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Original Article

Depression and Different Brain Areas: Neural Activity and Potential Mechanisms

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Abstract

Depression is a prevalent mental disorder that reduces the quality of life. It is associated with various psychological, behavioral, and physiological symptoms. A combination of genetic, epigenetic, and environmental factors could be traced in depression etiology. Depression affects various parts of the brain, becoming hypoactive and/or hyperactive. Various functions are impaired in depression due to the deregulated secretion of brain neurotransmitters, hormones, and growth factors. Moreover, it leads to immune system dysfunction and structural brain alterations. Therefore, administering proper and effective treatment for depression requires comprehensive knowledge of its underlying causes. All in all, the overview of the role of different brain areas and some of their influencing factors could be beneficial for the treatment of depression.

Keywords: Biochemical factors, Brain functions, Depression

Background

Major depressive disorder (MDD), also known as depression, is a common psychological disorder [1] and is indicated as one of the most prevailing problems in today's society [2]. Its global prevalence has increased to 320 million suffering from MDD [3]. As shown in Figure1, its most common symptoms include cognitive dysfunctions (e.g., impaired learning and memory), mood swings [4, 5], continuous low mood, feelings of worthlessness, anhedonia, social withdrawal, sleep disturbance, and suicidal thoughts [6, 7].

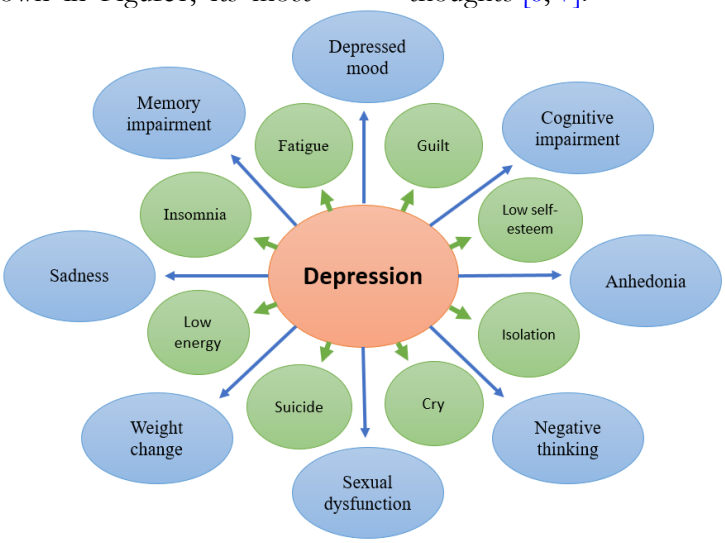

Figure1. Various psychological, behavioral, and physiological symptoms related to depression

Various factors, such as cellular, neurochemical, and neuroendocrine impairments, may cause depression [8]. Therefore, different methods are developed for its treatment, such as self-help, exercise, talking therapy, interpersonal psychotherapy, use of medications and medicinal plants, and polytherapy [9-12]. However, proper and effective treatment for depression requires a comprehensive knowledge of its causes. This is why in-depth knowledge about the main factors behind this disorder leads to better treatment choices. The overview of the role different brain areas and some of their influencing factors play could be beneficial for the treatment of depression (fig. 2); this study has thus attempted to provide an integrated summary of various brain areas and factors involved in depression.

Etiology of depression

Depression is a complex disorder with a combination of genetic, epigenetic, and environmental factors that lead to developing depression [8] (fig. 3).

Genetic factors and depression

Numerous family, twin, and adoption-related studies suggest a high potential for genetic predisposition to MDD [13]. Therefore, compared to early life experiences, genetic vulnerability seems to have a more significant role in developing depression [14]. In addition, reduced expression of the serotonin transporter gene increases the risk factor [15]. Moreover, *apolipoprotein E4*, *DE4A*, *FDX1L*, and *MYO15B* genes are linked to the potential risk of genetic depression [16, 17].

Epigenetic factors and depression

Several studies have indicated the role of prenatal and postnatal epigenetic factors in the neurodevelopment of different brain regions [hypothalamus, hippocampus, prefrontal cortex (PFC), and amygdala], neuroendocrine systems, behavior (depression or anxiety), and cognition (learning and memory) [8]. Early prenatal stress impairs corticotropin-releasing hormone (CRH), which in turn increases hypothalamic-pituitary-adrenal (HPA) axis activity and changes the serotonin system [18]. Thus, environmental factors during childhood could modify neural circuits, functions, and gene expression [8]. The neuroanatomical, neurochemical, and behavioral changes in depressed individuals could originate from the DNA methylation alterations in early life experiences [8].

