ANNUAL REVIEWS

Annual Review of Clinical Psychology

Epigenetics, Development, and Psychopathology

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Annu. Rev. Clin. Psychol. 2020. 16:327–50

First published as a Review in Advance on February 21, 2020

The *Annual Review of Clinical Psychology* is online at clinpsy.annualreviews.org

https://doi.org/10.1146/annurev-clinpsy-050718-095530

Keywords

epigenetics, neurodevelopment, gene transcription, early experience, gene × environment interactions, psychopathology

Abstract

Epigenetic mechanisms govern the transcription of the genome. Research with model systems reveals that environmental conditions can directly influence epigenetic mechanisms that are associated with interindividual differences in gene expression in brain and neural function. In this review, we provide a brief overview of epigenetic mechanisms and research with relevant rodent models. We emphasize more recent translational research programs in epigenetics as well as the challenges inherent in the integration of epigenetics into developmental and clinical psychology. Our objectives are to present an update with respect to the translational relevance of epigenetics for the study of psychopathology and to consider the state of current research with respect to its potential importance for clinical research and practice in mental health.

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INTRODUCTION

The rigor of the debate concerning the relative importance of genetic (nature) versus environmental (nurture) factors for individual differences in human traits has diminished over the past few decades. However, the resulting moratorium seems to better resemble a cease-fire than a meaningfully integrated approach to the origins of psychopathology. While there is an understanding that vulnerability to illness derives from gene × environment interactions, how best to integrate this appreciation into the study of mental health remains elusive. One obstacle is that of identifying the processes that define the ×: How exactly might environmental signals physically interact with the DNA material that makes up our genome?

The remarkable interest in epigenetics over the past decade derives from the idea that epigenetic mechanisms might explain how environment and genome operate in concert to define individual variation from the level of cellular function to complex traits. There are multiple compelling reviews on this topic (e.g., Boyce & Kobor 2015, Feng & Nestler 2013, Jones et al. 2018, Klengel & Binder 2015, Zhang & Meaney 2010). While we summarize the major aspects of this issue, our primary intent is to consider the next-generational question of how epigenetics might contribute to an understanding of the origins of psychopathology and advance intervention science and clinical practice. Rather than extensively catalog relevant papers, our discussion of the importance of epigenetics for clinical psychology emphasizes specific illustrative studies in detail. We aim to familiarize the reader with major conceptual and translational advances as well as to present a detailed discussion of the challenges in the field. Our objective is to bring the reader up to date with respect to the translational relevance of epigenetics to the study of psychopathology and its potential importance for clinical research and practice in mental health.

EPIGENETICS

Advances in the biological sciences have revealed a novel form of environmentally regulated plasticity in brain function that occurs at the level of the genome. This plasticity refers not to variation in nucleotide sequence, which remains largely invariant over the life span, but to the biochemical environment within which genetic information is transduced into cellular signals. This biochemical niche is the epigenome and can be considered as the software that directs the activity of the

Figure 1

(*a*) An environmental signal activates transcription factor binding to target sequences (i.e., transcription factor binding sites) that are specific for that transcription factor. Transcription factor binding then activates or represses gene transcription. (*b*) The nucleosome structure of chromatin is composed of ~146 base pairs of DNA wrapped around an octamer of histone proteins (Luger et al. 1997, Turner 2001). The nucleosome is commonly in a closed nucleosome state maintained by the physiochemical relation between the positively charged histone proteins and its accompanying negatively charged DNA. The blue strand represents one of the histone tails composed of amino acids that are common sites for epigenetic modification. Epigenetic modifications reveal DNA binding sites and permit transcription factor binding and transcriptional activation. Once complete, chromatin is repackaged, which involves reestablishing epigenetic signals. This repackaging is an opportunity to redesign some of the multiple epigenetic signals at that genomic region (Meaney & Ferguson-Smith 2010), thus modifying the subsequent probability of activation from that region. The process is analogous to synaptic plasticity, in which activity can influence future signaling capacity. Panel *b* adapted from an image by Song Tan, Penn State University (**http://www.personal.psu.edu/sxt30/gallery_protdna_alt.html**); CC BY-NC 3.0 US.

DNA sequence hardware. The epigenetic software is established during early development but is subject to updates that reflect the impact of environmental conditions and provide the basis for continuous adaptation in brain function.

Epigenetic mechanisms govern the biochemical cascade that begins with the DNA nucleotide sequence that produces various forms of RNA (i.e., the process of transcription). Messenger RNA (mRNA) produces the proteins (i.e., the process of translation) that are the principal cell signaling molecules. Variation across individuals in the operation of this cascade was historically ascribed to variation in nucleotide sequence. Indeed, sequence variation can influence the form and production of RNAs and their protein products, with effects on cellular function and health. This logic underlies the search for heritable sequence variations that are associated with disease states. However, this perspective ignores the remarkable complexity in the processes by which a gene is transcribed into an RNA product. Gene transcription or expression is a dynamically regulated event under the influence of epigenetic signals that control the operation of the genome (**Figure 1**). The obvious implication is that variation in the transcription of the genome within any cell can occur as a result of differences in the epigenetic software. The finding that epigenetic signals are modified by environmental conditions led to a wonderful integration of the biological and social sciences, reflecting the degree to which the study of human development and health has advanced beyond the darkness of the nature–nurture controversy.

Epigenetics and Development

The impact of epigenetic mechanisms can be understood by appreciating a fundamental problem in human development: How are more than 200 very different cell types produced from almost exactly the same genetic material? While every cell has the same genetic material, the portion that is actively transcribed differs across cell types; genes active in liver cells differ from those active

in neurons of the brain. The multiple cell types emerge during embryogenesis. The process of cell differentiation results in the specialization of cellular function reflected in the transcriptional profile, or transcriptome, of that cell type, which is the portion of the genome actively expressed within a cell. Liver cells specialize in energy metabolism through the processing of glucose and lipids. Genes associated with gluconeogenesis are active in liver cells and stably silenced in cells found in the brain. Brain cells establish the capacity for learning and memory, communication and social interactions, emotional reactions, and so forth, and thus rely on a different subset of the genome.

Epigenetic mechanisms govern the processes by which the various cell types acquire their distinct transcriptional profile and function in early development. Genes silenced in a particular cell type acquire chemical modifications, notably DNA methylation (see the section titled Epigenetic Mechanisms), that stably silence regions of the genome. The remaining, potentially active regions of the genome define the range of cellular function for that cell. The epigenetic signals that underlie this process of cell differentiation are highly stable. The loss of these signals results in the dedifferentiation of the cell, a process that causes organ dysfunction and diseases such as cancer. Since the development of vital organs is essential for life, the epigenetic signals that define cellular differentiation are largely invariant across humans. An estimate suggests that approximately 70% of DNA methylation marks across the genome show almost no variation across healthy adults of any population (Ziller et al. 2013). The study of individual variation in DNA methylation refers to the remaining portion that can vary across individuals without critically disrupting cellular identity.

