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INVITED REVIEWS

The epigenome and postnatal environmental influences in psychotic disorders

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Abstract
Objectives Schizophrenia spectrum disorders and bipolar spectrum disorders are the product of both heritable and non-heritable factors, the impact of which converges at different biological levels. Recent evidence from molecular approaches has provided new insights about how environmental exposures cause persistent alterations in the regulation of gene expression, particularly by so-called epigenetic mechanisms. The aim of this review is to provide an overview of findings of epigenetic studies in psychotic disorders, summarizing findings of human and animal studies on epigenetic alterations due to postnatal environmental exposures associated with psychotic disorders.
Methods Electronic and manual literature search of MEDLINE, EMBASE and PSYCHINFO, using a range of search terms around epigenetics, DNA methylation, histone modifications, psychoses, schizophrenia, bipolar disorder and environmental risks associated with psychotic disorders as observed in human and experimental animal studies, complemented by review articles and cross-references.
Results Despite several promising findings of differential epigenetic profiles in individuals with psychotic disorders in the studies published to date, the knowledge of the role of epigenetic processes in psychotic disorder remains very limited, and should be interpreted cautiously given various challenges in this rapidly evolving field of research.
Conclusions Integration of epigenetic findings into biopsychosocial models of the etiology of psychotic disorders eventually may yield important insights into the biological underpinnings of the onset and course of psychotic disorders.

Keywords Environment · Epigenetics · Psychotic disorders · Schizophrenia · Bipolar disorder · Postnatal

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Introduction

Schizophrenia spectrum disorders (SZ-s) and bipolar disorder (BD) are complex disorders with heritable and non-heritable constitutions. The heritabilities of SZ-s and BD are approximately 60–80 % [1]. The recent wave of large-scale genome-wide association studies (GWAS) and analyses of copy number variants has resulted in the discovery of a range of common and rare genetic variants that increase the risk of SZ-s and/or BD [2]. Although calculations using cumulative scores of genetic risk loci have shown that these scores may explain a small proportion of the disease variability, the bulk remains unexplained by genetic effects, thus suggesting that gene–gene interactions (i.e., epistasis) and gene–environment interactions may be involved [3, 4].

A large body of epidemiological findings has shown that a range of postnatal environmental exposures is associated with psychotic disorders [5]. In parallel, several lines of evidence from both human and animal studies have shown differentially dysregulated expression of the candidate genes associated with the pathogenesis of psychotic disorders [6, 7].

Recent studies in the domain of molecular biology have provided evidence that environmental exposures are able to alter the regulation of gene expression, particularly by so-called epigenetic mechanisms. Epigenetic mechanisms refer to chemical modifications to the genome that regulate gene expression independent of the changes in the DNA sequence. The concept of epigenetics is very relevant for social psychiatry and epidemiology, because it connects a broad range of environmental factors including experiences and social factors during life with biological mechanisms at the molecular level. Although epigenetic programming occurs to a large extent during early perinatal development (for review see [8]), accumulating evidence indicates that later postnatal environmental factors also induce gene expression changes through epigenetic mechanisms.

In this article, we first provide basic background information on epigenetic mechanisms. Second, to summarize findings from epigenetic studies in psychotic disorders and discuss the results of human and animal studies on epigenetic alterations in relation to postnatal environmental exposures associated with SZ-s and BD, we conducted an electronic and manual literature search of MEDLINE, EMBASE and PSYCHINFO, using a range of search terms around epigenetics, DNA methylation, histone modifications, psychoses, schizophrenia, bipolar disorder and postnatal environmental exposures associated with psychotic disorders, complemented by review articles and cross-references. Finally, we describe the current challenges and perspectives in the field of epigenetic research on psychotic disorders.

