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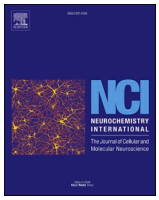

Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances

Rahul Mallick [a], Asim K. Duttaroy [b,*]

[a] A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Finland
[b] Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, POB 1046 Blindern, Oslo, Norway

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ABSTRACT

Changes in gene expression are involved in many brain functions. Epigenetic processes modulate gene expression by histone modification and DNA methylation or RNA-mediated processes, which is important for brain function. Consequently, epigenetic changes are also a part of brain diseases such as mental illness and addiction. Understanding the role of different factors on the brain epigenome may help us understand the function of the brain. This review discussed the effects of caffeine, lipids, addictive substances, physical activity, and pollutants on the epigenetic changes in the brain and their modulatory effects on brain function.

1. Introduction

Epigenetics (the Greek word "epi" means over/around) studies chemical processes that regulate gene expression by modulating DNA or its associated proteins without changing the underlying DNA sequence. Various enzymes add epigenetic marks to the DNA to signal specific genes to be active or silent, which drives cell and tissue differentiation. These epigenetic marks vary from person to person or tissue to tissue and from cell type to cell type within the tissue. Unlike DNA sequences, epigenetic modification is unique, changeable, and partially heritable (Wang et al., 2022). DNA methylation, histone modifications, and the actions of non-coding RNA molecules are epigenetic processes (Fig. 1). Epigenetic regulatory enzymes such as DNA methyltransferases, histone methyltransferases, and histone deacetylases catalyze these alterations (Han et al., 2019). Changes in the amino acid sequence of these enzymes have been demonstrated in studies to be closely associated with various diseases (Han et al., 2019).

The addition of a methyl (-CH_3) group to the fifth position carbon in the cytosine carbon ring (in the context of a CG dinucleotide [CpG site]) to form 5-methylcytosine is defined as DNA methylation (Youk et al., 2020). 70–80% of CpG sites are methylated in humans (Youk et al., 2020). Non-CpG methylation also occurs in the mammalian genome, specifically in the brain (de Mendoza et al., 2021). However, the functional implication of this methylation has yet to be made clear. Near the gene transcription starting site, CG content is enriched in specific stretches of DNA known as CpG islands. Most gene promoters are associated with CpG island (de Mendoza et al., 2021). Transcriptional initiation is inhibited by methylation of promoter-associated CpG islands (Hughes et al., 2020). DNA methylation directly blocks the binding of transcription factors to recognition sequences containing CpG sites and gene expression (Héberlé and Bardet, 2019). Removal and reestablishment of DNA methylation occur during gametogenesis and shortly following fertilization (Ivanova et al., 2020). DNA methylation is carried out by a family of enzymes known as DNA (cytosine-5)-methyltransferases, which are classified into three types: DNA (cytosine-5)-methyltransferase 1, DNA (cytosine-5)-methyltransferase 2, and DNA (cytosine-5)-methyltransferase 3 (Hervouet et al., 2018). DNA (cytosine-5)-methyltransferase 1 enzyme maintains the methylation process during cell division (Hervouet et al., 2018), while de novo methylation is maintained by DNA (cytosine-5)-methyltransferase 3a and 3b during early development (Hervouet et al., 2018). DNA (cytosine-5)-methyltransferase 3l is predominantly expressed during development to imprint genes and regulate DNA (cytosine-5)-methyltransferase 3a and 3b (Hervouet et al., 2018). The functions of DNA (cytosine-5)-methyltransferase 3l are still a mystery (Hervouet et al., 2018).

Histone determines the accessibility of stretched DNA to transcription-regulating molecules. The tight-bound stretch of DNA to

Abbreviations: CpG, CG dinucleotide; MRI, Magnetic resonance imaging; 5 mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine; PM, particulate matter.

* Corresponding author. Department of Nutrition Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway.
E-mail address: a.k.duttaroy@medisin.uio.no (A.K. Duttaroy).

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histones reduces the transcription activity. Amino acid tails of histones can be modified post-transcriptionally to modulate the interactions among histones, between histones and DNA, or support the recruitment of extra chromatin-modifying proteins (Zhao and Shilatifard, 2019). Histone modifications and the enzymes that carry them out can help in chromatin compaction, nucleosome dynamics, and transcription (Zhao and Shilatifard, 2019). These changes can be made in response to both internal and external stimuli. Histone acetylation, methylation, phosphorylation, and ubiquitination are the four most prevalent modifications written by histone acetyltransferases, histone methyltransferases, protein kinases, and ubiquitin ligases, respectively. Histone deacetylases, histone demethylases, protein phosphatases, and deubiquitinating enzymes, on the other hand, remove histone acetylation, methylation, phosphorylation, and ubiquitination, respectively (Morgan and Shilatifard, 2020).

Translation-unable RNAs are non-coding RNAs that participate in epigenetic regulation by recruiting histone- or DNA-modifying enzymes or directly modifying other RNAs or RNA-protein complexes (Bure et al., 2022).

