EPIGENOMICS
2026, VOL. 18, NO. 1, 137–150
https://doi.org/10.1080/17501911.2025.2572960

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REVIEW

Epigenomic alterations in psychiatric disorders and glioblastoma

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ABSTRACT

Brain disorders are among the most debilitating, costly and therapeutically challenging conditions worldwide. Therefore, there is a growing need for identification of biomarkers to support diagnostic, prognostic and therapeutic procedures. Technological advances are enabling increasingly precise, high-throughput profiling of epigenetic modifications, and the potential reversibility of epigenetic marks makes them a promising target for therapeutic intervention. Recent research on *in-vitro* models, *post-mortem* brain samples and peripheral tissues from living individuals has suggested that epigenetic mechanisms are involved in the pathogenesis of chronic mental illnesses, functioning as distal or proximal risk factors and mediating the long-term effects of environmental stressors on brain function. In brain cancers, including the highly lethal glioblastoma, epigenetic dysregulation (especially DNA methylation patterns) is already implicated in tumor classification as it contributes to cellular heterogeneity and may drive tumor progression. This review examines the multifaceted role of epigenomic regulation of brain gene expression, focusing on psychiatric disorders and primary brain malignancies such as glioblastoma. We summarize the technological advances that have enabled high-throughput and high-resolution exploration of the epigenome. Furthermore, we present the current knowledge of epigenomic signatures that may contribute to brain pathology and discuss their potential for biomarker discovery and the advancement of personalized medicine.

PLAIN LANGUAGE SUMMARY

Brain disorders are one of the most difficult problems in medicine. Epigenetics provides new pointers for their diagnosis and treatment. Epigenetics studies switching gene expression on or off without changing the DNA itself. Such changes are not permanent and can be influenced by the surroundings. New technology allows researchers to study epigenetic changes in human solid tissues, blood and cerebrospinal fluid. In psychiatric disorders, epigenetic changes can explain how stress affects brain function. In brain cancers, epigenetic changes like DNA methylation are used for diagnosis and classification. Here we explain how epigenetic changes help us understand brain function and disease. We also discuss how they point the way to more precise patient treatment.

ARTICLE HISTORY
Received 31 July 2025
Accepted 7 October 2025

KEYWORDS
Glioblastoma; major depressive disorder; schizophrenia; suicide; DNA methylation; non-coding RNA; histone modification; multiomics

1. Introduction

In the mammalian brain, complex developmental patterning and hardwiring of cells into stable functional networks must be orchestrated with a high level of plasticity to adapt to a constantly changing environment [1]. To meet these demands, the brain relies heavily on precise and dynamic epigenetic regulation. During neurodevelopment, cells acquire distinct epigenetic signatures that influence DNA accessibility and thus regulate cell type-specific gene expression. The term "epigenetics" refers to heritable DNA modifications that influence gene function without altering the underlying DNA sequence and are responsive to environmental stimuli. Typical mechanisms involve DNA methylation, post-translational histone modifications, chromatin remodeling and non-coding RNA-mediated gene regulation. These mechanisms have distinct influences on neuronal function, including neurotransmission and long-term potentiation [2]. It has been demonstrated that epigenetic dysregulation can disrupt neurodevelopment, immune response, memory formation and synaptic function, contributing to the development of various neuro- and psychopathologies [3].

The significance of psychiatric disorders extends beyond individual suffering toward public health implications. Psychiatric conditions, including major depressive disorder, bipolar disorder, and post-traumatic stress disorder, are associated with an increased suicide risk through various neurobiological mechanisms [4]. A recent study on suicide trends between 1990 and 2020 showed that, despite geographical variations, suicide remains a major global concern. While in most European countries, suicide rates are declining, significant increases were reported in the United Kingdom and non-European regions, including Asia and the United States. Suicide rates also differ between sexes: suicide rates in men are 2 to 5 times higher than in women. However, due to possible underreporting of suicide deaths, interpretation of these patterns should be approached with caution [5].

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Article highlights

- Epigenetic changes disrupt neuronal, immunological and developmental pathways in both psychiatric disorders and brain tumors.
- New technologies enable high-resolution, multi-omic, and spatial epigenomic studies of brain disorders.
- Epigenetics links neurodevelopment and immune signaling to the risk of psychiatric disorder risk across the lifespan.
- Glioblastoma shows immune pathway hypermethylation and therapy resistance.
- Epigenetic plasticity influences response to therapies in psychiatric disorders and glioblastoma, with drugs targeting DNA methylation and histone modifications showing promise.

In this review we address the hypotheses that epigenomic alternations disrupt neuronal, immunological, and developmental pathways, leading to development of psychiatric disorders (including suicidality) and glioblastoma. Key signaling pathways (Notch, Hedgehog, Wnt), normally regulated by chromatin dynamics, are disrupted across psychiatric conditions and glioblastoma; epigenetic flexibility in both psychiatric disorders and glioblastoma influences responses to pharmacological and immunological therapies.

1.1. Types of epigenetic modifications

DNA methylation is the most characterized epigenetic modification and the most commonly assessed in clinical samples. The addition of a methyl group at the 5-position of cytosine within CpG dinucleotides usually leads to gene silencing by preventing transcription factor binding to promoters. DNA methylation of the gene bodies associates either with increased or repressed gene expression, largely depending on the context [6]. Methyl-CpG-binding proteins also bind methylated DNA and recruit co-repressors to silence transcription. DNA methyltransferases (DNMTs), enzymes that methylate DNA, are responsible for maintenance (DNMT1) of methylation and *de novo* methylation (DNMT3a and DNMT3b). An additional level of DNA methylation complexity is associated with DNA methylation outside of the CpG positions. Already in embryonic stem cells DNA methylation can occur at dinucleotides where C is followed by A, C or T as well as CpG dinucleotides, but methylation of the non-CpG sites is mostly lost during differentiation [7]. Non-CpG methylation seems to be particularly characteristic for brain tissue and in the adult frontal cortex the non-CpG sites are present in significant numbers and were shown to be highly reproducible among different subjects [8]. In human brain, an oxidized form of DNA methylation – hydroxymethylation – is abundant. At first hydroxymethylation was understood as a step in DNA demethylation but further research showed that it plays an active role in regulation of gene expression and development of the brain [7].

Histones, the protein complexes around which DNA is wrapped to form nucleosomes, are also involved in the regulation of gene transcription. Post-translational modifications of histone tails (e.g., acetylation, methylation, ubiquitination) influence chromatin compaction. Histone acetylation by histone acetyltransferases (HATs) leads to the opening of chromatin structure, which facilitates transcription factor binding. In contrast, histone deacetylation by histone deacetylases (HDACs) represses transcription. Histone methylation on lysine and arginine residues can involve the addition of multiple methyl groups, resulting in a complex range of effects on gene regulation. Nucleosome positioning, and thus transcription, can also be altered by nucleosome remodeling complexes [9].

Among gene expression regulators are also non-coding RNAs (ncRNAs), a heterogeneous group of RNA molecules that are not translated into proteins. Both in cancer and neuropsychiatry, the most examined ncRNA type are microRNAs (miRNAs), which bind to the 3′ untranslated region of partially complementary mRNAs and cause target degradation or repression of translation. In some instances, miRNAs can also upregulate translation or switch between these two effects, depending on the cell cycle [10].

