

# Etiology of Depression: Biological and Environmental Factors in the Development of Depression

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## ABSTRACT

While depression affects 300 million people worldwide and is one of the most significant contributors to suicide, the mechanisms behind its onset remain unclear. This paper summarizes and discusses several biological and environmental factors that lead to the development of depression in an effort to demonstrate the intricate relationship between the various factors. First, an examination of the roles genetics and the external environment play in depression's occurrence is considered by comparing adoption studies. In the next section, biological mechanisms of depression, such as alterations in neurotransmitter systems and brain networks, are explored in an analysis of previous studies and by identifying areas that require further investigation. A discussion is included of how several environmental factors, including urbanization and childhood trauma, elevate the risk of depression in certain individuals along with genetic factors. The conclusion encapsulates how various factors interact with one another and calls for further research on the precise mechanisms behind the onset of depressive symptoms. This approach is crucial for understanding the cause of the depression and improvements in its treatment.

## **Introduction**

Major Depressive Disorder (MDD), also known as depression, is a highly complex psychiatric condition. Depression is diagnosed according to the DSM-5 criteria, a manual for assessing mental disorders. The most common symptoms of this disorder include depressed mood, loss of interest in daily activities, feelings of isolation, significant weight loss/gain, anhedonia, and a lack of motivation (Rakel, 1999). According to the National Institute of Mental Health, MDD often occurs with panic disorder and other anxiety disorders. While depression and anxiety have distinct clinical characteristics, their symptoms often overlap with each other, and this elevates the complexity of diagnosing and treating Depression. Major Depressive Disorder can be the result of a range of environmental and biological factors. Therefore, it is crucial to understand how these factors each play a role in depression in order to find better treatments for MDD. Since they often interact with each other to produce the effects, no single factor is the sole cause of Depression (Dean & Keshavan, 2017). In previous research, scientists have conducted studies on the biological mechanisms of depressive symptoms and examined the effects of environmental exposures and social environment, as well as the correlation between certain genes and the risk of developing depression. This paper will focus on studies that investigated the different biological and environmental factors of depression.

## Nature V.S. Nurture

The debate of Nature versus Nurture is often discussed in the etiology of depression. In the past, researchers have conducted numerous studies, particularly adoption studies, on the role of the rearing environment and genetics in depression. A recent experiment conducted in Sweden tried to answer this question. The study focused on whether depression risk was related more closely to genes or the environment with siblings and half-siblings who had at least

one depressed parent. In each pair, one sibling lived with their biological parents while the other was raised in an adoptive home described as supportive and generally advantaged. Results showed that when comparing individuals raised by their biological parents, children who were raised in adoptive homes with a high-quality rearing environment had a significantly reduced risk for major depression. However, this effect disappeared when an adoptive parent was depressed or when the adoptive home experienced the death of a family member or divorce during early life (Kendler K et al., 2020). Taken together, results suggest that the rearing environment plays a powerful role in impacting the risk for depression along with genetics. This study allows researchers to further understand the importance of the external environment and how nature and nurture each contributes to the onset of depression.

## Biological Factors

From a biological perspective, studies have shown that patients with major depression often have abnormalities with emotion processing. For instance, depression is associated with a hyper-activation of the Prefrontal Cortex (PFC) and hyper-reactivity of the amygdala, a part of the brain that is responsible for threat response, negative emotion, and anxiety. Simultaneously, there are alterations found in several neurotransmitter systems, such as the dopaminergic pathway that is responsible for rewarding feelings, leading to depressive symptoms in individuals (Bosch & Meyer-Lindenberg, 2015). The following sections will summarize how the biological mechanisms, including alteration in neurotransmitter levels, dysregulation of brain networks, and the HPA axis, contribute to depressive symptoms in patients.

### *Alterations in Neurotransmitter Systems*

Alterations and abnormalities of neurotransmitters could also result in depressive symptoms. A major theory for the etiology of depression proposes that depression is the result of alterations in levels of monoamine transmitters, including serotonin and dopamine (Dean & Keshavan, 2017). Studies have discovered that in depressed patients, serotonin levels are reduced, while antidepressants have been shown to increase levels of serotonin in the brain. Furthermore, depletion of tryptophan, a type of amino acid that helps to make melatonin and serotonin, is able to induce symptoms related to depression in patients who are treated for depression, while it has no effect on untreated patients. These results all suggest that increasing serotonin levels are essential for antidepressant effects, even though the reduced level of this neurotransmitter alone may not be adequate to produce the effect (Bell et al., 2021).

In addition, genetic abnormalities in serotonergic transmission have also been linked to depression. For instance, the promoter region of the SERT gene (5-HTTLPR) is associated with depression. Individuals who have the s/s genotype are more vulnerable to developing depression because the s allele is associated with a reduction in serotonin (Caspi et al., 2010).

