Weaver, Cell Dev Biol 2014, 3:1
DOI: 10.4172/2168-9296.1000132

Cell & Developmental Biology

Review Article Open Access

Epigenetics: Integrating Genetic Programs, Brain Development and Emergent Phenotypes

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Abstract

Adaptation to environmental changes is based on the perpetual generation of new phenotypes. Modern biology has focused on the role of epigenetic mechanisms in facilitating the adaptation of organisms to changing environments through alterations in gene expression. Inherited and/or acquired epigenetic factors are relatively stable and have regulatory roles in numerous genomic activities that translate into phenotypic outcomes. Evidence that dietary and pharmacological interventions have the potential to reverse environment-induced modification of epigenetic states (e.g., early life experience, nutrition, medication, infection etc.) has provided an additional stimulus for understanding the biological basis of individual differences in cognitive abilities and disorders of the brain. It has been suggested that the accurate quantification of the relative contribution of heritable genetic and epigenetic variation is essential for understanding phenotypic divergence and adaptation in changing environments, a process requiring stable modulation of gene expression. The main challenge for epigenetics in psychology and psychiatry is to determine how experiences and environmental cues influence the expression of neuronal genes to produce long-term individual differences in behavior, cognition, personality and mental health. To this end, focusing on DNA and histone modifications and their initiators, mediators and readers may provide new inroads for understanding the molecular basis phenotypic plasticity and disorders of the brain. In this review, we survey recent developments revealing epigenetic aspects of mental illness, as well as review some of the challenges of current approaches and some future directions in the field of behavioral epigenetics.

Keywords: Brain development; Epigenome; Chromatin plasticity; DNA methylation; Histone modification; Transgenerational inheritance

Early Life Development and Transmission of Phenotype

Human development not only involves the biological and physical aspects of growth, but also the cognitive and social aspects. Early in life, neuronal circuits are created and connections between neurons undergo remodeling as they develop their adult functional properties in response to intrinsic (genomic) and extrinsic (environmental) cues. The capacity of a single genotype to exhibit variable phenotypes in different environments is common across all species and is often highly adaptive and forms the basis for 'phenotypic plasticity'. Historically, the relationship between the genome and the environment has been presented under the framework of gene-environment interaction (or genotype-environment interaction, G×E). The challenge for developmental psychology and psychiatry has been to integrate findings from genetics into the study of personality and our understanding of the pathophysiology of mental illness. For example: (1) common genetic risk factors and rare mutations such as Single-Nucleotide Polymorphisms (SNPs) and variation in the number of nucleotide repeats such as Copy-Number Variants (CNVs) mapped in Genome-Wide Association Studies (GWAS) account for only a small fraction (1-2%) of the total risk for complex (non-Mendelian) inheritance of personality traits and neurodegenerative and neuropsychiatric disorders [1,2]; and (2) epidemiological studies that have attempted to examine the mechanisms and conditions under which genomic variation influences brain development and function have been confounded by complex cause and effect relationships (G×E interactions and non-germ-line inheritance) [3]. The large unaccounted heritability of personality traits and mental health suggests that additional molecular and cellular mechanisms are involved.

Epigenetic heritability is the transmission of phenotype in terms of gene expression through mitosis (and potentially meiosis) in the absence of changes in DNA sequence-hence the name epi- (Greek: επί- over, above) genetics [4,5]. The 'epigenotype' refers to mitotically heritable patterns of DNA methylation and modifications to chromatin proteins that package DNA. The advent of high-throughput techniques such as microarray- and sequencing-based approaches to study the distributions of regulators of gene transcription throughout the genome led to the collective description of the 'epigenome'.

The epigenome is highly dynamic-chromatin and DNA modification patterns show considerable heterogeneity within the tissues of an organism, differing between brain regions [6] and cell types, developmentally regulated and often induced by exposure to a range of external environmental factors [7] such that postnatal environmental factors (during early childhood and adolescence) can cause changes in molecular structures that mediate expression of genes conferring risk of mental health and chronic physical conditions [8-10]. Thus, the examination of genotype-epigenotype-environment interactions from a developmental perspective may determine the nature of gene mis-regulation in psychological disorders, which also has broad ranging implications for our understanding of and interrelations between social, physiological and pathological processes. This review will provide an overview of the main components of the epigenome and review themes in recent epigenetic research that have relevance for psychological theory, research and practice.

