*Psychiatria Danubina, 2026 Vol. 38, No. 3, pp 318-322 https://doi.org/10.24869/psyd.2026.318* *Commentary*
*© Medicinska naklada – Zagreb, Croatia*

# Beyond serotonin: rethinking the causes and diagnosis of depression

**León Trelles**

*Department of History and Philosophy of Science. Institute of Philosophy. University of the Republic, Montevideo, Uruguay*

*received: 1 September 2026; revised: 1 September 2026; accepted: 16 September 2026*

***Summary***

*Depression has frequently been investigated from a neurobiological perspective, particularly through hypotheses linking depressive disorders to alterations in serotonergic and other monoaminergic systems. Although this body of research provides evidence for an association between neurobiological mechanisms and depression, it does not by itself exhaust the range of factors involved in the emergence and maintenance of depressive states. In particular, socioeconomic and environmental conditions may influence psychological and cognitive processes associated with depression. This article argues that, even if serotonergic dysfunction contributes causally to depression, a neurobiological account cannot by itself provide an exhaustive explanation of the disorder. In this article, 1) some of the research linking the development of depression to dysregulation of serotonergic activity is reviewed. 2) It is then suggested that, even if the serotonergic hypothesis can be considered correct, it fails to account for how other types of factors, such as poverty, influence the development of depression. Finally, 3) it is argued that the serotonergic hypothesis also fails to distinguish between normal states of sadness and clinical cases of depression.*

***Keywords:*** *Depression; Psychiatric diagnosis; Philosophy of psychiatry; Mental Health*

* * * * *

## THE SEROTONERGIC HYPOTHESIS OF DEPRESSION: SOME PRELIMINARY REMARKS

Depression began to be studied as a phenomenon that could be explained through the functioning of neurobiological mechanisms in the 1960s (Tsou, 2021). Since then, the serotonergic hypothesis (now known as the monoamine hypothesis) has guided neurobiological research for decades. This hypothesis holds that depression is a phenomenon associated with deficient activity of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine. The first generations of antidepressants that were able to reduce depression were medications that increased the activity of these monoaminergic neurotransmitters (Tsou, 2021). It was even demonstrated that medications that reduced this neuronal activity could induce depression in patients (Hancock & McKim, 2018, p. 292).

Beginning with the second generation of antidepressants that emerged in the 1980s, particular attention was paid to serotonin. The serotonin hypothesis proposes that the feelings of sadness and loss of interest experienced by people with depression are associated with deficient serotonergic activity. Again, this hypothesis is also supported by the fact that serotonergic agonists can reduce depressive symptoms (Tsou, 2021).

On the other hand, research has found that individuals who are vulnerable to depression share a common characteristic: "insensitivity of postsynaptic 5-HT1A receptors, a factor that may even be more influential than the lack of serotonin activity itself" (Kring et al., 2017, pp. 145–146). It has also been found that a reduction in tryptophan levels, the main precursor of serotonin, can produce acute depressive episodes.

Furthermore, recent studies have shown that, as originally proposed by the "monoamine hypothesis," reduced activity of dopamine and norepinephrine is involved in the lack of energy and motivation that is closely associated with depression (Nestler & Carlezon, 2006; Moret & Briley, 2011; Stahl, 2002).

Research into the mechanisms that may explain depression is not limited to neuroscience. Neuroendocrinology, for example, examines how the nervous system interacts with the endocrine system, that is, how the nervous system regulates hormonal activity in the body. Research has shown that irregular functioning of the HPA axis (hypothalamic-pituitary-adrenal axis), the biological system involved in stress regulation, is also associated with depression. Hyperactivity of the HPA axis may lead to impairments in serotonergic activity (Drevets et al., 2007). Another interesting finding suggests that early-life experiences of stress sensitize the stress-response system, contributing to HPA-axis hyperactivity later in life and thereby increasing the likelihood of depression (Tsou, 2021).

Finally, genetics, as a field of biological research, has also investigated how certain genetic factors may influence the development of depression. Serotonin is transported by a protein known as 5-HTT (the serotonin transporter), which is encoded by the SLC6A4 gene (Hariri & Holmes, 2006). Researchers have therefore sought to associate this gene with serotonergic activity and, consequently, with depression. However, genetic research on depression has not produced conclusive evidence. Tsou (2021, p. 17) notes that "genetic research indicates that depression is moderately heritable, although evidence concerning the genetic mechanisms is inconclusive."