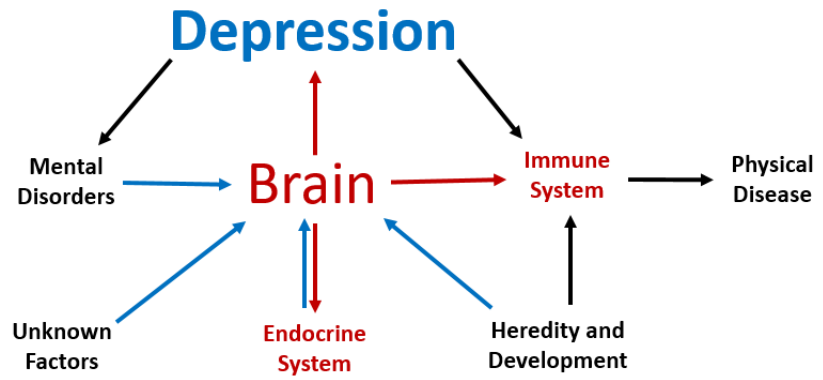

Figure2. A schematic diagram of depression and the involved systems [114]

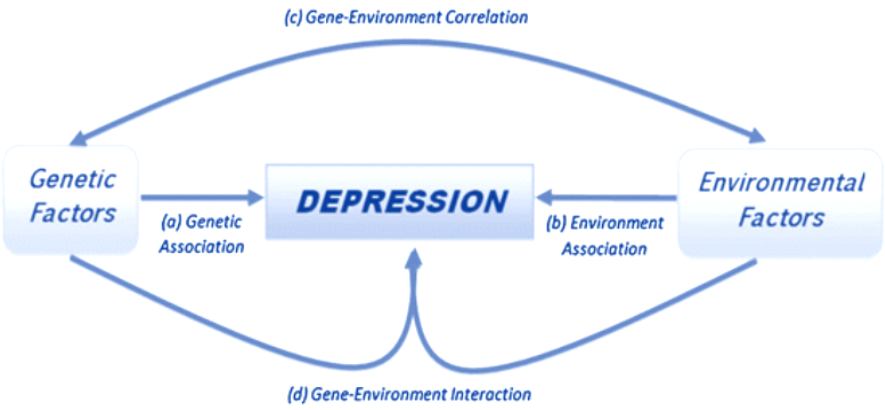

Figure3. Etiological paradigm of depression [115]

Environmental factors and depression

Different risk factors, including postnatal factors, cause depression among sociable humans. For instance, chronic stress diseases as the main factor, alcohol abuse, social isolation and deprivation, prior depressive episodes, low birth weight, malnutrition, and vitamin deficiency, particularly insufficiency of vitamin D and B12, could result in depression [5, 8, 19-21].

Unfortunately, genetic and epigenetic modifications require high costs. However, improvement in environmental factors seems to have decreased depression in subjects. Therefore, eliminating those environmental factors that caused and aggravated depression (i.e., stress, nutrition, etc.) could contribute to alleviation of depression and faster improvement in its treatment process.

Stress

Many studies have indicated the role of genetic and environmental factors in depression. The major environmental factor that, directly and indirectly, leads to depression is stress [8, 13]. Accordingly, it is defined as the environmental changes, internal or external, that would disturb homeostasis maintenance in the body [22]. Environmental stressors could worsen the prognostic indicators of depression [23], as many patients with a stressful lifestyle also experienced MDD episodes [24] (fig. 4).

Stress activates the HPA axis and sympathetic nervous system leading to the release of glucocorticoids and catecholamines into the blood [25]. Long exposure to glucocorticoids has neurotoxic effects on the brain [26]. Therefore, it could cause many neurological and psychological diseases similar to depression. Many studies have confirmed the relationship between depression and stress-related structural changes in the brain that alter mood and cause physical dysfunctions [4, 27, 28]. Therefore, chronic stress, which changes the body's homeostasis, could eventually lead to depression or worsened symptoms of depression.