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Received October 16, 2013; **Accepted** January 27, 2014; **Published** January 29, 2014

Citation: Weaver ICG (2014) Epigenetics: Integrating Genetic Programs, Brain Development and Emergent Phenotypes. Cell Dev Biol 3: 132. doi:10.4172/2168-9296.1000132

Epigenetic Control of Gene Expression: Molecules of Cellular Programming and Inheritance

The main challenge of a complex organism is how it regulates the expression of only a small set of genes from a vast repertoire of genomic sequences. Epigenetic mechanisms have evolved to offer a precise and stable control of gene expression and perpetuation of cellular phenotype over multiple generations, thus providing a link between single genotypes and multiple phenotypes. In terms of the underlying biochemistry, the epigenome is influenced by (1) distinct patterns of nuclear organization and chromatin structure, (2) global and local covalent modification of both histones [11] and DNA [12] and (3) the presence of specific macromolecules including small non-protein-coding RNAs [13-15]. These three systems have mostly been explored in the context of organism development, and have been shown interact to regulate gene function during cellular differentiation in embryonic and fetal development and throughout life [16]. However, it is now clear that experience, such as exposure to environmental toxins, maternal behavior, psychological or physical stress, learning, drug exposure or psychotrauma, leads to active regulation of the chemical and three-dimensional structure of DNA in the nervous system, i.e., that experience regulates epigenetic mechanisms in the CNS. Small RNAs encompass a wide variety of non-coding RNAs that have either been shown to regulate gene expression and cellular fate by controlling chromatin silencing and mRNA stability or translation in the nervous system, including piRNAs, microRNAs, small interfering RNAs (siRNAs), and small nuclear RNAs (snRNAs). These mechanisms have in common the exquisite capacity for nucleotide sequence-specific effects, allowing them to affect the function of particular genes with high specificity. This is a burgeoning area for all of biology, including (most recently) developmental pathology and neuropsychopharmacology [17].

A variety of other epigenetic molecular mechanisms are also in play in neurons including: ATP-dependent chromatin remodeling and regulation of the affinity of the histone octamer core particle with its associated DNA to promote gene transcription by loosening the chromatin 3-dimensional structure [18]; RE1-silencing transcription factor (REST)/REST core- pressor (CoREST)/Sin3A system in neuronal/non-neuronal cell fate determination [19]; LINE 1 (long interspersed nuclear element 1, aka L1) retro transposition insertional mutagenesis and regulation of transcription [20]; and prion-protein-like mechanisms as long-term controllers of synaptic efficacy [21]. These mechanisms, amongst others, allow individual neurons to achieve genomic diversity and distinction from their siblings, broadening the spectrum of cellular phenotypes driven by the single available genome.

This review focuses on DNA methylation and the predominant histone modifications, with emphasis on their dynamic interactions within the chromatin environment to form the complex epigenetic mechanisms that orchestrate the regulation of genes at the molecular level in mammalian cells.

The Primary Epigenetic Mark: Gene Silencing by DNA Methylation

Mammalian development requires DNA methylation, a heritable epigenetic mark of cellular memory believed to maintain a cell's unique gene expression pattern. DNA methylation is the proximal molecular mechanism that triggers gene silencing in cells associated with cell fate determination and perpetuation. Specifically, DNA methylation is a covalent modification that in the mammalian genome, largely occurs at cytosine residues in 5′-cytosine-phosphodiester-guanine (CpG)-3′ dinucleotides giving rise to 5-methylcytosine (5mC) in a cell-specific pattern [22-24]. However, based on recent discoveries it is clear that cytosine methylation also occurs at non-CpG sites. The enzymes that 'write' DNA methylation are DNA Methyl transferases (DNMTs), which catalyze the transfer of a methyl group from S-adenosyl-L-methionine (SAM or ado Met) to the cytosine [25]. In mammals, the DNMT family is composed of five proteins: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L [26]. These enzymes are all expressed in the Central Nervous System (CNS) and are dynamically regulated during development [27,28]. The DNMT1 maintenance methyl transferase prefers hemi-methylated DNA [29-31] and safeguards the methylome in dividing cells by faithfully copying the methylation pattern from parental to daughter strand during DNA replication [32,33]. The biochemical capacity of a specific chemical reaction to trigger self-perpetuation is the defining characteristic of a process involved in cellular information storage. Although DNA methylation in mammals is generally assumed to be similar on both alleles across the genome, Allele-specific DNA Methylation (ASM) reflects tissue-specific *cis*-regulatory influences of DNA polymorphisms on epigenetic status [34]. Epigenetic factors may also contribute to DNA sequence variation-the presence of a methyl group increases mutability of a cytosine base [35], and knockouts of DNMT1 exhibit a higher DNA mutation rate [36]. The production of sufficient methyl-donors is therefore of critical importance for the ontological role of DNA methylation.

DNA methylation of gene promoter regions or enhancer sites often correlates with transcriptional silencing [23,37-40]. The processes by which DNA methylation silences gene expression can generally be divided into two main mechanisms. In the direct mechanism of gene silencing, DNA methylation within transcription factor binding sites and enhancer elements displaces the binding of methylation-sensitive transcription factors to their cognate binding sites [41,42]. In the indirect mechanism, Methyl-CpG Binding Domain (MBD) proteins such as MeCP2, MBD1, MBD2, MBD3, and MBD4 'read' the methylation marks and bind to the methylated DNA [11,43-47]. These MBD proteins affect chromatin condensation by recruiting co-proteins such as SIN3A and histone modification enzymes, leading to chromatin compaction and transcriptional repression [48-52].

