal care.

In an earlier section, the ability of infant separation to produce lasting changes in depressive-like behaviors and methylation of the *Crh* gene (Franklin et al., 2010) was discussed. From this same study, anxiety and depression-related behaviors, as well as methylation changes, were also found to be present in offspring and grand-offspring derived from males that had experienced the initial separation (Franklin et al., 2010; Weiss et al., 2011). This is an

important observation because in rodents, the males do not provide infant care and are typically removed from a cage once successful mating has occurred. Subsequent studies from this line of work have revealed deficits in cognition and social interaction transmitted through the F3 generation, but also stress resiliency, suggesting both positive and negative long-term and transgenerational effects of early-life stress (Franklin et al, 2011). Paternal transmission of stress-related behaviors induced by social defeat have likewise recently been demonstrated (Dietz et al., 2011).

Another line of evidence supporting epigenetic transmission of acquired information comes from that manipulating the prenatal environment. Fetal alcohol-exposed rats exhibit deficits in expression of the *proopiomelanocortin* (*POMC*), an effect that coincides with increased methylation of the *POMC* promoter and persists in F2 and F3 generation males (Govorko et al., 2012). Offspring of pregnant guinea pigs treated with synthetic glucocorticoids show sustained alterations in CNS DNA methylation and gene expression (within the cerebellum), an effect likewise present in the next generation (Crudo et al., 2012). Providing some of the strongest evidence of the phenomenon of germ-line epigenetic inheritance, including altered stress responses for 3 to 4 generations removed from the initial environmental insult, are studies exposing pregnant dams to endocrine disruptors (Crews et al., 2012; Skinner et al., 2008) or high fat diets during gestation (Dunn & Bale, 2011).

Questions and challenges in the field

Animal studies over the past decade have given us fascinating insight into the relationship between environmental factors, experience-driven DNA methylation patterns, and behavioral outcomes. Discoveries as summarized in Figure 2 are consistent with the notion that epigenetic mechanisms underlie cause-effect relations in regard to neurobehavioral development and later stress-driven abnormalities. As applied to human development and psychopathology, epigenetic studies in humans too provide compelling evidence for DNA methylation alterations as a biological substrate through which a variety of factors can alter individuals for the long-haul (Figure 2). Though studies are being published at a rapid pace, behavioral epigenetics is still considered an emerging scientific field, and there are many unresolved issues and challenges that are certain to attract additional research. This final section serves as a forum to propose a handful of questions (arranged in no order of importance) that might drive future research (both with animal models and humans) to more clearly elucidate the role of epigenetics in development and psychopathology.

What are the natural pathways by which environmental stimuli preferentially alter DNA methylation in brain regions, and how are these changes then translated into altered gene networks, circuitry, and behavior?

Though it is clear that environmental factors have direct effects on gene expression and behavior via alterations in DNA methylation that appear to have some brain region specificity, we do not at present understand *how* this may be the case. We do know that postmitotic neurons express the enzymatic machinery necessary for modifying chromatin and DNA methylation states (Brown et al., 2008; Feng et al., 2005; Ma et al., 2009), providing a susceptible basis for environmentally-driven epigenetic modifications. Brain region, and cell-type specificity for that matter, would require qualitative, quantitative, and

spatial arrangement of mechanisms capable of orchestrating responses to similar stimuli, which appears to be in place. In the hippocampus for example, isoforms of *Dnmt* are known to vary by subregion (Brown et al., 2008) and cell-type (Feng et al., 2005; Siegmund & Connor, 2007). Though most studies have utilized a candidate gene approach to identify specific sites of DNA methylation changes (and rightly so, as this is a more sensitive approach for detecting methylation changes), an increasing number of studies that have utilized genome-wide approaches indicate changes are occurring at numerous gene loci. This would suggest changes in gene networks, with functional implications then for disruptions at the circuit and behavioral levels. *How* DNA methylation changes orchestrate these down-stream effects is not known, and is certainly an opportunity for future focus.

Do experiences within early-life developmental windows produce the greatest effects on DNA methylation?

Studies exposing either developing or adult animals to a variety of stressors demonstrate the remarkable ability of the CNS to alter its epigenetic status in response to environmental factors. At the same time this tells us that experiences do not have to be confined to early-life developmental periods in order to evoke DNA methylation changes. Whether sensitive periods early in life truly represent heightened periods of vulnerability to these types of changes is an issue that has not been systematically addressed. Expression profiles of *Dnmt1*, *3a*, and *3b* genes are detectable in neurons throughout the lifespan, though *Dnmt3a* is known to peak during the early postnatal period (Brooks, Marietta & Goldman, 1996; Feng et al., 2005; Goto et al., 1994). To directly answer this question, studies would need to incorporate a lifespan approach to provide information regarding when epigenetic modifications are more likely to occur or perhaps be attenuated in response to a specific stimulus or experience. Worth considering in this context is that it is possible that a much broader gene pool could be at play during sensitive periods (such as in early postnatal development or adolescence), while a more restricted gene pool is responsive to later-life factors.