Gender

The clinical manifestation of depression was reported at higher levels among women [29]. Surprisingly, some studies have also suggested the role of genetic factors in depression in women [17]. Psychiatric disorders are also linked to gender differences, especially at the onset of puberty until approaching menopause in women [30]. Since women are more likely to be diagnosed with depression, careful attention to different factors, such as their hormonal changes, is required before and during the treatment process.

Neural connections

Neural connections would be disrupted in depression [31]. Depression alters the organizational microstructure of white matter pathways in some brain regions, such as frontolimbic neural pathways [32], and might also be involved in neurodegeneration and aberrant neural network functions [33] (fig. 5).

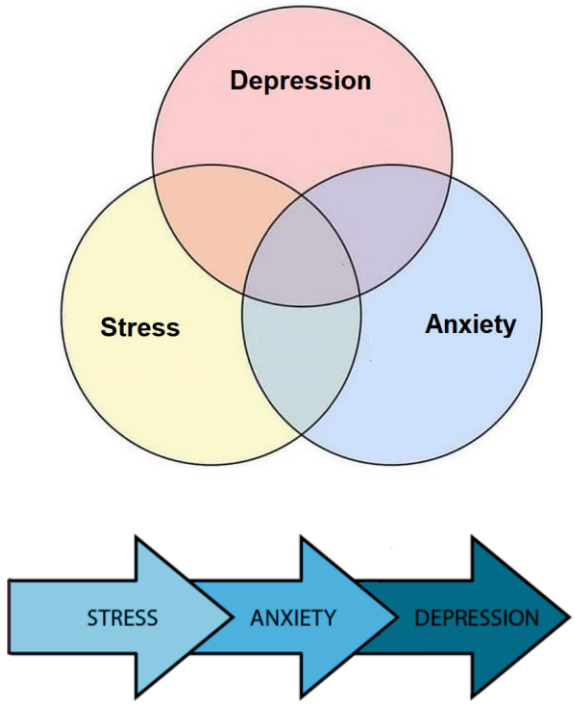

Figure 4. Stress, anxiety, and depression overlap. However, in the etiology of anxiety and depression, psychological stress is a major risk factor [54]

