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Review article

The Role of Neuroplasticity in the Etiology and Treatment of Depressive Disorders

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SUMMARY

Introduction/Aim. Depression is a mood disorder that prevents the patients from performing everyday activities, due to the constant presence of negative feelings. Depression is a worldwide medical disorder which is highly prevalent and has therefore become a huge financial burden for the health system. Biological, psychological, and social factors are most commonly described in the pathophysiology of depressive disorders, although the mechanisms behind depression are still not fully understood. Neuroplasticity is the ability of the nervous system to reorganize its structure and function in response to different stimuli. The aim of this paper was to summarize the available literature on neuroplasticity and its role in the pathophysiology and treatment of depressive disorders.
Literature review. Depression is often accompanied by chronic illnesses and is more prevalent in women than men. The most commonly used treatment options for depressive disorders are antidepressants, electroconvulsive therapy, and psychosocial therapy. Neuroplasticity has led to the development of a new clinical discipline called neurorehabilitation, and recent studies have shown a possible link between neuroplasticity and depression. It has been observed that different mechanisms behind neuroplasticity affect the structure of the limbic and paralimbic structures, especially the hippocampus, prefrontal cortex, and amygdala.
Conclusion. Limbic and paralimbic structures also undergo structural changes in depressed patients treated with electroconvulsive therapy and medications, which could lead to a better understanding of depressive disorders and how they should be treated.

Keywords: **depression, depressive disorders, neuroplasticity, hippocampus, amygdala**

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INTRODUCTION

Depressive disorders are a type of mood disorder that are characterized by a mood disturbance as a main feature. Depressive disorders, also known as unipolar depression, include major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified. Major depressive disorder (MDD) represents a period of at least two weeks during which an individual has either a depressed mood or a loss of pleasure or interest in most daily activities. The individual must also experience at least four symptoms which include feelings of guilt, difficulty in thinking or concentrating; having recurrent suicidal thoughts, plans or attempts; loss of energy; significant changes in sleep, psychomotor activity and/or weight and appetite (1). MDD is a very complex, clinically heterogeneous pathological condition in which the patients also experience significant cognitive and physical impairments. In addition, there are significant interindividual differences in the frequency, severity, and type of symptoms which are encountered (2). Women are at higher risk of experiencing an episode of major depression, compared to men. Depressive disorders are the worldwide cause of disability and have become a huge economic burden for the global health system. In addition, depression is often accompanied by other chronic illnesses (3). It has been established that biological, psychological, and social factors play key roles in the onset of depressive disorders. However, its underlying pathophysiology, especially on a molecular level, has yet to be fully understood (4, 5).

Neuroplasticity is defined as the ability of the central nervous system to modify its activity, in response to external and internal signals, by experiencing both structural and functional reorganization (6). The term neuroplasticity is credited by the Polish neuroscientist Jerzy Konorsky, who was the first one to give the definition of this process in 1948. He proposed a theory that claimed that the closeness of another neural circuit could activate or change the activities of the surrounding neurons (7). Neuroplasticity is regarded as a key factor for the development of the finest cognitive processes including memory, learning, and adaptation. It is considered that constant removal and/or recreation of neural connections is the fundamental principle of neuroplasticity. It has been observed that neuroplasticity plays a key role in restoring the normal motor function in patients who suffered a neural injury, which has led to the development of a new clinical discipline: neurorehabilitation (8). However, recent studies have found that neuroplasticity could also be included in the pathophysiology of depressive disorders, as well as the basis for understanding and modifying its complex treatment (9).

The aim of this review paper was to summarize the available literature on neuroplasticity and its role in the pathophysiology and treatment of depressive disorders.

DEPRESSIVE DISORDERS

Depressive episode has to be accompanied by either a substantial occupational, social or other functional impairment, or a clinically significant distress (1). It usually begins as subliminal depression, which in time becomes recurrent in approximately 85% of patients (10). This group of disorders usually starts at a younger age and is more common in females than males (11). The prevalence of depressive disorders has been increasing in the last few decades, and it is estimated that 20% - 25% of women and 7% - 12% of men suffer from some kind of depressive disorder during their lifetime (12).

