university of groningen

lncRNAs and miRNAs as Transcriptomic Biomarkers in the Pathophysiology of Mood Disorders

Bachelor's Thesis

Biology
Behaviour and Neurosciences
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Word count: 7793
Date of Submission: 21 July 2025
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1. Summary

Mood disorders like major depressive disorder (MDD) and bipolar disorder (BD) represent a significant global health burden, yet their diagnosis still primarily relies on subjective clinical evaluation, which results in high rates of misdiagnosis and treatment resistance. This highlights the critical need for objective biological markers that can aid in improving current clinical outcomes. This review aims to summarize the current findings on the role of non-coding RNAs (ncRNAs), specifically microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), as key transcriptomic regulators in the pathophysiology of mood disorders, as well as evaluate their potential as clinical biomarkers. ncRNAs are frequently dysregulated in MDD and BD, acting as a crucial link between the genetic predisposition and the clinical manifestation of these disorders. miRNAs and lncRNAs are mainly involved in biological mechanisms, such as: 1) synaptic plasticity and excitability, where miR-137 and lncRNA NEAT1 alter the synaptic structure of neurons; 2) neuroinflammation, where let-7e and miR-146a regulate critical immune pathways; 3) HPA axis regulation, where miR-124-3p modulates the stress response; and 4) olfactory dysfunction, where lncRNAs are implicated in both the neurogenesis and function of the olfactory system. While the field of transcriptomics has produced strong findings, there are many limitations that prevent the implementation of ncRNAs as clinical biomarkers, such as: the challenge of translating findings from in vitro to in vivo, contradictory findings on the role of specific molecules, and confounding effects of medication in patient studies. To address these limitations, future research must adopt a larger, longitudinal, multi-omic approach. In conclusion, ncRNAs play a key role in the molecular pathways underlying mood disorders, holding high potential as future biomarkers for diagnosis, prognosis, and treatment response prediction in the pathophysiology of mood disorders.

2. Introduction

2.1. Diagnostic challenges in psychiatry

The field of psychiatry continues to face the persistent challenge of accurately diagnosing, predicting the course of illness, and selecting effective treatments, which all contribute significantly to the global burden of disease (Goossens et al., 2021). In 2019, an estimated 970 million people worldwide were affected by a mental disorder. Amongst psychiatric disorders, mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) are a major cause of disability and mortality (World Health Organization, 2022). These disorders are associated with a substantial reduction in life expectancy, particularly in the case of BD, which can range from 10 to 20 years shorter than that of the general population (Chesney et al., 2014). This immense impact on public health underscores the urgent need for improvement in diagnosis, prognosis and treatment approaches, by increasing the effectiveness of current clinical tools, as well as introducing new ones.

While many medical conditions rely on quantitative assessment, psychiatric disorders are diagnosed based on clinical observation and self-reported symptoms. Based on this, patients are grouped into a certain diagnostic category, meaning a single diagnosis can cover a wide variety of symptoms. This diagnosis-based approach, combined with the heterogeneity and overlapping symptomatology that result from grouping symptoms into diagnoses, leads to high rates of comorbidity, which makes initial diagnosis unreliable and complicates treatment selection. Additionally, the molecular mechanisms that underlie mental disorders are still largely unknown, making the selection of effective treatments challenging (Garcia-Gutierrez et al., 2021). Even though pharmaceutical treatment is currently available for most psychiatric disorders, approximately 30% of patients show no significant improvement, requiring a dosage adjustment or medicinal switch to another drug (Goossens et al., 2021). These limitations are particularly evident in the aforementioned mood disorders, where diagnostic ambiguity and treatment resistance are common. Although the idea of a mood spectrum, with manic and depressive features occurring simultaneously, has been widely accepted for a long time, using a categorical approach has become more common as the diagnostic standard (McIntyre et al., 2018). A depressive episode is mainly characterized by a depressed mood and a loss of interest in daily activities for at least two weeks, while other symptoms could include decreased appetite, feeling of hopelessness, sleep disturbance, tiredness and thoughts of suicide. On the other hand, a mania episode consists of euphoria, irritability, impulsive behaviour, increased energy and decreased need for sleep (World Health Organization, 2022). MDD is characterized by at least one discrete depressive episode, while BD consists of episodes of mania or hypomania (milder form) that alternate with depression. The specific diagnosis is then further categorized into Bipolar I (BD I), which requires one episode of mania, and Bipolar II (BD II), which is defined by an episode of hypomania in addition to one major depressive episode (Gopalakrishnan et al., 2025).

The shared clinical representation of MDD and BD, depression, can often lead to diagnostic errors: early studies have shown up to 69% of BD patients receive a misdiagnosis of MDD, with a mean time of five to eight years for a diagnosis correction (Singh & Rajput, 2006). Consequently, effective treatment is further complicated by delays which could worsen symptoms and compromise daily functioning by elevating the risk of episode

chronicity (Gopalakrishnan et al., 2025). Given that the field of psychiatry is heavily limited by subjectivity, there is an urgent need for objective measures in order to improve diagnosis, prognosis, and treatment selection. Although the etiology and pathogenesis of mood disorders are not fully understood, there are overlapping patterns of gene expression in the dorsolateral prefrontal cortex of MDD and BD patients that support the hypothesis of a shared pathophysiology (Scarr et al., 2019). The discovery of biological markers could address core limitations by deepening the current knowledge of the underlying biology of mood disorders, while also providing an unbiased basis for clinical decisions (Nobis et al., 2020).

2.2. Transcriptomic biomarkers in psychiatric disorders

A biomarker is defined as any biological feature that can serve as an objective, measurable indicator for a physiological process, pathogenic condition or response to a therapeutic intervention (Nobis et al., 2020). In the field of psychiatric disorders, researchers have focused on biomarker discovery using functional neuroimaging, quantitative electroencephalography (qEEG), genetics and gene-expression profiling (Goossens et al., 2021). So far, these methods have produced potential molecular markers, such as gene mutations, RNA, and protein levels, that help differentiate the pathophysiology of MDD and BD. However, these findings have not yet been integrated into standard clinical diagnosis (Gibbons et al., 2020). Various biological systems, including the inflammatory, neurotransmitter, neuroendocrine, neurotrophic, and metabolic pathways, are affected in mood disorders, and can further be investigated through a range of 'omics' approaches like genomics, epigenomics, transcriptomics, proteomics, and metabolomics (Vismara et al., 2020). However, there is a current research gap between the genetic, mRNA, and protein literature, which could be explained by the dysregulation of non-coding RNAs. By acting as post-transcriptional regulators, ncRNAs might play a key role in explaining how clinical symptoms of MDD and BD develop from genetic backgrounds (Gibbons et al., 2020).

