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A Review of epigenetics in psychiatry: focus on environmental risk factors

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Abstract: Epigenetic modifications play a key role in development and cell type specificity. These modifications seem to be particularly critical for brain development, where mutations in epigenetic enzymes have been associated with neurodevelopmental disorders as well as with the function of post-mitotic neurons. Epigenetic modifications can be influenced by genetic and environmental factors, both known major risk factors for psychiatric disorders. Epigenetic modifications may thus be an important mediator of the effects of genetic and environmental risk factors on cell function.

This review summarizes the different types of epigenetic regulation and then focuses on the mechanisms transducing environmental signals, especially adverse life events that are major risk factors for psychiatric disorders, into lasting epigenetic changes. This is followed by examples of how the environment can induce epigenetic changes that relate to the risk of psychiatric disorders.

Keywords: epigenomics, psychiatry, DNA methylation, histones, major depressive disorder

Introduction

Psychiatric diseases have complex causes; both genetic and environmental risk factors are known to play a key role. In recent years, epigenetic mechanisms have been presented as the molecular basis for the biological embedding of environmental factors. As such, the field of epigenetics has become increasingly important in psychiatry. In this review, we present a summary of epigenetic mechanisms and their relevance to the brain, examples of how the environment can cause epigenetic changes, and the role of environmentally induced epigenetic changes in psychiatric disorders.

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Main text

Key concepts in epigenetics

“Epi,” the Greek prefix for “on top of” used in the context of genetics, describes mechanisms that work above or in addition to the DNA backbone, influencing the function of the genome without altering the DNA sequence. Epigenetic mechanisms influence how accessible certain DNA sequences are to regulators of gene transcription. Epigenetic mechanisms also package/condensate DNA so that it can fit into the cell’s nucleus.

To what extent certain DNA regions are accessible for gene transcription is regulated by chemical modifications of either the DNA itself, e. g., the methylation of cytosines, or of the histone proteins.

Our advance in epigenetic understanding is the result of the development of novel methods. As briefly summarized in the Glossary, there are various layers of epigenetic control: DNA methylation (DNAm), histone modification, non-coding RNAs and RNA modifications. For each, there are multiple types of tools available for study. Antibodies raised against 5-methylcytosine (using a method known as methyl-DNA immunoprecipitation) or recombinant methyl binding proteins (using a method known as methylated DNA island recover assay) can be used to pull down methylated fragments of DNA that can be analyzed using PCR or next-generation sequencing (NGS) approaches [1, 2]. However, these methods do not provide single base resolution. This can be achieved by converting non-methylated cytosine to uracil using sodium bisulfite. Methylated cytosine is protected, so that in the end, the readout compares cytosine (sign of methylation) vs. thymidine (from uracil = unmethylated) using different methods [3]. The most widely used are array-based systems that recognize this base change and whole genome sequencing. This method can also be used to examine other types of changes, such as hydroxymethylation, when combined with the use of other conversion methods. These methods also apply to RNA-based modifications. The most common method for detecting histone modifications is chromatin immunoprecipitation (ChIP). Here, an antibody to the specific histone modification is used to pull down associated DNA sequences. These are then analyzed using PCR, microarrays, or NGS (ChIP-Seq) [4]. Non-coding RNAs can be

studied using transcriptome tools such as qPCR, microarrays, and NGS. Their functions can be assessed with small RNA-mediated knockdown, while their locations can be determined using fluorescence in situ hybridization. There are three NGS methods available for analysis, i. e., ChIP-Seq, methyl-Seq, and ATAC-Seq.

It is important to bear in mind that epigenetic processes are both tissue- and cell-specific. Data compiled by large international consortia (such as for example the PsychENCODE project, <https://www.nimhgenetics.org/resources/psychencode>) will allow a detailed understanding of the brain region- and cell type-dependent complexity of epigenetic processes as they relate to psychiatric disorders.

Epigenetic changes in the brain

Epigenetic processes play a particularly important role in the brain, where a highly complex, primarily post-mitotic ensemble of cells must work together [5]. This is evident from monogenic diseases with mutations in genes that are central to epigenetic processes. They are associated with severe neurodevelopmental and psychiatric symptoms; for example, mutations in the methyl CpG binding protein 2 gene (*MeCP2*), which encodes a methyl-DNA binding protein essential for neuron function, are associated with Rett syndrome [6].

