AKADÉMIAI KIADÓ

Journal of Psychedelic Studies

8 (2024) 1, 28–42

DOI:
10.1556/2054.2024.00343

REVIEW ARTICLE

Ketamine and epigenetic processes in depression, intersection between serotonergic and glutamatergic pathways

ARGHAVAN NEPTON[1*], HESAM FARAHANI[2], MONNICA T. WILLIAMS[1,3], LINDA BOOIJ[4] and SONYA C. FABER[5]

[1] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada

[2] School of Linguistics and Language Studies, Carleton University, Ottawa, ON, Canada

[3] School of Psychology, University of Ottawa, Ottawa, ON, Canada

[4] Research Centre, Douglas Mental Health University Institute & Department of Psychiatry, McGill University, Montreal, QC, Canada

[5] Department of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

Received: November 8, 2023 • Revised manuscript received: January 19, 2024 • Accepted: February 14, 2024
Published online: March 29, 2024

ABSTRACT

Background: Hypotheses surrounding the etiology of depressive disorders encompass a wide range of biological changes that can occur in a depressed individual, from gene variations to epigenetic modifications and not only serotonergic mechanisms. Once again, the therapy response of the patient to antidepressants is connected to modifications in the epigenetic regulation of genes within the serotonergic system. The persistence of depressive symptoms points to the possibility that stable molecular adaptations in the brain, particularly at the epigenetic level, may be involved. *Methods:* Narrative review to first, discuss the historical evidence behind how serotonin (5-hydroxytryptamine, 5-HT) signaling and its associated actors are involved in various biological processes and second, examine the role of ketamine as one of the newer treatments for depression. *Results:* There is increasing evidence that responses to psychotherapy for mood disorders are correlated with epigenetic alterations. Although therapy response appears to be associated with epigenetic changes in genes regulating the serotonergic system, there are multiple lines of research that provide additional data implicating epigenetic alterations in the glutamatergic system. Also, the epigenetic regulation of target genes along the HPA axis are becoming more intriguing in linking mood disorders with environmental stressors, and warrant a closer look. Recent research suggests that ketamine's antidepressant effects may be linked to epigenetic alterations. Considering the multiple studies linking BDNF with depression, further exploration of its relation with ketamine in the context of epigenetic signaling is warranted. *Conclusion:* Understanding how and to what extent epigenetic mechanisms change gene expression and how these changes are influenced by environmental stressors may eventually allow mental health professionals to better understand the biological basis of depression as well as to gauge the efficacy, onset, durability and duration of therapies to treat mood disorders. Moreover, understanding the relation between serotonergic neurotransmission and epigenetic mechanisms of how these may be modified by ketamine should lead us to a greater knowledge of their therapeutic potential.

KEYWORDS

depression, epigenetic, glutamatergic systems, ketamine, methylation, psychedelics, serotonergic systems

*Corresponding author. Cellular and Molecular Medicine, University of Ottawa, Roger Guindon Hall, 451 Smyth Rd Ottawa, ON, K1H 8M5, Canada.
E-mail: Arghavan.nepton@uottawa.ca

INTRODUCTION

Depression is a psychiatric disorder that has a multifactorial etiology, influenced by both genetic and environmental processes, and their interactions (Alshaya, 2022; Gonda et al.,

2018). While the exact biological basis of depression remains incompletely understood, a variety of genes, neurotransmitters and brain regions that appear to be involved in the development and manifestation of the disorder have been identified over the last decades. Furthermore, an increasing number of studies have studied the role of epigenetic processes as a physiological mechanism of how genetic factors interact with the environment in relation to risk for depression (Booij et al., 2013).

Although it has long been held that monoamine mechanisms are involved in the neuropathogenesis of mood disorders, recent studies have called into question the causality between serotonin and depression with a systematic review demonstrating little support for the hypothesis that depression is caused by a decrease in serotonin concentrations or activity (Moncrieff et al., 2022). Nonetheless, in the first part of this review, we discuss the historical evidence behind how serotonin signaling and its associated actors have been thought to be involved, as they are indeed important in various biological processes, including those related to brain development, emotional control, stress response, and mood.

In the second half of this review, we pivot to one of the newer treatments for depression looking at the role of ketamine, the glutamatergic system and the associated role of brain-derived neurotrophic factor (BDNF) with focus on their epigenetic regulation. This review is not an exhaustive review of the epigenetic literature associated with depression; many reviews have been published (Albert, Le Francois, & Vahid-Ansari, 2019; Booij et al., 2013; Yuan et al., 2023), rather, we highlight literature on the epigenetic regulation of some relevant genes in the serotonergic pathway, the glutamatergic pathway and some recent genetic studies linking these two systems. Our lab has first-hand experience treating patients with major depressive disorder (MDD), with ketamine and we have a special interest in the intersection between mood disorders and racial trauma (Faber, Khanna Roy, Michaels, & Williams, 2023; Williams, Faber, & Duniya, 2022). We are particularly interested in the mechanisms behind the unprecedented efficacy with which ketamine is able to treat our patients and, as the tools to explore epigenetic mechanisms become more accessible, our lab is in the process of exploring these mechanisms.

Relation between mood disorders and the serotonergic system

Serotonin (5-hydroxytryptamine, 5-HT) signaling involving the serotonin transporter (5-HTT; also known as the SERT gene or SLC6A4), monoamine oxidase A (MAO-A), tryptophan hydroxylase 2 (TPH2), and 5-HT receptors (aan het Rot, Mathew, & Charney, 2009) (Fig. 1A) can be considered as among the most essential 5-HT-associated genes in mammals and have been demonstrated to play a role in brain development, emotional control, and stress response with 5-HT along with norepinephrine and dopamine being major monoamine neurotransmitters of the brain (Bowman et al., 2020).

The 5-HTT is responsible for the reuptake of serotonin at the presynaptic interface and although its role in serotonergic neurotransmission has long been indicated by Kanner and Schuldiner (Kanner & Schuldiner, 1987), it was not until 1994 that Lesch and co-workers sequenced and characterized the 5-HTT gene (Lesch et al., 1994). Because 5-HT is involved in regulating the stress response and decreased 5-HT activity increases dopaminergic transmission, altered regulation of the 5-HTT gene and its variants have been purported to increase vulnerability to stressful environments and thus intensify the possibility of mental disorders (Vahid-Ansari & Albert, 2021). There is a large body of research which describes the function of 5-HTT in psychiatric disorders. Findings reveal that genetic variants (i.e short or long forms) of the 5-HTT gene modulate serotonergic function (Canli & Lesch, 2007) (Fig. 1B), and that variation in the preceding genetic variants seem to be associated with diseases including major depressive disorder (MDD) and bipolar disorder type I (Abdolmaleky et al., 2014; Vahid-Ansari & Albert, 2021; Yokoyama, Bonham, & Sturm, 2015).

