Unraveling the Tapestry of Well-Being

The Intricate Dance of Mental Health and Epigenetics

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ABSTRACT

The advent of the 21st century has borne witness to the manifestation of concealed pandemics, characterized by chronic illnesses of significant societal consequence, which, while lacking the immediate visibility reminiscent of infectious diseases, pose considerable threats to public health. Among these concealed pandemics are mental health disorders, diabetes, cardiovascular ailments, oncologic conditions, and lung diseases. Despite their non-contagious nature, these afflictions exert profound and often interlinked impacts on individuals and societies.

This review explicitly addresses mental health disorders, and explores their intricate interplay with epigenetics, a domain that has ascended to prominence in contemporary research within this field. The central role of epigenetics in the development, progression, and treatment of mental health disorders is thoroughly examined. The emergent insights posit that epigenetic modifications function as a pivotal bridge, illuminating the intricate nature of mental health conditions.

Additionally, this research highlights the central role of the body in mental health, underscoring the relevance of body psychotherapy and bottom-up modalities. The review provides a crucial research foundation for understanding the significance of incorporating bottom-up/epigenetic approaches in treating and managing mental health conditions.

Keywords: hidden pandemics; chronic illnesses; public health; mental health disorders; epigenetics; development; treatment; societal consequence

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> ***Understanding epigenetics promises to shed light on various biological processes, from cellular differentiation to disease pathogenesis and the potential heritability of acquired traits.***

Non-communicable diseases (NCDs) are chronic diseases not caused by infectious agents and generally not transmitted from person to person. They are typically long-lasting, and often linked to lifestyle factors such as diet, physical activity, tobacco use, and alcohol consumption (Piovani & Nikolopoulos, 2022) (Figure 1). NCDs include a wide range of disorders, including cardiovascular disease (such as heart disease and stroke), diabetes mellitus, mental disorders, and oncologic and lung diseases (Piovani & Nikolopoulos, 2022). While NCDs are not traditionally "pandemics," they pose a significant global health challenge. Often responsible for a substantial portion of the global disease burden, they can have far-reaching social and economic impacts (Hadian et al., 2021). Preventing and managing NCDs involves health promotion, lifestyle modification, early detection, and appropriate medical care (Budreviciute et al., 2020).

Understanding the risk factors associated with NCDs is crucial for their prevention and management. NCD risk factors can be categorized into two broad groups: modifiable and non-modifiable. Non-modifiable risk factors include age, genetics, and family history (Budreviciute et al., 2020). However, modifiable risk factors are of particular concern, as they offer opportunities for intervention and prevention. Key modifiable risk factors for NCDs include unhealthy dietary habits, physical inactivity, tobacco use, and excessive alcohol consumption. Diets high in processed foods, saturated fats, salt, and sugar are associated with an increased risk of developing NCDs – particularly cardiovascular disease and diabetes (Budreviciute et al., 2020). Inadequate physical activity is linked to obesity, a known risk factor for multiple NCDs (Lee et al., 2012). Tobacco use remains a leading cause of preventable NCD-related deaths; smoking is a significant risk factor for lung cancer and cardiovascular disease (Mishra et al., 2022). Excessive alcohol consumption is associated with liver disease, certain cancers, and mental health disorders (Mishra et al., 2022).

Furthermore, social determinants and environmental factors play a pivotal role in the development of NCDs. Socioeconomic status, access to healthcare, education, and the physical environment influence an individual's risk of NCDs. These broader social and environmental factors often drive disparities in NCD prevalence and outcomes (Rasesemola et al., 2023).

Efforts to combat NCDs involve a multi-pronged approach encompassing health promotion, lifestyle modification, early detection, and appropriate medical care. Public health initiatives often focus on raising awareness about the impact of risk factors, implementing policies to reduce exposure to these factors, and encouraging healthier behavior. In clinical settings, early detection and management of NCDs are crucial for improving patient outcomes and preventing complications (Sousa Pinto et al., 2020). Integrating NCD management into mental health interventions becomes paramount in addressing the holistic well-being of individuals.