Epigenetics not only plays a central role in cell differentiation and development of the brain, but is also a mechanism that allows environmental factors to leave a memory trace on DNA. Negative life events significantly increase the risk of psychiatric disease. Negative experiences in childhood, such as loss of parents, maltreatment, and abuse, show the strongest effects [7]. Trauma in childhood is associated with a number of biological changes [8, 9]. These range from effects on the immune system and the stress hormone axis to differences in the cortical density of certain brain areas. But what mechanisms allow such long-term embedding of stress and trauma? Understanding the mechanisms that lead to these lasting effects will contribute to a better understanding of the pathophysiology of psychiatric disorders.

In a fundamental study, Weaver et al. investigated whether early life experiences could cause lasting biological changes through epigenetic mechanisms [10]. They reported that increased maternal care in young rats leads to decreased hippocampal DNAm in the promoter of the glucocorticoid receptor gene (*GR*), a central regulator of the stress hormone system, an effect that persisted into adulthood. This pivotal study stimulated the development

of the field of environmental and behavioral epigenetics. In follow-up studies, the same group showed that serotonergic signaling pathways were activated in pups by the mother's licking, which increased binding of transcription factors in the promoter region of the *GR* gene [11]. This led to reduced DNAm and thus increased *GR* transcription. Rats with lower maternal care showed higher DNAm in this promoter and decreased *GR* expression. This was paired with increased stress reactivity of the animals in adulthood and associated behavioral changes [12].

McGowan et al. reported similar results in a human study [13]. They investigated DNAm within the promoter region of the human *GR* gene in post-mortem hippocampal tissue of suicide victims with or without child abuse and controls. The authors found that differences in the methylation pattern of the human *GR* promoter was dependent on trauma exposure in a promoter region homologous to that studied in rats. Suicide victims who experienced abuse in childhood had significantly higher DNAm and lower *GR* expression than non-abused suicide victims. The *GR* promoter of abused suicide victims showed increased DNAm in a transcription factor binding site for the same nerve growth factor [13]. About 90 % of human and 70 % of rodent studies have shown higher methylation of the *GR* gene promoter in individuals with early negative life events [14].

However, it is clear that stress or trauma does not affect just a few genes, but must have genome-wide effects. This has been confirmed in a number of studies. Both differences in maternal behavior in rats and childhood abuse in humans show far-reaching genome-wide epigenetic effects in the hippocampus [15–17]. Lutz et al. suggested that changes in DNAm and hydroxymethylation may underlie the differences seen post-mortem in the myelination of the limbic system in individuals with a history of child abuse [18].

Epigenetic changes in peripheral tissues

It is of great interest how and whether certain environmental factors, known to increase the risk for psychiatric diseases, can be detected from changes in peripheral tissues. Since one of the main functions of epigenetic mechanisms is the establishment of cell-specific transcription patterns, epigenetic profiles vary between tissues [19]. Therefore, the epigenetic consequences of the early environment have been compared in the brain and blood of the same animals. The broad effect of early stress on DNAm profiles was observed both in the prefrontal cortex and in T cells of primates. However, these environment-associated

methylation profiles were very different and there were few direct overlaps [20]. For some candidate genes, similar changes in the blood and brain or nerve cells have been reported, including the above-mentioned *GR* gene promoter [14]. Ewald et al. isolated DNA from mice and found that glucocorticoid-induced changes in the brain were mirrored in the blood [21]. Nevertheless, it is the exception that epigenetic differences in peripheral tissues can be interpreted as central mechanisms.

Most of the current clinical and epidemiological epigenetics studies do not include brain samples. Rather, cells from peripheral tissues such as blood and oral mucosa are used, which has already led to the identification of numerous epigenetic associations with environmental influences [22, 23]. These associations can be seen as biomarkers, but, through their influence on the immune system, may also play a role as causal factors in the pathology of certain trauma-associated psychiatric and internal diseases [24, 25]. Such peripheral epigenetic profiles may also be associated with trauma-associated biological phenotypes, such as regulation of the stress response, and may mediate effects of trauma on these endocrine factors [26]. A number of studies have shown that socioeconomic status in childhood is associated with epigenetic signatures in peripheral blood in adulthood indicating altered immune regulation [27, 28]. Associations with trauma and abuse have been reported in a number of studies, but could not be verified in large, prospective studies [29]. A multitude of studies have also investigated the influence of prenatal environmental factors on epigenetic profiles at birth. Here, smoking during pregnancy and maternal prenatal depression and anxiety disorders were associated with epigenetic changes in cord blood [30, 31]. Prenatal risk factors, socioeconomic status, and post-natal negative life events are strongly correlated with each other, and as such make it difficult to isolate the influence of certain environmental factors in human studies. In addition, most studies give no direct indication as to whether these signatures are a marker for exposure alone or exposure-associated risk or resilience.