2. Emerging technologies in brain epigenomics

Research on brain disorders has traditionally relied on *post-mortem* brain samples, and until recently, the processes involved in embryonic and fetal human brain development remained largely inaccessible *in vivo*. *Post-mortem* tissue has major limitations, including difficulties in controlling for confounding factors (e.g., molecular changes due to the *post-mortem* interval, incomplete clinical histories), often small cohort sizes and the absence of longitudinal data on disease trajectories. The validity of translating these findings to tissues *in vivo* is unclear [11]. Therefore, there is a growing emphasis on utilizing integrative, high-resolution methods on well-defined cohorts to elucidate the molecular pathology of specific cases diagnosed with brain disorders. Recent technological developments have also enabled the investigation of developmental windows that were previously inaccessible in humans [12].

The term “epigenomics” refers to the genome-wide profiling of epigenetic modifications, enabled by advances in high-throughput sequencing technologies. Figure 1 presents an overview of established and emerging epigenomic methods. Accurate long-read sequencing has expanded the capacity to detect DNA methylation directly and comprehensively, as it can generate longer reads of single native DNA molecules without the need for amplification, and can therefore assess multiple epigenetic modifications along a single chromatin fiber within one continuous read. Novel assays have been developed for analyzing chromatin states, integrating data on DNA methylation, chromatin accessibility, transcription factor binding and histone modifications. Long-read methods are also applied in multi-omics studies to investigate the relationship between chromatin states and transcriptional dynamics [13].

The development of various single-cell epigenomic methods followed by sequencing has enabled the exploration of dynamic and transient biochemical processes that constitute neurodevelopmental trajectories. Among such methods are: single-cell Assay for Transposase-Accessible Chromatin (scATACseq), single-cell chromatin immunoprecipitation

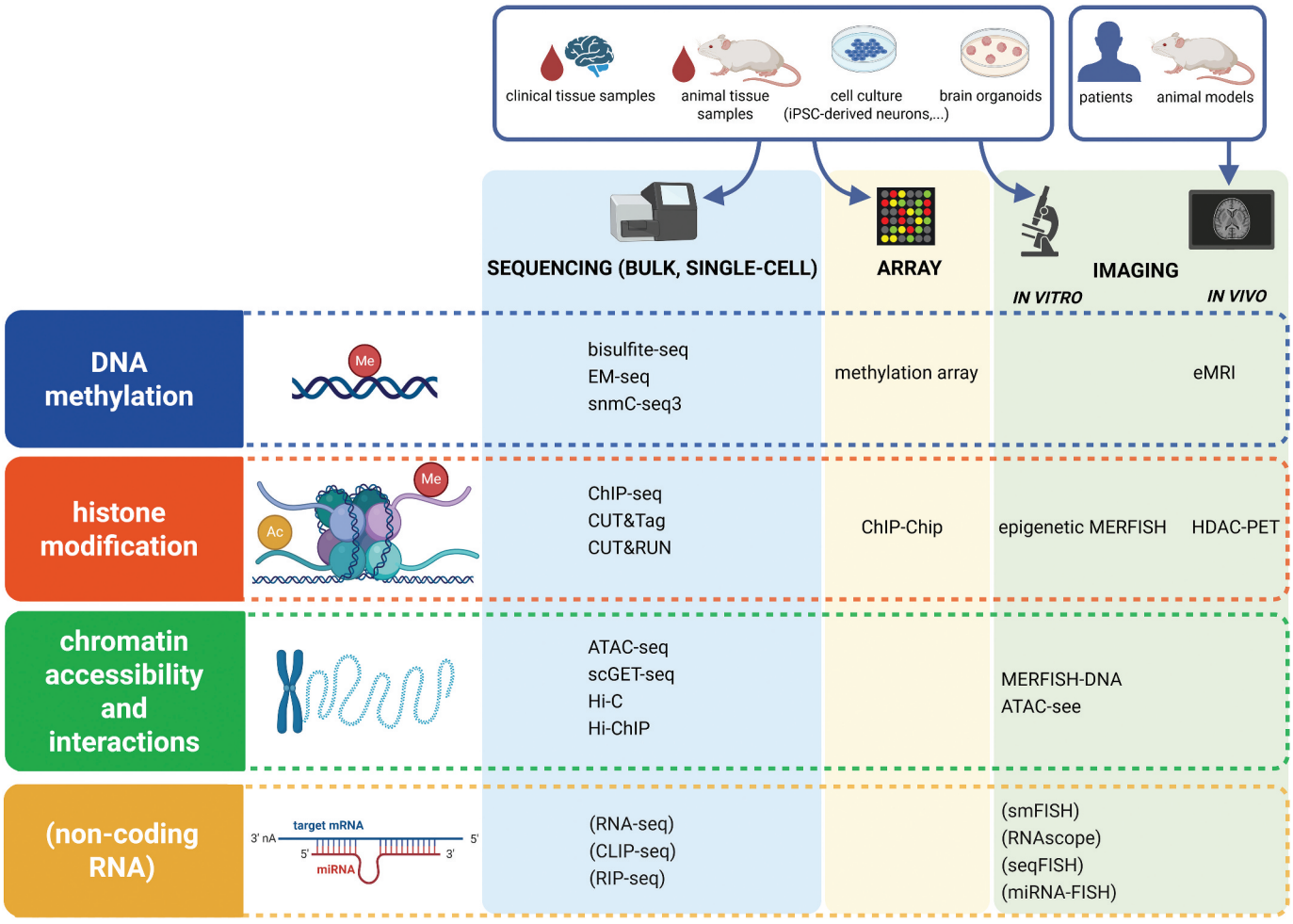

Figure 1. Overview of epigenomic methods. This figure presents experimental techniques that profile different layers of the epigenome (rows on the left), including DNA methylation, histone modifications, chromatin accessibility, and non-coding RNA levels. The presented techniques can be applied to various biological sources, including clinical samples. Techniques are grouped by methodological approach (columns), and the majority of techniques that include sequencing have been adapted for the single-cell level. Brackets indicate techniques that are not strictly epigenomic, but transcriptomic and relevant for examining non-coding RNAs. Compared to bisulfite sequencing, the newer method of enzymatic methyl sequencing (EM-seq) is less damaging to DNA, can also assess 5-hydroxymethylcytosine, and requires lower input. Single-nucleus methylation sequencing (snmC-seq3) enables epigenomic profiling of individual nuclei from complex tissues, such as brain tissue. Array-based methods are less frequently used in epigenomic research as they are limited to predefined probes. Chromatin immunoprecipitation sequencing (ChIP-seq) is a standard method for the genome-wide identification of histone modifications and histone-DNA interactions. In comparison, newer techniques, including CUT&Tag and CUT&RUN, require less sample input, provide better resolution and are more cost-effective. Assay for transposase-accessible chromatin with sequencing (ATAC-seq) detects open chromatin regions across the genome, while chromosome conformation capture with sequencing (hi-C) is better suited for examining 3D genome architecture. Single-cell gene expression and trait sequencing (ScGET-seq) simultaneously profiles gene expression and chromatin accessibility. Hi-ChIP combines features of hi-C and ChIP-seq to detect chromatin interactions, such as enhancer – promoter loops, mediated by specific histone modifications. Epigenomic MERFISH is an adapted version of MERFISH (multiplexed error robust fluorescence in situ hybridization), a technique for multiplexed RNA imaging in individual cells, that also allows imaging of histone modifications. *in vivo* epigenetic imaging methods, including epigenetic MRI, are not yet widely used in epigenomic research due to their high cost and low resolution. Created in BioRender. Šmon, J. (2025) https://biorender.com/qr89k5u.