As development progresses, individual tissues expand as a function of cell proliferation. However, cells faithfully recapitulate the fate of the progenitor across cell division. Liver cells give rise to liver cells. The epigenetic signals that define the destiny of the cells are reproduced in the progeny. Cell lineage is thus maintained over the course of proliferation. The recapitulation of the epigenetic signals across cell division reflects the heritability of epigenetic signals. But this is mitotic heritability, which explains why the definition of epigenetics often includes reference to these signals as heritable. It does not imply meiotic heritability, which would bear on the issue of intergenerational transmission.

There are also more subtle differences in gene expression between cells within the same population. Epigenetic mechanisms define not only the differences between liver cells and neurons but also the variation that occurs within these populations. The brain comprises multiple forms of glial cells and neurons, each with a generally stable range of function. There are cells that are morphologically very different, that synthesize and release specific neurotransmitter molecules, and that make specific forms of connections. This more subtle level of specialization is also associated with unique epigenetic profiles (Rizzardi et al. 2019).

The next level of variation, the one most relevant for this review, is that occurring between individuals within a specific cell type. This individual variation in cell function is reflected in patterns of genomic transcription linked to epigenetic signals (Husquin et al. 2018). The epigenetic signals associated with variation in cellular function across individuals are the most significant for individual differences in health outcomes and thus for the clinical and intervention sciences.

Epigenetic Mechanisms

The transcription of DNA into RNA is actively regulated by the binding of transcription factors to specific DNA regions (transcription factor binding sites) to activate or repress transcription (**Figure 1*a***). While **Figure 1** depicts strands of DNA as linear for the sake of simplicity, the reality is very different (Luger et al. 1997, Turner 2001). The nucleosome structure of chromatin

(**Figure 1*b***) reveals the packaging of DNA; note that this restrictive configuration is maintained, in part, by electrostatic bonds between the positively charged histones and the negatively charged DNA. The nature of the chromatin structure is critical. This closed chromatin configuration limits transcription factor binding and the active regulation of transcription.

Epigenetic signals modify chromatin configuration through chemical modifications to either the histone proteins or the DNA. An increase in transcription factor binding to DNA and the subsequent activation of transcription require epigenetic modifications to chromatin in order to relax the histone–DNA bonds, promoting an open chromatin configuration that permits transcription factor binding and transcriptional regulation. Epigenetic signals thus determine the accessibility of chromatin to transcription factors, a process that can be dynamic and, importantly, reversible (Meaney & Ferguson-Smith 2010).

Histone modifications. Dynamic changes in chromatin structure occur through biochemical modifications of histone proteins at the amino acids that form the histone tails (**Figure 1*b***). There are several such modifications, including acetylation, phosphorylation, methylation, and ubiquitylation (Maze et al. 2013). Specific enzymes catalyze each of these modifications to regulate the chemical properties at specific histone regions (Hake & Allis 2006). For example, histone acetyltransferase transfers an acetyl group onto specific lysines on the histone tails that diminish the positive charge at that site, opening chromatin and enhancing the access of transcription factors to DNA binding sites. Histone acetylation is commonly associated with active transcription.

Histone deacetylases (HDACs) oppose the effects of histone acetyltransferases. HDACs remove acetyl groups and prevent acetylation, maintaining a closed chromatin structure and thereby decreasing both transcription factor access to DNA and gene expression. Histone modifications thus gate transcription factor binding to DNA through chemical modifications to chromatin.

Histone acetylation and deacetylation are dynamic processes regulated by additional epigenetic modifications. One such modification is histone methylation, a more stable modification that also occurs at amino acid sites in the histone tails (Kouzarides 2007). Histone methylation attracts protein complexes that then close or open chromatin. Histone methylation marks can attract either histone acetyltransferases, thus favoring transcription, or HDACs, thus causing transcriptional silencing. Histone methylation can therefore serve as a platform for additional molecules to form complexes, opening or closing chromatin to affect transcriptional activity. Methylation or demethylation at individual histone sites is catalyzed by specific enzymes regulated by intracellular signaling pathways that are sensitive to environmental conditions. Importantly, because of the more stable nature of histone methylation, this class of epigenetic modifications can serve to maintain enduring environmental effects on transcription and behavior (e.g., Feng & Nestler 2013).

DNA methylation. DNA methylation is a chemical modification of DNA formed by the addition of a methyl group (CH_3) onto cytosines, most commonly those bound to guanines to form CG sequence couplets (Deaton & Bird 2011, Razin & Riggs 1980; but see Lister et al. 2013). DNA methylation in gene regulatory regions where transcription factors bind is typically associated with transcriptional repression. The relationship between DNA methylation and transcription in regions such as the gene body is more complex (Maunakea et al. 2010, Shenker & Flanagan 2012) and can be positively associated with transcription through as-yet-unknown processes. However, note that DNA methylation is not universally associated with the silencing of gene transcription.

DNA methylation in regulatory regions can repress gene transcription through multiple pathways (Klose & Bird 2006). Broad regions of densely methylated DNA compact to form heterochromatin that precludes transcription factor binding in order to sustain silencing of a

selected portion of the genome (see the preceding section). We focus more on euchromatin regions of the genome that can be dynamically activated. A common manner in which DNA methylation regulates activity within the euchromatic regions is subtle and involves additional epigenetic signals. The presence of CG methylation attracts methylated DNA binding proteins to the DNA (Klose & Bird 2006); these, in turn, attract a cluster of proteins to form a repressor complex including active mediators of gene silencing, such as the HDACs that prevent histone acetylation. DNA methylation can thus be associated with a diminished capacity to open chromatin.

DNA methylation is established by multiple forms of DNA methyltransferase (DNMT) proteins. During early development, DNMT-1 establishes stable DNA methylation patterns and mediates the fidelity of these patterns during cell proliferation. DNMT-1 is closely associated with cell and tissue differentiation. DNMT-3a, by contrast, remains active over the life span and is associated with dynamic variations in DNA methylation established beyond the point of cell specialization. Importantly, DNMT-3a is dynamically regulated by environmental conditions and mediates effects on behavioral outcomes (e.g., Elliott et al. 2016) as well as on learning and memory (e.g., Morris & Monteggia 2014). There also exist multiple cell signaling pathways activated by environmental conditions that result in the removal of the methylation mark or demethylation (Bhutani et al. 2011, Kohli & Zhang 2013, Zhu 2009). An important point here is the reversibility of DNA methylation signals. Cells in the central nervous system bear the capacity for remodeling DNA methylation at any phase of the life cycle, a process that underlies neuronal plasticity (Guo et al. 2011, Herb et al. 2012, Meaney & Ferguson-Smith 2010).