An important concept is that global levels of DNA methylation and gene specific DNA methylation profiles are dynamic and vary spatially and temporally throughout life, especially during epigenetic remodeling in early development. The methylated maternal and paternal genomes are demethylated at fertilization and specific patterns of methylation are then re-established progressively commencing in the early post-conception period [26]. The removal of epigenetic marks is essential to ensure the totipotency required for sustaining further development. The *de novo* establishment of DNA methylation is performed by methyl transferases DNMT3A and -3B, and modulated by DNMT3L, which lacks direct catalytic activity [26].

Besides DNA cytosine methylation, other chemical modifications of cytosine in DNA have also been documented to exist, including 5-hydroxymethylcytosine (hmC) formation and methyl-cytosine oxidation to generate 5-formylcytosine and 5-carboxyl-cytosine. The functional role(s) of these novel modifications are not fully established, and this is a hot area of investigation in the field at present. 5hmC accounts for ~40% of modified cytosines in neurons, increases in the brain with postnatal age and is produced in response to neuronal activity [53,54]. A central dogma of the epigenetics field has been that once DNA methylation patterns are established upon the genome in terminally differentiated cells, those modifications are permanent

and essentially immutable. However, of late it has become clear that so-called active cytosine demethylation also occurs, wherein a previously methylated cytosine can undergo a net reconversion back to the un-methylated state. This mechanism appears to be particularly prominent in two places: in the mature nervous system and in the fertilized zygote undergoing generation of totipotent embryonic stem cells (in other words, in the two most highly plastic tissues in the body). Current models propose that 5hmC is an intermediate base in active DNA demethylation processes that operate during important reprogramming phases of mammalian development [55]. Genome-wide profiling revealed that 5hmC is enriched at promoters and gene bodies, and its enrichment on gene bodies is positively correlated with gene expression in the human brain [56]. In the human genome, 5hmC is highly enriched on exons and Untranslated Regions (UTRs), but depleted on introns and intergenic regions [57]. In addition, fetus-specific and adult-specific Differentially hydroxyl methylated regions (DhMRs) in exons and CpG islands have been identified [57]. In the brain, 5hmC makes the neurons highly plastic and highly adaptable so that they can receive signals and trigger long-lasting functional changes [58]. While further studies are required to determine additional regulatory functions of 5hmC independent from that of 5mC, these studies imply that 5hmC-mediated epigenetic regulation may broadly impact human brain development, and age-related dysregulation of DNA methylation could contribute to memory deficits and the molecular pathogenesis of neuro developmental disorders.

Histones Modifications: Regulation of Chromatin Structure and Fine-Tuning of Gene Function

Histone posttranslational modifications are the second major category of epigenetic biochemical mechanisms in mammalian cells. Genomic DNA in mammalian cells is packaged with specific proteins termed histones to form protein/DNA complexes called chromatin. The basic unit of chromatin is the nucleosome, which is composed of ~ 146 Base Pairs (bp) of DNA wrapped around an octamer of the four core histones (H2A, H2B, H3, and H4). The core histones are tightly packed in globular regions, with amino-terminal tails that extend from the globular region, making them accessible to histone modifying enzymes (discussed further below) [59]. Gene expression can be controlled through several types of histone posttranslational modifications, including lysine acetylation [60], lysine mono/di/tri-methylation [61], arginine mono/di-methylation, serine/threonine phosphorylation, histone mono-ubiquitination [62], and histone poly-ADP-ribosylation [63]. Another protein, termed linker histone H1, interacts with DNA links between nucleosomes and functions in the compaction of chromatin into higher-order structures that comprise chromosomes. This organization of chromatin allows DNA to be tightly packaged, accurately replicated, and sorted into daughter cells during cellular division.

Additionally, individual isoforms of histone monomers (histone variants) can also be replaced in the octamer, a regulatory mechanism termed histone subunit exchange, an integral component of physiological brain activity. For example aging is associated with a progressive increase in markers of DNA breaks in neurons. One such marker is the histone variant γH2A.X, which is typically associated with severe DNA damage and the activation of cell death pathways. However, γH2A.X may also help recruit the DNA repair machinery and fulfill physiological functions in epigenetic processes that regulate chromatin structure and gene expression [64]. Subunit exchange and posttranslational modifications trigger either increases or decreases in transcription, depending upon the particular modification, the particular histone isoform involved, and even the context of other histone modifications in which the modification resides.

Interpretation of Epigenetic Modifications: Toward Cracking the Code

The relationship between regional patterns of histone modifications and locus-specific transcriptional activity provides evidence for the existence of a 'histone code' for determining cell-specific gene expression programs, wherein histone modifications are interpreted in situ as a combinatorial code regulating gene transcription rates at specific loci across the genome [65]. The 'Encyclopedia of DNA Elements' (ENCODE) project [66] has generated a wealth of information on genome-wide binding sites of numerous transcription factors, histone modifications and chromatin accessibility across multiple human cell lines [50,67]. These studies have provided evidence for certain transcription factors (e.g., c-Jun, GATA1, NRF1) located exclusively within eu-chromatin and associated with transcriptional activation, while others (e.g., ZFN274, KAP1, SETD B1) predominantly within heterochromatin and associated with gene silencing. However, further studies are required to identify additional factors that determine cell-type-specific binding profiles and control of the human genome [68].