Women are more prone to suffering from depressive disorders, especially during pregnancy and postpartum period. It is believed that women who had depressive episodes during their pregnancy are more likely to develop post-partum depression. Although it still has not been fully understood why women are at higher risk of suffering from depressive disorders, it is believed that this is the result of both social and biological factors (10). Recent studies have suggested that genetic factors could be responsible for the difference in prevalence between genders. The most commonly used studies for separating genetic and environmental factors are the twin studies. These studies have shown that adolescence is a crucial period for the appearance of the first signs of depression, especially in girls. This could be the result of the activation of certain genes in females, that trigger different biological and psychological changes, which in turn lead to the beginning of depression. Although several attempts have been made to identify possible genetic loci responsible for the gender difference in depression, further research has to be done to get a better understanding of this problem. Currently, the most studied genes are those associated with serotonin and dopamine system.

However, there is still not enough evidence to fully support the genetic hypothesis, and future research should be focused on better understanding of the interaction between genes and the environment (13). Low socio-economic status (poverty, lack of education, type of occupation) is also considered to be a risk factor for depressive disorders and a possible prevalence difference between genders (10). Certain chronic diseases, such as multiple sclerosis and epilepsy, are also thought to be the risk factors for developing some types of psychiatric diseases, especially depressive disorders (14). Studies have shown that most people who suffer from depression also have some type of anxiety disorder. The concurrence of anxiety and depressive disorders makes the patients more dysfunctional which in turn complicates the therapy, as the patients will probably become more resistant to the standard treatment (15).

Although the pathophysiology of depressive disorders is still not fully understood, most theories claim that concentrations of certain neurotransmitters, and dysfunction of the hypothalamic-pituitary-adrenal axis are the key factors for developing depressive disorders. Pathological changes in the metabolism in the limbic system as well as paralimbic structures in the prefrontal cortex are associated with the onset of major depression (4). Neuroimaging methods have shown that there is a difference in the volume of the hippocampus between people suffering from depression and healthy individuals (16). It has been suggested that hippocampus undergoes the process of atrophy in patients with depressive disorders, which could be the result of the glucocorticoid-mediated neurotoxicity (17, 18). Dysfunction of the hypothalamic-pituitary-adrenal axis increases glucocorticoid levels during exacerbation of depressive disorders, which eventually damages hippocampal tissue and reduces the number of its neurons (18). In addition, biological theories suggest that people with depressive disorders have significantly lower levels of neurotransmitters (norepinephrine, serotonin, and dopamine) in the central nervous system, especially in the structures related to the limbic system (19). Some studies have also found a possible connection between depressive disorders and increased secretion of pro-inflammatory cytokines. Researchers have found that major depressive disorder is more commonly found in patients suffering from some type of chronic inflammatory condition (rheumatoid arthritis, type 2 diabetes, etc.) compared to healthy individuals (20). Although the mechanisms behind this are still unclear, a possible reason could be the impaired metabolism of tryptophan, the essential amino acid and precursor of serotonin. Oxidation of tryptophan is usually catalyzed by tryptophan dioxygenase intrahepatically, and less often extrahepatically by indoleamine 2,3 dioxygenase (IDO). Proinflammatory cytokines such as TNF-α and INF-γ stimulate the activity of IDO, which is found to be enhanced in patients with atherosclerosis, rheumatoid arthritis, obesity, and heart diseases. Chronic activation of IDO is associated with depressive behavior (20). In patients with major depressions, there is an elevation in the levels of interleukin 6 and C reactive protein, as well as a slight increase in the levels of interleukin 1β and tumor necrosis factor (21).