There are multiple variations in DNA methylation. One of them, methylcytosine, can be transformed into hydroxymethylcytosine, which can also bind methylated DNA binding proteins and regulate transcription (Branco et al. 2012, Mellén et al. 2012). This epigenetic modification is enriched in the brain (Jin et al. 2011, Kriaucionis & Heintz 2009) and is associated with synaptic genes and dynamic regulation in early development (Ruzov et al. 2011, Szulwach et al. 2011). This form of DNA methylation is readily subject to demethylation, suggesting a more dynamic state. Another interesting twist is the methylation of cytosines that occurs at non-CG couplets, especially cytosine–adenine sites (Guo et al. 2014, Lister et al. 2013). This form of DNA methylation is highly responsive to environmental conditions, including environmental enrichment (Zhang et al. 2018). Non-CG methylation is highly enriched in the brain as well as in stem cells, suggesting that it might characterize cells that are in a state of plasticity. Additional derivatives of DNA methylation include 5-formylcytosine and 5-carboxylcytosine, which appear to influence the developmental regulation of genome function (Iurlaro et al. 2016, Wu & Zhang 2017). Much remains unknown about these cytosine modifications, as well as non-CG methylation. The important point is that DNA methylation varies in its absence and presence at specific sites across the genome, as well as in its chemical forms.

RNA signaling. The DNA sequences that code for proteins account for only 2–3% of the more than three billion or so nucleotides of the human genome. The remaining portion came to be ingloriously known as junk DNA. It is now apparent that this genomic trash produces important types of cellular signaling molecules collectively known as noncoding RNAs. Noncoding RNAs are transcribed sequences that vary in length and function, often working in concert with other epigenetic signals to form complexes to alter the activity of the classical DNA–mRNA–protein cascade. We provide a few illustrative examples of the many forms of RNAs that act as cellular signals.

MicroRNAs (miRNAs) are short (~22–25 nucleotides in length), single-stranded RNA molecules that can directly repress transcription (Treiber et al. 2019). miRNAs also interact with proteins to form RNA-induced silencing complexes that determine the stability of mRNA and can inhibit the translation of mRNA to protein. The expression of various forms of miRNAs

is influenced by environmental conditions, including chronic stress with downstream effects on synapse formation and function, learning and memory, and socioemotional function. For example, exposure to chronic social stress in mice alters the transcription of several miRNAs in the striatum, which then determines stress-induced social avoidance (Dias et al. 2014). The association of certain genetic variants with highly heritable mental or neurological disorders involves effects on the expression of selected miRNAs (Devanna et al. 2018). Long noncoding RNAs (lncRNAs), as the name implies, are longer (>200 bp) and more numerous (~50,000 in the human genome) forms of RNA. lncRNAs are especially abundant in neural tissues; they regulate the processing of mRNAs to produce subtly different transcripts from the same gene. lncRNAs are linked to mental health conditions in humans (Zuo et al. 2016).

Summary. There is considerable interdependence across the various epigenetic signals. Methylated DNA recruits enzymes that alter histone modifications. Likewise, histone modifications determine the capacity for DNA methylation at specific sites (e.g., Ooi et al. 2007). miRNAs' influence on both DNA methylation and histone modifications (and, conversely, DNA methylation or histone modifications) affects miRNA transcription. Histone modifications can attract miRNAs to specific sites that then directly repress transcription (e.g., Li 2008). Thus, epigenetic modifications can communicate in order to control cellular function via a common regulatory network (Iorio et al. 2010).

This brief overview is far from complete. We have not discussed many histone modifications or variant forms of the core histone proteins themselves, which are dynamically regulated and functionally important for transcription. The spacing and composition of the nucleosome are variable and linked to transcription (Maze et al. 2015). We have not considered an entire class of epigenetic signals, namely polycomb complexes (Schuettengruber et al. 2017), or epitranscriptomics, which refers to chemical modifications to RNA molecules (Nainar et al. 2016). Moreover, the relationship between epigenetic marks and transcription varies depending on genomic context (Meaney & Ferguson-Smith 2010). The important point for the purpose of this review is simply that many modifications to DNA and its chromatin environment function as an additional layer of genomic information. Collectively, these modifications alter the structure and chemical properties of chromatin and thus transcription. Importantly, while the underlying DNA sequence remains largely static across development, these multiple epigenetic modifications are dynamically regulated and responsive to changes in the environment. Epigenetic information is also specific to certain cell types, allowing for localized environmental effects and specific outcomes.

ENVIRONMENTAL EPIGENETICS

Early-life experience shapes stable, individual differences in brain function that underlie the psychological processes that define the quality of mental health. Epidemiology has traced the developmental origins of individual differences in vulnerability to mental disorders (Dube et al. 2003, Gur et al. 2019, O'Donnell & Meaney 2017). Likewise, exposure to chronic stress during later periods of life leads to sustained alterations in physiology and behavior that persist well beyond the duration of the stressor (Nestler et al. 2016). The challenge is to identify the mechanisms by which environmental signals establish and sustain conditions of vulnerability.

The enduring effects of early experience were thought to be mediated through influences on neural circuitry established during development and sustained into adulthood. Neuroscience was strongly influenced by studies of the development of sensory systems that show pronounced critical periods during which the relevant neural systems are established and thereafter are largely immutable to experiential influences. This perspective has been replaced by one that views

environmentally induced plasticity as a feature of brain function across the life span, especially in cortico-limbic regions that underlie cognitive–emotional and social functions as well as learning and memory (McEwen et al. 2015). Human neuroimaging studies as well as studies with model systems document the remarkable lifelong capacity of neural connections for experience-dependent remodeling. For example, neuroimaging studies reveal dynamic plasticity in neural connectivity and function in response to psychotherapy in adults (Marwood et al. 2018). These findings led to a remarkable fusion of developmental and clinical psychology with neuroscience. But in light of this perspective of the dynamic brain, how can we understand the biological basis for the enduring effects of early experience? And how might we capture this information as the basis for both understanding the nature of vulnerability and enhancing our ability to more effectively deliver prevention or therapeutic modification?

Environmental Regulation of the Epigenome

The environmental conditions of early life determine adult patterns of gene expression and biological function, well beyond the duration of the relevant environmental condition (Bateson et al. 2004, Gluckman & Hanson 2007, Meaney 2001, Seckl & Holmes 2007). How do environmental conditions and the accompanying cellular signals stably affect gene expression? This issue is particularly important for the brain, where enduring alterations in cellular function are essential for normal activity, including learning and memory. The central role of the brain is to guide the function of the organism in accordance with life history to ensure survival and reproductive success (Meaney & Ferguson-Smith 2010). The ability to master such adaptation to circumstance relies upon the plasticity of genomic structure and function in neurons and glial cells. The implicit hypothesis is that environmental signals alter the epigenetic signals underlying the transcriptional plasticity that sustains variation in neural function.

Studies on rodent models suggest that such effects are mediated by enduring epigenetic modifications (an epigenetic memory of environmental conditions during development) that subsequently alter gene expression and cellular function. We review such studies examining the relevance of environmentally regulated epigenetic signals for the function of the hypothalamic–pituitary–adrenal (HPA) axis (**Figure 2**). We adopt this focus because of the convergence of this literature with research with human subjects (see the section titled Translational Studies in Environmental Epigenetics) and because the HPA system's role as a stress mediator is relevant for a wide range of mental disorders.

