Review Article

A Review on the role of neuroplasticity in neurodegenerative disorders and its possible pharmacological and non-pharmacological interventions

Abstract

Neuroplasticity is the capability of brain cells to interchange as well as modify for the ultimate cause of higher proficiency to acclimatize to the new situations. Neuroplasticity also plays a very pivotal role in the development and then further progressing of neurodegenerative disorders. The severe adjustments in neural plasticity caused by high pressure, anxiety and other terrible stimuli like stress play a considerable role in the onset and cause of depression. This comprehensive review explores the pivotal role of neuroplasticity in neurodegenerative disorders, shedding light on the dynamic adaptive processes of the nervous system in response to pathological conditions. The paper synthesizes current research findings to elucidate the intricate interplay between neuroplasticity and the progression of neurodegenerative diseases. Furthermore, it delves into potential pharmacological and non-pharmacological interventions aimed at modulating neuroplasticity to ameliorate or mitigate the impact of these disorders. By examining diverse strategies, from pharmaceutical interventions to lifestyle modifications, this review contributes to a nuanced understanding of the multifaceted mechanisms underlying neurodegeneration and offers insights into promising avenues for therapeutic development.

Keywords: Neuroplasticity, Anxiety, Pharmacological, multifaceted, therapeutic

Introduction:

Neuroplasticity can be defined as the ability of brain to exchange and remodel for cause of higher capability to adapt to new situations which sometimes known as neural plasticity or brain plasticity[1]. No matter the fact that the concept of neuroplasticity is pretty new, it is one of the most critical discoveries in neuroscience and has deep linkage with pharmaceutical sciences as it is concerned with all the brain diseases and pathways to some extent [2]. It deals with the capacity of brain to reorganize its response to intrinsic or extrinsic stimuli with the aid of changing its structure, capabilities, or connections after accidents, consisting of a stroke or traumatic brain harm (TBI)[3].The reality is that neuronal networks are not fixed, but occurring and disappearing dynamically at some point of our lives. It occurs when the brain is rewired to function differently from how it did previously[4]. These alterations might be like new connections made along individual neuronal pathways such as cortical remapping or neural circulation. Other types of neuroplasticity include cross-modal reassignment, homologous area adaptation, and map expansion modifications brought on by learning a new skill, knowledge acquisition, environmental factors, practice, and psychological

stress are all examples of neuroplasticity[5]. Neuroplasticity leads to many different occurrences, such as habituation, sensitization to a certain position, medication tolerance, even recovery following brain injury[6]. Neuroscientists long believed that neuroplasticity only appeared in children; however studies conducted in the later part of the 20th century revealed that many adults also exhibit neuroplasticity[7]. Also the neurotransmitters influence the neuroplasticity to some level as they are essential components of synapse as synapse cannot be preceded without neurotransmitters directly dealing with several modifications in neuroplasticity. The most interesting neurotransmitters involved are acetylcholine, dopamine, and serotonin in mediating neuroplasticity. Neuroplasticity is a life-long process that mediates the structural and functional reaction of dendrites, axons, and synapses to experience from new things like learning[8]. Despite the idea that the human brain is adaptable and heavily depends on, neural plasticity, an essential mechanism of neuronal version and novelty, is disrupted and despair in neuronal disorders. The severe adjustments in neural plasticity caused by high pressure, anxiety and other terrible stimuli like stress play a considerable role in the onset and cause of depression [10].Effective neuronal plasticity additionally relies upon on neurotrophins, which are regulatory factors that help improvement and survival of brain cells. Brain-derived neurotrophic issue (BDNF) is the neurotrophic factor mainly localized in the CNS. Certainly, a few research have shown that the level of BDNF inside the serum of BD patients are decreased on every occasion and patients go through a period of sadness or mania leading to bipolar diseases[11].While the loss in neuroplasticity is slow at some point of regular aging but sometimes this loss is elevated dramatically, causes neurodegenerative diseases like Alzheimer and dementia within a decade of onset of cognitive symptoms[12].Neuroplasticity within the young minds is very strong as we discover various ways to map our brain using all the connections[15].

Mechanistic approach involved in neuroplasticity:

Neuroplasticity is the brain's ability to alter itself continually throughout a person's life, and it may be demonstrated at various levels, with behavioral adaptations and learning and memory at the top of the hierarchy, linking structural changes with functioning[16]. Clinically, it refers to the process of neurological changes that occur following an accident, such as a stroke or traumatic brain injury (TBI). An elemental key premise underlying neuroplasticity is the flexibility of synaptic connections that are continually being removed or rebuilt, with the balance of these opposing processes being primarily reliant on the activity of the neurons. The activity dependency of synaptic plasticity is a crucial idea in general neuroplasticity as well as memory and learning theories that focus on experience induced changes in synaptic functionality and structure[17]. These modifications might be positive (restoration of function following injury), neutral (no change), or negative (can have pathological effects). Synaptic plasticity theory has also expanded to encompass more of the developing complexity of synaptic transmission, which includes: metaplasticity, spike timing dependent and homeostatic plasticity[16, 18].

