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Neuroplasticity in Depressive Disorders: The Role of BDNF in Linking Pharmacotherapy and Physical Activity

Maciej Mamczur
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
https://orcid.org/0009-0000-2789-1235
maciej.mamczur@gmail.com

Michał Szczepański
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
https://orcid.org/0009-0001-8586-3790
mszczepanski0202@gmail.com

Dominik Maciej Feret
Independent Public Health Care Complex No. 1 in Rzeszów,
ul. Czackiego 3, 35-051 Rzeszów, Poland
https://orcid.org/0009-0004-3174-2784
feret.dominik@gmail.com

Marcin Kuliga
College of Medical Sciences, University of Rzeszów, Poland
al. Tadeusza Rejtana 16C, 35-310 Rzeszów
https://orcid.org/0009-0004-3452-7377
marcinkuliga@gmail.com

Daniel Zapasek
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
https://orcid.org/0009-0006-1383-1825
daniel.zapasek@interia.pl

Julia Słowik
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland
https://orcid.org/0009-0003-3821-5090
jj16@interia.eu

Mateusz Bajak
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland
https://orcid.org/0009-0006-8237-1295
mateuszbk88@gmail.com

Damian Sowa
Clinical Provincial Hospital No. 2 in Rzeszow, Poland
Lwowska 60, 35-301 Rzeszów, Poland
https://orcid.org/0009-0003-0980-9324
damian_sowa@wp.pl

Julia Inglot
Clinical Provincial Hospital No. 2 in Rzeszów, Poland
Lwowska 60, 35-301 Rzeszów, Poland
https://orcid.org/0000-0002-6604-7229
inglotjulia@gmail.com

Jadwiga Inglot
Clinical Provincial Hospital No. 2 in Rzeszow, Poland
Lwowska 60, 35-301 Rzeszów, Poland
https://orcid.org/0000-0002-3071-4392
inglotjadzia@gmail.com

Corresponding Author: Maciej Mamczur, maciej.mamczur@gmail.com

Abstract:
Introduction: Depressive disorders are among the most prevalent mental health conditions globally, affecting millions of people. Despite extensive research, the exact pathophysiology of depression remains unclear. Recent evidence suggests that neuroplasticity, particularly the

role of brain-derived neurotrophic factor (BDNF), plays a crucial role in both the onset and treatment of depressive disorders.

Aim of Study: This review explores the relationship between neuroplasticity and depression, focusing on BDNF as a central biomarker and potential therapeutic target. It also examines how antidepressant therapies and physical activity influence neuroplasticity and BDNF levels, offering insights into novel approaches for treating depressive disorders.

Material and Methods: A literature review was conducted using PubMed and Google Scholar databases, focusing on peer-reviewed articles with the keywords: "neuroplasticity", "BDNF", "depression", "antidepressants" and "physical activity".

Conclusions: Neuroplasticity, particularly through BDNF signaling, plays a critical role in the pathogenesis and treatment of depression. Elevated BDNF levels promote synaptic plasticity, neurogenesis, and recovery of brain function. Antidepressant treatments enhance neuroplasticity by increasing BDNF levels. Antidepressants and physical activity both influence neuroplastic processes, with BDNF serving as a key mediator.

Keywords: Neuroplasticity, BDNF, Depression, Antidepressants, Physical activity.

Introduction.

Depressive disorders represent one of the most prevalent groups of mental health conditions worldwide. It is estimated that 3.8% of the global population and 5% of adults experience depression, with women being approximately 50% more likely to be affected than men [1]. Over 264 million people are estimated to suffer from depressive disorders [2]. A depressive episode is characterized by a period lasting at least two weeks during which a depressed mood, diminished ability to experience pleasure, and loss of interest in daily activities occur, along with symptoms such as disrupted sleep patterns, appetite changes, excessive guilt or low self-esteem, low energy levels, and reduced concentration [3]. Depressive disorders result from the interaction of psychological, social, and biological factors, although the precise pathomechanism remains incompletely understood [1], [4]. Long-standing theories primarily focus on monoamine neurotransmission disturbances, the neuroinflammation and oxidative

stress hypothesis, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, and stress response pathway dysfunction [5]. However, standard monoaminergic pharmacological treatments show limited efficacy and variable response rates, with 10-30% of patients experiencing treatment-resistant depression [6]. Other theories are insufficient to fully explain the origin and treatment of depressive disorders, thus raising questions about the validity of the aforementioned hypotheses as the primary causes of depression and prompting further investigation into its pathomechanism. A recently developed theory is the involvement of neuroplasticity in the pathomechanism and treatment of depressive disorders, with brain-derived neurotrophic factor (BDNF) playing a central role in these processes. Impaired neurotrophic signaling in synaptic plasticity and the neurotrophin response induced by antidepressant medications have been suggested as potential, previously unexplored factors in depressive disorders, with BDNF highlighted as a key neurotrophic factor [7].

