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Review Article

The Role of Brain-Derived Neurotrophic Factor in Different Psychiatric Disorders and Neurodegenerative Diseases

Suzan A. Hamza[1*], Namir I. A. Haddad[1], Gheyath AL Gawwam[2]

[1] Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.
[2] Department of Neurology, College of Medicine, University of Baghdad, Baghdad, Iraq.
* Corresponding author's email: suzan.adnan@sc.uobaghdad.edu.iq.

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ABSTRACT

Brain-derived neurotrophic factor is a widely studied neurotrophins found throughout the mammalian central nervous system. These neurotrophins regulate numerous aspects of neuronal and oligodendroglia development and function, including axonal growth, synaptic plasticity, differentiation, proliferation, survival, and apoptosis. Brain-derived neurotrophic factors have a significant impact on neurodegenerative disorders, synaptic plasticity, and the formation and maintenance of a normal brain circuit. Precise regulation of Brain-derived neurotrophic factor concentrations, including their controlled release at the transcriptional and translational levels, is essential for the correct functioning of the central nervous system. This review provides a summary of the role of Brain-derived neurotrophic factor in various neurological and mental disorders. In addition, to its role in memory recognition by increasing neuronal proliferation and survival in the perirhinal cortex, a vital area for recognizing objects in memory.

Introduction

Several polypeptide factors are essential for neuronal plasticity, survival, neurite outgrowth, and differentiation, and one of these is brain-derived neurotrophic factor (BDNF) [1]. Multiple mammalian studies have focused on BDNF because of the multiple cellular processes it controls in oligodendroglia cells and neurons during development and maturation, such as differentiation, proliferation, survival, axonal growth, and synaptic plasticity [2]. Two regions of the central nervous system (CNS) that contain high concentrations of the neurotrophins neuron growth factor (NGF) include the hippocampus and the prefrontal cortex (PFC). The precursor pro-BDNF can be stored in axons and dendrites and then transformed into BDNF during synthesis. The last BDNF protein is generated via cleavage, which might take either within or outside of cells. Furthermore, exercise determines whether pro-BDNF and mature BDNF are released [3, 4]. Neurons, which can be in several parts of the brain, including the cerebellum, striatum, hippocampus, amygdala, and cortex, are the principal cellular sources of BDNF. The immune system cells that express and secrete BDNF include microglia, astrocytes, endothelial cells, and megakaryocytes. Because the blood-brain barrier is permeable in both directions, BDNF can be released into the bloodstream from both peripheral and cerebral sources. Research in both animals and humans has shown that BDNF levels in the blood correlate with brain BDNF levels [5-8]. Because there is significant control over BDNF expression, even healthy people can have widely varying BDNF levels. Variations in BDNF expression have been linked to both normal and abnormal ageing and mental diseases, particularly in sections of the brain critical for memory processes, like the hippocampus and para hippocampal regions [4]. Several neurodegenerative diseases have been linked to altered BDNF levels and signaling pathways [9]. With the greatest concentrations seen in the frontal cortex and hippocampus, the major effort was investigating the BDNF effects on the CNS. Recent research have demonstrated that BDNF exists in various peripheral organs, including the kidneys, spleen, heart, intestines, thymus, and lungs [10, 11].

Synthesis and expression of BDNF

There are numerous steps involved in the synthesis and maturation of BDNF, and the production of different precursor isoforms is one of them. A protein of 247 amino acids, BDNF has been well-preserved. It is produced and shaped in the endoplasmic reticulum as pre-pro-BDNF, weighing between 32 and 35 kilodaltons. After being transported to the Golgi apparatus, the signal sequence of the pre-region is quickly removed, resulting in the formation of the isoform pro-BDNF (28–32 kDa). The pro-BDNF undergoes further cleavage to produce the mature isoform (mBDNF, 13 kDa). The pro-BDNF and m-BDNF isoforms together are secreted into the extracellular space, Figure (1) [12].