Besides synaptic plasticity, hippocampal neurogenesis is also one of the considerable mechanisms in structural neuroplasticity. The cellular precursor shown in the hippocampus, particularly in the subgranular zone of the dentate gyrus, is a kind of

astrocyte that exhibits cell proliferation markers[19, 20]. Neurotrophin levels, such as brain-derived neurotrophic factor (BDNF), influence the proliferation of these cells[21]. Glutamatergic and Cholinergic systems are the two prominent systems among the functional molecular changes. In the glutamatergic system, N-methyl-D-aspartate (NMDA) receptors are crucial mediators of activity- dependent synaptic plasticity which is involved in cognitive processes including learning and memory[22]. In the hippocampus, the diheteromeric structure comprising GluN1-N2A and GluN1-N2B subunits predominates. High concentrations of β-amyloid plaques in the hippocampus are known to cause enhanced replacement of NMDA Glu-N2A subunits with Glu-N2B in Alzheimer's disease[23]. Previous research has shown that the cholinergic system is important for LTP (long term potentiation) modulation and induction, as the α7 cholinergic receptor induces the synthesis and release of the neurotransmitters involved in LTP formation, such as glutamate, in presynaptic neurons[24]. In both healthy and pathological states, the alpha7 cholinergic nicotinic receptor plays critical roles in neuroplasticity, neuroprotection and memory recovery. As the α7 receptor is capable of activating phosphoinsitide 3-kinase (PI3K), its activation causes an increase in the phosphorylation of the protein kinase Akt. The binding of BDNF and NGF neurotrophins to their respective receptors may also activate the PI3K/Akt pathway[25]. Among all neurotrophins, brain derived neurotrophic factor (BDNF) distinguishes out as a synaptic plasticity regulator in the adult brain, with structural and functional effects spanning from short to long term. BDNF signaling deficiencies have a role in the development of various important illnesses and disorders including Huntington's disease, Alzheimer's disease, and depression. Depressive illnesses are closely related to BDNF modulation of both glutamatergic and serotonergic transmitter systems; hence, understanding the mechanisms of such impairment could bring novel ways in treatment of neurological diseases[26, 27].

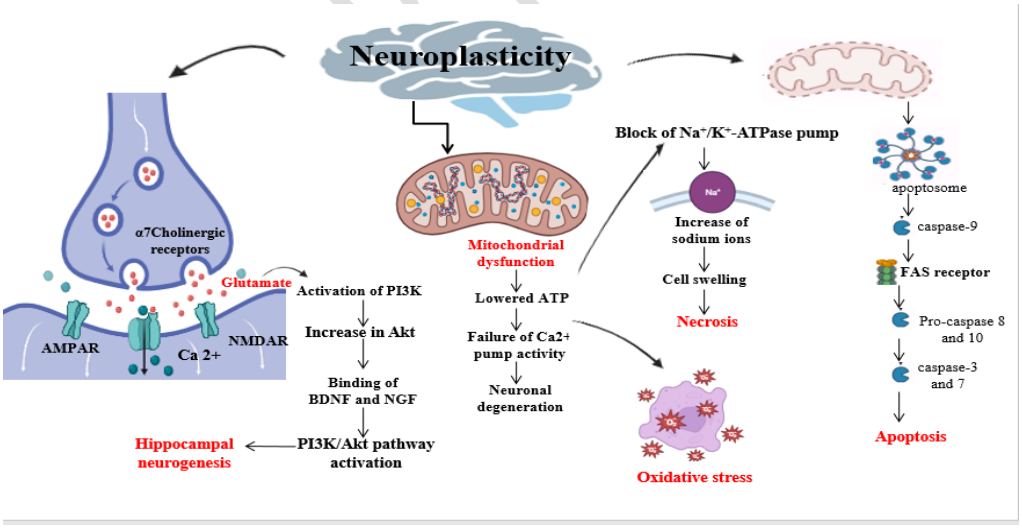

Fig1: Mechanistic approach of neuroplasticity including mitochondrial dysfunction, Hippocampal neurogenesis,Oxidative stress, Block of Na^{+}/K^{+}-ATPase pump, necrosis and apoptosis of cells

Another mechanistic approach underlying the concept of neuroplasticity is functional reorganization which includes equipotentiality and diaschisis. Equipotentiality is the premise that if one side of the brain suffers damage, the opposing side of the brain can compensate for the lost function. Researchers found that unilateral injuries to a region of the left side of the brain produced speech loss despite the opposite side remaining unharmed. Furthermore, it was hypothesized that relearning particular functions, such as speaking, was simpler for a kid than for an adult. This notion evolved into equipotentiality, which means that if the injury occurs early on, the brain may be able to compensate for lost functions[18]. On the other hand, diaschisis refers to the idea that injury to one portion of the brain might result in a loss of function in another owing to a linked pathway[18].

