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Research Paper

Neuroplasticity in Depression: A New Cure for the Future

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ABSTRACT

Major depressive disorders are the leading cause of disability worldwide. The most effective treatment for depression in today's generation is neuroplasticity. Neuroplasticity mainly explains the structural and functional alterations in the brain in response to different stimuli, such as stress, anxiety, depression, and many other mood disorders. Depression, or major depressive disorder, is a common mental disorder where an elevation or deviation of mood plays a great role in a person's day-to-day life and also affects the lifestyle. It mainly involves a depressed mood or loss of interest in all activities for a prolonged period of time. Depression is a chronic as well as a recurrent disease. Neuroplasticity, also known as neural plasticity, is the modified structural capacity of the nervous system to modify its response according to intrinsic or extrinsic stimuli by making alterations in the structural or functional processing's or connectivity after any kind of injury. For example: stroke, accidents, traumatic brain injury, etc. Neuroplasticity has helped a lot in the rewiring of the brain through new skill adaptability and mood enhancement.

Keywords: *Neuroplasticity, Depression, New Cure, Future*

Before knowing about neuroplasticity, it is important to know about the term "plasticity." Plasticity is defined as the potentiality of a very weak structure to be changed by external foreign stimuli, so strong as not to mold at once. However, the nervous tissue of the human brain is gifted with a tremendous capacity for plasticity, which in turn can help in treating many mood disorders [1]. A long time ago, scientists believed that the brain did not change after childhood; however, later on, it came to light that the brain does change even during the adult period. The brain is basically designed to be customized in the early part of life and to implement those algorithms and that circuitry for the rest of its life, so the brain can change in adulthood, provided that there is an emphasis on some perceptual event. In other words, if we want to change our brain in adulthood, let's take into consideration that we want to be less anxious or want to learn a new skill. The key thing is to bring focus to some particular perception of something that's happening during the learning process. The reason for this can be the chemical systems involved, like acetylcholine, which comes from two nuclei at the base of the brain called the 'Neucleus Basalis'. When we think about something very intensely, acetylcholine gets released from the basalis at the selective neuron that is involved in that certain behavior, and it marks those

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for change. In a network of neurons, neurons are the fundamental unit that transmits responses in order to get intrinsic and extrinsic information. During plasticity, neurons are the dynamic processes that occur in response to external stimuli, injuries, emotions, and so on. This neural function plays a very vital role in the process of neuroplasticity [2]. Neuroplasticity mainly explains the structural and functional alterations in the brain in response to different stimuli, such as stress, anxiety, depression, and many other mood disorders. Depression, or major depressive disorder, is a common mental disorder where an elevation or deviation of mood plays a great role in a person's day-to-day life and also affects their lifestyle. It mainly involves a depressed mood or loss of interest in all activities for a prolonged period of time. Depression is a chronic as well as a recurrent disease [3]. The prevalence rate of depression in today's generation is at its peak. Women are more likely to have depression than men. According to studies, 3.8% of the population is experiencing depression, including 5% of adults. 4% of men, 6% of women, and 5.7% of adults older than 60 are going through depression worldwide. Approximately 280 million people in the world have depression, according to recent studies [4]. Depression not only disturbs mental behavior but also causes pathophysiological disorders such as cardiac diseases, cerebrovascular diseases, and nervous system impairment. Unfortunately, till now, there have been no effective treatments for this disease. Currently, the most effective treatments for depression are antidepressants, psychotherapies, and other treatment methods, which have very life-threatening side effects. According to the new findings of antidepressants, the new antidepressants are based on the monoamine hypothesis, in which serotonin (5HT), norepinephrine (NE), and the dopamine neurotransmitter system are involved. The available antidepressants, whether in combination or alone, have shown a delayed response with a very limited duration of efficiency. Hence, it is important to explore the pathophysiological effects of depression. Through a lot of studies and research, it has been found that there is a correlation between depression and neural plasticity through their mechanisms. It's important to know how neuroplasticity is linked with depression [5]. Neuroplasticity occurs through cellular mechanisms in the brain, which take place due to learning and memorizing. This neurogenesis can take place in the brain cells in certain locations of the brain, like the hippocampus, the olfactory bulb, and the cerebellum [6].