Abbreviations: iPSC: induced pluripotent stem cell; Seq: sequencing; EM-seq: enzymatic methyl sequencing; SnmC-seq3: single-nucleus methylation sequencing; ChIP-Seq: chromatin immunoprecipitation with sequencing; ChIP-Chip: chromatin immunoprecipitation on chip (microarray); CUT&Tag: Cleavage Under Targets and Tagmentation; CUT&RUN: cleavage under targets and release using nuclease; ATAC-seq: assay for transposase-accessible chromatin with sequencing; scGET-seq: Single-cell genome and epigenome by transposases sequencing; Hi-C: chromosome conformation capture with sequencing; Hi-ChIP: chromosome conformation capture and chromatin immunoprecipitation with sequencing; CLIP-seq: cross-linking and immunoprecipitation with sequencing; RIP-seq: RNA immunoprecipitation and sequencing; eMRI: epigenomic MRI; MERFISH: multiplexed error robust fluorescence in situ hybridization; HDAC-PET: histone deacetylase positron emission tomography; smFISH: single-molecule fluorescence in situ hybridization; miRNA: microRNA.

(scChIPseq), single-cell Cleavage Under Targets and Tagmentation (scCUT&Tag), single-cell High-throughput Chromosome Conformation Capture (scHiC), and single-cell bisulfite sequencing. Parallel profiling across multiple molecular layers, including genomic, transcriptomic, proteomic, and epigenomic (e.g., multi-omics), is likely to prove even more informative. However, these methods have lower throughput compared to single-omics assays, and integrating this data remains challenging [14,15]. Incorporating spatial context, e.g., by combining spatial transcriptomics with epigenomic profiling, has enabled the construction of spatiotemporal atlases of the developing human brain [16] and is increasingly used to explore cell-type-specific gene regulation and regionally distinct epigenetic alterations in both brain cancer and psychiatric disorders [17,18]. As the brain is difficult to dissociate into intact cells, isolating nuclei better preserves the integrity of the epigenome, and methods such as single-nucleus methylation sequencing (snmC-seq3) allow high-resolution mapping of interactions between chromatin organization and DNA methylation. The overlap between chromatin loop-

connected, cell-type-specific regulatory regions and common genetic risk variants associated with various disorders (e.g., schizophrenia) may help identify mechanisms by which genetic variations contribute to disease development [19]. Recently, the epigenomic multiplexed error robust fluorescence *in situ* hybridization (MERFISH) method, an imaging-based method for the visualization of spatiotemporal epigenomics at the single-cell level, was used to map active promoters and putative enhancers in mouse brain [20]. Improved *in vitro* models, including human induced pluripotent stem cells (iPSC)-derived neurons and iPSC-derived brain organoids, offer ethically acceptable platforms for large-scale research of neural processes and are increasingly being used in concert with multi-omic tools to model neurodevelopment under controlled conditions [21].

Noninvasive imaging techniques may enable *in vivo* monitoring of epigenetic changes in human tissues. For example, epigenetic MRI (eMRI) offered noninvasive visualization of regional DNA methylation in newborn pigs *in vivo* [22]. Positron emission tomography (PET) imaging of chromatin-modifying enzymes can track histone deacetylation in real-time in the human brain [23]. In future research, the use of peripheral tissues from living participants and integrating multi-omic data with detailed clinical, behavioral, and imaging data will be essential for enhancing the replicability and predictive value of research on brain disorders [24].

3. Developmental and immune pathways in psychiatric disease risk

3.1. Neurodevelopment, environmental influences and epigenetic modulation in psychiatric disorders

Development of the human brain extends over a prolonged period; it starts in the prenatal stage at about 3 weeks, and is completed when an individual comes to its fourth decade [25]. Critical periods of brain development are the prenatal period and adolescence. During fetal development and in early childhood, synaptogenesis is reinforced, followed by synaptic pruning occurring during adolescence [26]. The brain's development is based not only on the genetic blueprint, but is modified by environmental factors, such as sensory stimuli, parent-child relationships, stress, and psychoactive substances, through epigenetic mechanisms. An interesting natural 'experiment' showing the impact of epigenetic mechanisms are monozygotic twins. These are born with identical genetic makeups, but during their life they are exposed to different environmental stimuli leading to manifestation of different (disease) phenotypes. Studies on schizophrenia highlight genetic factors as the most important in the etiology of disease, but monozygotic twins show only 50% concordance for the disease with environmental factors playing a modulating role [27].

DNA methylation patterns in somatic cells are established very early – just after fertilization. Initially they are erased from the pre-implantation embryo, which means that the time surrounding conception is likely a critical window for influencing DNA methylation. Therefore, environmental exposures before and during conception could influence individual's health later in life [28]. In human history some adverse events, like famines with well-defined duration (e.g., the Dutch Hunger Winter of 1944–45), provided evidence that prenatal famine has effects on disease incidence, which could be linked to DNA methylation changes of certain genes, like *IGF2* [29]. More specific effect of early-life adversity (ELA) on DNA methylation has been shown for genes of the hypothalamic-pituitary-adrenal (HPA) axis, which is crucial for stress regulation; its increased and prolonged activity has been associated with depression [30]. In rodent models [31] and in humans [32], increased DNA methylation of the glucocorticoid receptor gene (*NR3C1*) and subsequently lower expression of mRNA was determined to be due to ELA. Another important mediator of gene – environment interactions in stress-related psychiatric disorders is the FK506-binding protein 5 gene (FKBP5), encoding a co-chaperone molecule that modulates various signaling pathways in response to stress, including the HPA axis (33). ELA can interact with genetic variation in FKBP5 to influence the risk of disease development by altering transcriptional regulation. Mechanistically, stress-induced demethylation of glucocorticoid-responsive elements in introns 2, 5, and 7 of this gene has been shown to increase its transcriptional responsiveness to glucocorticoids (34). In animal models and studies on human postmortem brain tissue, increased FKBP5 transcription in the brain has been linked to maladaptive behavior and psychiatric disorders (35), including suicide (36). Alcohol, caffeine and tobacco also influence fetal growth [28] and have effects on DNA methylation and on adolescent substance use [33]. In addition, immune activation during pregnancy due to maternal viral infections has been linked to different neurobehavioral phenotypes. Increased risk for schizophrenia in the offspring has been associated with maternal virus infections with influenza and herpes simplex [34]. In animal models, the effect of viral infection with viral mimetic poly(I:C) was studied. It showed an important effect on the GABAergic system, further affecting cognitive and behavioral abnormalities whereby viral infection increased DNA methylation and hydroxymethylation of the *GAD1* and its isoform *GAD2* that code the enzyme glutamic acid decarboxylase (GAD). Methylation changes were associated with increased binding of methyl CpG-binding protein 2 and decreased gene expression. The infection-causing *GAD1* DNA methylation changes were correlated with impairments in working memory and social interaction [35].

Differences in DNA methylation patterns between sexes have been determined in variety of diseases [36], including in brain disorders. An important gene for maintaining brain plasticity is brain-derived neurotrophic factor (*BDNF*). Its altered expression and DNA methylation patterns have been associated with depression, schizophrenia, anxiety [37] and even suicidality [38]. Sex-specific patterns of *BDNF* methylation showed higher methylation in female schizophrenia patients compared to males [39]. Another important aspect of sex-specific epigenomic regulation is reproductive senescence, for example menopause. Menopause has been linked to an acceleration of epigenetic aging patterns, including global DNA hypomethylation [40]. In animal models, age-related DNA-methylation changes and gene expression patterns of genes involved in hormone signaling, glutamate signaling,

and melatonin and circadian pathways in hypothalamus occurred before the manifestation of perimenopause. These changes could contribute to understanding of the neurological symptoms associated with perimenopause [41].