External factors e.g., physical activity, diet, and drugs, strongly influence epigenome (Galkin et al., 2023; Toranõ et al., 2016). These modifications can impact any development phase and modulate disease susceptibility (Galkin et al., 2023; Toranõ et al., 2016). Epigenetics may influence biological changes, but nurture strongly impacts biological activities and behavior (Fig. 2). Various studies demonstrated the crucial role of histone modifications and non-coding RNAs in memory formation in the brain and other forms of neuroplasticity (Dias et al., 2015; Levenson and Sweatt, 2005; Saab and Mansuy, 2014; Sillivan et al., 2015). In addition, existing variability in DNA methylation can modulate brain activities (Rasmi et al., 2023). Albeit cell-specific nature of these dynamic epigenetic processes in human brain function and behavior are quite unknown. Therefore, epigenetic mechanisms will help better understand unexplained variability in neural phenotypes and precise molecular mechanisms that may drive the emergence of inter-individual variability in brain activities. The human genome's epigenetic modification is the subject of this article, focusing on how it links to the effects of physical activity, micronutrients, caffeine, toxins, and addictive substances, which addresses critical aspects of human health, genetics, and lifestyle choices. The selection criteria of the mentioned factors can potentially inform healthcare, public policy, and personal decision-making, ultimately contributing to improved health outcomes and a deeper understanding of our genetic and epigenetic makeup.

2. Epigenetics and adult brain function

Recent studies have demonstrated that epigenetic processes are vital for brain function. The impact of epigenetics on imaging genetics embraced the significance of environmental factors in associations between brain function and sequence variants. Table 1 demonstrates that psychiatric epigenetic studies targeting methylation within or near a gene's promoter correlate with diminished gene expression and downstream neural phenotypes. These studies indicate that DNA methylation patterns are influenced by an individual's specific environment, which explains the reason for variability in brain function than DNA sequence-based variation alone (Liu et al., 2018). However, where and how these methylation patterns start and how the mapping of methylation patterns in peripheral tissues onto the patterns in the brain are still burgeoning fields. Despite variation in methylation, epigenetic marks are partially heritable and modifiable in response to environmental factors (Liu et al., 2018).

Due to having similar DNA sequences in every cell (except in rare cases) of an organism (Vijg, 2014), derived DNA from peripheral tissues should be similar to DNA in the human brain. In contrast, epigenetic marks vary between cell types and tissues. Whether methylation

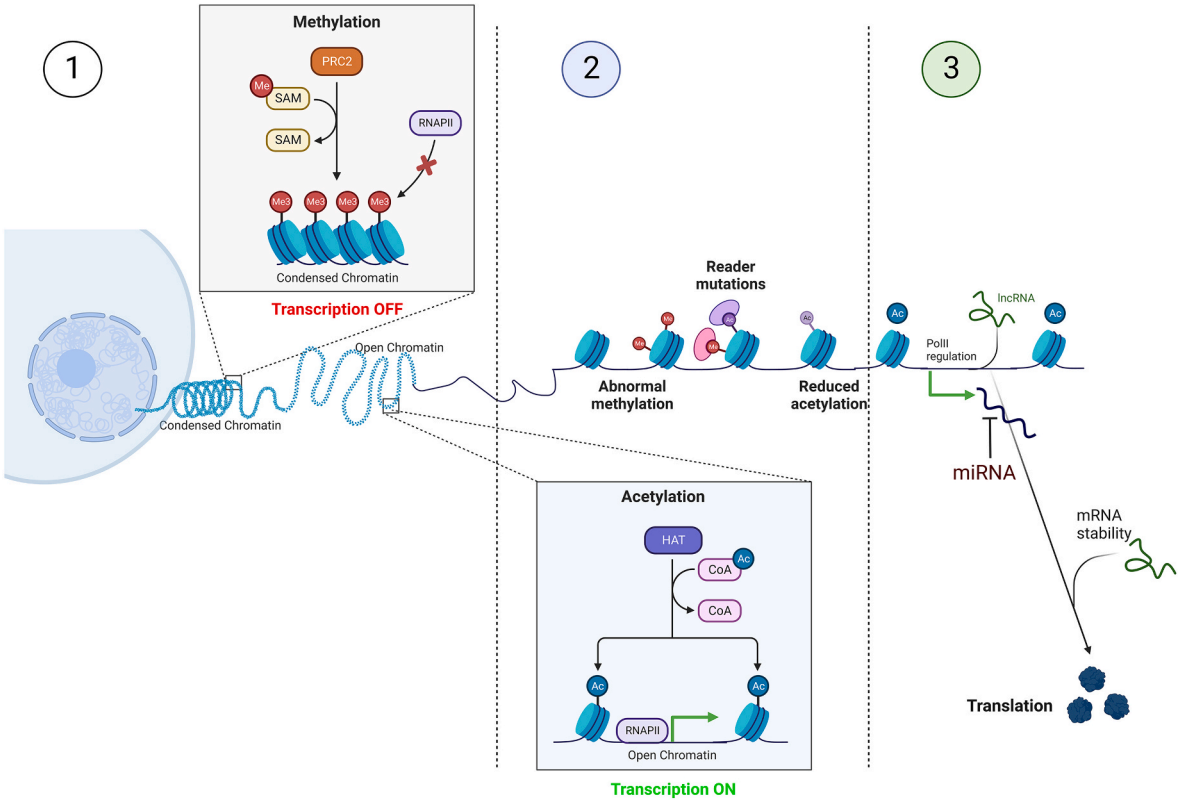

Fig. 1. Epigenetic processes
Most common epigenetic processes: (1) DNA methylation, which inhibits the transcription process (2) Histone modification, such as methylation and acetylation (histone acetylation results in relaxation of the chromatin and ultimately greater transcription) (3) non-coding RNAs block transcription and/or translation process.