The association of the serotonergic system with mood disorders has made these receptors attractive pharmacologic targets and as such, 5-HT receptor-specific agonists and antagonists have been developed as a treatment for mental disorders. The 5-HT_{1A} receptor has inhibitory control over 5-HT neuronal activity, which means that the binding of

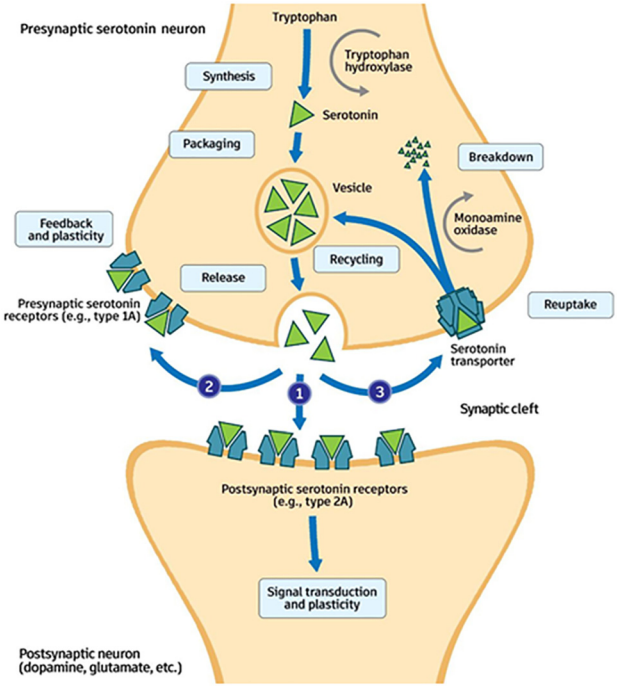

Fig. 1A. Serotonin neuron releases 5-HT into the synaptic cleft where it performs a variety of functions. (1) It attaches to the 5-HT receptors on other neurons and activates the postsynaptic 5-HT receptors initiating signal transduction. (2) It binds to the presynaptic 5-HT receptors on the neuron that released it, providing feedback and regulating neuronal plasticity. (3) It taken up by the 5-HTT of the neuron which initially released it (presynaptic serotonin neuron) and is recycled. Adapted from aan het Rot et al. (2009)

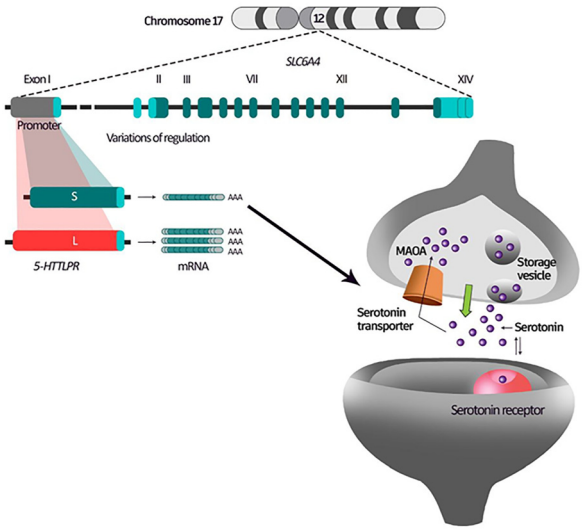

Fig. 1B. Depiction of the 5-HTT gene's long and short polymorphism and 5-HT release, reception, and recycling in neurons. The long (L) 5-HT receptor LPR variant (shown in red) of the 5-HT receptor gene transcribes significantly more mRNA and protein than the short (S) variant (shown in blue). This causes the synaptic cleft to fill up with excessive amounts of 5-HT. Adapted from Canli and Lesch (Canli & Lesch, 2007)

5-HT to this receptor serves to reduce the further release of 5-HT through a feedback mechanism. It is also referred to as an autoreceptor and is the most well-studied of the 5-HT receptors. In attempts to link these biochemical mechanisms to mental conditions, studies have indicated that individuals with MDD and suicide victims with MDD have greater levels of 5-HT_{1A} in 5-HT neurons of the dorsal raphe (Hesselgrave & Parsey, 2013; Stockmeier et al., 1998). 5-HT_{1A} also functions as a postsynaptic receptor and is found expressed in main brain areas such as the cortical, hippocampal, and hypothalamic regions, all of which have been found to be associated with a variety of functions, including anxiety, depression, and stress (Albert & Vahid-Ansari, 2019). Several lines of evidence converge to show correlations between low or altered serotonergic function and traits such as aggression and impulsivity (Banlaki et al., 2015). The preceding findings lead to the hypothesis that the primary role of the serotonergic circuit was to "rescue" the organism from aversive or dangerous situations, and any reduction in serotonergic function could lead to increased tolerance for undesirable stimuli, endangering the organism (Banlaki et al., 2015).

There are however many indications that the serotonin theory of mood disorders has not provided a complete picture of depression. Pharmaceutical antidepressants, primarily classified as selective 5-HT reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), were commonly used as first-line treatment for depression (Sun et al., 2021) since the initial approval of Prozac by the FDA in 1987. However, studies indicate that the level of response to antidepressants is highly individually variable (Cusin et al., 2002; Dong et al., 2016; Ferrari et al., 2013; Lin et al., 2014) with only one to two-thirds of patients showing improvement in the first round of treatment (Dong et al., 2016; Sun et al., 2021). A recent systematic review with a total of more than 10,000 patients showed no sufficient empirical evidence supporting the hypothesis that depression is caused by abnormalities in 5-HT levels or activity (Moncrieff et al., 2022). These studies rather showed that the impact of stressful life events significantly influenced the risk of developing depression, with the occurrence of more stressful life events corresponding to a higher likelihood of depression (Chiappelli et al., 2021).

Overall, literature indicates that depression should be understood as influenced by multiple genetic and environmental factors, with 5-HT signaling as an important but just one piece of the puzzle. It is also important to note that the role of 5-HT in depression remains incompletely understood and requires additional active research. In sum, hypotheses surrounding the etiology of depressive disorders encompass a wide range of biological changes that can occur in a depressed individual, which may include diverse factors ranging from gene variations to epigenetic modifications, and not only serotonergic mechanisms should be taken into account.

Epigenetics

Epigenetic regulation refers to modification in gene expression that can be inherited by the next generation without affecting the DNA sequences that encode for those genes (Hochberg et al., 2011). Epigenetic modifications are assumed to be at least partly reversible and can alter how the organism reads a DNA sequence. Understanding how and to what extent epigenetic mechanisms change gene expression and how these changes are influenced by environmental stressors may eventually allow mental health professionals to better understand the biological basis of depression as well as to gauge the efficacy, onset, durability and duration of therapies to treat mood disorders.

Early life stress or trauma leading to depression has been hypothesized to result in epigenetic modifications of serotonergic system genes, growth factor genes, hormones and genes in the glutamatergic pathways (Parade et al., 2017). The persistence of depressive symptoms points to the possibility that stable molecular adaptations in the brain, particularly at the epigenetic level, may be involved. Examining the epigenetic modifications of these genes may therefore help shed light on the nature-nurture relationship in depression (Soga et al., 2021). Epigenetic changes are purported to lead to imbalanced levels of proteins that regulate central nervous system processes by affecting DNA transcription and/or mRNA translation. With the advancement of new technologies and knowledge, epigenetic research has become more feasible to explore within the field of psychiatry.