As a field, transcriptomics represents large-scale study of the transcriptome, which is highly dynamic as a function of spatiotemporal gene expression of various genes being actively expressed or repressed at a given time. The transcriptome can offer a more direct and accurate view of current pathological states, unlike the genome, which is far less dynamic (Gururajan et al., 2016). For example, transcriptomic biomarkers have been recognized as a potential diagnostic tool for a long time and were originally called 'sentinels of disease', as transcriptome profiles in the blood showed an overlap of approximately 80% to those in various organs (Liew et al., 2006). In terms of classification, the transcriptome consists of protein-coding messenger RNA (mRNA) and non-coding RNA (ncRNA). After transcription, approximately 98% of the genes in the genome are in the form of ncRNA. They are broadly categorized by transcript length into short RNAs (<50 nucleotides), medium RNAs (50-200 nucleotides), and long RNAs (>200 nucleotides) (Fig. 1) (Hao et al., 2022).

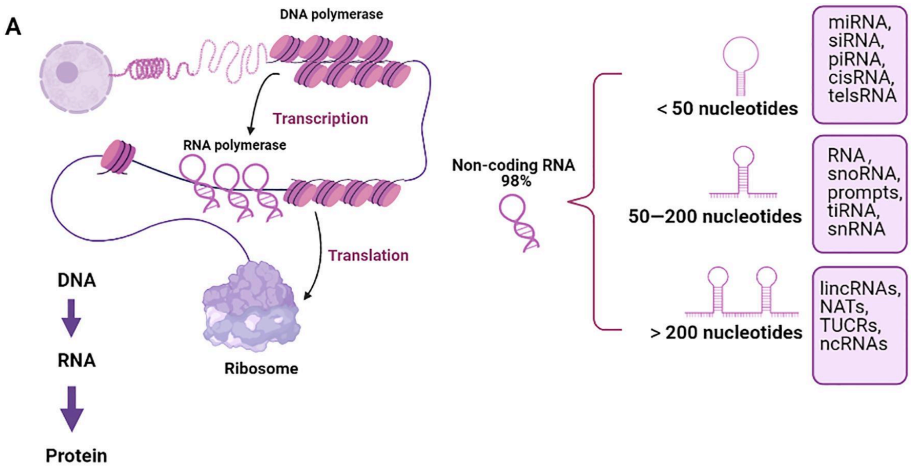

Figure 1. An overview of the transcription and translation of DNA into proteins (left), and the classification of non-coding RNA (right) by transcript length.

2.3. Biogenesis and function of miRNAs and lncRNAs

While the pathophysiology of psychiatric disorders is complex, recent research has demonstrated that both miRNAs and lncRNAs are frequently dysregulated in patients with mood disorders, relating to changes in biochemical pathways that are affected in both disorders (Gibbons et al., 2020). miRNAs are small non-coding RNAs of approximately 22 nucleotides that can control up to 30-60% of mammalian protein-coding genes in a specific region, making their specific regulatory system hard to decipher (Gururajan et al., 2016). The biogenesis of miRNA begins in the nucleus, where it is first transcribed into a primary miRNA (pri-miRNA), then cleaved to a shorter precursor miRNA (pre-miRNA), which is then exported to the cytoplasm. The pre-miRNA is further processed by the Dicer-Argonaute complex, creating the mature miRNA duplex, which is loaded onto the RNA-induced silencing complex (miRISC). The mechanism of miRNAs consists of guiding the miRISC to bind to a target mRNA in order to silence gene expression. It can either inhibit translation initiation by blocking the eIF4IF complex at the 5' end of the mRNA or it can stimulate mRNA degradation by recruiting deadenylase complexes PAN2-PAN3 and CCR4-NOT at the 3' poly(A) tail

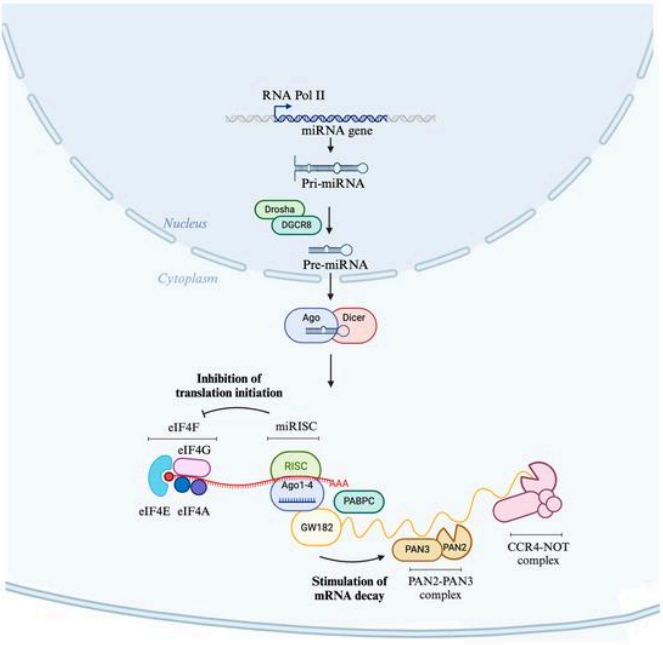

Figure 2. miRNA biogenesis and gene-silencing mechanisms.

of the mRNA to destabilize it (Fig. 2). Through these powerful silencing mechanisms, miRNAs play a key role in the central nervous system by regulating processes such as neuroinflammation, synaptic plasticity, and the stress response, and providing a molecular basis to psychiatric disorders (Kaurani, 2024). For example, as proven by a key study by Zhang et al. (2017), miRNAs have the ability to pass the blood-brain barrier and act as post-transcriptional regulators of gene expression in depression.

In contrast to miRNAs, long non-coding RNAs (lncRNAs) are more complex structures of over 200 nucleotides. While their biogenesis shares some key features with mRNAs, they are uniquely regulated through distinct pathways that produce highly cell-type specific lncRNAs. For example, a large proportion of lncRNAs arise from divergent transcription, which is initiated by bidirectional promoters that present an asymmetric distribution of splicing and polyadenylation signals near the promoter. lncRNAs can then be further regulated at post-transcriptional maturation (Quinn & Chang, 2015). A key example is the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1), which will be discussed later in the context of neuronal excitability (Barry et al., 2017), that lacks a poly(A) tail and instead forms a stable triple-helix structure, critical for their function and localization to nuclear paraspeckles. The functions of lncRNAs are also highly diverse and are mainly categorized into cis and trans regulation. In cis regulation, lncRNAs act on neighboring genes at their site of transcription, for example by recruiting protein complexes to epigenetically silence genes, mediating chromosome looping to bring distant enhancers and promoters together, physically blocking transcription, or silencing entire chromosomes. In trans regulation, lncRNAs act away from their site of origin through their complex structures, serving as molecular scaffolds, as miRNA sponges, or as direct nucleic acid templates (Fig. 3) (Quinn & Chang, 2015). Therefore, lncRNAs play a key role in the pathogenesis of mood disorders by regulating fundamental processes, such as neurotransmitter and neurotrophic factor signaling, synaptic plasticity and excitability, and olfactory function.

