Title: DNA methylation signature as a biomarker of major neuropsychiatric disorders

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Abstract

DNA methylation is a broadly-investigated epigenetic modification that has been considered as a heritable and reversible change. Previous findings have indicated that DNA methylation regulates gene expression in the central nervous system (CNS). Also, disturbance of DNA methylation patterns has been associated with destructive consequences that lead to human brain diseases such as neuropsychiatric disorders (NPDs). In this review, we comprehensively discuss the mechanism and function of DNA methylation and its most recent associations with the pathology of NPDs-including Major depressive disorder (MDD), schizophrenia (SZ), autism spectrum disorder (ASD), bipolar disorder (BD), and attention/deficit hyperactivity disorder (ADHD). We also discuss how heterogeneous findings demand further investigations. Finally, based on the recent studies we conclude that DNA methylation status may have implications in clinical diagnostics and therapeutics as a potential epigenetics biomarker of NPDs.

Keywords: DNA methylation, Major depressive disorder, Schizophrenia, Bipolar, ADHD, Autism, Brain disease

Introduction

Neurological conditions are mental disorders that are typically attributed to diseases that originate from the nervous system (1). These disorders affect the health of affected individuals and influence their ability to learn, work and emotionally cope. Mental disorders can be categorized in degenerative diseases (like multiple sclerosis (MS), Parkinson's, and Alzheimer's), mood disorders and psychosis (e.g. bipolar disorder (BD) and schizophrenia (SZ)), as well as, childhood neurodevelopmental disorders (like attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (2). Much effort is being made over the last decade to understand the role of biological mechanisms in mental disorders (3,4). Although genome wide association studies (GWAS) have been the most widely used strategy to discover new candidate loci involved in the molecular signature of psychiatric disorders (5,6), epigenetic signatures are starting to be considered as a key genetic biomarker . DNA methylation is one of the most broadly studied epigenetic modifications and has been considered as heritable and reversible changes (7). DNA

methylation includes adding methyl group (CH3) from S-adenosyl methionine (SAM) using DNA methyltransferases (DNMTs) and formation of the carbon-5 of cytosines (5mC). There are two families of DNMTs: maintenance DNMTs such as DNMT1, and *de novo* DNMTs including DNMT3A, DNMT3B, and DNMT3L. DNMT1 initiates methylation on hemi-methylated DNA strands during cell divisions, whereas *de novo* DNMTs establish new methylation status (**Fig. 1**) (8). On the other hand, a class of proteins called TETs (ten-eleven translocation, TET1, TET2, and TET3) catalyze DNA demethylate and convert 5mC into 5-hydroxymethylcytosine (5hmC). The actions of DNMTs and TETs result in establishing and maintaining specific DNA methylation signatures in different cell types (9). Another protein in the DNA methylation pathway is MeCP2 (methyl CpG binding protein 2) that binds to 5mC and 5hmC (10). These sets of protein complexes are important for changing chromatin states during transcription (**Fig.2**).

Previous findings have indicated that DNA methylation regulates gene expression in the central nervous system (CNS). Moreover, improper recognition and regulation of DNA methylation result in various damaging consequences that have been reported in human brain diseases such as NPDs (11–13).

In addition to its role in regulating protein-coding genes, DNA methylation can regulate the expression and function of non-coding RNAs including long non-coding RNAs (lncRNAs). For example, Xist is a lncRNA that promotes random X-inactivation in 4-8 cell stage embryos (14). The *Xist* gene promoter contains the CpG island, whose methylation pattern determines whether the X chromosome is active (15). Sati et al. have investigated the DNA methylation status surrounding promoter regions of protein-coding genes and lncRNA loci. They found significantly enhanced DNA methylation downstream of lncRNAs promoter but it did not associate with the

lncRNAs expression (16). However, how DNA methylation controls lncRNA expression in the CNS is still unknown.

Furthermore, DNA methylation can control genome stability by regulating the expression of repetitive sequences like LINE 1 (long interspersed nuclear element-1) (17). Investigations have reported that LINE 1 is more active in the brain compared with other cells and tissues which may influence the expression of neuronal genes in the brain (18). Increased activity of LINE 1 has previously demonstrated correlations with multiple brain diseases including both degenerative and psychiatric diseases (19). In this review, we aimed to summarize the most recent findings about the DNA methylation biomarkers in several NPDs including MDD, BD, SZ, ADHD, and ASD (**Table 1**).

DNA Methylation Regulates Brain Function

Several studies have reported that there is a correlation between DNA methylation levels and transcriptional activity in the brain, suggesting that DNA methylation plays a crucial role in regulating brain functions. For instance, DNA methylation patterns change during differentiation of embryonic stem cells (ESCs) into nerve progressive cells (NPCs) and differentiation of NPCs into neurons (20). In addition to neurogenesis, differentiation of astrocytes is regulated by DNA methylation. Demethylation of GFAP (glial fibrillary acidic protein) promoter is required for the differentiation of astrocytes from neuroepithelial cells (21).

DNA methylation, also, controls neural migration and axonal/dendritic outgrowth. For instance, DNA methyltransferase DNMT1 appears to play a regulatory role in GABAergic interneuron

migration (**Fig. 3**). DNMT1 induces the survival and migration of GABAergic interneurons (22,23). In line with this, *de novo* methylation by DNMT3b is important in controlling the protocadherins (*PCDHS*) genes in the neurodevelopmental pathways (24). PCDHS, cell-surface adhesion proteins, are mainly expressed in the brain and play significant functions in neuronal survival (25), dendritic patterning (26), and neural development. They are involved in multiple NPDs including SZ, ASDs, and depression (27,28).

Also, DNA methylation functions in memory processing in the hippocampus and cortical regions. In the rat hippocampus, fear conditions promoted alteration in DNA methylation during memory formation. The inhibition of DNMTs by inhibitors including 5-aza-2′-deoxycytidine and zebularine demonstrated that methylation patterns of *BDNF* and *REELIN* genes (neuronal plasticity-inducing genes) altered (29). Besides, DNMT3a and DNMT3b mRNAs are increased after fear conditions in the brain, but, when zebularine or 5-aza-2′-deoxycytidine (DNMT inhibitors) were injected into the hippocampus after fear conditions, the elimination of fear response was observed, indicating that hypermethylation of DNA is needed for memory formation (30). In line with this, it has been reported that fear conditions disturb the DNA methylation status of three genes (i.e. *calcineurin*, *EGR1*, and *REELIN*), which are associated with memory and have large CpG islands in their promoters (31).

F. Rizzardi et al. have found different mCG islands in neurons that are rich in binding sites of transcription factors regulated by synaptic activity including MEF2C, FOS, and JUN, some of which quickly detect and react to methylation marks. These results indicate a correlation between synaptic activity and epigenetic modification in the binding sites of transcription factors (32).

A study by Mo et al. has indicated that there are significant differences between the levels of gene expression and the levels of DNA methylation in different types of neurons of the mouse brain. They have used the INTACT method (isolation of nuclei tagged in specific cell types) for isolating and investigating the transcriptome and methylome of some neuronal subtypes including vasoactive intestinal peptide-expressing, parvalbumin-expressing interneurons, and excitatory pyramidal neurons in the mice brain (33). Such methods can be used to study patterns of DNA methylation during brain function and disease and to produce models of NPDs to find suitable genetic and epigenetic biomarkers for diagnostic and therapeutic purposes.

Effects of stress in DNA methylation

The term stress refers to the psychological response elicited when an individual perceives themselves to be under threat or challenge and is generally beneficial, eliciting a range of behavioral and physiological changes aimed at addressing the perceived threat (34). Experiences of chronic and/or severe stress during early childhood, often also conceptualized as early life stress, childhood adversity, child maltreatment, or childhood trauma, have persistent and pervasive consequences for development (35). However, chronic and/or extreme stress results in extended activation of these psychological, behavioral, and physiological stress response systems leading to dysregulation and negative psychological and behavioral outcomes. Acute stress disorder is also a stressful condition that describes posttraumatic stress reactions that occur in the first month following a trauma (36). Various studies have shown that stress such as acute/chronic stress and early-life stress play a critical role in pathophysiology of psychiatric disorders and could increase risk of them (37,38). Different kinds of stress can regulate epigenetics, in particular, DNA

methylation, which may modify gene expression and therefore disease phenotypes (39). In fact, early-life stress (e.g. childhood abuse and stress-related disorders) have perdurable effects on DNA methylation of some genes, especially those involved in the hypothalamic–pituitary–adrenal (HPA) axis (40,41).

In addition, in vitro and in vivo studies have found differential methylation of *BDNF, SLC6A4, LINE-1* and *TH* in association with sustained work-related stress and chronic lifestyle stress (42–45).