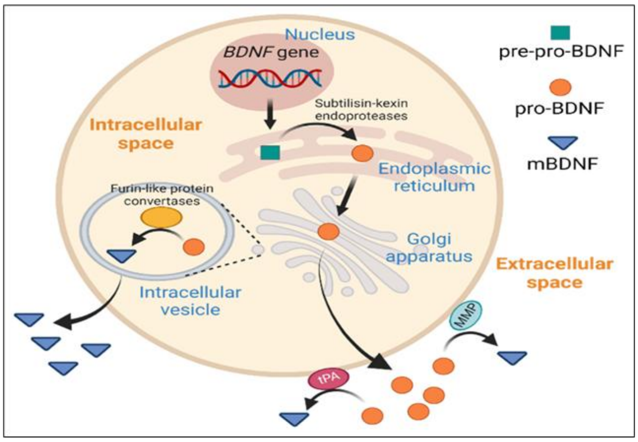

Figure 1: Synthesis of pro-BDNF and mature BDNF (mBDNF).

The pro-BDNF can undergo conversion by metalloproteinases 2 and 9, plasmin, and extracellular proteases [13]. Both the neuronal and non-neuronal cells express the secretory protein BDNF. In neuronal cells, the BDNF immuno-reactivity was found in numerous regions of the central nervous system in addition to the peripheral and enteric nervous system [14-18]. In non-neuronal tissue, the BDNF is synthesized in cells of the immune system, like T cells, B cell and monocytes, muscle cells, thymus, heart, liver and spleen [19-21].

The expression of BDNF in various tissues is controlled during development. Moreover, both normal and abnormal physiological states, along with interventions like physical activity, low oxygen levels, psychological stress, epileptic convulsions, and reduced blood flow, enhance the production of BDNF in specific tissues [22-25].

The human BDNF gene exists on chromosome 11p14.1 and comprises 11 exons (I-XI) and 9 promoters. These promoters control the developmental and regional production of several alternatively spliced mRNA isoforms. The BDNF precursor protein's main coding sequence is found only in exon IX, located at the 3' end of the gene locus [26]. The coding sequence of BDNF is translated into a pre-pro-protein, which contains an N-terminal pre-domain that directs the mRNA to the rough endoplasmic reticulum (rER) the pre-sequence cleaves co-translationally, synthesizing the immature un-cleaved pro-BDNF protein in the ER. The transcription of the BDNF gene into different mRNA variants is closely controlled by the increase in Ca2+ levels generated by electrical activity in neurons [27]. The unique mRNA variations can be carried into dendrites, where localized synthesis and release of BDNF can be limited to particularly active sections of the dendrites, thus enhancing synaptic plasticity in a manner that relies on BDNF. Because of this, BDNF may precisely shape maturing and growing synaptic networks through activity-dependent local synthesis and secretion [28].

Secretion of BDNF

To carry out its functions, BDNF requires secretion via the appropriate cell type at the correct time and location. In contrast to other growth factors, mostly released through a continuous process, the newly produced BDNF is directed towards a controlled pathway that relies on neuronal activity and Ca^{2+} -dependent signaling [29-31]. Once synthesized, BDNF is held in dense core vesicles (DCVs) until it is released in response to an increase in cytoplasmic Ca^{2+}levels, which acts as a stimulus for the process. Two sources can raise a concentration of Ca^{2+} to trigger the release of BDNF: the Ca^{2+} outside the cell and the Ca^{2+} inside various organelles. While the release of BDNF activated by glutamate in brain slices or primary neuronal cultures relies on the release of Ca^{2+} from internal Ca^{2+} reserves, the secretion of BDNF in response to action potential is contingent upon external Ca^{2+} [32-34]. After being released, BDNF and pro-BDNF attach to two different groups of receptors. Initially, brain-derived neurotrophic factor (BDNF) forms a strong connection with a specific member of the tropomyosin receptor kinase family, known as the TrkB receptor. This is a protein that spans across the cell membrane and could add phosphate groups to tyrosine residues, a process known as tyrosine kinase activity. This protein triggers the activation of three signaling pathways, namely Ras/Rap-MAPK, PI3K-AKT, and PLCg-PKC cascades, the activation of these cascades occurs in a ligand-dependent manner, meaning that it requires the presence of the ligand [35-37]. However, pro-BDNF, along with further pro-neurotrophins and neurotrophins, interacts with the p75NTR receptor, which is a dimerization member of the tumor necrosis factor receptor (TNFR) superfamily. The BDNF-TrkB pathway plays a crucial role in controlling and synchronizing several cellular functions, including the survival, growth, and differentiation of neurons during development, activity-dependent changes in the strength of connections between neurons, and the processes involved in memory and learning in the mature central nervous system [38, 39].