3.2. Neuroimmune interactions in psychiatric disorders

Recently, the field of research into psychiatric and neurological disorders has been expanding. One of the important areas of study is immunology and the links between the immune response and the development and course of mental disorders – immunopsychiatry. The term "immune privilege" was coined in the 1940s by the renowned biologist Peter Medawar to describe the ability of an organ or tissue to not have a classical immune response to a certain stimulus [42]. This may represent an evolutionary advantage, as misregulation or over-activation of the immune system could be harmful. For example, in the central nervous system (CNS), where the division potential of new cells is limited, activation of killer cells or neutrophils could cause irreversible changes [43].

It was long believed that some organs, such as the brain, are completely separated from the rest of the body in terms of the immune system, making a strict division between the brain and peripheral immune system. After years of research we are beginning to achieve a better understanding of the unique and complex bidirectional communication between the immunological processes of brain and the periphery [44]. Nevertheless, brain immunity has distinct features. Under normal physiological conditions, the immune cells of the peripheral immune system cannot be found in the brain. The main cells of the brain's immune response are microglia, which act as local phagocytes, exerting surveillance through pattern recognition receptor (PRR) mechanisms and cytokine expression. Microglia also act as gatekeepers – a recent study has shown that microglia can attract peripheral immune response cells such as T cells through chemotaxis in the event of brain injury [45]. Microglia are heterogeneous, and their function and phenotype can be adapted based on the changes in the brain microenvironment, residing in either a more resting state (monitor and maintain) or an activated state (phagocytosis and cytokine production) [44]. Both resting and activated states of the microglia serve an important function in the brain. The problem arises when the activation of microglia is unwarranted, for example, due to chronic stress-induced signaling molecules rather than pathogens or cellular damage. Reactive microglia produce increased levels of cytokines, further inducing astrocytes and increasing neuroinflammation [46].

Although the CNS is distinct from the peripheral immune system, a growing body of research is highlighting the role of epigenetics in this complex interplay between the peripheral immune system, microglia residing in the CNS, and the risk of psychiatric and neurological diseases. In the presence of external stimuli, such as in response to injury, various infections, or chronic inflammation, the peripheral immune system is activated. This activation leads to the release of cytokines produced by macrophages and other peripheral immune cells. Cytokines can cross the blood-brain barrier and trigger microglial activation, with additional cytokines being produced in the CNS [44]. Studies also indicate the important effect of epigenetics on the microglia during early life development, with epigenetic regulation playing a crucial role in shaping the identity and function of microglia. Furthermore, epigenetic regulation modulates neuroimmune contributions to neuro-psychiatric disorder risk. Numerous animal models of neuroinflammation and neurodegeneration suggest that chronic stress and inflammation during pregnancy affect microglia plasticity and later affect microglia cellular memory [47]. Epigenetics thus influences the formation of microglia *in utero* and in addition the function and formation of microglia are later influenced by our environment and experiences [47].

Another under-recognized aspect of the immunology of psychiatric disorders is the complement system, traditionally regarded as part of innate immunity. For a long time, it was assumed that the main role of the complement system was defense against pathogens. Today, however, we are increasingly recognizing the role of the complement system in the development, homeostasis and pathology of the CNS. The complex complement cascade consists of over 50 soluble and membrane-bound proteins. The complement components found in the blood are mostly produced by the liver. Locally, in the brain, individual complement components are produced by different cell types such as astrocytes, microglia and neurons. Complement can be activated in three pathways: classical, alternative, or lectin. Complement activation must be carefully regulated and controlled, as inappropriate regulation can have serious consequences for the host tissue [48]. Complement is very important during early brain development as it is critically involved in the process of synaptic pruning. Synapses that are destined to be removed are marked by components such as C3 and C1q, which are recognized by microglia. This process is crucial for the proper formation of neuronal circuits, and dysregulation of this process can lead to various pathological conditions; indeed inadequate synaptic pruning has already been linked to neurodevelopmental disorders. Complement is not only important during development, but also in adulthood. In adults, complement in the brain is involved in brain plasticity, memory and the process of forgetting [49]. Overall, the complement system is an important neuroimmune mediator that links immune activation to psychiatric and neurodegenerative diseases through its influence on synaptic regulation and neuroinflammation. In schizophrenia, multiple studies have been conducted on the C4 component, mainly investigating the genetic variations and their possible association with schizophrenia. Recently, DNA methylation of C4A has been investigated in plasma of patients with schizophrenia. Plasma levels of C4 were increased compared to the control group, and correlations were observed between plasma levels and DNA methylation levels of C4A [50]. Multiple complement-involved genes (such as *C1R*, *C1S*, *C7*, *C4A* and *CFI*) have been identified as differentially expressed in the brain of schizophrenia patients compared to control subjects. No DNA methylation analysis was completed, but these changes in gene expression do allow for speculation about the epigenetic mechanism involved [51].

4. Epigenomic alterations associated with psychiatric disorders

Chronic psychiatric disorders, including major depressive disorder (MDD), schizophrenia, bipolar disorder and post-

traumatic stress disorder (PTSD), are among the most prevalent chronic diseases worldwide and thus present an important public health burden [52]. The importance of the gene-environment interactions in the pathogenesis of these multifactorial disorders is becoming increasingly recognized, and epigenetics may provide a molecular framework for their effects. Chronic psychiatric disorders are frequently co-occurring and may share common etiologies and epigenetic patterns, however, distinct epigenetic signatures are also likely present and could serve as valuable biomarkers in personalized medicine [53].

4.1. The epigenetics of MDD and suicidality

MDD is a chronic, usually episodic psychiatric illness with a global prevalence over 300 million [54]. Suicide accounts for over 720,000 deaths annually and is frequently, but not always, linked to chronic psychiatric disorders, of which MDD is the most notable [55]. Numerous studies have associated both MDD and suicidality with both central and peripheral inflammation, characterized by elevated levels of pro-inflammatory cytokines. Environmental stressors have been proposed to trigger inflammatory responses that disrupt glial function and synaptic processes, thereby increasing the risk for MDD development. Epigenetic mechanisms, among which DNA methylation is the most examined, may mediate this interaction. The relationship between epigenetic regulation and inflammation may be bidirectional, as inflammation itself can induce further epigenetic alterations [44].

A recent meta-analysis of epigenome-wide association studies (EWAS) identified various differentially methylated positions associated with MDD, implicating pathways involved in synaptic plasticity, immune signaling, and calcium homeostasis [56]. Similarly, an epigenome-wide meta-analysis revealed altered DNA methylation patterns in the brains and blood of individuals who died by suicide [57]. In a recent genome-wide DNA methylation study of depression, a co-methylation network analysis revealed a module enriched in immune-related pathways, which also correlated with Interleukin 6 (IL-6) levels and telomere length [58]. Importantly, blood DNA methylation profiles have shown potential as predictive biomarkers for long-term outcomes in MDD. The enrichment of these profiles in pathways related to autoimmune disease and inflammation suggests that epigenetic regulation of immune-related processes may serve as a stable indicator of disease trajectory [59]. Regarding histone modifications in MDD, the most explored modification is the histone 3 lysine 4 trimethylation (H3K4me3). A recent targeted study assessed H3K4me3 differences in the promotors of immunity-related genes in peripheral blood mononuclear cells of MDD patients. Decreased H3K4me3 levels in immunity-related genes, including Toll-Like Receptor 4 Gene (*TLR4*), were linked to MDD, and these alterations were not reversed by 4-week antidepressant treatment [60]. Furthermore, multiple types of non-coding RNAs (ncRNAs) have been associated with depressive behavior and suicidality in animal models and humans, e.g., miR-16, miR-135a, and others, targeting transcripts involved in serotonergic, dopaminergic, glutamatergic and polyaminergic signaling pathways. While most studies have focused on microRNA (miRNA), various ncRNA species likely function within interconnected networks, and their collective impact on gene regulation should be further examined [61].