Also with relevance to the importance of utilizing a lifespan approach, evidence has emerged that experiences do not always translate into immediate changes in DNA methylation, but that changes can evolve after an appreciable delay. For example, separation of infant mice produce changes in *AVP* DNA methylation that are not detectable during infancy, but rather, seem to evolve over the course of development only to be present within adult tissue (Murgatroyd et al., 2009). Adding further complexity, we also know that DNA methylation patterns naturally change with maturation and aging processes (Numata et al., 2012; Penner et al., 2010; Siegmund & Connor, 2007). Both of these phenomena then likely have significance in terms of “stress incubation” and direct vs. indirect trajectories leading to later behavior change or the onset of psychiatric disorder.

Are better animal models needed to fully realize the translational implications of DNA methylation?

Our knowledge regarding the role of epigenetic modifications in mediating behavioral effects has been mostly derived from rodent models that exclude any confounds of genetic variability and where the behavior outcome is fairly uniform. It is important to consider that

in humans, however, genetic polymorphisms exist and it is often the case that experiences that produce a particular outcome in some people do not in others. Thus, functional polymorphisms are predicted to add an extra layer of complexity to understanding how behavioral outcome is moderated by life experiences, and it may be the case that polymorphisms service as predispositions that make individuals more susceptible to subsequent epigenetic alterations and disease. The flip side of this is that certain polymorphisms could also serve as a protective factor against epigenetic alterations.

Though keeping animals in constant conditions to understand the association between an early-life experience and later outcome has obvious value, this experimental design excludes the reality of complex social environments and the summing effects of total life experiences that we know profoundly influence human behavior. One way that animal research could address this issue is to incorporate both early-life and later-life stress exposures in various models to determine outcomes associated with cumulative stress and epigenetic loads. Furthermore, it should be evident from the developmental animal studies reviewed here that rodent models have focused on mother-pup interactions and how the dynamics within this context can influence DNA methylation and subsequent development. In humans it is not the case that only mothers interact with their children, and a broader social context (fathers, grandparents, childcare facilities, etc.) then has an ability to leave its imprint on DNA methylation and gene expression patterns. Animal models with communal nesting and environmental complexity may be a way to capture this.

Does DNA methylation play an important role in why males and females often have different outcomes from the same experience?

Some of the evidence reviewed in earlier sections suggests that epigenetic activity indeed plays an important role in sex-specificity and susceptibility to stress. This may be due to developmental windows in which some genes have the potential to be differentially marked between male and females. For example, DNA methylation of the *ER-α* gene for example is higher in female rodents than males at postnatal day 1 (Schwarz, Nugent & McCarthy, 2010). mRNA and protein levels of *Dnmt3a* (Kolodkin & Auger, 2011) and MeCP2 (Kurian, Forbes-Lorman & Auger, 2007) within the infant amygdala are higher in females than in males, but by postnatal day 10 these sex differences have disappeared. *Dnmt3a* is highest in the female and male cortex at postnatal day 10, while *Dnmt1* is highest after weaning (PN25) (Westberry, Trout & Wilson, 2010). Within the MPOA, gene promoters involved in sexual differentiation of the brain show differential epigenetic patterns between males and females at both an embryonic and early postnatal stage (Matsuda et al., 2011). It stands to reason that developmental epigenetic studies that incorporate both sexes will reveal substantial etiological information regarding sex-specific development of behavior.

Can we target the epigenome for behavioral benefits?

A new-type of therapy aimed at correcting epigenetic “defects” has received considerable attention. In so-called epigenetic therapy, investigators aim to use drugs like 5-Azacytidine, Zebularine, Sodium Butyrate, and Trichostatin A to relax chromatin structure in order to provide gene transcription accessibility. The ability of these drugs to correct epigenetic patterns was first recognized in cancer treatment, but the scope of their application has

continued to be broadened to include enhancing cognition and treating specific symptoms of various psychiatric disorders. HDAC inhibitors for example have been successfully used to reverse deficits in synaptic plasticity, learning and memory, and stress-related behaviors (for a review see (Abel & Zukin, 2008)).

In several of the aforementioned developmental studies investigators have successfully modified patterns of DNA methylation in the adult brain that were associated with early-life experiences (Roth et al., 2009; Weaver et al., 2004). The ability of epigenetic therapy to reverse gene deficits (and behavior) that were either set up in infancy or in cognitively impaired animals is a remarkable finding in its own right. Since these studies have only examined the effects of epigenetic therapy on gene patterns or behavior on a rather short-time scale (hrs. to days later), whether this strategy would be successful as a standalone treatment to stably (i.e. life-long) reverse aberrant DNA methylation and behavior patterns is not known. Animals would need to be followed for long periods of time (another point arguing for a lifespan design in studies), and perhaps through multiple generations. This approach is not only necessary to help us understand trajectories of psychiatric disorders, but to understand when, where, and how to successfully intervene. Whether behavioral therapies, such as environmental or social enrichment, would be better suited for such a long-term application, or in combination with drugs targeted at epigenetically modifying programs of genes, is also a question open for investigation.