There are four mechanisms that cause epigenetic changes. First, there is *DNA methylation*, the most well-known epigenetic change which involves the addition of a methyl group to the DNA molecule. This change can affect

gene expression by making certain genes more or less accessible to the cell's machinery. DNA methylation occurs when a methyl group (CH_3) is added to DNA, thereby modifying gene expression. The process occurs when a CH_3 is transferred to the 5-carbon (C-5) of the cytosine ring in DNA, resulting in 5-methylcytosine (5-mC). This prevents transcription factors from binding to DNA, and thus high methylation levels are linked to the suppression of gene expression, increasing or decreasing the levels of transcription (Soga et al., 2021) (Fig. 2). Secondly, there is *Histone Modification/Acetylation*. Histones are proteins that package DNA into a compact structure called chromatin. Modification of histones can affect gene expression by changing the structure of chromatin, making it more or less accessible to transcription factors. Given that histone proteins manage the tightness of chromatin coils, and a tightly packed chromatin prevents regulatory factors from accessing DNA, the number of genes that are expressed can be controlled by modifying histones. Thirdly, there is the process of *Chromatin Remodeling* which refers to changes in the structure of chromatin that can affect gene expression. This can be achieved through the action of enzymes that add or remove chemical groups from histones, or by physically moving nucleosomes (the building blocks of chromatin) along the DNA molecule. Finally, there is *Non-coding RNA*. These are small RNA molecules that do not code for proteins but can regulate gene expression by binding to messenger RNA (mRNA) and preventing it from being translated into protein (Crabtree, 2020).

There are several lines of evidence establishing an association between DNA methylation of 5-HT-associated genes and mental disorders as well as evidence showing an epigenetic influence on the therapeutic response to medications in clinical populations (Parade et al., 2017; Shen et al., 2020). However, the regulation of the serotonergic gene family has been shown to have multiple layers. Several critical 5-HT pathway genes also have variants or polymorphisms which influence their activity and these have been purported to have effects on mood disorders. Additionally, there are overlapping epigenetic switches within these same groups of genes (Shen et al., 2020; Wang, Zhang, Lv, et al., 2018).

The preceding epigenetic mechanisms are assumed to offer increased flexibility for an organism to dynamically modulate mood states above and beyond genetic polymorphism. The reversibility of DNA methylation gives the organism the opportunity to respond to the environment. This means that even if polymorphic variation (i.e., short and long promoter variants of serotonergic genes) may influence neuroticism or OCD (Walitza et al., 2011) (Fig. 3), de-methylation layered atop, may provide an additional mechanism to modify gene expression and contribute to regulation or rebalancing of the mood state. The promise of understanding epigenetic regulation of genes, is the idea that directed changes may be made in the environment (through psychotherapy or medications) that can allow monitoring of therapeutic changes to the mood state.

SLC6A4 or 5-HTT: Studies on the promoter of the 5-HTT gene (SLC6A4) have led to several studies that have shed light on genetic and epigenetic mechanisms in this system (Caspi et al., 2003). Studies found that the levels of 5-HT in the synapse are directly influenced by the SLC6A4

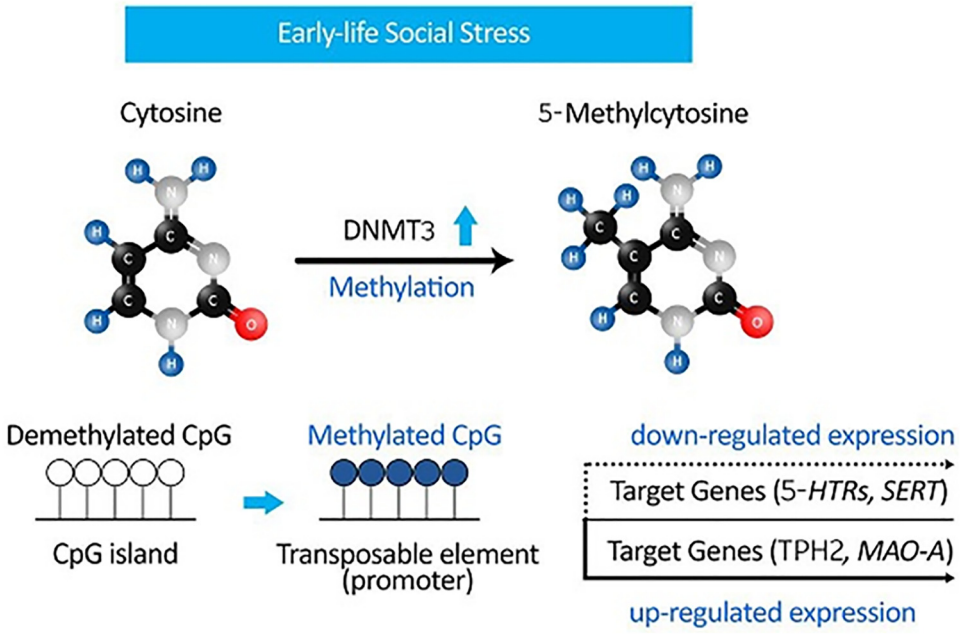

Fig. 2. After being exposed to early-life social stress, DNA methylation of CpG islands in the genetic code silences gene expression. Methylation is caused by a methyltransferase (DNMT3) adding a methyl group at the 5-carbon of the cytosine ring. When methylation happens on a transposable element, it suppresses gene transcription associated with that element. 5-HTRs (5-HT receptors); SERT (5-HTT); TPH2; MAO-A (Soga et al., 2021)

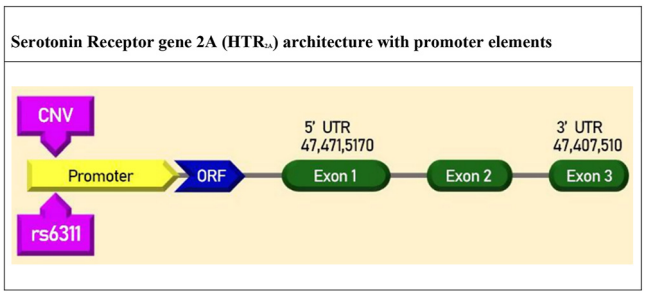

Fig. 3. The HTR_{2A} gene alignment with its promoter region (not to scale). The transcriptional control region (yellow) of the gene that encodes the 5-HT receptor 2A has been found to influence the occurrence, the onset, and the severity of OCD. The locus involved is a single nucleotide polymorphism (SNP), −1438G/A (rs6311). Carriers of one copy (deletion) of the copy number variant (CNV) were associated with a very early onset OCD (Walitza et al., 2011)

which in turn appears to be associated with mood. Abdolmaleky et al. (2014) furthermore found that in individuals with schizophrenia, the SLC6A4 promoter (already known to have S (short) and L (long) promoter variants) is hypomethylated, causing decreased expression (Abdolmaleky et al., 2014). When non-coding regions outside of the SLC6A4 promoter region were examined to locate other epigenetic modifications in individuals with mood disorders, the CpG island upstream of exon 1 and the island shore region were found to be hypermethylated in schizophrenia (Abdolmaleky et al., 2014; Ikegame et al., 2020). The data also indicated that hypermethylation of the SLC6A4 promoter was correlated with increased sensitivity to both positive and negative effects of cocaine in contrast to participants with decreased methylation of the promoter (Longtain et al., 2022). This means that the genetic form of this promoter, which is also regulated by its methylation state, may have an affiliation with mood states including depression and posttraumatic stress disorder (PTSD). Given that stress plays a decisive role in the epigenetic modifications in the brain (Gudsnuk & Champagne, 2012), it seems reasonable to expect a role for early-life social stress in the epigenetic regulation of this gene (Soga et al., 2021).