4.2. The epigenetics of PTSD

PTSD is a chronic psychiatric disorder that develops in response to traumatic experiences, affecting approximately 6–10% of the general population and 35% of individuals with significant lifetime trauma exposure [62]. Emerging research points to an important role of the immune system in the development of PTSD, and inflammation, associated with sympathetic system dysregulation, has been recognized as a key characteristic of this disorder. Despite this, the interactions between the central and peripheral immune systems and the biological processes driving the immune imbalance in PTSD are still not well understood. Elevated levels of peripheral pro-inflammatory markers, such as IL-6, tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP) etc., have been found in patients with PTSD compared to controls, and these may be resistant to psychotherapy and pharmaceutical treatment [63].

Recent studies have explored epigenetic alterations in PTSD, also in connection to immunity. A cross-sectional meta-analysis of EWAS studies revealed 11 CpG sites associated with PTSD, implicating immune response- associated genes such as aryl hydrocarbon receptor repressor gene (*AHRR*) and Toll interacting protein gene (*TOLLIP*), with 5 sites exhibiting brain-blood correlation in methylation patterns. Increased DNA methylation of the *AHRR* promoter also associates with decreased kynurenine levels [64]. Another recent large-scale study examined cell type-specific DNA methylation patterns associated with PTSD. In peripheral blood samples, novel PTSD-associated CpGs were identified across immune cell types, with some of these CpGs mapping to genes previously implicated in GWAS. Altered DNA methylation patterns were most evident in B cells, and PTSD-related inflammation may alter the epigenetic regulation of immune cells [65]. Histone modifications associated with PTSD and ncRNA expression levels are less explored, and the lack of replicable results encumbers the interpretation of such studies. Certain histone modifications in the proximity of genes such as glucocorticoid receptor (*GR*) gene, interferon gamma gene (*IFNG)* etc., may be involved in PTSD pathogenesis. Recently, H3K4me3 has been linked to the upregulation of Wnt Family Member 10B (*WNT10B*), a key regulator of the Wnt/β-catenin signaling pathway involved in immune response. It has also been shown that the long ncRNA LINC00926 recruits the histone methyltransferase to the *WNT10B* promoter, enhancing its expression [66].

4.3. The epigenetics of schizophrenia

Schizophrenia is a chronic psychiatric disorder and a leading cause of disability in young people, affecting approximately 1% of the global population. While this neurodevelopmental disorder has a strong genetic basis with an estimated heritability of 80%, the contributions of environmental factors (e.g., cannabis use, prenatal infections, obstetric complications and

psychosocial stress) are well documented. Studies on *post-mortem* brain tissue as well as peripheral tissues have proposed that epigenetic factors mediate the effects of environment on schizophrenia risk [67].

Altered function of enzymes involved in chromatin remodeling has been implicated in schizophrenia. A recent proteomics study on iPSC-derived forebrain neurons from schizophrenia patients identified increased acetylation of histones H2A.Z and H4, which correlated with findings in *post-mortem* brain tissue. Inhibiting BET family proteins which interact with acetylated histones may offer a therapeutic strategy by correcting schizophrenia-associated transcriptional abnormalities [68]. Furthermore, decreased cortical expression of genes involved in GABAergic neurotransmission, such as reelin (*RELN*) and glutamic acid decarboxylase 1 (*GAD67*), has been associated with schizophrenia. Candidate gene approaches have identified hypermethylation of their promoter regions in *post-mortem* samples of schizophrenia patients, which may be caused by environmental risk exposure, as suggested by animal studies. Promoter hypomethylation of catechol-O-methyltransferase (*COMT)*, a gene involved in dopamine metabolism, and promoter hypomethylation of SRY-box transcription factor 10 (*SOX10)*, which is involved in oligodendrocyte differentiation, has also been noted [67]. Epigenome-wide analyses have identified multiple schizophrenia-associated loci, including those related to neurotransmission and inflammation (e.g., within the strawberry notch homolog 2 (*SBNO2*) gene, a regulator of IL-6 signaling) [69]. Furthermore, epigenetics may help explain the sex differences in schizophrenia onset and severity, as sex-specific methylation patterns were identified in various genes, including glutamate receptor subunit 3B (*NR3B*, hypomethylated in males), Janus kinase and microtubule interacting protein 1 (*JAKMIP1*, hypermethylated in females) and potassium inwardly rectifying channel subfamily J member 6 (*KCNJ6*, hypermethylated in males) [67]. Studies on histone modifications in schizophrenia are scarce; altered expression of histone-modifying enzymes have been linked to schizophrenia, and studies on *post-mortem* samples have associated changes in histone acetylation H3acK9/K14 and H3K4me3 level with the altered expression of several schizophrenia-related genes, including *GAD67* [67]. The role of ncRNA regulation in schizophrenia is increasingly becoming an area of interest. MiRNAs play important roles in neurodevelopment and the 22q11.2 deletion, a rare genetic variation that affects 1% of schizophrenia patients, affects the *DGCR8* gene, which is involved in miRNA processing [70]. Some of the differentially expressed miRNAs include miR-181b, miR-107 (targeting *RELN*), miR-15 family, miR-34a, miR-130b and many more [67].

5. Epigenomics in brain cancer

The leading cause of death among women aged 20 years and younger and men aged 40 years or younger is brain cancer [71]. Brain cancers can be benign, i.e., noncancerous, or malignant, i.e., cancerous. Because of the complexity of malignant tumors their diagnosis is challenging. However, as they can trigger lethal diseases, timely diagnosis is crucial for better quality of life and longer patient survival.

Even though brain tumors represent less than 2% of all primary tumors, they are accountable for 7% of the years of life lost from cancer before the age of 70 years [72]. According to the WHO [73], brain cancers are classified into four grades [71]: 1, low grade glioma, slow growing, less aggressive tumors which can be completely cured with surgery; 2, slow growing tumors that may spread to surrounding tissues and can recur after surgery or treatment; 3, fast growing tumors that can damage nearby tissues for which besides surgery, radiation and chemotherapy are recommended; and 4, fast growing and spreading infiltrative tumors with abnormal vascular growth and necrotic areas associated with poor prognosis. Of these, the grade 4 glioblastoma is the most common type of brain cancer.