Importantly, histone posttranslational modifications regulate this structure in order to modulate transcription of the associated gene. One of the most thoroughly studied modifications of histone tails is the acetylation at lysine residues, which is associated with transcriptional activation. Acetylation on histone tails is mediated by the opposing enzymatic activities of Histone Acetyl transferases [HATs; i.e., CREB-binding protein (CBP)] and Histone Deacetylases (HDACs; i.e., the class I HDAC2) [69]. For example, acetylation of histone H3 on lysine 9 (H3K9Ac) of gene promoter regions or enhancer sites by HAT enzymes is generally associated with an 'open' euchromatin structure and transcriptional activation [70,71]. On the other hand, removal of the acetyl group (de-acetylation) by HDAC enzymes is generally associated with a 'closed' heterochromatin structure and gene silencing [72]. As well, residues on histone tails may be mono- (me1), di- (me2) or tri-methylated (me3) [73]. The biological effect of each modification depends on both the identity of the modified residue and the extent of methylation. For example, methylation of histone H3 on lysines 4 and 36 (H3K4 and H3K36) is generally associated with an euchromatin structure and transcriptional activation, whereas methylation of histone H3 on lysines 9 and 27 (H3K9 and H3K27) is generally associated with a heterochromatin structure and gene silencing [74]. Methylation of histone tails is controlled by the opposing enzymatic activities of histone methyl transferases (HTMs; i.e., EZH2, G9a, MLL, Suv39H1) [75-77] and Histone Demethylases (HDMs; i.e., JARID1d, Utx) [78,79].

The relationship between DNA methylation and chromatin modification is believed to be bilateral: 5mC can serve as a mark for directing chromatin state which itself can equally define DNA methylation [80]. This suggests that the active targeting of histone-modifying enzymes responsive to signaling pathways in the cell determines the state of histone modification and level of expression of the underlying genes. The implications of this kind of molecular/cellular information processing within neurons, through which a given pattern of chromatin changes from transient effects on gene regulation to more persistent epigenetic programming of gene expression by DNA methylation is only beginning to be considered and addressed at present and discussed below.

Epigenetic Marks: Linking Maternal Nutrition and Child Health and Beyond

There are several indications of experience-dependent heritable changes in the CNS epigenome-many associated with the quality of nutritional programming early in life. The fetal-origins hypothesis suggests that maternal and fetal nutrition can have a profound and sustained impact on the health of the offspring in adult life [81,82]. Critical phases exist in early development during which chemical, biological and physical insults (i.e., nutritional restriction, gestational diabetes, maternal stress) exert permanent effects on intrauterine growth, physiology, metabolism and health of offspring through remodeling of tissue morphology [82]. Moreover, it appears that nutrients and bioactive food components can influence the epigenome either by directly inhibiting enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions. Diet-derived methyl donors and cofactors are necessary for the synthesis of SAM, which serves as the donor of methyl groups for DNA methylation, thus environmental factors that alter early nutrition and/or SAM synthesis can potentially influence adult metabolism via persistent alterations in DNA methylation [83-87]. For example, fetal deficiency in the essential amino acid methionine and dietary folate (found in fresh fruits and vegetables), as well as genetic variants in Methylene tetra hydrofolate Reductase (MTHFR, a regulatory enzyme in folate metabolism) have been shown to alter intracellular SAM levels [88,89] and to be linked to the increased risk of many serious health conditions [90]. In this regard, early life nutrition has the potential to influence epigenetic programming in the brain not only during early development but also in adult life, thereby modulating health throughout life.

The best evidence relating to the impact of adverse environmental conditions on human development and long-term health comes from follow up studies of the offspring of women pregnant during two civilian famines of World War II: The Siege of Leningrad (1941-44) [91] and The Dutch Hunger Winter (1944-1945) [92]. In the Netherlands famine, previously adequately nourished women were subjected to low caloric intake and associated environmental stress. Women exposed to famine in late pregnancy gave birth to smaller babies [93] who had an increased risk of insulin resistance later in life [94]. Following the famine, offspring who were starved prenatally were found to have impaired glucose tolerance in adulthood when food was more abundant [92]. Famine exposure at different stages of gestation was associated with an increased risk of obesity, dyslipidemia, and coronary heart disease, and second generation offspring of females exposed in the first trimester *in utero* did not have the expected increase in birth weight with increasing birth order [93]. Interestingly, when examined sixty years later, the growth-regulatory gene IGF-2 in individuals prenatally exposed to famine was hypo-methylated by comparison to their unexposed same sex siblings [95]. Together these studies demonstrate that not only the magnitude but also the timing of exposure to environmental factors plays an important role in mediating expression of phenotype.