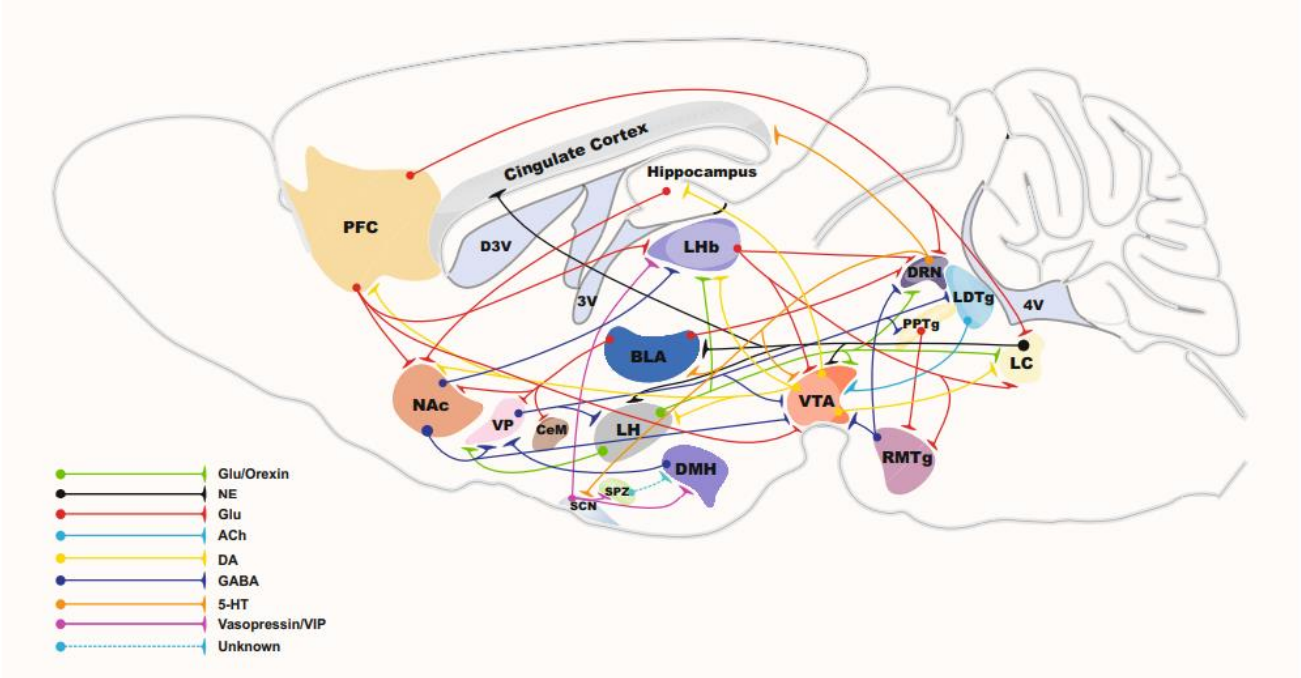

Figure 5. A conceptual scheme for the major brain network circuit involved in depression-related behaviors and neurotransmitter secretion from different brain nuclei [116]

Role of different brain structures in depression

Some neurobiological, structural, and functional abnormalities have been observed in several limbic [amygdala, hippocampus, and nucleus accumbens (NAc)], non-limbic, or para-limbic [cortical areas, subgenual anterior cingulate cortex (sACC), and ventromedial PFC (vmPFC)] structures that were involved in the prefrontal and cingulate cortices [8, 34] (fig. 6).

Patients with MDD had a smaller volume of the medial orbitofrontal cortex (mOFC or gyrus rectus) [35]. The activity in the dorsal system [hippocampus, dorsolateral PFC (DL-PFC), and dorsal anterior cingulate cortex (dACC)] is reduced in depression. In similar conditions, increased activity has been observed in the ventral system (amygdala, insula, ventral striatum, subgenual cingulate cortex, ventral parts of the ACC and PFC) [34, 36].

In people with depression, morphological alterations, including neural atrophy, reduced number of glial cells, dendritic spines, brain metabolism, brain volume, and dendritic arborization have been reported in several cortical and limbic areas like PFC and hippocampus [8, 25, 37]. Similarly, some changes were observed in the gray matter volume, neural organization, electro-physiological activity, and neurotransmitter receptors in the mentioned brain regions [34]. As shown in Figure 7, despite the hyperactivation of some brain areas in depression, other regions may become hypoactive [38]. As such, several brain regions changed in patients with depression, including the limbic system, hippocampus,

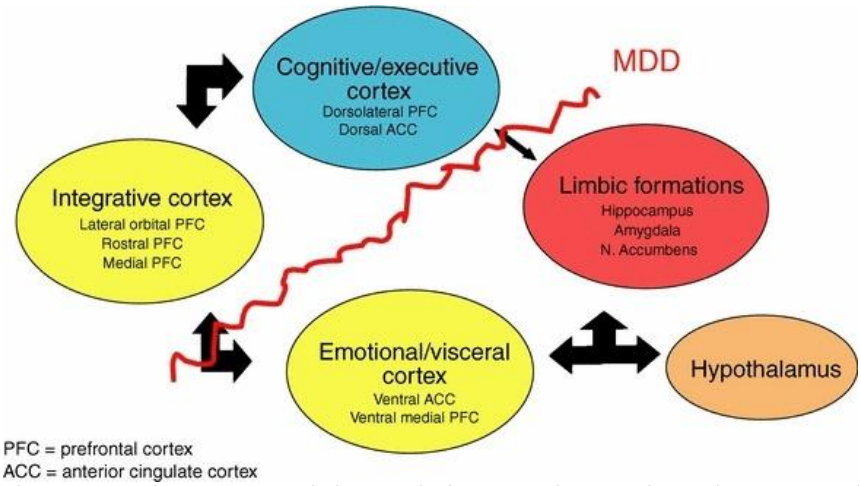

Figure 6. Limbic regions have reciprocal connections with the "para-limbic" cortical areas, subgenual anterior cingulate, and vmPFC [117]