5-HT_{1A}: Just as in the 5-HTT gene, epigenetic regulation of 5-HT genes appears to play a role in mood disorders. Level of methylated 5-HT_{1A} gene appears to be associated with MDD. Several studies have found interactions between methylation in the 5-HT_{1A} gene and MDD in humans. For example, in bipolar depression, higher levels of DNA methylation of the $5HT_{1A}$ promoter in leukocytes has been reported (Carrard et al., 2011). In a blood sample study, a relation was found between stress-induced 5-HT_{1A} gene hypomethylation (of CpG668 site) and antidepressant resistance in treatment-naive individuals with MDD (Wang, Lv, Mao, et al, 2018). Studies have found that the altered response of individuals with MDD to antidepressants is related to the DNA methylation of the 5-HT_{1A} promoter which is modulated by stress (Arias et al., 2005; Le Francois et al., 2008).

HTR_{2A}: For individuals with depression, genotyping of HTR_{2A} polymorphisms may be a promising tool for estimating the outcome and side-effects of antidepressants (Wan et al., 2020). The HTR_{2A} gene is downregulated by several antidepressant medications, and correlates with the step by step decrease in clinical manifestations in depression (Wan et al., 2020). The analysis by Wan et al. concluded that the 1438A/G polymorphism is linked with a higher response to antidepressants while the rs7997012G/A polymorphism correlates with higher antidepressive remission (Wan et al., 2020). HTR_{2A} has also been hypothesized to play a role in the outcome of antipsychotic therapy. Patients with schizophrenia have long been treated with antipsychotic drugs. It is important to note that when referring to antipsychotic medications, it is specific to second-generation antipsychotics that possess antagonistic activity at 5-HT2A sites. However, similar to antidepressants, responses to antipsychotic drugs exhibit considerable individual variability (Tandon, Nasrallah, & Keshavan, 2010).

Epigenetic responses found to correlate with response to therapy

Increasing evidence suggests that responses to psychotherapy for mood disorders are correlated with epigenetic alterations. Research has revealed that changes in the methylation at the promoters of certain genes can in some cases predict response of the patient to antidepressants, and that classical antidepressants can also induce changes in the epigenome (Parade et al., 2017), it has been suggested that this effect may play a crucial role in the efficacy of treatment (Engelmann et al., 2022; Shen et al., 2020).

Studies have shown the effectiveness of antidepressants such as escitalopram in both recovering humans and rats are due to beneficial epigenetic modifications (Seo et al., 2016; Wang, Zhang, et al., 2018). Husum and Mathé documented the effective impact of lithium treatment in reversing the effects of early-life social stress in the adult rat hypothalamus (Husum et al., 2002). Since this treatment reverses environmental effects, it can be imputed to be an epigenetic effect, similarly to other studies showing effective treatment through chemical agents such as Valproic acid (Pinheiro et al., 2012), or dopamine receptor 3 (Drd3) agonists (Shin et al., 2018). However, as noted above, it is of critical importance to note that the response to treatment has shown prominent individual variability and the results from animal studies cannot yet be effectively implemented in human treatment (Soga et al., 2021).

Although therapy response appears to be associated with epigenetic changes in several genes in the serotonergic system, there are multiple lines of research that provide additional data implicating epigenetic changes in genes involved in other signaling pathways (Arčan et al., 2022; Webb, Phillips, Ho, Veldic, & Blacker, 2020) with studies providing data among others, showing overlapping involvement of genes in both the serotonergic and glutamatergic systems. Some of the work is reviewed below.

Negative life experiences and the intricacies of HPA axis regulation in the context of stress response modulation

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key system involved in the body's response to stress, can occur when a person experiences a negative life event. The HPA axis then becomes activated, leading to the release of cortisol, a stress hormone. Corticosteroid hormones play a crucial role in regulating cognitive and emotional processes through influencing the central nervous system. Over time, chronic stress leads to sustained high levels of cortisol and other stress-related hormones (Reshetnikov et al., 2022) which can result in an increased susceptibility to mood disorders such as anxiety and depression (Muvuka et al., 2020; Williams, Chapman, Wong, & Turkheimer, 2012). Chronic activation of the HPA axis has been linked to changes in brain structure *such as* the prefrontal cortex (PFC) which is involved in the regulation of these mood disorders and is affected by repeated stress. This negatively influences PFC cognitive processes which are notably mediated by glutamatergic pathways (Bludau et al., 2019; Chiappelli et al., 2021; Seo et al., 2017; Wang et al., 2022).

Relation between mood disorders and the glutamatergic pathways

NR3C1: Candidate gene NR3C1 (the glucocorticoid receptor gene) is a key gene in the HPA axis and has attracted particular interest, and is associated with regulating the central nervous system's response to external stress stimuli and mood (Arčan et al., 2022). NR3C1 encodes for the glucocorticoid receptor (GR) a transcription factor that belongs to the nuclear hormone receptor family and plays a critical role in regulating the physiological response to stress. Mutations in NR3C1 have been associated with a range of diseases, including depression, anxiety, bipolar disorder, and post-traumatic stress disorder (Farrell et al., 2018). Studies investigating depressive disorders resulting from early-life stress have focused on the methylation of the glucocorticoid receptor gene (NR3C1). Recent studies have also identified genes that may be involved in the epigenetic modulations of depression which have effects in both the serotonergic and glutamatergic systems (Alameda et al., 2022).

The S100A10 gene encodes the calcium binding **p11** protein, which is essential in the regulation of 5-HT signaling in the brain and modulates receptor signal transduction pathways in both mice and humans by regulating among others, 5-HT trafficking and localization to the cell membrane. p11 is expressed in various types of neurons, including GABAergic, cholinergic interneurons and monoaminergic, cholinergic, glutamatergic, and GABAergic projection neurons. *P11 however also binds to the mGluR5 receptor* and increases its surface availability, providing a potential mechanism underlying the antidepressant-like activity of mGluR5 antagonism (Gał et al., 2022; Seo et al., 2017). Many researchers speculate that the S100A10 gene is associated with depression (Gał et al., 2022).

Studies have shown that p11 is involved in the etiology of depression and the mechanism of action of antidepressants. p11 mRNA and protein are downregulated in the brains of depressed humans, suicide victims, and a mouse model of depression (Gał et al., 2022; Seo et al., 2017). Although p11 protein levels or gene expression in patients with depression are only slightly elevated and in one recent study did not reach statistical significance (Gał et al., 2022), other recent studies have found a significant increase in methylation of P11 CpG sites in patients with major depressive disorder compared to healthy controls (Wang et al., 2022). Recent research highlights the crucial role of S100A10/p11 in depression, specifically in non-neuronal cells like astrocytes and microglia, challenging the traditional neuronal-centric focus. Studies by Chen, Oh, and Kim (2022) and Milosevic et al. (2017) reveal the expression and dysregulation of S100A10/p11 in astrocytes and microglia, indicating their involvement in the pathophysiology of depression. These findings emphasize the significance of non-neuronal elements, suggesting potential therapeutic avenues by targeting S100A10/p11 in astrocytes and microglia for a more comprehensive approach to treating depression (Chen et al., 2022; Milosevic et al., 2017).