Mechanisms of Neurodegeneration involved in neuroplasticity:

Mitochondrial dysfunction:

Mitochondria have significant roles in regulating neuroplasticity events, such as neuronal differentiation, neurite outgrowth, neurotransmitter release, and dendritic remodeling, through the production of energy. Evidence shows that mitochondrial failure is visible in neurodegenerative diseases because it lowers ATP creation, with mitochondria accounting for around 90% of ATP production[28]. Aside from energy metabolism, mitochondria are critical regulators of apoptotic pathways. The transport of mitochondria is critical for neuron survival due to the necessity for their optimal distribution in areas with a higher need for ATP and calcium, such as the synapse. Because the creation and transmission of synapses need a high energy demand created by mitochondria present in axonal terminals and neuronal dendrites of pre and post synaptic terminals, the quantity of ATP produced directly interacts with synaptic plasticity[29]. Insufficient ATP synthesis in the cell might result in failure of Ca2+ pump activity in the plasma membrane and the endoplasmic reticulum with Ca2+ exhaustion. As a result, oxidative stress can limit the mitochondria's capacity to produce ATP[30]. BclxL, a member of the Bcl2 protein family, functions as an anti apoptotic protein by inhibiting the release of mitochondrial cytochrome c, hence promoting caspase activation and, eventually, programmed cell death. As a result, it is not unexpected that mitochondrial dysfunction and signaling are implicated in reduced neuroplasticity and neuronal degeneration in Alzheimer's disease, Parkinson's disease, mental disorders, and stroke[27].

Necrosis:

Cell death through necrosis is a degenerative process, that when engaged, it stimulates the immune system response. This difference in the composition of cell produces an inflammatory mode of response, with stimulation of immune system factors such as lymphocytes, macrophages, ILS and transcription factors (TNF)[31]. Furthermore, activation of this system impacts surrounding cells and the environment, which might result in chain death. During necrosis, mitochondrial function changes, lowering ATP synthesis and, as a result, blocking the Na^{+}/K^{+}-ATPase pump, producing cell swelling owing to an increase of sodium ions in the cell cytoplasm[32]. Necrosis was always thought to be an unintended cell death caused by a physicochemical insult. However,

recent genetic data and the development of pharmacological inhibitors of the process have revealed the presence of several necrosis regulatory routes. One of the most common kinds of programmed cell death, for example, necroptosis has implicated in neurological illnesses, and its inhibitor, necrostatin 1, has been proven to be useful in degenerative conditions such as Huntington's disease sclerosis. Necrostatin 1 was shown to play a function in neuropathic pain, and it was also discovered that this tiny molecule reduced neuroinflammation and necrotic cell death[33]. It was also demonstrated that intravenous treatment of necrostatin 1 decreased amyloid-aggregation and alleviated cell death associated with Alzheimer's disease pathogenesis. As a result, Nec-1 and necrosis inhibitors have therapeutic potential in neurodegenerative disorders and chronic pain.

Apoptosis:

Apoptotic cells contain distinct morphological features such as chromatin condensation, DNA breakage, lack of attachment to neighboring tissue, and specialized structures such as microvilli. The creation of cytoplasmic vacuoles happens during the apoptotic process, which means that the cell loses liquid and separates into microscopic fragments known as apoptotic bodies[32]. Apoptosis can be induced by either an extrinsic pathway involving the activation of death receptors in the cell membrane or an internal (or mitochondrial) pathway involving intracellular stress. Apaf-1 is an apoptosome complex that needs the presence of cytochrome c, which is produced by mitochondria during apoptotic activation[34]. Once the apoptosome develops, caspase-9 cleaves and induces the cleavage of additional caspases, such as caspase-7 and caspase-3. Bcl-2 family members are found in the mitochondria (intrinsic pathway), the organelle that governs cell death. Cytochrome c, together with Apaf-1 and pro-caspase-9, produces the apoptosome, which triggers the apoptosis cascade[35]. Ultimately, activation of Bax or Bak results in the development of the apoptosome, which causes cell death by the action of caspases[35]. The extrinsic route, which is known to include death receptors, is another sort of pathway that produces neuroplasticity. TNF and TNF-related apoptosis-inducing ligand are their ligands, and TNFR-1 and FAS/CD95 are their receptors. In the case of the Fas receptor, this protein binds to intracellular caspases such as pro-caspase-8, resulting in the creation of a complex known as the death-inducing signaling complex[36]. This complex will cause autoclaving and activation of the other caspases, which may have a disruptive impact, such as interfering with the mitochondrial pathway or causing neuronal alteration or death.

Oxidative stress:

Another mechanism that might cause cell death is oxidative stress, which occurs when the synthesis of oxidizing agents surpasses the capacity of antioxidants. Oxidative stress causes oxidation of cellular elements such as lipids, proteins, and DNA, which results in cell death[37]. When compared to other tissues, nervous tissues are more vulnerable to this type of damage due to high calcium flow through the neurons; the presence of excitatory amino acids, primarily glutamate; and the high rate of molecular oxygen consumption and deficiency in antioxidant defenses. Free radicals are unbound electron entities that rapidly react with other compounds[38]. They are thought to be the primary cause of widespread aging and the decrease of biological functioning, and they

are responsible for both physical and mental aging. They act more intensively and quickly in the brain, causing disorders ranging from moderate memory loss to neurodegenerative illnesses[28].