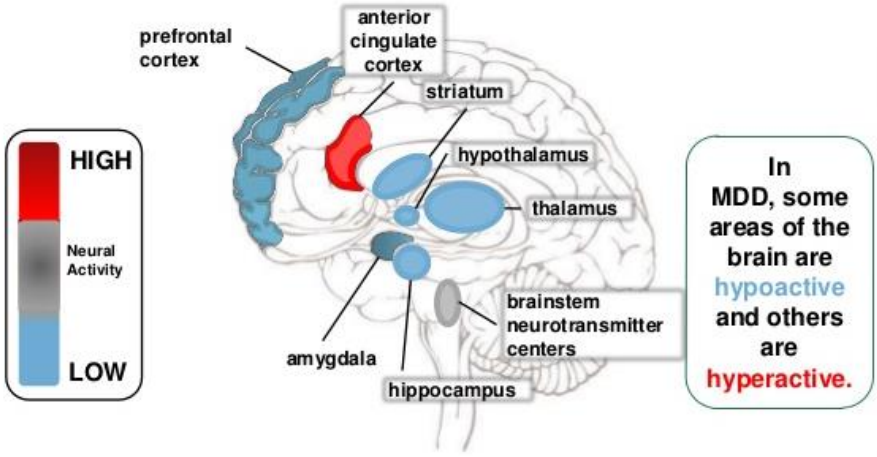

Figure 7. Some brain areas are hypoactive, whereas other regions are hyperactive in depression

amygdala, and PFC [39]. For instance, those patients who committed suicide had different connections between the left anterior limb of the internal capsule (ALIC), left middle frontal cortex (mFC), orbitofrontal cortex (OFC), and left thalamus [40]. Therefore, evaluating different parts of the brain via imaging techniques before, throughout, and after the treatment process could help estimate the treatment effect.

Limbic region

The limbic system is a set of brain structures that collectively affect emotions, behavioral patterns, memory, and olfactory modality [41]. Any structural changes in this system would be associated with depression [8, 42].

Hippocampus

The hippocampus, a significant part of the limbic system, is involved in the pathophysiology of depression [43]; for example, hippocampal volume was reported to have decreased in depression [44]. The changes in hippocampal function may also influence other limbic structures, including the PFC, amygdala, ventral tegmental area (VTA), and NAc, which are associated with the state of mood and emotions [45]. Moreover, depression causes memory impairment, possibly in association with decreased hippocampal plasticity [12, 46]. The hippocampal connections to key frontal and subcortical regions (amygdala, hypothalamus, basal ganglia, and PFC) indicate that the hippocampus is involved in regulating mood [41]. Consequently, any hippocampal dysfunctionality could result in inappropriate emotional responses [14].

Amygdala

The amygdala is a brain area that processes threats and regulates emotions [47]; therefore, abnormal amygdala activity plays a role in the severity of depression [14]. Increased amygdala blood flow and metabolism were observed in subjects with depression [47]. The volume, glial density, and glia/neuron ratio were reduced in the amygdala of depressed patients [41, 48]. Chronic stress increased the spine density, synaptogenesis, and metabolism in the amygdala [49]. Moreover, serotonin transporters were significantly reduced in the amygdala of depressed patients [8].

Para-limbic regions

Prefrontal cortex (frontolimbic)

The vmPFC controls the autonomic nervous system, cognition, and emotions [20]. Apart from a decreased activity in the DL-PFC, the ventral prefrontal and para-limbic structures presented increased activity in depression [47]. The depression rate had a reverse correlation with the left dorsal PFC activity [47]. Similarly, the ventrolateral (i.e., anterior cingulate) and orbital areas of the PFC had abnormal blood flow and metabolism in depression, where many interconnections were observed with the amygdala, dorsomedial nucleus of the thalamus, and ventral striatum (both ventromedial caudate and NAc) [50].

Raphe nuclei

Dorsal and median raphe nuclei neurons are the primary serotonin sources in the forebrain [51]. Brain imaging studies have shown that serotonin transporters were decreased in the midbrain raphe nuclei in MDD [52].

Other structures

Depression changes the volume of some brain regions, such as the thalamus and insula [53, 54]. For instance, a decreased size of the striatum and caudate nuclei was observed [41]; these areas also exhibited lower ventral striatum activity in depression [55]. Therefore, the limbic system seems more involved in depression than the para-limbic system.

4. Neurobiology of depression

A vast range of neurobiological changes in the brain is associated with depression, including the release of neurotransmitters, hormones, inflammatory factors (cytokines), and neurotrophic factors [14, 56-58]. Some of these neurobiological factors are indicated in the present study, as will be observed in the following sections.