Epigenetic mechanisms

Epigenetic mechanisms dynamically regulate the transcription and expression of genes during life and are responsive to environmental factors. The transcription of DNA into messenger RNA (mRNA) is influenced by dynamic epigenetic marks that are mostly located in or around these genes regions. DNA methylation and histone modifications are the most studied epigenetic processes in this context, although the expression of the genes can also be regulated by many other epigenetic factors. Most recently, post-transcriptional epigenetic regulation through so-called noncoding RNAs, including microRNAs [9], has gained a lot of attention not in the least by the potential to use them for manipulation of gene transcription [10]. Methylation of DNA predominantly occurs at a cytosine (C) nucleotide next to a guanine (G) nucleotide producing 5-methyl cytosine (5mC). High levels of methylation in regions rich in CG dinucleotides in promoter regions of genes disrupt the binding of transcription factors and thereby, in general, decrease the transcription of the corresponding genes. In repressor areas these effects are reversed and methylation leads to decreased repression and therefore increased expression. Thus, DNA methylation can switch the transcription of genes "on" or "off". DNA methylation is mediated by the family of DNA methyltransferases (DNMTs) including DNMT1, DNMT3a and DNMT3b [11] and is co-dependent on the availability of methyl-donor molecules, among which for example is folic acid. Over the last few years, it has been observed that 5mC can undergo further epigenetic processing into 5-hydroxymethylcytosine (5hmC) by the ten–eleven translocation (TET) family of proteins [11], after which 5hmC can be further processed into 5-formylcytosine and 5-carboxylcytosine [12] and, eventually, fully de-methylated cytosine.

Modifications to the chromatin (the complex of DNA and proteins that together make up the contents of the nucleus of a cell) comprise the second main epigenetic mechanism. Chromatin is composed of DNA wrapped around nucleosomes, each of which consists of histone proteins and their tails. The accessibility of the transcriptional machinery to the chromatin (needed for active gene transcription) can be altered by chemical modifications of histone tails (i.e., histone acetylation, methylation, phosphorylation, SUMOylation and ubiquitylation at lysine (K) or arginine (R) residues of the histones). Depending on the specific position of the histone tail residue and the nature of the chemical modification and, moreover, the combination of histone modifications, such chromatin changes are linked to either enhanced or decreased accessibility of the DNA for gene transcription and, thus, to altered gene transcription. In general, histone 3-lysine 4 mono-, di- and tri-methylation (H3K4me, H3K4me2, H3K4me3), H3K9me and H3K27me marks are associated with an open chromatin structure and active transcription of the genes, while di-, tri-methylated H3K9 and H3K27 are linked to gene repression [13].

Epigenetic alterations in psychotic disorders

Although there are several indirect approaches for investigating the involvement of epigenetic mechanisms in epidemiological studies, for example using proxy measures of X-inactivation [14], or frequency of pregnancy as a proxy measure of vitamin B12 status [15], nowadays a range of available methods and techniques are available to investigate the epigenetic machinery at the molecular level more directly. Molecular investigations of epigenetics may

thus consist of: (1) analyses of a certain epigenetic mark at a global level, e.g. providing data on the average level of global methylation of a given specimen, (2) interrogations of the epigenetic profiles (such as DNA methylation or histone acetylation) at individual genetic loci, either using a candidate gene or genome-wide approach and (3) genetic association studies or gene expression studies of genes regulating the epigenetic machinery.

Global epigenomic alterations

One explorative approach for studying epigenetic involvement is to measure the global status of a certain epigenetic mark throughout the DNA without specifying which specific genes or genomic regions are altered. A first wave of studies using this approach has not (yet) been able to find consistent patterns of aberrant global epigenetic profiles in patients diagnosed with psychotic disorders, although the majority of studies on global DNA methylation to date have found a lower level of global methylation in different tissue types. For example, global methylation analyses in post-mortem frontal cortex tissue indicated decreased global DNA methylation of SZ-s and BP patients compared to controls, while global methylation in germline DNA of BP patients was also decreased [16]. Studies on global DNA methylation in blood of patients with SZ-s compared to matched healthy controls observed that global DNA methylation profiles of peripheral leukocytes were also decreased [17, 18]. However, no differences in global analysis of DNA methylation of peripheral blood DNA samples obtained from patients with SZ-s or BD have been reported [19–21]. Interestingly, global methylation analyses of maternal and paternal X-alleles in DNA derived from blood showed that MZ twins discordant for BD had greater differences in global methylation than concordant MZ twins [22], suggesting that DNA methylation may indeed be involved in the disorder.