Using a wider approach to locate depression associated genes, a recent meta-analysis comparing the effects of social stress on transcriptome alterations in mice with alterations found in humans with depression and PTSD, reveals interesting findings (Reshetnikov et al., 2022). The study identifies three gene families that consistently exhibit altered expression in both organisms: glucocorticoid-responsive genes, neuroinflammation genes, and genes related to oxidative stress. Notably, four genes, including FKBP5, Il1r, Lpr8, and Txnip, show consistent changes in expression direction between the mouse model and human samples, all of which are known to be linked to the development of mental disorders.

FKBP5: FKBP5 is a key stress-responsive regulator of the hypothalamic-pituitary-adrenal axis that restricts glucocorticoid receptor function. Methylation of the FKBP5 gene is associated with stress regulation and is influenced by early stress exposure (Beach et al., 2022). Demethylation of FKBP5 was associated with exposure to community danger in African Americans, and was also found in the children of Holocaust survivors (Beach et al., 2022; Yehuda et al., 2016). Two CpG sites, *cg20813374 and cg00130530*, have been identified as potential reporters of early stress (Reshetnikov et al., 2022). Both human and animal studies have demonstrated a correlation between FKBP5 gene variants and environmental factors, particularly early-life stress, in the development of psychiatric disorders, suggesting that epigenetic mechanisms play a role in regulating FKBP5 expression (Beach et al., 2022; Reshetnikov et al., 2022). The negative experiences in early childhood can have lasting impacts on health, and minoritized individuals may be more vulnerable to these effects due to their increased exposure to contextual stressors such as neighborhood violence. These stressful experiences can result in prolonged physiological responses that can cause long-lasting changes in gene

function. The study aimed to investigate the impact of exposure to community danger, parental harshness, and discrimination on methylation of two CpG sites on FKBP5, a gene that responds to stress, in young adults who had reported these experiences at age 10. The findings showed that exposure to community danger was linked to demethylation of the two CpG sites on FKBP5, which have been previously associated with stress and aging (Beach et al., 2022). Interestingly, circling back around to the key players in serotonergic and glutamatergic pathways, a recent study found that after 100 days of SSRIs treatment, the methylation of promoter CpG sites of FKBP5, but also BDNF, NR3C1, and SLC6A4 were significantly reduced (Mohammadi et al., 2022).

Taken together, studies indicate that the epigenetic regulation of target genes along the HPA axis are becoming more intriguing in linking mood disorders with environmental stressors, and warrant a closer look (Alameda et al., 2022) (Fig. 4).

Ketamine interaction with serotonergic system/ glutamatergic system and epigenetics processes

Another substance with effects in the glutamatergic pathway which has garnered much recent attention is ketamine. The psychotomimetic, anesthetic, and analgesic effects of ketamine have been described to be mediated by antagonism at the N-methyl D-aspartate receptor (NMDA) and the results of recent published studies showed significant improvements in depression symptoms among individuals after receiving ketamine treatment (Michaels, Lester, de la Salle, & Williams, 2022). This has resulted in a possible breakthrough designation in therapy for depression, for at least some individuals (Calabrese, 2019; Matveychuk et al., 2020).

Although not considered a "classic" psychedelic, ketamine can be classified as a psychedelic substance because its administration results in mood-altering experiences characterized by alterations in perception, emotions, and cognition. These effects may include enhanced emotional receptivity, increased sensory awareness, and shifts in mood states (Rochester et al., 2022). On a physiological level ketamine appears to have multiple effects in the brain by which it may have an impact on depression (Hess et al., 2022). Although ketamine was originally assessed to be an antagonist of N-methyl-D-aspartate receptors (NMDARs), it has become increasingly clear that this function alone does not fully explain the observed antidepressant effects (Hess et al., 2022). Unlike responses to antidepressants such as SSRIs and SNRIs that take several weeks to months, ketamine induces an acute pharmacological increase in monoamine concentration. A single dose of ketamine however, has been shown to induce prompt and persistent antidepressant effects for 1–2 weeks in both humans and animals. These considerations have helped shift the focus of research on the

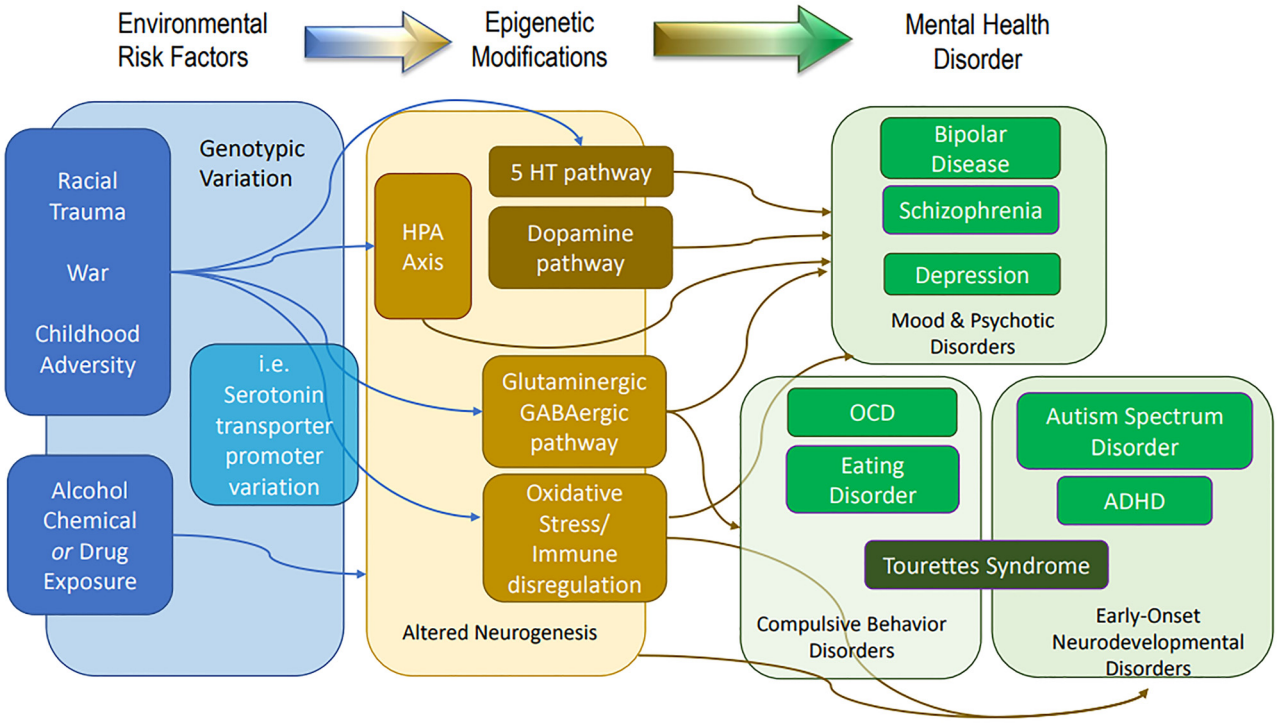

Fig. 4. This diagram summarizes the evidence on the links between childhood trauma, genotypic variation, changes in DNAm, and the development of psychiatric conditions. The figure shows that there are different biological pathways affected by childhood adversity that can lead to changes in DNA methylation (DNAm) which are also functionally related (Serotonergic, Dopaminergic pathways, Glutamatergic & GABAergic pathway, Neurogenesis, Immune system and Oxidative stress), which in turn can be associated with the development of psychiatric conditions (Alameda et al., 2022)