At the same time that these studies emerged, other research investigated the possibility that depression may be a symptomatology that responds to particular social conditions. Following the research conducted by Ridley et al. (2020), the following section presents some arguments in favor of the view that poverty, as one specific social condition among others, directly contributes to the development of depression.

## DEPRESSION AS A RESPONSE TO SOCIAL CONDITIONS

Recent studies on depression (Ridley et al., 2020) have indicated that people with lower incomes are between 1.5 and 3 times more likely to experience depression or anxiety than the rest of the population. The study also suggests that there may be a causal relationship between poverty and the development of depression and anxiety. It therefore proposes that the concerns and uncertainties generated by situations of poverty are directly related to the development of conditions such as depression. The mechanisms mediating the relationship between depression and poverty are multiple and can be summarized as follows (Ridley et al., 2020, p. 1):

1. Concerns and uncertainties arising from financial insecurity can worsen mental health. The study suggests that providing health or employment insurance may reduce rates of depression within a given society.
2. Poverty may lead people to grow up in inadequate housing, exposing them to a range of adverse environmental factors, such as pollution and extreme temperatures (Dean et al., 2018). These conditions may, among other consequences, lead to serious difficulties in falling asleep.
3. Experiencing poverty during childhood increases the likelihood of inadequate nutrition and, consequently, the risk of impaired cognitive development and a predisposition to mental illness in adulthood.

Studies of this kind highlight the relationship between depression and the environment in which the person who develops the condition is situated. Social causes (poverty, in this case) cannot simply be explained in terms of impaired serotonin regulation. Poverty is a socioeconomic condition that is neither genetically acquired nor an inherent dysfunction of a particular brain. Nevertheless, poverty can shape the development of mental states and alter the functioning of cognitive capacities, ultimately leading behavior to be indirectly influenced by these socioeconomic conditions. As with many other illnesses, both mental and physical, depression can have negative economic consequences for those who experience it, insofar as it may negatively affect their ability to perform paid work. Unlike physical illnesses, however, depression also directly affects the way people think (Ridley, 2020). Indeed, depression can impair certain cognitive functions, such as attention, and may even affect the brain's capacity to process information (Mani et al., 2013). Depression can distort certain memories and alter people's beliefs about their own abilities (Gotlib & Joormann, 2010). These cognitive difficulties can, in turn, affect the way individuals make decisions, ranging from job-seeking to incentives to save money or pursue education.

Just as people with depression are more likely to recall negative events and to experience difficulties in forgetting negative information once it has captured their attention (Gotlib & Joormann, 2010), it could be argued that depressed individuals update their beliefs in a more pessimistic manner than non-depressed individuals. Ridley (2020) argues that this evidence is consistent with the idea that depression causes pessimistic beliefs while, at the same time, pessimistic beliefs contribute to the development of depression.

Based on this type of research, my first suggestion is that depression should be understood within a theoretical framework that goes beyond what is established by serotonergic hypotheses. Depression may therefore need to be understood as a phenomenon that cannot be reduced to a neurochemical imbalance occurring at the level of the brain. Explanations and research derived from sociological and/or cognitive approaches may complement the explanations offered by research focused on serotonergic hypotheses (Gruica, 2026; Gruica, 2025).

In this regard, I suggest that taking into account the social dynamics involved in the development of depression may shed light on how possible treatments should be conceptualized. Moreover, if certain social conditions directly contribute to the development of depression, this may suggest that, in some cases, particular attention should be paid to the environmental conditions in which a person diagnosed with depression is situated.

Thus far, I have shown how certain social conditions may be associated with the emergence and development of depression. In the following section, I will examine how psychiatry, through the use of diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), may sometimes fail to take into account specific stressors experienced by individuals and consequently misdiagnose symptoms that are not associated with the presence of a clinically significant depressive disorder.

## DEPRESSION OR SADNESS?

In addition to pointing out that specific social conditions may help explain the onset of depression, other research has indicated that symptoms that are, in fact, expected responses to particular stressful circumstances are often diagnosed as mental disorders. In this regard, one of the most influential books on the subject is *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Depressive Disorder* (Horwitz & Wakefield, 2007). The authors argue that psychiatry often confuses the normal state of sadness with the mental disorder known as depression. This occurs because psychiatry itself overlooks the relationship between symptoms and the context in which they emerge. Psychiatric diagnosis of depression assumes that symptoms alone can indicate the presence of the disorder (Table 1), which creates the problem that normal responses to stressful circumstances may be mistakenly characterized as symptoms of clinical depression (Horwitz & Wakefield, 2007).