Rodent models elucidated the mechanisms for the enduring effects of variation in mother–offspring interactions on gene expression and phenotypic outcomes. In the rat, maternal care comprises nursing bouts during which the mother licks/grooms her pups, which regulates pup physiology and growth (Hofer 2005, Levine 1994). There are marked and highly stable individual differences in the frequency with which lactating rats lick/groom their offspring. The adult offspring of mothers exhibiting increased levels of pup licking/grooming (LG) (i.e., high-LG mothers) show reduced fearfulness and more modest HPA responses to stress compared with offspring of low-LG mothers (Anacker et al. 2014, Bagot et al. 2012, Caldji et al. 1998, Francis et al. 1999, Liu et al. 1997, Weaver et al. 2004). Cross-fostering and intervention studies confirm the direct effect of maternal care on behavioral and HPA responses to stress (Caldji et al. 2000, 2003; Francis et al. 1999; Weaver et al. 2004). The difference in HPA response to stress in the adult offspring of high- and low-LG mothers is mediated by a maternal effect on the expression of the glucocorticoid receptor (*GR*) gene in the hippocampus (**Figure 2**) (Hellstrom et al. 2012; Liu et al. 1997; Weaver et al. 2004, 2007). GR is a transcription factor that when bound by glucocorticoids is activated and translocated to the cell nucleus, where it binds specific regions of the DNA to regulate

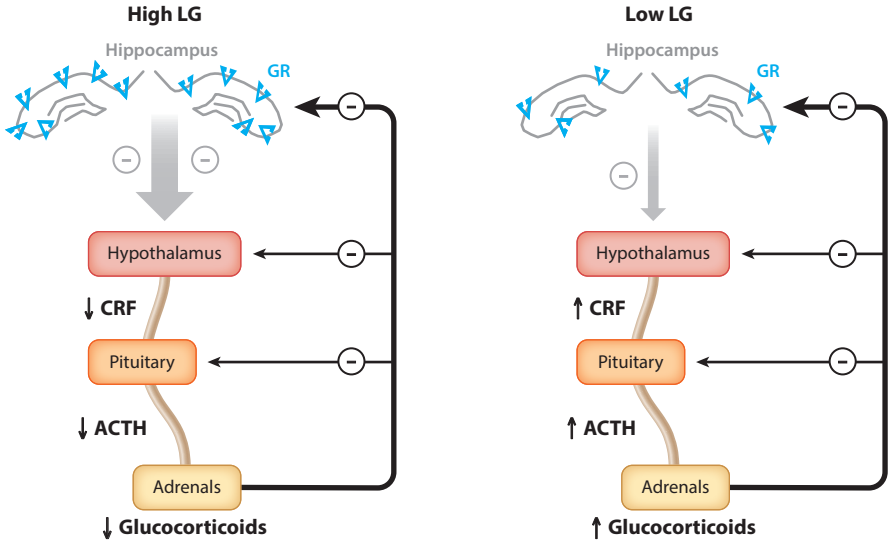

Figure 2

The influence of glucocorticoid receptor (GR) expression on hypothalamic–pituitary–adrenal axis responses to stress in the adult offspring of high- and low-licking/grooming (LG) rat mothers. The relative increase in hippocampal GR expression (*cyan triangles*) in the adult offspring of high-LG mothers leads to greater feedback inhibition of hypothalamic corticotropin-releasing factor (CRF) and more modest responses to stress, reflected in lower stress-induced secretion of both pituitary adrenocorticotrophic hormone (ACTH) and adrenal glucocorticoids.

transcription. GR activation in the hippocampus initiates a negative-feedback signal that inhibits corticotropin-releasing factor (CRF) expression in the hypothalamus. Since CRF activates the pituitary–adrenal stress response, negative-feedback regulation moderates the magnitude of the stress response. The offspring of high-LG mothers show increased hippocampal GR expression, more efficient negative-feedback regulation of CRF, reduced hypothalamic CRF expression, and more modest HPA responses to stress (**Figure 2**).

The *GR* gene includes an exon 1 region that contains multiple promoters, each of which can activate GR transcription (McCormick et al. 2000). Maternal LG activates a cell signaling cascade that establishes the level of methylation at the exon 1_7 promoter site over postnatal development and remains stable into adulthood (Hellstrom et al. 2012). The difference in DNA methylation of the exon 1_7 promoter occurs in a region that binds the transcription factor nerve growth factor–induced factor A (NGFI-A), which activates GR transcription (Weaver et al. 2007). Adult offspring of high-LG mothers show reduced levels of exon 1_7 methylation at the NGFI-A binding site, increased NGFI-A binding, and increased GR transcription. DNA methylation at this GR promoter site is also accompanied by differences in histone modifications that enhance transcription (Hellstrom et al. 2012; Weaver et al. 2004, 2007; Zhang et al. 2013).

Early experience produces enduring epigenetic modifications at multiple components of the HPA axis. Prolonged maternal separation in the mouse alters the methylation state of the promoter for the arginine vasopressin (*AVP*) gene, increasing hypothalamic AVP release and HPA responses to stress (Murgatroyd et al. 2009). This epigenetic programming of AVP expression involves calcium/calmodulin signaling that produces a hypomethylation at the AVP promoter, which in turn sustains the increased capacity for stress-induced AVP release and increased HPA activation.

Variations in maternal care in the rat also stably alter CRF signals through epigenetic modifications in the glutamate neurons that activate CRF release from the hypothalamus (Singh-Taylor et al. 2018). Maternal regulation of HPA function also includes effects at the level of the pituitary gland (Wu et al. 2014). Maternal separation of mouse pups causes an enduring hypomethylation of the *POMC* gene that encodes for proopiomelanocortin, from which adrenocorticotrophic hormone is derived, resulting in increased basal and CRF-induced levels of HPA activation (**Figure 2**). These findings reveal that the quality of maternal care epigenetically programs transcription at multiple levels of the HPA axis to regulate both basal and stress-induced activity. The epigenetic programming of HPA activity is not limited to periods of early development. Mice subjected to chronic social defeat stress display decreased DNA methylation in the *CRF* gene, leading to sustained upregulation of *CRF* in neurons of the hypothalamus (Elliott et al. 2010).

Translational Studies in Environmental Epigenetics

Translational studies using postmortem human brain samples addressed the question of whether early-life adversity in humans is linked to stable epigenetic regulation of transcription. The strength of these studies lies primarily in their use of brain tissue but also in their ability to focus on selected regions and even discrete cell types. Since childhood maltreatment is associated with altered HPA function (Heim et al. 2000, 2001), such studies often focus on this system, permitting a comparison with results from model systems.