Regarding global profiles of histone modifications, studies using peripheral blood cells have observed increased H3K9me2 and reduced H3K9 acetylation in those with SZ-s compared to controls, as well as a negative correlation between global H3K9me2 levels in lymphocytes and age at onset for patients with SZ-s [23]. In addition, increased global levels of histone 3 arginine 17 methylation (H3R17me) in the prefrontal cortex (PFC) have been observed in a subgroup of patients with SZ-s displaying hypometabolism in this brain region [24].

Epigenomic alterations in candidate genes

Most epigenetic studies in psychiatric disorders have thus far focused on aberrant epigenetic profiles in selected candidate genes, i.e., with a priori evidence for a possible role in major psychosis, including genes involved in certain neurotransmitter systems (dopaminergic, glutamatergic and GABAergic systems), synaptic plasticity, oxidative stress and oligodendrocyte viability and myelination. These studies on candidate genes have provided important first insights into possible epigenetic dysregulation in the psychotic disorders. Here, we discuss a selection of the main findings of the first studies on candidate genes involved in different neurobiological systems. The dopamine hypothesis of psychosis is long-standing and dopaminergic genes have been candidates for hypothesis-driven research for decades [25]. Hypomethylation of the promoter region of membrane-bound isoform of catechol-O-methyltransferase (MB-COMT, a major metabolizing enzyme of dopamine) in the DNA derived from frontal lobe and saliva has been observed in patients with SZ-s and BD [26, 27], while no differences were observed in the cerebellum of these patients [28]. Another recent study has shown that the promoter region of the soluble isoform of COMT (S-COMT) was hypermethylated in peripheral blood leukocytes of patients with SZ-s [17]. Methylation in a genomic region regulating the transcription of the D2 dopamine receptor (DRD2) was observed to differ between non-affected twin pairs and twin pairs discordant for SZ-s [29]. A recent study has furthermore shown increased levels of methylation in the promoter regions of the *DRD2* and *D4* dopamine receptor genes in peripheral blood lymphocytes of patients with SZ-s compared to controls [30]. However, another study on 48 sibling pairs discordant for SZ-s found no alterations in methylation of the regulatory region of *DRD2* in patients versus their siblings [31]. In addition to the dopamine hypothesis of psychosis, the glutamate hypothesis has gained much attention over the last decades. Metabotropic glutamate receptors (GMRs) play important roles in synaptic plasticity and long-term potentiation and are involved in the pathogenesis of SZ-s. Hypermethylation in the promoter region of *GMR2* and *GMR5* genes has been observed in DNA from peripheral blood of patients with SZ-s [32].

Several lines of evidence have also indicated dysregulation of the GABAergic system in psychotic disorders. A series of studies on a glutamic acid decarboxylase GAD67 (main enzyme responsible for decarboxylation of glutamate into GABA) have shown decreased *GAD67* mRNA expression in the prefrontal cortex and cerebellum in both SZ-s and BD [33, 34]; in addition, it was shown that reduced *GAD67* mRNA expression was associated with chromatin-associated DNA methylation changes at the promoter region of *GAD1*, the gene encoding GAD67 in SZ-s [35]. However, in brain tissue of patients with SZ-s, reduced *GAD67* mRNA expression in cortical GABAergic interneurons can also be related to the concomitant increased levels of DNMT1 [36].

Genes involved in neuroplasticity and oligodendrocyte functioning may also be implicated in the etiology of psychotic disorders. For example, evidence suggests a role for brain-derived neurotrophic factor (BDNF) in the pathophysiology of SZ-s and BD, although the epigenetic processes regulating the expression of the different *BDNF* exons are complex and very dynamic [37]. In peripheral blood cells of patients with SZ-s, hypermethylation at the promoter I of the *BDNF* gene has been observed compared to controls [38], specifically male patients displayed higher levels of methylation. In a recent study, hypermethylation of the promoter region of BDNF exon I was observed in patients diagnosed with type II BD [39]. Thus, taken together, this first wave of epigenetic analyses of candidate genes in different tissue types has shown evidence for numerous epigenetics alterations in SZ-s and BP.