Role of neurotransmitters in depression

Many neurotransmitters alterations affect the mood states and lead to depression [59] (see fig. 4). For instance, the changes in the amount of monoamines (i.e., serotonin, norepinephrine, and dopamine) lead to depression [37, 56, 60]. Additionally, the down-regulation and desensitization processes of pre- and post-synaptic norepinephrine and serotonin receptors change in depression [37].

Serotonin

Serotonin plays a vital role in various brain functions, including mood, anxiety, aggression, sleeping habits, appetite, sexual desire, and especially learning and memory [61, 62]; that is because serotonergic neurotransmission deficits are linked to depression [44]. According to some reports, reduced serotonin levels were not observed in all depressed patients [63]. Neurogenesis was decreased with lower serotonin levels in the dorsal raphe of the rodents in depression [56]. Furthermore, reduced serotonin neurotransmission was observed in most forebrain regions, including the medulla oblongata, raphe nucleus, frontal cortex, and hippocampus [8, 64]. However, the serotonergic activity enhanced in pons in similar conditions [64]. The impaired serotonin input to other brain areas, including DL-PFC, subgenual PFC, and amygdala, could lead to mood impairment and depression [65]. In addition, significant changes in neural activity were observed in several serotonin-related brain regions (e.g., dorsal raphe, septal region, habenula, amygdala, and OFC), indicating that tryptophan plasma levels were related to depressed moods [47]. Various studies on the effects of serotonin reuptake inhibitors administration have confirmed the role of serotonin in alleviating some depression symptoms [11].

Norepinephrine

Several studies proved the involvement of low concentrations of plasma norepinephrine in depression [60]. The neural response occurs via up-regulation of the postsynaptic receptors to reduce monoamine transmission as a compensatory mechanism for depression [66]. It is notable that most therapeutic drugs for depression target monoaminergic systems [67].

Dopamine

Dopamine is the major mediator of the pleasure and reward system [47] and it is indicated as a motivational factor of behavior [39]. In the mesolimbic pathway, as a key reward circuit, the dopaminergic neurons project from VTA to NAc, hippocampus, PFC, and other forebrain areas [47, 56, 68]. These dopaminergic neurons also play a crucial role in mediating stress response, which is the main MDD cause [69].

Glutamate

Glutamate is a major excitatory neurotransmitter in the nervous system [64, 70] and is responsible for regulating mood states [56]. Moreover, it is essential for dendritic development and neural growth [70]. The glial cells (i.e., astrocytes, oligodendrocytes, and microglia) have a key role in regulating glutamate signaling in depression [71, 72]. Notably, depression is associated with reduced glutamate function in the prefrontal regions [71].

The ionotropic N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors are involved in the glutamate release [59]. The NMDA receptor antagonists act as potent and fast-acting antidepressants [56] by regulating moods, possibly through neuroplasticity maintenance [56], leading to the alleviation of depression-related symptoms [47]. Therefore, the pharmacologic stimulation of AMPA receptors facilitates depression recovery [47].

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is implicated in depression [25]. Previous studies have frequently mentioned the varying GABA levels in the brain of patients with depression [73]. Anxiety and depressive disorders seem to deregulate GABAergic signaling [64], GABA transporter expression, and enzyme involvement of GABA metabolism in depression [13].

Substance P

Substance P is pathologically involved in depression [74, 75], where levels of serum substance P are enhanced [76]. However, its antagonists had no antidepressive effects [77].

Due to the potential role of different neurotransmitters in provoking the occurrence of depression, it is necessary to use various drugs for the treatment of depression in such a way that they could affect different neurotransmitters, especially for resistant and severe types of depression.

Role of hormones in depression

According to previous studies, depression is associated with changes in neurotransmitters. However, the alteration of some hormone circadian rhythms leads to depression as well [36].

Glucocorticoids

Abnormal activation of the HPA axis is implicated in depression [25, 78]. Glucocorticoids could contribute to depression pathogenesis by decreasing synaptic plasticity and augmenting vulnerability to neural death in the hippocampus [79]. Several factors, including monoamine dysfunction, neurogenesis decrease, synaptic neuroplasticity, increased neurodegeneration, and various changes in different brain regions, are linked to depression. These factors are associated with the Glucocorticoid Theory of Depression [37].