Neuronal cells are the most extensively studied among those capable of secreting BDNF. However, numerous findings suggest that astrocytes and microglia can secrete BDNF to [40]. Bones and muscles play a crucial role in the secretion of peripheral BDNF; since resistance training induces more significant stress on bones and muscles, leading to increased expression of BDNF in peripheral tissues. This BDNF is then transported to the brain through the bloodstream and affects the brain after crossing the blood-brain barrier [23, 24]. BDNF secretion is regulated by various stimuli, including neuronal electrical activity, such as depolarization caused by increased extracellular concentration of K+, high-frequency stimulation (HFS), or theta-burst stimulation (TBS). Additionally, neuropeptides (neurotrophins, CGRP) and diverse compounds (glutamate, ATP, capsaicin, adenosine) also play a role in controlling BDNF secretion [40].

Essential role of BDNF in Brain

Multiple studies provide evidence for the essential function of BDNF signaling in both normal and abnormal learning and memory processes [41,42]. The neuro-protective properties of brain-derived neurotrophic factors (BDNF) have been extensively demonstrated in the hippocampus, a cerebral area primarily implicated in cognitive processes such as learning and memory. Memory and learning are both improved when BDNF TrkB signaling sets off a cascade of intracellular procedures that activate many signaling pathways. Among these processes are the following: neuronal survival, synaptic formation, and neuronal generation [43–45]. The formation and maintenance of long-term memories are both impacted by BDNF. The reason behind this is because it can alter the strength of neuronal connections through binding to receptors on the membrane of neuronal cells and release in reaction to neural activity [46]. In addition, fluctuations in synaptic connections and a rise in dendritic spine number, size, and complexity are known to facilitate long-term potentiation (LTP) and memory retention [47]. By regulating the structural changes involved in spatial and recognition memory processes, the proteins produced by the BDNF-TrkB signaling pathway significantly contribute to improved memory functions. In addition, research has shown that BDNF is essential for the maturation of memory recognition skills because it promotes the neurons growth and survival in the perirhinal cortex, an area of the brain that is fundamental for recalling specific objects from memory [48].

Role of BDNF in some Psychiatric Disorders and Neurodegenerative Diseases

BDNF is a promising biomarker currently being considered for its potential significance in diagnosing and treating neurodegeneration. Multiple methodologies have been examined to assess the potential use of BDNF as a biomarker in neurodegenerative disorders that demand decision-making in clinical practice. BDNF has been recognized as a potential biomarker that can be found in the bloodstream and used to indicate the presence of schizophrenia, depression, and neurodegenerative disorders. Although numerous experimental investigations validate its significance as a marker for the development of various diseases, there are limited papers detailing strategies to establish the possibility of using it as a clinical prognostic indicator. One approach quantifies BDNF levels in different biological samples, such as blood, cerebrospinal fluid, or post-mortem brain tissue. Changes in serum levels of BDNF have been observed in epilepsy, mental disorders, and neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, and multiple sclerosis [49, 50].

Role of BDNF in Depression

The complex and varied nature of depressive disorder has led to various hypotheses regarding its pathogenesis, which is still not fully understood. A protein crucial for neuroplasticity, synaptic transmission, and neuronal survival, brain-derived neurotrophic factor (BDNF) has been the center of intense research within the neurotrophic hypothesis [51,52]. Evidence suggests that decreased BDNF expression in important brain areas, like the hippocampus and prefrontal cortex, may contribute to the development of depressive symptoms [53,54], and BDNF level changes have been linked to the pathophysiology of depression. According to proponents of the neurotrophic hypothesis, depression is associated with larger processes of neuronal shrinkage and synaptic loss, and the pathophysiology of the condition revolves around the hypo regulation of BDNF and the ensuing impairment of neuroplasticity [55]. In line with this theory, multiple investigations have shown that depressed individuals' blood BDNF levels are lower than those of healthy controls. Plasma BDNF levels and depression severity had an inverse relationship, and the intervention substantially raised BDNF levels. Also, there was an inverse relationship between the two variables as well as between the two changes in BDNF levels and depression severity [56, 57]. Suárez-Cuenca *et al*. found that higher plasma BDNF levels before hemodialysis reduces the risk of mild depression in patients with CKD under renal replacement therapy [58]. Also, in comparison to the non-diabetic controls, type 2 diabetics showed low levels of brain-derived neurotrophic factor (BDNF) and a high burden of depression. A substantial decrease in BDNF levels was linked to severe depression in type 2 diabetic individuals [59].