The most commonly used treatment options for depressive disorders are psychosocial therapy, electroconvulsive therapy and antidepressants. First-line medications are selective serotonin reuptake inhibitors (SSRI), due to their safety profile, although other drugs such as selective norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, and venlafaxine are also widely used (22). The three most commonly used types of psychosocial therapies are interpersonal, supportive, and cognitive behavioral therapy. Although they can be used as monotherapy, in patients with more severe forms of depression, there is a need for a combination of medications and psychotherapy (23). Electroconvulsive therapy is still used as a treatment for depressive disorders, especially in patients with symptom remission of a major depression. Also, researchers have found that relapse rate is significantly lower in patients who underwent electroconvulsive therapy, compared to other treatment options (24). Recently, there has been an increase in the use of intermittent theta burst stimulation (iTBS), a type of repetitive transcranial magnetic stimulation, in the treatment of cognitive symptoms in depressive disorders. Torres et al. concluded that iTBS leads to an increase in the left hippocampal volume in bipolar patients with depressive symptoms, which is associated with the improvement of non-verbal memory. This finding indicates that there is a possible connection between the hippocampal volume and neuroplasticity in prefrontal and temporal area of the cerebral cortex, which could prove to be beneficial for the improvement of cognitive impairments in bipolar, depressive patients when treated with iTBS (25). Unfortunately,

although there are numerous treatment options, approximately one-third of the patients with major depression are not able to achieve significant symptom remission. Also, those who do achieve it, most often experience relapse of the symptoms in the following years. Difficulties in treatment and prognosis of depression are most often the result of the significant etiological heterogeneity among patients, and because the treatment options for patients who experience relapse are mostly non-specific. Researchers are still unable to determine why some patients initially respond well to the treatment but fail to remain stable, or why there is a significant difference in how patients respond to pharmacological and non-pharmacological treatment options (26).

NEUROPLASTICITY

Removal and recreation of neural synapses are considered to be the key factors for stimulation of the neuroplasticity (8). Studies have shown that there is a huge variability of the mechanisms behind neuroplasticity. Apart from the reorganization of the neural synapses, neuromodulator systems are also crucial for neuroplasticity. The noradrenalinergic and dopaminergic systems are essential for neuroplasticity of the cerebral cortex (27). Acetylcholine has been linked to neuroplasticity in response to behavior-related stimuli. Cortical cholinergic neurons release more acetylcholine when animals are performing a task which requires more attention and focusing (28). Norepinephrine has been observed as a possible inductor of the neuroplasticity in the auditory regions of the cortex (27). Certain enzymes such as protein kinases, proteases and protein phosphatases are also vital for the process of neuroplasticity, especially in its relation to the long-term memory by modulating transduction of signals between different parts of the central nervous system (8). One of the most studied forms of the neuroplasticity is long-term potentiation (LTP). LTP was demonstrated on the animal hippocampus in 1974, and it has since been proven to be crucial for inducing cortical plasticity and formation of the memory, as well as for the learning process (8, 28). Proinflammatory cytokines have been associated with homeostatic synaptic plasticity. Inflammation of the central nervous system affects neuroplasticity, and has therefore been linked as a possible factor in the pathophysiology of neurological and psychiatric diseases (8).

NEUROPLASTICITY AND PATHOPHYSIOLOGY OF DEPRESSION

Neuroplasticity has led to the development of a new clinical discipline - neurorehabilitation, which is based on restoring motor function in patients with neural damage by reorganization of neural synapses. However, recent findings are implicating that neuroplasticity may have a significant role in the pathophysiology of depressive disorders (8, 9).

In patients with depressive disorders, dysfunction of the neuroplasticity can lead to the changes in volume of the hippocampus, apoptosis of its neurons, as well as changes in hippocampal neurogenesis. These pathological changes are likely the result of chronic stress which affects hippocampal synaptic plasticity. Chronic stress decreases the branching of the neural dendrites and affects the hypothalamic-pituitary-adrenal axis by increasing the levels of glucocorticosteroids, which impairs the hippocampal plasticity. Previous studies have found that severe stress affects long-term potentiation and enhances depression in rodent models. Hippocampus, part of the limbic system, is an extremely important structure responsible for generating memory, emotions, and other cognitive functions (29). It has been observed that patients with a greater number of depressive episodes have smaller hippocampal volumes, compared to healthy individuals. There is evidence that people with late-onset depression (which begins after the age of 50), also have smaller volumes of the entorhinal cortex (30). Impaired hippocampal neurogenesis has also been proposed as a possible risk factor for developing depressive disorders. Even in adulthood, new neurons are still being formed in the hippocampal region, especially in its part called the dentate gyrus, where it has been estimated that every day about 700 granule cells are added in healthy individuals (31). Although it is still not fully understood why neurogenesis continues to occur in this part of the brain and not in others, researches suggest that a potential answer lies in understanding of cellular and molecular mechanisms that enable neurogenesis in this part of the dentate gyrus under physiological conditions (32). Wang et al. (33) used high-resolution magnetic imaging (MRI) to register potential changes in the dentate gyrus in 17 male veterans with post-traumatic stress disorder (PTSD). They found that the participants with PTSD had a volume loss in the dentate