In a more recent study, Comes et al. have reported that epigenome-wide methylation across time in patients with BD is associated with recent, non-traumatic stressful life events. They identified a single significant, CpG site at *POU6F2*, which has been related to several psychiatric disorders, intelligence and educational attainment (46). In this context, early life stress (ELS) has been indicated to be correlated with enhanced risk for many psychiatric disorders including MDD, BD, and posttraumatic stress disorder (PTSD) (37). For instance, ELS is known as the main cause of MDD and recently, ELS is considered to have been interacted with DNA methylation for influencing brain structure and function which will lead to changes in emotions and behaviors (47). These effects were exerted via regulating risk genes. For example, Ziegler et al. reported that MDD patients had lower methylation levels at *MAO* (Monoamine oxidase) A than healthy controls (48). Therefore, hypomethylation of *MAO A* may be a risk factor for MDD. On the other hand, hypomethylation of *MAO A* may result in depression through stress (49). MAO is a key enzyme that regulates the metabolism of monoamine transmitters, such as norepinephrine, 5-hydroxytryptamine (5-HT), and dopamine in the brain, affecting gene expression to regulate functions of neurons (50). An *in vivo* study demonstrated that the methylation level of the *5-HT1A* (serotonin 1-A receptor) promoter affects gene expression. In fact, stress enhanced the mRNA

level of *5-HT1A* in the prefrontal cortex of CUMS mice. These regulatory effects by stress are mediated through the methylation of the -681CpG site (51). In addition, ELS and adult life stress are associated with the modification of DNA methylation in other genes related to mood regulation including *NR3C1, SLC6A4, and OXTR* (52). *OXTR* (Oxytocin receptor) is the main regulator of stress and anxiety. Hormonal changes lead to changes in the DNA methylation of the *OXTR* promoter during pregnancy, thereby influencing maternal behavior (53). In this regard, the relationship between stress throughout pregnancy and epigenetic modification of offspring DNA was also investigated (54). Two genes involved in regulating stress response are *NR3C1* and *NR3C2* (nuclear receptor subfamily 3 group C member 1 and 2). Lower DNA methylation at *NR3C2* found in placental tissue was associated with maternal early pregnancy depressive disorder and symptoms (55). *MAO A* variations, on one hand, and Early-life adversities, on the other, affect the DNA hypermethylation of *NR3C1* which results in depression in females (56). Overall, these studies show the link between DNA methylation of multiple loci and ELS.

Chronic stress has also demonstrated variation of DNA methylation patterns in the brain (57). Profiling of DNA methylation of the dentate gyrus at putative regulatory regions across the mouse genome from mice exposed to 14 days of social defeat revealed two differentially methylated regions (DMRs). One DMR was located at intron 9 of Drosha, with reduced methylation in stressed mice, and the other DMR at an intergenic region of chromosome X, with increased methylation in stressed mice (57).

The effects of acute stress on DNA methylation in rats brains revealed a decrease in global DNA methylation in hippocampus, cortex and periaqueductal gray (PAG) of sedentary animals and an increased expression of *Bdnf* in PAG, suggesting that acute stress evokes adaptive changes in global DNA methylation of rat brain that are independent of the expression of the *Dnmt1* gene but

might be linked to abnormal expression of the *Bdnf* gene (58). A study has shown that promoting DNA methylation of *c-fos* and *egr1* promoters via S-adenosyl methionine (SAM) administration, the endogenous methyl-donor for DNA methylation, it is possible to significantly hamper the consolidation of immobility behavior after forced swim (FS) paradigm in rats (59). This suggests stress-increased Dnmt3a repressive activity represents an example of adaptive acute stress-coping process based on transcriptional constrain of plasticity genes in the brain.

DNA Methylation in major depressive disorder

One of the most common psychiatric disorders is MDD with a prevalence of 4.4% (60). Current predictions demonstrate that depression will be a major cause of disease burden by 2030 (61). Although the etiology of MDD remains unknown, it is a multifactorial, complex disorder. Increasing evidence indicates that epigenetic modifications including DNA methylation are essential in the pathobiology of MDD. The metabolic enzyme for the monoamine neurotransmitters, MAO A/MAO B are the prime candidates for the investigation into the role of DNA methylation in MDD. In MDD, increased *MAO A* expression and decreased serotonin and norepinephrine brain levels are considered to be the major causative factors. Functional polymorphisms of the *MAO A* gene and genes in the serotonin signaling pathway are linked to MDD. Depression in females may result from a dysregulated epigenetic programming of *MAO A*. In females, depression is related to hypomethylation in the first exon region of the *MAO A* gene (62). Also, female depressive patients showed significantly decreased methylation at ten methylated sites (CPGs) representing parts of exon I and intron I of the *MAO A* gene, compared with age-matched healthy female controls (56). DNA methylation levels have a major impact on depression. Interestingly, there are relatively few studies on DNA methylation of the gene encoding *MAO B*. Nevertheless, there is evidence for depression and changes in *MAO B*

methylation patterns. In single-zygote twins without major depression, the initial association between a *MAO B* promoter CpG site and depressive symptoms could not be corrected in multiple tests (56,63). In fact, different environmental stress factors will affect the DNAm of different CpGs, which will affect the phenotype of depression.

Adult hippocampal neurogenesis is functionally also important for stress-induced social avoidance and depression (64). Knockdown of *Bdnf* in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis (65). In this regard, neurogenic-related genes (e.g. *Dlg4, Drd2, Nos1, Nrxn1,* and *Sox10*) have indicated vulnerability to the effects of stress and depression by DNA methylation (66). An *in vitro* analysis (67) showed that neonatal maternal separation attenuates the capacity of adult neural precursor cells to differentiate into neurons; increases expression of *Dnmt1*, but not 3a or 3b; reduces expression of RARα, but not β subtype; and increases methylation of RARα promoter. In this study, RARα increased neural differentiation and blockade of RARα reduced neural differentiation induced by retinoic acid. These findings elucidate the impact of environmental factors on adult neurogenesis in hippocampus through DNA methylation modifications relevant to stress and depression (67).

Several studies have investigated the association between DNA methylation and impaired neuroplasticity in depression. For instance, *in vivo* and *in vitro* studies have demonstrated alterations of DNA methylation of *Bdnf* in MDD. These studies suggest that hypermethylation of *Bdnf* leads to a decrease in its expression in MDD (68–71). In this regard, a human study identified increased levels of *Bdnf* promoter methylation correlated with decreased cortical thickness in patients with MDD, which leads to neurodegenerative changes. It suggests that the methylation of *Bdnf* might have an effect on the disruption of the fronto-occipital white matter tract. On the other hand, hypermethylation of *Bdnf* and decreased cortical thickness of the prefrontal and occipital

regions, could be correlated with regulating emotion, executive functions and depressive mood (71). This effect of *Bdnf* activity in the prefrontal cortex in depression could be exerted through the *Bdnf*-neurotrophin receptor tyrosine kinase 2 signaling pathway, consequently, promoting the molecular vulnerability in depression (72).

In another study, the three genes *Lingo-3, Pou3f1*, and *Itgb1* that are implicated in myelination and mediates oligodendrocyte and axonal interactions, had a significant difference in methylation levels in individuals with depression. These results show that early life adversity (ELA) may lead to myelin alterations. On the other hand, ELA can control critical behavioral and emotional systems and is involved in the pathobiology of MDD and other psychopathology (73,74).

Interestingly, Weder et al. and Kaufman et al. indicated that differential methylation of some genes including *ID3* (DNA-Binding Protein Inhibitor ID–3), *GRIN1* (Glutamate Receptor, Ionotropic N-methyl-D-aspartate (NMDA) 1), *TPPP* (Tubulin Polymerization Promoting Protein), and *OTX2* (Orthodenticle homeobox 2) emerged as predictors of depression. Indeed, epigenetic changes in biologically related genes including *ID3, GRIN1, OTX2* and *TPPP* genes may confer risk for depression (75,76). The expression level of *ID3* is enhanced in the pituitary in response to chronic stress (77), and it has been implicated in neurogenesis and in neural plasticity (78). *TPPP* is involved in oligodendrocyte differentiation, myelinating oligodendrocytes and white matter maintenance in the brain (79,80). The expression level of *GRIN1* is reduced in response to stress in the frontal cortex from animal models of depression. In addition, *GRIN1* plays a key role in memory, synaptic plasticity, fear conditioning and pathophysiology of MDD and anxiety disorders (81,82). *OTX2* plays a role in brain development and the development of depressive-like behaviors in a mouse model of early life stress (83). Meanwhile, *OTX2* regulates the characteristics of serotonergic and dopaminergic neurons during embryonic development (84). In this regard, other

studies aimed to elucidate the role methylation of several genes such as *SLC6A4, NR3C1*, and *OXTR* in MDD.

In human lymphoblast cell lines, increased promoter methylation of *SLC6A4* (5HTT) resulted in reduced expression of *SLC6A4* mRNA (84,85) and consequently led to changes of emotional behavior. What is more, in other investigations, there was a correlation between DNA methylation in *SLC6A4* promoter and MDD (86,87). Molecular study conducted by Booji et al. demonstrated that the alterations of the *SLC6A4* gene implicated in the development and function of human brain regions (88). Additionally, it plays important roles in the control of emotional aspects of behavior and serotonergic signaling through transporting 5-HT from synaptic spaces into presynaptic neurons (89).