Molecular mechanisms

A number of molecular mechanisms that influence how environmental factors may alter the epigenome have been described. Maternal touch, serotonergic neurotransmission, and transcription factor activation can lead to epigenetic changes in the DNA of activated neurons [11].

Epigenetic effects of stress hormones may also be important for the lasting effects of adverse life experiences. Stress and adversity have been shown to lead to both acute

and chronic activation of this system [32]. The GR is a nuclear receptor that acts as a transcription factor and can trigger a genome-wide transcriptional response as well as epigenetic changes at the DNA binding sites of the GR [33, 34]. Activation of the GR is associated with a reduction in DNAm at the enhancer elements within the *FKBP5* gene locus, which may lead to a weaker inhibition of transcriptional activation by a subsequent stimulus. Importantly, the same enhancers show reduced DNAm in individuals exposed to early trauma [35]. In fact, administration of dexamethasone (a selective GR agonist) has been shown to lead to highly dynamic and reversible changes in DNAm at these enhancer sites, and these changes are regulated by the same genetic variants that interact with early adversity to increase the risk for psychiatric disorders [36]. It will be important to understand which factors contribute to the stabilization of these epigenetic changes in the context of genetic and environmental risk factors throughout development. Exposure to glucocorticoids in the context of developmental stress likely affects a number of loci. Provencal et al. reported lasting changes in DNAm when a human hippocampal progenitor cell line was exposed to dexamethasone during (but not following) neuronal differentiation. These cytosine–guanine dinucleotide (CpG, see the Glossary) sites were enriched among enhancers and promoters. This is in line with the finding that these lasting changes in DNAm were not accompanied by changes in baseline gene transcription, but by an enhanced transcriptional responsiveness of genes in proximity to the affected CpG sites [37]. This suggests that exposure to stress hormones during development can alter the setpoint of the response to subsequent stress exposures and therefore may alter trajectories of risk and resilience.

Neuronal activation is known to lead to persistent epigenetic changes, which underlie the processes of learning and memory. Inhibitors of DNAm enzymes prevent long-term potentiation in synapses, indicating that DNAm is an important step in strengthening synaptic connections and thus learning [38].

Epigenetic inheritance

Originally, it was thought that all epigenetic marks are erased in the germline; however, mounting evidence has indicated that epigenetic changes can be heritable. Data from animal studies, but also from studies on the descendants of Holocaust or other genocide survivors [39, 40], indicate that the parent or grandparent environment can be associated with epigenetic differences in the offspring [41].

Several mechanisms of transgenerational transmission have been proposed [42, 43]. Firstly, parental exposure to stress and trauma experiences can lead to differences in parent–child interaction. Disturbed mother–child bonds have been reported for women with trauma in their own childhood, and this could lead to long-lasting epigenetic changes analogous to those seen in animal models. A second path of transmission is during pregnancy. Childhood trauma experienced by the mother is associated with physiological changes in pregnancy, including altered stress hormone levels, and could initiate epigenetic consequences in utero [44]. Alternatively, the effects of exposure to negative environmental events could be passed on to the offspring via the germ line. Indeed, stress exposure can lead to changes in micro-RNA (miRNA) levels in sperm, which influence epigenetic patterns in the developing embryo [45].

Gene–environment interactions

In addition to strong main genetic effects reported as risk factors for all psychiatric disorders [46], a number of studies have shown that genetic factors may alter the effects of childhood trauma on the long-term risk of psychiatric disease [47], although data in large cohorts have not confirmed many candidate gene–adversity interactions in depression [48]. Epigenetic changes represent a molecular mechanism by which gene variants and the environment converge. For example, we were able to show that in individuals with certain functional genotypes in the *FKBP5* gene, a reduction of DNAm in important regulatory sequences of this gene was associated with exposure to early trauma. This genetic regulation of environmentally associated epigenetic changes is paralleled by a change in the risk for a number of psychiatric disorders [49]. This mechanism of a convergent influence of the environment and gene variants on epigenetics, especially DNAm, extends not only to *FKBP5* but to a variety of genes. Two independent studies have shown that joint influences of gene variants and prenatal environmental factors, and not the environment alone, are the strongest determinants of variability in DNAm at birth [50, 51]. In fact, genetic variants that show strong influences on perinatal DNAm in the interaction with the prenatal environment were enriched in genetic variants associated with psychiatric disorders in large-scale genome-wide association studies (GWAS), supporting the disease relevance of genetic regulation of environmental epigenetic consequences [50].