gyrus, which was consistent with the theory that chronic stress inhibits hippocampal neurogenesis.

The prefrontal cortex is a structure closely associated with depression. In patients with chronic depression, functional neuroimaging studies have shown differences in the neural activity of different parts of the prefrontal cortex. Its ventromedial parts showed hyperactivity, while its dorsolateral parts were underactive (31). PET scans have shown increased metabolism in the ventromedial prefrontal cortex in patients with depressive disorders, and the metabolic rate correlated with the severity of the symptoms. Neuroimaging studies have found a decrease in the volume of the ventromedial prefrontal cortex in depressive patients, most commonly localized to the left. This suggests that the volume of the lower left ventromedial prefrontal cortex could potentially serve as a biomarker for depression (34). Ongür et al. (35) found a selective reduction in the number of glial cells and density in subgenual parts of the prefrontal cortex in patients with familial forms of depression, by examining human brain tissue. This finding correlates with a predominately left-localized reduction in the volume of the prefrontal gray matter, shown by MRI imaging.

Another structure that is included in the pathogenesis of depression is the amygdala. Unlike the hippocampus and prefrontal cortex, in depressive patients the rate of neuroplasticity is increased in the amygdala. The volume of the amygdala is increased in patients with depression, compared to healthy individuals, as well as glucose metabolism (36). Vyas et al. (37) found that chronic immobilization stress in rats causes significant atrophy of the dendrites in the hippocampus, whereas in the basolateral parts of the amygdala it causes dendritic hypertrophy. These dendritic changes were only spotted on the stellate and pyramidal neurons of the basolateral amygdala, possibly because these types of neurons are excitatory ones. Romanczuk-Seiferth et al. (38) used structural MRI to measure the volume of the amygdala, and found that healthy first-degree relatives of patients with depressive disorders have significantly larger volumes of the gray matter in the bilateral amygdala. Qiu et al. (39) studied the potential connection between functional connectivity of the amygdala in six-month old infants with depressive symptoms diagnosed in mothers. Both structural and resting-state functional MRI were used. The results of this study showed that infants born to mothers with depressive disorders had a greater functional connection between the amygdala and other parts of the limbic system, including the left temporal cortex and ventromedial prefrontal cortex. This connectivity pattern is highly similar to the one found in adults and adolescents with major depressive disorders.

NEUROPLASTICITY AND TREATMENT OF DEPRESSION

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is shown to be able to enhance neuroplasticity by increasing the volume of the hippocampus and causing morphometric changes in both the hippocampus and the amygdala (40). On a molecular level, ECT activates presynaptic glutamatergic neurons and inhibits gamma-aminobutyric acid (GABA) neurons. The release of glutamate in the synaptic cleft activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and inhibits N-methyl-D-aspartate (NMDA) receptors. Upon activation, AMPA receptors release brain-derived neurotrophic factor, which in turn activates protein kinase B. Activated protein kinase B speeds up the neurogenesis process by sending the signal to mTORC1. Additionally, these molecular changes activate inositol 1,4,5-trisphosphate receptor (IP3R) and stimulate the release of calcium ions, which in turn partially open the voltage-gated potassium (BK) channels. Opened BK channels cause the hyperpolarization of the postsynaptic neuron, which consequently expresses an antidepressant effect (41).