A few studies investigated the DNA methylation signature of *NR3C1* in different kinds of tissues, including brain, blood, placenta, saliva, and buccal swab from cases with depression disorder (90). Genome-wide DNA methylation profiling of peripheral leukocytes from MDD patients showed DNA methylation differences at 363 CpG sites, of which *GSK3B* was one of the most related genes, as it is implicated in not only MDD but also in the therapeutic mechanism of antidepressants (91).

There is also evidence of the crucial involvement of the glucocorticoid receptor (GR) in the development of MDD. GR is a ligand-activated transcription factor which plays a critical function in the HPA axis. The dysfunction of GR in the brains and the genetic variations in *NR3C1* gene, encoding GR, were associated with schizophrenia, bipolar disorder and other psychiatric illnesses (92). Several studies observed that the DNA methylation levels of *OXTR* (oxytocin receptor) increased in depressed women (93,94). Current studies demonstrate that the polymorphisms of

OXTR influence the HPA function. Also, *OXTR* modulates some physiological and behavioral processes in depression neuropathology (95).

Glial cells account for at least 75% of brain cells, and are implicated in a range of psychiatric disorders, including alcoholism, schizophrenia , depression and suicide (96,97). In particular, astrocytic dysfunction is evident in depressive psychopathologies, including suicide. Piling evidence suggests astrocytic dysfunction in depression, however, little is known about the underlying etiological mechanisms. Nagy et al showed that astrocytic markers *GFAP, ALDH1L1, SOX9, GLUL, SCL1A3, GJA1* and *GJB6* were downregulated in prefrontal cortex samples from MDD subjects (98). Among intragenic DMRs, those found in *GRIK2* (glutamate receptor, ionotropic kainate 2) and *BEGAIN* (brain-enriched guanylate kinase-associated protein) were most significant and also showed significant correlations with gene expression (98). All these findings suggest alteration of DNA methylation patterns in different cell types in impaired brain regions in MDD.

DNA Methylation in bipolar disorder

BD is characterized by shifts in mood, energy, and activity levels (mania and depression episodes) which influences an individual's ability to carry out daily tasks. Some forms of BD can be easily misdiagnosed with SZ, MDD, Borderline Personality Disorder as well as major clinical and economic consequences (99–101). Thus, over the past years, researchers have focused on identifying BD diagnosis from a molecular point of view to create distinct clinical patterns of disease as well as new and more specific treatments. To this end, identification of molecular biomarkers for diagnosis and clinical observations is required.

Despite extensive efforts, the molecular basis and pathophysiology of BD are not well known and no specific genes are confidently associated with the progression of the disease. Therefore, BD is a complex situation with the interaction of highly susceptibility genes with many environmental factors (102). These interactions are mediated by epigenetic mechanisms such as DNA methylation (99).

The literature reveals that the DNA methylation of several genes such as *PDYN* (precursor of the dynorphin peptide), *BDNF*, *DNMTs* and *MeCP2* (methyl CpG binding protein 2) plays an important role in the pathobiology of BD (99,103–105). The PDYN is a precursor of the dynorphins, peptide neurotransmitters that are ligands for the *KOP* (κ-opioid receptor), which have depressogenic effects in both animals and humans. Disruption of the PDYN/dinorphin/KOR system is involved in several psychiatric disorders including bipolar disorder, schizophrenia, drug addiction and depression (106).

Based on this, increased DNA methylation at the *PDYN* promoter following a reduction of *PDYN* gene expression, which was observed in cases with BD (87,103), results in *KOP* remaining inactive. This in itself can be a good therapeutic strategy to control episodes of mania and depression in BD.

BDNF is a neurotrophin that is highly expressed in the brain and has a crucial role in dendritic arborization, neuronal survival and differentiation, synaptic plasticity, memory consolidation, and learning (107). ProBDNF (precursor BDNF) interacts with p75 NTR receptor, which promotes long-term depression (LTD) and activates apoptosis. By contrast, mature BDNF binds to tyrosine kinase receptors (TrkB) and l simplifies long-term potentiation (LTP), induces cell survival, and enhances spine complexity (108). Some studies have associated BDNF with plastic changes,

including modulation of the trafficking and N-methyl-d-aspartate receptors (NMDARs) expression in synaptic strength (109) suggesting that BDNF may represent an crucial element of the cellular mechanism promoting memory formation and maintenance by facilitating synaptic reinforcement (110,111). Other studies suggest that BDNF may play an important role in the disrupted cellular resilience observed in BD. Reduced expression of BDNF results in dysregulation of the intracellular signaling pathways, including PI3K/Akt, PLC/PKC, and Ras/Erk pathways (111). Indeed, BD has been associated with alterations in several markers implicated in resilience and neuroplasticity, such as oxidative stress factors, synaptic, apoptotic, neurotrophic and inflammatory markers (112).

In this context, different studies showed that the CpG methylation level of the *BDNF* gene was significantly varied between BD subjects and controls (113). Some of these CpGs overlapped with transcription factor binding sites in the BDNF promoter, suggesting a possible role for DNA methylation in the regulation of *BDNF* gene expression. Although hypermethylation of BDNF has been observed in the post-mortem frontal cortex of BD patients compared with controls (114), in another study there was no difference in the DNA methylation of *BDNF* between BD patients and controls, which indicates that this marker may not be generalized to all populati (115). These findings suggest that the BDNF methylation status might play a regulatory role in shaping of the neuronal signaling cascade.

One of the most investigated genes in NPDs is MB-COMT (membrane-bound catechol-O-methyltransferase), which plays roles in synaptic dopamine degradation in the CNS. Dopamine is a neurotransmitter, which has cognitive functions in the brain. In the post-mortem brain samples of patients, there were lower levels of DNA methylation at its prompter along with higher expression, resulting in an enhancement in the rate of dopamine degradation and decreasing

dopaminergic state in the frontal lobe (116–118). Similarly, the MB-COMT hypomethylation has been shown in saliva, suggesting its potential role as an epigenetic biomarker for the disorder (117). Therefore, the investigations with respect to the methylation patterns of MB-COMT allow research of interactions between dopaminergic neurotransmission and cognitive functions in BD patients.

The pattern of DNA methylation in the serotonin receptor and transporter genes such as the serotonin receptor 1A (5-HTR1A) and the serotonin transporter (5-HTT) as well as GAD1 (glutamate decarboxylase 1) have also altered in BD. DNA methylation in these genes enhanced in post-mortem brain samples and leukocytes of BD patients resulted in a decrease of their expression in patients (119–121). 5-HTR1A binds the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) and regulates hyperpolarization and firing rate of the postsynaptic neuron (122). Cases with BD shared the large, fast hyperpolarization followed by a resting period before the neuron can fire again. This large, fast hyperpolarization Speeds up this cycle, resulting in fast and sustained neuron firing. That means in BD cases, the threshold for a neuron fire drops after-hyperpolarization (123). Altogether, these findings suggest that the methylation of 5-HTR1A may be involved in fast hyperpolarization and neuron firing processes in BD. Interestingly, there is cross-talk between BDNF and serotonin receptors. For example, enhanced expression of BDNF was observed in the mice knock-out for serotonin receptor 5-HT2B (124) that may result in antidepressant effects in BD.

In this regard, a study has evaluated the pattern of methylation at the *FKBP5* (FK-506 binding protein 5) gene in BD patients, unaffected siblings, and controls. The methylation of FKBP5 negatively regulates the activity of the glucocorticoid. Moreover, there was a negative correlation between the levels of DNA methylation at CpG sites and the number of previous manic episodes

(125,126). These methylation modifications are likely due to the presence of glucocorticoid receptor resistance in BD patients, which results in an abnormal activity of the hypothalamus-pituitary-adrenal axis and stress resilience (127). Hypomethylation at the HCG9 (HLA complex group 9) locus has also been found in BD patients (128). Lower DNA methylation of this gene has been reported in the germline and WBC (white blood cells), recommending it as a potential biomarker of BD (129).

Several other studies have also examined the pattern of DNA methylation of other genes in BD patients. Some of these genes, such as *RELN (130,131)* and *DTNBP1 (132)* indicated hypermethylation, which is correlated with less expression of these two genes in BD patients compared to controls. However, hypomethylation of the *DTNBP1* promoter has been reported in patients after drug treatment (133). RELN is an extracellular matrix glycoprotein that regulates synapse structure and function as well as dendritic spines and cognitive function. In addition, RELN controls the promotion and maintenance of the neuron's structure and function especially GABAergic and glutamatergic neurons and their interplay in BD (**Fig. 3**)(84).

In two other studies, the levels of *DISC1, DISC2* and *MALAT1* lncRNAs were analyzed in PBMCs of BD patients. Decreased levels of *DISC1* as well as *MALAT1* and enhanced levels of *DISC2* were reported in BD subjects compared with controls. These results indicated that the expression of *DISC1*, *DISC2* and *MALAT1* lncRNAs was associated with an increased risk of BD and might be involved in the neurobiology of BD. Using computational analysis, it was demonstrated that modification of the expression of these genes could be due to DNA methylation (134,135).