Methylome-wide association studies

There are over 25 million CpG sites/loci in the genome [40] and the first wave of methylome-wide approaches generally limit methylation analyses to those loci that have a higher probability of being biologically informative. Quantitative profiling of methylation of thousands—millions of genetic loci covering the entire genome in one assay has been performed for the first time for psychotic disorders in 2008, using DNA from the frontal cortex from individuals diagnosed with SZ-s and BD and from matched controls [16]. This methylome-wide association analysis (MWAS) indicated psychosis-associated DNA methylation differences in numerous loci, particularly in genes involved in glutamatergic and GABAergic neurotransmission as well as in brain development. Another MWAS has been performed in DNA samples from peripheral blood cells from a cohort of MZ twin pairs discordant for major psychosis [19]. This study identified various aberrant methylated regions in the genome that were associated with psychosis. One interesting differentially methylated locus identified by this twin study was in the promoter of ST6GALNAC1. This locus was hypomethylated in the affected individuals in DNA from blood, but also in an independent sample of postmortem brain tissue from patients diagnosed with psychotic disorder [19]. An MWAS of medication-free patients with SZ-s and controls also demonstrated differentially methylated regions in the promoter region of several genes that were associated with SZ-s such as beta-1,3-glucuronyltransferase 2 (*B3GAT2*), *HDAC4* and diacylglycerol kinase (*DGKI*) [41]. A very recent MWAS on DNA from peripheral blood cells from a large sample of 1,479 SZ and control participants found evidence for differential methylation in the loci of several genes that have previously already been linked to the pathogenesis of SZ. Interestingly, differential methylation in the gene *FAM63B* (Family with Sequence Similarity 63, Member B) was replicated in another relatively large sample of 1,033 cases and control subjects [42].

Genetic variants and altered expression of genes of the epigenetic machinery

Because (1) distinct proteins, mRNA molecules and enzymes regulate the epigenetic processes and machinery and (2) these proteins are themselves also a product of genes, the involvement of the epigenetic machinery in the etiology of psychotic disorders can also be investigated using (a) genetic association studies assessing whether variants in genes regulating epigenetic processes are associated with SZ-s and/or BD and (b) mRNA and protein expression studies of genes centrally involved in DNA methylation and histone tail alterations.

Investigations of mRNA expression of the main DNA methylating enzymes DNMT1 and DNMT3a showed that peripheral lymphocytes of patients with SZ-s had higher levels of DNMT1 and DNMT3a [43]. Increased DNMT3A1 expression in telencephalic GABAergic interneurons of patients with SZ-s was found in another study [44]. A genetic association study of the DNMT3B gene indicated that the rare variant in one tagging single-nucleotide polymorphism (SNP), rs6119954, was associated with early onset SZ-s [45]. Investigations on the levels of methyl-group donors and cofactors affecting DNA methylation have furthermore pointed at aberrant methylation in SZ-s and BD. Several studies have detected differences in the levels of S-adenosyl methionine (SAM), a methyl donor, and other molecules part of the one-carbon metabolism pathway (i.e., homocysteine and folate) in patients with major psychosis [46, 47]. A recent meta-analysis of 48 genetic association case–control studies showed that a common variant (*MTHFR* C677T) in the gene encoding methylenetetrahydrofolate reductase, a crucial molecule in the folate-dependent one-carbon cycle which regulates the availability of methyl groups, increased the risk of SZ-s, bipolar disorder and unipolar depressive disorder and may thus reflect a shared genetic vulnerability factor [48]. Interestingly, a recent study has found a dose-dependent association between *MTHFR* C677T and three other genes and the severity of negative symptom only among patients with SZ-s with low folate levels [49]. Moreover, another subsequent study has shown that administration of folate plus vitamin B12 supplementation was able to improve negative symptoms of SZ-s, specifically in carriers of a certain MTHFR genotype; symptom improvement was found for T/T and C/T carriers of *MTHFR* C677T, but not for C/C carriers [50].

