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Neurobiological and Environmental Contributors to Depression and its Subtypes

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Abstract

Depression major depressive disorder (MDD) is a complex and multifaceted mental health issue with diverse symptoms and heterogeneous aetiology. Identifying the exact cause and mechanism of depression in different individuals can be challenging. This paper provides a concise overview of depression as a prevalent and growing global health concern, drawing on evidence from textbooks and peer-reviewed articles. Then reviews the existing literature on the four major contributors to major MDD: genes, neurotransmitters, stress, and immunological factors. Furthermore, this paper proposes avenues for future research aimed at gaining a more comprehensive understanding of the multifactorial nature of depression.

Keywords: Major Depressive Disorder; Genetic; Neurotransmitters; Inflammation; Stress; CPH Axis; Hypercortisolemia; PFC; Amygdala

Abbreviations: MDD: Major Depressive Disorder; APA: American Psychiatric Association; GWS: Genome-Wide Sequencing; DA: Dopamine; NA: Noradrenaline; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Selective Serotonin and Noradrenaline Reuptake Inhibitors; NRIs: Noradrenaline Reuptake Inhibitors; HPA: Hypothalamic Pituitary Adrenal axis; SNS: Sympathetic Nervous System; FMRI: Functional Magnetic Resonance Imaging; ACTH: Adrenocorticotropic Hormone; CRF: Corticotropin-Releasing Factor; GR: Glucocorticoid Receptor; PFC: Prefrontal Cortex

Introduction

Depression

Negative situations and disappointments are inevitable parts of life. While most people accept and embrace these conditions and move on, some individuals experience intense despondency that persists and can make them feel like life is not worth the trouble. Major depressive disorder (MDD) is one of the most prevalent psychiatric issues, adversely impacting people's feelings, thoughts, behavior, and physical health [1]. As a result, individuals with depression often struggle to enjoy life events and fulfill their personal and social responsibilities. According to the World Health Organization [2], MDD was the third major contributor to the global disease burden in 2008, highlighting the need for early diagnosis and interventions to reduce this burden. To understand why MDD develops and reduces the risk of its occurrence, it is essential to comprehend the causal factors and aetiology of this disorder. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [3], depression is typically characterized by at least five of the following symptoms, experienced for a minimum of two weeks: despondency (i.e., a prolonged feeling of sadness and low mood), anhedonia (i.e., a loss of interest in nearly all activities that were once enjoyable), changes in sleep patterns or appetite, persistent exhaustion, low self-esteem, trouble concentrating and making decisions, and, in more severe cases, feelings of hopelessness and recurrent thoughts of self-harm or suicide.

The DSM [3] specifies that among the other depressive symptoms, despondency and anhedonia must be observed or self-reported. Numerous studies, including those by Albert [4] and Schuch et al. [5], have revealed that MDD is more prevalent among females than males. This discrepancy is attributed to a range of biological, social, and cultural factors, such as hormonal changes, socioeconomic status, cultural expectations, and gender-based violence [4]. However, the rate of depression-related deaths due to

suicide in men is reported to be three times higher than in women [6]. It is worth emphasizing that, in most cases, the diagnosis and treatment of MDD are still based on symptoms, as accurate knowledge about its mechanism and pathology is still lacking [7].

Genetic factors

Familial studies have convincingly demonstrated a high contribution of genetic factors to the risk of developing MDD. For instance, Sullivan et al. [8] suggested that the prevalence of depression following environmental exposure is approximately 30-40% higher in children of parents with depressive disorders. Various approaches, including genome analysis, linkage studies, and genome-wide sequencing (GWS), have been used to identify specific gene variants that increase the predisposition to MDD. McGuffin et al. [9] investigated genome linkage in 497 subjects with recurrent MDD and observed linkage on several loci in the genome. One of the most extensively studied genes for its moderating function on the impact of environmental stress and reducing the risk of depression is the serotonin transporter promoter polymorphism gene (5-HTTLPR) [10]. The 5-HTTLPR polymorphism has two common alleles, short (S) and long (L), which differ in their transcriptional efficiency [11]. Individuals who carry two copies of the short allele (SS genotype) have been found to have a higher risk for depression, particularly in response to stressful life events, compared to individuals who carry one or two copies of the long allele (SL or LL genotypes) [12].