Glioblastoma is an incurable cancer with median survival of 15 months and a 5-year life expectancy of less than 7% [74,75]. Glioblastoma can be diagnosed with MRI, where it appears as a contrast-enhancing mass with irregular borders, with PET scans, that can determine growth extent, aggressiveness, and may assist in treatment planning, and CT, which can identify structural abnormalities and detect brain masses by revealing its size, location, and effects on surrounding structures [71]. In addition, omics data can also assist in glioblastoma diagnosis and treatment. Immune evasion protects glioblastoma cells from the cytotoxic immune response. In this regard, using 22 pairs of formalin-fixed paraffin-embedded sequential (FFPE) tissue samples from glioblastoma patients and a larger cohort of 112 primary and recurrent glioblastomas by Klughammer et al [76], Tompa et al investigated CpG methylation in promoters, genes, and pathways with restricted resolution bisulfite sequencing (RRBS) and bioinformatic analyses [77]. When comparing recurrent to control and primary glioblastoma samples, the authors identified hypermethylated parts of the innate and adaptive immune system. For example, there were higher methylation levels of the IL-7 signaling pathway and response to IL-7 in recurrent glioblastomas. Significantly higher methylation levels of IL-7 receptor α-subunit was found in recurrent compared with primary glioblastomas. The authors suggest that the progressive suppression of IL-7 receptor-mediated pathway as means of immune escape can also be a therapeutic target. Epigenetic modifications are common in glioblastoma. Such patterns help in tumor classification, diagnostic accuracy and informed treatment.

5.1. DNA hypomethylating agents

Immunotherapy with immune checkpoint inhibitors is used for the treatment of different cancers such as metastatic melanoma, non-small cell lung cancer and renal carcinoma [72], but is not as effective in glioblastoma. This may be a result of the phenotypic diversity of glioblastoma, the immune environment of the brain, the presence of brain resident microglia but also the blood brain barrier. Compared with brain metastasis from extracranial tumors, the tumor microenvironment (TME) of glioblastoma shows an abundance of tumor-associated macrophages, tissue-resident microglia, and monocyte-derived macrophages recruited from the peripheral circulation [78,79]. In this regard, approaches for reprogramming the TME of glioblastoma with epigenetic interventions are

becoming more attractive. One such approach is the use of hypomethylating agents that can restore the expression of genes which can help in anticancer treatment [80]. Lofiego et al compared gene expression and methylation profiles of glioblastomas and melanoma brain metastasis to identify differentially expressed genes, their modifications upon treatment with the DNA hypomethylating agent (DHA) guadecitabine and the role of DHA in increasing glioblastoma immunogenicity [74]. Their results showed that in glioblastoma cells, inhibiting MHC class II antigen presentation leads to an enrichment in genes correlated to tumor growth, invasion and extravasation. Immune pathways involved in the activation, proliferation and migration of T and B cells were among the most frequently activated in glioblastoma after guadecitabine treatment. Treatment with guadecitabine shifted glioblastomas to a more immunogenic phenotype. Moreover, DNA-activated immune-related upstream-regulators were enriched for biological processes involved in the regulation of cytokine and chemokine production, inflammatory response, and type I/II/III IFN-mediated signaling. The authors suggest that guadecitabine can be used for making glioblastoma more immunogenic and responsive to immunotherapy. Similarly, Ma et al showed that the DNMT inhibitor 5-aza-2′-deoxycytidine, i.e., the DNA hypomethylating agent decitabine (DAC), increases neoantigen and cancer testis antigen (CTA) mRNA expression *in vitro* through DNA hypomethylation [72]. They observed increased neoantigen presentation by MHC class I in tumor cells leading to increased neoantigen and CTA-specific T-cell activation and killing of DAC-treated cancer cells. The authors examined immunogenic antigen expression using the commercially available glioblastoma cell line U87 and primary samples from 4 glioblastoma patients. At least for two analyzed genes in particular, NY-ESO and SLC6A12, the changes at the transcriptomic level were also observed at the proteomic level. Changes in gene expression were observed in dose-dependent and treatment-duration effects (24 *versus* 48 h). The examined cell lines expressed several immune checkpoint inhibitor ligands including PD-L1 before and after DAC treatment. The authors suggest that DAC can improve the immunogenicity of glioblastoma by increasing neoantigen and CTA expression *in vitro*. In a different study, Gallitto et al examined the combination of decitabine and temozolomide (TMZ) for glioblastoma treatment [80]. Decitabine is interesting for glioblastoma, as it can cross the blood-brain barrier and reach CSF levels up to 50% of plasma levels. The authors used 11 patient-derived glioblastoma cell lines and determined IC_{50} of TMZ before and after DAC treatment. In 6 of 11 cell lines the IC_{50} of TMZ significantly decreased after DAC treatment regardless of the MGMT status (methylated or unmethylated). Gallitto et al examined protein expression levels of MLH1, MSH6 and MSH2 in DAC-treated cells and non-treated controls. They observed that an increased MLH1 protein expression level was associated with DAC sensitization to TMZ. They also investigated CpG methylation changes within a 2.5 kb segment of the *MSH1* promotor region in 3 sensitized and 3 desensitized cells lines. Compared to the sensitized cells, desensitized cells presented with significantly higher levels of methylation across multiple CpGs in the upstream region of the promoter. By increasing DNA mismatch repair (MMR) activity, DAC potentiates TMZ cytotoxicity in glioblastoma. This can be useful since TMZ is the main course of treatment for glioblastoma patients.

6. Molecular alterations occurring in psychiatric disorders and brain cancer

Epigenetic dysregulation can affect immune interactions, synaptic plasticity and neural cell lineages, contributing to pathological states. Common epigenetic alterations in the brain can thus be found in distinct disease categories, including psychiatric disorders and brain malignancies, as presented in Figure 2. Notably, neurodevelopmental signaling pathways including Notch, Hedgehog, and Wingless (Wnt) signaling, which are tightly regulated by chromatin dynamics, are disrupted in adult patients with neuropsychiatric disorders and also in glioblastoma, although in divergent contexts. *NOTCH4* gene polymorphisms, as well as variants of NOTCH pathway components, have been associated with schizophrenia in certain populations, and epigenetic analyses have suggested differentially methylated regions of NOTCH pathway genes in schizophrenia, which may be linked to aberrant connectivity, a characteristic of the disorder [81]. Furthermore, downregulation of the hedgehog signaling pathway has been associated with depression [82]. The upregulation of the aforementioned pathways promotes tumor progression and resistance to chemotherapeutics in glioblastoma [83]. The polycomb repressive complex 2 (PRC2), with its catalytic subunit Enhancer of zeste homolog 2 (EZH2), orchestrates epigenetic repression of neuronal differentiation genes in glioblastoma stem-like cells, and EZH2 inhibition improved survival in animal glioblastoma models [84].

Epigenetic alterations of transcriptional regulators such as the BDNF have been associated with schizophrenia and MDD [37,38,85]. BDNF is a neuronal growth factor, a regulator of immune response and may exert a pro-tumorigenic role in glioblastoma. High-neural glioblastoma was recently associated with elevated serum BDNF levels, possibly due to BDNF secretion from malignant cells or glioma-induced neuronal hyperactivity. In contrast, low-neural glioblastomas exhibited immune-enriched profiles [86]. Reduced expression and promoter hypermethylation of the *BDNF* gene, as well as repressive histone modifications, were associated with depression, suicide and schizophrenia [37,38,85]. *DISC1*, a gene involved in neurodevelopment and synaptic plasticity that was originally linked to schizophrenia via the (1; 11) (q42; q14.3) translocation, was also found to be highly expressed in glioblastoma, and *DISC1* downregulation decreased glioblastoma cell migration and invasion [87]. Furthermore, *RELN* is downregulated both in schizophrenia and glioblastoma [88,89]. Epigenetic alterations in immunity-related genes are associated both with neuropsychiatric disorders and brain cancer. The creation of an immunosuppressive TME is characteristic of glioblastoma, and methylome-wide studies have shown that recurrent glioblastomas exhibit hypermethylation of promoters linked to immune-related pathways, including IL-7 signaling [77]. Increased levels of pro-inflammatory cytokines, possibly due to epigenetic mechanisms [90], have been linked to depression, suicide and schizophrenia [91–93]. Research into common molecular mechanisms disrupted