A cluster of common genetic variants in the histone-regulating gene jumonji, AT rich interactive domain 2 (*JARID2*), was among the strongest hits in recent GWAS analyses [51]. Furthermore, a de novo copy number variant (CNV; a deletion or duplication of a DNA segment) in a histone H3 Lys 9 (H3K9) methyltransferase-encoding gene (*EHMT1*) has been implicated as a risk factor for SZ-s [52]. Other genetic association studies observed no association between histone deacetylase 2 and 3 (*HDAC2* and *3*) genes and risk of SZ-s in a Chinese population [53], while a study examining *HDAC3, 4* and *10*, showed one SNP in *HDAC4* to increase the risk for SZ-s in a Korean population [54]. Besides these genetic findings, gene expression studies on histone modifying enzymes have provided further evidence for involvement of histone tail alterations in psychotic disorders. Higher mRNA levels of *HDAC1* but not *HDAC2*, *3*, *4*, *6* and *9* were observed in the prefrontal cortex [55], hippocampus and medial temporal lobe in SZ-s subjects [33]. In patients with BD, mRNA expression of *HDAC4* was elevated particularly during a depressive state, although mRNA expressions of *HDACs 6* and *8* were reduced in both depressive and remission states [56].

MicroRNA molecules are very small non-coding RNA molecules that can repress the translation of other mRNA molecules, and many miRNA species have currently been identified [57]. Interestingly, recent GWAS on SZ-s and on other psychiatric disorders have identified miRNA-137 as a risk locus for several psychiatric disorders [58]. A strong association between the MIR137 rs1625579 variant and severe cognitive deficits has been shown in patients with SZ-s [59]. Furthermore, there is evidence that the MIR137 rs1625579 variant is associated with age of onset and subsequent phenotypic heterogeneity in individuals with SZ-s [60]. Moreover, it has been shown that the same variants in MIR137 may be associated with structural alterations in a number of brain regions involved in the pathogenesis of psychotic disorders [61].

Together, these epigenetic, genetic association and gene expression studies are in line with the notion that alterations in the epigenetic machinery may mediate transcriptional changes that contribute to the risk for psychotic disorders [62].

Postnatal environment and epigenetic reprogramming

Epigenetic mechanisms play a crucial role in adaptive regulation of gene expression during neurodevelopment and aging [63, 64]. Studies in recent years have shown that the psychosocial environment and social stress in particular can induce changes in gene expression during key developmental periods and adult life via epigenetic mechanisms [65], and that environmental exposures during certain periods in postnatal life alter risk of developing psychotic disorders. To date, no studies have yet been able to directly connect distinct environmental exposures with altered epigenetic profiles and psychosis. However, numerous animal and some human studies have provided evidence that postnatal environmental factors associated with SZ-s or BD are associated with differential epigenetic profiles, and here we describe some of the main findings in this field.

Epigenetic changes and adversities in early postnatal life

Environmental exposures during early postnatal life have been associated with several mental disorders including SZ-s and BD. Parental care is one such factor and it has been shown that parental care affects the epigenetic status of several genes, including those associated with psychotic disorders. A series of experimental animal studies have shown strong associations between variations in maternal care and epigenetic alterations of genes involved in hypothalamic–pituitary–adrenal (HPA) axis function and hippocampus-related learning and memory processes. A landmark study in 2004 showed that differences in postnatal maternal care in rats led to hypermethylation in the promoter region of the glucocorticoid receptor gene (*NR3C1*) in the offspring, which was negatively correlated with *NR3C1* mRNA expression and behavioral phenotypes that persisted into adulthood [66]. Glucocorticoid receptors (GR) play a key role in the regulation of the HPA axis through a negative feedback mechanism, which is also closely associated with mesolimbic dopaminergic neurotransmission [67]. It has been observed that subjects with SZ-s show a down-regulation of *NR3C1* mRNA in cortical and hippocampal regions of the brain [68], and that childhood trauma is associated with a blunted cortisol response to stress [69]. Subsequent animal experiments indicated that methyl supplementation during early postnatal life could reverse the epigenetic and gene expression changes induced by maternal care in the offspring [70]. Interestingly, hippocampal transcriptomic studies in rats identified over 900 genes that were regulated by maternal care [71]. Consistent with the results in animal studies, findings from a human study showed an increased overall percentage of DNA methylation in *NR3C1* in blood lymphocytes that was strongly associated with the number of childhood traumatic events in patients with BD [72]. Moreover, increased methylation of the promoter region of *NR3C1* in DNA derived from leukocytes was significantly associated with severity of childhood maltreatment in 99 healthy subjects [73], while differential DNA methylation levels have been detected in more than 2,600 CpG sites in DNA from saliva of abused children as compared to controls [74]. Post-mortem hippocampus samples obtained from suicide