Additionally, the dopaminergic system is known to play a crucial role in emotion processing and is associated with various psychiatric disorders, including depressive disorders [13]. An increasing amount of research, including neuroimaging, post-mortem, and linkage studies, has examined the potential link between the function of the dopamine receptor subtype 4 (DRD4) and the development of MDD [14-17]. Several studies have found a strong association between DRD4 and depressive symptoms. For example, a meta-analysis conducted by Lopez-Leon and colleagues in 2005 revealed a significant link between DRD4 and the occurrence of MDD. Xiang et al. [18] measured the level of DRD4 mRNA in the basal nucleus of patients with MDD and demonstrated that it was significantly higher in these patients than in participants in the control group. Propper et al. [19] reported that drugs that disrupt the activity of DRD4 precipitate depressive episodes, including impaired motivation and low mood. However, other studies disputed this association. For instance, in Frisch et al. [20] and Persson et al. [21] studies, no significant association between DRD4 genotype and depressive symptoms was observed. A meta-analysis conducted by Wang [22] reviewed nine different studies on the association between apolipoprotein ε4 (APOE) polymorphisms and depression. The findings from this meta-analysis confirmed that the APOE ε4 allele was significantly associated with depression and that patients carrying the APOE ε4 allele show more severe depressive symptoms. However, results from other studies [23,24] found no correlation between APOE ε4 and MDD. Therefore, no conclusive correlation has been established between depression and APOE ε4.

In a study conducted by Anttila et al. [25], it was confirmed that the GNB3 gene was associated with the development of depressive symptoms in females, but no association was observed in men. However, results from another study conducted on 146 MDD patients in Japan by Kato and colleagues [26] showed no significant association between carrying the GNB3 gene and experiencing MDD. According to Zięba, et al. [27] Several studies confirmed the association between Methylenetetrahydrofolate reductase (MTHFR 677T) gene and MDD. MTHFR 677T gene is involved with the secretion of folate and consequently the production of some neurotransmitters in the body. Some of these studies, such as Slopien et al. [28], which used a self-report method to collect data from 172 postmenopausal women between 42 and 65 years in Poland, reported a significant association between the MTHFR 677T gene and MDD. However, other studies such as Hong et al. [29], which studied 178 MDD and 85 non-MDD candidates, and Pan et al. [30], which investigated 170 MDD and 83 non-MDD candidates over 60 years old, did not find a significant association between the MTHFR 677T gene and MDD. These genes are not the only ones suggested to have an impact on the development of MDD. According to Zięba et al. [27], about 600 different genes have been suggested to have a correlation with MDD. Additionally, other studies, such as Shi et al. [31], suggest that there is no genome-wide association with MDD.

Neurotransmitters

Low mood and diminished pleasure are commonly recognized as primary symptoms of MDD, which have been found to be closely linked with altered connectivity in the limbic and cortical regions of the brain. The agents responsible for providing connections in the loop of prefrontal cortex, amygdala, and hippocampus are neurotransmitters [32]. Of over 100 neurotransmitters that have been identified in the body, monoamine neurotransmitters, including serotonin (5-HT), dopamine (DA), and noradrenaline (NA), play a significant role in regulating brain states [33]. According to the monoamine hypothesis of depression, the underlying physiological basis of depression is linked to low levels of serotonin, norepinephrine, and/or dopamine in the central nervous system [34]. Numerous studies have supported this theory [15,33,34]. However, the findings are still mixed, and the precise role of these neurotransmitters in the aetiology of depression remains complex and not yet fully understood. For instance, a meta-analysis conducted by Ruhé et al. [35] on 90 depletion studies found that artificially lowering monoamine neurotransmitter levels in healthy individuals does not necessarily lead to low mood. A more recent study conducted by Wild [36] analyzed the findings of 17 previous studies and indicated that there might not be a connection between antidepressants and

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serotonin. The study suggested that SSRI antidepressants, which are supposed to increase serotonin levels in the brain, might only have a placebo effect.

Based on this theory, several classes of antidepressant drugs have been developed, including monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), and selective serotonin and noradrenaline reuptake inhibitors (SNRIs). These drugs are meant to increase the concentration of monoamine neurotransmitters by inhibiting their reuptake within the synaptic cleft [37]. Some of the most compelling evidence supports the efficacy of these drugs in improving mood and reducing depressive symptoms [38]. However, there is evidence that challenges the effectiveness of antidepressants. For example, a meta-analysis carried out by Kirsch [39] indicated that the difference in effectiveness between antidepressants and placebo was relatively small, and the clinical significance of this difference was uncertain. Other studies have also indicated that the efficacy of antidepressants may be overstated due to publication bias and selective reporting of positive results [40].