What is Neuroplasticity?

The term neuronal plasticity was first used by the scientist of neuroscience, ‘Santiago Cajal', in the early 1900s to characterize non-pathological changes in the structure of the adult brain. Neuroplasticity is the ability to rewire the functions of the brain, starting from early synaptic plasticity, either strengthening (long-term potentiation) or weakening (long-term depression) in response to intrinsic and extrinsic stimuli by synaptic transmission, synapse formation or retraction, axonal sprouting, axonal regeneration, dendrite growth and formation, and also neurogenesis. In easy words, neuroplasticity, also known as neural plasticity, is the modified structural capacity of the nervous system to modify its response according to intrinsic or extrinsic stimuli by making alterations in the structural or functional processing’s or connectivity’s after any kind of injury. For example: stroke, accidents, traumatic brain injury, etc.

***Types*:**

Mainly, there are two types of neuroplasticity. They are structural neuroplasticity and functional neuroplasticity.

Structural Neuroplasticity:

The capacity of the brain to modify its neural connections as modified new neurons are continuously produced and racially mixed into the central nervous system throughout life based on their type. Structural plasticity mainly refers to the brain's capacity to adjust the neuronal analysis and structural overview of neuronal connectivity. It mainly works at the cellular level through many dynamic changes in the cellular structures that have a functional impact. Structural plasticity is very limited and has a very high preferable degree of unchangeable response, which is an important characteristic of the mammalian central nervous system. as it makes sure that neural circuits remain steady and the important or specific neuron connection remains protected. This is the reason why neurons are unsustainable. This is the reason why the mammalian central nervous system has low regeneration and repairable capacity. It is the adjustment between the adaptability and stability of the brain to work at full power.

The main role or mechanism of neuroplasticity is responsiveness to the experiences we alter in everyday life, what our senses capture, and how we use them in our daily lives. That's the importance of learning and memorizing. The experience that we gather stays throughout our lifetime and gets engraved into our brains in such a way that it allows us to adapt our behavior [6-8]. The main example is the change in the proportion of the gray matter or the strength of the synapse in the brain [6,7].

Mechanism of Structural Neuroplasticity:

The physiological aspect of the brain changes throughout life depending on what we learn and adapt, and the main thing is age. The stability between structural brain plasticity and equilibrium denotes a healthy brain; any unbalanced characteristics lead to brain tumors, psychiatric disorders, and neurodegenerative diseases [9]. The mechanism of structural neuroplasticity starts with precise changes ranging from synaptic remodeling and myelination of axons to more dynamic changes like the growth and development of new neurons called neurogenesis. The mechanism and the occurrence of structural plasticity vary for different mammalian species [7,8].

Synapse Remodeling

Synapses are intrinsically compliant, i.e., modifiable through the changes that can take place in the dendritic spines; they are the membranous protrusions along the neuronal dendrites, which form effective contacts with adjacent axons of neurons. Dendritic axons are highly plastic, which means they can be modified. Its size and shape constantly change in response to neuronal activity [9]. Spines get formed excessively after birth. It goes through substantial pruning during the postnatal period, but mostly remains stable during adulthood, providing a structural blueprint for long-term memory storage. The synaptic remodeling decreases in the adult brain, but the ability of the synapse to grow is too high to have functional significance and shows a lifelong impact on behavioral adaptation. With the increase in age, the dendritic spines may swell or shrink, and a new formation of spines can take place. Spines either get stabilized or may get thinner with age [8,9]. According to studies, the fast growth of new spines takes place in the adult brain due to motor task learning and novel sensory experiences, but most of the dendritic spines remain pruned. The non-working spines start working after repeated stimulation and are interpreted into a functional circuit. Newly modified spines remained long-lasting without any training; this showed that the stabilization of new spines put up a memory consolidation in context to the newly learned motor skills. Synaptic remodeling processes induce a small but permanent change, refining the neuronal circuit for long-lasting memory adaptation and behavioral adaptation.