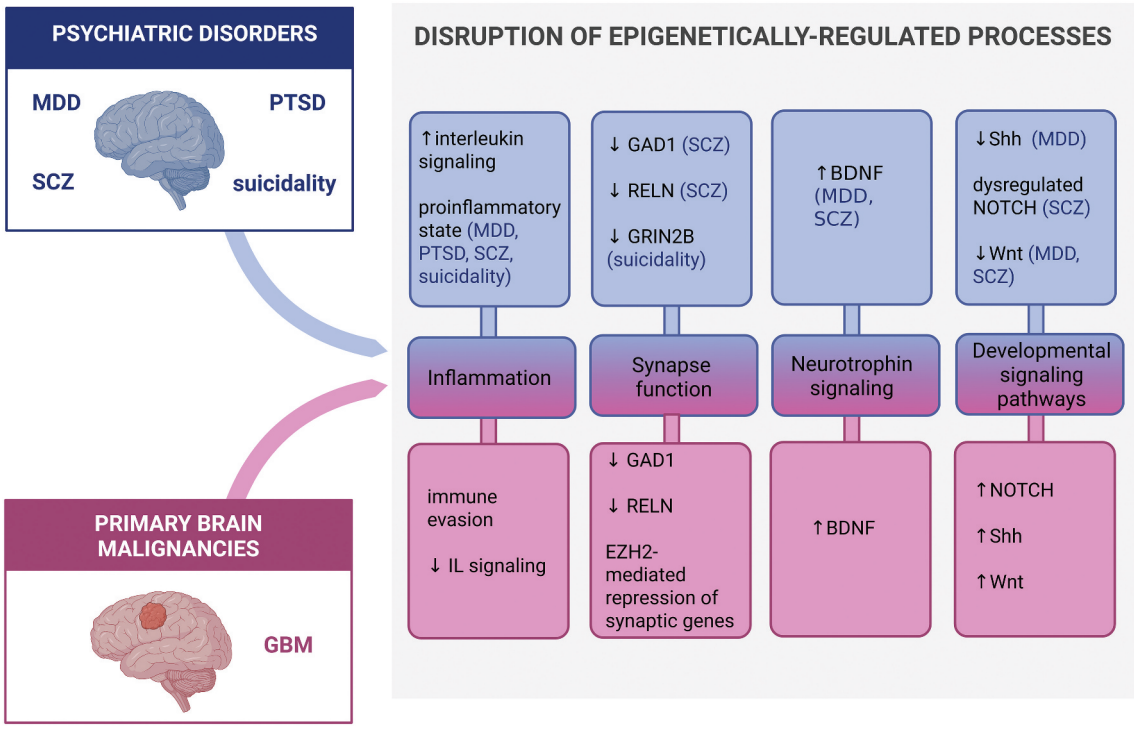

Figure 2. Common molecular processes disrupted in psychiatric disorders and brain malignancies. A number of processes that are epigenetically disrupted in psychiatric disorders, including major depressive disorder (MDD), post-traumatic stress disorder (PTSD), schizophrenia (SCZ), and suicidality, are also involved in the pathophysiology of glioblastoma (GBM). Examples include (neuro)inflammation, synapse function, neurotrophin signaling, and neurodevelopmental signaling (e.g., Notch, wingless, and hedgehog signaling). In the majority of cases, these processes are affected in divergent directions (e.g., immune suppression in glioblastoma and proinflammatory state in neuropsychiatric disorders). This overlap highlights the far-reaching effects of key signaling pathways and suggests a potential for shared biomarkers and cross-disciplinary therapeutic strategies. Created in BioRender. Šmon, J. (2025) https://BioRender.com/p0qzs5c.

Abbreviations: MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SCZ: schizophrenia; GBM: glioblastoma; IL: Interleukin; BDNF: brain-derived neurotrophic factor; GAD1: glutamate decarboxylase 1; RELN: reelin; GRIN2B: glutamate ionotropic receptor NMDA type subunit 2; Shh: Sonic hedgehog; Wnt: Wingless/Integrated; NOTCH: Notch signaling pathway; EZH2: enhancer of zeste homolog 2; PRC2: polycomb repressive complex 2.

in various brain disorders may provide novel insights into mechanisms of cellular plasticity, immune modulation, and therapeutic resistance, as well cross-disciplinary biomarkers.

7. Challenges, opportunities and implications for diagnostics and therapy

Across psychiatric disorders and brain cancer, converging insights relevant for diagnostics and treatment can be identified [94]. First, epigenetic patterns mediate environmental influences on genetic predisposition, which makes them desirable biomarkers in precision medicine [95]. Furthermore, they show potential in diagnostics due to their responsiveness to environmental changes, and both pharmacotherapy and psychotherapy have been shown to alter DNA methylation patterns [96]. Epigenetic alterations occur across multiple psychiatric and brain disorders and thus show potential as cross-diagnostic biomarkers. The advancement of computational and high-throughput epigenomic techniques may facilitate interdisciplinary research into epigenetic biomarkers. An example of a promising approach is the identification of gene networks with coordinated DNA methylation patterns in multiple biological pathways, altered in various brain disorders [97]. However, problems regarding specificity, tissue source, and cost-effectiveness should be addressed in future research; for example, brain and blood methylation patterns may not reliably correspond to each other [98,99]

The involvement of immune-related epigenetic alterations across both disease categories examined in our review indicates that immunomodulatory therapies targeting epigenetic mechanisms warrant priority investigation [100]. In a methylome-wide study of Dutch adolescents with and without PTSD, trauma-focused psychotherapy in treatment responders altered methylation pattern in a genomic region related to the *PAX5* gene, implicated in inflammation and neurodevelopment [96]. Clozapine, an atypical antipsychotic used in schizophrenia treatment, has been associated with DNA methylation changes over the first six months of exposure [101]. Therapeutics directly targeting epigenetic modifications are currently not used in clinical psychiatry due to concerns about their broad effects on gene expression and safety. However, preclinical studies suggest that HDAC inhibitors may produce antidepressant-like effects [102].

While biomarker evaluation is not yet integrated into the diagnostics of chronic psychiatric disorders, the development of minimally invasive tools for risk stratification and the evaluation of therapeutic response presents an important goal in personalized psychiatry. Inconsistencies in sample characteristics, small cohort sizes, and methodological variation may hinder cross-study comparisons and the replication of findings. Additionally, it is difficult to control for confounding factors,

such as the effects of *post-mortem* biological changes. To identify reliable biomarkers, future studies should investigate the concordance of epigenetic signatures between brain and peripheral tissues [103].

Machine learning approaches are increasingly being used to facilitate biomarker discovery. In a recent study, a blood-based epigenetic biomarker signature for schizophrenia was developed via a three-step automated machine learning (ML) pipeline: methylomic data was analyzed and putative biomarkers were validated in the blood of 30 first-episode, drug-naïve schizophrenic patients and 30 controls. The ML approach identified key methylation biomarkers (hypermethylation of Insulin Like Growth Factor 2 MRNA Binding Protein 1 (*IGF2BP1*) and hypomethylation of Proteasome Activator Subunit 4 (*PSME4*)), and an optimized five-feature biosignature, incorporating also age and sex, distinguished schizophrenic patients from controls with an area under the curve (AUC) of 0.755 [104]. Furthermore, single-cell epigenomics show promise in advancing our understanding of cell-type-specific regulatory mechanisms in the brain, which may aid biomarker discovery by revealing how epigenetic alterations differ across neuronal and glial subtypes in psychiatric disorders [16].