Furthermore, there are several pieces of evidence that point to the effect of altered dopaminergic transmission and the mesolimbic pathway toward depression. For instance, studies have found that some symptoms related to depression are a result of a malfunctioned reward system and that some antidepressant agents could increase dopamine levels in the brain. Therefore, it is clear that dopamine plays an essential role in mood regulation and feelings of pleasure (Dean & Keshavan, 2017). A study conducted in 2009 defined depression as a disease of the mesolimbic system when an individual experiences great stress or loss develops a dysfunctional reward system, and this led to anhedonia and lack of motivation.

To conclude, the different neurotransmitters, such as serotonin and dopamine, are all related and impact each other in the brain. For instance, both dopamine and norepinephrine (NE) could increase serotonin release from the dorsal raphe nucleus. These findings suggest that monoamine neurotransmitters do not operate independently. Instead, they are interconnected and an alteration in one of the neurotransmitters could affect the other two in the development of depression (El Mansari et al., 2010). All of the biological mechanisms discussed previously are connected with each other and can lead to alterations in the neurocircuitry in the brain, which can be observed by depressive symptoms.

### *Stress*

Stress is often a risk factor for Depression. Stressful life events could potentially lead to depressive symptoms in vulnerable individuals, and childhood abuse or neglect could result in depression in adulthood. Studies with animals have shown that chronic stress could lead to behavioural abnormalities in rodents, including decreased sucrose intake, anhedonia, and decreased motivation (Willner, 2005). Abnormalities in the HPA axis are also associated with a hyperactive response to stress in depressed human patients. This often results in cortisol release, which is a response to the lower levels of stress and chronically increased cortisol levels (Dean & Keshavan, 2017). This increase could impact the ability of the hippocampus to adapt to a constantly changing environment. Moreover, the medial prefrontal cortex (mPFC), hippocampus, and amygdala have also been altered by an increase in glucocorticoids, a hormone that is responsible for reducing inflammation and suppressing the immune system. Studies have also discovered that chronic stress could reduce activity in the mPFC. However, as this region is involved in emotion processing, inactivity of the mPFC could lead to insufficient processing of negative affect. Although these effects allow individuals to avoid stress and external threats, when the outside environment is interpreted as dangerous, this leads to a lack of interest in the external world (Myers et al., 2014).

The relation between chronic stress and depression can also be explained by psychological concepts. The attachment theory, presented by Bowlby, focuses on the emotional bond between children and their caregivers. While attachment provides a sense of security, individuals will experience great distress when they are separated from their caregiver. Over time, when the attachment figure is not found by the individual, they gradually give up on finding their caregiver (Dean & Keshavan, 2017). This concept suggests that individuals who experienced early loss may deviate to an insecure attachment type as they develop a fear of abandonment, and this leads them to become hypersensitive to losses. Depression can occur when the abandoned individual expresses great anger toward the attachment figure combined with love, which generates guilt at the same time. In this way, depression can be seen as self-punishment for feelings of forbidden anger (Holmes, 2013). This conclusion highlights the important role of family during childhood and how insecure attachment contributes to the onset of depressive symptoms later on in life.

Based on all the previous studies discussed, stress has been shown to have a long-lasting impact on the regulation of the HPA axis that leads to a vulnerability toward later stressors that acts as a predisposition to depressive symptoms in the future. Therefore, it can be concluded that chronic stress could induce changes in the brain, including the affective processing circuits, which creates a predisposition to depression. These findings provide an important framework for future research of the biological mechanisms behind stress and how this factor contributes to the onset of depression.

### *Brain Networks*

Several networks in the brain play a distinct role in depression, as their interactions have been impacted by dysregulations. For instance, the reward network is a set of neural pathways responsible for motivation, associative learning, and a range of other behaviours involving pleasure. Studies have found that the VTA dopaminergic projection in the reward system that projects via the Medial Forebrain Bundle (MFB) to the Nucleus accumbens (NAc) and the prefrontal cortex (PFC) is responsible for mediating seeking behaviours. Therefore, it is suggested that the dysfunction of this projection running via the MFB is associated with anhedonia and lack of motivation. The affect network is responsible for emotion processing and human fear, and as a result, the network is related to separation distress, sadness, anxiety, and grief. Feelings of rejection and isolation involve increased activity of this network, which correspond with several depressive symptoms.