Nutrition also affects paternal epigenetic programming of offspring, as evidenced through records of a population in from northern Sweden, which revealed a link between grandparental and parental periods of low or high food availability and disease risk [96-99]. This work highlighted the possible importance of food availability during the paternal grandparental pre-pubertal Slow Growth Periods (SGP), between age 8-10 in girls and 9-12 in boys. Mortality due to cardiovascular disease or diabetes increased in men if the paternal grandfather was exposed to high food availability during his SGP [96,97,99], an effect later extended to paternal grandmother-granddaughter pairs and transmitted in a gender-specific fashion [99,100].

However, multi-generational epigenetic effects in human populations are scarce, mainly because 1) phenotypic records have rarely been collected, and 2) the inevitable difficultly in being able to define the relative contributions of genetic, epigenetic and common environmental or learned behavioral confounders. Animal models of maternal care have helped to provide a mechanistic understanding of the impacts of early life adversity, allowing for control of genetic variation and a temporal dynamics of environmental exposures.

Maternal Care and Epigenetic Programming of Phenotypic Differences in Behavior

The quality and stability of the early social context has profound influences on long-term emotional and psychological health, and appears to be mediated, in part, by the closeness or degree of positive attachment in parent (typically mother)-infant bonding and parental investment [101]. The synchrony of parental investment, including nutrient supply provided by the parent, during the critical postpartum period provides the individual with an evolutionary advantageous ability to physiologically adjust (or 'program') gene expression profiles contributing to the organization and function of neural circuits and molecular pathways that support (a) biological defensive systems for survival (e.g. stress resilience), (b) reproductive success to promote establishment and persistence in the present environment and (c) adequate parenting in the next generation [102].

Associations between early life experiences (including parent-infant bonding), Hypothalamus-pituitary-adrenal (HPA) axis activity, brain development and health outcome provide important clues into the neurobiological mechanisms that mediate the contribution of stressful experiences to personality development and the manifestation of illness. The HPA axis shapes the endocrine response to stress in addition to its role in many other physiological processes, including immune and metabolic function. As such, the HPA axis plays an adaptive role by maintaining allostasis (i.e., stability amid change) in the face of challenging environmental conditions. Importantly, the relationship between early life experience and long term health is mediated by maternal influences on the development of neuroendocrine systems that underlie HPA and behavioral responses to stress. Accumulating evidence indicates that this 'biological embedding' involves persistent changes in gene regulation via epigenetic mechanisms.

Maternal behavior in the rat during the first weeks of life provides the nurturing environment that is crucial for survival of the young and allows the dam to meet the physiological demands of prolonged care of the offspring. In rat pups, maternal nurturing (licking and grooming) during the first week of life is associated with long term programming of individual differences in stress responsiveness, emotionality, cognitive performance and reproductive behavior [103-107]. As adults, the offspring of mothers that exhibit increased levels of pup Licking and Grooming (LG) over the first week of life show increased expression of the Glucocorticoid Receptor (GR) in the hippocampus (a brain structure associated with stress responsivity as well as learning and memory) and a lower hormonal response to stress by comparison to adult animals reared by Low LG mothers [104,106]. In adulthood, the female offspring of mothers that exhibit increased levels of pup LG (i.e., High LG mothers) over the first week of life are themselves high in maternal LG behavior towards their pups and likewise, the offspring of Low LG mothers are low in maternal LG behavior towards their

pups [106]. These effects are essentially reversed by cross-fostering, suggesting a direct effect of maternal care [104,106].

Interestingly, the effects of maternal care on the behavioral and neuroendocrine responses to stress appear to depend on epigenetic programming of gene expression in the brain. The offspring of High and Low LG mothers display lifelong alterations in 5mC patterns and chromatin H3K9Ac status in the exon 1_7 promoter, an upstream regulatory region that regulates the expression of the coding regions of the GR gene in the hippocampus [108]. These group differences emerge over the first week of life, are reversed by cross-fostering, remain stable through life and are potentially reversible in adulthood [108]. These studies, among others, suggest that the maternal behavior stimulates a neural pathway that activates specific transcription factors, directing the epigenetic machinery (chromatin and DNA modifying enzymes) to specific targets within the genome [109-112]. The ability of maternal behavior to affect several behavioral phenotypes in the offspring, including maternal care, provides a mechanism by which acquired and stable behavioral traits can be propagated across generations through epigenetic modifications of DNA and chromatin structure in a loci- and tissue-specific manner.