Thyroid hormone

There is a link between thyroid disorders and depression [80], as thyroid hormone concentrations are involved in the severity of depressive episodes [81]. For instance, although hypothyroidism decreases anxiety and depression-like behaviors, an opposite result was observed in the hyperthyroid rats [82]. As a treatment strategy for depression, levothyroxine could be used [83]. Although some studies reported levothyroxine to have improved mood without causing hyperthyroid symptoms in depressive subjects [84], other studies showed no significant relationship between thyroid disorders and depression [85, 86]. Nevertheless, there is still insufficient evidence to support thyroid hormones as a suitable treatment strategy for unipolar depression [87].

Estrogen

Ample evidence exists for the high incidence of depression among women due to serum estrogen and even progesterone levels [88, 89]. However, menopause, pregnancy, menses, and fluctuating hormones increase the occurrence rate of depressed mood states in women [89, 90]. As such, estrogen therapy improves the mood of women after menopause [4]. Serotonin and noradrenaline levels were enhanced after menopause, and estrogen participated in regulating the serotonin receptors in the brain [89, 91]. It is noteworthy that estrogen increases serotonin levels by enhancing serotonin synthesis and decreasing its reuptake [89].

Testosterone

The relationship between depression and serum testosterone levels remains unclear. A weak association between testosterone concentrations and depression has been observed [92]. However, it should be mentioned that salivary testosterone levels have been lower in patients with depression [93].

Parathyroid hormone

Some patients with hyperparathyroidism exhibited mood swings [94]. It is reported that vitamin D deficiency increases serum parathyroid hormone (PTH) levels, a hormone that is commonly accompanied by depression [95]. Some other studies suggested no association between the levels of PTH and vitamin D in depression [96].

Oxytocin and antidiuretic hormone

Oxytocin seems to be involved in regulating anxiety and the HPA axis. An increase in the plasma levels of oxytocin in depression has been reported [97]. Similarly, antidiuretic hormone levels increased in a hyperactive HPA axis in depression conditions [98, 99].

Melatonin

Melatonin is involved in regulating the circadian rhythms and biological clock. A disturbed circadian rhythm could increase the risk of depression [100], and nocturnal concentrations of melatonin have been higher in patients with MDD [101].

Insulin

Insulin increases serotonin in the brain through different mechanisms, including enhanced serotonin synthesis rate and tryptophan entry into the brain, thus, affecting mood states in depression [102].

According to the effects of different hormones on developing depression, a laboratory examination is necessary before initiating the treatment. In this regard, hormone therapy could simultaneously be considered along with other types of drugs. Since the functional level and blood maintenance of different hormones affect the body's physiologic system more than the neurotransmitter secretion, the changes in neurotransmitter secretion in specific brain regions seem more accessible than the changes in hormone secretion.

Role of other biochemical factors in depression

Inflammatory factors (Cytokines)

An elevated level of circulating immune markers (e.g., cytokines) has an immunological function, and is also important for the formation of neural structures and circuits [8]. Cytokines cause major changes in systems relevant to the development of depression, such as the HPA axis and sympathetic nervous system [37]. Therefore, the immune system has a critical role in neurodevelopment [8], as depressed patients exhibit an increase in autoimmune disorders [56]. Cytokines are divided into different categories: interleukins (pro- and

anti-inflammatory ILs), chemokines, tumor necrosis factors (TNFs, TNFα), interferons (IFNs, IFNα), and transforming growth factors (TGFs, TGF-β) [37]. The overexpression of pro-inflammatory cytokines is reported in the brain of many patients with depression [56, 79, 103]. There is also a strong association between depression and peripheral inflammatory diseases [104]. The inflammatory cytokines reduced monoamine levels in depressed patients through increasing tryptophan metabolism [56]. The activation of the immune system and neuro-inflammation could cause a deficiency in the dopaminergic mesolimbic pathway and dysfunction in the prefrontal glutamatergic system. This leads to anhedonia, loss of motivation, psychomotor retardation, fatigue, and cognitive deficits [79, 105]. Some cytokines (like IL-6) modulate neuro-transmission and activate the HPA axis leading to depression [106]. Moreover, plasma levels of anti-inflammatory cytokines were reduced in depression [79]. The patients under cytokine immunotherapy, for instance, those receiving IFNα, presented a higher risk of developing depression-related symptoms [25].