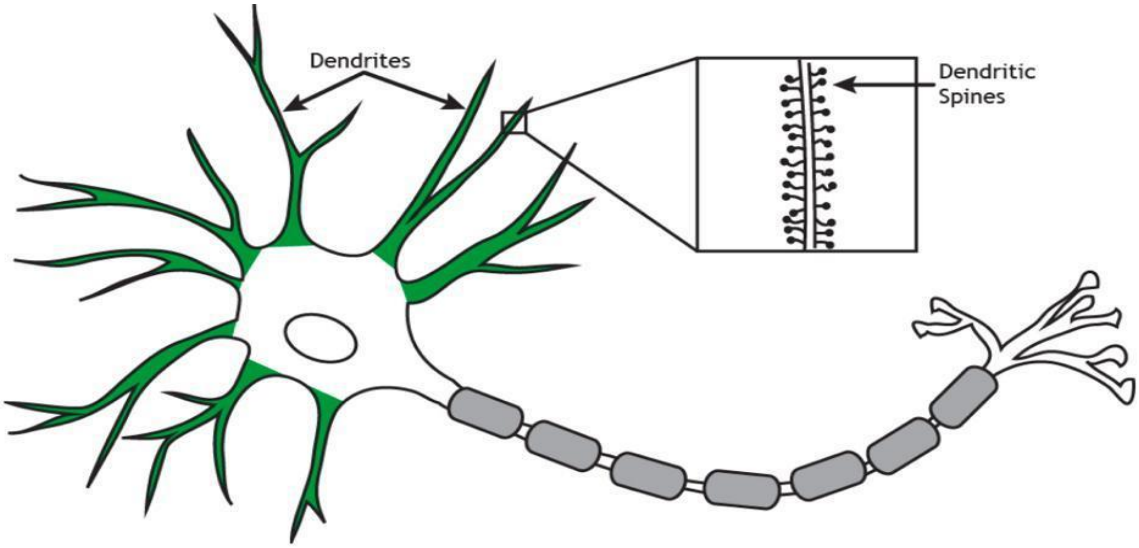

Fig-1: Synapse Remodeling

Myelin Plasticity and White Matter

CNS white matter indicates an intense form of neural plasticity, which has been termed "myelin plasticity". It is already well known that oligodendrocyte generation and the addition of new myelin internodes continue throughout new adulthood, the enhancement of which promotes myelin thickening. These new myelin internodes may be required for the myelination of previously unmyelinated axons, myelin sheath replacement, or even myelin remodeling. It was seen that motor skill learning not only changed the white matter structure but also the presence of the mind in active myelination. Therefore, it is seen that myelin production is extremely important as a neuroplastic change in the learning process. White matter is mainly found in the deeper tissues of the brain, most probably the subcortical region. It mainly consists of axons, which are the nerve fibers, or neurons. These nerve fibers are surrounded by a type of sheath or covering called the myelin sheath. The white matter gets its color from the myelin sheath. It also protects the nerve fibers from injury [9,10].