Mental health as a silent pandemic

Among the diseases mentioned above, mental health disorders stand out as a silent pandemic within the larger NCD landscape. Mental health is a complex and multifaceted aspect of human well-being, encompassing conditions such as depression, anxiety, schizophrenia, and bipolar disorder, and influenced by a combination of genetic, environmental, and psychological factors. These conditions are classified according to gene-specific transcriptional changes in various limbic brain re-

Figure 1. *Risk factors that kill 7 out of 10 people worldwide, WHO https://www.who.int/news*

The image is adopted from the Report: (in?)Vincible Pandemics, 2022. Georgieva, M., Momekov, G., Stamenova, D. and Sharkov, A.

gions involved in controlling stress responses, reward processing, and cognitive functions (Nestler et al., 2016). On a global scale, mental health disorders are one of the primary contributors to disability (Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, 2020; Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019,2022). On a worldwide scale, mental health is becoming more and more globally recognized as an issue in modern society (Trivedi et al., 2014). Economic elements, political aspects, culture, and individual and social manners influence mental well-being. The increasing number of people with mental health illnesses can even have a direct national effect on social and economic development (Allen et al., 2014).

At present, scientists lack a complete understanding of the origins of mental health disorders. Considering the complex nature of the brain, combined with how mental illness affects thoughts, behavior, and feelings, it is no surprise that getting to the bottom of how mental illness develops still remains a challenge. Psychology, psychiatry, and neuroscience take on different aspects of the complex relationship between a person's behavior, emotions, thoughts, out-of-control actions, and the biology of the brain. Scientists in different fields have gathered their knowledge to discover the cause of mental disease. This could lead to more advanced therapies and treatments, and potential cures. Among the fields involved in mental health research is epigenetics, which investigates changes in gene expression that do not involve alterations to the DNA sequence. It has emerged as a key player in understanding the development and manifestation of mental health disorders (R. Kumsta, 2019). The intricate interplay between epigenetic modifications and the development, progression, and response to therapeutic interventions in mental health conditions suggests that targeting these epigenetic mechanisms could offer novel and effective treatment strategies. By unraveling the complexities of epigenetic regulation, we gain valuable insights that may pave the way for personalized and targeted therapies, thus potentially revolutionizing the treatment landscape for mental health disorders.

Epigenetics unveiled: Navigating the dynamic mechanisms beyond DNA sequences

Epigenetics is a dynamic and fascinating field within genetics and biology that seeks to unravel the intricate mechanisms underlying how gene expression is regulated without changes in the DNA sequence itself. In essence, epigenetics explores the "above" or "beyond" genetics, encompassing a multitude of molecular processes that influence how genes are turned on or off – a phenomenon that plays a pivotal role in development, health, and disease (Hamilton, 2011). At its core, epigenetics denotes gene expression and cellular identity changes that are heritable through cell division, but do not involve alterations in the underlying DNA sequence. These changes are essential for the normal functioning of an organism, as they guide cells to specialize into different types, repair damaged DNA, and respond to environmental cues. Epigenetic modifications are reversible and responsive, enabling organisms to adapt to their surroundings and experiences. They are often likened to additional layers of instruction written on the genetic code that help interpret genetic information (Kumari et al., 2022).

The most well-known epigenetic modification is DNA methylation. A methyl group (CH_3) is added to the DNA molecule, typically to cytosine nucleotides found in specific CpG islands sequences. DNA methylation serves as a repressive mark, silencing gene expression by making it more challenging for the cellular machinery to access the DNA. However, DNA methylation can be context-dependent, influencing gene expression differently depending on its location and the surrounding molecular cues (Jin et al., 2011).

Histone modifications represent another prominent epigenetic mechanism. Histones are proteins around which DNA is wrapped, forming a structure known as chromatin. Chemical changes to these histone proteins can either promote or inhibit gene expression. Acetylation of histones, for instance, generally relaxes the chromatin structure, making it easier for genes to be transcribed and expressed. At the same time, methylation can have varied effects, depending on the specific histone and the modification site. These histone modifications work with DNA methylation to fine-tune gene regulation (Handy et al., 2011).