Can peripheral measures really tell us anything about the brain?

As DNA methylation alterations continue to be linked to psychiatric disorders, this has led to the idea that peripheral measures of DNA methylation (including from blood samples or cheek swabs) can serve as a proxy for brain changes that have already occurred or even as a predictive biomarker for the probability of some outcome or individual responsivity to some type of clinical treatment. As highlighted in an earlier section, a growing body of work has noticeably demonstrated a link between blood-DNA methylation profiles and a risk for and current diagnosis of psychiatric disorder. Since there is accumulating evidence that epigenetic modifications occur with incredible specificity across tissue-and cell-types (Davies et al., 2012; Iwamoto et al., 2011; Ladd-Acosta et al., 2007), however, this questions the ability of peripheral measures of DNA methylation to serve as an accurate and reliable proxy for changes occurring the brain, and thus the reality of using DNA methylation as a biomarker.

Though the link between peripheral and central measures has not been unequivocally established, evidence we do have at present suggests blood-DNA methylation profiles do show promise of serving as valuable diagnostic biomarkers. For example, it was shown in one study that methylation patterns of the rodent *COMT* gene were directly correlated in peripheral blood mononuclear cells (PBMCs) and the PFC (Ursini et al., 2011). Methylation in the PBMCs however did not correlate with patterns in the hippocampus (though they were in the same direction) or striatum. In the largest cross-tissue and inter-individual comparison of blood and brain methylation patterns in humans, investigators found that though DNA methylation at specific gene loci were found to differ between tissue types

(blood, cortex, cerebellum, etc.), strong correlations between DNA methylation for blood and brain tissue were present (Davies et al., 2012).

Conclusions

Paradigm-shifting research in the past decade has provided evidence that epigenetics serve as candidate pathways by which experiences can leave their mark on genes to drive sustained changes in behavior. Though we still lack a complete understanding of the cause-and-effect role of epigenetic mechanisms in health outcomes and disease, evidence is clear that epigenetic alterations are biological consequences of early-life and later-life environmental input. Furthermore, the evidence at hand suggests these alterations likely play a role in the development of and enduring nature of psychopathology. Though a complete picture has yet to emerge, our charge now is to incorporate the insights we have gained from these studies into programs and policies, an action point increasingly making its way into the literature (Birnbaum & Jung, 2011; Hackman, Farah & Meaney, 2010; Rothstein, Cai & Marchant, 2009). These include those of the public health sector, such as programs designed to help alleviate socio-economic disparities and child advocacy programs aimed at helping infants and young children cope with early-life adversity. What we have learned regarding epigenetics and health outcomes has previously under-appreciated legal and ethical implications, which could include litigations regarding multi-generational environmentally-driven health effects. Finally, in the realm of medical policy this should include policy decisions regarding diets (including infant formula) and chemical exposure, medical experiences such as *in vitro* fertilization, and funding of research aimed at early detection and interventions to restore normal brain function and health.

In conclusion, epigenetic studies over the past decade have contributed fascinating insight into the role of DNA methylation (and chromatin for that matter) as a rich source for interactions between our environment and static genome. The birth of epigenetics research has provided an exciting new level of analysis for understanding tenets central to the discipline of developmental psychopathology. Further research using human study populations and animal models, especially those with clinical relevance, promises a greater understanding of the regulatory role of epigenetic processes in aspects of brain development relevant to the etiology of and resilience to psychiatric disorders. The current momentum in the field also points towards the applicability of using epigenetics, along with genetic polymorphisms, in providing individualized medicine and predicting more effective responses to treatments.

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Figure 1.

DNA compaction and methylation. (A) DNA in the nucleus is wrapped around histone proteins, forming what is referred to as chromatin. This provides a highly ordered packaging state of DNA to serve as a building block of chromosomes. (B) DNA methylation occurs at cytosine residues of cytosine-guanine (CG) dinucleotides that are often clustered within gene regulatory regions. DNA methylation is an epigenetic mechanism typically associated with gene suppression, as methyl groups can either interfere with the binding of transcription factors necessary to promote gene transcription and/or recruit repressor proteins that promote a compact chromatin state not permissive to gene transcription. There are reports however of DNA methylation being associated with active gene transcription (Chahrour et al., 2008; Uchida et al., 2011).

Figure 2.

Summary of psychological and social-contextual factors known to produce DNA methylation alterations. *Top panel*- Experiences known to produce behavioral change in both developing and adult rodents that have been linked to altered DNA methylation and gene expression profiles. These epigenetic changes occur in many brain regions with known relevance to psychopathology, several of which are depicted here. *Bottom panel*- Many of these animal findings have translated to similar observations in humans. A growing number of psychiatric disorders, several of which are listed here, have also been associated with DNA methylation alterations.