In addition to the studies that have examined DNA methylation patterns at specific loci in patients with BD, several reports have evaluated the whole-genome methylation. Rao et al. have found

global hypermethylation in the post-mortem frontal cortex from BD patients compared to controls [98], whereas, Huzayyin et al. (136) and Soeiro-de-Souza et al. (137) have reported global hypomethylation in lymphoblasts and whole blood of BD patients, respectively. However, Bromberg et al. found no differences in global methylation patterns between leukocytes from BD patients and controls (138). Several other studies analyzed genome-wide methylation in different post-mortem brain regions (139,140) and blood (141–143) from BD subjects and healthy controls. Eventually, the overall clinical relevance of changes in global methylation to the neurobiology of BD needs further investigation.

DNA Methylation in schizophrenia

SZ is considered a complex and relatively common disorder with high heritability. Many genes, several environmental factors, and some epigenetic factors are involved in the neuropathology of this disorder (144). One of these epigenetic factors is DNA methylation that regulates gene expression. Changing DNA methylation patterns appear to affect brain development and function, and subsequently, cognition and behavior that ultimately lead to NPDs such as SZ (145).

Findings from different genetic studies indicate DNA methylation plays a potential role in neurobiological mechanisms in SZ. For example, several studies found significant differences in the DNA methylation patterns of some loci involved in neurodevelopment, GABAergic neurotransmission, and other pathways associated with SZ etiology (31). In a GWAS of DNA methylation study, differences were observed in the DNA methylation patterns between monozygotic (MZ) twins discordant for SZ (146), suggesting the epigenetic changes associated with the etiology of SZ disease. Several investigations focused on the DNA methylation patterns in SZ patients either in the post-mortem brain or peripheral samples. For instance, Grayson et al.

and Guidotti et al. have reported in separate studies that the levels of *RELN* and *GAD67* mRNA and protein decreased in the prefrontal cortex of SZ cases, and appeared to be related to the increased methylation level of their promoters (130,147). Animal models display that reduced *RELN* expression impacts on synaptic plasticity and cognition, resulting in deficits in active avoidance tasks, LTP, dendritic spine densities, and excitatory postsynaptic responses to glutamate receptor agonists (130). Changes in *GAD67* mRNA expression disturb neurotrophin signaling, neuronal activity, glutamatergic and dopaminergic neurotransmission. The reduced expression of *GAD67* decreases the number of neurons and GABA concentrations in SZ (148). *SOX10* (an oligodendrocyte-specific transcription factor) was downregulated in the prefrontal cortex of SZ subjects, which is correlated with hypermethylation of *SOX10 (149).* Downregulation of *SOX10* results in dysfunction of oligodendrocyte genes and myelination pathways in SZ brain samples (150). COMT (catechol-O-methyltransferase), which implicates in the metabolism of dopamine, has also been reported as a candidate gene in SZ. The microdeletion of the *COMT* locus has shown correlation with SZ pathogenesis (151). However, the DNA methylation patterns of this region in SZ is still controversial. Although a group of researchers found the hypomethylation of *COMT* promoter and upregulation of *COMT* mRNA in the left frontal lobes of SZ patients (116), another study observed no association between the methylation levels of *COMT* and SZ in the cerebellum, suggesting differences in *COMT* expression related to SNP variations (152).

In relation to this, two genes, *GAD67* and *COMT* are involved in dopamine and GABA activities, therefore, there may be cross talks between these two genes for regulating glutamatergic and dopaminergic neurotransmission.

The modification of DNA methylation in the promoter of other genes such as *HTR2A* (serotonin receptor 2A) and *FOXP2* (a transcription factor required for language development) has also been

observed in the post-mortem brain of SZ samples (153,154). Unlike post-mortem brain samples, peripheral tissue samples from living patients can be accessed with minimally invasive techniques. For example, Kinoshita et al. have compared the levels of DNA methylation in leukocytes between 24 SZ subjects and 23 healthy controls. They observed that there were 234 disease-associated loci with differential methylation status (155), including *RELN* (encoding the serine protease reelin), a widely investigated gene in SZ, and *FAM63B*, involved in the differentiation of neuronal cells (156). Indeed, FAM63B hypomethylation and a locus on chromosome 16 have been reported as epigenetic risk factors in SZ (157). The function of *FAM63B* in the neuropathology of SZ remains unknown. Former investigations have revealed that *FAM63B* plays a role in neuronal differentiation and dopaminergic gene expression as well as the circadian clock through the microRNA network (157). Modification of DNA methylation pattern in *FAM63B* may impair these functions and initiate SZ.

Previous studies have reported the alterations of DNA methylation in *ST6GALNAC1, GABRB2* (β2 subunit of GABA (A) receptor) in post-mortem brain samples and blood or saliva samples from SZ patients. *ST6GALNAC1* encodes an enzyme named α-N-acetylgalactosaminide α-2,6-sialyltransferase 1 that transfers sialic acid to O-linked N-acetylgalactosamine residues, but without a clear function (146,158).

The alteration of DNA methylation in response to different drugs suggests that this epigenetic mark may have a function in response to the therapeutic biomarkers. Olanzapine leads to DNA methylation alterations in cadherin gene families as well as dopamine receptors including *DRD1, DRD2* and *DRD5*. These alterations were correlated with reduced stress-induced locomotor activity in a rat model (159). Likewise, Melka et al have revealed that olanzapine induces the modification of DNA methylation in cadherin/pro-cadherin genes, which in turn influences the

antipsychotic response in rats (160). Quetiapine, an antipsychotic drug, can regulate the DNA methylation at the *SLC64A* promoter in SK-N-SH cells (161). Furthermore, valproic acid reduces the DNA methylation at the promoters of *Reln* and *Gad67* in the mouse brains (162).

In addition to these studies in animal models, a few results have also been obtained from human subjects. In a cohort study, haloperidol increased the levels of DNA methylation in blood from SZ patients (163). Hypomethylation of the *DTNBP1* promoter was found in the post-mortem brain of SZ samples after antipsychotic treatments (133).

Despite these findings, further investigation will be required using larger sample sizes to understand the DNA methylation patterns in the post-mortem brain, peripheral blood, and saliva from SZ subjects. Also, the alteration of DNA methylation can be useful for finding potential biomarkers for the diagnosis and treatment of SZ disease.

DNA Methylation in attention deficit/hyperactivity disorder

ADHD is one of the most prevalent child psychiatric disorders characterized by cognitive and motivational deficits (164). Genetic and environmental factors, as well as epigenetic patterns, have been suggested to be involved in the pathogenesis of ADHD (164,165). Until now, a few epigenetic investigations have been performed in ADHD children. For instance, Walton et al. observed that DNA methylation at birth was linked to symptoms of ADHD at the age of 7–15 years. They found the CpG islands into some genes including *PEX2, SKI* and *ZNF544* which were related to the later ADHD. Although the roles of these genes in ADHD are still unclear, the analysis of the gene networks demonstrated a complex network associated with neurodevelopmental processes (166).

Also, the methylome-wide analysis performed in boys with ADHD suggests that DNA methylation changes at the *VIPR2* (vasoactive intestinal peptide receptor 2) and *MYT1L* (myelin transcription factor 1-like) genes are associated with regulation of cholinergic and monoamine neurotransmission (167,168). *MYT1L*, which is involved in the myelin and nervous system formation [168], is a pro-neuronal transcription factor. *MYT1L* reprograms fibroblasts into neurons (169). Although *MYT1L* functions in brain development are not well-known, based upon its biological function *MYT1L* is linked to major depressive disorder (170) and SZ (171).

Several works on DNA methylation patterns in ADHD have investigated several loci (including *DRD4, COMT, NGFR, SLC6A4, BDNF, DPP10, ANKK1,* and *TPH2*) (172–175). The *COMT* (catechol-o-methyltransferase) gene appears to be involved in monoamine signaling at cortical synapses. There were two CpG sites on this locus that were associated with ADHD (174,176).

DPP10 (dipeptidyl peptidase 10), an enzyme that regulates the expression of voltage-gated potassium channels, affects dopaminergic tone and the pathogenesis of NPDs such as SZ, ADHD and ASD (177,178). DPP10 is a component of the Kv4 channels (voltage-gated potassium channels) which regulate neuronal excitability, firing frequency and signal processing in CNS (179).

Heinrich et al. found an association between the DNA methylation of *TPH2* (tryptophan hydroxylase 2) and ADHD behavior (176). Guillemin et al. observed that the *TPH2* promoter is differentially methylated in adults, indicating aggressive behavior in childhood (180,181). In the brain, *TPH2* is a rate-limiting enzyme in the production of 5-HT (Serotonin 5-hydroxytryptamine). 5-HT plays critical roles as neurotransmitter or neuromodulator in the CNS and PNS. Furthermore, the expression levels of *Bdnf* mRNA are enhanced in adult Tph2−/− rats. In fact,

hyposerotonergia promotes neuronal plasticity by upregulating *Bdnf* in the hippocampus (182). These events can occur when *Tph2* is hypermethylated which means the hypermethylation of *Tph2* results in reducing *Tph2* expression, decreasing serotonin production, and enhancing *Bdnf* expression.