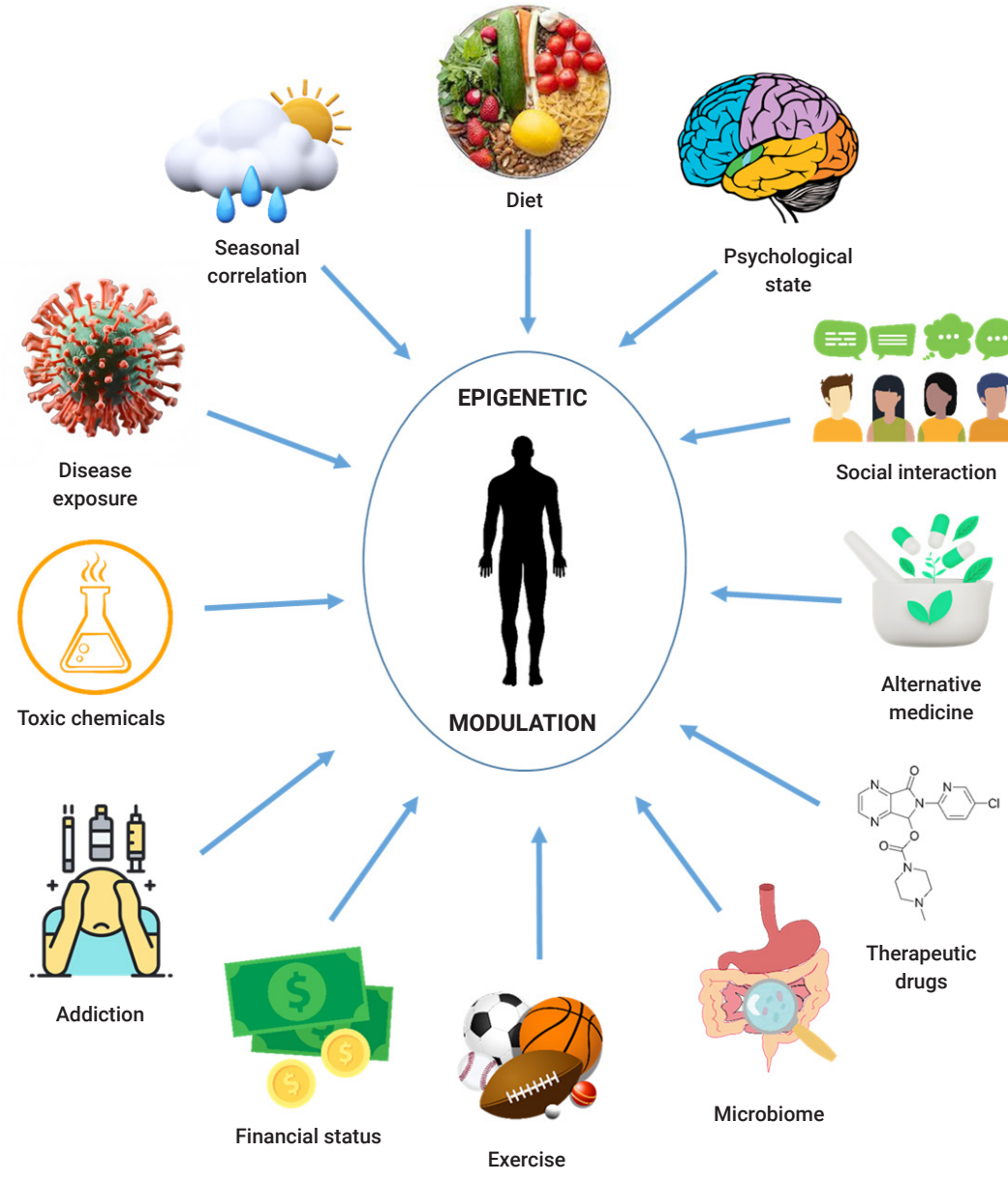

Figure 2. *Key factors inducing epigenetic modulation.*

This schematic illustrates the diverse array of environmental, lifestyle, and other external factors that contribute to the dynamic regulation of epigenetic modifications, which influence gene expression and cellular function.

Non-coding RNAs, a diverse class of RNA molecules that do not code for proteins, also contribute significantly to epigenetic regulation. For example, microRNAs and long non-coding RNAs can bind to messenger RNAs (mRNAs) that degrade or block their translation into proteins. This process can effectively reduce the expression of a particular gene or set of genes (Wei et al., 2017).