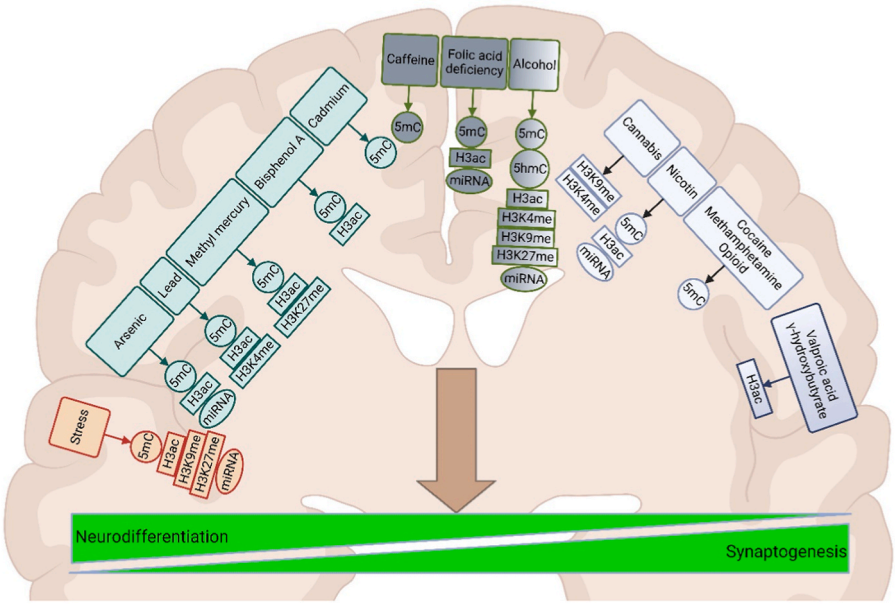

Fig. 2. Influence on brain development and functions by aversive environmental exposure
The continuous increment of different types of environmental factors influences epigenetic marks, including DNA methylation (5 mC, 5hmC) and histone modification (H3ac, H3K4me, etc.) to affect synaptogenesis and neurogenesis together affect the brain function and neuropsychiatric disease at a given time of the life.

patterns measurable in DNA derived from peripheral tissues vary from methylation patterns in brain needs to study further. Despite having varied methylation status among tissues, few studies demonstrated blood-brain correlations in DNA methylation (Nishitani et al., 2023). The exact mapping of entire brain and peripheral tissues methylomes remains unknown. Several questions need to figure out to know better the epigenetics of human brain functions. Are the mechanisms of different methylation processes in the brain and the peripheral tissues similar or different? How does small-scale inter-individual variability in DNA methylation affect gene expression, are the other epigenetic marks than DNA methylation correlate between brain and peripheral tissue, and do the activities of DNA (cytosine-5)-methyltransferase 1 through several cell divisions share the similar developmental origin of cells or reflect experiences in adulthood, determining best proxy peripheral tissue for DNA methylation in the brain, the correlation between the temporal stability of DNA methylation markers in the brain and peripheral tissue methylomes demands further studies. Then epigenetic marks can be used for diagnostic purposes accurately.

3. Epigenetics and brain memory function and dysfunction

Several enzymes have been found to modulate DNA or histone proteins for proper neuronal signaling for learning and memory (Park et al., 2022). Epigenetic processes support long-term memory formation (Feng et al., 2010; Korzus et al., 2004). Cognitive impairments can be reversed by drugs acting on defective epigenetic components (Gräff et al., 2010; Koshibu et al., 2009, 2011). Thus, it's clear that epigenetic processes can modulate memory performance. Epigenetic therapies could be potential therapeutic strategies for memory and cognitive function disorders (Franklin and Mansuy, 2010; Gräff and Mansuy, 2008, 2009; Urdinguio et al., 2009). For example, histone deacetylase inhibitors (histone-modifying enzymes) could be beneficial in treating memory impairment, age-related cognitive decline, Alzheimer's disease, etc. (Peleg et al., 2010).

4. Epigenetics and brain development

As epigenetic modulations are the basis for cellular development, impetuous changes of the nervous system during prenatal and postnatal development are influenced by environmental conditions. Thus, innate genetic programming and sensory experiences maintain the functional neuronal circuits and brain development. Environmental influence impacts natural variability in the quality and quantity of interactions between mother-infant, which modulates the infant's response to living conditions later in life and can influence their response to stress and aversive conditions (Table 2). Changes in these responses have been found to be correlated to the development of anxiety and depression (Beery and Francis, 2011). In addition, variability in maternal care stabilizes epigenetic modifications that remain beyond the period of maternal care (Weaver et al., 2004). Severe chronic stress during early life alters a mother's behavior in adulthood and ultimately influences children's behavior across generations. Depression, impulsive behavior, and altered social skills are common in adults who experienced separation from their mothers in childhood (Franklin et al., 2010; Weiss et al., 2011). Significant brain epigenetic profile alteration (results in changes in the methylation profile of stress-related genes) occurs in those who experience childhood abuse and commit suicide later in life (McGowan et al., 2009). Experiences during adulthood also modulate epigenome, even in the case of (monozygotic) twins (Fraga et al., 2005). These behavioral changes have been found to be correlated with the alteration of epigenetic processes, specifically in DNA methylation in various genes in the brains, which demonstrates that early stress modulates epigenome in various cells and tissues that transmit on subsequent generations. Epigenetic divergence, known as epigenetic drift, can happen with or without environmental influence.