McGowan et al. (2009) and Labonte et al. (2012b) showed decreased *GR* expression in samples of hippocampus from suicide completers with histories of childhood maltreatment compared with controls (sudden, involuntary fatalities). Psychological autopsies (forensic interviews with family members) established the subjects' developmental history and mental health status (Zouk et al. 2006). There was no association between a history of mood disorders or substance use and hippocampal *GR* expression. Rather, decreased hippocampal *GR* expression was associated with a history of childhood maltreatment. Molecular analyses revealed decreased activity of various *GR* promoters, of which there are several, as a function of childhood maltreatment that correlated with differential DNA methylation patterns. The exon 1_F promoter sequence is of particular interest because it is the ortholog of the rat exon 1_7, is highly expressed in hippocampus, and contains an NGFI-A binding site (McGowan et al. 2009, Turner & Muller 2005). The exon 1_F sequence showed increased DNA methylation, decreased NGFI-A binding, and decreased *GR* expression as a function of childhood maltreatment. Studies in independent human samples using peripheral rather than brain samples report comparable associations between early-life adversity and *GR* methylation at the same exon 1_F promoter (Radtke et al. 2011, Tyrka et al. 2012). A systematic review concluded that 89% of human studies were directionally consistent with early adversity, predicting increased DNA methylation of *GR* reported in human brain (Turecki & Meaney 2016).

The English and Romanian Adoptees Study (Sonuga-Barke et al. 2017) and the Bucharest Early Intervention Project highlight the profound influence of the early care environment on vulnerability for mental disorders (McGoron et al. 2012, Nelson et al. 2007). Kumsta et al. (2016) identified a differentially methylated region in *CYP2E1* in buccal cell DNA from adolescents with a history of extended institutionalization relative to individuals who had been briefly institutionalized. DNA methylation of this site associated with IQ and social cognition. Likewise, Non et al. (2016) found associations between institutionalization and DNA methylation of the *SLC6A4* and FK506 binding protein 5 (*FKBP5*) genes (the former codes for the serotonin transporter) in buccal cell DNA from adolescents in the Bucharest Project, consistent with reports that children deprived of parental care show distinct epigenetic changes. Naumova et al. (2012) observed that ~4% of CG sites across the genome show differential methylation as a function of institutional rearing. While

the functional effects of these epigenetic changes on vulnerability for psychopathology have not been reported, these studies provide proof of principle that extreme forms of childhood experience are reflected in DNA methylation patterns in humans.

Additional genome-wide analyses of DNA methylation reveal pervasive effects of childhood adversity on the methylome (Essex et al. 2013, Labonte et al. 2012a, Mehta et al. 2013, Yang et al. 2013). Labonte et al. (2012a) reported differential methylation of multiple gene promoters in hippocampal neurons associated with cellular/neuronal plasticity as a function of childhood maltreatment. Yang et al. (2013) reported an even greater number of differentially methylated targets affected by childhood abuse in salivary DNA from maltreated youths; however, this analysis was conducted closer in time to the exposure. Maternal stress, especially early in infancy, is likewise predictive of DNA methylation profiles assessed in buccal epithelial cells of 15-year-olds (Essex et al. 2013).

Epidemiological studies establish associations between exposure to adversity and broad variations in the epigenome in human subjects but do not inform about the nature of the underlying biology: how adversity-related epigenetic signals might alter neural function to promote psychopathology. Lutz et al. (2017) addressed this issue using postmortem human brain samples with epigenetic, transcriptional, and anatomical approaches, focusing on the anterior cingulate cortex (ACC) derived from individuals with known childhood histories. The structure and function of the ACC are affected by exposure to childhood adversity (Teicher & Samson 2016). The genomic regions in which DNA methylation revealed a strong association with childhood maltreatment included *LINGO3*, *POU3F1*, and *ITGB1*, which are genes related to myelin formation and were apparent in myelin-related oligodendrocytes, but not in neurons (Lutz et al. 2017). The transcriptional analyses showed that myelin- and oligodendrocyte-related genes were differentially expressed as a function of childhood maltreatment. This observation led the authors to hypothesize that childhood maltreatment may selectively affect oligodendrocytes and the process of myelination. Lutz et al. (2017) observed that childhood maltreatment was associated with a reduction in the thickness of axons and their myelin sheaths, a finding that links the epigenetic and transcription results to alterations in the morphology of oligodendrocytes, and that myelination of the axons may serve as a substrate for mediating the long-term consequences of childhood maltreatment. Finally, these authors demonstrated that the offspring of rat mothers that showed decreased levels of maternal care revealed decreased expression of myelin-related genes in the ACC (Lutz et al. 2017). These convergent findings suggest that early-life adversity shapes cell-specific molecular processes, which in turn influence brain structure and function in brain regions closely associated with adversity-related psychopathology.

Issues with Tissues: Cell Type Specificity

A major challenge for translational research is the degree to which DNA methylation profiles vary across peripheral sources of DNA, such as saliva, blood, or buccal epithelial cells, or inform about epigenetic mechanisms in brain. As noted above, cell type–specific patterns of DNA methylation are fundamental to cell differentiation, such that DNA methylation profiles differ across cells (Deaton & Bird 2011, Varley et al. 2013). This specificity poses a challenge to researchers studying DNA methylation in the context of child development, where access to neural tissue is unavailable other than in the postmortem state.

A number of studies addressed this issue by directly comparing DNA methylation profiles in blood and brain (Davies et al. 2012, Edgar et al. 2017, Farre et al. 2015, Provençal et al. 2012, Ursini et al. 2011). Provençal et al. (2012) used a genome-wide approach to describe the long-term effects of the early rearing environment on DNA methylation in the blood and brain of

adult rhesus macaques. Maternal versus peer rearing produces persistent and marked changes in behavior and stress reactivity (Stevens et al. 2009) associated with differential methylation of 1,981 probes in the prefrontal cortex but only 227 sites in a selected peripheral T cell population that were weakly correlated to those in brain (Provençal et al. 2012). In humans, Davies et al. (2012) provided a comprehensive description of DNA methylation in six cortical regions, the cerebellum, and matched peripheral whole-blood samples. DNA methylation within each brain region clustered and was distinct from that in blood. Remarkably, individual differences in DNA methylation identified in blood were well correlated with individual differences in brain samples ($r = 0.66$–0.76). This study contrasts with the findings of Provençal et al. (2012), who examined direct correlations of absolute methylation levels across tissues rather than individual differences across tissues. However, an important caveat of the Davies et al. (2012) study, and of genome-wide analyses in general, is that large regions of the genome (e.g., retrotransposons) should be highly methylated regardless of cell type. The inclusion of such regions into analyses inevitably inflates the degree of correspondence across cell types.

Edgar et al. (2017) established an innovative blood–brain DNA methylome resource that facilitates a direct comparison of the cross-tissue concordance of DNA methylation levels in blood and brain. The Blood-Brain Epigenetic Concordance (BeCon) tool provides variance and concordance estimates across ~450,000 CG sites contained on a human DNA methylation array using data from individuals with paired blood and brain samples. Such resources using a wider range of peripheral tissues will be required to address issues of cross-tissue concordance for early-life adversity effects on DNA methylation.