Epigenetic changes are initiated and maintained by a host of enzymes and protein complexes that add or remove these modifications. DNA-methyltransferases, for instance, add methyl groups to

DNA, while demethylases remove them. Similarly, histone acetyltransferases and histone deacetylases regulate histone acetylation levels (Han et al., 2019).

Epigenetic modifications are highly dynamic and responsive to both internal and external cues. They are essential during development to guide the differentiation of cells into various tissue types, ensuring that genes are switched on or off at the correct times and locations (Gopinathan & Diekwisch, 2022). Epigenetics also plays a significant role in response to environmental factors (Figure 2). For instance, diet, stress, exposure to toxins, and social interactions can all induce epigenetic changes that influence health and disease (Alegría-Torres et al., 2011). Recent data show that interventions such as psychotherapy, pharmacotherapy, mindfulness practices, and lifestyle modifications impact the epigenetic modifications, especially those associated with mental health conditions.

For example, research in the field of psychiatry has investigated how antidepressants may influence DNA methylation patterns or histone modifications (Šalamon Arčan et al., 2022). Additionally, behavioral interventions like stress reduction through mindfulness meditation have been associated with positive epigenetic changes linked to improved mental well-being (Verdone et al., 2023). Physical exercise, nutrition, and other lifestyle modifications have also shown the potential to influence epigenetic processes associated with mental health (Plaza-Diaz et al., 2022). While the field is still evolving, these findings suggest a dynamic relationship between treatments/interventions and epigenetic mechanisms, highlighting the potential for interventions to not only address symptoms but also impact the underlying biological processes associated with mental health disorders.

Importantly, epigenetic modifications can be heritable. When cells divide, they must faithfully replicate the genetic code and the epigenetic marks. Errors in this process can lead to developmental disorders or predisposition to diseases such as cancer. Conversely, the inheritance of acquired epigenetic changes from one generation to the next is an active area of research. Such epigenetic inheritance could have profound implications for our understanding of evolution and the interplay of genetics and the environment (Hamilton, 2011). These modifications are essential for proper development, health, and disease prevention. Understanding epigenetics promises to shed light on various biological processes, from cellular differentiation to disease pathogenesis and the potential heritability of acquired traits. There is an opportune point to emphasize the significance of understanding epigenetics for developing effective treatments (Roth, 2013). The heritability of epigenetic modifications, as mentioned in this paper, underscores the importance of these marks in maintaining proper development, health, and disease prevention. Recognizing the potential heritability of acquired epigenetic changes positions epigenetics as a crucial factor in the interplay of genetics and the environment. In the context of mental health disorders, where the intricate nature of these conditions involves a combination of genetic predispositions and environmental influences, understanding and targeting epigenetic mechanisms becomes pivotal. Insights into how epigenetic changes are inherited or modified through interventions not only contribute to our understanding of disease pathogenesis but also offer promising avenues for developing tailored and effective treatments. Thus, integrating the knowledge of epigenetics into treatment approaches holds the potential to advance precision medicine, and improve therapeutic outcomes for individuals with mental health disorders (Grezenko et al., 2023).

Sculpting the mind: The dance of genes and well-being

One of the many fields in which epigenetics plays a role is mental health. Various mental health disorders have been associated with epigenetic mechanisms like changes in histone modifications, DNA methylation, and miRNAs. The development of mental disorders is linked to epigenetics through events like traumatic stress exposure, but at the same time through favorable circumstances created by salutary environments that exert a positive impact (Szyf, 2009; Yehuda et al., 2005).

Anxiety development and stress

Stress has long-term effects on gene expression and neural development (Lester et al., 2016; Palmisano & Pandey, 2017). This influence is especially prominent during gestation (Lester & Marsit, 2018). Anxiety symptoms have proven to be elevated based on changes in DNA methylation patterns