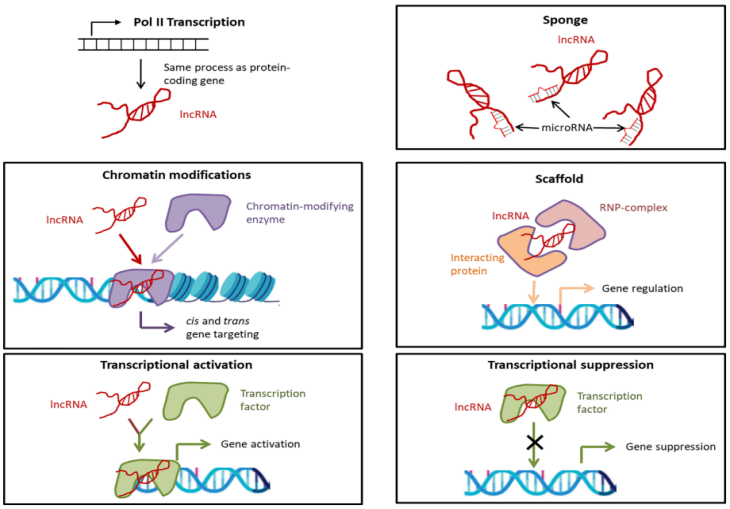

Figure 3. lncRNA biogenesis and functions (Yoshino & Dwivedi, 2020).

Therefore, the aim of this review is to investigate how ncRNAs, specifically miRNAs and lncRNAs, contribute to the pathophysiology of mood disorders, and to evaluate their potential as clinical biomarkers for diagnosis, prognosis, and treatment response.

3. Main findings: non-coding RNA mechanisms in mood disorders

3.1. MicroRNAs (miRNAs)

The following sections will explore the role of microRNAs (miRNAs) in the pathophysiology of mood disorders, through three key mechanisms. First, miRNAs are the central regulators that mediate signaling pathways involved in neuroinflammation, presenting both pro-inflammatory and anti-inflammatory properties. Second, multiple miRNAs expressed in the brain particularly contribute to the formation of structural and functional synaptic plasticity, especially during depressive episodes, altering the brain's ability to respond to stimuli. Third, miRNAs manipulate the expression of genes involved in the stress response through hypothalamic-pituitary-adrenal (HPA) signaling (Choudhary et al., 2024). Table 1 contains the list of the miRNAs that are associated with these mechanisms and that are presented in this review.

Name	Study model	Source	Target	Reference	Findings
let-7e, miR-146a, miR-155	Humans	Peripheral immune cells	TLR4, NF-κB signaling proteins	Hung et al. (2019)	Downregulation of all three miRNAs in MDD patients; Low let-7e & miR-146a correlate with low depression, while miR-155 correlates with severe depression; Antidepressant treatment increases all three;
miR-155	Mice (KO model)	Hippocampus	Pro-inflammatory cytokines (IL-6, TNFα)	Fonken et al. (2016)	miR-155 KO reduces anxiety and depression-like behaviours, and lowers hippocampal inflammation;
miR-155	Human dendritic cells	Cell culture	TAB2	Ceppi et al. (2009)	Acts as a negative feedback brake on TLR signaling through anti-inflammatory role; Decreasing miR-155 leads to increases in pro-inflammatory cytokines;
miR-16	Humans, rats	CSF, blood	SERT mRNA	Song et al. (2015)	MDD patients: CSF miR-16 downregulation (not blood miR-16); Rats: neutralizing miR-16 induces depression-like behaviours;
miR-16	Rats (MD & CUPS models)	Hippocampus	BDNF	Bai et al. (2012)	MD model: miR-16 upregulation, BDNF downregulation; CUPS model: no changes;
miR-223	Mice, humans	Hippocampal neurons	NR2B & GluA2 mRNAs	Morquette et al. (2019)	Neuroprotective role by reducing NR2B and GluA2 expression, inhibiting NMDA-induced calcium influx and preventing glutamate hyperexcitation;

miR-335	Humans, NPCs	Blood, cell culture	GRM4	Li et al. (2015)	MDD patients: blood miR-335 downregulation, leading to high GRM4; Antidepressant treatment normalizes both;
miR-137	Mice (KO model)	Forebrain	EZH2	Yan et al. (2019)	Loss of miR-137: dendritic/synaptic overgrowth, reduced LTP, and anxiety/depression-like behaviours due to EZH2 upregulation;
miR-92a, miR-485	Rats (CU/MS model)	Dorsal hippocampus	Genes in axonal guidance & cAMP signaling	Muñoz-Llanos et al. (2018)	Upregulation of both miRNAs after 14 days of chronic stress; The effect is independent of corticosterone, and impacts nervous system function and behaviour;
miR-124-3p	Rats (CORT model), humans	Prefrontal cortex, blood serum	NR3C1, AMPA receptors (Gria3, Gria4)	Roy et al. (2017)	Chronic stress and MDD cause epigenetic upregulation of miR-124-3p, leading to a downregulation of NR3C1 and impairing the HPA axis; Antidepressants reverse the effect;
miR-124, miR-34a-5p , miR-135, miR-451-a	Humans	Serum, plasma	Cortisol, serotonin, oxidative stress markers	Al-Rawaf et al. (2021)	A specific set of dysregulated miRNAs in depressed older adults correlates with HPA axis hyperactivity, low serotonin and high oxidative stress;
miR-124	Aplysia	Neuron culture	CREB1	Rajasethupathy et al. (2009)	Downregulation of miR-124 by serotonin; Lower suppression of CREB1, involved in long-term memory;

Table 1. List of miRNA studies and their findings.

3.1.1. miRNA regulation of neuroinflammation

Neuroinflammation is a complex response within the central nervous system (CNS) that involves resident glial cells, primarily microglia and astrocytes, that in turn produce inflammatory cytokines in reaction to various threats (Slota & Booth, 2019). miRNAs function as critical fine-tuners of key immune and inflammatory pathways, and their dysregulation is increasingly associated with the pathology of neuroinflammation in mood disorders. They work through key mechanisms such as controlling Toll-like receptor (TLR) signalling pathways, and its downstream effector nuclear factor kappa B (NF-κB) (Fig. 2). The activation of TLRs by microbial ligands can induce the upregulation or downregulation of specific miRNAs, which in turn, directly target components of the TLR pathway. Consequently, the dysregulation of miRNAs is linked to neuroinflammation pathology, which makes them modifiable targets for controlling inflammatory responses that mediate changes in mental states in mood disorders (Quinn & O'Neill, 2011). The study by Hung et al. (2019) investigated the role of let-7e, miR-146a, and miR-155 in the neuroinflammation associated with major depressive disorder (MDD). By analyzing their expression in peripheral immune cells using qRT-PCR, they found that the expression of all three miRNAs was significantly