Similar processes at comparable epigenetic labile regions could explain why the adult offspring of high and low LG dams exhibit wide spread differences in hippo campal gene expression and cognitive function [112]. Recent findings have shown that maternal care influences levels Glutamic Acid Decarboxylase (GAD)-the rate-limiting enzyme in GABA synthesis-in the hippocampus through epigenetic programming of a GAD gene promoter [113]. Compared with the offspring of high LG mothers, those reared by low LG dams showed reduced hippo campal GAD1 mRNA expression, increased cytosine methylation and decreased H3K9Ac of the GAD1 promoter. Likewise, the adult offspring of low LG mothers show enhanced binding of MECP2 to the Brain-derived Neurotropic Factor (Bdnf) promoter in the hippocampus (Weaver et al., unpublished data), decreased hippo campal BDNF mRNA and protein expression, reduced hippo campal neuronal survival, reduced hippo campal synaptogenesis and synaptic plasticity [114-116]. Consequently these offspring perform worse in tests of spatial learning and object recognition by comparison to adult animals reared by high LG dams [116,117]. This is consistent with recent studies demonstrating that exposure of infant rats to stressed caretakers that predominately displayed abusive behaviors (e.g., dragging, rough handling) produces offspring with increased BDNF IV promoter methylation and decreased in forebrain BDNF mRNA expression throughout life, with evidence of trans-generational inheritance of these traits in the abused female offspring [118]. Central infusion of the DNA methylation inhibitor zeburaline increases forebrain BDNF mRNA expression in the abused offspring to levels comparable to the non-abused offspring. A recent study found evidence of sex-specific DNA methylation changes in BDNF and reelin in the medial prefrontal cortex of offspring subjected to an adverse maternal environment that emerge in the transition between adolescence and adulthood [119]. Interestingly, the effect of maternal care on cognitive function in the offspring of low LG mothers is largely reversed with peri-pubertal exposure to an enriched environment [117,120,121], implying that epigenetic labile regions in the rat brain remain environmentally responsive well beyond the perinatal period.

These studies demonstrate that early life experiences can trigger lifelong persisting epigenomic changes in the brain of an individual, an observation that has clear implications for how epigenetic mechanisms might contribute to CNS health and pathogenesis over the lifespan.

Conserved Epigenetic Sensitivity to Early Life Experience in Humans: It's In Your Blood

Several studies have attempted to determine to what extent are the findings from model animals transferable to humans. Examination of post-mortem brain tissue from healthy human subjects found that the human equivalent of the GR gene promoter (NR3C1 exon 1F promoter) is also unique to the individual [122]. A similar study examining newborns showed that methylation of the GR gene promoter maybe an early epigenetic marker of maternal mood and risk of increased hormonal responses to stress in infants 3 months of age [123]. Although future studies are required to examine the functional consequence of this DNA methylation, these findings are consistent with our studies in the neonate and adult offspring of low LG mothers that show increased DNA methylation of the promoter of the GR gene, decreased GR gene expression and increased hormonal responses to stress [108]. Examination of brain tissue from suicide victims found that the human GR gene promoter is also more methylated in the brains of individuals who had experienced maltreatment during childhood [124]. These finding suggests that DNA methylation mediates the effects of early environment in both rodents and humans and points to the possibility of new therapeutic approaches stemming from translational epigenetic research. Indeed, similar processes at comparable epigenetic labile regions could explain why the adult offspring of high and low LG dams exhibit wide spread differences in hippo campal gene expression and cognitive function [112]. Taken together, these data suggest that increased GR methylation could represent a general epigenetic mark of early-life stress that could be observed in different psychiatric populations exposed to early-life adversity and experiencing emotional and/or mood deregulation.

This type of research is however has been hampered by the inaccessibility of human brain samples. The translational potential of this finding would be greatly enhanced if the relevant epigenetic modification can be measured in an accessible tissue. Recently Perroud et al showed that increased DNA methylation of the human GR gene promoter in peripheral blood lymphocytes was associated with increased loading of childhood maltreatment in people with borderline personality disorder, suggesting that peripheral blood could represent a proxy of the epigenetic modifications of the GR gene promoter occurring in the CNS [125]. In support of this, the same group examined blood samples from adult patients with bipolar disorder, who also retrospectively reported on their experiences of childhood abuse and neglect and found that the degree of DNA methylation of the human GR gene promoter was strongly positively related to the reported experience of childhood maltreatment decades earlier [126].

These studies have the potential to open a range of exciting new possibilities: given the large effect size and consistency of this association, measurement of the GR promoter methylation may effectively become a blood test measuring the physiological traces left on the genome by early experiences. While this simple blood test cannot replace current methods of diagnosis, this unique and addition information adds to our knowledge of how disease may arise and be manifested throughout life. It is tempting to imagine that in the near future such epigenetic marks will form a useful guide for predicting important outcomes, such as response to treatment and suicidal behavior.

Regulation of Synaptic Transmission, Neuronal Plasticity and Cognitive Function

Epigenetic mechanisms influences genomic activities in the brain to produce long-term changes in synaptic signaling, organization and

morphology, which in turn support cognitive function [127]. Neuronal activity in the hippocampus of mice induces active DNA demethylation or *de novo* methylation [128], and targeted knockouts of DNA *de novo* methyl transferases cause learning and memory impairments [129]. DNA methylation has also been implicated in the maintenance of long-term memories, as pharmacological inhibition of DNA methylation abolishes remote memories [127,130]. Consistent with this idea, over expression of TET1 protein (which promotes 5hmC formation and active demethylation) results in increased expression of several neuronal memory-associated genes and impaired contextual fear memory [58]. These findings indicate the importance of covalent DNA modifications in mediating synaptic plasticity and cognitive functions, both of which are disturbed in psychological illness. Changes in histone modifications can also influences long-term memory formation by altering chromatin accessibility and the transcription of genes relevant to learning and memory. Memory formation and the associated enhancements in synaptic transmission are accompanied by increases in histone acetylation [131] and alterations in histone methylation [132], which promote an active chromatin state. Conversely, a neuronal increase in histone de-acetylase activity, which promotes chromatin compaction, results in reduced synaptic plasticity and impairs memory [133]. Pharmacological inhibition of histone deacetylases augments memory formation [133,134]; further suggesting that histone (de) acetylation regulates this process.