5. Epigenetic factors impacting brain and behavior

5.1. Physical activity

Physical activity modulates brain plasticity and functions by releasing factors from contracting muscles in children and adults into circulation (Biddle and Asare, 2011; Hillman et al., 2008; Lees and Hopkins, 2013; Ma et al., 2017; Niederer et al., 2011; Rodriguez-Ayllon et al., 2019; Schmidt-Kassow et al., 2014; Suwabe et al., 2017; van Praag, 2009). Regular aerobic exercise reduces the DNA methylation of

Table 1
Summary of imaging epigenetics study.

Methods	Year	Gene	Findings
Structural magnetic resonance imaging (MRI)	*2013*	*FKBP5*	*Upregulated FKBP5 methylation reduces volume of the right hippocampal head* (Klengel et al., 2013).
	2014	*BDNF*	*Upregulated BDNF promoter methylation reduces white matter integrity in patients with major depressive disorder* (Choi et al., 2015).
		SLC6A4	*Increased methylation in a functional element of the SLC6A4 promoter upregulates hippocampal volume* (Dannlowski et al., 2014).
	2015	*SLC6A4*	*Increased SLC6A4 methylation was associated with childhood trauma and decreased hippocampal volume* (Booij et al., 2015).
Functional MRI	*2011*	*COMT*	*Reduced methylation of the Val158 COMT allele diminishes cortical efficiency in a working memory task, particularly in the context of stress* (Ursini et al., 2011).
	2012	*OXTR*	*Raised methylation of the OXTR gene promoter increases the activity in the temporal-parietal junction and dorsal anterior cingulate cortex during a social perception task* (Jack et al., 2012).
	2014	*SLC6A4*	*Increased SLC6A4 promoter methylation increases amygdala reactivity to threatening faces* (Nikolova et al., 2014).
		COMT	*Increased COMT promoter methylation upregulates left dorsolateral prefrontal cortex activity during a working-memory task across patients with schizophrenia and controls* (Walton et al., 2014).
		NR3C1	*Increased NR3C1 promoter methylation upregulates the activity in the right ventrolateral prefrontal cortex and cuneus, as well as reduced performance, in a memory task in healthy men* (Vukojevic et al., 2014).
	2015	*SLC6A4*	*SLC6A4 methylation modulates the activity differently in the insula, operculum, hippocampus and amygdala in an emotional attention-shifting task* (Frodl et al., 2015).
		OXTR	*Upregulated methylation of the OXTR gene promoter increases the activity in the amygdala, insula and fusiform gyrus, as well as decreases the amygdala connectivity with regulatory regions during threatening face processing* (Puglia et al., 2015). *Decreased OXTR methylation upregulates amygdala activity during social-phobia related word processing in individuals with social anxiety disorder* (Ziegler et al., 2015).
Positron emission tomography	*2012*	*SLC6A4*	*Increased SLC6A4 promoter methylation reduces 5-HT synthesis in the orbitofrontal cortex* (Wang et al., 2012).
		MAOA	*Increased methylation near the MAOA promoter was associated with lower MAOA activity in healthy men* (Shumay et al., 2012).

various genes (Barrès et al., 2012; King-Himmelreich et al., 2016; Ling and Rönn, 2014; McGee et al., 2009). Studies suggested that brain capillaries regulate positive effects on mental health and abilities in neurogenic niches that supply growth factors (e.g., VEGF, GDF11, BDNF) to activate cellular survival pathways to induce gene transcription responsible for neuroplasticity (Chen and Russo-Neustadt, 2009; Niederer et al., 2011). For instance, Exercise influences BDNF chromatin regulation, DNA demethylation of the BDNF promoter IV, and phosphorylation of MeCP2 to stimulate BDNF mRNA and protein synthesis (Gomez-Pinilla et al., 2011). Different neurotransmitters (e.g. GABA, glutamate, serotonin) are also secreted by neurons in the neurogenic niche (Niederer et al., 2011). Studies found strong links among physical activity, brain health, and epigenetic mechanisms that affect neurogenesis, brain plasticity, and function (Christiansen et al., 2016; Fernandes et al., 2017; Horvath et al., 2015; Hunter et al., 2019; Lista and Sorrentino, 2010; Schenk et al., 2019; van Praag, 2008; van Praag et al., 1999; Woelfel et al., 2018). It's clear now that inactivity is epigenetically deleterious.