completers with reports of childhood abuse had increased CpG methylation of the *NR3C1* promoter, which was also associated with a decrease of *NR3C1* mRNA levels [75]. Thus, environmental impact on epigenetic programming of the HPA axis seems to have persistent influences on gene expression and behavior. In line with this, institution-reared children compared to family-reared controls showed DNA methylation differences in genes involved in immune response and cellular signaling systems [76], and that childhood trauma was associated with decreased levels of DNA methylation in the gene encoding the FK506 binding protein 5 (FKBP5), another important regulator of the stress response system [77]. Interestingly, this association depended on genetic variation in *FKBP5* as carriers of the risk allele in *FKBP5* intron 7 showed lower levels of DNA methylation that led to stronger FKBP5 induction and to GR resistance [78]. This phenomenon is called allele-specific methylation, which may occur frequently [79]. Although methylation status of *FKBP5* remains to be investigated in psychosis, genetic variations in the *FKBP5* gene have recently been shown to moderate the risk of psychotic symptoms after early trauma [80].

Another rodent model of parental care is the maternal separation model, in which the offspring is repeatedly separated very early during life from their mothers. Maternal separation in mice induces HPA-axis overactivity via increased MeCP2 phosphorylation and persistent hypomethylation in the arginine vasopressin (*AVP*) gene associated with increased gene expression in the parvocellular division of the paraventricular nucleus [81].

Findings from both animal and human studies together suggest that adversity in early life may lead to persistent epigenetic marks on specific genes associated with psychotic disorders.

Epigenetic changes and adversities in adulthood

A large body of studies has identified the role of epigenetic mechanisms in alteration of gene expression, particularly in genes involved in dopaminergic neurotransmission, HPA axis and neuroplasticity after normal and abnormal exposures and experiences. With respect to psychosis, it has been postulated that chronic exposure to social defeat (SD) may lead to sensitization of the mesolimbic dopamine system and thereby increase the risk for SZ-s [82]. In rodents, repeated exposure to defeat is known as an animal model for physical and psychosocial stress, which is associated with a strong impact on the HPA axis and neuroplasticity-related genes such as BDNF, via epigenetic mechanisms [83, 84]. It has been observed in several studies that animals show a striking differential susceptibility to the effects of chronic SD at the behavioral, biochemical and molecular levels [85]. Interestingly, this differential susceptibility was associated with altered activity of the mesolimbic dopaminergic system, mediated via epigenetic modulation of BDNF gene expression [86], and with DNMT3a-mediated neuroplasticity in the nucleus accumbens [87], which is thought to represent a key region in mediating psychosis. The hypothesis that similar mechanisms may operate in human beings exposed to social defeat may be supported by findings that humans exposed to acute psychosocial stress show alterations of DNA methylation of *BDNF*, at least in DNA from peripheral blood cells [88] and that social stressors impact the dopamine system in humans [89, 90]. Studies attempting to directly relate social stress exposure to altered neural activity (including dopaminergic neurotransmission using PET markers) and epigenetic status are currently ongoing. Thus, evidence accumulates that exposures to social stressors in puberty, adolescence and adulthood can influence behavioral, cellular and molecular phenotypes and that these influences are mediated by epigenetic mechanisms.

Epigenetic changes and drug use

The use of drugs such as methamphetamine, cocaine and cannabis has consistently been associated with SZ-s and BD [91, 92], and evidence from human studies has highlighted long-lasting alterations in gene expression in subjects exposed to psychostimulants [93, 94]. Recent studies have provided evidence for epigenetic modifications in the genome following psychostimulant use in both human cohorts and animal models. For example, prolonged use of methamphetamine is associated with an altered expression level of the major DNA methylating enzyme, DNMT1, in rats [95], and in rodents acute and chronic cocaine administration increased histone acetylation in the nucleus accumbens and decreased HDAC5 activity [96]. Although cannabis use in the developmental stage of life is a well-established environmental risk factor for psychosis [97], no studies have yet examined the link between cannabis use, epigenetic regulation and risk of psychotic disorders. However, it is tempting to suggest a role for epigenetic factors, especially given the recent observation that Δ^9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, induces expression of HDAC 3 [98].