In another study by van Mil et al., the association of methylation values of a few candidate genes with ADHD behavior was analyzed in childhood. These genes, including *NR3C1* (glucocorticoid receptor), *MTHFR* (methylenetetrahydrofolate-reductase), *DRD4* (Dopamine Receptor D4) and 5-HTT (serotonin transporter protein), *IGF2DMR* (insulin-like growth factor 2), *H19*, and *KCNQ1OT1* (potassium channel protein) impact on different nervous pathways (174). For instance, *NR3C1* has an important function in the brain's response to stress. It regulates the influences of stress exposure and following cortisol production on ADHD (183).

The results indicated the reduction of DNA methylation levels was associated with an increase in the scores of ADHD symptoms. However, multiple descriptions may help further clarify the association between lower levels of DNA methylation and ADHD symptoms. First, several environmental factors such as toxins and drugs (184–186) might underlie the epigenome status. Second, genetic factors might influence the association between DNA methylation and ADHD symptoms. Thus, environmental factors and the polymorphisms present in these loci should be investigated (174).

The methylation levels of another locus, *DAT1* (Dopamine transporters), were associated with symptoms of hyperactivity and impulsivity in ADHD subjects (187). In the striatum tissue from rats with ADHD, DNA methylation of *DAT1* was negatively associated with its protein expression (188). Furthermore, the methylation of *DAT1* in blood has been correlated with DAT availability

in impulsivity and the basal ganglia in monkeys (189). However, it is still unclear whether methylation of *DAT1* in the blood is associated with the availability of DAT or protein expression in the human brain and with inattention or hyperactivity symptoms in ADHD patients (190).

DNA Methylation in autism spectrum disorder

ASD is a group of developmental disorders characterized by stereotypic behavior, social-communication difficulties, narrow interests, and sensory difficulties (191). It has been estimated that the prevalence of ASD is one in 59 individuals in the United States. The ratio of male/female of the disorder is 4.5 to 1 (192). The concordance of ASD among identical twins is high, suggesting complex inheritance and etiologic role of genetic factors (193,194). A combination of genetic, epigenetic and environmental factors plays important roles in ASD pathogenesis. Previous studies demonstrate the modification of DNA methylation in ASD subjects. For example, *PRRT1* (proline-rich transmembrane protein 1) and *TSPAN32* (Tetraspanin32) genes have indicated hypomethylation in the cerebellum and temporal cortex in the brains of ASD patients (195–197).

PRRT1 (also known as SynDIG4) is a component of AMPAR (AMPA receptor) complexes. There are some AMPAR complexes at synapses that are thought to regulate memory and learning. AMPAR content and excitatory synaptic strength are controlled by PRTT1 (198). Loss of PRRT1 has been reported to increase the number of synapses and decrease synaptic strength (199), leading to synaptic dysfunction in ASD. Presumably, *PRRT1* hypermethylation has the same effect.

Zhubi et al. have reported the enhanced mRNA levels of *TET-1, TET-2,* and *TET-3* (epigenetic proteins Tet methylcytosine dioxygenases), and reduced levels of DNMT1 (DNA

methyltransferase 1) in ASD brains. The increased binding of *MECP2* and *DNMT1* to the *GAD1* and *RELN* promoters could be the cause of their lowered expression in ASD patients (197). Besides, Pu et al. have shown that the C677T polymorphism in the *MTHFR* (methylenetetrahydrofolate reductase) gene is associated with an increased risk for ASD development. The MTHFR enzyme produces 5-methyl-tetrahydrofolate which has an important function in DNA methylation during the development of the neural system (200).

Likewise, Hannon et al. have analyzed the variations of methylation in the blood from 1263 infants (50% develop to ASD). They found two CpG sites located on chromosome 8 associated with later ASD (201). A genome-wide analysis of DNA methylation was performed in the blood from 50 MZ twin pairs with and without ASD. There were many differentially methylated sites associated with ASD. Moreover, significant correlations were observed between DNA methylation and quantitatively measured autistic traits between cases and controls (202). However, in a meta-analysis study of the blood from ASD subjects and controls, no single CpG site demonstrated a significant difference in DNA methylation signature was observed (203). Some studies have reported the results of methylation analysis in brain samples. For instance, in a genome-wide methylation study, 58 differentially methylated regions (DMRs) have been found in the frontal cortex of ASD subjects and healthy controls. These DMRs included GABAergic system-associated genes, such as *GABBR1* and *ABAT*, and brain-specific MicroRNAs (204). An earlier study performed by the same group (196) showed that there were many hypomethylated CpGs and hypermethylated CpGs in two cortical regions, Brodmann area 10 (BA10) and Brodmann area 24 (BA24), of ASD subjects, respectively. Hypomethylated genes, including *ITGB2* (*C3R*), *SPI1*, *TNF-α*, *C1Q*, *IRF8m*, and *C3*, were overexpressed in the ADS brains and involved in synaptic pruning and microglial cell specification, while hypermethylated genes were correlated with

synaptic membrane (196). In a recent investigation, the significant differences in DNA methylation patterns have been identified in cortical regions from idiopathic ASD patients. The results demonstrated these DMRs, associated with ASD, implicated in the neuronal regulation, synaptic signaling, and immune system (205). Although the post-mortem brain is related to NPDs such as ASD, it is not easily accessible and will be impaired by the post-mortem influences on DNA methylation. Therefore, the use of peripheral tissues like blood can be useful for the study of neurological disorders.

Furthermore, DNA methylation can control genome stability by regulating the expression of repetitive sequences like transposon elements (206). Two groups of researchers in individual studies using genome-wide Alu methylation and transcriptome profiling (207,208) reported the significantly altered Alu methylation patterns in ASD cases compared with matched controls. They suggested that the changes in the methylation pattern of Alu elements can lead to alteration of their retrotransposition, which, in turn, results to changes in the target genes and downstream molecular networks which are negatively correlated with the pathogenesis of ASD (**Fig. 4**).

Taken together, these findings have opened new perspectives for understanding the molecular mechanisms of ASD pathogenesis and identifying new epigenetic biomarkers for ASD. However, future studies of different ASD-associated loci are necessary to provide evidence for potential roles of DNA methylation status in ASD neurobiology.

Conclusions and perspective

Overall, the findings compiled in this review indicate there are significant alterations in the status of DNA methylation in patients with NPDs. DNA methylation has been discussed from various dimensions including the study of methylation patterns as peripheral biomarkers, the assessment of methylation alterations in response to treatment, and the evaluation of global and genome-wide methylation in the general population as well as, in twin studies. However, the differences, roles, and functions of DNA methylation in human diseases, especially NPDs are still a mystery. In this review, we provided a description of how DNA methylation patterns are related to various pathways involved in the neuronal system such as β-adrenergic signaling, neurogenesis, synapse formation and plasticity, synapse signaling, corticotropin-releasing hormone signaling, and glutamate receptor signaling.

A limitation of previous studies is that the studied patients received drug treatments, while these medications could influence the status of methylation. Follow-up studies can help to understand the molecular mechanisms of the drug effects on methylation levels. Another limitation of the DNA methylation investigation is the existence of changes in the methylation status across different tissues such as the brain, peripheral blood, saliva, etc. Therefore, further research is needed to confirm alterations of the DNA methylation in various tissues. In the long term, establishing cross-talk between DNA methylation and molecular knowledge of NPDs may provide deep knowledge about epigenetic biomarkers that lead to the development of novel procedures for diagnosing and treating neuronal problems.

Search strategy and selection criteria

The studies were identified by searching the PubMed/MEDLINE, Google Scholar, and Sciencedirect databases for peer-reviewed journal articles that were published by September 2019. To identify additional relevant citations, we conducted forward searches in the Web of Science database. The abovementioned databases were searched with the following combinations of keywords: “psychiatric disorder”, “neuropsychiatric”, “schizophrenia”, “bipolar”, “attention/deficit hyperactivity”, “autism”, “ASD”, and “DNA methylation”, “epigenetic change”, “DNA modification”, “methylation”, and “biomarker”. We included only references published in English within the past 5 years, except for key or landmark and case studies in the field. The final reference list was made on the basis of relevance to the theme of this review.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' contribution

I. S. conceived of and designed the study. Z. Sh. and I. S. drafted the manuscript. Z. Sh., I. S. and Z. B.H. revised the manuscript critically and contributed to drawing the figures. N.V.T. contributed to reviewing and revising the manuscript. The authors approved of the version of the manuscript to be published.

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Table 1. The list of DNA methylation studies in psychiatric diseases.