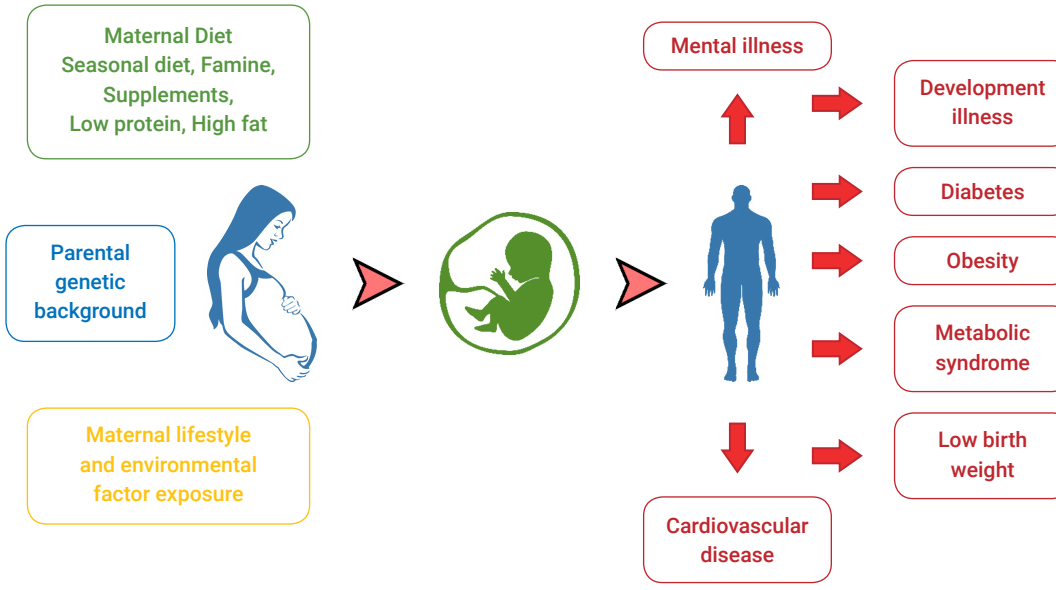

Figure 3. *Maternal factors driving epigenetic changes.*

This diagram highlights the crucial maternal influences, including diet, stress, and environmental exposure, which play a pivotal role in shaping epigenetic modifications during pregnancy. These changes can have lasting effects on the developing fetus and may impact long-term health outcomes.

linked to the hypothalamic-pituitary-adrenal (HPA) axis (McGowan et al., 2009; Shimada-Sugimoto et al., 2015). Cortisol increase in newborns has also been connected to DNA methylation changes referred to as maternal depression, which leads to HPA stress response increase in newborns (Oberlander et al., 2008). Another interplay between stress and DNA methylation changes has been discovered through a long-term twin study, which showed how the serotonin transporter gene (SERT) DNA methylation was increased in victims of bullying (Ouellet-Morin et al., 2013). miRNAs have also been considered a mediator of behavior typical in anxiety. By increasing miR-101a-3p expression in low-anxiety rats, researchers observed an increase in anxiety behaviors (Cohen et al., 2017).

Maltreatment during childhood

Child abuse is associated with physical and emotional offense and neglect, as well as sexual abuse. By testing blood samples from 45-year-old British males, who were divided into two groups of abused and non-abused, a variation in DNA methylation patterns was discovered (Figure 3). These changes were also linked to the development of diseases like diabetes, cancer, and other age-related diseases later into adulthood (Suderman et al., 2014). Suicide victims who were also victims of childhood abuse were discovered to have a specific methylation pattern as well. The neuron-specific glucocorticoid receptor (NR3C1) promoter from post-mortem hippocampus samples was discovered to be hyper-methylated when compared to controls (McGowan et al., 2009). The development of borderline personality disorder (BPD), post-traumatic stress disorder (PTSD), and major depressive disorder (MDD) is also connected to the severity, frequency, and age of onset of maltreated children. These early life events were associated with hyper-methylation of the exon 1(F) NR3C1 promoter, which permanently impacts the HPA axis (Perroud et al., 2011).