In the context of glioblastoma, epigenetic alterations are fundamental as they can be reversible and also because they allow for the cellular type to be shaped based on gene activation or repression. For example, a subset of glioblastoma cells named glioblastoma stem cells (GSC) present with more dynamic and decondensed chromatin organization that is correlated to a more flexible transcriptional program [105]. The plasticity of GSC is referred to as "morphological and functional flexibility" and allows them to adapt to different TME and survive in the presence of chemotherapeutic agents [75]. In glioblastoma, heterogeneity is present also in the TME and includes hypoxic (with low oxygen levels), perivascular and invasive niches. Epigenetic changes can alter the level of gene transcripts and with that the amounts of proteins produced, including those responsible for tumor progression and maintenance [106]. In GSC, intrinsic (i.e., affecting DNA, RNA and chromatin) and extrinsic (TME) processes maintain their plasticity. These cells constantly switch between more and less differentiated states leading to a cell population that ensures tumor persistence [106]. Some even consider "GSCs" a function and not an entity [107]. This means that some cells are plastic and able to adapt depending on the circumstances and microenvironment. This can explain the heterogeneity and cellular adaptation of glioblastoma as glioblastoma is among the most heterogeneous tumors, being characterized by the existence of multiple cell subpopulations each with their own genotypic and phenotypic characteristics [75]. This heterogeneity is also guided by different inter- and intra-tumor epigenetic profiles. The cellular plasticity and cells' ability to interchange between one type and another may also be among the reasons for therapy failure. For example, after TMZ treatment, GSC cells have been observed to switch to a drug-resistant phenotype. Epigenetic modifications which are commonly detected in glioblastoma are *MGMT* promoter methylation and decreased chromatin accessibility.

DNMT inhibitors (DNMTi) such as the previously mentioned decitabine but also azacytidine [108] have been examined for their potential in treating glioblastoma either alone or in combination with TMZ. Histone methylation and demethylation also aid in therapy resistance and are explored as a possible mechanism for improving therapeutic efficacy. Singh et al showed that inhibiting histone lysine demethylase (KDM), in particular KDM1A (LSD1), decreases neurosphere formation and GSC cell viability, promotes differentiation, and increases endoplasmatic reticulum stress therefore inducing apoptosis and enhancing sensitivity to TMZ [109]. For glioblastoma the LSD1 degrader BEA-1 and its cofactor coREST have been granted orphan drug designation by the FDA. Moreover, poly (ADP-ribose) polymerase (PARP) inhibitors, which are implicated in stabilization of DNA replication forks, single-stranded and double-stranded DNA breaks, and modulation of chromatin structure, are also being considered as a therapeutic target. Finally, in the context of therapy, RNAs such as miRNAs have also been explored as epigenetic targets. For example, miR-17-3p, miR-340, and miR-222 are critical miRNAs that modulate glioblastoma cell viability *in vitro* and *in vivo* [110]. In addition, miR-198 (*MGMT*), miR-101 (*GSK-3beta*), miR-1268a (*ABCC1*), miR-381 (*ABCG2*, *ABCC3*, *ABCC5*), miR-137 (*LRP6*), miR-126-3p (*SOX2*), and miR-128-3p (*c-Met*, EMT) that promote glioblastoma sensitivity to TMZ, have also been examined [111].

8. Study limitations

In this review, we discuss the potential of epigenetic alterations for research, diagnosis and treatment of psychiatric disorders and brain cancer, specifically glioblastoma. However, our work has several limitations in particular: 1) the broad scope of the article which describes two heterogeneous brain conditions, psychiatric disorders and glioblastoma; 2) epigenetic changes are attractive biomarker candidates because of their reversibility. Yet, their sensitivity to environmental influences questions their reproducibility and can make them unstable and unreliable for clinical use; 3) samples used in the cited papers originate from *in vitro* systems, *post-mortem* or peripheral tissues which may not reflect the full complexity of the brain *in vivo*; 4) even though new technologies such as long-read sequencing, single-cell epigenomic and multi-omics methods have helped us to understand human disease to a deeper extent, they also have methodological variabilities and bioinformatics challenges which complicate study cross-validations; 5) despite the potential of epigenetic changes for personalized care, at this point their clinical translation is delayed because of the low number of validated biomarkers, lack of standardization across sample cohorts as well as legal and ethical regulations. Overall, while the use of epigenetic signatures shows potential for clinical implementation, current results need to be critically evaluated and validated on large-scale studies to prove their clinical utility.

9. Conclusion

Epigenetic changes affecting neurological development, immune regulation and cellular plasticity are key factors in the development and progression of psychiatric disorders

and brain tumors. Recently, remarkable progress has been made in high-throughput, single-cell, spatial and multiomic technologies that have enabled more precise mapping of these changes and the discovery of potential biomarkers and therapeutic targets. These epigenetic changes thus represent promising targets for the discovery of biomarkers that could influence risk prediction, diagnosis and choice of therapy. However, current findings are mostly preclinical and derived from autopsy or in vitro studies, and their clinical application is still a long way off. Although the potential for personalized psychiatry and precision neuro-oncology is considerable, its generalizability is limited by reproducibility, tissue availability and methodological variability. These findings suggest a systems view of brain disease, where common epigenetic mechanisms link traditionally separate pathologies in a mosaic fashion. They offer an opportunity for future research, early diagnosis and the development of targeted interventions, but rigorous validation and ethical oversight are required for widespread clinical application.

10. Future perspective

In the future, we expect that increasing insight into the epigenomic architecture of the human brain, enabled by advancements in high-throughput, spatial, single-cell and computational technologies, will enable in-depth exploration of the brain across developmental stages, in health and various diseases. Concerning psychiatry, we expect that epigenomic profiling, in combination with other -omic modalities, clinical data and possibly ML models, may aid the stratification of patients into biologically-defined subgroups. This would present a paradigm shift toward precision psychiatry, where diagnosis and choice of treatment could be aided by individual biomarker profiles. However, clinical use of machine learning models raises ethical concerns, including data privacy, which should be addressed. In neuro-oncology, epigenomic profiling may be more routinely integrated into clinical workflows, aiding in early diagnosis, therapy response prediction, and personalized treatment planning for glioblastoma and other brain cancers with poor prognosis, which is of the highest priority. Epigenetic drugs, including targeted DNMTi and RNA modulators, may become a part of combinatorial treatment strategies aimed at overcoming resistance and immune evasion. Overall, we expect the field to continue moving toward an integrative, systems-level approach to brain disorders, with epigenetic dysregulation linking various, traditionally unclearly connected, pathologies. Therefore, with increasing safety and precision, epigenetic therapy may also be explored in other types of brain disorders.

Acknowledgments

The authors wish to acknowledge the funding bodies. The funders had no role in the preparation or publication of the manuscript. The authors wish to thank Dr. John Hancock for critical appraisal and scientific English editing of the manuscript.

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Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

The authors would like to thank the Slovenian Research and Innovation Agency for funding the Research Programme grants No P1-0390 and P3-0083; Research Project grants No N3-0349, J3-4533 and BI-ME/25–27–013, and Young Researcher Grant to JŠ. The funders had no role in the preparation or publication of the manuscript.

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