Recently, there has been a growing interest in using ketamine as a non- monoaminergic mechanism for the treatment of depression, especially when traditional antidepressant medications fail. Studies suggest that ketamine can rapidly improve depressive symptoms by blocking the action of glutamate and resetting neural circuits disrupted in depression [41,42]. However, it should be noted that ketamine is still considered an experimental treatment and should only be administered under medical supervision due to potential side effects such as dissociation, hallucinations, and addiction risk [43,44]. One important issue with the synaptic explanation for the mechanism of antidepressants is that, while these medications increase the level of neurotransmitters in the synapse within days of administration, it takes several weeks for them to reduce depressive symptoms [1]. Therefore, it can be inferred that decreased levels of neurotransmitters may contribute to the mechanisms underlying depression, but they are not its exclusive etiological factor. Additionally, GABA as the main inhibitory neurotransmitter and, glutamine as the major inhibitory neurotransmitter control neural excitation and information flow in the brain and therefore are involved in a wide range of cognitive and emotional processes [45,46]. Based on evidence from numerous studies, an imbalance of GABA and glutamate can compromise cognitive and mental health [47,48]. Imaging studies indicate that there may be a reduction in glutamate transmission in specific areas of the prefrontal cortex in patients with MDD. Kang et al. [49] also supported these findings through post-mortem studies, which revealed a decrease in synapse number and expression of synaptic markers in the dorsolateral PFC of MDD subjects.

Stress

The third pathway to depression is stress. It activates the hypothalamic-pituitary- adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in the release of stress hormones such as cortisol. Elevated levels of cortisol, or hypercortisolemia, have been linked to neuropsychiatric disorders, including depression. Studies have reported that over 80% of depressed individuals have significantly higher cortisol concentrations [50] and that more than 50% of people with higher cortisol levels develop depressive symptoms [51]. The effect of hypercortisolemia on important regions of the brain associated with emotion and cognition, such as the hippocampus, prefrontal cortex (PFC), and amygdala, may explain how it leads to the development of depressive symptoms. Chronically elevated cortisol levels have been linked to changes in the structure and function of glutamate neurons, which can alter glutamate transmission in the synapses. This can cause a reduction in the length and branching of dendrites of pyramidal neurons, leading to a decrease in the volume of important brain regions such as the hippocampus and prefrontal cortex, including the subequal and anterior cingulate cortex [52]. Additionally, chronic stress has been shown to decrease the expression of the glucocorticoid receptor (GR) gene which makes the HPA-axis feedback system less sensitive to levels of circulating glucocorticoids. As a result, the hypothalamus continues to release corticotropin-releasing factor (CRF), which leads to increased release of adrenocorticotropic hormone (ACTH) from the pituitary gland, and ultimately increased cortisol release from the adrenal glands. This dysregulation of the HPA axis can contribute to cognitive deficits, memory deterioration, and depressive symptomatology [14].

Moreover, the PFC oversees important decision making, emotional regulation, rational thinking, and self-esteem. Its volume reduction may lead to emotional dysregulation, impulsivity, impaired executive function, apathy, and anhedonia [53]. This symptom reinforces the association between stress and depression, as evidenced by Kumar et al. [53] where there is a linear association between PFC volume and the severity of depression. Additionally, the amygdala, which plays a prominent role in emotional and behavioural responses, increases in both size and function because of hypercortisolemia, leading to anxious behaviour [54,55]. While studies have reported that individuals with depressive symptoms have larger amygdala volumes compared to non- depressed individuals, some studies argue against this conclusion [56]. Altered structures of the hypothalamus, PFC, and amygdala lead to hypothalamic hyperactivity, which may ultimately cause MDD through complex neural pathways involving dopamine, norepinephrine, and fear response in the amygdala [56]. Overall, studies have shown a strong link between chronic stress and the development of MDD, with stress being recognized as a significant contributing factor to the onset of depressive symptoms. The manifestation of this

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symptom in individuals experiencing stress further underscores the need for effective stress management strategies to mitigate the risk of developing depression.

Additionally, it highlights the importance of early identification and intervention for those experiencing symptoms of MDD, as the longer it goes untreated, the greater the risk for more severe and long-lasting effects on mental and emotional well-being. Santarelli and colleagues [57] conducted a study that showed how antidepressants are involved in the growth of new brain cells in the hippocampus of adult mice. They blocked the effects of antidepressants in mice by using X-rays on the hippocampus and found that mice without a certain receptor did not respond to antidepressants. This suggests that antidepressants cause changes in the brain, such as the growth of new brain cells, over a period of weeks. In rats, certain proteins involved in brain cell growth were affected by antidepressant treatment. Although some studies have shown that a particular signalling pathway may be involved, more research is needed to fully understand how antidepressants work in growing new brain cells.