In humans genetic defects in genes encoding the DNA methylation and chromatin machinery exhibit profound effects on cognitive function and mental health [135]. For example, ATRX a severe, X-linked form of syndromal mental retardation associated with Alpha Thalassaemia (ATRX syndrome) is caused by a mutation in a gene that encodes a member of the SNF2 sub-group of a super family of proteins with similar ATPase and helicase domains involved in chromatin remodeling [136] and is associated with DNA methylation aberrations [137]. In addition, functional polymorphisms of genes involved in folate metabolism-such as Methylene tetra hydrofolate Reductase (MTHFR), a regulatory enzyme in folate metabolism—have been shown to alter intracellular SAM levels and linked to the increased risk of psychiatric disorders [88,89]. However the two best characterized examples are Rett syndrome, a progressive neuro developmental disorder and one of the most common causes of mental retardation in females which is caused by mutations in the X-chromosome-linked gene MeCP2 [138], and Rubinstein–Taybi Syndrome (RTS), a multiple congenital anomaly syndrome in males and females which is caused by mutations in the histone acetyl transferase gene CBP [139]. Both MeCP2 and CBP are highly expressed in post-mitotic neurons and are involved in regulating neural gene expression [140,141].

The phosphorylated (active) form of MeCP2 binds broadly throughout the genome, affecting chromatin state, dendritic and synaptic development and hippocampus-dependent memory [142,143]. Mice with truncated MeCP2 exhibit genome-wide H3 hyper acetylation (H3Ac), neuronal atrophy, increased anxiety, cognitive deficits and social withdrawal, which can be further exacerbated by forebrain knockout of *BDNF* [144]. Remarkably, many of the physiological, cognitive and emotional deficits associated with MeCP2 mutant mice are reversed by ectopic *Bdnf* expression, demonstrating a functional interaction between MeCP2 and *Bdnf* in Rett disease progression [145]. Although originally thought to selectively recognize 5mC and mark genes for repression [146,147], a recent study identified MeCP2 as the major 5hmC-binding protein in the mammalian brain and demonstrated that MeCP2 bound 5hmC facilitates gene transcription [148]. A certain Rett-causing mutation, called R133C-which is responsible for a relatively milder form of the disorder-disrupts MeCP2's binding to 5hmC. These findings support a model in which 5mC, 5hmC and MeCP2 constitute a cell-specific epigenetic mechanism for regulation of chromatin structure and gene expression, which may be disrupted in Rett syndrome.

Mutations of the CBP HAT domain in several Rubinstein-Taybi syndrome (RTS) cases are associated with genome-wide histone hypo-acetylation and cognitive dysfunction in adulthood [149]. The learning and memory deficits are attributed to perturbed neural plasticity [150], however, RTS individuals also exhibit early cognitive dysfunction [151] and display neural dysgenesis, including cortical abnormalities [152]. Similar to RTS in humans, mice with a heterozygous null mutation of CBP perform poorly in cognitive tasks and show decreased genome-wide histone acetylation [153]. The potential role for CBP was examined in neural precursors born in the sub-ventricular zone of the lateral ventricles of the developing murine cortex, which sequentially generate neurons, astrocytes and oligodendrocytes [154]. Phosphorylation of CBP by atypical protein kinase C (aPKC) was found to act as an epigenetic switch to promote precursor differentiation. Interestingly, this epigenetic mechanism is perturbed in the fetal brains of CBP haplo insufficient mice, which, as pups, exhibit early behavioral deficits in ultrasound vocalization following maternal separation [154]. These findings provide a novel mechanism whereby environmental cues, acting through histone modifying enzymes, can regulate stem cell epigenetic status and thereby directly promote differentiation, which regulates neurobehavioral development.

Together, these studies demonstrate that mis regulation of epigenetic modifications and their regulatory enzymes is capable of orchestrating prominent deficits in neuronal plasticity and cognitive function, abnormalities relevant to many psychological disorders.

Influence of Chromatin Plasticity on Major Neuropsychiatric Disease

Epigenetic events that alter chromatin structure to regulate programs of gene expression have been associated with depression-related behavior and action of antidepressant medications, with increasing evidence for similar mechanisms occurring in *post-mortem* brains of depressed individuals. The 'chronic social defeat' model of depression is a behavioral paradigm in which the animal is exposed to a more aggressive animal of the same species [155]. When brought together again, chronically exposed animals tend to avoid contact with the aggressor [156]. In mice, this social avoidance resulted in increased transcriptionally repressive H3K27me2 levels and decreased expression of hippo campal Bdnf splice variants (Bdnf III and Bdnf IV) important in mediating depressive responses [157]. Similarly, chronic social defeat stress was found to increase the repressive mark H3K9me3 in the hypothalamic orexin (hypocretin) gene promoter-a neuropeptide implicated in normal emotion processing [158]. Chronic administration of the widely used antidepressant imipramine increased markers of transcriptional activation H3K9/K14ac and H3K4me2 and reversed the repression of the *BDNF* transcripts induced by defeat stress [157,159]. Other classes of antidepressants have also been shown to enhance H3K4me2 levels [160].