pathophysiology and drug development for MDD from the monoaminergic system to the glutamatergic system (Kawatake-Kuno, Murai, & Uchida, 2021). However, ketamine also provides a link between these two signaling systems. In addition to its effects in glutamatergic signaling pathways, studies show that ketamine interestingly also has effects on 5-HT (Bowman et al., 2020; Dore et al., 2019). Ketamine appears to be an enhancer of monoamine signaling (Ago, Yokoyama, Asano, & Hashimoto, 2022). Recent publications indicate that these additional effects are targeted at strengthening downstream alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling transmission, and in both traditional and rapid-acting antidepressants, increased excitatory neurotransmission, notably involving AMPARs, appears to be a common downstream target required for antidepressant efficacy (Hess et al., 2022).

In regards to serotonergic neurotransmission, ketamine's antidepressant-like effects are negated by depletion of 5-HT. These and other data suggest ketamine administration transiently increases 5-HT neurotransmission by modifying the balance of excitatory and inhibitory neurotransmission in a specific location in the brain (raphes nucleus) (Pehrson, Roberts, Khawaja, & McNair, 2022). There are several lines of evidence demonstrating involvement of at least four 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_4) in the unique effects of ketamine (Pehrson et al., 2022), with the data suggesting that the two receptors 5-HT_{2A}, and 5-HT_4 have an independent ability to trigger rapid antidepressant effects. In contrast, effects on 5-HT_{1A} and 5-HT_{1B} receptors seem to be downstream effects (Pehrson et al., 2022).

BDNF: Critically, brain derived neurotrophic factor (BDNF) signaling appears to play a prominent role in ketamine's effects on depression and the serotonergic system. In regards to the above mentioned four 5-HT receptors known to be affected by ketamine, BDNF appears to be activated by 5-HT_{2A}, and 5-HT_4, which have been demonstrated to be relevant for ketamine induced effects on synaptic plasticity, with the two receptors 5-HT_{1A} and 5-HT_{1B} in contrast, increasing their function or expression in response to BDNF, possibly to support the observed greater synaptic plasticity.

There may also be an epigenetic effect of ketamine on BDNF signaling (which would also lead to an enhancement of downstream AMPA receptor signaling), as there is strong evidence that depression causes a decrease in hippocampus synaptic plasticity, and that ketamine therapy increases synaptic plasticity (Widman & McMahon, 2018). One mechanism for influencing synaptic plasticity in the brain is through up-regulation of BDNF (Tomassoni-Ardori et al., 2019), and in this vein, reversing BDNF deficiency significantly decreased depression symptoms in depressed patients (Kato et al., 2018). However, ketamine operates differently by specifically inhibiting a particular group of N-methyl-D-aspartate receptors (NMDARs) located in gamma aminobutyric acid (GABA)ergic interneurons, although the exact mechanisms of this action are not fully understood. This inhibition results in the disinhibition of the pyramidal target neurons that are involved in glutamate signaling, leading to an increase in Ketamine extracellular glutamate and elevated non-cell autonomous glutamatergic synaptic transmission with AMPA potentiation. This results in the stimulation of tropomyosin-related kinase B (TrkB), a target of BDNF, which activates the mechanistic target of rapamycin complex 1 (mTORC1). The TrkB receptor, a key tyrosine kinase receptor, plays a central role in MDD by mediating the effects of BDNF. In the context of MDD, reduced BDNF-TrkB signaling contributes to neuronal atrophy and compromised synaptic plasticity, particularly in regions crucial for mood regulation (Li et al., 2022). Ketamine, as an NMDA receptor antagonist, induces an initial elevation in glutamate levels, triggering BDNF release. Subsequent binding of BDNF to TrkB activates intracellular pathways, including MAPK and PI3K, promoting synaptic plasticity and neurogenesis. This restoration of neurotrophic support and synaptic growth is believed to underlie ketamine's rapid and sustained antidepressant effects, offering a potential therapeutic avenue for addressing depressive symptoms in MDD through the BDNF/TrkB pathway (Kadriu et al., 2020). Moreover, ketamine may rapidly induce the translation of BDNF in certain brain areas, partially by reducing the phosphorylation and activation of eukaryotic elongation factor (eEF2). Increasing evidence indicates that the metabolite (2R,6R)-hydroxynorketamine [(2R,6R)-HNK] operates separately from ketamine by stimulating glutamate signaling at presynaptic sites. Similar to SPs, this heightened neural activity leads to the release of BDNF, which is then followed by a temporary activation of the mTOR pathway and an increase in the expression of various proteins that operate at glutamatergic synapses (Kadriu et al., 2020) (Fig. 5). Consequently, this results in the functional strengthening of glutamatergic synapses. A recent scientific review presents a comprehensive analysis of various studies exploring the epigenetic alterations observed in samples from depressed patients and animal models (Park et al., 2019). Among these, DNA methylation is the most extensively studied modification, with particular attention given to exon I of the BDNF gene. Correlations were found between depression and stress-related epigenetic alterations in the BDNF gene (Park et al., 2019). Xing et al. compared the levels of methylation of BDNF exon I in blood samples from MDD patients and healthy controls revealing that methylation levels in exon I may be utilized to identify patients with depression (Xing et al., 2021). Furthermore, Liu and colleagues found in contrast that methylation in BDNF exon VI was correlated with MDD and antidepressant-induced remission - however, only in female patients (Liu et al., 2021). Although one of these studies investigated exon I and the other exon IV, both found an association between the methylation at various areas within the BDNF gene and MDD.