An important finding emerging from the BeCon analysis is that the correspondence between peripheral tissues, in this case blood and brain, depends upon the genomic region—it is higher for some than for others. This might be expected. The processes by which interindividual variation in DNA methylation at certain regions is established in brain and peripheral tissues might be similar (e.g., stress-related hormonal signaling). Studies with human peripheral samples investigating the effects of early-environmental adversity on GR methylation report findings that are generally consistent with those reported in postmortem brain (e.g., Turecki & Meaney 2016) and examine promoter regions identical to those assessed by McGowan et al. (2009). Similarly, Kundakovic et al. (2015) used both rodent and human samples to investigate the effects of in utero bisphenol A (BPA) exposure, which disrupts neurodevelopment with sustained behavioral effects. Prenatal BPA induced DNA methylation changes in the transcriptionally relevant regions of the *BDNF* gene in the hippocampus and blood of mice. These modifications at the BDNF region were observed in the cord blood of humans exposed to high maternal BPA levels in utero. The findings are consistent with the idea that, at specific genomic regions, DNA methylation in the blood may predict that occurring in brain and reflect early-life environmental exposures. Ursini et al. (2011) used a comparable approach to reveal correspondence between the effects of stressful life events on blood and prefrontal cortex on methylation levels at the *COMT* gene. Other environmental effects might produce variation in DNA methylation through far more tissue-specific effects. A detailed analysis of genome-wide epigenetic modifications in the mouse showed that environmental enrichment produces very different patterns of DNA methylation in brain regions as closely related as the dorsal and ventral hippocampus (Zhang et al. 2018).

There is no simple answer to the question of cell type variation. An appropriately conservative interpretation of existing studies with peripheral samples is that such findings reflect the capacity for the relevant environmental condition to modify the epigenome. Whether that effect is relevant in brain and for observed effects on brain function remains unknown. Studies combining human analyses with relevant model systems and focusing on candidate genomic regions can be informative (e.g., Kundakovic et al. 2015, Ursini et al. 2011). Finally, we note that researchers attempting

to define the biological mechanisms that underlie environmental influences on neurodevelopment and mental health will view this complication very differently from those seeking biomarkers that reflect experience and predict outcomes.

The Importance of Genotype in Studies of the Epigenome

Twin and multigenerational studies suggest a direct genetic influence on DNA methylation (Gertz et al. 2011, Kaminsky et al. 2009). DNA sequence directly determines the degree of DNA methylation at many sites across the genome (Deaton & Bird 2011) and is an important determinant of the epigenetic landscape (Lienert et al. 2011). There are widespread effects of genotype on DNA methylation in the human brain (with some evidence that genotype–methylation associations are conserved across peripheral and neural tissues) (Ng et al. 2017).

Genotype may influence DNA methylation in a number of ways. DNA sequence variation can introduce or remove CG couplets to add or remove sites for methylation. Genetic polymorphisms can result in sequence variation that influences transcription factor binding, and the degree to which environmental signals linked to transcription factor activation might influence DNA methylation. Recall that transcription factor binding can affect DNA methylation (Lienert et al. 2011, Stadler et al. 2011), particularly at regions of the genome that regulate transcription. Genotypic variation may also act at a distance (i.e., in *trans*) to influence activity in cell signaling pathways that affects DNA methylation (Bonder et al. 2017, Klengel et al. 2013).

An obvious question concerns the extent to which interindividual variation in specific epigenetic signals across the genome reflects gene × environment interactions in comparison to direct effects of genotype or environmental condition. This issue was addressed in two large analyses. Teh et al. (2014) used DNA from newborns' umbilical cords to survey the genome for genetic polymorphisms and DNA methylation, as well as extensive measures of the maternal environment. Maternal intrauterine environmental factors included maternal body mass index, symptoms of depression and anxiety, glucose tolerance, nutrients, and birth outcomes (birth weight and gestational age). The analysis focused on those regions of the genome that showed marked interindividual variation in DNA methylation [variably methylated regions (VMRs)]. Multiple regression models examined whether interindividual variation in each of the VMRs was best explained by the genetic factor, an environmental factor, or an interaction between the gene and the environment. Controlling for ethnic variation, 15% of the VMRs were best explained by a main genetic effect, 85% were best explained by a gene × environment interaction model, and none was best explained by an environmental factor alone (note the use of the term "best," which implies the strongest model but not that the model accounted for all of the variance). A more recent comprehensive analysis (Czamara et al. 2019) across four independent cohorts, using neonatal blood with the same statistical modeling, resulted in very similar estimates of the importance of gene × environment influences and also provided evidence of additive effects of genetic and environmental influences.

Estimates of the relative impact of genetic, environmental, and gene × environment interaction influences will inevitably vary across tissues and age. However, these studies underscore the importance of the gene × environment effects for variation across the human methylome (Klengel et al. 2013, Meaney 2010). The implications are important for studies in epigenetic epidemiology that associate specific environmental exposures with variation in DNA methylation across the genome [i.e., epigenome-wide association studies (EWASs)]. The gene × environment findings suggest that the EWAS approach is limited for exposures that show genotypic moderation. Where genotypic moderation is less influential, EWAS exposure–outcome analyses may be more valuable. For example, Liu et al. (2018) surveyed genome-wide DNA methylation levels in blood as a function of alcohol consumption and identified reliable epigenetic signatures, including at sites in a gene that codes for a GABA-B (gamma-aminobutyric acid B) receptor, which is implicated in alcohol

dependency. These findings reveal a putative objective marker of alcohol consumption for clinical treatment programs.

Studies of candidate genes also reveal evidence for gene × environment interactions, with a focus on environmental conditions and genomic regions relevant for mental health. Analyses from the Iowa Adoption Study (Beach et al. 2010) demonstrated that exposure to childhood sexual abuse and *SLC6A4* polymorphism interact to predict decreased methylation of a CG within the *SLC6A4* gene. Another targeted analysis focused on a polymorphism in the *BDNF* gene that results in valine–methionine amino acid variation at position 66 in the coding region of the gene. This so-called Val/Met 66 variant is associated with anxiety disorders in humans (Casey et al. 2009). Li et al. (2015) found a strong association between antenatal maternal anxiety and epigenome-wide DNA methylation that was modified by the Val/Met 66 *BDNF* variant. Infants carrying the Met/Met genotype showed an approximately threefold-greater number of variably methylated CG sites associated with maternal anxiety.