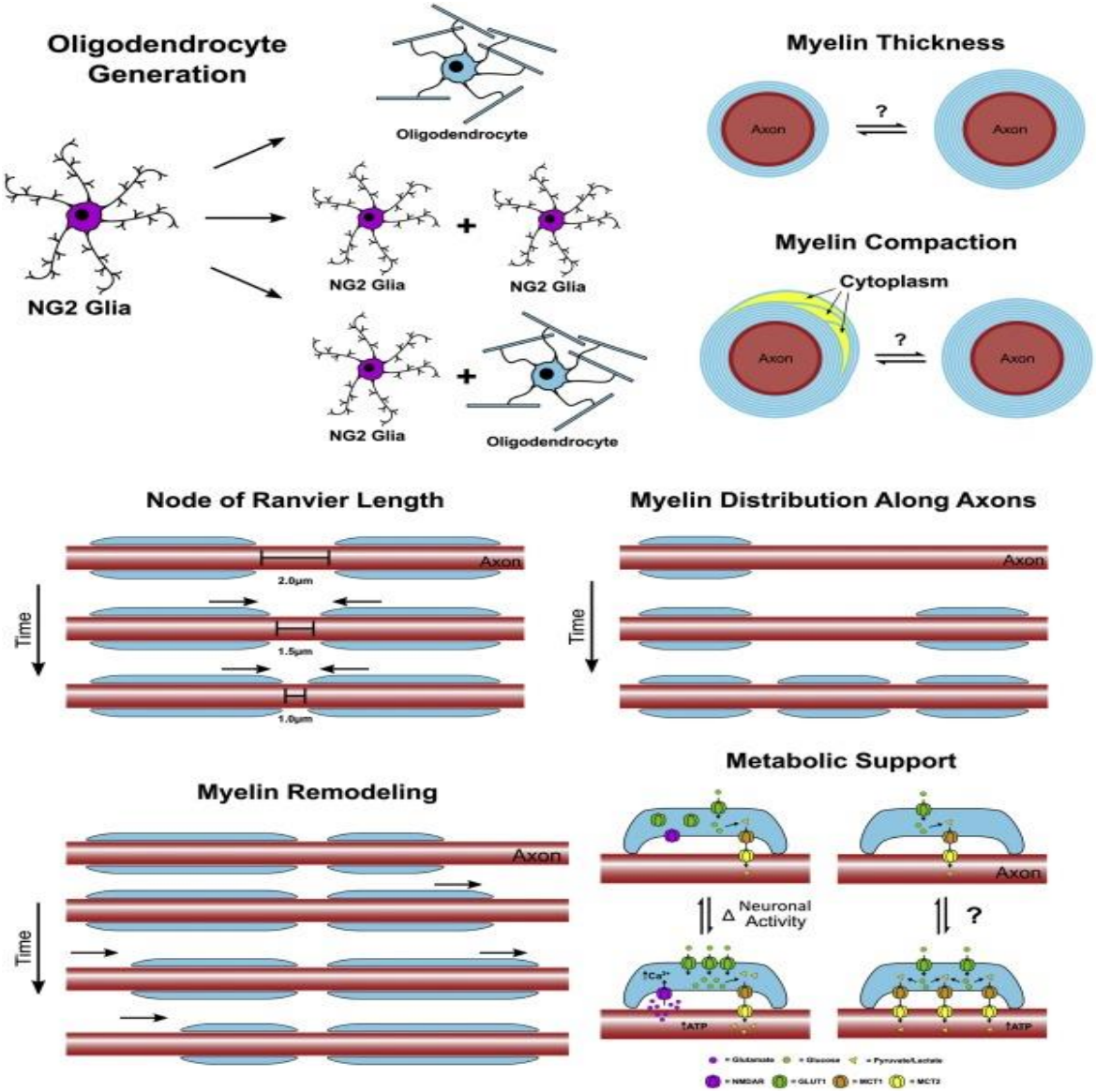

Fig-2: Myelin plasticity in adulthood

Neurogenesis

Neurogenesis is defined as the process by which new neurons are formed in brain cells. The main function of these new cells is to receive and process information from the outside world and pass information throughout the body. Neurons mainly communicate via electrical or chemical signals that travel through the synapse of the brain cells. Connections that get formed through neural networks help us learn. Neurogenesis is possible only in specific brain regions where cellular and molecular structuration allow neuronal development to occur. In humans, the work of neurogenesis degrades with age. Till now, it has been seen that human neurogenesis can always be changed according to the enforcement we put in the brain and also according to the new skill development and experience a person gathers [10,11].

Functional Neuroplasticity

It is the brain's ability to locomote functions of the brain from a damaged area of the brain to undamaged areas. The molecular-level modifications are made in functional neuroplasticity

through neurotransmitter signaling, receptor levels, ion channel properties, and many more. The main mechanisms of functional neuroplasticity are:

- Synaptic strengthening
- Intrinsic plasticity

Synaptic Strengthening

Functional synaptic plasticity considers alterations in the properties of signaling through synapses, mostly in the form of changes in the synaptic strength in response to patterns of neuronal activity, either by making it strong or by weakening the connectivity of the synapse between two neurons. Synaptic strengthening mainly occurs in a form called long-term potentiation. In this process, when two neurons connect with each other and fire, the responsiveness of the postsynaptic neuron increases. One more process is synaptic weakening or long-term depression, where it responds to decreased activity. In this state, synapses become less efficient and less able to elicit a response in the post-synaptic neuron. In this way, connections between two neurons weaken.