lower in patients with MDD. let-7e was found to directly negatively regulate the expression of TLR4, playing an important role in the pro-inflammatory signaling cascade as an anti-inflammatory regulator. miR-146a is another essential anti-inflammatory mediator that was found to prevent an overactive immune response through attenuating NF-κB signaling, by targeting key inflammatory signaling proteins (IRAK1, IRAK2, TRAF6). Low expression of both let-7e and miR-146a is negatively correlated with depression severity (HAMD-17) and would be expected to lead to the excessive production of pro-inflammatory cytokine IL-6, as shown by previous research (He et al., 2013; Wei et al., 2016). The expression of miR-155 was also found to be decreased, but its baseline levels were positively correlated with depression severity. This suggests that low miR-155 may reflect a state of chronic inflammation, which has a different signature than the typical upregulation seen in inflammatory responses, serving as a potential indicator of disease progression. However, after four weeks of antidepressant treatment, the levels of all three miRNAs significantly increased, suggesting their involvement in both MDD pathophysiology and therapy response (Hung et al., 2019). miR-155 has been the subject of many studies, due to its role as one of the master regulators of inflammation. A previous study by Fonken et al. (2016) investigated the role of miR-155 in depression using knockout (KO) mice. The study found that, contrary to the previous findings in humans where low levels of miR-155 were associated with more severe depression, knocking out miR-155 in mice significantly reduced anxiety and depression-like behaviour. The improvements were associated with a reduced inflammatory signature in the hippocampus of KO mice, which showed decreased mRNA expression of the pro-inflammatory cytokines IL-6 and TNFα (Fonken et al., 2016). Another study by Ceppi et al. (2009) has also investigated the function of miR-155, providing a potential mechanism for its complicated role. By using lipopolysaccharides (LPS) to activate TLR4 signaling in human monocyte-derived dendritic cells, then silencing miR-155 using a specific inhibitor, they found out that knocking down miR-155 resulted in a significant increase in the expression of pro-inflammatory cytokines, such as IL-1β and IL-6. The study identified TAB2, an adaptor in the TLR/IL-1 signaling cascade, as a direct target of miR-155, which suppresses pro-inflammatory responses. They concluded that miR-155 is part of a negative feedback loop with an anti-inflammatory role, which aligns with the study by Fonken et al. (2016), where the absence of miR-155 resulted in less inflammation and less depressive-like behaviours (Ceppi et al., 2009).

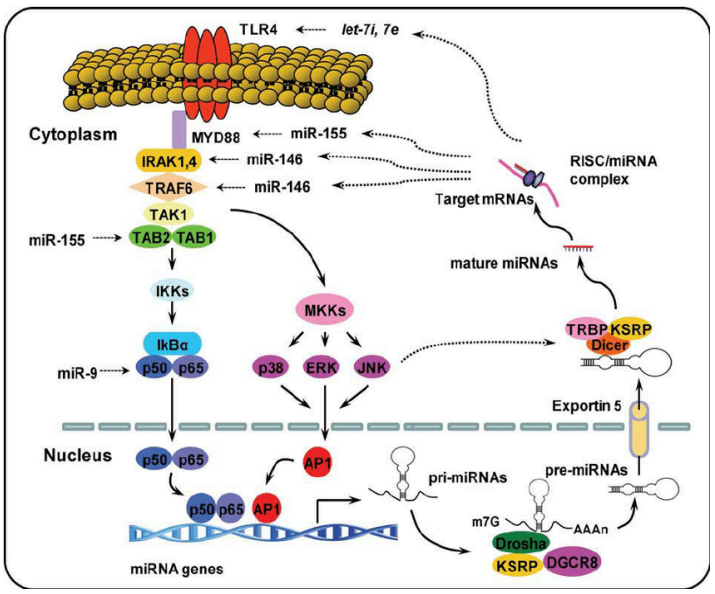

Figure 4. The regulation of TLR4 signaling by miRNAs (let-7e, miR-146a, miR-155), and its further activation of NF-κB signaling (Zhou et al., 2011).

3.1.2. miRNA regulation of synaptic plasticity

In synaptic plasticity, as shown by Wan et al. (2015), specific pre-miRNAs are transported to certain areas in order to regulate the translation of mRNA, in response to localized stimulation or injury. Therefore, levels of locally upregulated or downregulated miRNA can lead to impaired synaptic plasticity, which is strongly linked to the pathogenesis of mood disorders. There are two types of synaptic plasticity: functional and structural plasticity, which are strongly interlinked for transmission efficiency and memory storage (Gao et al., 2022).

(a) Synaptic functional plasticity

miRNAs directly influence synaptic functional plasticity by the regulation of neurotransmission through altering the density and activity of transporters, and modifying the function of transporters responsible for neurotransmitter reuptake (Gao et al., 2022). The serotonin transporter (SERT), a monoamine transporter protein, regulates neurotransmission by reducing the concentration of serotonin (5-HT) in the extracellular fluid of nerve cells (Fakhoury, 2015). A study by Song et al. (2015) investigated the role of miR-16, a regulator of SERT mRNA, in MDD. The analysis was conducted by collecting CSF and blood samples from MDD patients and healthy controls, which were used to measure the levels of miR-16 and serotonin. It was found that miR-16 levels were significantly lower in the CSF of depressed patients, which correlated with more severe depression symptoms and lower CSF serotonin. To confirm the findings, an animal study was performed in healthy rats where miR-16 was neutralized, leading to depression-like behaviours, lower CSF serotonin, and increased levels of SERT. In both humans and rats, there was no significant difference in the blood levels of miR-16, suggesting that its role is specific to the brain's serotonin system, where lower miR-16 levels induce depression-like behaviours (Song et al., 2015). However, opposite results were found in an earlier study by Bai et al. (2012) where they investigated two models of rats: MD (maternal deprivation) rats for early-life stress, and CUPS (chronic unpredictable stress) rats for adulthood stress, by measuring the levels of miR-16 and BDNF expression in the hippocampus. They found that although both MD and CUPS rats exhibited depression-like behaviours through behavioural tests, MD rats showed significantly higher expression of miR-16 and lower expression of BDNF in the hippocampus when compared to healthy controls, while CUPS rats showed no significant changes in the expression of either miR-16 or BDNF. This suggests that the upregulation of miR-16 which subsequently results in downregulation of BDNF, might be a mechanism that is only associated with certain stressors. In this study, only the MD rats showed a difference in expression, meaning that only early-life stress induced depression-like behaviours, but not adulthood stress (Bai et al., 2012).