5.2. Abusive substances

Despite adverse consequences, compulsive seeking and taking of abusive substances (e.g. psychostimulants, opiates) is termed drug addiction (Koob and Volkow, 2016). Epigenetic modulation plays a crucial role in the vulnerability of drug addiction. All abused or chronic use of drugs act on mesolimbic dopamine circuitry in the fundamental cell type within the nucleus accumbens as well as midbrain ventral tegmental area and innervation of medium spiny neurons to induce long-lasting structural, electrophysiological, and transcriptional changes via epigenetic maladaptations (Feng et al., 2014; Hyman et al., 2006; Kelley and Berridge, 2002). Hyperacetylation of histones (H3 and H4) in nucleus accumbens due to an imbalance between histone acetyltransferases (e.g. cAMP response element binding protein-binding protein) and histone deacetylases due to acute or chronic exposure to abusive drugs facilitates rapid expression of associated genes at the specific locus to contribute to addiction (Barrett and Wood, 2008; Botia et al., 2012; Ferguson et al., 2013, 2015; Kumar et al., 2005; Levine et al., 2011; Malvaez et al., 2011; Pandey et al., 2008; Renthal et al., 2007, 2009; Schroeder et al., 2008; Shen et al., 2008; Shogren-Knaak et al., 2006; Taniguchi et al., 2012). Further research demands to know the consequences of gene-specific histone-post translational modifications within the context of drug addiction. Alcohol addiction has been found to modulate epigenetically. Excessive alcohol drinking not only affects individuals but also affects their offspring throughout various stages of their development. Excessive alcohol exposure during pregnancy leads to fetal alcohol spectrum disorder and induces various epigenetic changes (Resendiz et al., 2013; Ungerer et al., 2013). Excessive alcohol exposure during pregnancy induces DNA methylation at 5-methylcytosine (5 mC) and 5-hydroxymethylcytosine (5hmC) during embryonic and brain development (Chen et al., 2013; Guo et al., 2011; Ito et al., 2011; Kriaucionis and Heintz, 2009; Liu et al., 2009; Tahiliani et al., 2009; Zhou et al., 2011a). Alcoholism also raises histone 3 acetylation globally and changes miRNA expression in neural stem cells in a cell-type and stage-specific manner (Kim and Shukla, 2006; Miranda, 2012; Pal-Bhadra et al., 2007; Shukla et al., 2007; Wang et al., 2009). Opium, an old analgesic medication, causes severe effects on the offspring's nervous system by increased methylation at the *OPRM1* promoter region (Chorbov et al., 2011; Das et al., 2004). Prenatal exposure to methamphetamine, another known abusive drug, led to oxidative stress in the embryonic brain and postnatal neurodevelopment and cognitive and behavioral defects (Jeng et al., 2005; Kwiatkowski et al., 2014). Prenatal methamphetamine exposure results in differentially methylated regions in the hippocampal DNA of adolescent offspring and leads to abnormal behavior (Itzhak et al., 2015). The hypermethylated and hypomethylated differential methylated regions are enriched for "cerebral cortex GABAergic interneuron differentiation" and "embryonic development."

5.3. Cannabis

Chronic cannabinoid exposure maintains protracted effects. The epigenome provides the cellular context for cannabinoid exposure to modulate the functionality of genes and related behavior (Szutorisz et al., 2016; Szutorisz and Hurd, 2016, 2018). Epigenetics contribute to

Table 2
Studies on prenatal exposure to environmental agents related with epigenetics changes.

Agents	Histone modification	DNA methylation	miRNAs	Outcomes
Alcohol	*H3Kac, H3K4me, H3K9me, H3K27me* (Pal-Bhadra et al., 2007; Shukla et al., 2007; Subbanna et al., 2013)	5 mC, 5hmC (Chen et al., 2013; Garro et al., 1991; Otero et al., 2012; Ouko et al., 2009; Wolff et al., 1998)	*miR148, miR152, miR21, miR153, miR335* (Kutay et al., 2012; Sathyan et al., 2007)	• *Delayed formation in the neural tube, forebrain, hindbrain* (Zhou et al., 2011b) • *Delayed maturation and diminished size of hippocampus* (Chen et al., 2013) • *Declined neuron cell number, cortical plate, thickness* (Zhou et al., 2011b)
Arsenic	*H3ac* (Cronican et al., 2013)	5 mC (Intarasunanont et al., 2012; Kile et al., 2012; Xie et al., 2007)	*let 7a, miR16, miR17, miR20a, miR20b, miR26b, miR96, miR98, miR107, miR126, miR195, and miR-454* (Rager et al., 2014)	*Interrupted spatial and episodic memory, as well as fear conditioning performance* (Cronican et al., 2013)
Bisphenol A	*H3ac* (Yaoi et al., 2008)	5 mC (Yaoi et al., 2008)	*N/A*	*Delay the perinatal chloride shift in cortical neurons* (Yeo et al., 2013)
Caffeine	*N/A*	5 mC (Buscariollo et al., 2014; Dan Xu et al., 2012)	*N/A*	*Growth retardation* (Dan Xu et al., 2012)
Cannabis	*H3K4me, H3K9me* (Dinieri et al., 2011)	*N/A*	*N/A*	*Upregulated opiate reward sensitivity in adult* (Dinieri et al., 2011)
Cadmium	*N/A*	5 mC (Castillo et al., 2012; Kippler et al., 2013; Sanders et al., 2014)	*N/A*	*Decreased birth weight and height* (Castillo et al., 2012)
Folic acid deficiency	*H3ac* (Akchiche et al., 2012)	5 mC (Guéant et al., 2013)	*miR124, miR302a* (Kerek et al., 2013; Liang et al., 2012)	*Brain size reduction, growth retardation* (Kerek et al., 2013)
Lead	*H3ac, H3K4me* (Bihaqi et al., 2011)	5 mC (Bihaqi et al., 2011; Schneider et al., 2013)	*N/A*	*Increased neurodegeneration in primate* (Bihaqi et al., 2011)
Methyl mercury	*H3ac, H3K27me* (Onishchenko et al., 2008)	5 mC (Bose et al., 2012; Onishchenko et al., 2008)	*N/A*	*Depression like behaviour* (Onishchenko et al., 2008)
Methamphetamine	*N/A*	5 mC (Itzhak et al., 2015)	*N/A*	*Increased cocaine reward and hyper-locomotion as well as diminished conditional fear* (Itzhak et al., 2015)
Nicotine	*H3ac* (Levine et al., 2011)	5 mC (Breton et al., 2009; Maccani et al., 2013; Suter et al., 2010, 2011)	*miR16, miR21, miR146a* (Maccani et al., 2010)	• *Increased aggression, locomotion in adult male* (Yochum et al., 2014) • *Birth weight reduction* (Suter et al., 2011)
Opioid	*N/A*	5 mC (Chorbov et al., 2011)	*N/A*	*N/A*
Stress	*H3ac, H3K9me, H3K27me* (Dalton et al., 2014; Réus et al., 2013)	5 mC (Champagne and Curley, 2009; Darnaudéry and Maccari, 2008; Heim and Binder, 2012; Szyf, 2013)	*miR16, miR9, miR29a, miR124, miR132, miR212* (Bai et al., 2012; Uchida et al., 2011)	*Induces depressive-like behaviors, altered response to aversive environments* (Champagne and Curley, 2009; Franklin et al., 2010)
Valproic acid	*H3ac* (Balmer et al., 2012; Monti et al., 2010)	*N/A*	*N/A*	*Diminished birth rate, reduced sociability, and social preference* (Kim et al., 2011)
γ-hydroxybutyrate	*H3ac* (Klein et al., 2009)	*N/A*	*N/A*	*N/A*