Klengel et al. (2013) provided a remarkable model of allele-specific demethylation of the *GR* gene coregulator FKBP5 in adults exposed to childhood trauma. The *FKBP5* gene produces a protein that binds to GR and prevents GR signaling, thus moderating the cellular impact of glucocorticoids. GR activation increases the expression of FKBP5 by binding to a specific DNA binding site and enhancing transcription of the *FKBP5* gene. This process essentially serves as a negative-feedback mechanism to protect against excessive glucocorticoid activation. The Klengel et al. (2013) study built on previous research showing that a single-nucleotide polymorphism (SNP) in *FKBP5* moderated the association between severe childhood adversity and risk for posttraumatic stress disorder (PTSD) (Binder et al. 2008). The SNP in the *FKBP5* gene influences the broader organization of the chromatin surrounding the *FKBP5* gene in a manner that influences the physical interaction between the GR binding site on the DNA and the region that actively regulates *FKBP5* transcription. Since stress enhances GR signaling, this *FKBP5* genetic variant determines the magnitude of stress-related GR binding to DNA and the effect at the level of the *FKBP5* gene. The GR effect not only includes the activation of *FKBP5* expression but also remodels the DNA methylation profile at another site on the *FKBP5* gene that controls expression. GR binding to DNA dynamically alters DNA methylation at multiple sites across the genome (Thomassin et al. 2001). The *FKBP5* genetic variation influences the capacity for GR activity at *FKBP5*, thereby determining the magnitude of the stress-induced GR signal on the DNA methylation state of the *FKBP5* gene—a truly elegant example of the biology of a gene × environment interaction (Klengel et al. 2013). The net effect of this process is to determine the capacity of the stress-induced change in FKBP5 to effectively regulate HPA function through modulation of the GR signaling.

EPIGENETIC SIGNALS AND PSYCHOPATHOLOGY

A biomarker is a measurable indicator of the risk for or presence of a specific condition. Epigenetic signals are putative disease biomarkers, especially DNA methylation, which is the most stable and measurable epigenetic mark in humans. This idea is being actively explored in cancer treatment. A biomarker can serve at least three distinct clinical objectives by providing an objective marker of a clinical state, reflecting the risk of a condition, and predicting a clinical treatment outcome.

DNA Methylation as a Biomarker of Clinical Condition and Risk

PTSD is characterized by altered HPA function reflected in stably reduced levels of circulating cortisol (Yehuda et al. 2001). Low cortisol levels are associated with enhanced GR-induced

negative-feedback suppression of HPA activity, as reflected by a low-dose dexamethasone (DEX) suppression test (Daskalakis et al. 2013, Yehuda et al. 2004). The efficacy of DEX-induced negative-feedback suppression is mediated by binding of DEX to the GR. Combat veterans with PTSD show increased GR expression compared with veterans without PTSD (Yehuda et al. 2004), a difference that is specific to PTSD symptoms (e.g., Matić et al. 2013).

The GR is part of a complex that includes moderators such as FKBP5 (discussed in the preceding section). *FKBP5* expression is reduced in PTSD, which would enhance GR signaling, consistent with findings of enhanced GR sensitivity in PTSD. Individuals with PTSD who carry an *FKBP5* polymorphism associated with a risk of PTSD also show increased glucocorticoid negative-feedback sensitivity and dampened HPA activity (Mehta et al. 2011). As described above, a genetic variant in the *FKBP5* gene that is associated with an epigenetic alteration of this gene as a consequence of childhood abuse confers risk for PTSD (Binder et al. 2008, Klengel et al. 2013). Likewise, genetic variants that govern GR function are associated with a risk of PTSD (Brouwer et al. 2006, Hauer et al. 2011, van Rossum et al. 2006). Thus, genetic and epigenetic variations associated with the GR–FKBP5 complex are related to glucocorticoid negative-feedback sensitivity, altered HPA activity, and the risk for PTSD. These molecular markers predict the risk for PTSD. In two studies, van Zuiden et al. (2011, 2012) observed that GR levels in the blood of military personnel prior to deployment were higher among those with a high level of postdeployment PTSD symptoms. Yehuda et al. (2009) showed that reduced *FKBP5* expression prior to deployment was also a risk factor for PTSD in response to deployment. A study of survivors of the September 11, 2001 World Trade Center attacks also showed lower *FKBP5* gene expression levels in those with PTSD (Yehuda et al. 2009) compared with those without PTSD or, interestingly, with remitted PTSD (Sarapas et al. 2011, Yehuda et al. 2009).

The increased GR expression and greater GR sensitivity in combat veterans with PTSD are accompanied by decreased methylation of the exon 1_F *GR* gene promoter in peripheral blood cells (Yehuda et al. 2015). Clinical symptoms of PTSD and reduced levels of plasma cortisol following DEX and 24-h urinary cortisol excretion were inversely correlated with the level of *GR* gene promoter methylation (Yehuda et al. 2015). Studies of Rwandan genocide survivors also reveal significant associations between methylation of the same *GR* gene promoter and symptoms of PTSD (Vukojevic et al. 2014). In another sample of subjects, Vukojevic et al. (2014) provided evidence of an association between the level of *GR* gene promoter methylation and both memory formation and arousal during the encoding of emotionally negative stimuli. Methylation of the GR region is also associated with activation of the ventrolateral prefrontal cortex during cognitive testing, consistent with analyses implicating this region in the neurocircuitry of PTSD (Hayes et al. 2012). The importance of glucocorticoids in the regulation of memory formation under conditions of strong emotional arousal is an attractive explanation for the relation between GR signaling and PTSD (de Quervain et al. 2009). The functional BclI polymorphism of the *GR* gene is associated with variation in glucocorticoid sensitivity (van Rossum et al. 2003), emotional memory in healthy individuals (Ackermann et al. 2013), traumatic memories, and PTSD symptoms (Hauer et al. 2011). These findings suggest that the differential methylation of promoters that regulate GR–FKBP5 expression is related to profiles of HPA activity and neural processing of emotional conditions that appear to predict vulnerability for PTSD.

Another promising line of translation research focuses on maternal depression. Variation in estrogen sensitivity is a putative risk mechanism for maternal depression (Guintivano et al. 2014) especially in women with a history of psychiatric illness. Mehta et al. (2014) identified 116 different gene transcripts involved in estrogen signaling. Remarkably, these transcripts predicted the risk of postpartum depression with 88% accuracy in a high-risk cohort (Mehta et al. 2014). Women

with the most dynamic change in the expression of estrogen-sensitive genes showed the greatest risk of postpartum depression.

Guintivano et al. (2014) developed a predictive biomarker of peripartum depression on the basis of DNA methylation at two CG sites within two different genes, *HP1BP3* and *TTC9B*, both of which are regulated by estrogen. DNA methylation at these sites predicted postpartum depression with a high degree of sensitivity (~80%) (also see Osborne et al. 2016). The direction of association between DNA methylation of *HP1BP3* and depressive symptoms depended on the presence or absence of maternal antenatal depression. While both loci predicted postpartum depression, methylation of *HP1BP3* identified women at risk of clinical symptoms across the peripartum period. The ability to distinguish between women with stable, high symptoms and women who experience postpartum onset is an interesting characteristic of this biomarker that could inform treatment. Frokjaer et al. (2015) showed that manipulating estradiol levels gives rise to a significant increase in depressive symptoms (Frokjaer et al. 2015, Mehta et al. 2018). Such manipulation produces changes in DNA methylation of ~50% of the 116 estrogen-sensitive genes identified by Mehta et al. (2018). Such findings converge on sex hormone sensitivity, indexed by dynamic changes in gene expression and DNA methylation, as a predictor of subsequent risk of depressed mood.