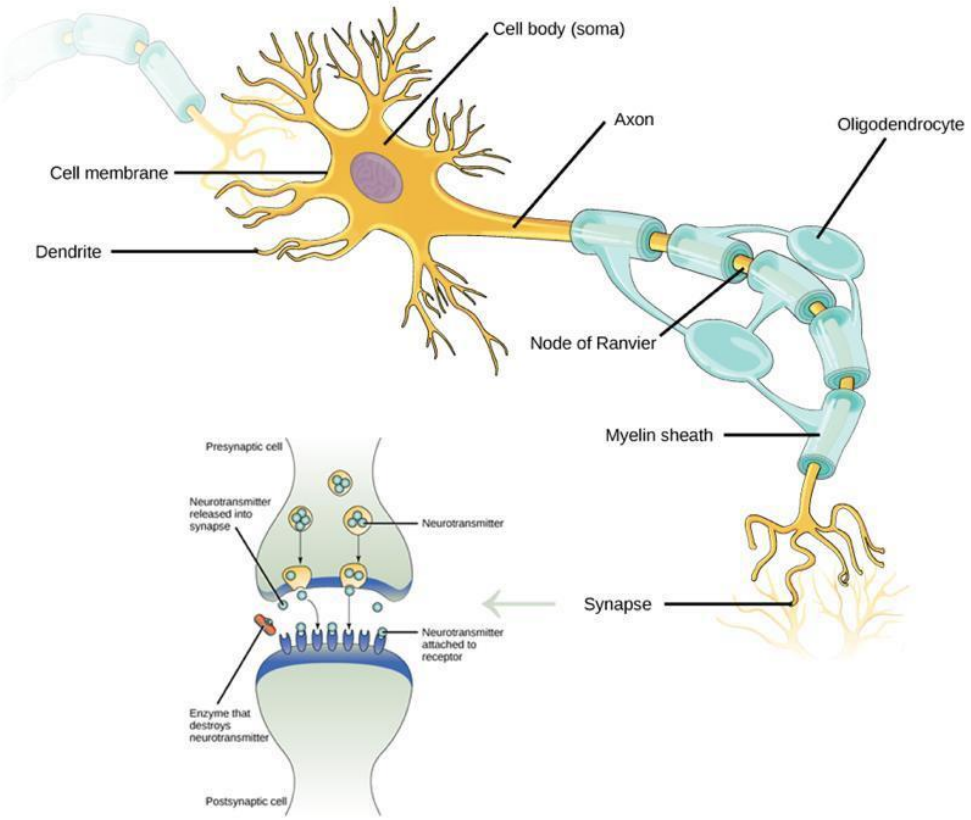

Fig-3: Synaptic Strengthening

Intrinsic Plasticity

Intrinsic plasticity is the modification of the electrical properties of neurons by synaptic activity through the action potential. Intrinsic plasticity refers to the changes in the excitability of the neurons, i.e., the likelihood that a neuron will fire [12,13].

Role of Neuroplasticity in Depression

In this generation, depression is said to be the most common mental illness. According to the evidence gathered, depression may cause a change in neuroplasticity in certain parts of the brain. This depends on how severe the symptoms have arisen. Depression somehow matches

up with the atrophy of neurons in the cortical and limbic brain regions that help in controlling and regulating the mood and emotions in a person. The pathological aftermath of depression states that, according to the researchers, significant modifications mainly take place in the structure of gray matter and white matter in the frontal lobe, hippocampus, temporal lobe, thalamus, striatum, and amygdala of depressed individuals. The main pathophysiology of depression is that damage or obstruction occurs in the functional circuit connecting the different regions of the brain, instead of one anomaly [11]. It is seen that the hippocampus of depressive patients is smaller in size as compared to those of healthy ones. It is already known that the hippocampus is associated with memory and cognitive processes in the brain. In depressed patients, the gray matter decreases due to the deviation of emotions and impaired cognitive characteristics in a depressive patient [12,13].