Maternal depression

Mothers navigating the challenges of both pre- and postnatal depression contribute to the unique terrain of their infants' epigenetic landscape, setting the stage for potential long-term consequences (Slomian et al., 2019). This modified epigenetic profile has been correlated with disruptions in social and behavioral functioning, compromised cognitive abilities, and an increased susceptibil-

ity to psychiatric disorders as offspring progress through life. However, there is a glimmer of hope within this intricate interplay. The impact of these epigenetic modifications is not entirely deterministic or irreversible. Recent research indicates that the harmful effects of maternal depression on an infant's epigenome can be at least partially mitigated. A critical factor in this remediation lies in the maternal-infant relationship, where expressions of affection and responsiveness to the child's social-emotional needs play a pivotal role. When mothers actively engage in nurturing behavior, such as addressing distress, providing a positive touch, and fostering emotional connection with their infants, they initiate a process of epigenetic resilience. This highlights the environment's powerful influence in shaping a child's epigenetic development (Severo et al., 2023). The provision of a supportive and emotionally rich environment can act as a potent counterforce that helps alleviate the adverse consequences of early-life epigenetic modifications associated with maternal depression. In essence, these findings underscore the intricate dance between nature and nurture, emphasizing the importance of a nurturing environment in mitigating the potential long-term effects of altered epigenetic landscapes induced by maternal depression. Mothers' responsiveness and care can be a powerful catalyst for positive epigenetic adaptations, ultimately contributing to their offspring's well-being and mental health (Vaiserman & Koliada, 2017). Specifically, the role of a nurturing environment in mitigating the long-term effects of altered epigenetic landscapes induced by maternal depression highlights the importance of interventions that address the environmental and interpersonal aspects of mental health. These data align well with the principles of bottom-up treatments, emphasizing the significance of addressing the foundational aspects of an individual's experiences and relationships (Lee et al., 2022).

In the context of mental health disorders, particularly those linked to early-life experiences, interventions that focus on creating supportive environments and fostering positive relationships become crucial. Understanding how responsive and caring environments can catalyze positive epigenetic adaptations provides a strong rationale for integrating bottom-up approaches in mental health interventions (Schiele et al., 2020). This holistic perspective, encompassing biological and environmental factors, enriches the discourse on effective treatment strategies.

Major depressive disorder

This is one of the most common mental diseases, affecting more than 350 million people worldwide, and is predicted by the World Health Organization (WHO) to become the second main factor of disability, following ischemic heart disease (Yuan et al., 2023). It is characterized by suicidal thoughts, feelings of guilt, impaired cognitive function, agitation, sleep disturbance, changes in appetite, and other symptoms. Following the COVID-19 pandemic, cases of MDD have increased tremendously (Santomauro et al., 2021). Genome-wide association studies (GWAS) have identified 80 MDD-contributing loci, which have only a negligible effect on the contribution of disease development (Levey & Stein, 2021). Generally, the inheritability of MDD accounted for only 35% (Baselmans et al., 2021). Results from epidemiological studies have strongly suggested the contribution of environmental factors to disease development. These can be stressful experiences later and early in life (Kessler, 1997; Phillips et al., 2015). Different epigenetic biomarkers involving DNA methylation, histone modifications, and specific miRNAs have been identified (Yuan et al., 2023). These could be helpful for the identification of disease progression and its development. For example, depression was found to be modulated by the hyper-methylation of the promoter for the *BDNF* gene (Januar et al., 2015).

Schizophrenia

The rise of schizophrenia has been associated with both genetics and environment (Smigielski & Jagannath, 2020). One of the main focuses of epigenetic research regarding schizophrenia is DNA methylation. A longitudinal study using monozygotic twins demonstrated psychotic symptom differences that began at the age of twelve, and showed differences in DNA methylation patterns when comparing the twins (Fisher et al., 2015). Additionally, biomarkers for schizophrenia detection have been identified. Ma et al. have pointed out three specific miRNAs – miR-22-3p, miR-92a-3p, and miR-137 – which could be used in combination to detect disease, be useful in both diagnosis and treatment monitoring (Ma et al., 2018).

Addiction

Epigenetics has long been associated with addiction, involving different epigenetic mechanisms like histone acetylation, DNA methylation, and non-coding RNAs for different substances like alcohol, cocaine, methamphetamine, and amphetamine (Hamilton & Nestler, 2019). It has been speculated that epigenetics seeks behavior mediation by regulating dopamine in the neurological system. The hypothesis has been made as to whether epigenetics could be used to battle addiction (Hamilton & Nestler, 2019). Cocaine addiction has been linked explicitly to histone acetylation increase, which influences and elevates addictive behavior, therefore suggesting that epigenetics is involved in facilitating cocaine abuse (Maze & Nestler, 2011). Methyl supplementation in rats has been shown to halt cocaine-seeking behavior (Wright & Hollis, 2015).