The exact implications of the reduced BDNF levels in depression are still uncertain. The impermanent correlation between serum BDNF levels and the antidepressant effect tends to be indirect. Both ketamine and Electroconvulsive therapy progressively rise serum BDNF levels, whereas their antidepressant impact is observed to occur rapidly at [60]. Two investigations have demonstrated a decline in brain-derived neurotrophic factor (BDNF) levels in platelets of patients diagnosed with major depressive disorder (MDD) [61,62]. A separate study demonstrated a substantial drop in platelet BDNF levels compared to the control group. The BDNF levels were brought back to a normal state by using SSRIs treatment, as compared to the control group [63]. Collectively, these investigations provide compelling evidence that fluctuations in serum levels of BDNF indicate modified BDNF secretion from blood platelets. Therefore, due to the resemblances in the control of BDNF synthesis in megakaryocytes and neurons, there may be similarities between the brain, BDNF in the bloodstream, and its release. However, a decrease in the expression of BDNF and TrkB has been seen in the hippocampus and prefrontal cortex of post-mortem brain tissues of individuals who died by suicide [64,65]. Furthermore, multiple meta-analyses have provided evidence supporting the link between the Val66Met polymorphism and an elevated vulnerability to developing mood disorders [66–68].

Finally, a report demonstrated that individuals who had the Met allele of the BDNF gene have a higher propensity to develop depression [69]. Depression is thought to be caused by a disturbance in the transmission of serotonin signals in the brain. Modifications in synaptic serotonin concentrations and receptor numbers are linked with modified synaptic plasticity and neurogenesis [70, 71].

Role of BDNF in Schizophrenia

Schizophrenia is a complicated mental condition that affects approximately 1 in 222 adults, corresponding to a prevalence rate of 0.45% [72]. The condition has a global impact due to its chronic nature, significant alterations in personality, and impairments in cognitive functions such as working memory, attention, and executive function. These factors lead to a decreased quality of life and a high rate of disability among patients [73]. Cognitive impairments in individuals with chronic schizophrenia have been associated with several factors, such as the intensity of psychotic symptoms, age, medication, and levels of BDNF. Atake *et al*. conducted a study to examine the relationships between these characteristics in a cohort of patients [74]. They observed that the levels of BDNF in the blood were positively connected with working memory, attention, processing speed, motor performance, and executive function.

A new meta-analysis, which examined 21 studies including a total of 2,449 individuals with schizophrenia-spectrum disorders, investigated the association between BDNF levels and cognitive impairment in schizophrenia. The findings revealed a slight but substantial correlation between BDNF levels and cognitive functioning. When considering cognitive abilities, there was a substantial correlation between BDNF levels and performance in verbal memory, working memory, processing speed, and verbal fluency [75]. Ahmed *et al.* conducted two distinct meta-analyses, examining both the BDNF gene and its levels. The first study examined the correlation between the Val66Met polymorphism and neuro-cognition in individuals diagnosed with schizophrenia. The outcomes indicated no significant difference between the genotype groups regarding most neurocognitive domains. In the second study, the researchers examined the relationship between cognition and the peripheral expression of BDNF. They discovered small but significant associations between reasoning and problem-solving aspects [76,77]. Male patients diagnosed with schizophrenia have exhibited inferior performance on specific assessments measuring immediate and delayed memory in comparison to their female counterparts. Consequently, the male patients have exhibited lower BDNF levels than the female patients [78]. Peripheral levels of BDNF can serve as a valuable biomarker for assessing cognitive function in individuals with schizophrenia. These levels can be easily measured from a blood sample, specifically from plasma or serum. Furthermore, they have the potential to fluctuate during different stages of the illness and in response to various pharmacological and non-pharmacological treatments [79].

Role of BDNF in Alzheimer disease

One of the biggest problems that healthcare systems are facing is the increasing prevalence of AD among the elderly. There are about 50 million individuals worldwide who are thought to have dementia, with 22% of those aged 50 and above experiencing AD dementia, AD prodromal dementia, and AD preclinical dementia [80]. The development of AD involves multiple factors, but a crucial role is played by the buildup of ß amyloid (Aß) deposits in the brain as senile plaques, together with the presence of over-phosphorylated tau protein in the form of neurofibrillary tangles [81, 82]. Previously, it was widely assumed that the buildup of Aß was responsible for triggering and speeding up the progression of the disease, but it was thought to be unrelated to the tau protein. On the other hand, recent findings indicate that these two processes are interconnected and work together in a mutually beneficial way [81]. In their thesis on the pathophysiology of AD, Busche *et al*. discuss the synergistic effect of Aß and tau protein, known as Aß-tau synergy. They highlight that the specific mechanism underlying these interactions remains unclear. The authors fail to acknowledge the potential influence of BDNF, which we believe deserves attention [81]. BDNF's involvement in the development of AD seems to be multifaceted. BDNF depletion is linked to higher levels of tau phosphorylation, Aß accumulation, neuro-inflammation, and neuronal death [83].