Joshi et al. (42) performed a study on 43 patients with major depression to track possible changes in the structure or volume of the hippocampus and the amygdala. Neuroimaging methods showed that patients with depression had smaller hippocampal volumes, compared to healthy individuals. After conducting ECT, volumes of both the hippocampus and the amygdala increased, and significant morphometric changes were observed in the anterior parts of the hippocampus and basolateral amygdala, whereas all measures remained stable in the control group. Pirnia et al. (43) measured the cortical thickness in depressed patients who were undergoing ECT by using MRI. They observed that, over the course of the ECT, along with the symptom improvement, MRI detected an increase in the thickness of the limbic system and paralimbic structures.

No changes in the cortical thickness were detected in healthy individuals. Researchers concluded that ECT stimulates neuroplasticity in limbic and paralimbic structures, and that a change in the thickness could be a predictor of the success of the treatment. Similar results were observed in studies with adult monkeys receiving electroshock therapy (analog of ECT). Prolonged electroshock therapy caused an increased proliferation in the subgranular zone of the hippocampal dentate gyrus, which implicated that this type of therapy stimulates the process of neurogenesis in the hippocampus (43).

Antidepressant medications

Hippocampal plasticity is considered to be closely related to the pathophysiology of depressive disorders. Hippocampal synaptic plasticity, one of the most important function of the human brain, is impaired in depressed patients. This is mostly due to the fact that LTP, a crucial part of the neuroplasticity, is diminished due to a decrease in the concentration of the required growth factors and downregulation of the synaptic proteins. Monoaminergic antidepressants are thought to have a protective effect on the hippocampal synaptic plasticity (29). Normann et al. (44) studied the effects of SSRI on hippocampal synaptic plasticity in rats. They found that SSRI have protective effect on the synaptic plasticity in hippocampus, possibly by modulating the activity of Ca^{2+} channels. Another significant alteration in depressed patients is the reduced volume of the hippocampus. These changes in the hippocampal volume can possibly be a result of a neurodegeneration caused by increased glucocorticosteroid levels. The hippocampus volume may change after taking certain types of antidepressants for an extended period of time (29). Zung et al. (45) observed that in bipolar patients with symptoms and signs of depression, long-term use of lithium led to an increase in the left hippocampal volume, compared to patients who were not using lithium. Boldrini et al. (46) found that the use of SSRI and tricyclic antidepressants caused an increase in the proliferation of neural progenitor cells in the anterior human hippocampal dentate gyrus. A few years later, Boldrini et al. (47) again performed a similar research, where they observed that the size of hippocampal volume as well as the number of mature dentate gyrus granule cells can be increased by long-term SSRI treatment. SSRI are proved to be especially potent in stimulating hippocampal neurogenesis in depressed patients (48, 49). The volume of the hippocampus significantly decreases as a result of the defective neurogenesis process, which is considered to be closely related to the beginning of depression. Furthermore, a higher rate of apoptosis is thought to be related to the smaller hippocampus volume. Two distinct mechanisms could account for the increase in hippocampus volume in SSRI-treated patients. Firstly, blood glutamate levels were lower in SSRI-treated patients, which lowered neurotoxicity, the resulting damage, and death of the hippocampus cells. Additionally, SSRI stimulate neurogenesis and significantly increases the number of neural progenitor cells (29, 50). Wang et al. (51) studied the effects of long-term use of fluoxetine (SSRI antidepressant) and observed that its prolonged use stimulated LTP in the dentate gyrus and accelerated maturation of immature nerve cells in the hippocampus. Fluoxetine treatment increases the activity of several growth factors, including brain-derived neutrophic factor and vascular endothelial growth factor. The release of these factors, preceded by desensitization of 5-HT1A and 5-HT1B serotonin autoreceptors, stimulates proliferation of neural progenitor cells and enhances maturation of hippocampal neurons. Studies have shown that tricyclic antidepressants (most commonly imipramine and desipramine) can also modulate hippocampal neurogenesis in depressed patients, by decreasing the expression of cyclin-dependent kinase inhibitor (p21). The expression of p21 in the subgranular zone of the hippocampal dentate gyrus blocks the process of neurogenesis. Tricyclic antidepressants down-regulate the expression of p21, allowing the proliferation of neural progenitor cells and consequently increasing the volume of this part of the hippocampus (40, 52). Venlafaxine, a dual serotonin/norepinephrine reuptake inhibitor, is shown to protect hippocampal neurogenesis from stress and to suppress hippocampal apoptosis by the upregulation of the brain-derived neurotrophic factor (29, 40). The levels of brain-derived, a dimeric protein, are especially high in the cerebral cortex and hippocampus, and it is therefore considered to be crucial in the pathophysiology of mental illnesses. It can cross the blood–brain barrier and its levels in the blood correlate with its levels in the cerebrospinal fluid (53). Recent findings suggest that this factor could be a significant biomarker for the diagnosis of different psychiatric disorders. A meta-analysis compared the concentrations of brain-derived neuro-