Diseases involved in neuroplasticity:

Depression:

Depression is an illness characterized by persistent sadness and a loss of interest in activities that you normally enjoy, accompanied by an inability to carry out daily activities, for at least two weeks to many months[39]. A depressive episode is different from regular mood fluctuations like anxiety, stress, insomnia and sleeping sickness [40].This depressive episode can be categorized as mild, moderate, or severe depending on the number and severity of symptoms, as well as the impact on the individual's functioning. The usual term confused with the depression is the state of anxiety which is a different sort of mental disorder Anxiety is a feeling of fear, dread, and uneasiness[41]. Trouble concentrating or thinking about anything other than the present worries all are the denoting terms of anxiety. The other disorder which is usually a cause and factor of anxiety and depression, also effect neuroplasticity is the insomnia. Insomnia is a common disorder that can make it hard to fall asleep or cause you to wake up too early and not be able to get back to sleep[42]. The condition can be short-term (acute) or can last for a long time (chronic). Acute insomnia lasts from 1 night to a few weeks. Insomnia is chronic when it happens at least 3 nights a week for 3 months or more [43]. Insomnia may be the primary problem, or it may be associated with other medical conditions or medications like depression and anxiety. The other term Sleep apnea causes you to stop breathing periodically throughout the night, interrupting your sleep a cause of negative plasticity[44][46]. A large variety of transmitter theories have been put forward over the years has recently been discussed.

Recent studies on the link between the depression and neuroplasticity has shown that low level of some neurotransmitters leads to the negative neuroplasticity (degradation of neuronal pathways). In experimental studies the depressed person is shown to have low level of dopamine (Happy hormone). Dopamine is the neurotransmitter released in your brain which makes you feel happy; dopamine helps nerve cells to coordinate themselves properly. *Homovanillic acid* (*HVA*) is also an important factor, or a major catecholamine metabolite that is produced by a consecutive action of monoamine oxidase and catechol-O-methyltransferase [47].The situation of decreasing dopamine and HVA leads to incompletion of synapses (a passage of message conduction) is a major reason of decrease in neuronal neuroplasticity. The level of dopamine decreases due to increased reuptake of dopamine and HVA or due to down regulation of the receptors of dopamine lead to the insensitivity of the receptors[48]. If the synapses fail to progress due to the low level of dopamine and HVA this disturbance lead to neuroplastic basis of depression because brain cannot reorganize and recollect its connection and remain in the state of sadness and lower activity.

The second basis is the level of serotonin and its metabolite, 5-hydroxyindolaceticacid (5-HIAA); these neurotransmitters are greatly concerned with the neuroplasticity as they are involved in the conversion, reorganization or conduction of nerve impulses from

spinal cord to brain. The decrease level of these neurotransmitters hinders the normal passage of synapses leading to the neuroplasticitic changes in patient with in the central nervous system[49]. On the basis of methodologically well-standardized studies, it would seem that, on average, depressed persons show approximately 25 % lower 5-HIAA concentrations in spinal fluid than healthy subjects. On the other hand, the findings of several research groups would indicate that a low 5-HIAA concentration in spinal fluid is connected with increased suicidal behavior and aggression. The information regarding multiple serotonin receptors and brain serotonin subsystems will contribute that the decrease in dopamine, homovanillic acid, 5-hydroxyindolaceticacid, serotonin lead to various neuropsychiatric disorders caused by neuroplasticity, including depression and anxiety states by disturbing the neuronal pathways[50].Findings related to imipramine binding sites(serotonin binding site) in the presynaptic neuronal endings and in thrombocytes are of special interest[12]. There is clear evidence that in patients with depression and in persons who have committed suicide, the functioning of this binding site (so called imipramine receptor) may be impaired and altered which result in the breakdown of brain connections a major mechanism seen in neuronal plasticity. The binding site of imipramine is closely related to the re-uptake mechanism located in serotonin neurons. In patients with depression, changes found in imipramine binding site (also called serotonin binding site) may thus reflect disorders in 5-HT transporter activity and a central serotonin turn over deficit cause disturbance in synapses. Molecular studies performed on patients with depression seen that disturbance in the binding sites of neurotransmitters also lead to depression and anxiety due to disturbance in normal synapses process caused by negative neuroplasticity[51].

Depression can be a result of several functional disorders of the endocrine regulatory systems caused by neuroplasticity. The activity of the hypothalamus hypophysis axis (a gland responding in stress conditions) varies frequently in healthy subjects and depress patients. Abnormalities in several hypophysis hormones have been indicated in negative neuroplasticity leading to depression due to excessive stress as this type of patient cannot handle stress properly[52]. Changes in the functioning of the CRF-ACTH axis can thus have an extensive effect on the functioning of the brain because it has deep connection with neuronal growth leading to degradation of specific parts of brain (negative neuroplasticity).[11] Research upon brain functions, neuroplasticity and the immune system gives a unique opportunity to increase our knowledge of the mechanisms and interactions of these functional settings. During recent years a number of studies have been performed on the possible association between psychiatric disorders, such as depression, stress and specific immune-related disorders [53]. The studies shown that a decrease lymphocyte function after stress and excess period of sadness is also a cause of negative neuroplasticity lead to depression. However, current results shown the possible association between depression or neuroplasticity and increased morbidity and mortality due to these disorders involving the immune system are largely conflicting [54]. The corticosteroid overdrive and noradrenergic hyperactivity in neuronal connection cause degeneration of brain parts, which may ultimately impair the normal functions of the immune system. Thus, decreased lymphocyte numbers have been reported in depressive patients. However, some patients suffering from major depression may be T-immuno suppressed and this link

indicates the synaptic disturbances in these patients caused by negative neuroplasticity[55].