regulating the endocannabinoid system, which is critical in controlling different synaptic communication and plasticity in healthy brain and different neuropsychiatric disorders over short and long period (Batool et al., 2019; Bayraktar and Kreutz, 2018; D'Addario et al., 2013; Dambacher et al., 2013; Dillon, 2012; Meccariello et al., 2020; Weaver, 2014). Table 3 demonstrates the epigenetic mechanisms of developmental cannabis exposure. These studies suggest that cannabis exposure during multiple stages of development modulates epigenetic mechanisms to change neural and behavioral phenotypes. Cannabis acts through the germ line to modulate synaptic development and behavior

Table 3
Studies on cannabinoid exposure related with epigenetics dysregulation.

Cannabinoid types	Epigenetic modifications	Exposure period and models	Studied brain region and effects
Δ9-tetrahydrocannabinol	*H3K4me2, H3K9me3 Promoter, gene body*	Prenatal male rats Adolescent male rats	↓ *Drd2* mRNA levels in nucleus accumbens of adult brain (Dinieri et al., 2011) ↑ *Penk* mRNA levels in nucleus accumbens shell of adult brain (Tomasiewicz et al., 2012)
	Global H3K9me3 levels, promoters	Adolescent female rats	↓ mRNA expression of genes related to endocannabinoid system and synaptic plasticity in prefrontal cortex of adult brain (Cuccurazzu et al., 2018)
	H3K4me2, H3K9me3, Global H3K14ac levels	Adolescent and adult female rats	Brain region-specific and age-specific alterations of histone modifications at different times after exposure in hippocampus, nucleus accumbens and amygdala of adolescent and adult brains (Prini et al., 2017)
	CpG DNA methylation at promoters, intergenic regions, especially in gene bodies	Adolescent female and male rats	Altered methylation at loci implicated in synaptic plasticity, including the *Dlg4* gene network of nucleus accumbens in adult brains (Watson et al., 2015)
	DNA methylation at promoter	Adult male rats	↓ DNA methylation of synaptic *Dlgap2* in nucleus accumbens of adult brains (Watson et al., 2015)
WIN-55,212–2 cannabinoid agonist	*Intragenic DNA methylation*	Adolescent male mice	↑ DNA methylation and ↓ mRNA expression of *Rgs7* in hippocampus of adult brains (Tomas-Roig et al., 2017)
	Chromatin accessibility (ATAC-seq) at promoter, gene body *Global DNA methylation levels*		↑ Accessibility at *Npas2* and splicing at prefrontal cortex of adult brain (Scherma et al., 2020). ↑ DNA methylation and ↑ DNMT expression at prefrontal cortex of adult brain (Ibn Lahmar Andaloussi et al., 2019).
HU-210 cannabinoid agonist	*microRNAs*	Adolescent male mice	Expression of various microRNAs altered at entorhinal cortex of adolescent male rat (Hollins et al., 2014)

across generations (Szutorisz et al., 2014; Watson et al., 2015).