Damage to the frontal lobe and thinning have commonly been associated with depression. Studies have confirmed that after treatment with antidepressants, there is an increase in the volume of gray matter and proper neural activity in the regions of the brain that are most probably associated with the symptoms of depression. Since it was observed by Michael Merzinich that our brain is highly plastic, which means the nerve cells of the brain can be changed or adjusted, we can say that the neurons of the brain are modifiable. This change takes place in response to intrinsic and extrinsic factors. When it was discovered by scientists that neurons can be developed through the human hippocampus, a new ray of hope arose for a new kind of therapeutic treatment for depression as well as patients going through mood disorders. The suppression of neuroplasticity takes place in the hippocampus due to the high level of plasmatic cortisol. According to a study, it was observed that excessive glucocorticoids can cause impairment in the function of the glial cells by increasing glucose transportation in astrocytes, limiting their capacity to aid neurons, and causing impairment in the glutamate accumulation of the synapses. Sadness and negative effects in depressed patients can lead to disruptions in the activity of the prefrontal and parietal cortex. The activity that takes place in the sublingual cingulated increases. Any kind of disruption in this neurological pathway can lead to the effects of negative mood and altered emotional responses. Stress and a high level of cortisol can induce atrophy in certain regions of the brain. It has been found through research that prolonged stress can cause impairment in the development of the dendritic spines and synaptic connectivity in the amygdala. This most probably affects the brain in a negative way and causes a negative neuroplasticity effect, enhancing the recall of negative emotions and fear learning mechanisms.

In recent studies, DMN has shown greater variability in the pathological system of depression. DMN (Default Mode Network) is a system of connected brain areas that shows increased activity when a person is not focused on what is happening around them. Recently, it has been observed that depressed patients show overactivation of the function of DMN. Certain antidepressants mainly help with the mechanism of neuroplasticity. Its main function is mainly to repair the neurally impaired circuits, strengthen synapses in certain brain areas, or normalize glutametase levels. In cases of major depressive disorders, neuroplasticity is badly affected, which involves difficulties in the hippocampus involved in learning and memory, the prefrontal cortex helping in attention, concentration, and memory in the amygdala [14].

The Neurotrophic Factors and Neural Plasticity

The first neurotrophic factor, NGF, was discovered in the 1950s. BDNF was discovered in the 1980s, and these two compounds established the neurotrophin family; the other two neurotrophins are NT3 and NT4, which were discovered.

The release of neurotrophins is activated by neuronal activities. They mainly see through the functions of neuronal survival and differentiation, synaptogenesis, and plasticity in an activity-dependent way.

The physiological response to the neurotrophins is mainly arbitrated by their binding to the tyrosine kinase receptor family (Trk) and the p75 neutrophin receptor. NGF binds to TrkA; BDNF and NT4 bind to TrkB. When tyrosine kinase receptors are bound to neurotrophins, ligand-receptor dimerization and autophosphorylation will be induced.

BDNF is first synthesized as proBDNF. BDNF activates the tyrosine kinase receptor and subsequently promotes neuronal survival, neuroplasticity, and synaptogenesis through different signaling pathways. Activated Trk receptors circuit tyrosine kinase substrates, including P13K and PLC [14].

In the peripheral nervous system, neurotrophic factors are consecutively released in minute amounts by the target cells to regulate survival and process the outgrowth of developing neurons. To act as a mediator of activity-dependent plasticity in the central nervous system, neurotrophins need to be released and act in an activity-dependent manner. Neurotrophins are regulators of activity-dependent plasticity. Neurotrophins and their proforms mediate synaptic strengthening and dendritic retraction. This dual action is regulated by the neuronal activity that controls the expression and secretions of BDNF, the cleavage of proBDNF, and plasma membrane translocation. When two axons are competing for the intervention of two target neurons, a functional connection eventually forms between the two active neurons, and the less active neurons retract. Neuronal activity promotes the release of BDNF and pro-BDNF.pro-BDNF.

CONCLUSION

Neuroplasticity can be a cure for depression as it increases skill development in human beings. The new adaptivity that people are trying to develop now is an important factor in neuroplasticity. Newer investigational molecules have shown subtle promise in their anti-depressant effects, like the age-old antidepressants and somatic treatment modalities, and these strengthen our belief in the neuroplastic hypothesis of this order. Antidepressant therapies also have the power to overdrive the negative neuroplasticity caused by depression, which in turn has evidenced that antidepressants and neuroplasticity both enhance the mood of an individual in a regular lifestyle. More focus should be given to the non-pharmacological aspect, in which neuroplasticity plays a vital role.

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Conflict of Interest

The author(s) declared no conflict of interest.

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