Immunological factor

The immune system's response to physical illness is another potential factor that may contribute to depression. Numerous experimental and clinical studies have demonstrated a significantly higher incidence of MDD among individuals with serious physical illnesses compared to the general population [58]. This association is even stronger among those with neurodegenerative, infection, and autoimmune disorders [59], particularly when the physical illness is more severe [60]. It appears that physical illness can act as a stressor for patients, triggering HPA axis hyperactivity and leading to elevated cortisol levels and activation of stress-induced pathways, like other prolonged stressors [61]. Furthermore, physical illnesses, injuries, and inflammations can trigger the production of cytokines in the body. Cytokines are proteins that help control inflammation and regulate immune responses, produced by various immune cells like T-cells and B-cells [62]. However, an excessive number of cytokines can lead to more inflammation. High levels of cytokines can stimulate the immune system to produce more immune cells and increase blood flow to the affected area, resulting in characteristic signs of inflammation like swelling, redness, and heat. In addition, certain cytokines can activate other immune cells to produce more cytokines, resulting in a vicious cycle of inflammation and tissue damage [63].

Moreover, certain types of cytokines have been shown to cross the blood-brain barrier and bind to receptors in the brain, activating signalling pathways that cause the behavioral changes seen in sickness behavior. Sickness behaviors, as proposed by Maier and Watkins [64], include a set of behaviors such as lassitude, coldness, fatigue, lack of appetite, withdrawal from social activity, and sleep disturbance, which are common during times of physical illness. These behaviors are a natural way for a physically ill person to fight or cope with the illness and conserve energy to fight the disease, even though they may overlap to some degree with depressive symptoms. In addition, cytokines also affect HPA activation and interfere with the production of neurotransmitters, mainly serotonin, which may contribute to MDD [65]. While several studies have confirmed elevated levels of pro-inflammatory cytokines and a direct association between the level of pro-inflammatory cytokines and the severity of MDD in patients, other studies have failed to report such a direct correlation between pro- inflammatory cytokines and MDD [63].

These inconsistencies in findings about the relationship between MDD and inflammatory cytokines raise questions about the causal role of inflammatory cytokines in depression and argue that the stress-induced pathway is the only contributor to MDD in physically ill patients. According to Dantzer [66], major depressive disorder (MDD) resulting from cytokine-induced sickness behavior only occurs in vulnerable individuals. This vulnerability may be innate due to genetic factors or acquired through environmental factors such as stress or sociocultural context. Shattuck et al. [67] discuss how cultural norms and values can shape sickness behavior. The authors surveyed a US sample of 1,259 individuals to study the various factors that shape sickness behavior across sex and racial/ethnic groups. They found that low income and stoic endurance of pain and discomfort were associated with higher sickness behavior scores. Familism was positively associated with sickness behavior in men, but not women. The study suggests that social contexts of sickness across demographic groups may have implications for pathogen transmission and recovery times, potentially contributing to health disparities [68].

Conclusion

Depression is a complex and multifaceted disorder with heterogeneous aetiology. It is characterized by a range of symptoms that vary widely in their severity and duration, and it affects millions of people worldwide. Over the years, researchers have attempted to identify the various factors that contribute to the development of depression, including genetic, neurochemical, environmental, and immunological factors. However, the results from these studies are often mixed and inconclusive, suggesting that depression may be influenced by a complex interplay of multiple pathways. One of the most widely studied pathways that contribute to depression is the genetic pathway. Researchers have identified several genes that may play a role in the development of depression, including the serotonin transporter gene and the dopamine receptor gene. However, the extent to which these genes contribute to depression is still a matter of debate, as many people who carry these genes do not develop the disorder Another pathway that has been implicated in depression is the neurochemical pathway, specifically the dysregulation of neurotransmitters such as serotonin, norepinephrine, and dopamine. Although many antidepressant medications target these neurotransmitters, the mechanisms by which these drugs

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work are still not well understood. Stress is another pathway that has been shown to contribute to depression. Chronic stress can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased cortisol levels, which have been linked to depressive symptoms. Additionally, chronic stress can lead to changes in brain structure and function that may contribute to the development of depression.

Finally, there is evidence to suggest that the immune system may also play a role in depression. Studies have shown that inflammation, which is regulated by the immune system, may contribute to the development of depression. Additionally, some antidepressant medications have been shown to have anti-inflammatory effects, suggesting that the immune system may be a promising target for future drug development. Overall, the future of MDD research is focused on improving our understanding of the complex interplay between biological, psychological, and environmental factors that contribute to the disorder and developing more effective and personalized treatments. Future research can focus on developing a more personalized approach to treat depression by identifying specific risk factors in individuals. Advancements in genomic technology and data analysis can help identify novel genes and pathways associated with depression. Furthermore, a more in-depth investigation of the immune system's role in depression can lead to novel therapeutic targets. Non-invasive imaging techniques, such as functional magnetic resonance imaging (FMRI), can help in identifying the brain regions associated with depression, providing valuable insights into the brain's pathophysiology in depression. Finally, a more extensive investigation into the gender differences in depression can lead to more personalized interventions.

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