In addition to the serotonin system, miRNAs also regulate the brain's primary excitatory neurotransmitter system, which is essential in synaptic plasticity. The upregulation of glutamate can cause neuronal toxicity and lead to neuronal death, as shown by Sequeira et al. (2009), where the NR2A (Grin2a) subunit of the NMDA (N-methyl-D-aspartate) receptor was significantly upregulated in the brains of depressed and suicidal patients. Besides NR2A, other glutamate receptor subunits were found to be dysregulated in depression. Morquette et

al. (2019) found that miR-223 has a neuroprotective effect in preventing glutamate-induced hyperexcitation: by targeting the mRNAs of NR2B and GluA2 in order to reduce expression, it inhibits NMDA-induced calcium influx in hippocampal neurons. Other types of miRNA, such as miR-335, target the metabotropic receptor GRM4 (glutamate receptor metabotropic 4). In healthy controls, miR-335 regulates GRM4 by suppressing its expression. However Li et al. (2015) found that in the blood of MDD patients, miR-335 was significantly downregulated, impairing its ability to suppress GRM4, leading to high levels. The mechanism of this miRNA is based on a regulatory feedback loop, demonstrating that GRM4 can also negatively regulate the expression of miR-335. To test the efficacy of a certain antidepressant, citalopram, on the cellular mechanism, researchers first applied the drug to human neural progenitor cells (NPCs) for seven days, which resulted in regulated high levels of miR-335 and low levels of GRM4. MDD patients were then treated with the drug for four weeks, yielding the same results, where both levels returned to normal (Li et al., 2015).

(b) Synaptic structural plasticity

MiRNAs play a critical role in synaptic structural plasticity, by regulating the expression of synapse-associated proteins and active regulatory factors, which consequently influences the shape and number of dendrites and their spines (Gao et al., 2022). For example, Yan et al. (2019) investigated the in vivo effects of miR-137 by generating a forebrain-specific miR-137 knockout (cKO) mouse model, since it has been known that a decrease in miR-137 has been implicated in MDD but the exact cellular basis of this mechanism is still unknown. Through the analysis of cultured hippocampal neurons, the study found that decreased levels of miR-137 cause significant dendritic and synaptic overgrowth. The mice also presented altered synaptic plasticity, specifically a significant reduction in long term potential (LTP). To further investigate the cellular mechanism, the researchers identified enhancer of zeste homolog 2 (EZH2), a target of miR-137, to be significantly upregulated in the forebrain of cKO mice. It was then revealed that after EZH2 was knocked down using a lentivirus with short hairpin RNA (shRNA), the mice experienced a decrease in depression-like behaviours, reduced dendritic complexity, length, and density, as well as an amelioration in impaired LTP. The study concluded that the loss of miR-137 contributes to anxiety and depression-like behaviours in mice, through the upregulation of EZH2 (Yan et al., 2019). Another study by Muñoz-Llanos et al. (2018) examined how chronic stress alters miRNA expression in the dorsal hippocampus of rats, due to its important role in post-translational regulation of gene expression and in several hippocampus-dependent functions, as well as the ways it relates to depression pathophysiology. Using microarray analysis on the dorsal hippocampus of rats that underwent daily restraint stress for 7 to 14 days, they compiled a transcriptomic profile of various miRNAs with altered expression based on the duration of exposure to stress. Two miRNAs, miR-92a and miR-485, were significantly upregulated after 14 days of stress. However, when replicating this experiment by chronically administering corticosterone, they found that the results were not the same, and that the miRNA changes are not only due to the stress hormone. An in silico bioinformatics analysis was performed to understand the relevance of the findings, which showed that the targets of miR-92a and miR-485 are involved nervous system functioning, behaviour, as well as axonal guidance and cAMP signaling. It was

concluded that exposure to chronic stress can lead to a time-dependent shift in miRNA expression in the hippocampus, and that the upregulation of miR-92a and miR-485 could contribute to depression pathophysiology (Muñoz-Llanos et al., 2018).

3.1.3. miRNAs modulation of the hypothalamic-pituitary-adrenal (HPA) axis

Chronic stress can lead to hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, which has been strongly associated with the development of depression. The system is regulated at multiple levels: the hypothalamus secretes the corticotropin releasing factor (CRF), which stimulates the pituitary release of adrenocorticotropic hormone (ACTH), triggering the adrenal release of glucocorticoids. These hormones then interact with multiple target tissues, but also provide negative feedback to the brain by binding to glucocorticoid receptors and controlling the stress response (Ding et al., 2023). For example, Roy et al. (2017) investigated the role of miRNA-124-3p in key stress response pathways involved in MDD. Using a rat model that mimics chronic stress by corticosterone (CORT) administration, they found a significant increase in the expression of miRNA-124-3p in the prefrontal cortex. The increase was shown to target and suppress several key targets, including Gria3 and Gria4, members of the AMPA receptor family, and the NR3C1 glucocorticoid receptor, which plays a key role in maintaining the equilibrium of the HPA axis in response to stress. This is due to an epigenetic mechanism, specifically the hypomethylation of the promoter of the miRNA-124-3p gene. The study was also replicated in humans, through the analysis of postmortem brain tissue from patients with MDD, as well as the blood serum of living unmedicated MDD patients, where the same pattern was then observed for both miRNA-124-3p upregulation and glucocorticoid receptor downregulation. Importantly, treatment with the antidepressant fluoxetine in stressed rats reduced the stress induced by the increase of miR-124-3p, highlighting this pathway as a potential therapeutic target (Roy et al., 2017). However Al-Rawaf et al. (2021) found that hyperactive HPA axis responses can have effects at a larger scale on the central nervous system. They found that older adults with depression had significantly increased levels of the stress hormone cortisol, as well as significantly reduced levels of serotonin when compared to healthy controls, indicating HPA axis hyperactivity. Then using qRT-PCR, they found that the expression of four miRNAs, miR-124, miR-34a-5p, miR-135, and miR-451-a, all correlated positively with elevated cortisol levels and negatively with reduced serotonin levels. This relationship was further associated with a state of elevated oxidative stress, as cortisol levels also correlated positively with pro-oxidant markers and negatively with antioxidant genes. The findings suggest that the dysregulation of the specific set of miRNAs is associated with a hyperactive HPA axis and reduced serotonin, which are key features of the pathophysiology of depression (Al-Rawaf et al., 2021). A previous study by Rajasethupathy et al. (2009) has also confirmed the negative correlation between miR-124 and serotonin. The researchers also found a potential mechanism by which serotonin could control synaptic function through miR-124. Using a sensory-motor neuron culture from Aplysia, they found that the repeated application of serotonin caused a significant downregulation in miR-124 in the presynaptic neuron. miR-124 was found to directly target and repress cAMP response element binding protein 1 (CREB1), which is involved in long-term memory. Therefore, when serotonin downregulates

miR-124, it relieves the inhibition on CREB1, allowing levels to increase and promote long-term changes in the synapse. The researchers also found a potential feedback loop, through which CREB1 may further regulate the expression of miR-124. It was concluded that serotonin can control synaptic function through a specific molecular cascade that is regulated by miR-124, allowing an increase in CREB1 levels that promoted long-term changes necessary for memory formation (Rajasethupathy et al., 2009).