5.4. Micronutrients

Research focusing on dietary impact on gene expression via epigenetic mechanisms on brain development and neuropsychiatric diseases/disorders is evolving (Canani et al., 2011; Levi and Sanderson, 2004; Prado and Dewey, 2014; Roseboom et al., 2006). Studies found that neuropsychiatric diseases during adulthood were linked with prenatal exposure to inadequate nutrition (Roseboom et al., 2006; St Clair et al., 2005; Susser et al., 1996; Susser and Lin, 1992). Early malnutrition induces lasting epigenetic changes in the brain, leading to behavioral consequences and diseases/disorders in later life (Canani et al., 2011; Kundakovic and Jaric, 2017). For instance, studies found an association between maternal iron deficiency and the risk of autism spectrum disorders among offspring due to epigenetic modulation (Insel et al., 2008; Schmidt et al., 2014). The effects of folic acid on epigenetics through the methionine pathway to generate methyl donors for DNA and histone methylation might support fetal neural tube development (Akchiche et al., 2012; Berry et al., 1999; Guéant et al., 2013; "Use of Folic Acid for Prevention of Spina Bifida and Other Neural Tube Defects—1983-1991," 1991). N-3 polyunsaturated fatty acids (PUFAs) are also known to control DNA methylation state globally and via gene-specific methylation of promoter sequences during development (Heberden and Maximin, 2019). Higher intake of n-3 PUFAs during pregnancy supports fetal brain development (Basak and Duttaroy, 2022). Despite some studies on epigenetic changes in neurodevelopmental-related genes (Kundakovic et al., 2013; Toledo-Rodriguez et al., 2010), there is no established epigenetic mechanism for how the environment does have confounding effects on neurodevelopment disorders. Therefore, more studies need to be done to deepen the knowledge about the relationship between nutrition, epigenetics, and neurodevelopment.

5.5. Caffeine

As an adenosine receptor blocker, caffeine is a widely used stimulant worldwide. Caffeine accumulation aggravates stress response (Yeomans et al., 2007). Chronic caffeine ingestion activates the maternal and placental renin–angiotensin system (RAS) and induces p53-dependent placental apoptosis, which leads to fetal intrauterine growth retardation (Huang et al., 2012). Soellner and colleagues have demonstrated that chronic prenatal caffeine exposure interrupts novel object recognition and radial arm maze behaviors in adult rats (Soellner et al., 2009). Caffeine exposure during pregnancy inhibits the development and function of the fetal hypothalamic-pituitary-adrenal axis-associated neuroendocrine metabolism (Liu et al., 2012; Xia et al., 2014; D. Xu et al., 2012b, 2012a; Xu et al., 2011). Prenatal caffeine exposure inhibits fetal adrenal steroidogenesis by blocking the enzymes (StAR/P450scc, 3β-HSD, P450c21, and P450c11) due to altered epigenetic modifications (DNA methylation and histone acetylation) of the promoter region for the transcriptional activator SF-1 (Yan et al., 2014). However, further studies might clarify the role of epigenetic modification by caffeine.

5.6. Pollutants

Different types of pollution are increasing daily due to industrialization, which is contributing to causing various diseases or disorders. For example, tobacco smoking is the most common pollutant that modulates early neurobehavioral development. Prenatal smoking increases children's risk of attention deficit hyperactivity disorder due to *DAT1*, *DRD4*, and *CHRNA4* gene variations (Becker et al., 2008; Kahn et al., 2003; Todd and Neuman, 2007). The epigenetic effects transmitted intergenerationally due to smoking predict family dysfunction and poor health (Miles and Weden, 2012; Seeman et al., 2010; Taylor et al., 2006). However, the necessity of a better understanding of underlying microprocesses doesn't preclude policies, sanctions, and universal public health campaigns against childhood exposure to tobacco smoke in domestic settings.

Traffic-related air pollution is also a significant source of air pollution in urban areas, particularly for particulate matters (PMs) [according to size, categorized as "coarse" (PM_{10}), "fine" ($PM_{2.5}$) μm, and "ultrafine" ($PM_{0.1}$), having an aerodynamic diameter less than 10 μm, less than 2.5 μm and less than 0.1 μm, respectively], which is composed of gases like nitrogen oxides (e.g., NO_2, NO_x) and sulfur dioxide (SO_2) as well as black carbon, absorbed metals, and polyaromatic hydrocarbons of various size fractions (Johnson et al., 2021; Rider and Carlsten, 2019). Traffic-related air pollution modulates brain development and function through DNA methylation (Rider and Carlsten, 2019). Studies found that prenatal exposure to $PM_{2.5}$ results in thinning of the cortex in many regions of the brain and impaired inhibitory control, which is related to neurobehavioral dysfunctions such as addictive behavior and attention deficit hyperactivity disorder due to altered DNA methylation, including global hypomethylation, gene-specific changes in methylation process as well as downregulated expresión of miR-21, miR-146a, and miR-222 (Johnson et al., 2021).

Lead toxicity is also quite common. Lead exposure is commonly caused by food, water, tobacco smoke, air, dust, and soil. The fetus can be exposed via placental transfer ("Scientific Opinion on Lead in Food," 2010; World Health Organization, 2010). Surprisingly, bioavailable lead is absorbed better in infants than adults and developmental neurotoxicity is a significant health effect of lead exposure ("Scientific Opinion on Lead in Food," 2010; Tarragó and Brown, 2017). Lead can interrupt epigenetic modulation (Khalid and Abdollahi, 2019). In newborns, prenatal lead exposure results in genomic DNA methylation (*CLEC11A, DNHD1, LINE1*) (Pilsner et al., 2009; Wu et al., 2017). Epigenetic modulations, including DNA methylation, influence *BDNF* expression across tissues, including the brain and blood (Ikegame et al., 2013; Kundakovic et al., 2015; Stenz et al., 2015). Therefore, BDNF can be used as a peripheral biomarker of psychiatric disorders (Kundakovic et al., 2015; Stenz et al., 2015). However, further research might explain lead exposure-mediated psychiatric diseases.