Bipolar disorder:

Bipolar disorder can be generalized into two main subtypes: BD type I and BD type II. BD type I is linked with at least one manic episode, characterized by increased energy, libido, and grandiose thinking followed by hypomanic or severe depressive episodes[56]. By contrast, BD type II is characterized by no manic episodes and at least one hypomanic and depressed episode. Because it supports the brain's cognitive processes; attention, memory and specific cognitive functions —the parietal lobe (PL) plays a major role in the course of BD[57]. Despite substantial study, the etiology of bipolar illness remains unknown, however genetic and environmental variables have been linked to the development of this condition. Sensory-motor interactions have the ability to revive neuroplasticity, which was previously believed to be latent in the adult neocortex, which has the potential to modify the pattern of neural connections[57, 58]. Neuroplasticity, which is referred as the development of new brain cells, or reconstructing the existing neural circuits induced by several factors, which have manifest to strengthen connectivity in a bipolar depressed brain[59]. Lithium has neurotrophic and neuroprotective benefits; magnetic seizure treatment lowers cortical inhibition; mindfulness-based cognitive therapy (MBCT) strengthens mindfulness and emotion management; and physical exercise promotes happiness, serenity, and greater cognitive performance[60].

Bipolar disorder is well known to contain neurocognitive impairments; this is particularly true when psychosis is included, as opposed to BD alone. Research indicates that distinct activity and connectivity in the precuneus, inferior parietal lobe and inferior frontal lobe in response to affective stimuli may be interpreted as potential risk markers for BD[61, 62]. The prefrontal cortex's (PFC) structural and functional plasticity has demonstrated the brain circuitry's incredible ability to adapt to behavioral events, especially throughout early infancy and adolescence[62].According to recent findings, the primary neuropathological insights in BD appear to be modifications in neuronal plasticity, specifically in cell resilience and connectivity[57]. Data from several streams of research points to BDNF as a significant contributor to the pathophysiology of BD. A growing amount of research suggests that BDNF is connected to the way that mood stabilizers and antidepressants work. In addition, BDNF is also involved in a variety of neural processes during the development of both humans and animals. Primarily, BDNF is important for neurogenesis, neuronal survival, and the proper maturation of neural development pathways. In adults, long-term memory consolidation depends on BDNF in addition to dendritic development and synaptic plasticity[66].

The genomic structure of BDNF is quite complex. It is thought that the exact control of BDNF production is mediated by this complex set of genomic promoters. Research indicates that people with significant depression may have lower levels of BDNF messenger RNA (mRNA) expression in their peripheral blood mononuclear cells[67]. Furthermore, studies have demonstrated a decrease in the expression of BDNF

messenger RNA (mRNA) in peripheral blood mononuclear cells of individuals suffering from significant depression. Evidence suggests that BDNF gene's involvement in chromatin remodeling may be linked with the detrimental effects of stress and with antidepressant response. More precisely, a study about a mouse model of depression showed that chronic defeat stress, exhibits a downregulation of *Bdnf* mRNA expression in the hippocampus. This impact was mediated by repressive histone methylation, which in turn caused the production of Bdnf transcripts III and IV to decline[68]. A subsequent study revealed that in rat cortical neuronal cultured cells, the mood stabilizers valproate and lithium enhanced Bdnf transcript III. Together, these findings provide compelling evidence that mood stabilizers and antidepressants may have significant influence on the control of BDNF transcription[69,71,66].

Aging:

Aging is a complex and multifactorial phenomenon associated with progressive loss in function across multiple systems, including sensation, cognition, memory, motor control, and behavioral capacity[73, 74]. Aging can occur at molecular, cellular, and histological levels in various organs, specifically at the central nervous system (CNS) and particularly in the brain. In recent times, however, an alternative perspective has become evident that, based on considerable experimental work, demonstrates that as people age, brain plasticity proceeds with negative consequences begin to dominate brain functioning[75]. Neuroplasticity, which is the nervous system's capacity to rearrange its connections, structure, and function in response to both internal and external stimuli. In addition to acting as a modulator of responses to neuronal damage and attrition, it serves as a substrate for memory and learning (compensatory plasticity). This continuous process in reaction to neuronal activity and injury has been linked with alterations in structural and functional processes of dendrites, axons, and synapses. The compensation mechanism for neuron loss in the aging brain is through expanding dendritic arbors and synaptic connections. However, mechanisms of neuroplasticity may vary with age, and occur in many variations and in many contexts, while common areas of plasticity that emerge across diverse CNS conditions include experience dependence and circuit training[76, 77].