Regarding methamphetamine use, a study on rats discovered that the drug-induced histone hypo-acetylation repressed transcription and encouraged the addiction process. The authors used valporic acid to reverse this effect, which had an inhibiting effect on histone deacetylation, thus leading to hypo-acetylation (Jayanthi et al., 2014). The study on methamphetamine use in rats, demonstrating the reversal of drug-induced histone hypo-acetylation with valproic acid, suggests a potential avenue for therapeutic intervention. This knowledge could inform the development of pharmacological interventions targeting histone deacetylation to mitigate the addiction process in individuals with methamphetamine use disorders. Alcohol use disorder (AUD) was also associated with both DNA hyper-methylation and hypo-methylation in different promoter regions (Zhang & Gelernter, 2017), indicating the complex epigenetic changes involved in this condition. This opens up possibilities for holistic treatment approaches that combine lifestyle modification with traditional therapeutic methods for individuals with AUD. Interestingly, exercise has been found to alter epigenetic modifications associated with AUD, which could be incorporated into counseling therapy (Chen et al., 2018). These data underscore the diverse range of interventions that could be explored, from pharmacological agents targeting specific epigenetic processes to lifestyle interventions like exercise, thus highlighting the multifaceted nature of addressing substance use disorders through the lens of epigenetics.

Epigenetic modifications in mental health therapy and diagnostics

Research confirms that environmental factors could induce enduring epigenetic change. From a clinical perspective, peripheral tissue alterations could be used as diagnosis biomarkers and monitoring therapy. These epigenetic therapies include DNA methylation, mRNA modifications, miRNA, and histone modification mechanisms (Engel et al., 2018; Volk et al., 2016). Recognizing the importance of epigenetics in stress-related psychiatric disorders like PTSD and MDD unravels novel drug development targets. Research has already shown how epigenetics could be implemented in antidepressant therapy. The use of valporic acid has been documented to lead to changes in global chromatin modifications (Vialou et al., 2013). These include the hyper-acetylation of histoneH3/H4, DNA methylation, and 2MeH3K9 hypo-methylation (Perisic et al., 2010). Another common drug used to treat MDD – amitriptyline – can cause DNA demethylation and reduction in the enzymatic activity of DNA methyltransferases without affecting global histone acetylation (Zimmermann et al., 2012). Currently, miRNAs are thought to be involved in antidepressant therapy through the action of various drugs. One of the most commonly used therapies for MDD, a class of drugs known as serotonin-selective reuptake inhibitors (SSRIs) is thought to be supported by the action of miRNA-16, which also targets the serotonin transporter (SERT), as do the SSRIs (Heyer & Kenny, 2014). Repression of miRNA-16 results in elevated SERT expression. Therefore, miRNA-16 has a contributing therapeutic action for SSRI antidepressant therapy (Baudry et al., 2010).

Conclusion

A spectrum of mental health disorders, including anxiety, depression, stress, schizophrenia, and addiction has been intricately linked to the burgeoning field of epigenetics (Kumsta, 2019). Noteworthy instances of epigenetic imprinting have also been documented in stress and trauma, as exemplified by the enduring impact observed in Holocaust survivors and their descendants (Yehuda et al., 2016). The transformative role of epigenetics in reshaping approaches to mental health disorders is becoming increasingly evident. This paradigm shift is manifested through individualized treat-

ment strategies, comprehensive therapeutic interventions, and precision-targeted therapies. Central to this transformative potential is the inherent reversibility of epigenetic changes, a feature actively leveraged in these therapeutic modalities. Encouragingly, groundbreaking strides have been made in identifying promising treatment options for complex conditions such as depression and schizophrenia. Collectively, the influence of social stressors spans critical developmental stages, encompassing prenatal, early childhood, puberty, adolescence, and adulthood. This multifaceted influence extends beyond behavioral manifestations, shaping both cellular and molecular phenotypes. Crucially, these impacts are mediated by a repertoire of epigenetic mechanisms, underscoring the dynamic interplay between environmental stressors and the epigenetic landscape (Grezenko et al., 2023). Ongoing research in this dynamic field continues to unveil novel therapeutic avenues, promising continued evolution in the landscape of mental health treatment strategies.

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