The effects of imipramine on H3K9/K14ac appear to associate specifically with HDAC5 activity [157]. Over expression of *Hdac5* reversed the imipramine-induced antidepressant increase in H3K9/K14ac and Bdnf splice variant transcription [157]. These results provide support for the efficacy of HDAC inhibitors against depression. Accordingly, several HDAC inhibitors, including sodium butyrate

[157], Entinostat (MS-275) [161], and Suberoylanilide Hydroxamic acid (SAHA) [161], as well as reduced hippo campal *Hdac5* expression have been found to exert antidepressant effects in models of chronic social defeat [162]. Consistent with these findings, in the Nucleus Accumbens (NAc), chronic social defeat stress decreased *Hdac5* mRNA levels and imipramine treatment increased *Hdac5* mRNA levels [163]. Accordingly, *Hdac5* KO animals showed depression-associated behavior but no effects of imipramine treatment. Additionally, NAc levels of Hdac2-but not of Hdac1 or Hdac3-were down regulated after chronic social defeat in mice and in human *post- mortem* NAc samples from individuals with a history of clinical depression [161].

Different types of HDAC inhibitors may be effective as antidepressants by each modifying distinct cellular targets. For example, chronic antidepressant treatment with fluoxetine increases Hdac2 mRNA levels accompanied by H3K9/K14ac levels and also enhances MeCP2 and MBD1 transcription in the rat forebrain, including the frontal cortex, hippocampus and striatum [164]. The antidepressant-dependent increase in MeCP2 was specific to GABAergic interneurons [164]. This finding is of particular interest, since abnormal GABAergic transmission and abnormalities in GABA-related gene methylation have been linked to MDD and suicidal behavior in humans. Depressed patients who committed suicide have higher levels of methylation in the GABA-A α1 receptor subunit [165] and *BDNF* exon IV [166] promoter regions, and increased *DNMT3b* mRNA and protein in the prefrontal cortex compared with control individuals who died of other causes [165]. Indeed, there is increasing evidence that aberrant gene transcription resulting from altered epigenetic regulation is associated with the pathophysiology of suicide. Ribosomal RNA (r RNA) promoter methylation [167,168] has been shown to be increased in the hippocampus (but not the cerebellum) of suicide victims who were victims of abuse during childhood compared to controls [169]. Thus, it is tempting to speculate that there is an epigenetically determined reduced capacity for protein synthesis (required for learning and memory) in the brains of suicide victims.

Epigenetic mis-regulation is also consistent with various clinical and epidemiological features of neuropsychiatric diseases, including discordance of monozygotic (identical) twins, fluctuating clinical course, sexual dimorphism in incidence and severity, parent-of-origin effects, coincidence between disease onset and the time of major hormonal changes in the organism, decline of clinical symptoms in aging patients with Schizophrenia (SCZ) and Bipolar Disorder (BPD), and the non-decreasing incidence of SCZ despite the significantly reduced reproductive fitness of the affected individuals [170,171]. Epigenome-wide studies have identified several dozen sites with DNA methylation alterations, some of which are sex-specific, in genes involved in brain development and neurotransmitter pathways, which had previously been associated with major psychosis [172]. Interestingly, many of theses epimutations maybe inherited or acquired before tissue differentiation in embryogenesis [173].

Concluding Remarks

Phenotype is maintained through multiple interactions between the dynamics of cellular-level function in response to intrinsic (genomic) and extrinsic (environmental) cues. Physiological and neuro developmental systems continually receive, transform and update information regarding the demands of the environment. Rapidly growing evidence from basic research indicates that epigenetic regulation underlies these processes in brain development and phenotypic plasticity, and that cognitive dysfunction occurs upon epigenetic mis-regulation. However, as discussed in this review, the epigenome is not static and can be molded by developmental signals, environmental perturbations and disease states, which present an experimental challenge in the search for epigenetic risk factors in neuropsychiatric disease. Though determining how epigenetic mechanisms serve as the interface between genes and experience (or nature and nurture) is certainly a daunting endeavor, the combination of genetic association maps studies with epigenome-wide developmental studies will hopefully identify novel molecular mechanisms to help explain inheritance of certain personality and behavioral traits and the emergence of neuropsychiatric illness. Accordingly, we are only beginning to understand how early experiences influence key biological systems—genetic, neural, endocrine and immunological—over the long term to produce social gradients in life course trajectories of health and human development.

Acknowledgments

We would like to thank Dr. Shelley E. Brown for her helpful comments and numerous constructive suggestions throughout the preparation of this manuscript.

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