Taken together, however, BDNF appears to be an important target in depression research and the implication of the research is that medication-induced methylation alterations in the BDNF gene may influence response to treatment. Supporting these findings, Zhou et al. found in a

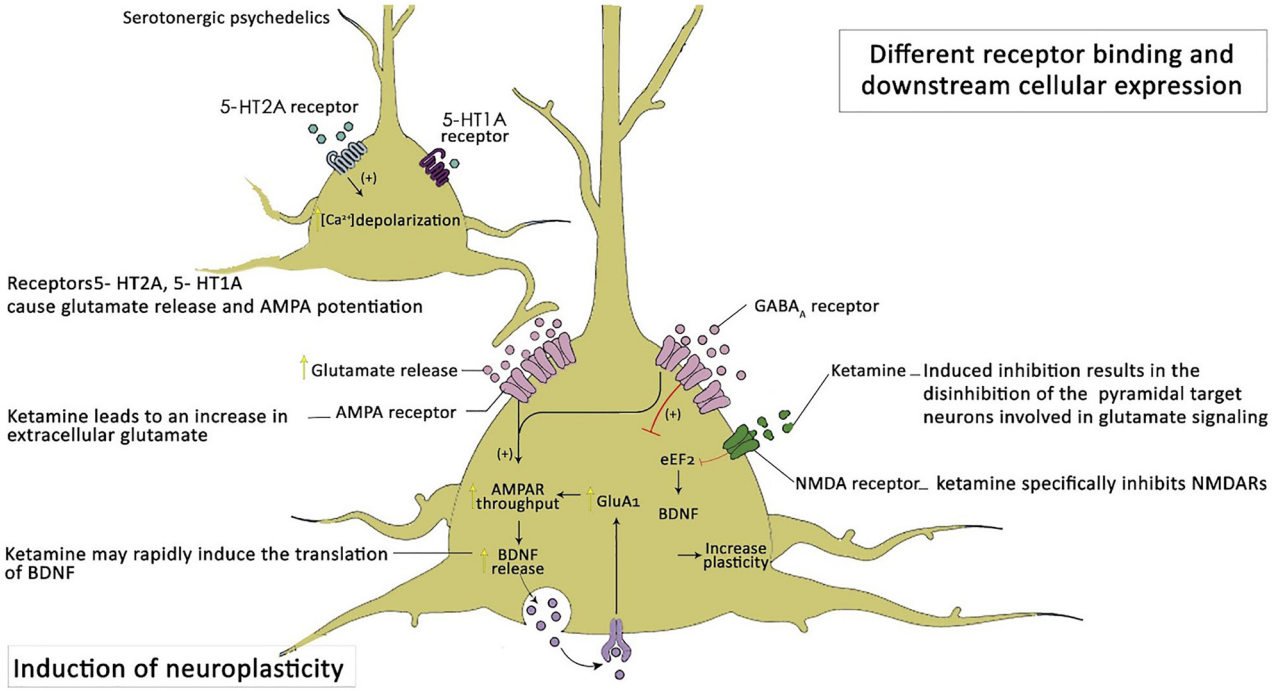

Fig. 5. The way in which ketamine and serotonergic psychedelics (SPs) affect the brain's cellular mechanisms may converge at glutamatergic synapses. The mechanism of action of SPs primarily involves activating certain receptors (5-HT2A, 5-HT1A) that cause glutamate release and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) potentiation. This results in the stimulation of tropomyosin-related kinase B (TrkB), a target of brain-derived neurotrophic factor (BDNF), which activates the mechanistic target of rapamycin complex 1 (mTORC1) (Kadriu et al., 2020). GPCR, G protein-coupled receptor; mGluR, metabotropic glutamate receptor; PSD95, post-synaptic density protein 95

systematic review, evaluating all DNA methylation associated with clinical improvement caused by antidepression medications (Zhou et al., 2021) that the only methylation positively correlated with clinical improvement in MDD was in the BDNF gene (Bandeira et al., 2021).

In another study by Duclot and Kabbaj (2015) exploring the molecular basis of MDD and antidepressant response, there is growing attention to epigenetic mechanisms influencing the BDNF/TrkB pathway, epigenetic modifications, such as DNA methylation. While TrkB was previously described in relation to BDNF, TrkB is also relevant as a neurotrophic signaling pathway and its potential implications for MDD and antidepressant response. TrkB is the receptor for BDNF, and its activation plays a key role in mediating the biological effects of BDNF. The interaction between BDNF and TrkB is essential for neuronal survival, differentiation, and synaptic plasticity. The findings suggest that alterations in the epigenetic regulation of TrkB may contribute to the neurobiological changes observed in MDD (Duclot & Kabbaj, 2015). Further investigation into the epigenetic regulation of TrkB, both in the context of MDD and response to antidepressants, could provide additional insights into the complexities of neurotrophic signaling in depression. Understanding how TrkB expression and function are modulated by epigenetic mechanisms may contribute to a more comprehensive understanding of the molecular pathways involved in MDD and its treatment.

Intriguingly, tying several of these lines of inquiry together, in a recent study which randomly subjected rats to SNI (spared nerve injury) or sham surgery, Liu and colleagues showed that reduced BDNF expression, induced by epigenetic mechanisms (DNA methyltransferases (DNMTs)), lead to pain and depression, which could be alleviated by ketamine (Liu et al., 2021). This would establish ketamine as playing a role as an epigenetic modulator of depression, confirming studies that showed that by restoring BDNF DNA methylation, ketamine treatment would have the ability to reduce relapse of fear in PTSD (Murrough, Abdallah, & Mathew, 2017). A majority of scientific investigations have reported increased DNA methylation in the BDNF gene among individuals diagnosed with depression, although a small number of studies have reported a decrease in DNA methylation, the primary consensus is that modifications to BDNF methylation are linked to the presence of depressive symptoms (Arčan et al., 2022).

Considering the multiple studies linking BDNF with depression, further exploration of its relation with ketamine in the context of epigenetic signaling is warranted.

The need for further clinical studies of ketamine and the epigenetic regulation of depression

A decade of preclinical studies have shown that blocking 5-HT transmission can block the antidepressant effects of

ketamine, demonstrating that ketamine's antidepressant effects are at least in part associated with 5-HT availability. Evidence from animal studies showed that ketamine increases extracellular 5-HT by blockade of the 5-HTT (SLC6A4) (Yamamoto et al., 2013). The mechanism that causes this is unclear in humans therefore, *it is of high interest to examine epigenetic effects of therapy for depression on the* 5-HT *pathway genes and explore the role of ketamine.* Other studies have found that ketamine treatment can increase the expression of genes involved in neuroplasticity and synaptic function; in particular, ketamine may by epigenetic mechanisms directly or indirectly rapidly induce the translation of BDNF in areas of the brain involved in mood regulation and cognition (Gill et al., 2021). It is likely that DNA methylation is a mechanism by which ketamine treatment influences regulation of genes in the serotonergic pathway (transporter and 5-HT receptors). Based on the current studies, in regards to gene-methylation specific epigenetic changes which may be induced after treatment with ketamine, we would also expect to see changes as well in other genes, particularly of those involved in the glucocorticoid-responsive or oxidative stress and neurotransmitter and/or inflammation genes. In particular, further investigation of the genes in Table 1 is warranted.