Neuroplasticity.

Neuroplasticity refers to the processes in the nervous system involved in development, repair, learning, and memory, encompassing synaptic plasticity, neurogenesis, and cellular growth and remodeling [8]. In other words, it is the nervous system's response to internal or external stimuli through structural and functional reorganization [5]. Neuroplasticity underlies the regeneration of the nervous system after various pathological processes and injuries, enabling remarkable functional recovery, especially in young individuals [8]. Neuroplasticity processes are influenced by environmental factors, particularly during sensitive periods, with the primary sensitive period being early postnatal life and prenatal development. The dynamics of individual development exhibit various peaks in neuroplasticity modulation during childhood, adolescence, and adulthood, which can be significantly altered early in life due to adversities caused by unfavorable environmental factors [9]. Interestingly, neuroplasticity mediated by BDNF has been associated with social adversities in childhood, which accelerate the maturation of social network circuits, potentially serving as an adaptation to a changing, unfavorable environment [10]. The body's response to stress modulates neuronal plasticity through intracellular changes in the nervous system, and chronic stress exposure may have long-term effects on brain structures [9]. On a cellular level, synaptic plasticity is defined as the ability to change the strength and efficiency of synaptic connections. This results in short-term modifications that, with sufficient duration and continuity, become long-term and lead to structural changes in synaptic organization and number, effectively remapping the nervous

system's function. At the tissue level, neuroplasticity can activate alternative neuronal circuits that form specific pathways to recover lost brain functions [11].

Neuroplasticity in the Context of Depressive Disorders.

Impaired regulation of neuroplasticity processes can contribute to a broad spectrum of neuropsychiatric disorders, including depressive disorders [8]. The mechanism of depressive disorder pathogenesis and its treatment can be explained through the concept of neuroplasticity as a cascade of intracellular signal transmission. It has been shown that adverse experiences and stress can impair brain function, particularly in the hippocampus; however, chronic antidepressant therapy can reverse the inhibition of neurogenesis in the hippocampus [12]. A link has also been established between stress and decreased synaptic complexity in the prefrontal cortex and hippocampus [7]. A significant observation is the reduced hippocampal volume in patients with depression, which may present this phenomenon as a biological marker of depressive disorders. Additionally, a decrease in the volume of the prefrontal cortex (PFC) has been observed [13], [14]. Notably, in depressive disorders, key elements associated with plasticity disturbances also include neuroinflammation and dysregulation of multiple neurotransmitters such as serotonin, dopamine, norepinephrine, GABA, and glutamate.

BDNF as an Indicator of Neuroplasticity.

An effective indicator for assessing neuroplasticity processes at the cellular level is the neurotrophin family, which primarily includes brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) [15]. The most crucial indicator of neural plasticity widely used in research is BDNF. This neurotrophin regulates the proper development and function of the nervous system, overseeing neuronal maturation and synapse formation. Studies have shown that BDNF is a more reliable biomarker for assessing the severity of depressive disorders than serotonin [2]. BDNF expression in the central nervous system (CNS) is widespread, providing a basis for its profound impact on synaptic plasticity development and brain function. The BDNF protein is encoded by distinct BDNF gene transcripts from 9 different promoters, with each transcript potentially affecting specific regional and temporal outcomes of BDNF's action [16]. BDNF is synthesized in neuronal and glial cell bodies and then transported to synaptic terminals for release [17]. It has been shown that high mRNA and BDNF protein levels are particularly present in the hippocampus, amygdala, cerebral cortex, and hypothalamus, where it regulates

synaptic transmission through long-term potentiation (LTP), a process that changes synaptic conformation, enhancing synaptic conductance [11]. BDNF interacts with two distinct receptors: TrkB and p75NTR [5], with BDNF mainly exerting its effects through interaction with the TrkB receptor. A reduction in TrkB expression is associated with anxiety-like behaviors [12]. The signaling of the BDNF-TrkB complex enhances synaptic efficacy through both presynaptic and postsynaptic mechanisms [16]. Reduced BDNF levels have been observed in the hippocampus and prefrontal cortex in both rodents exposed to stress and in post-mortem analyses of patients with depression. Furthermore, antidepressant treatment has been shown to reverse the reduced BDNF levels in patients with depression, considering that antidepressant medications act inversely on BDNF expression in the hippocampus and prefrontal cortex compared to stress and low mood states [14].

Pharmacotherapy of Depression in the Context of Neuroplasticity.