Moreover, neuroimaging studies have also found functional abnormalities in the affect regulation neurocircuitry in depressed patients, which involves altered connectivity between the PFC, amygdala and hippocampus. It is suggested that depression develops when the affect regulation system does not have a sufficient ability to process strongly negative affect, and this leads to feelings of hopelessness and despair. The default mode network is functional if the individual is not performing any type of action, which is associated with increased ruminations in depression

(Fenoy et al., 2021). As each of the networks is involved in different aspects of the development of depression, it is crucial to gain further knowledge on their interactions with other networks or regions and the precise mechanisms behind them.

## Environmental Factors

Several environmental factors could increase the risk of depression, ranging from the physical aspects to the social environment. They often interact with each other when producing the effects and no single factor is the sole cause of depression.

### *Urbanization*

The physical aspects of the environment, such as noises, pollutants, and urbanization, play a significant role in elevating the risk of depression in genetically vulnerable individuals. Several environmental exposures, including air pollution, noise, and natural disasters, could negatively influence the specific gene expression for depression vulnerability (Bosch & Meyer-Lindenberg, 2015).

Air pollution is one of the environmental exposures that could directly cause alterations in the brain, which may lead to depressive symptoms. Air pollutants, including diesel emissions, carbon monoxide, and nitrogen oxides, are widely emitted from vehicles and industries. While most of the pollutants enter the human body directly through inhalation, some can also enter through the skin and reach the brain directly. Recent research has found the neurological effects of air pollutants on the developing brain. Moreover, studies have also shown that air pollution exposure among children and teenagers is associated with central nervous system inflammation and changes in important brain regions. (Calderón-Garcidueñas, L et al., 2012) This result emphasizes the need to recognize the dangers posed by air pollutants which its implications need more research on.

Air pollutants may also influence neural plasticity, which could result in cognitive, memory, and behavioural abnormalities. A recent study showed that PM<sub>10</sub> and PM<sub>2.5</sub> were associated with an increased prevalence of suicide, a behaviour often displayed by depressed patients. In other studies on the relation between air pollution and mental health, similar results were concluded. However, other factors should also be considered in the research process in order to establish the association between air pollutants and suicide. These studies corroborated a positive association between air pollution and depression, which validated the hypothesis that exposure to air pollutants was one type of environmental exposure that could increase the risk of developing depression (Bosch & Meyer-Lindenberg, 2015).

Noise is also a common complaint in urban areas. Noises such as loud traffic and construction sounds could result in annoyance and other negative emotions, and this could induce psychological responses that are related to depression. Studies that measured the relationship between noise levels and depressive symptoms found that the most common issue related to noise is sleep disturbance, which is a risk factor for depression. (Sygna et al., 2014) Another large-scale study discovered that exposure to aircraft, railway, or traffic sounds increases the risk of depression or antidepressant prescription. However, though there is evidence of some associations between noise exposures and depression and is corroborated with large samples, more research needs to be done to confirm the relationship without the effect of other factors and establish the biological mechanisms behind the association.

Overall, urbanization in today's society plays a significant role in increasing the risk of depression. While urban living offers numerous benefits, including improved sanitation and healthcare, it is a more stressful environment than rural areas. Environmental exposures in cities, such as air pollution and noise, could lead to alterations in the brain. Recent studies have shown that urban living leads to impacts on brain structures and functions that are important for emotion processing, social cognition, and stress (Lederbogen, F et al., 2011). In fact, mental illness is a commonly reported issue in urban areas, and depression is one of the disorders that is often found in citizens who are exposed to urban environments during childhood.

On the other hand, another study demonstrated that while urbanization was associated with depressive symptoms, depression was less prevalent in more urbanized areas. This is likely due to the lack of knowledge in mental

health and lack of resources for residents in less urbanized areas, which makes it more difficult for them in terms of combating depression (Wang et al., 2018). However, these results cannot support the casual relationship between the extent of urbanization and depressive symptoms because the data were cross-sectional. Therefore, more research needs to be conducted in order to verify whether urbanization is a causal risk factor for depression, and what aspects of urbanization are directly related to the onset of depressive symptoms. Until additional evidence for harmlessness is established, these exposures should be limited to prevent a further alarming rate of depression.

### *Early Life Trauma*

Traumatic experience during childhood is prevalent in society worldwide. Studies have discovered that approximately 20-25% of women and 8-9% of men experience sexual abuse in early life, while emotional abuse and neglect are likely to be much higher than sexual and physical abuse but are harder to measure (Saveanu & Nemeroff, 2012). Research has shown that depression and other types of mood disorders are directly impacted by stressful events during childhood. In a community-based study, women who experienced childhood abuse demonstrated an increased risk of depression compared to women with no experience of abuse (McCauley J, 1997). Individuals with a history of early life abuse are more prone to other disorders as well, including PTSD, panic disorder, anxiety, bipolar disorder, and schizophrenia (Bremner JD et al., 1996). Additionally, a cross-sectional study showed that exposures to childhood stressors are associated with impaired cognitive performance and alterations in brain structures compared to individuals who did not experience childhood abuse. Traumatic childhood experiences could directly impact an individual's mental health in adulthood. For instance, sexual abuse is associated with multiple mental health disorders and an increased risk for suicide in later life (Jakubczyk et al., 2014), and family conflicts are damaging to children's cognitive development (Saleh A et al., 2017). Even in the clinical course of depression, patients who are victims of early life trauma have a lower rate of recovery and a longer period of depression (Heim C et al., 2008). These results showed a significant relation between early life adversity and depression, which allows researchers to find better and more personalized treatment for depressed patients.