Table 1. Selected protein coding genes regulated by epigenetic mechanisms that are associated with mood

Signaling pathway	Gene	Function	Ref.
Serotonin	*5-HTT/ SLC6A4*	**Serotonin transporter gene**; The main role of the 5-HTT in the central nervous system is to regulate serotonergic signaling by transporting serotonin molecules from the synaptic cleft back into the pre-synaptic terminal for reuse. This transporter plays a critical role in controlling the availability of 5-HT to other receptors in the serotonergic systems. Obsessive-Compulsive Disorder and Anxiety are some of the diseases linked to the SLC6A4 gene. The pathways associated with this transporter include Transmission across Chemical Synapses and Nuclear receptors meta-pathway. The transporter is responsible for the re-uptake of 5-HT, and it changes its shape to move the molecules.	Berger et al. (2009), Lv and Liu (2017)
Serotonin	*5-HT$_{1A}$*	**5-Hydroxytryptamine Receptor 1A**; encodes a G protein-coupled receptor for 5HT. located primarily in limbic brain areas.it's key role is the regulation of dopamine and 5-hydroxytryptamine levels in the brain which affects mood, behavior and neural activity. Also functions as a receptor for various drugs and psychoactive substances. Increased methylation at sites in the promoter have been associated with MDD risk.	Albert and Vahid-Ansari (2019)
Serotonin	*HTR$_{2A}$*	**G-protein coupled receptor for 5-hydroxytryptamine**; Functions as a **receptor** for various drugs and psychoactive substances, including mescaline, psilocybin. Affects neural activity, cognition, perception and mood under contextual stress. PTSD and MDD symptoms associated with methylation of this genotype at two CpG sites (−1420 and −1224).	Parade et al. (2017), Wan et al. (2020)
Serotonin	*TPH2*	**Tryptophan Hydroxylase 2**; Genetic variation of these gene may be associated with psychiatric diseases such as bipolar affective disorder and major depression. Among its related pathways are superpathway of tryptophan utilization and Monoamine transport. Promoter hypermethylation is associated with elevated early-life stress.	Ottenhof et al. (2018)
Hormone Receptor	*NR3C1*	**Receptor for glucocorticoids (GC)**; has a dual mode of action: as a transcription factor that binds to glucocorticoid response elements (GRE), both for nuclear and mitochondrial DNA, and as a modulator of other transcription factors. Increased DNA methylation in promoter of NR3C1 gene at 1-F at CpG 38 site in depressed patients has been associated with early life adversity.	Timmermans et al. (2019)
Neuro-transmitter	*BDNF*	**Brain Derived Neurotrophic Factor**; DNA methyltransferases (DNMTs) reduced BDNF expression and it is associated with mood disorder.	Liu et al. (2021), Xing et al. (2021)
Serotonin Glutamatergic	*S100A10*	**Calcium binding p11 protein**; which is essential in the regulation of 5-HT signaling in the brain; also binds to the mGluR5 receptor.	Wang et al. (2022), Seo et al. (2017)
Glutamatergic	*FKBP5*	**FKBP Prolyl Isomerase 5**; stress-responsive regulator of the hypothalamic- pituitary-adrenal axis that restricts glucocorticoid receptor function. Disorders associated with FKBP5 include MDD.	Reshetnikov et al. (2022)

Ketamine: with or without psychotherapy?

In regard to the process of administering ketamine, there has been some debate on whether or not including psychotherapy in ketamine therapy is necessary (Hasler, 2020). It is important to understand that there are several clinical models for the use of ketamine for mental health indications. The most common is the infusion model, where patients come to a clinic at regular intervals for IV ketamine from a physician (Calabrese, 2019; Zarate et al., 2006). This can be provided with or without adjunctive psychotherapy. However, more recently, ketamine-assisted psychotherapy (KAP) has been advanced and an alternative and perhaps more effective treatment model (Dore et al., 2019; Halstead, Reed, Krause, & Williams, 2021). This includes lower doses, given with therapists present while experiencing the effect of the drug and immediately after for psychedelic integration of the experience.

Authoritative ethical guidelines released by several groups emphasize the importance of therapist involvement in the delivery of ketamine therapies of any type.

In discussing the ethics of ketamine administration, Ryan and Bennett (2020) note that ketamine is a potent psychoactive drug renowned for its unique dissociative and psychedelic qualities. Professionals in the field of ketamine treatment recognize the crucial requirement for tailored psychological support throughout the entire process, encompassing pre-treatment, administration, and post-treatment care (Ryan & Bennett, 2020). Likewise, the collective viewpoint among Canadian experts underscores the perilous nature of administering substances that induce a Non-ordinary State of Consciousness (NOSC) without sufficient training and procedural support. In the absence of proper guidance during a NOSC, coupled with inadequate follow-up and integration measures, there exists a heightened risk of eliciting adverse mental and physical responses in participants, potentially leading to complications and, tragically, even severe consequences (Rochester et al., 2022).

The role of the psychotherapy component in epigenetic changes has yet to be determined. Understanding these relations and their epigenetic mechanisms should lead us to a greater knowledge of ketamine's therapeutic potential.

Future direction: ketamine and epigenetic modification as therapy?

While progress has been made in understanding both biochemical and epigenetic processes in depression, there is still much that needs to be researched. In particular more research is needed to understand the specific biochemical and epigenetic mechanisms and confirm the role of currently identified genes that contribute to depression, as well as to identify new targets for therapeutic interventions. Despite extensive and promising research on the BDNF and other genes, reliable biomarkers, whether proteomic or (epi) genetic, that can actually be used in a clinical setting, remain to be identified (Arčan et al., 2022).

The promise of understanding the epigenetic regulation of genes, is the idea that changes may be made in the environment that can alter methylation patterns of key genes which may correlate with the mood state, or function as biomarkers for recovery. The duration and efficacy of such interventions may eventually be able to be assessed dynamically through non-invasive assays, to assess ideal interventions and assess which therapies, pharmaceuticals or combinations are most efficient.

Experiments are ongoing in our lab to measure these epigenetic changes in a cohort of patients receiving ketamine-assisted psychotherapy and standard therapy for MDD. The studies are designed to provide a basis for future experimental trials which may be able to further the understanding of how early life stresses are connected with responses to psychedelic substances such as ketamine, and map their interaction with serotonergic genes. Such research into the neurological mechanisms of psychedelic substances may lead us to a better understanding of the therapeutic potential of ketamine which could shed light on other psychedelic substances and their mechanism of action.

Finally, our study brings together neurobiologists studying the epigenetic processes in the lab and health professionals treating depression with ketamine and is bridging the gap between neuroscience and clinical practice. This interdisciplinary approach is providing insights into the relationship between epigenetic modifications, neurotransmission systems such as serotonergic and glutamatergic, and therapeutic responses to ketamine-assisted psychotherapy. Such interdisciplinary collaborations are the key to understanding the biological underpinnings of depression and tailoring more effective and personalized treatment strategies for our patients.

Funding: This research was undertaken, in part, thanks to funding from the Canada Research Chairs Program, Canadian Institutes of Health Research (CIHR) (PI M. Williams). Award number: CRC-2018-00239.

Author contributions: Arghavan Nepton and Hesam Farahani share first-authorship due to equal contributions. Arghavan Nepton played a lead role in resources and supervision, and an equal role in writing of original draft, and writing of review and editing. Hesam Farahani played an equal role in writing the original draft and writing of review and editing. Sonya C. Faber played a major role in writing, investigation and project administration of original draft and editing. Monnica T. Williams and Linda Booij played a supporting role in review and editing.

Competing interests: S Faber declares that she is an employee of Angelini pharma and has an interest in the GmbH Bioville. There are no competing interests to declare. The authors report no conflicts of interest.

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