The hypothesis of the pathomechanism of depressive disorders as a disruption of neuroplasticity, manifested by a reduction in BDNF levels, can be indirectly confirmed by the fact that depressive disorders are treated with antidepressant drugs, which influence neural plasticity through changes in BDNF levels. Furthermore, it has been shown that appropriate levels of BDNF are necessary for obtaining a positive effect from antidepressant treatment. Although antidepressants increase the levels of monoamines within a few hours, the desired effect usually takes several weeks to manifest, which is explained by the phenomenon of hippocampal neurogenesis, requiring appropriate time during which synaptic regulation processes occur [14]. Studies consistently emphasize the role of BDNF as a link and key factor between antidepressant treatment and brain plasticity changes. A correlation has been demonstrated between the increased expression of BDNF mRNA and TrkB in the hippocampus and cerebral cortex and the use of conventional pharmacotherapy based on antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs). It is believed that the basis of antidepressant treatment lies in dendritic remodeling and synaptic contacts in the regions of the hippocampus and prefrontal cortex [5]. A study involving the injection of BDNF into the mesencephalon produced an effect similar to antidepressants in rodents, and later it was shown that a single infusion of a low dose of BDNF in the DG or CA3 region of the hippocampus induced an effect similar to antidepressants within 3 days [16]. A correlation was also examined in which antidepressant and anxiolytic effects were triggered in rodents after subcutaneous peripheral administration of BDNF [18]. Studies on rodents with the NMDA receptor antagonist ketamine showed that it could induce a rapid antidepressant effect

by increasing the release and expression of BDNF and VEGF in the hippocampus and prefrontal cortex (PFC), increasing the number and function of synapses in these areas [6]. Increased BDNF expression in the visual cortex of adult, visually impaired rats was the result of fluoxetine therapy. The therapy also restored plasticity between neurons in the visual system [5]. A meta-analysis of 11 studies evaluating the difference in serum BDNF levels between individuals with and without depression and 8 studies comparing serum BDNF levels before and after antidepressant therapy provided strong evidence that BDNF levels were lower in individuals with depression than in the healthy control group. Similarly, higher levels of BDNF were observed in individuals after antidepressant therapy [19]. In another study, a similar meta-analysis was conducted: 38 studies on BDNF levels in individuals with and without depressive disorders and 21 studies on the correlation between BDNF levels and antidepressant treatment were analyzed. BDNF levels were reduced in people with depression, and pharmacotherapy increased serum BDNF levels in individuals with depressive disorders [20]. It has also been proven that serotonin can stimulate the expression of BDNF [5]. A possible correlation between the effectiveness of antidepressant therapy in patients with depression and the presence of the BDNF Val66Met polymorphism was also examined. A higher response rate to SSRI therapy was shown in patients with the Val66 allele compared to those carrying the Met allele, highlighting individual differences in neuroplasticity [5]. The literature indicates that the increase in BDNF/TrkB signaling as a result of antidepressant therapy can induce a state of neuroplasticity similar to that of youth, which allows for the reorganization of social circuits and provides a safe background for subsequent psychotherapy [10].

The Role of Physical Activity in the Treatment of Depressive Disorders.

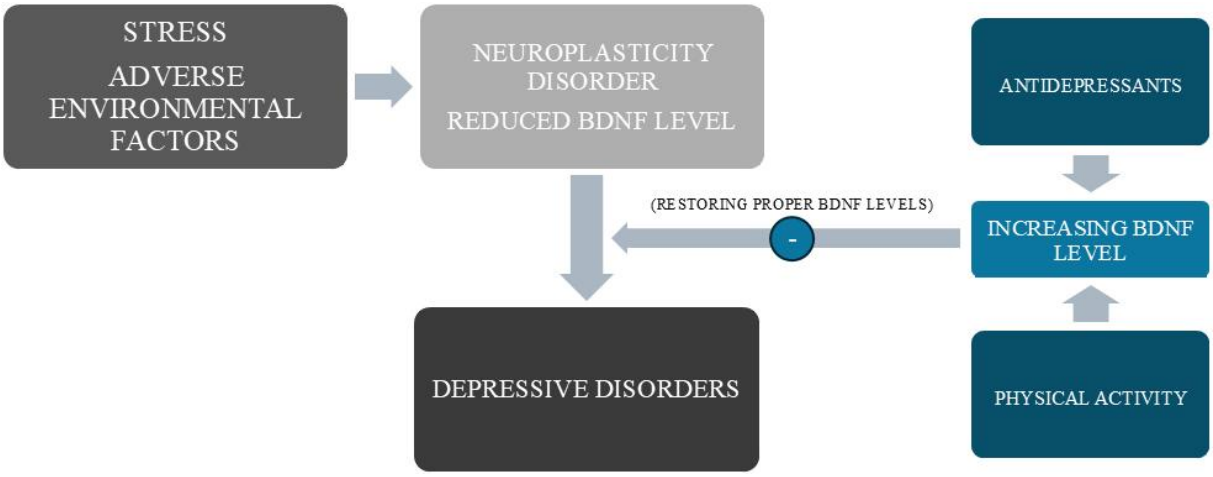
There is substantial evidence indicating that regular physical activity is associated with a reduced risk of experiencing a depressive episode and alleviating symptoms of already existing mild or moderate depression [21]. A review examining the relationship between physical activity and depressive and anxiety disorders, including 21 observational studies and data from 42,293 participants, confirms that individuals engaging in more frequent and intense physical activity tend to have a lower incidence of depression and anxiety [22]. The results of many studies indicate that physical activity is a valuable adjunct to conventional methods of treating depressive disorders. Neuroimaging studies have shown that depressive disorders significantly impair the function of the reward system, contributing to a reduced ability to feel pleasure. The reward system includes a circuit that consists, among other things,