A limited number of meta-analyses have validated the role of BDNF in the progression of AD. Two separate meta-analyses conducted by Qin *et al.* and Ng *et al*. demonstrated that individuals with AD exhibited reduced BDNF in their blood compared to the control group [83,84]. Due *et al.* showed that BDNF is reduced in the blood, cerebrospinal fluid, hippocampus, and cortex of patients with AD[85]. From a clinical perspective, it is necessary to identify an AD biomarker that is highly responsive to diagnose the disease in its early stages, prior to the onset of clinical symptoms. Additionally, this biomarker should be fast and non-invasive. Consequently, researchers have shown interest in Brain-Derived Neurotrophic Factor (BDNF) [86]. Ng *et al.* disproved these hopes by showing that the decline in peripheral BDNF concentration is only observed in the advanced stage of AD. This decrease is likely a result of the prior increase in BDNF secretion, which is part of the compensatory and neuroprotective mechanism. Only when these mechanisms are exhausted does the decrease in BDNF levels in the blood occur [84]. Xie *et al.* questioned the use of BDNF as a marker for detecting AD or moderate cognitive impairment (MCI), which is a transitional stage between normal aging and dementia, in their meta-analysis. The researchers moreover demonstrated that AD is linked to reduced concentrations of peripheral BDNF. However, study of the ROC curve indicated that peripheral BDNF concentrations may not be an ideal biomarker for diagnosing AD or MCI due to its lower AUC, lower sensitivity, and poor specificity [87].

Role of BDNF in Multiple Sclerosis

Multiple Sclerosis (MS) is a prevalent autoimmune disorder characterized by inflammation and degeneration of the central nervous system (CNS). This leads to the loss of myelin and the gradual buildup of impairment over time. It is predominantly found in the northern hemisphere and has a higher incidence in women than men. The typical age range for patients diagnosed with multiple sclerosis is often around 20 and 45 years old. Furthermore, the condition is more frequently observed in younger people. Remarkably, studies have consistently shown that the overall occurrence and the predominance of females have steadily risen over the past few decades [88-90]. Multiple sclerosis likely has a complex etiology that includes a wide range of factors, including genetics and the environment. The brain-derived neurotrophic factor role in controlling neuroinflammation and promoting neuroprotection has led to substantial research into BDNF in multiple sclerosis (MS). In mouse models, it has been shown to increase myelin protein production, oligodendrocyte lineage cell development, and neuronal recovery from damage or deterioration, and axon growth [91-93]. Research comparing people with MS to those without the disease has shown conflicting findings on the variations in blood BDNF levels. Some research found higher levels, while others found reduced levels [94,95]. Both the duration of the illness and the method of testing may impact on the variability in results, according to certain publications [96]. New research shows that during the relapse phase, BDNF concentrations rise in those with relapsing-remitting multiple sclerosis. This rise in BDNF levels is linked to the healing of lesions, as indicated by studies [95, 97, 98].

In contrast, several investigations have found that during the relapsing phase, the levels of BDNF are typically elevated in peripheral blood mononuclear cells (PBMC) and serum [99, 100]. Nevertheless, Azoulay *et al.* discovered a lower concentration of BDNF in the serum of RRMS patients, with no discernible variation between the remission and relapse stages [101]. Levels of BDNF in the serum and cerebrospinal fluid (CSF), as well as the production of BDNF by PBMC, are lower in individuals with MS compared to those without the condition [102, 103]. Consistent with neuropathological research [104,105], immune cells in patients with relapsing-remitting multiple sclerosis (RRMS) produce more BDNF compared to those with progressive MS. This suggests that the progression of MS may be caused by a lack of neuroprotection and neurorepair capabilities in the presence of persistent injury [100, 103].