3.2. Long non-coding RNAs (lncRNAs)

The rest of the sections will explore the role of long non-coding RNAs (lncRNAs) in the pathophysiology of mood disorders, through another three key mechanisms. First, lncRNAs can regulate neurotransmitters and neurotrophic factors, influencing brain development and disease. Second, various lncRNAs can modulate synaptic plasticity by altering synaptic function, through local action after being transported to specific sites, and by changing the threshold for neuronal excitability. Third, lncRNAs manipulate the process of neurogenesis in the olfactory bulb, as well as the gene networks involved in the olfactory transduction pathway (Zhong et al., 2023). Table 2 presents the list of the lncRNAs that are associated with these mechanisms and that are presented in this review.

Name	Study model	Source	Target	Reference	Findings
NONHSAG 045500	Human neuroblastoma cells	Cell culture	SERT mRNA	Liu et al. (2018)	Overexpression inhibits SERT expression, while its KD increases SERT expression; Regulator of the serotonin system;
BDNF-AS	Human & mouse cell lines, mice	Cell culture, hippocampus, frontal cortex	BDNF gene	Modarresi et al. (2012)	Acts as a natural repressor of BDNF transcription; BDNF-AS KD upregulates BDNF, increasing neuronal proliferation and survival;
MIR155H G	Mice (CUMS model)	Hippocampus	miR-155	Huan et al. (2021)	Decreased in depressed mice; Acts as a sponge, preventing miR-155 from repressing BDNF; Overexpression has antidepressant effect;
Various lncRNAs	Mice (learned helplessness model)	Hippocampus	Synapse-related mRNAs	Li et al. (2018)	Identified 340 differentially expressed lncRNAs in a depression model; 57% correlate with synaptic function mRNAs;
AP1AR-DT	Mice, human twins	Mouse mPFC, human blood	NEGR1 gene promoter	Li et al. (2024)	Upregulated in BD; Overexpression causes anxiety and depression-like behaviours by reducing spine density and repressing NEGR1 via competition with NRF1;

SLAMR	Mice, rats (fear conditioning model)	CA1 hippocampal neurons	CaMKIIα protein, local translation	Espadas et al. (2024)	Activity-dependent lncRNA transport to synapses; Role in structural plasticity and memory consolidation by increasing local translation and CaMKIIα activity;
NEAT1	Human iPSC-derived neurons	Cell culture	K+ channel proteins (KCNAB2, KCNIP1)	Barry et al. (2017)	Regulates neuronal excitability; KD leads to hyperexcitability and increased expression of ion channel genes;
Various lncRNAs	Rats (learned helplessness model)	Hippocampus	Olfactory trans-duction pathway genes	Wang et al. (2019)	Enrichment of lncRNA networks for olfactory transduction pathway in both depression-vulnerable and depression-resilient rats;
T-UCstem1	Postnatal mice	Olfactory bulb	miR-9	Pascale et al. (2020)	Controls neurogenesis in the OB; KD decreases progenitor proliferation but increases final number of new neurons in the OB by acting as a sponge for miR-9;

Table 2. List of lncRNA studies and their findings.

3.2.1. lncRNA regulation of neurotransmitters and neurotrophic factors

(a) Neurotransmitters

The pathogenesis of various mental disorders such as major depressive disorder (MDD) is closely linked to a general decrease in neurotransmitters, such as 5-hydroxytryptamine (5-HT) (Hao et al., 2022). LncRNAs have been identified as essential regulators in these systems, for example, by controlling the transport of the monoamine transporter 5-HT. The study by Liu et al. (2018) investigated the role of three different lncRNAs previously associated with MDD (Cui et al., 2016), NONHSAT142707, NONHSAG045500, and ENST00000517573, by examining their ability to regulate the central neurotransmitter serotonin (5-HT) transporter (SERT). The research was conducted in vitro using human neuroblastoma cells, overexpressing the three lncRNAs in plasmids and using small interfering RNAs (siRNAs) to interfere with their expression. After measuring expression levels of SERT mRNA using qRT-PCR, they found out that the overexpression of any lncRNA significantly inhibited the expression of SERT, while only the interference of NONHSAG045500 significantly increased SERT expression. They concluded that NONHSAG045500 can act as an essential regulator of the serotonin transporter, proving to be a potential therapeutic target by the modulation of the serotonin system. Although the findings have to be replicated in vivo, the dysregulation of NONHSAG045500 could be involved in the pathological alterations of 5-HT transmission in MDD (Liu et al., 2018).

(b) Neurotrophic factors

Another focus has been the lncRNA mediated regulation of neurotrophic factors, particularly the brain-derived neurotrophic factor (BDNF), which is often found in brain tissues such as the amygdala and the hippocampus. BDNF is vital for neuronal development, differentiation, survival, and growth, and is also known to be dysregulated in MDD (Hao et al., 2022). One primary mechanism is regulating direct gene expression, as shown by the early study of Modarresi et al. (2012), in which they identified BDNF-AS as a lncRNA that directly regulated the expression of BDNF. Through a series of experiments, they found out that BDNF-AS functions as a natural repressor of BDNF transcription by altering the chromatin structure of its gene locus to make it less accessible. In vitro, the researchers knocked down BDNF-AS in human and mouse cell lines, which resulted in a significant upregulation of BDNF mRNA and protein levels, along with a significant reduction in repressive chromatin marks and the BDNF promoter. In vivo, they used an inhibitory oligonucleotide to block BDNF-AS, which also led to a significant increase in BDNF mRNA and protein levels in the hippocampus and frontal cortex. This increase also resulted in more neuronal proliferation and survival. The study concluded by establishing that BDNF-AS suppressed BDNF expression and that inhibiting this lncRNA may offer a novel strategy to upregulate BDNF (Modarresi et al., 2012). Another important mechanism of lncRNAs is through competitive inhibition with miRNAs. The interplay between BDNF, miRNA (miR-155) and lncRNA (MIR155HG) was investigated by Huan et al. (2021). Using a CUMS (chronic unpredictable mild stress) mouse model, they first observed that in the hippocampus of depressed mice, the levels of BDNF and lncRNA MIR155HG were significantly decreased, while miR-155 levels were significantly increased. They then found out that MIR155HG directly binds and negatively regulates the expression of miR-155. Normally, miR-155 would bind to BDNF mRNA and repress it, but under MIR155HG regulation, BDNF can fully exert its protective benefits. This was confirmed in vivo using viral vectors to manipulate gene expression in the hippocampus, showing that both the overexpression of MIR155HG and the inhibition of miR-155 expression can alleviate depression-like behaviour of CUMS mice. While the downstream mechanism remains unclear, this study concluded that MIR-155HG has an antidepressant effect, proving that the MIR-155HG/miR-155/BDNF axis plays an important role in the pathophysiology of MDD (Huan et al., 2021).