The criteria specifying the symptoms that must be present to justify a diagnosis of depression largely disregard any reference to the context in which the person is experiencing these symptoms. Consequently, responses that are to be expected in the face of stressful circumstances may be mistakenly characterized as symptoms of depression. These authors suggest that psychiatry should be able to establish a clear distinction between genuine disorders and symptoms that are expected responses to stressful circumstances. Horwitz and Wakefield (2007) argue that contemporary psychiatry has largely overlooked this distinction, and that what is now considered an epidemic of depression in the West "has been made possible by a change in the psychiatric definition of depressive disorder that often allows sadness to be classified as illness, even when it is not" (p. 6).

The question that then arises is how it would be possible to distinguish between symptoms associated with a normal state of sadness and those associated with a depressive disorder. These authors argue that three components are essential to a normal state of sadness: first, the state is associated with a specific stressful context; second, its intensity is proportional to the level of stress causing it; and third, it comes to an end once the stressful circumstances disappear or the individual manages to adapt to them. This last characteristic indicates that a "normal state of sadness" may persist until the conditions generating stress in an individual's life change (Horwitz & Wakefield, 2007, p. 29). Certain events, such as the loss of a loved one, can produce a normal state of sadness, and although its duration may vary, it gradually subsides over time (Brown, 1993). Other events, such as the dissolution of a romantic relationship or the loss of employment,

**Table 1:** DSM-5 diagnostic criteria for major depressive disorder

| **Five or more symptoms during the same 2-week period. At least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.** |
|---|
| 1. Depressed mood most of the day, nearly every day. |
| 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. |
| 3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day. |
| 4. Insomnia or hypersomnia nearly every day |
| 5. Psychomotor agitation or retardation nearly every day, observable by others. |
| 6. Fatigue or loss of energy nearly every day. |
| 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day. |
| 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day. |
| 9. Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide. |

Source: Adapted from DSM-5 (APA 2013). Table extracted from Hyman (2021)

can produce a temporary state of sadness that improves rapidly following positive changes in the individual's circumstances (Horwitz & Wakefield, 2007). This does not mean that a normal state of sadness is necessarily always transient. As long as stressful circumstances persist in a person's life, the symptoms may continue over time: "sadness persists in contexts such as troubled marriages, oppressive jobs, persistent poverty, or chronic illnesses because the stressful circumstances that produced it do not change" (p. 29). Therefore, a normal state of sadness does not necessarily have to be shorter in duration than a depressive state itself. In this respect, psychiatry, through the use of diagnostic manuals such as the DSM, risks producing false positives when it fails to distinguish precisely between a normal state of sadness and a depressive state. Indeed, if references to context were completely abandoned in psychiatric diagnoses, then any state of sadness could potentially be regarded as a symptom of depression (Horwitz & Wakefield, 2007).

This distinction also raises a problem for the serotonergic hypothesis. Even if alterations in serotonergic activity are causally involved in depressive states, such alterations would not, by themselves, establish whether a particular state of sadness constitutes a clinical disorder. A person experiencing sadness in response to the loss of a loved one, unemployment, or persistent poverty might undergo neurobiological changes associated with stress and mood regulation without necessarily suffering from a depressive disorder. Thus, identifying a serotonergic dysfunction cannot by itself distinguish pathological depression from an appropriate response to adverse circumstances. The serotonergic hypothesis may therefore contribute to explaining how depressive states are biologically mediated, but it does not provide sufficient criteria for determining when sadness should be understood as a mental disorder.

One alternative worth exploring would be to consider the possibility that the neurochemical imbalance occurring in the brain during depression is, in fact, an adaptive response of the organism to particular environmental demands, such that it may represent one way in which an individual adapts to the environment in which they live (see Garson, 2016, 2021).

# CONCLUSION

Throughout this paper, I have reviewed the evidence linking the development of depression to alterations in serotonin activity. I have argued that reducing the explanation of depression exclusively to these biological factors is insufficient.

First, the evidence reviewed concerning the relationship between poverty and depression shows that social and economic conditions directly influence the onset and maintenance of the disorder through mechanisms such as economic uncertainty, exposure to adverse environmental conditions, inadequate nutrition, and greater exposure to trauma and violence. These non-biological factors do not invalidate the serotonergic hypothesis, but they do show that the latter is explanatorily incomplete when considered in isolation. Depression, understood in this way, cannot be understood solely as a neurochemical dysfunction located in an individual's brain; rather, understanding it requires taking into account the social environment in which the individual develops.