trophic factor (BDNF) in blood between patients with eight different psychiatric conditions (including depression) and healthy individuals. The findings demonstrated that nearly all of the patients had significantly lower levels of BDNF compared to the healthy population. Only those suffering from post-traumatic stress disorder had higher amounts of this factor (54). The results of this meta-study indicate that BDNF could be a useful biomarker in the diagnosis of depression and that its reduced levels would indicate the activity of the disease. Additionally, the levels of brain BDNF are influenced by antidepressants, especially SSRI. Studies have shown that a positive reaction to SSRI therapy is accompanied by an elevation in BDNF levels in the cerebral cortex and hippocampus. Patients taking ketamine for depression also have this beneficial impact. All these findings suggest that BDNF could also serve as a predictor of a positive response to antidepressant treatment (55).

Li et al. (56) studied the potential effects of ketamine on prefrontal cortex and the amygdala in patients with treatment-resistant depression by measuring standardized uptake values (SUV) of glucose metabolism by 18F-FDG positron-emission tomography. Patients with this type of depression often have hypoactivity of the prefrontal cortex and hyperactivity of the amygdala. The results showed that patients treated with ketamine had an increase in SUV of the prefrontal cortex and a decrease in SUV of the amygdala. Ketamine has a significant effect on the process of synaptogenesis, by drastically increasing the number of synapses and improving their functionality. This result is possibly due to the facilitation of the glutamatergic neurotransmission caused by ketamine. Ketamine quickly increases transmission of glutamate in the prefrontal cortex and the concentration of activity-regulated cytoskeleton-associated protein (Arc protein), which is essential for the adequate synaptogenesis. In the presence of brain-derived neutrophic factor, glutamate stimulates synaptogenesis by enhancing the mTOR signaling pathway and the production of the synaptic proteins (56,57). Medications that can also affect amygdala in depressed patients are citalopram and quetiapine (29).

The studies reviewed in this paper show that modern antidepressant treatment has a potent effect on the process of neuroplasticity in the brain areas of interest (hippocampus, amygdala, prefrontal cortex). Electroconvulsive therapy stimulates the process of neuroplasticity, mostly by increasing the volume of both hippocampus and the amygdala. Also, this kind of therapy alters the morphology of the regions examined in this article by regulating the activation of several receptors on postsynaptic and presynaptic neurons, which increases synaptic plasticity. Additionally, a prolonged use of ECT increases the thickness of the limbic system and paralimbic structures, which is considered to be a good indicator of the outcome of the treatment.

Based on a review of the literature, it can be concluded that antidepressants significantly affect neuroplasticity, with the SSRI class of antidepressants having the strongest influence. SSRI stimulate hippocampal neurogenesis and prevent the apoptosis of neural cells by lowering the amount of neurotoxicity. All these changes lead to a significant increase in the hippocampal volume. Also, this group of antidepressants stimulates LTP in the dentate gyrus and accelerates maturation of immature nerve cells in the hippocampus. The analysis of the papers reviewed found that tricyclic antidepressants can also modulate hippocampal neurogenesis in depressed patients, mostly by decreasing the expression of p21 in the subgranular zone of the hippocampal dentate gyrus, which in turn allows the proliferation of neural progenitor cells and increases the volume of the hippocampus. This review also found that ketamine could have a significant effect on neuroplasticity in depressed patients, most probably by increasing the transmission of glutamate in the prefrontal cortex, which improves the functionality of the synapses.