According to an adoption study on the effect of parental depression, parents with major depression were associated with a greater risk of disorders in both adopted and non-adopted children, and environmental influences during childhood contribute to an increased risk in families with a depressed mother (Tully E. C., 2008). It is suggested that even in a non-biological relationship, there is an association between maternal depression and risk for adolescent depression. Even in families where the depressed mother is not genetically related to the child, there is an environmental liability that may interact with genetic factors to create risks for depression (Tully E. C., 2008). In this way, parents play a significant role in children's mental development. However, because the factor of genetics was not considered in the study, further studies need to be conducted on whether parental depression has a long-lasting effect on an individual's mental health as they age into adulthood to detect genetic influences in non-adopted families.

### Gene-Environment Interactions

According to previous studies, there is also a strong relation between genetic predispositions and early life trauma during critical stages of cognitive development. While early life experiences could increase the risk of depression, individuals may respond differently to the same events due to the difference in genetic factors (Saveanu & Nemeroff, 2012). Caspi and his colleagues were the first researchers to identify a gene-environment interaction. Their studies have shown that individuals with the s/s genotype of the SERT (5-HTTLPR) gene discussed previously have an increased risk for depression.

On the other hand, another study conducted by Polanczyk investigated the protective effect of the CRHR receptor toward depression. They discovered that individuals who have two copies of the TAT protective haplotype CRHR 1 gene may end up having an impaired activation of fear memory consolidation, and this results in relatively unemotional processing of memories during stressful life events. Therefore, this may act as a protection for individuals

who experienced early life trauma from depression in adulthood. In comparison, individuals who are carrying zero copies of the allele are at a greater risk for being affected by stressful experiences (Polanczyk G et al., 2009).

Another group of researchers investigated another gene-environment interaction of the CRHR 1 and the SERT gene. They found that there is an interaction between the two genes and early life abuse that could predict depression in later life. For instance, individuals carrying risk alleles of both genes, which are the s/s allele and zero copies of the CRHR 1 protective allele, have shown significant depressive symptoms at less severe levels of childhood trauma than individuals with no or one of the risk alleles. In contrast, the CRHR 1 allele was more common among individuals with a history of early life trauma but did not exhibit depressive symptoms in later life (Ressler KJ et al., 2009). Therefore, it can be concluded that there is an association between the stress caused by childhood abuse and depression, though it can be mediated by genetic mechanisms. Further research could be conducted on the role of other genes in the difference in an individual's vulnerability to depression.

Furthermore, the Diathesis-Stress Model views depression and other psychiatric disorders as “developmental derailments that evolve over time” (Dean & Keshavan, 2017). The model suggests that depression is not caused by one factor in isolation, instead, a vulnerable individual who experienced a negative response to stress repeatedly can cause the pre-existing vulnerability to manifest itself. Depression will be only brought out by environmental stressors along with genetic predisposition and not only the latter (Beck, 2008). While stress causes hyperactivation of the HPA axis and acts as a predisposition towards a reduced response to stress, it does not lead to depressive symptoms directly. In this way, it is the combination of the environmental stressors and the pre-existing vulnerabilities that bring about depression.

## Conclusion and Further Directions

Overall, the paper summarizes several biological and environmental factors that contribute to the development of depression, including gene-environment interactions. Although the external environment could act as a stimulus for the onset of depression, certain genetic predispositions can elevate an individual's vulnerability to the disorder. While research has deepened our understanding of which biological factors are involved in depression and the fact that they interact with each other, it remains unclear exactly how they do so on a molecular level. It is reasonable to investigate the role of each individual factor in the development of depression, but it would be impossible for researchers to understand how various biological factors interact with each other without discovering the detailed mechanisms behind them. Therefore, there are still some questions that scientists still need an answer to: How exactly does stress reduce monoamine levels? Do the biological mechanisms lead to depression, or are they actually a result of the condition? And how much do nature and nurture each contribute to the risk of depression? It is crucial to understand the precise environmental and biological mechanisms in order to find better treatments and ways to alleviate depression.

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