Alzheimer's disease:

Alzheimer's disease is a progressive brain disorder characterized by memory loss (dementia) in which brain loses its capacity to carry out simple tasks. Alzheimer's disease is the most common cause of dementia which is a gradual decline in memory, thinking behavior and social skills. Memory loss is the key symptom of Alzheimer's disease. Early signs include difficulty remembering recent events or conversations. But it gets worse with time and other symptoms develop as the disease progresses. Alzheimer's disease signs towards the shrinking of brain and brain cells leading towards neuronal death caused by negative neuroplasticity effect [93][94].The major cause of an Alzheimer's is the damage of various parts of the brain caused by neuroplasticity changes hence Alzheimer has a deep linkage with neuroplasticity. The major mechanism is the loss of connections between nerve cells (neurons) in the brain due to break down of neuronal pathways as happen in negative plasticity (degradation of brain).The disturbed pathways also cause disturbance in the activity of neurons.

Neurons transmit messages between different parts of the brain, but not to specific part (target sites) but in faulty areas leading to loss in the functioning of brain gradually. Hence, deterioration of the memory by the loss of neuroplasticity is a major cause of Alzheimer's disease[95][96].

Parkinson's disease:

Parkinson's disease is a brain disorder that causes unintended or uncontrollable movements, such as shaking, stiffness, and unsteadiness due to disturbance in balance and coordination in various brain parts usually caused by loss in neuroplasticity (the degradation process of brain).As the disease progresses, patients may have difficulty in walking and talking. Symptoms usually begin gradually and worsen over time. Patient may also have mental and behavioral changes, sleep problems, depression, memory difficulties, and fatigue [101].

Diagnostic approaches to psychological disorders:

Brain Imaging tests mainly include CT scan, MRI and PET scans providing detailed images of your brain parts and all diagnostic tests concern about the loss of neuroplasticity in brain regions. They can detect brain activity and areas of disease or damage along with sites of blockage of synapses so we can easily detect which type of psychological disorder patient is suffering from [59].The most important is a computerized tomography (CT) scan provides a series of X-ray photographs taken from distinctive angle of your brain and uses computerized processing system to create cross-sectional pictures (slides) of the various parts of the brain including the blood vessels and soft tissues inside your brain. CT scan provides exact statistics than simple X-rays diagnosis [50]. Magnetic resonance imaging (MRI) is one of the most commonly used diagnostic tests in neurology and neurosurgery. MRI scanners create images of the brain with the use of a huge magnetic and radio waves.

PET (positron emission tomography) scan is an imaging technique that uses radioactive material to diagnose a variety of brain disorders. In general, PET scans may be used to evaluate normal functioning of neurons for the presence of disease or not. PET may also be used to evaluate the function of neurotransmitters in brain [14].

Dopamine active transporter scan (DaT scan), a diagnostic test helps in the detection of Parkinson's disease as well as depression. In this the tracers used for DaT scan adhere itself to the dopamine transporter, a receptor found on dopamine releasing neurons. Several hours after the tracer has been injected, special imaging equipment scans the brain to detect the normal level of dopamine [15]. The disturbances in dopamine level in brain indicate the effect of negative neuroplasticity (degradation of dopamine neurons) hence we can detect Parkinson's disease and depression easily[17].

Pharmacological interventions for diseases related to neuroplasticity:

The key therapeutic aims for **insomnia** are to increase sleep quality and quantity while also eliminating associated daytime deficits[21]. In these cases, adequate cognitive behavioral therapy (CBT) should be undertaken. In individuals with chronic insomnia, combined CBT and medication had no consistent advantage or disadvantage over CBT

alone. Hypnotics presumably act either by blocking neurotransmitters that promote arousal or facilitating the neurotransmitters that drive sleep. Hypnotic agents (benzodiazepines and non-benzodiazepines) facilitate GABA receptors[22]. Most of the agents that block wake promotion are histamine antagonists (usually H1 receptor antagonists, such as diphenhydramine, doxepin, low-dose mirtazapine, novel selective H1 receptor antagonists, and 5 HT2A antagonists). Orexin receptor antagonists also produce sleepiness with much greater and longer effects in man[63]. Ramelteon, a synthetic melatonin receptor agonist (MT1 and MT2 receptors), is FDA-approved for the treatment of sleep-onset insomnia in adults, and for sleep maintenance insomnia only by the European Community Agency, but is not approved for use in children and adolescents. It is likely that hypnotics work by inhibiting the neurotransmitters that stimulate wakefulness or by promoting the neurotransmitters that promote sleep.