3.2.2. lncRNA regulation of synaptic plasticity and excitability

Previous studies have shown that a decrease in synaptic density in the brain is closely associated with the onset of depression. This decrease is caused by a downregulation of synapse-related genes, especially in the case of patients with severe depression. It has also been shown that lncRNAs regulate synaptic function (Kang et al., 2012), highlighting the important role of lncRNAs in the pathophysiology of mood disorders. The study by Li et al. (2018) used a learned helplessness mouse model to investigate the role of lncRNA hippocampal regulation in depression pathology. Through RNA-sequencing, they identified 340 lncRNAs that were differentially expressed in helpless mice, revealing that the changes were highly correlated with the regulation of mRNAs involved in synaptic functions. Approximately 57% of the lncRNAs, including specific ones such as Gomafu, Gm26859,

1700109K24Rik, Gm16364, and RP24-502E20.5, were linked to 18 different synapse related functions, including synapse assembly, synaptic plasticity, and dendritic spine morphogenesis. These findings suggest that lncRNA might be implicated in mediating synaptic dysfunctions that are involved in depression pathophysiology. Another study by Li et al. (2024) provides a direct causal link between the upregulation of the lncRNA AP1AR-DT and bipolar disorder (BD). By overexpressing AP1AR-DT in the medial prefrontal cortex (mPFC) of mice, they started exhibiting anxiety and depression-like behaviours. The overexpression of AP1AR-DT caused a reduction in both neuronal spine density and the frequency of spontaneous excitatory postsynaptic currents, directly linking the behavioural change to synaptic dysfunction. By analyzing the brain transcriptome of the mice, they found that AP1AR-DT physically binds to the promoter of the neuronal growth regulator 1 (NEGR1) and competes with the transcriptional activator NRF1 to suppress the expression of NEGR1. The study also showed that restoring NEGR1 expression was enough to ameliorate both the impaired synaptic function and the anxiety and depression-like behaviours, confirming the role of the lncRNA in this specific pathway (Li et al., 2024).

In addition to regulating gene expression in the nucleus, lncRNAs can also be transported to specific subcellular locations to act locally. Espadas et al. (2024) identified an activity dependent lncRNA, Synaptically Localized Activity Modulated lncRNA (SLAMR), that becomes enriched in CA1 hippocampal neurons following fear conditioning in mice and rats. They found that SLAMR promotes structural plasticity: its overexpression increases dendritic complexity and spine density, while its silencing has the opposite effect. Using live-cell imaging, the researchers found that SLAMR is actively transported along dendrites by the molecular motor KIF5C, then recruited to individual synapses. Its mechanism involves post-transcriptional regulation, as SLAMR was found to increase local protein synthesis by enhancing the activity of the synaptic protein CaMKIIα. Finally, by selectively knocking down SLAMR expression in the CA1 region of the mice hippocampus, only the consolidation of contextual fear memory was impaired, without affecting its acquisition, recall, or spatial memory, highlighting its behavioural relevance (Espadas et al., 2024).

Regarding other specific mechanisms, alterations in the subunit stoichiometry of ion channels could induce neuronal excitability and plasticity, by changing the threshold for action potentials, which could manifest as a mood instability (Rusconi et al., 2020). According to Barry et al. (2017), lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) is a key regulator of neuronal excitability. Using a human proteome microarray, they found that NEAT1 binds directly to potassium channel-interacting proteins, such as KCNAB2 and KCNIP1, which are known to reduce neuronal excitability. Then they knocked down NEAT1 in human iPSC-derived cortical neurons, which led to neuron hyperexcitability through a significantly increased depolarization-induced calcium influx. Further transcriptome sequencing also revealed that NEAT1 knockdown in activated neurons is enough to significantly increase the expression of multiple ion channel gene sets, providing a potential molecular mechanism for this dysfunction (Barry et al., 2017). Neuronal hyperexcitability is a feature that is often seen in bipolar disorder (BD) patients, which was proved to be rescued by lithium treatment in a recent study by Khayachi et al. (2024).

3.2.3. lncRNA involvement in olfactory dysfunction

Olfactory disturbances are increasingly recognized as a significant factor in the pathology of mood disorders, as patients with loss of smell are more likely to suffer from anxiety or depression (Marin et al., 2023). The study by Wang et al. (2019) investigated lncRNA and mRNA networks that are associated with vulnerability and resilience to stress-induced depression. They used a learned helplessness rat model and created a co-expression network of differentially expressed lncRNAs and mRNAs in the hippocampus of depression-vulnerable (LH) and depression-resilient (NLH) rats. The findings consisted of two significantly enriched pathways, specifically the olfactory transduction pathway with 44 DEGs, and a neuroactive ligand-receptor interaction, which correlated with both LH and NLH phenotypes. Olfactory receptor 8 (olr8) and olfactory receptor 510 (olr510) were identified as the top-ranked genes that were associated with the LH state. The study concluded that the dysfunction in olfactory processing is strongly linked to the development of depression, which consists of a change in the olfactory bulb and the limbic system that results in an abnormality in emotional cues. Besides the dysfunction in the olfactory pathway, they also mentioned other affected non-related pathways, including G-protein coupled receptor signaling, dopamine transport, and cell cycle regulation (Wang et al., 2019). Another study by Pascale et al. (2020) also investigated the role of lncRNAs in the neurogenesis of the postnatal mouse olfactory bulb (OB). First, by knocking down lncRNA T-UCstem1 in postnatal mice, they found a decrease in the proliferation of neuronal progenitors in the proliferative subventricular zone (SVZ), which resulted in a significantly higher number of new neurons that integrated in the olfactory bulb 14 days later. Conversely, by overexpressing U-TCstem1, they observed an opposite effect, which increased progenitor proliferation in the SVZ at the expense of neuron production. The study also found a potential mechanism which is mediated by the interaction of T-UCstem1 with miR-9, as mutating the miR-9 binding sites on the lncRNA reversed its effects on both progenitor proliferation and the final number of neurons in the olfactory bulb (Pascale et al., 2020). While olfactory dysfunction in mood disorders is still an emerging field, especially in bipolar disorder (BD), Li et al. (2023) found that BD patients have significant olfactory impairments, showing decreased olfactory sensitivity (OS) and olfactory identification (OI) compared to healthy controls. OS was significantly lower in patients with BD I compared to both BD II patients and controls, suggesting its use as a potential biomarker in subtype differentiation. The researchers also identified correlations between olfaction and symptom severity, as poorer OS was associated with more severe depression in BD II patients, while better OI was associated with more severe mania in BD I patients. While the study by Li et al. (2023) establishes a clear link between BD and significant olfactory dysfunction, an underlying mechanism has not been found, representing a research gap that could potentially be explained by the regulatory role of lncRNAs.