Disease	Genes	Number and Type of sample	Results	Reference
Major Depression Disorder	BDNF	peripheral blood mononuclear cells (PBMCs) from 286 patients with Depression (major or minor depressive disorder)	increased DNA methylation at BDNF. No significant methylation-genotype interactions were found.	[57]
	BDNF	Peripheral blood samples from 20 patients with major depression and 18 healthy controls	Differentiation based on the DNA methylation profiles of CpG I of the BDNF gene may be a valuable diagnostic biomarker for MDD.	[193]

	BDNF	Serum samples from 65 patients with recurrent MDD and healthy controls.	Higher levels of BDNF promoter methylation may be closely associated with the reduced cortical thickness among patients with MDD.	[58]
	LINGO3, POU3F1, and ITGB1	Postmortem brain samples from 78 human subjects and from 24 rodent model of the impact of early-life environment	decreased DNA methylation in the LINGO3 and POU3F1	[61]
	ID3, GRIN1, and TPPP	Saliva samples from 94 children with depression and 96 healthy children	DNA methylation changes in ID3, GRIN1, and TPPP genes may confer risk for depression in children.	[62]

	SLC6A4 (5HTT)	lymphoblast cell line	methylation at this CpG in the 5′ region of gene associated with decreased levels of 5HTT mRNA	[72]
	SLC6A4 (5HTT)	Whole blood from 33 adult patients with MDD and 36 healthy controls	Greater 5HTT methylation in the depressed patients	[73]
	5-HTT	Blood samples from 94 patients MDD	DNA hypomethylation of the 5-HTT might impair antidepressant treatment response in Caucasian patients with MDD.	[74]
	OXTR	Blood from 269 cases with Postpartum depression (PPD) and 276 controls	There was an interaction between rs53576 and methylation in the OXTR gene amongst women who did not have depression	[79]

			prenatally but developed PPD	
	OXTR	43 depressed women recruited and 42 healthy, female subjects	female patients with MDD had decreased DNA methylation of OXTR at exon 1 compared to healthy controls. The association between depression and methylation level was regulated by OXTR rs53576 genotype.	[80]

	NR3C1	saliva samples from 181 mothers and infants	The methylation of NR3C1 promoter in infants is elevated in the presence of increased maternal postnatal depression following low prenatal depression	[77]
Bipolar disorder	PDYN and BDNF	post-mortem brain of 35 individuals, and 21 PBMCs from of these subjects.	increased DNA methylation at PDYN promoter and reduction of PDYN gene expression, higher methylation levels in PBMCs (82%) than in the brain tissues	[88]
	PDYN and BDNF	peripheral blood mononuclear cells from 99 BD-I and BD-II, and from 42 healthy controls	increased DNA methylation and reduction of PDYN and BDNF gene expression. A significantly positive correlation in promoter DNA methylation was observed in all subjects	[82, 87, 97]

		between PDYN and BDNF	
COX-2 and BDNF	postmortem frontal cortex from 10 BD and 10 AD patients and 10 controls per group	hypo- and hypermethylation of CpG islands in COX-2 and BDNF promoter regions, respectively.	[98]
BDNF	peripheral blood mononuclear cells from 207 MDD subjects, 59 BD subjects and 278 control subjects.	The BDNF exon I promoter methylation resulted to be significantly increased in MDD cases compared to BD cases and control subjects	[99]

MB-COMT	115 post-mortem brain samples from the frontal lobe of schizophrenia and bipolar disorder patients, compared with the controls	increase in transcript levels of MB-COMT in schizophrenia and bipolar disorder patients compared with the controls	[100, 101]
MB-COMT	saliva from 20 SCZ, 20 BD and 25 control subjects.	Reduction of DNA methylation of MB-COMT gene promoter and an increased gene expression methylation	[101]
5-HTR1A and 5-HTT	post-mortem brains from 35 controls, 35 SCZ and 35 BD, and 100 saliva samples from 30 controls, 30 SCZ, 20 BD and 20 first degree relatives of SCZ or BD	increased DNA methylation and reduction of gene expression	[102, 103]

GAD1 regulatory network genes	Postmortem human hippocampus tissue samples from 8 patients with schizophrenia, 8 patients with bipolar disorder, and 8 healthy control	Within the GAD1 regulatory network, 146 sites were differentially methylated	[104]
FKBP5	peripheral blood cells	increased DNA methylation	[108, 109]
HCG9	22 postmortem prefrontal cortex samples from SCZ patients; 27 samples from BPD patients; and 32 samples from controls	significant differences in DNA modification at CpG 29, located in the second intron of HCG9, between BPD and controls	[110, 111]

HCG9	post-mortem brains, peripheral blood cells and germline (sperm)	Two brain tissue cohorts showed lower DNA methylation in bipolar disease patients compared with controls	[112]
RELN	caudate nucleus (CN) and putamen (PT) tissues from 27 NPS, 20 SZP, 14 BP individuals	Hypermethylation of GAD67 and reelin promoter, downregulation.GAD67 and reelin transcription, increase of DNMT1 expression in GABAergic neurons of SZ and BDP patients	[114]
DTNBP1	Frontal-Cortex Brain-Tissue Samples from 35 SZP, 35 BP, ana 35 controls	increased DNA methylation	[115]

KCNQ3	post-mortem brains from 35 SCZ and 35 BD patients, and 35 controls	Reduction of DNA methylation and increased expression, BD patients with psychotic depression exhibited higher degree of methylation versus other BD patients	[116]
PPIEL	lymphoblastoid cells derived from the twins (16 BPI patients, 7 BPII patients, and 18 control subjects)	higher DNA methylation level in female BD patients compared with control females. In PPIEL, DNA methylation level was significantly lower in BPII patients than in controls. The expression level of PPIEL was significantly higher in bipolar II disorder than in controls.	[194]

FAM63B	blood samples from 459 BP cases and 268 controls.	Reduction of DNA methylation in BD cases compared to controls and increased expression	[195]
genome-wide DNA methylation	postmortem frontal cortex	global hypermethylation	[98]
genome-wide DNA methylation	lymphoblast's and whole blood	global hypomethylation	[119, 120]
genome-wide DNA methylation	leukocytes	no differences in global methylation	[121]
genome-wide DNA methylation	different post-mortem brain regions	differentially methylated	[122, 123, 171]

	genome-wide DNA methylation	blood	differentially methylated	[124-126]
Schizophrenia	RELN and GAD67	occipital cortex samples from 10 SZP patients and 10 healthy controls	There was increased methylation at positions -134 and 139, which is particularly important for regulation	[130, 131]
	RELN	prefrontal cortices samples from 14 SZP patients and 13 control	No detectable DNA methylation was observed in both gray and white matter	[115, 196]
	SOX10	Postmortem prefrontal cortices from 13 SZP and 15 healthy controls	CpG island of SOX10) was highly methylated in brains of SZP patients correlated with reduced expression of SOX10	[134]

	COMT	115 post-mortem brain samples from the frontal lobe of schizophrenia and bipolar disorder patients, compared with the controls	increase in transcript levels of MB-COMT in schizophrenia and bipolar disorder patients compared with the controls	[100]
	COMT	60 post mortem cerebellum samples from SZP individuals, bipolar disorder, depression, and no history of psychopathology	no differences in COMT methylation patterns and expression in any of the psychiatric diagnoses examined.	[137]
	FOXP2	postmortem brain from 293 SZP patients and 340 controls.	In patients, there was hypermethylation in the left parahippocampus gyrus than in the right one.	[138]

	HTR2A	post-mortem brains of with 35 SZP and 35 BP patients and 35 control subjects	expression of HTR2A in individuals carrying the C allele of T102C was higher than TT genotype. DNA hypermethylation of HTR2A was at and around the -1438A/G polymorphic site, but was hypomethylated at and around T102C polymorphic site in SZP and BP compared to the controls.	[139]
	RELN and FAM63B	peripheral leukocytes from 24 SZP patients and 23 healthy controls	Reduced DNA methylation in SCZ at numerous loci across the whole genome in peripheral leukocytes	[140, 141]
	ST6GALNAC1	peripheral blood from 11 SZP twins and 11 BP twins	numerous DNA methylation differences associated with both SZP and BP	[129]

	GABRB2	Leukocytes from 150 schizophrenia and their parents (150 mothers; 150 fathers)	increased methylation in the neighborhood of SNP rs1816071, and methylation differences between SZP patients and controls.	[143]
	5HTR2A	saliva samples	CpGs of the −1438A/G polymorphism site, −1420 and −1223 were >95% methylated. The CpG at T102C polymorphic site and neighboring CpGs were ~70% methylated both in the patients and controls.	[197]

	COMT	saliva from 20 SCZ, 20 BD and 25 control subjects.	Reduction of DNA methylation of MB-COMT gene promoter and an increased gene expression methylation	[101]
Attention-deficit/hyperactivity disorder (ADHD)	VIPR2 and MYT1L	saliva from two sets, a discovery set (46 ADHD, 46 control) and a confirmation set (10 ADHD, 10 Controls).	Reduced CpG methylation in the saliva of children with ADHD	[152]
	NR3C1, MTHFR, DRD4 and 5-HTT, IGF2DMR, H19, and KCNQ1OT1	Blood from 426 children	Reduced DNA methylation levels of the 7 genes were associated with more ADHD symptoms	[159]
	genome-wide DNA methylation	blood	differentially methylated sites	[151]