Antidepressants can counteract the detrimental neuroplasticity that depression induces. Antidepressant medication should be beneficial for all individuals with depression in order to attain clinical remission. According to recent research, people on antidepressant treatment who are clinically remitted also tend to have higher quality of life[24]. An increase in the functional connectivity in both subcortical and neocortical regions—differing portions of the prefrontal cortex—has been found in individuals who have received antidepressant medication. Research has indicated that antidepressant medications have the opposite impact on neuroplasticity. Antidepressants have been shown to boost functional connectivity, increase neurogenesis in the hippocampus, and change cellular signaling. An increase in neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), mediates this effect by activating tyrosine kinase receptors and initiating an intracellular cascade that includes mitogen-activated protein kinase, cAMP-dependent protein kinase A, and other molecules[25]. In a comparative research, participants receiving citalopram or escitalopram, two selective serotonin reuptake inhibitors, demonstrated reduced limbic activity and restoration of front parietal network activity during a cognitive task. Elevated serotonin levels at synapses can initiate intracellular processes that enhance neuronal plasticity. It has been demonstrated that escitalopram treatment raises blood levels of brain-derived neurotrophic factor (BDNF), which in turn stimulates hippocampal neurogenesis[126]. Treatment with tianeptine was shown to enhance granule cell proliferation and inhibit the retraction of apical dendrites of hippocampal pyramidal neurons via interacting with the NMDA receptor. Similar outcomes were shown when fluoxetine was used to inhibit the effects of stress in the prefrontal cortex. Ketamine is an NMDA glutamate receptor antagonist that has garnered popularity as a potential novel antidepressant medication in recent years. It has been established that long-term ketamine use increases dopamine levels and synthesis. The main issue with ketamine treatment is that it can have psychotomimetic effects[67].

According to a theoretical definition, Cognitive Enhancer Drugs (CEDs) are substances that can improve cognitive abilities in **brain aging**. This systematization allows CEDs to be categorized as substances intended to potentiate more particular cognitive domains, primarily affecting general or psychological components of cognition[68]. Methylphenidate and modafinil, in this regard, are excellent representatives of a class of compounds that generally alter psychological traits including alertness, focus, and

memory. Methylphenidate works by activating the cortical dopaminergic and noradrenergic transmission networks, which is how it promotes attention or "vigilance." This mechanism of action was initially reported in preclinical settings and then validated by PET in human investigations[29]. It has been demonstrated that oral methylphenidate (0.25 mg/Kg) treatment promotes a 50% blockage of the dopamine transporter[130]. Another medication that affects vigilance or "attentional" states is modafinil. The substance was initially described as a way to combat narcolepsy-related excessive drowsiness. Extracellular dopamine concentrations rise as a result of modafinil's binding to forebrain dopamine transporters. By blocking the enzymes that break down acetylcholine, known as acetylcolinesterase inhibitors, or AChEIs, classical CEDs improve the cholinergic tone of the brain[31]. In older, healthy participants, rivastigmine has been demonstrated to have a deleterious effect on episodic memory while improving motor learning and visuospatial abilities. Memantine, galantamine, and donepezil are examples of drugs that target the clinical phases of **Alzheimer's disease** with noticeable cognitive symptoms. These drugs are suggested for mild to moderate AD or for moderate to severe AD. Cholinesterase inhibitors and N-methyl-D-aspartic acid (NMDA) receptor antagonists are the two currently authorized medications for the symptomatic treatment of AD[132]. Both of these medications, however, only offer very brief symptomatic relief, and their effectiveness decreases dramatically as the illness worsens. Only galantamine, donepezil, tacrine, rivastigmine, and memantine have received approval for the treatment of AD among the cholinesterase inhibitors at present[133]. Previous research by the authors revealed that donepezil increased cholinergic activity in the brain inhibits neuroinflammation induced by an experiment through the α7-nAChRs/phosphatidylinositol-3-kinase-Akt pathway, indicating that this system could serve as a foundation for the development of new drugs to reverse neuroinflammation[34]. The use of traditional anti-amyloid medications is frequently combined with therapeutic approaches that target secondary mechanisms other than the pathologies caused by amyloid and tau. Lithium has several modes of action, one of which is inhibition of glycogen synthase kinase 3-β (GSK3-β). Numerous pathways, including those involving inflammation, neuronal polarity, and cell membrane signaling, are regulated by GSK-3β[26]. It has been shown that long-term lithium or valproate medication reduces the transcription of Homer1b/c in brain areas that are uniquely linked to the pathophysiology of BD. Lithium is still recommended as one of the first-line monotherapies for bipolar prophylaxis due to the compelling evidence that it lowers the frequency and intensity of relapses. It works well to avoid manic episodes as well as depressed ones; however, it seems to work better in preventing mania[35]. Lithium has several therapeutic benefits, one of which is immune system regulation. This entails bringing elevated proinflammatory cytokine levels in affective episodes back to normal, leading to a state of both clinical and neurobiological remission. Additionally, there is proof that antipsychotic medications with anti-manic characteristics have neuroprotective qualities. Olanzapine, Risperidone, and Quetiapine are recommended as first-line monotherapy when treating mania and mixed episodes acutely[36]. This is especially true if symptoms are severe or accompanied by aberrant conduct. Olanzapine has been shown to affect Glu neurotransmission, as evidenced by an increase in serum Glu levels and the Glx/creatine ratio in the ACC of schizophrenia patients. Finally, riluzole, a glutamatergic modulator licensed to treat amyotrophic lateral

sclerosis (ALS), has showed potential as monotherapy or augmentation therapy. Open-label research also revealed that riluzole in conjunction with lithium might be useful in the treatment of bipolar depression[36].