LIMITATIONS OF THE STUDY

This study has several limitations. The majority of the original research reviewed in this study was based on a smaller sample size of depressed patients. Control groups were usually healthy individuals with no confirmed pshychiatric condition, which is seen as a restriction in several studies where it was recommended that patients who were not receiving treatment for depression should be included. Also, there was heterogeneity among the participants in terms of age, duration of the depression, comorbidites, and previous treatment modalities. A few of the reviewed research used human postmortem brain tissue or animal models. The results of these investigations need to be validated and further investigated in live people suf-

fering from depression. Additionally, due to heterogeneity of the patients, it is impossible to exclude impact of other factors on the process of neuroplasticity. The process of neuroplasticity in the brain regions reviewed in this study can also be altered by the aging process, gender differences, task learning, stress, diet, and the use of various non-psychiatric drugs, all of which are impossible to fully exclude when studying the process of neuroplasticity in depressed patients.

CONCLUSION

Depression is one of the most prevalent psychiatric disorders worldwide, which has extremely negative effects on the quality of life and prevents patients from engaging in everyday activities. The pathophysiological mechanisms behind depression are still not fully understood. Neuroplasticity is a phenomenon that allows the brain to change its structure and activity in response to different types of stimuli. Recent studies have shown that neuroplasticity may be a key factor in the development of depressive disorders, as well as a predictor of the successful treatment and prognosis of these disorders. Further investigations could be aimed at discovering a stronger connection between neuroplasticity and different types of antidepressant treatments, possibly by using different neuroimaging methods which can detect volumetric changes in the hippocampus, amygdala, and prefrontal cortex in patients treated with antidepressants and/or ECT. Also, by using rodent models or human brain tissue of patients with depressive disorder, could be focused further research on the use of immunocytochemistry techniques to study the process of neurogenesis in cerebral areas reviewed in this article. Future studies could also focus on the BDNF and how different treatments for depression disorders affect blood levels of this protein.

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Uloga neuroplastičnosti u etiologiji i lečenju depresivnih poremećaja

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SAŽETAK

Uvod/Cilj. Depresija je afektivni poremećaj koji sprečava obolele osobe da obavljaju svakodnevne aktivnosti, budući da podrazumeva konstantno prisustvo negativnih emocija. Depresija je kao jedan od najučestalijih mentalnih poremećaja na svetu postala ogroman finansijski teret za zdravstveni sistem. Najčešće se kao etiološki faktori depresivnih poremećaja opisuju biološki, fiziološki i socijalni faktori, mada patogenetski mehanizmi koji dovode do depresije još nisu u potpunosti proučeni. Neuroplasticitet je sposobnost nervnog tkiva da reorganizuje svoju strukturu i funkciju kao odgovor na različite stimuluse. Cilj ovog rada bio je da sumira dostupnu literaturu o neuroplastičnosti i o njenoj ulozi u patofiziologiji i lečenju depresivnih poremećaja.

Pregled literature. Depresija se najčešće javlja sa različitim hroničnim oboljenjima i češća je kod žena nego kod muškaraca. Antidepresivi, elektrokonvulzivna terapija i psihosocijalna terapija predstavljaju najčešće terapijske opcije koje se koriste u lečenju depresije. Neuroplasticitet je doveo do razvoja nove kliničke discipline – neurorehabilitacije. Najnovija istraživanja ukazuju na postojanje veze između neuroplasticiteta i depresije. Različiti mehanizmi koji su u osnovi procesa neuroplasticiteta utiču na limbičke i paralimbičke strukture, naročito na hipokampus, prefrontalnu moždanu koru i amigdalu.

Zaključak. Činjenica da limbičke i paralimbičke strukture podležu strukturnim promenama kod obolelih od depresije koji uzimaju antidepresive ili koriste elektrokonvulzivnu terapiju može dovesti do boljeg razumevanja depresivnih poremećaja i načina na koji ih treba lečiti.

Ključne reči: **depresija, depresivni poremećaji, neuroplasticitet, hipokampus, amigdala**