of the nucleus accumbens, ventral tegmental area, orbitofrontal cortex, and the previously mentioned amygdala, hippocampus, and prefrontal cortex. It has been shown that physical activity modulates reward processing by regulating neurotransmitter levels in the reward system circuits [21].

Neuroplasticity and BDNF, and Physical Activity.

Numerous preclinical and clinical studies demonstrate the relationship between physical activity and increased plasticity and neurogenesis through mechanisms involving BDNF – the same protein that connects the effects of antidepressants with the reduction of depressive symptoms [Figure 1], [23]. Many of the positive aspects of physical activity on mental health and the functioning of the nervous system arise from its impact on maintaining appropriate levels of BDNF, particularly in the hippocampus [24]. Furthermore, physical exercise optimizes the function and levels of key neurotransmitters: serotonin, dopamine, norepinephrine, as well as glutamate and GABA [23]. Consequently, changes in neurotransmission indirectly modify BDNF gene expression in areas such as the hippocampus, amygdala, and nucleus accumbens [24]. Moreover, regular physical activity reduces neuroinflammation and increases resistance to stress, as well as alleviates dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, whose regulation is responsible for the volume loss in the hippocampus. A number of studies seem to confirm the correlation between chronic aerobic exercise and an increase in peripheral BDNF levels, blood volume in the dentate gyrus, gray matter in the prefrontal cortex and cingulate gyrus, and hippocampal volume [25]. Studies also indicate that in rodents subjected to physical activity 5 days a week for 4 weeks, synthesis and release of BDNF in the dentate gyrus were increased. Additionally, the increase in hippocampal size resulting from regular physical activity correlates with an improvement in spatial memory performance in both healthy individuals and those with neurodegeneration [26]. Interestingly, a 2020 study highlighted the existence of undefined BDNF isoforms in human satellite cells, with their levels rising along with BDNF mRNA in the muscles from 24 to 72 hours after physical exercise [27].

Figure 1. A simplified pathway linking stress, neuroplasticity dysfunction, and depressive disorders: the therapeutic role of antidepressants and physical activity in restoring BDNF levels.



Conclusion.

Depressive disorders represent a significant global health challenge, necessitating ongoing research into their pathophysiology and therapeutic strategies. Recent advances highlight the crucial role of neuroplasticity, particularly through brain-derived neurotrophic factor (BDNF) signaling, in both the onset and treatment response of depressive disorders. Antidepressant therapies not only modulate neurotransmitter systems but also activate BDNF-mediated neuroplastic processes, which promote synaptic remodeling and neurogenesis in brain regions critical for mood regulation, such as the hippocampus and prefrontal cortex. BDNF may thus serve as both a crucial biomarker and a therapeutic target in the management of depression. Emerging evidence also suggests that lifestyle interventions, such as regular physical activity, can enhance BDNF expression, offering an adjunctive approach to pharmacotherapy. This underscores the potential of integrating physical activity into treatment strategies for depression. However, further research is needed to delineate the precise molecular mechanisms underlying BDNF's role in depression and explore novel therapeutic approaches to increase its activity, ultimately improving outcomes for individuals with depressive disorders.

Disclosure:

Author's contribution:
Conceptualization: Maciej Mamczur, Dominik Feret
Methodology: Maciej Mamczur, Michał Szczepański
Investigation: Maciej Mamczur, Marcin Kuliga
Software: Maciej Mamczur, Damian Sowa

Check: Michał Szczepański, Marcin Kuliga, Julia Słowik
Formal analysis: Julia Inglot, Jadwiga Inglot, Mateusz Bajak
Writing – rough preparation: Maciej Mamczur, Dominik Feret
Writing – review and editing: Marcin Kuliga, Jadwiga Inglot, Damian Sowa
Resources: Maciej Mamczur, Daniel Zapasek, Julia Słowik
Data curation: Maciej Mamczur, Daniel Zapasek, Mateusz Bajak
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Project administration: Maciej Mamczur, Dominik Feret

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