These studies point to the transcriptional regulation of estrogen-sensitive genes in the prediction of maternal perinatal depression. However, there are limitations. The findings are limited to relatively small cohorts of women, mainly of European ancestry, selected predominantly on the basis of a previous history of psychiatric illness. The studies focused exclusively on maternal depression and did not consider the contribution of maternal genetic variation to risk prediction. Doing so is especially important in light of the burgeoning literature that demonstrates the large contribution of SNPs to variation in DNA methylation (Czamara et al. 2019, Do et al. 2017, Garg et al. 2018, Gaunt et al. 2016, Teh et al. 2014). Future studies should include genotype as well as the wealth of psychosocial risk factors (e.g., financial insecurity, stressful life events, lack of social support, partner difficulties) to best identify women at risk of adverse perinatal mental health outcomes.

DNA Methylation as a Predictor of Clinical Outcomes

A preliminary study (Yehuda et al. 2013) reveals the potential that epigenetic measures of the *GR* and *FKBP5* genes hold for clinical studies. The level of *GR* gene promoter exon 1_F methylation predicted treatment outcome among combat veterans with PTSD in response to psychotherapy. Interestingly, the level of exon 1_F methylation did not vary in relation to treatment response, suggesting that it may function as a trait rather than a state measure. A trait measure might reflect an increased state of risk for PTSD. However, this finding does not imply that the epigenetic modifications that regulate GR signaling are immune to treatment. Methylation of the *FKBP5* gene did not predict treatment response but did vary with recovery. This finding reflects the capacity for therapy-induced modifications of the epigenetic marks that regulate the expression of genes involved in regulating GR signaling and underscores the potential value of these signals as biomarkers of changes in clinical condition.

The strongest contribution of a biomarker is its ability to predict differential treatment outcomes. Treatment effects of antidepressant medication vary considerably across patients, and predictive biomarkers for the clinical response would greatly benefit clinical practice by decreasing the evaluation period for drug efficacy and allowing for potential matching of patients with treatment. The Canadian Biomarker Integration Network in Depression (CAN-BIND) initiative examined genome-wide patterns in baseline DNA methylation in leukocytes as predictors of an

antidepressant response to escitalopram in patients with major depressive disorder (Ju et al. 2019). This study is, to our knowledge, the first genome-wide methylation analysis of antidepressant response. An analysis of genome-wide patterns of DNA methylation at baseline identified sites in two genes, *CHN2* and *JAK2*, that significantly distinguished responders from nonresponders following an eight-week treatment period. The difference at the *CHN2* site was replicated in an independent study. Both genes are interesting candidates. *JAK2* encodes for a tyrosine kinase involved in cytokine signaling that mediates inflammation, a process strongly implicated in depression. *CHN2* codes for a protein involved in controlling axon-pruning processes during neurodevelopment. As the authors acknowledge, this is certainly a preliminary study, but one that provides a template for a critically important line of research (Ju et al. 2019). The findings are also consistent with the hope that epigenetic marks might serve as dynamic predictors of clinical outcomes.

CONCLUSIONS AND FUTURE DIRECTIONS

Research with model systems and, more recently, in human translational studies reveals the impact of environmental conditions across the epigenome. Epigenetic processes remain an attractive mechanism that could explain the enduring effects of early experience on genomic transcription and health outcomes. The studies reviewed here illustrate the potential value of epigenetic measures as biomarkers, with emerging evidence that specific signals might predict and perhaps track clinical outcomes. The most compelling studies are those that integrate epigenetic measures into a broader and clinically relevant research program that permits multidimensional analyses. For example, the Lutz et al. (2017) and Vukojevic et al. (2014) studies described above provide the basis for working models on which to base hypothesis-driven studies and link molecular signals to specific neural outcomes at the level of structure and function. Other examples are studies, such as those reviewed in the sections on PTSD, that position epigenetic analyses within a strong framework of clinical phenotyping.

We emphasize that environmental regulation of the epigenome is a new field of study and that there remain very significant gaps in our knowledge base. Perhaps the most significant need is for longitudinal studies that exploit the capacity for dynamic variation in the epigenome to track epigenetic signals and mental health status over the course of development in relation to environmental conditions. The prospective studies of the risk of PTSD in military personnel exemplify the merit of this approach. Likewise, there is a surprising dearth of such studies in the context of clinical treatment. Filling these and other gaps will be critical for advancing the translational science. The CAN-BIND study described above demonstrates the potential value of epigenetic measures for precision in mental health treatments.

Finally, we note that perhaps the potentially most interesting opportunity for epigenetics in the study of development and psychopathology remains to be explored. The significant role of gene × environment interactions in determining individual variation in epigenetic states may be a source of frustration for EWASs but could be critical for advancing clinical and intervention science. While childhood adversity predicts an increased risk for psychopathology, there is considerable evidence for interindividual variation in susceptibility. Circumstance is not necessarily fate. This differential susceptibility derives, at least in part, from genetic influences (Belsky et al. 2009). The ability of specific epigenetic marks to reflect the interaction between genotype and an environmental exposure relevant for a specific mental health outcome might position the epigenome as the ideal location in which to search for objective measures of risk at the level of the individual. Exploring this avenue would be particularly valuable for the identification of risk in young children and for the advancement of prevention science beyond reliance on either genetic or environmental exposure alone. The same argument could justify epigenetic measures as predictors

of treatment outcomes in which individual characteristics shaped by gene × environment interactions determine who might respond best to a selective course of treatment. These opportunities should serve to guide the next generation of translational epigenetic research programs.

SUMMARY POINTS

1. Interindividual variation in the DNA methylome reflects gene × environment interactions and thus lies at the interface of nature and nurture.
2. Epigenetic regulation of transcription involves intricate interactions among multiple epigenetic signals and cannot be reduced to a single biochemical modification.
3. Epigenetic signals, including DNA methylation, reflect experiences that are associated with the risk for psychopathology and remain an attractive mechanism underlying the enduring effects of early experience on genomic transcription and health outcomes.
4. Preliminary studies illustrate the potential value of epigenetic measures as biomarkers to predict and perhaps track clinical outcomes. These studies address the critical challenge of leveraging epigenetic research to advance intervention science and clinical practice.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

M.J.M. is supported by grants from the Hope for Depression Research Foundation, the Canadian Institutes for Health Research, the National Medical Research Council (Singapore), the Natural Sciences and Engineering Research Council of Canada, the Webster Foundation, and the JPB Foundation and by core funding from the Agency for Science, Technology and Research (A*STAR, Singapore). M.J.M. and K.J.O. are fellows of the CIFAR Child and Brain Development Program. K.J.O. is supported by the Canada First Research Excellence Fund Healthy Brains for Healthy Lives initiative at McGill University, the Jacobs Foundation, and the Fonds de recherche du Québec—Santé.

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