Given replicated evidence that genetic variants in AKT1 may moderate the impact of cannabis exposure on psychosis, testing whether cannabis exposure alters the epigenetic profile of AKT1 may be warranted [99, 100].

Epigenetic inheritance

The classical concept that the molecular biology of transgenerational inheritance only involves genetic factors has

recently been challenged by findings in animal studies that environmentally induced epigenetic profiles can also be transmitted to several generations of offspring after the original exposure. This field has re-opened the Lamarckian concept of heritability of acquired traits and has received significant attention, particularly because rodent studies have provided suggestive evidence that the dramatic impact of maternal separation was persistent in some of the abnormal behaviors and in methylation changes across three generations [101], and that epigenetic profiles and behavioral expression of conditioned-fear paradigms can be transmitted to subsequent generations [102]. Thus, these findings may have strong implications for understanding the heritability of environmental influences on behavioral traits and psychiatric disorders, including psychotic disorders. It should be noted here that, although there is some evidence for inheritance of the impact of environmental exposures across generations in humans, the underlying mechanisms remain largely unknown. It needs to be established whether epigenetic inheritance is indeed relevant for humans. Although such studies are very challenging to conduct, one could envision that it may be possible to prospectively collect DNA samples and rich phenotypical data in adult humans over a time period with clear exposures to robust environmental factors, and collect the same material from their offspring, testing whether a given environmental exposure induces epigenetic profiles and phenotypes that are specifically transmitted to offspring whose conception took place after the exposure of the parent and not to offspring whose conception took place before the exposure of the parent.

Integrative model

Accumulating evidence that gene-by-environment interactions mediate and moderate vulnerability to psychiatric illness has changed the conventional understanding of the etiology of psychotic disorders [103]. Besides genetic variants that moderate the impact of environmental influences on gene expression and behavioral phenotypes, recent evidence has shown that epigenetic mechanisms