Autism spectrum disorder	PRRT1 and TSPAN32	cerebellum and temporal cortex of brains from 19 autism cases and 21 controls	reduction of DNA methylation	[180, 181]
	ITGB2 (C3R), SPI1, TNF-α, C1Q, IRF8m and C3,	Brain tissue samples from 13 autism cases and 12 controls	reduction of DNA methylation, there is an inverse correlation between gene expression and DNA methylation within the individuals	[181]
	genome-wide DNA methylation	blood from 1263 infants	differences in neonatal DNA methylation associated with later ASD, there was a significant association between increased polygenic burden for autism and methylomic variation at specific loci.	[186]

genome-wide DNA methylation	blood from 50 MZ twin pairs of ADHD	differentially methylated sites, significant correlations between DNA methylation and quantitatively measured autistic trait scores across	[187]
genome-wide DNA methylation	frontal cortex	differentially methylated sites	[189]
genome-wide DNA methylation	cortical regions	differentially methylated sites	[190]

Figures

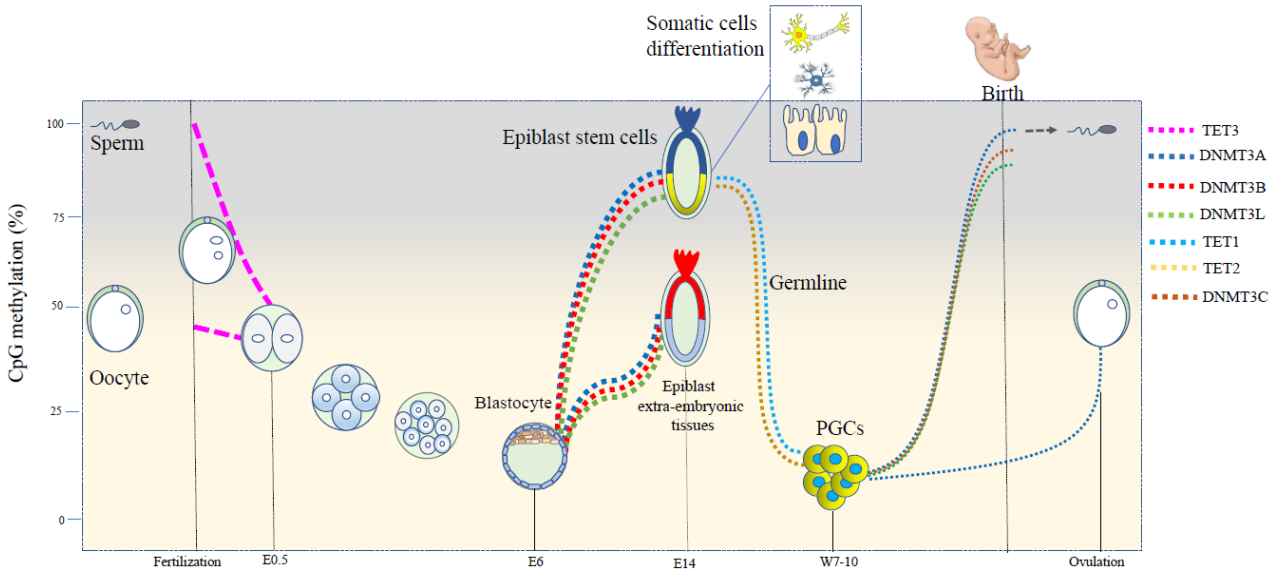

Figure 1. **Human embryonic and germline DNA methylation reprogramming**. The methylcytosine dioxygenase TET3 is active in the fertilized zygote, leading to hydroxymethylation and active DNA demethylation. Following passive demethylation (dashed line), DNA methylation has the lowest level at the blastocyst phase, which is followed by DNA (cytosine-5)-methyltransferase 3A (DNMT3A)-mediated and DNMT3Bmediated *de novo* DNA methylation after blastocyst implantation. In addition, DNMT3L is expressed at this point but is not critically essential to methylate the embryonic DNA. In extra-embryonic tissues, DNMT3A, DNMT3B, and DNMT3L are expressed less than in the embryo proper, which associates with relative DNA hypomethylation. After implantation, in the epiblast, a population of stem cells is specified for the germline, where they undergo two stages of DNA demethylation: one passive and one mediated by TET1 and TET2. Male gametes become highly methylated before birth through the activity of DNMT3A and DNMT3L. The oocyte gains methylation after meiosis and before ovulation through the activity of DNMT3A.

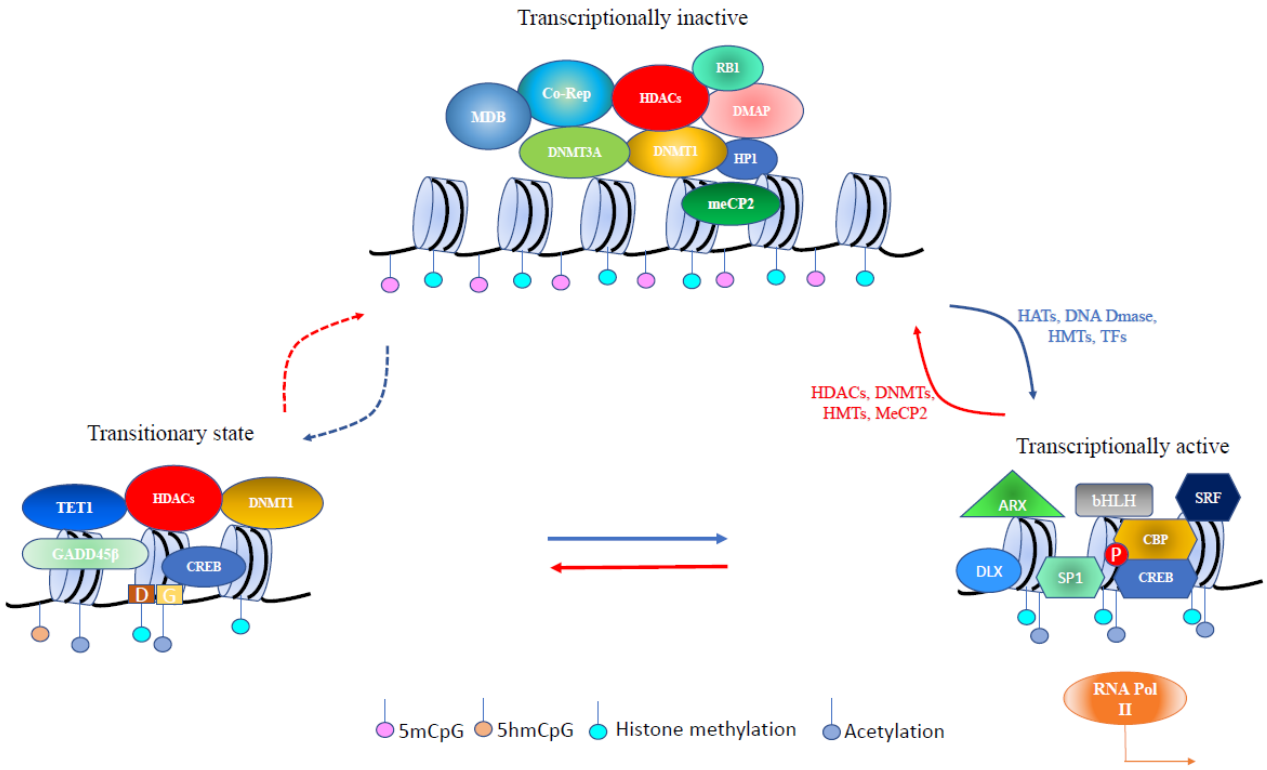

Figure 2. DNA- and histone-binding proteins mediate modifications of the chromatin status. This illustration depicts the transitions between a transcriptionally inactive state (left) and a transcriptionally active state (right). The transcriptionally inactive state is identified by DNA methylation and the binding of multiple inhibitory proteins, such as DNA methyltransferase 1 (DNMT1) and 3A, methyl-binding domain proteins (MBDs, MeCP2), co-repressors, and modified histones related to repressive chromatin marks (e.g. H3K9me2, H3K9me3, H3K27me2, H3K27me3). In the intermediate state, the DNA/protein complex is determined by the binding of DNMT1 to unmethylated CpGs and ten-eleven translocase-1 (TET-1) bound to 5-methylcytosines (5mCs) and 5-hydroxymethyl cytosine (5hmCs). In the transitional state, DNMT1 is bound to histone deacetylases (HDACs) and excess DNMT3A transforms that to the inactive state (left). The binding of TET1 to hydroxymethylated CpGs in the intermediate state supports stable suppression until the entrance of GADD45b, which employs proteins necessary for DNA

demethylation (deaminases and glycosylases). DNA demethylation is escorted by extra histone modifications (mediated by HATs and HMTs). Hydroxymethylated CpGs are additionally modified and removed. In this model, HDAC inhibitors enhance the disruption of the inactive state and depending on the availability of GADD45b, DNA demethylation arises. In the active (open) state, various transcription factors (TFs) bind and occupy their specific DNA recognition sites enabling transcription. Some of the transcription factors are shown bound to the intermediate state (such as CREB, which upon phosphorylation (P) recruits the histone acetyltransferase CBP). Transcriptionally active promoters are represented as an open chromatin structure characterized by the presence of acetylated (H3K9ac, H3K14ac) and methylated (eg, H3K4me1, H3K4me3, H3K9me1, H3K27me1, H3K79me1, etc) histones. The model highpoint repressive roles for DNMT1 and TET1, which depends upon the availability of accessory proteins (DNMT3A and GADD45b, respectively) to modify their function in postmitotic neurons. Based on localization studies of DNMT1 in GABAergic neurons and GADD45b in pyramidal neurons, these mechanisms are likely unique to specific types of neurons depending on the neurotransmitter phenotype. ARX, aristaless-related homeobox; bHLH, basic helix-loop-helix transcription factors; CBP, CREB-binding protein; Co-Rep, co-repressor proteins; CREB, cyclic AMP response element-binding protein; D, deaminase; DLX, distal-less homeobox; DMAP1, DNA methyltransferase 1-associated protein; DNA DMase, DNA demethylase; G, gycosylase; HATs, Histone acetyl transferases; HMTs, histone methyl transferases; HP1, hetrochromatin protein 1; me1, monomethyl; me2, dimethyl; me3, trimethyl; MeCP2, methyl CpG-binding protein 2; P, phosphoryl group; RB1, retinoblastoma 1; SP1, promoter-specific transcription factor; SRF, serum response factor; TFs, transcription factors.