Neurotrophic factors

Brain-derived neurotrophic factor (BDNF) and other members of the neurotrophic factor family, including the neurotrophin-3 and nerve growth factor, affect cellular functions [107, 108], which seem to be linked to the clinical manifestations of depression [55]. In addition, BDNF has a crucial role in the neurobiology of depression [8, 79]. It regulates neural morphology and physiology, and structural complexities [107]. In several studies, reduced BDNF levels were reported in MDD patients [35, 56]. However, their over-expression in the forebrain excitatory neurons of the hippocampus, neocortex, and amygdala was seen with less depressive-like behavior [33, 107, 109].

Brain functions in depression

Neuroplasticity

Depression is associated with changes in neuroplasticity, neurogenesis, and neurotransmitters in certain corticolimbic structures, such as the hippocampus and PFC [25, 107]. Neuro-psychological studies indicate that cognitive impairments are related to the frontal lobe functions in depression [52].

Reward system

Rewards could motivate the recipient to obtain survival necessities [110]. The VTA, NAc, midbrain, vmPFC, posterior cingulate cortex, ACC, anterior insula, and thalamus are involved in the reward system, whose alterations could generate anhedonia [56, 111] as one of the depression-related symptoms [93]. According to some studies, dopaminergic neurotransmission was diminished in depression [112].

Behavioral patterns

Depression has several psychological, behavioral, and physiological symptoms. These symptoms include dark moods, negative thinking, cognitive dysfunctions, irritability, sadness, social isolation, insomnia, fatigue, impaired concentration, low self-esteem, guilt, crying uncontrollably, appetite disturbance, constipation, weight fluctuation, libido loss, sexual dysfunction, lack of energy, motivation and memory impairment, slower speech, anhedonia, feelings of worthlessness, and finally suicidal thoughts [37, 56, 103]; which is why it is associated with higher rates of morbidity, mortality, and increased risk of suicide as well [14, 113].

At last, the role of different brain areas, systems, and biochemical factors in depression are summarized in Figure 8.

Etiology of depression	Genetic factors		
	Epigenetic factors		
	Environmental factors	Stress	
		Gender	
Neural connections and depression	Brain structures	Limbic region	Hippocampus
			Amygdala
		Para-limbic regions	Prefrontal cortex (frontolimbic)
			Raphe nuclei
			Striatum
			Other structures
Neurobiology of depression	Neurotransmitters	Serotonin	
		Norepinephrine	
		Dopamine	
		Glutamate	
		GABA	
		Substance P	
	Hormones	Glucocorticoids	
		Thyroid hormone	
		Estrogen	
		Testosterone	
		Parathyroid hormone	
		Antidiuretic hormone	
		Oxytocin	
		Melatonin	
		Insulin	
	Other biochemical factors	Inflammatory factors (cytokines)	
		Neurotrophic factors	
Brain functions in depression	Neuroplasticity		
	Reward system		
	Behavioral patterns		

Figure 8. A summary diagram of how depression affects different brain aspects

Conclusions

Depression is a mental disorder caused by biochemical and morphological alterations in different brain areas, in which the limbic system is more involved than the para-limbic one. Changes in neurotransmitter secretion in specific brain regions also seem to be more accessible compared to hormone secretion fluctuations. Overall, a combination of different genetic, environmental, and epigenetic factors are involved in the development of this disorder. The genetic and epigenetic modifications would require high costs. Therefore, it seems that the best available strategy for depression treatment is making changes in environmental factors, which could alter the secretion of brain neurotransmitters and different hormones. As a result, an alternative lifestyle with exercise, balanced nutrition, and the use of medications with low side effects are proposed as the best approach to depression treatment. However, making a proper decision for the best treatment scheme needs comprehensive knowledge of the physiopathology of depression. A therapist should therefore investigate all the underlying factors through various tests before prescribing different drugs. At last, it is strongly recommended to avoid one-dimensional treatment procedures and consider all the influencing factors in depression for a more effective treatment strategy.

Compliance with ethical guidelines

All ethical principles were considered in conducting the present study.

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Authors' contributions

All authors participated in drafting of the article and approved the final version.

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None.

Conflicts of Interest

The authors declare no conflict of interests.

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