Studying the role of BDNF in cognitive deterioration associated with this condition is crucial. This is achieved by comparing patients with Val66Met polymorphism, which reduces BDNF production by 18-30%, to the general population [106]. Multiple sclerosis (MS) prognosis and the rs6265 BDNF single nucleotide polymorphism (SNP) have been the subject of multiple investigations. There may be more processes involved in BDNF gene regulation; however, the results of these studies are inconsistent with one another [107]. New research in epigenetics has shown that methylation and other epigenetic mechanisms play a crucial role in controlling many important biological processes. As far as the Expanded Disability Status Scale is concerned, the rs6265 SNP is not indicative of a worse outcome [108]. Regardless of the polymorphism, a lower proportion of methylation in the BDNF gene is associated with a higher chance of significant impairment. A lower probability of achieving an EDSS score of 6.0 is linked with reduced gene suppression, whereas more methylation functions as a gene suppressor. Patients with severe inflammation may benefit from de-methylation therapy, which increases BDNF release and promotes better CNS function. A higher severe impairment score is the usual outcome for these patients due to the rapid depletion of brain functional reserves [108]. BDNF methylation is seen as an epiphenomenon of disease activity, specifically neuroinflammation. Therefore, it could be useful in distinguishing individuals with a greater level of inflammation from those with a lesser level. If these findings are corroborated by additional research, the methylation of BDNF rs6265 polymorphism could serve as a reliable prognostic indicator in multiple sclerosis, enabling early identification of patients with a more severe form of the disease compared to those with a milder form [108, 109].

Role of BDNF in Parkinson's disease

Parkinson's disease (PD) is a multifaceted, long-lasting, very debilitating neurodegenerative disorder and the most rapidly progressing brain ailment globally. The aetiology of Parkinson's disease (PD) remains elusive, while it has been associated with specific hereditary variables and modifiable risk factors such as environmental toxin exposure, insufficient exercise, and low levels of physical activity [110, 111]. Both animal and human models have shown that exercise has a physiological effect on gene expression, namely genes related to increased neuronal proliferation, enhanced survival, and decreased inflammatory response [112-114]. Physical activity increases the expression of neurotrophins such as nerve growth factor, glia derived neurotrophic factor (GDNF), the formation of GDNF-producing cells (glia), and the activation of BDNF-induced TrkB signaling in lymphocytes [115]. Physical activity inhibits the decrease in activity of the BDNF signaling pathways in the substantial nigra and striatum. As a result, it provides protection to dopaminergic neurons in the basal ganglia [116-119] and other regions of the brain such as the bed nucleus of the stria terminalis, septum, cerebellum (nucleus of solitary tract), dentate gyrus of the hippocampus, and cerebral cortex [120, 121]. BDNF controls the levels of dopamine and the activity of dopaminergic cells in striatum [122.] Conversely, dopaminergic input influences the responsiveness of striatal spiny neurons to BDNF [123]. Individuals with Parkinson's disease (PD) have reduced levels of brain-derived neurotrophic factor (BDNF) in the nigrostriatal pathway, in comparison to age-matched individuals without neurological disorders [124,125]. This drop in BDNF levels may make the brain more susceptible to degeneration [112]. There is a hypothesis that suggests that the rise in circulating BDNF levels caused by exercise could be used as a therapeutic treatment for PD [113].

Conclusion

Although BDNF is present in organs other than the central nervous system (CNS), including the intestines, thymus, spleen, kidneys, lungs, and heart, its effects on the CNS were initially studied, with the hippocampus and frontal cortex exhibiting the highest concentrations of BDNF. Several experimental investigations have indicated that BDNF acts as a marker for the aetiology of various psychiatric illnesses and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and schizophrenia.

Numerous surveys have indicated the potential for quantifying its concentrations in different biological specimens, including blood, cerebrospinal fluid, and post-mortem brain tissue. This would provide a better understanding of the disease's activity and prognosis.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability

This article is a narrative review and does not involve new data generation. Any materials, extracted tables, or synthesized information used to support the findings of this review are available from the corresponding author upon reasonable request. This statement supports transparency and good scholarly practice consistent with indexing requirements.

Author Contributions

All authors contributed equally to the conception of the review, literature search, data interpretation, manuscript drafting, and final approval of the paper

All authors meet the ICMJE criteria for authorship and agree to be accountable for all aspects of the work.

ORCID

Suzan Hamza 0009-0008-9522-5849
Namir Haddad 0000-0002-5851-5926
Gheyath AL Gawwam 0000-0002-5614-7680

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