The majority of pharmacologic therapies for Parkinson's disease motor symptoms are dopamine-based. Initial therapy includes levodopa preparations, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors. Anticholinergic drugs (e.g., trihexyphenidyl) are effective for young people with pronounced tremor, but they must be used with caution due to the risk of side effects, particularly those involving cognition[37]. Although levodopa improves function, it increases the risk of dyskinesia, especially at larger dosages. MAO-B inhibitors and dopamine agonists provide less symptom alleviation but lessen the risk of dyskinesia. Several drugs can be used in conjunction with levodopa. Unlike levodopa, which requires increasingly frequent dosage over time, MAO-B inhibitors and dopamine agonists are dosed 1 to 3 times daily (depending on medication and formulation) throughout the illness course. Catechol-O-methyltransferase inhibitors and MAO-B inhibitors suppress enzymes that breakdown dopamine, extending levodopa's benefits. Quetiapine is the easiest antipsychotic medicine to administer; hence it is extensively used in clinical practice despite the lack of efficacy found in clinical trials. The likelihood of effectiveness and adverse effect profiles are used to choose appropriate medical therapies for nonmotor complaints. In conclusion, treatments such as deep brain stimulation and therapy with levodopa-carbidopa enteral suspension can benefit those who have drug-resistant tremor, symptoms that increase after the medicine wears off, and dyskinesias[37].

Non-pharmacological interventions for diseases related to neuroplasticity:

First of all change in lifestyle is the most important factor which involves alter food options to your thinking habits [110]. One of the important aspect of non-pharmacological treatment is, Naturopathy, a system of treatment strives to find the cause of disease by understanding the body, mind and spiritual energy. In this we concern the life style changes for betterment of neurological connections and move towards natural or more organic things that help improving patient mental health. Chinese or oriental methods are also present which divide the brain into five elements all concerning to potentiate the neural connections of brain leading to increased focus and concentration diverting negative thoughts caused by neuroplasticity in depression[41] .This procedure is helpful in bipolar disorder, brain aging and Alzheimer’s disease. The certain types of organic herbs are also prescribed which targeting the various brain regions and potentiate them according to patient mental condition [22].

Physical and mental exercises are very helpful to treat psychological disorders as theses exercise have direct connection with the neuroplasticity[53]. Cognitive training including learning new skills and practicing focus on some point or topic leads to enhance neuroplasticity as these exercises involve creating new pathways along with previous neural connections prolonging synapses process help increasing neuroplasticity. Travel towards nature also heals brain physiology and get over from depression like states including anxiety. Meditation a simple practice of turning your attention to a single point of reference can involve focusing on breathing or brain

sensations. It means turning your attention away from distracting thought and focusing on the present moment help in improving the health of neurons and release of transmitters [64]. This is very helpful in the positive neuroplasticity and treatment of depression. Yoga practices based on exercises and meditation procedures also facilitate the enhancement of physical or mental health. This therapy is used to relive patient from stress for peace of mind. Yoga includes different positions or postures either sitting or standing in fresh environment help calming your mind and soul also smoothens neuronal connections majorly helpful in brain aging[115]. Behavioral therapy is also helpful it means altering behavior of psychological patient which is done in rehabilitation centers or by help of caring staff [86].

Aromatherapy is the use of selected fragrances to alter mood and restore energy of body and mind. It is used to relieve tensions or give soothing effects. Phytochemicals are a chemical compounds that occur naturally in plants[77] it is believed that these chemicals help prevent psychological diseases and stimulate the release of neurotransmitters like dopamine ,enhancing neuroplasticity leading to treatment of depression, bipolar disorder, brain aging along with Alzheimer's and Parkinson's disease. Calorie restriction and changing your eating habits has a great influence on your mind and soul. Calorierestriction is a dietary strategy that reduces the energy intake from foods and beverages without incurring malnutrition. It is very important concept these days .Calorie restriction also involves avoiding synthetic and packed food along with many kinds of beverages leading towards aging[89]. A new study finds that reducing caloric intake may slow the pace of brain aging as well according to some biomarkers [97].Occupational Therapy is an important non pharmacological treatment of Parkinson' disease. As Parkinson's progresses, everyday tasks may become difficult for patients. Occupational therapy can help them manage everyday tasks and maintain their independence for as long as possible, as well as improve their quality of life. Occupational therapy can help people with Parkinson's disease stay active in daily routine by balancing neuroplasticity.

Conclusion:

By this review we have investigated into the convoluted interaction amid neuroplasticity as well as disorders such as neurodegenerative disorders as, psychiatric disorders,in addition to neurological injuries. Both pharmacological as well as non-pharmacological intrusions have arisen as vital treatment in using neuroplasticity for therapeutic purposes. Some pharmacological agents directing as an explicit neurotransmitters and encouraging neurotrophic factors display potential in moderating synaptic plasticity as well as neuronal connectivity. In the meantime, non-pharmacological mediations, counting as cognitive training, physical exercise, as well as neuromodulation practices, have confirmed activities to persuade valuable structural as well as functional variations in brain.Notwithstanding the advancement made considerate neuroplasticity. Additional research is needed to unravel the intricate mechanisms underlying neuroplasticity in diverse disorders as well as to enhance pharmacological and non-pharmacological interventions for individual as well as targeted treatment approaches.

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