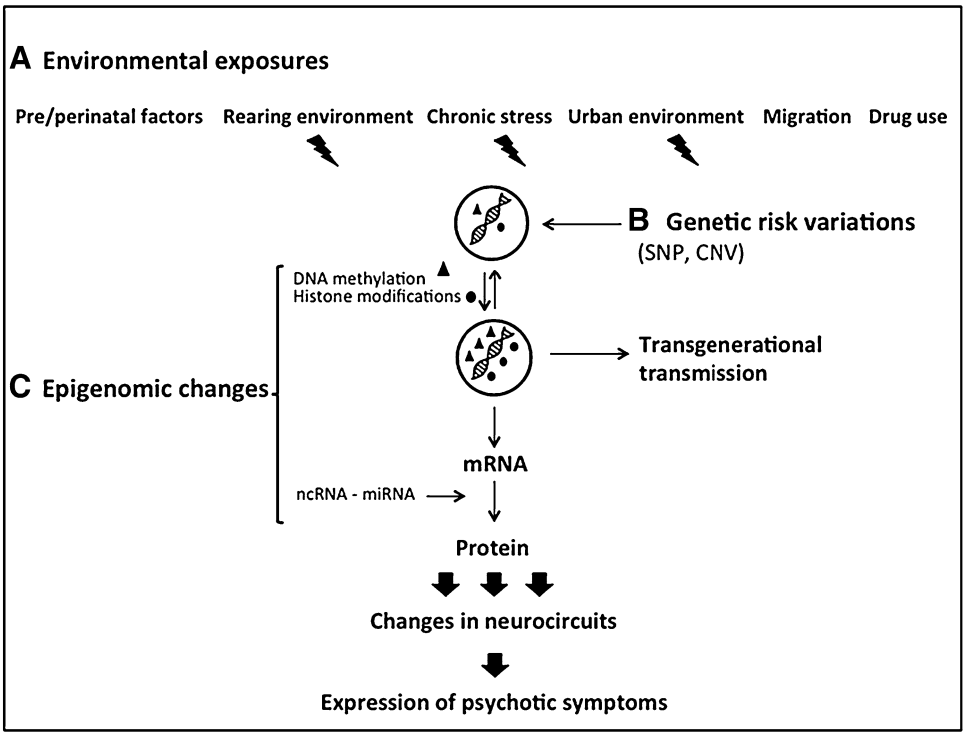

Fig. 1 Schematic illustration of an integrative model of gene–environment interplay in the etiology of psychotic disorders. The impact of environmental exposures (*A*) is mediated by both genetic (*B*) and epigenetic (*C*) factors. Current studied genetic and epigenetic variations comprise single-nucleotide polymorphisms (SNPs), copy number variations (CNVs), DNA methylation, histone tail alterations and noncoding RNA (ncRNA) including microRNA (miRNA). While genetic variants are stably transmitted from parent to offspring, epigenetic marks can be inherited or acquired over life as a result of environmental exposures and life experience. Environmental influences on the development of disease can depend on particular variations of a gene, while differential exposures to environmental factors can lead to altered expression of genes via epigenetic modifications. The net result of these processes on gene expression determines the anatomy and activity of neurocircuits and ultimately mediates the dynamic changes in the expression of psychotic symptoms, which may evolve to psychotic disorders

may moderate as well as mediate environmental influences across the lifespan. Figure 1 illustrates a current model integrating genetic, environmental and epigenetic factors in the etiology of psychotic disorders. Inherited genetic and epigenetic profiles constitute the molecular basis of an individual to develop over the life course, during which environmental exposures interact with genetic and epigenetic profiles, and may furthermore lead to long-term alterations of the epigenome, altering expression of genes influencing behavioral and experiential phenotypes of individuals. Furthermore, mounting evidence suggests the existence of allele-specific epigenetic differences in genes associated with psychosis constituting a further element in the dynamic interplay between the environment, genome and epigenome. In this respect, a very recent study pointed out that mild isolation stress during adolescence in rodents affected behavioral parameters as well as mesocortical dopaminergic neurons through increased DNA methylation of the gene encoding tyrosine hydroxylase (i.e., a necessary enzyme in the production of dopamine), but only when combined with a relevant genetic risk (a genetic variant of DISC-1) [104].

Taken together, the integration of epigenomic, genetic and environmental data in translational studies may further enhance our understanding of the etiology and inheritance of psychotic disorders.

Challenges and future prospects

Although epigenetic mediation of environmental factors in the development of SZ-s and BD has generated considerable recent interest, little evidence is currently available and, when available, epigenetic findings should be interpreted cautiously. In this respect, it is important to realize that (1) most of the findings mentioned above have not (yet) been replicated and were obtained with limited samples sizes, (2) molecular methodologies assessing epigenetic profiles are developing rapidly and the 'normal' epigenome is still largely unknown, (3) most studies on environmentally induced epigenetic changes were performed on animals and (4) the current wave of human studies has mainly been performed on chronic patients. Another major challenge lies in the limited availability of brain tissue for epigenetic studies. However, recent data suggest that epigenetic profiles in peripherally accessible cell types such as blood, buccal epithelial cells and saliva may be worthwhile. These data indicated that (1) between-individual differences in DNA methylation are correlated across brain and blood [105] and the association with many traits is conserved between these tissues [106] and (2) the role of DNA methylation in tissue-specific gene expression may be largely limited to differentially methylated regions with a distinctive profile regarding the location and CpG density [105, 107]. Technical improvements in the epigenetic profiling regarding coverage of most (and even all) CpG sites in the genome and distinguishing better between different epigenetic processes such as methylation and hydroxymethylation are pushing the field forward in this respect [108, 109].

Nevertheless, no studies have yet examined the direct link between environmental exposures such as cannabis use, migration and urbanicity with epigenetic profiles and risk of psychotic disorders. Longitudinal cohort studies with data collection on environmental exposures, genetic predisposition and epigenetic profiles are therefore needed. Given the confounding effects of several diseases-related exposures such as medication and social disadvantage, it will be crucial to conduct such studies in a prospective manner in the general population, high-risk groups and first -episode patients.

Taken together, the current state of the literature points out that genes and environment do not act independently and that the nature–nurture dichotomy is much less rigorous as previously thought. Integration of what has often been seen as separate approaches holds new promise for studies of psychiatric disorders, in general, and psychosis, in particular.

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