Another known pollutant is bisphenol A. Due to industrialization, the endocrine-disrupting chemical bisphenol A induces neurotoxicity through ingesting contaminated foods and drinks or inhalation (Chianese et al., 2017). Bisphenol A interrupts androgenic activities via binding with steroid receptors, e.g., estrogen receptor α, estrogen receptor β, estrogen-related receptor γ, androgen receptor, GPER30, etc (Chianese et al., 2017; Murata and Kang, 2018; Tavares et al., 2016; Vandenberg et al., 2013). Bisphenol A and its analogs change methylation of CpG islands in the promoter regions of specific genes or the genome-wide methylation in fetal and adult brain through DNA methyltransferases modulation, while is transmitted across the generations (Doshi et al., 2011; Drobná et al., 2018; Wolstenholme et al., 2011; Yaoi et al., 2008). Bisphenol A and its analogs modulate histone methylation and acetylation to affect chromatin remodeling by NAD + -dependent deacetylase sirtuin 1 (Chen et al., 2017; Doherty et al., 2010; Eichenlaub-Ritter and Pacchierotti, 2015; Viré et al., 2006). Even Bisphenol A mediated post-transcriptional modification of other RNA species by non-coding RNAs (e.g., microRNA, long non-coding RNA, circRNA) affects brain physiology in health and disease (Godlewski et al., 2019; Leighton and Bredy, 2018; Noack and Calegari, 2018; Sekar and Liang, 2019; Shi et al., 2017). Bisphenol A-induced impaired hippocampal neurogenesis correlates with upregulated DNA methylation of the CREB-regulated transcription coactivator 1 (Jang et al., 2012). Bisphenol A also increases histone H3 acetylation in the cerebral cortex and hippocampus to promote memory and cognitive dysfunction (Bale, 2015; Keverne, 2014; Kumar and Thakur, 2017). Not only gestating mothers but also paternal exposure to bisphenol A influences fetus development [as spermatozoa use non-coding RNAs to carry paternal hereditary information] (Dobrzyńska et al., 2015; Guerrero-Bosagna et al., 2013; Kuruto-Niwa et al., 2007; Mendonca et al., 2014). Bisphenol A exposure causes sex-specific, dose-dependent (linear and curvilinear),

and brain region-specific changes in the expression of epigenetic regulators (DNMT1 and DNMT3A) as well as genes encoding estrogen receptors and estrogen-related receptor-γ (Kundakovic et al., 2013). Bisphenol A increases DNA methylation levels in the promoter region of the *GRIN2B* gene (Alavian-Ghavanini et al., 2018). Bisphenol A has been shown to induce hypermethylation of the 5-prime end promoter region of the *BDNF* gene in female offspring but enhances DNA methylation of the transcriptional regulators of the glucocorticoid receptors *FKBP5* was found within the hippocampus of male rats to influence spatial learning and memory capabilities (Alavian-Ghavanini et al., 2018; Cheong et al., 2018; Kitraki et al., 2015). Interestingly, bisphenol A exposure in the fetal stage did not significantly affect hippocampal DNA methylation (Aiba et al., 2018). Overall, bisphenol A induces behavior-related and sex-specific epigenetic modifications predominantly targeting the expression pattern of sexually dimorphic genes. However, further studies are needed to determine the exact dose range and exposure time during development by which bisphenol A can induce epigenetic modifications.

5.7. Hypoxia

Maternal and fetal hypoxia in pregnancy disorders influences normal fetal development and pathological processes (Pouyssegur and López-Barneo, 2016). Various reviews accredit maternal-fetal hypoxia affects organogenesis and brain functions (Faa et al., 2016; Newby et al., 2015; Schlotz and Phillips, 2009). Abnormal levels of fetal hypoxia provoke epigenetic modulation that modifies target gene expression (Cerda and Weitzman, 1997; Luo et al., 2006). However, more mechanistic studies are necessary to study hypoxia-mediated direct and indirect effects on fetal development, gene expression, epigenetic changes in specific genes, and consequences later in life.

6. Conclusions

This thorough review sheds light on the complex interplay between epigenetic modifications and their substantial impact on brain functions. The critical impacts of the micronutrients, physical activity, caffeine, toxins, and harmful substances in the brain's epigenetic landscape are now evident. The intricate links between epigenetic changes and behavioral outcomes emphasize the possibility of targeted therapies that could harness the power of epigenetic control to improve cognitive function and attenuate the detrimental consequences of substance addiction and environmental pollutants. Despite strong evidence of the different roles of epigenetic alterations in gene expression and phenotypic outcomes, translating the findings from animal studies to the health effects of environmental exposure to humans needs to be improvised. To untangle the intricacies of epigenetic modifications and their long-term impact, there is still a need for interdisciplinary collaboration, advanced technical breakthroughs, and longitudinal investigations.

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