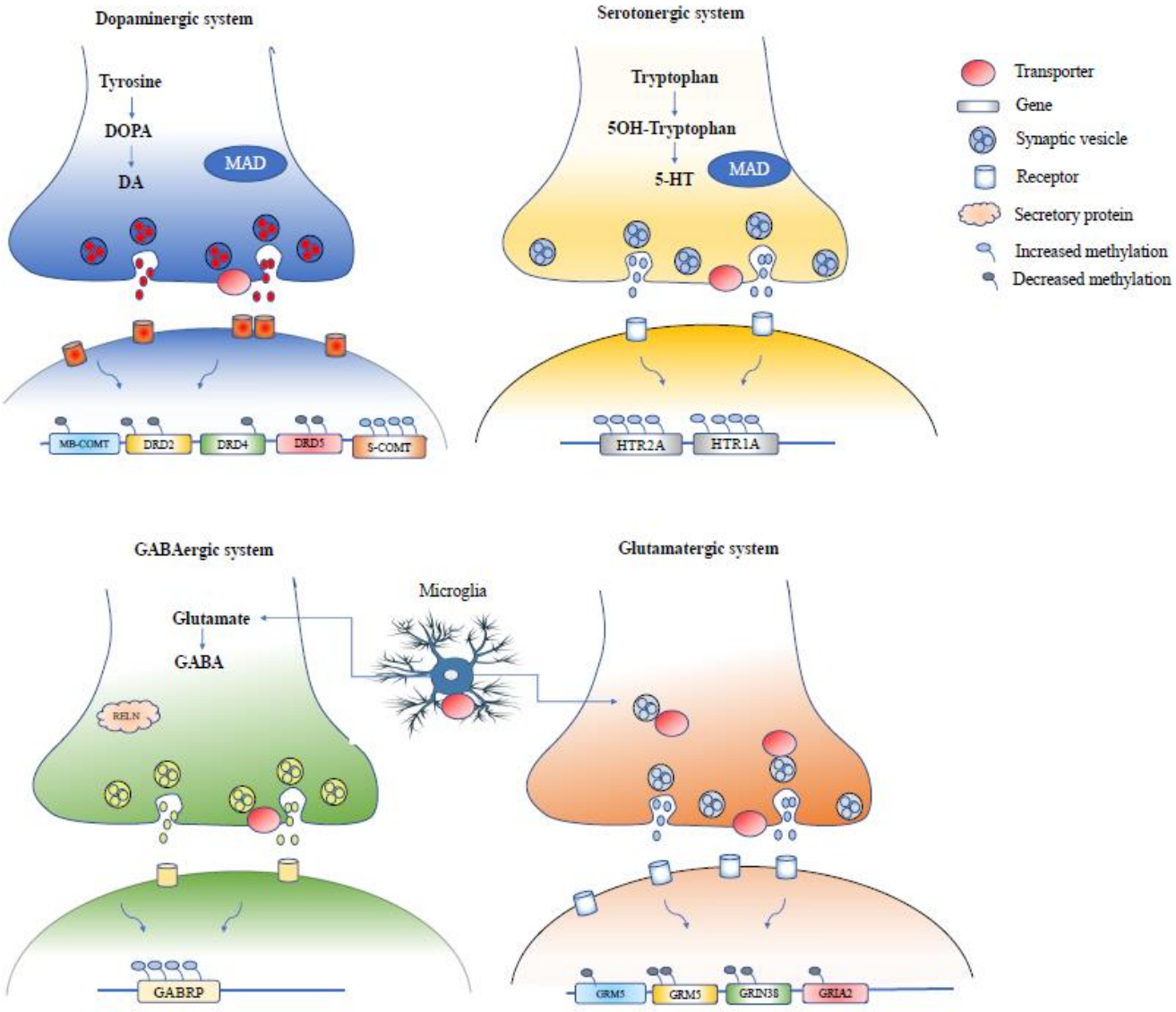

Figure 3. A schematic illustration of the DNA methylation changes on genes associated with the neurotransmitters in SZ and BD.

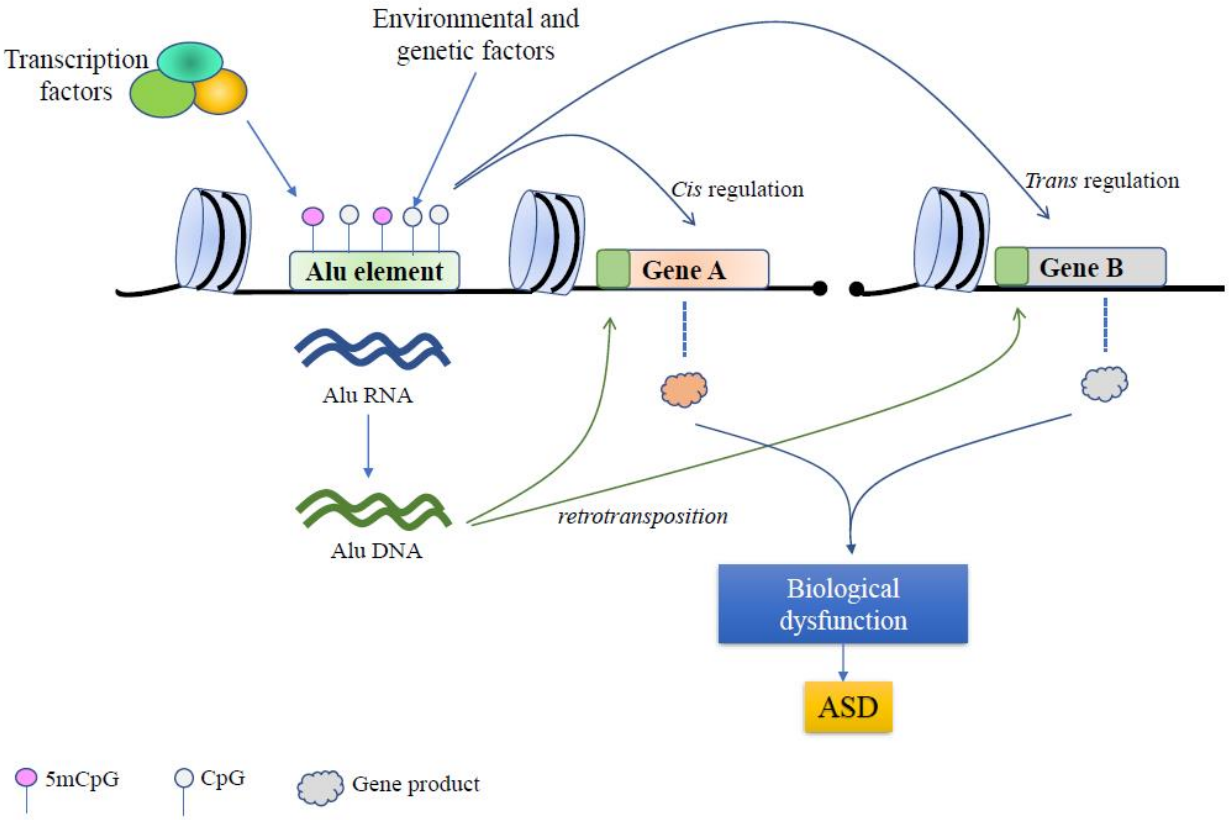

Figure 4. **A schematic representation of the role of Alu elements methylation in ASD**. This model explains that exposure to environmental factors or disturbance of other DNA methylation regulatory mechanisms results in alteration of DNA methylation status in Alu elements. These alterations in transcription factor binding and, possibly in combination with other Alu regulatory mechanisms, lead to the disturbance of the expression and retrotransposition of Alu elements. Dysregulated Alu retrotransposition affects the target genes through cis- or trans-regulatory mechanisms, which, in turn, change gene expression and gene regulatory mechanisms negatively associated with ASD pathogenesis.