4. Discussion

4.1. Key findings and limitations

This review highlights that non-coding RNAs, specifically miRNAs and lncRNAs, play key roles in the molecular pathways of mood disorders. They act as critical regulators of core biological processes that are often dysregulated in MDD and BD: neuroinflammation, synaptic plasticity and excitability, HPA axis dysregulation, and olfactory processing.

While holding great potential, there is a contradictory nature regarding some of the findings. For example, some studies have resulted in opposite data that might suggest that the role miR-16 is dependent on the context. Song et al. (2015) reported that CSF miR-16 was significantly lower in both MDD patients and rats than in healthy controls, resulting in low CSF serotonin levels, while blood miR-16 showed no significant difference. Another study by Bai et al. (2012) used two stress models, MD for early-life stress and CUPS for adult stress, that resulted in different molecular mechanisms. Although both models induce depressive behaviours, the upregulation of miR-16 resulted in BDNF downregulation only in the MD rats, but not in the CUPS rats. This finding reinforces the idea that the pathophysiology of depression is extremely complex. As other studies (Larsen et al., 2010; Razzoli et al., 2009) have also reported divergent findings on the levels of BDNF following the aftermath of different stressors, the discrepancy in BDNF might be explained by the fact that the timing and nature of various stressors could cause divergent depressive phenotypes due to different molecular pathways. Another example would be the contradictory findings on miR-155 in inflammation. While Hung et al. (2019) found that lower levels of miR-155 in human peripheral immune cells correlated with more severe depression, Fonken et al. (2016) found that knocking out miR-155 in mice had a protective effect, reducing both anxiety-like behaviours and hippocampal inflammation. Additionally, Ceppi et al. (2009) contradicts the potential protective effect seen in knockout mice, showing that silencing miR-155 in dendritic cells increases the production of pro-inflammatory cytokines. This discrepancy could be explained by the different roles that miR-155 could play in acute versus chronic inflammation. The review by Su et al. (2016) provides a potential mechanism by consistently identifying miR-155 as a major regulator in pro-inflammatory pathways. In response to various inflammatory stimuli, miR-155 is upregulated in microglia, macrophages, and monocytes, which activates the transcription factor p53 that suppresses the mRNA of c-Maf and induces an inflammatory state in the microglia. Furthermore, in a mouse model of the neurodegenerative disease ALS, genetic depletion of miR-155 delayed disease progression and significantly prolonged survival (Butovsky et al., 2014). In conclusion, the role of miRNAs can differ based on cell types, as miR-155 may have a pro-inflammatory role in the microglia, but a different purpose in peripheral dendritic cells.

While the potential of transcriptomic biomarkers is significant, there are certain core limitations that prevent the integration in clinical practice. There is the issue of reproducibility, that refers to the fact that many findings from in vitro studies do not translate to in vivo contexts, and most in vivo research has only been conducted in rodent models, complicating their clinical relevance. The studies that have been performed in humans only include extremely small sample sizes that are limited due to the invasive procedures necessary to measure transcriptomic markers (Gururajan et al., 2016). This is further

complicated by the discrepancy in the ability of the peripheral and central nervous systems to reflect accurate ncRNA changes, as the study by Song et al. (2015) has found that miR-16 was only altered in the CSF of MDD patients, but not in their blood. Another limitation refers to medication as possible confounders, as Hung et al. (2019) has demonstrated that antidepressant treatment can significantly alter ncRNA levels. Finally, this review has been limited by the significant research gap in both lncRNAs and bipolar disorder. The current majority of literature is focused on MDD, leaving particular key features of the mood spectrum unexplored. The exact mechanism and function of lncRNAs is also not known due to its complex nature. For example, Zhang et al. (2021) identified different lncRNAs in depression model mice, compared to normal mice. While the predictive functions of lncRNAs suggest its involvement in oxygen binding, cellular transport, protein binding, and metabolic regulation, there is no direct evidence that confirms any lncRNA is a key mechanism for the development of mood disorders. Despite these limitations, the current findings strongly suggest that the dysregulation of these ncRNAs can act as a strong link between molecular profiles and the clinical symptoms of MDD and BD, presenting the ability to act as potential biomarkers for diagnosis and treatment response.

4.2. Future directions

As current limitations emerge from the incomplete understanding of the mechanism of ncRNAs and the way they contribute to the pathophysiology of mood disorders, future studies should aim on achieving a larger scale, performed in a longitudinal manner. Such methodologies could help track the expression of ncRNAs over the course of the illness, by uncovering the specific nature of a biomarker in diagnosis, prognosis, or treatment selection. More studies should also explore multi-omic data integration, as single molecular layers often provide an incomplete picture. The review by Mokhtari et al. (2022) suggests that integrating genomics, epigenomics, transcriptomic, and proteomics, could uncover complex relationships between clinical phenotypes, through advanced methods such as matrix factorization and deep learning algorithms. For example, recent research has indicated that the intestinal flora might play a role in the pathophysiology of depression, through its interplay with epigenetics (Hao et al., 2022). According to Gao et al. (2020), the intestinal microbiota can directly regulate lncRNA lncLy6C by increasing its expression to promote cell differentiation through the production of butyrate metabolites. Since dysregulation in the microbiota-gut-brain-axis is often seen in depression, the combination of intestinal flora and lncRNAs could be a potential area of research that would provide more insight into the pathogenesis of depression (Gao et al., 2020).

As for novel areas of research, there have been many studies on both lncRNA-mediated regulation of growth factors and growth factor-mediated depression, however few studies have investigated the mechanism through which lncRNAs affect depression through the direct regulation of a certain growth factor. Zhang et al. (2020) has identified lncRNA NR2F1-AS1 as a key regulator of angiogenesis in breast cancer. By acting as a sponge for miR-338-3p, it prevents it from suppressing the insulin-like growth factor-1 (IGF-1). This leads to an increase in the production of IGF-1 and the activation of the IGF-1R/ERK signaling pathway, which promotes the proliferation of endothelial cells and the

subsequent formation of new blood vessels. However an earlier study by Mitschelen et al. (2011) has highlighted the fact that IGF-1 is also a critical molecule for maintaining normal brain function and mood. They demonstrated that a long-term deficiency of IGF-1 can induce depression-like behaviour in mice, as the hippocampus relies on the IGF-1 supply from the blood, which is not compensated when levels are low. Therefore, the aim of developing a cancer treatment would be to decrease IGF-1 in order to inhibit angiogenesis, however this would also reduce the amount of circulating IGF-1 that is available to the brain, which is essential for neurological health. In conclusion, while the field of ncRNAs is still challenged by various limitations, miRNAs and lncRNAs hold great potential in improving personalized psychiatry, where diagnosis, prognosis, and treatment strategies, can be assessed by objective biomarkers.

5. Appendix

Throughout the writing of the thesis, the artificial language model Gemini was used to summarize and extract key information from scientific articles, to provide feedback and to improve grammar as a rephrasing tool.

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