In addition to environmental factors, genetic variants can also influence DNAm. Methylation quantitative trait

locus (mQTL) analysis provides a systematic view of the common genetic variation found on DNAm. A number of studies, including the study by Hannon and colleagues [52], have catalogued such mQTLs in different tissues; their results are publicly available (<https://www.ebi.ac.uk/ega/home>). This database can be used to interpret the functional consequences of common genetic variation. This will undoubtedly improve our understanding of the relationship between DNAm variation, gene expression, and complex traits.

Epigenetics in psychiatric disorders

Major depressive disorder (MDD) is one example of a psychiatric disorder with established increased risk through exposure to adverse life events [53, 54]. Epigenetic mechanisms have been proposed as mediators of the lasting increases in MDD risk following exposure to an adverse life event [49].

Animal studies in which histone deacetylase (HDAC) was inhibited first suggested that epigenetics plays a crucial role in MDD. Covington et al. reported that HDAC showed robust antidepressant properties when infused into the nucleus accumbens of mice following social defeat stress [55]. To date, there are only a handful of post-mortem studies that have examined histone modifications in MDD. In the prefrontal cortex, elevated levels of histone 3 lysine 4 trimethylation (H3K4me3, a marker of gene activation) were reported at the synapsin gene family in MDD [56]. Altered H3K4me3 levels in promoter regions of some candidate genes (*ARG2*, *OAZ1*, *OAZ2*, and *AMD1*) were reported in the prefrontal cortex [57]. However, no genome-wide analysis of histone modifications has been reported in MDD. Among epigenetic modifications, DNAm has been most studied in MDD. A systematic review (of 61 studies in peripheral tissue) concluded there was evidence for DNAm differences at selected loci [58]. Most consistently, candidate gene studies found that patients with MDD had hypermethylation in the loci containing the genes for brain-derived neurotrophic factor (*BDNF*) and the serotonin transporter (*SLC6A4*). Genome-wide methylation studies reported that DNAm at some loci is significantly associated with MDD, but no consistent changes in direction nor position have been identified. The lack of consistency highlights the importance of sufficient cohort sizes, a longitudinal study design, and robust experimental and statistical methods. Overall, there is very limited evidence for altered DNAm in peripheral blood of MDD patients. MDD-associated epigenetic changes in RNA are of growing interest since Engel et al.

recently showed that the N6-methyladenosine mRNA modification is dysregulated in the blood of patients with depression [59].

As mentioned above, epigenetic changes are thought to be important in learning and memory formation. As such, they may also play a role in the development of pathological behavior observed in psychiatric disorders. Epigenetic changes have been investigated in the context of fear conditioning [60] and may explain the pathophysiology of post-traumatic stress disorder (PTSD). In PTSD, intrusions of trauma-associated memory content occur together with a disturbed extinction of associations with negative experiences. Stable epigenetic changes may contribute to these hard to erase memories.

Large GWAS have pointed to epigenetics as an important pathomechanism in psychiatric disorders by a number of genome-wide significant associations as well as pathway analyses. For example, histone methylation was the pathway showing the strongest associations when combining data from schizophrenia, bipolar disorder, and MDD [61]. Another large GWAS identified *miR-137* as one of the strongest associations with schizophrenia [62].

Dynamic epigenetic changes

Epigenetic changes, especially DNAm, were long regarded as predominantly irreversible. However, in recent years it has become clear that effects controlled by environmental influences on DNAm are dynamic. Several studies have shown that epigenetic changes invoked by a negative early environment can be reversed, with animal studies suggesting that early-life stress-induced epigenetic changes can change through life. For example, Weaver et al. showed that the epigenetic changes caused by a lack of maternal affection were reversible later in life using methyl donors and cross-fostering [63]. In a longitudinal human study in families likely to maltreat children, parent participation in a preventive psychosocial intervention in the months after birth was associated with epigenetic changes in the offspring at the age of 27 years [64]. A handful of studies could also show that psychotherapy is associated with peripheral epigenetic changes [65–68].