Second, I have argued that the absence of contextual references in current diagnostic criteria (*DSM-5-TR*) creates a concrete risk of overdiagnosis. States of normal sadness that are proportional to an identifiable stressor and tend to resolve once that stressor disappears or the individual adapts to it may be mistakenly classified as major depressive episodes.

Taken together, these two points—the explanatory insufficiency of the serotonergic hypothesis in accounting for social conditions, and the difficulty faced by psychiatric diagnosis in distinguishing sadness from depression—suggest the need for a broader theoretical framework that does not dismiss neurobiological evidence but complements it with social and contextual variables

***Ethical considerations:*** Ethical approval was not required for this study

***Conflicts of interest:*** No conflict of interest is associated with this article.

***Funding sources:*** No funding was received.

## References

American Psychiatric Association (APA) (2013). *Diagnostic and statistical manual of mental disorders: DSM-5-*. Washington DC.

American Psychiatric Association (APA) (2022). *Diagnostic and statistical manual of mental disorders: DSM-5-TR*. Washington DC.

Brown, G. W. (1993). Life events and affective disorder: Replications and limitations. *Psychosomatic Medicine, 55*, pp. 248-259.

Dean, E. B., Schilbach, F., & Schofield, H. (2018). Poverty and cognitive function. In C. B. Barrett, M. R. Carter, & J.-P. Chavas (Eds.), *The economics of poverty traps* (pp. 57–118). University of Chicago Press.

Drevets, W. C., Thase, M. E., Moses-Kolko, E. L., et al. (2007). Serotonin-1A receptor imaging in recurrent depression: Replication and literature review. *Nuclear Medicine and Biology, 34*(7), pp. 865-877.

Garson, J. (2016). *A Critical Overview of Biological Functions*. Springer International Publishing.

Garson, J. (2021). The Developmental Plasticity Challenge to Wakefield's View. En L. Faucher & D. Forest (Eds.), *Defining Mental Disorder*. The MIT Press, pp. 335-352.

Gruica, T. (2026). Pharmacological Alienation and the Phenomenological Self: SSRI Use, Bodily Attunement, and Phenomenological Psychiatry, *Psychiatria Danubina.*

Gruica T. (2025). *Embodied Cognition and Authenticity: A Heideggerian Perspective on Psychopathology*. Karl-Franzens University of Graz.

Gotlib, I. H., y Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology, 6*, pp. 285-312.

Hancock, S. D., y McKim, W. A. (2018). *Drugs and Behavior: An Introduction to Behavioral Pharmacology* (8th ed.). Pearson.

Hariri, A. R., y Holmes, A. (2006). Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Sciences, 10*(4), pp. 182-191.

Horwitz, A. V., y Wakefield, J. C. (2007). *The loss of sadness: How psychiatry transformed normal sorrow into depressive disorder*. Oxford University Press.

Hyman, S. E. (2021). Psychiatric Disorders: Grounded in Human Biology but Not Natural Kinds. *Perspectives in Biology and Medicine, 64*(1), pp. 6-28.

Kring, A. M., Davison, G., Neal, J. M., y Johnson, S. L. (2017). *Abnormal Psychology: The Science and Treatment of Psychological Disorders*. John Wiley & Sons.

Mani, A., Mullainathan, S., Shafir, E., y Zhao, J. (2013). Poverty impedes cognitive function. *Science, 341*, pp. 976-980.

Moret, C., y Briley, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment, 7*(1), pp. 9-13.

Nestler, E. J., y Carlezon Jr., W. A. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry, 59*(12), pp. 1151-1159.

Ridley, M., Rao, G., Schilbach, F., y Patel, V. (2020). Poverty, depression, and anxiety: Causal evidence and mechanisms. *Science, 370* (6522).

Stahl, S. M. (2002). The psychopharmacology of energy and fatigue. *Journal of Clinical Psychiatry, 63*(1), pp. 7-8.

Tsou, J. Y. (2021). *Philosophy of Psychiatry*. Cambridge University Press.

*Correspondence:*
*León Trelles*
*Department of History and Philosophy of Science.*
*Institute of Philosophy. University of the Republic,*
*Montevideo, Uruguay*
*leontrelles5@gmail.com*

*Published under*
*https://creativecommons.org/licenses/by-nc-nd/4.0/*