Some positron emission tomography (PET) ligands can be used to measure in vivo epigenetic changes in the brain. For example, the ligand [(11C)M]Martinostat detects the activity of HDACs, important epigenetic regulators. Such ligands have already been successfully tested in neuroimaging of humans [69, 70].

Clinical relevance of epigenetic mechanisms: biomarkers and new targets for drug development

Research supports the fact that environmental factors can trigger long-lasting epigenetic changes. Clinically, changes in peripheral tissues could serve as biomarkers for diagnostic purposes and therapy monitoring. There is a wide range of possibilities that include DNAm as well as circulating miRNAs and mRNA [59, 71]. The insight that epigenetic factors play an important role in stress-related psychiatric disorders such as MDD or PTSD also opens up a number of new targets for drug development. Drugs that interact with epigenetic enzymes have shown initial positive results in an animal model [72, 73]. These drugs contain HDAC inhibitors (HDACi) and some drugs, e. g., valproic acid, have known HDACi activity. Specific HDACi show promising results in animal models, and studies in patients are planned [74, 75].

Evidence has suggested that other forms of commonly used treatment, such as psychotherapy and electroconvulsive therapy, may also act through epigenetic mechanisms. One possibility could be to couple such substances with psychotherapy. These substances would then only intervene in cells and gene loci where epigenetic changes occur within the framework of therapy and the formation/strengthening of synaptic connections [76].

A model emerges where genetic and environmental risk factors, and their interactions, could drive aberrant epigenetic mechanisms targeting stress response pathways, neuronal plasticity, and other behaviorally relevant pathways implicated in psychiatric disorders.

Conclusions for practical application

1. Epigenetic modification represents a new therapeutic target, be it pharmacological or psychotherapeutic.
2. Epigenetic changes in peripheral tissues may hold promise as biomarkers for diagnostics, treatment monitoring, and disease progression.
3. In the future, PET ligands might allow epigenetic changes in the brain to be measured. HDACs ligands have been successfully tested in humans [69].
4. Although promising, epigenetic approaches still face a number of unsolved issues. Epigenetic substances have unspecific effects on all genes and lead to either more or less methylation, yet epigenetic changes observed in psychiatric patients go in both directions,

with increases and decreases of specific epigenetic marks, depending on the locus. Therefore, drug development should focus on substances that have a specific and dynamic effect.

Glossary of epigenetic mechanisms

DNA methylation

DNA methylation (DNAm) regulates gene expression through direct modifications of the DNA. Nucleotides located primarily, but not exclusively, in sequences of cytosine–guanine dinucleotides (CpGs) are covalently modified [77]. Non-CpG methylation seems to be restricted to specific cell types, such as pluripotent stem cells, but also neurons and glial cells [78]. Increased DNAm is associated with a less accessible DNA sequence and when this occurs in the promoter region of a gene, this is associated with decreased gene expression. Additionally, hydroxymethyl groups and other chemical DNA modifications (formyl or carboxyl groups) have been described, of which hydroxymethylation occurs preferentially in neurons [5, 79]. Hydroxymethylation has been associated with increased gene transcription.

Chromatin modification

Histones are an important component of the epigenome, responsible for packaging DNA in chromatin. Histone phosphorylation, acetylation, and methylation at specific amino acid residues regulate how accessible the DNA is, i. e., how tightly or loosely wrapped the DNA is, and thus gene transcription [80]. The addition or removal of these post-translational changes is mediated by a number of enzymes, including histone acetyltransferases and histone deacetylases (HDACs). Depending on the chemical reaction, these changes can either promote or inhibit gene transcription.

Non-coding RNAs

Non-coding RNAs play a role in nullifying mRNA. Long non-coding RNAs regulate gene expression by modifying the structure and thus the stability of chromatin. Short interfering RNAs mediate post-transcriptional gene silencing via RNA degradation. Micro-RNAs (miRNAs) finetune gene expression by targeting mRNA. MiRNAs enforce their effects through direct binding to the 3'-untranslated region

of the mRNA of their target gene. This leads to an impairment of the synthesis of the encoded protein and faster degradation of the mRNA [81, 82].

RNA modifications

The epitranscriptome describes epigenetic changes affecting RNA. It represents another layer of epigenetic regulation that influences almost all aspects of RNA, including maturation, stability, distribution, and translation. RNA modifications appear on almost all types of RNA, including mRNA, tRNA, rRNA, and small nuclear RNA (snRNA) [83]. The most common and best described RNA modification is the methylation of adenosine on mRNA, forming N⁶-methyladenosine [84].

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