# Brain-derived neurotrophic factor (BDNF) as a Potential Biomarker for Neuropsychiatric Disease

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Diagnostic neuropsychiatry is often subjective, relying primarily on questionnaires and interviews to identify disorders; a potential solution, biomarker research, which aims to identify specific genes and molecules that are related to specific neuropsychiatric disorders, has shown promise in adding objectivity into the diagnostic process. In particular, a protein known as brain-derived neurotrophic factor (BDNF) has demonstrated both positive and negative correlations with several neuropsychiatric disorders, including depression, bipolar disorder, borderline personality disorder, and schizophrenia. BDNF's role in neuroplasticity may link it to the presentation of cognitive symptoms within and across disorders. This paper reviews the fundamentals of BDNF as a molecule, presents an analysis of its applications to these disorders, and discusses the potential complications of incorporating BDNF-based diagnostics into clinical practice to reduce diagnostic subjectivity. Future directions to address the issues of biomarker specificity, testing standardization, and other general limitations of BDNF as a biomarker are presented and discussed.

**Keywords:** brain-derived neurotrophic factor, psychiatry, diagnosis, biomarker.

## Introduction

The 5th edition of the Diagnosis and Statistical Manual of Mental Disorders *(Diagnostic and Statistical Manual of Mental Disorders)*[1] and the 11th edition of the International Classification of Diseases (International Classification of Diseases) guide doctors all over the[2] world in psychiatric diagnosis, defining human behaviors associated with mental disorders. One significant issue with current diagnostics, though, is that basing diagnosis on behaviors alone can result in stigmatizing labels, misdiagnoses, and overall, oversimplified explanations of psychiatric conditions[3], which have long been known to be multifaceted in their causes. Environmental factors, chemical factors, social factors, and genetics all play a role in the development of mental disorders[4]. This is a main reason why organizations such as the United States National Institute of Mental Health (NIMH) have been promoting initiatives such as the[5] Research Domain Criteria (RDoC), which aim to better understand mental illnesses by incorporating biological systems into their classification frameworks . Thus, multiple approaches should be used to accurately diagnose and treat patients with neuropsychiatric illnesses. One potential approach to improving diagnostic psychiatry is utilizing BDNF as a biomarker for various neuropsychiatric conditions to add objectivity to diagnostics. This paper discusses said approach through a thorough literature review of credible journal articles related to BDNF and its link to various neuropsychiatric conditions. The scope of this paper focused on 4 primary disorders: depression, bipolar disorder, borderline personality disorder, and schizophrenia, and the primary limitation of this research included a lack of homogeneity in papers reviewed. However, such limitations are addressed in the discussion section.

Biomarker research aims to identify specific genes and molecules that are related to specific neuropsychiatric disorders, which can add objectivity into the diagnostic process. In particular, a protein known as brain-derived neurotrophic factor (BDNF)[6] has demonstrated both positive and negative correlations with several neuropsychiatric disorders, including depression, anxiety, bipolar disorder, borderline personality disorder, schizophrenia, Alzheimer's, and autism spectrum disorder. BDNF's role in neuroplasticity may link it to the presentation of cognitive symptoms within and across disorders. This paper will present an overview of BDNF and its biological mechanisms before delving into each of the major classes of psychiatric disorders and explaining how BDNF may be relevant to their phenomenology and can be useful in diagnosis. Following this, a consideration of the limitations of BDNF being used as a biomarker will be discussed.

### *General Context*

BDNF, which stands for Brain-Derived Neurotrophic Factor, is a protein that plays a crucial role in the growth, development, and maintenance of neurons (nerve cells) in the brain. BDNF is a member of the neurotrophin family of proteins, which are responsible for promoting the survival, differentiation, and func-

tion of neurons. BDNF is involved in various processes in the brain, including neurogenesis (the formation of new neurons), synaptic plasticity (the ability of neuronal connections to change and strengthen), and the overall health and maintenance of neurons[7]. It acts as a growth factor, supporting the survival of existing neurons and promoting the growth and differentiation of new neurons. BDNF is widely distributed throughout the brain and is involved in various functions, such as learning, memory, and mood regulation[8]. Therefore, BDNF may positively correlate with hippocampal volume. BDNF is also important for the development and maintenance of the nervous system, particularly during critical periods of brain development[9].

### *Molecular Pathway of BDNF*

BDNF is initially produced as a precursor molecule called proBDNF. When the gene for BDNF is activated, the DNA sequence containing this gene is transcribed into a messenger RNA (mRNA) molecule. The mRNA is then transported to the cytoplasm of the neuron, where it undergoes translation, resulting in the synthesis of proBDNF. After synthesis, proBDNF undergoes a series of intracellular trafficking events. It is packaged into vesicles within the cell body of the neuron and transported along the axon to the synapse (the junction between two neurons). At the synapse, proBDNF is processed and converted into its active form, mature BDNF (mBDNF). The mechanisms underlying this conversion are complex and involve proteolytic cleavage (the enzymatic hydrolysis of a peptide bond) by enzymes such as plasmin and tissue-type plasminogen activator (tPA)[10]. Once converted, mBDNF is released from the presynaptic neuron into the synaptic cleft. After its release, mBDNF interacts with specific receptors on the surface of the postsynaptic neuron.

The two main receptors for BDNF are tyrosine kinase B receptor (TrkB) and p75NTR (p75 neurotrophin receptor)[10]. TrkB is the primary receptor involved in BDNF's signaling pathway. Binding of mBDNF to the TrkB receptor leads to receptor dimerization (or bonding), which activates intracellular signaling pathways. The main signaling pathways activated by BDNF include the MAPK/ERK pathway (mitogen-activated protein kinase/extracellular signal-regulated kinase) and the PI3K/Akt pathway (phosphatidylinositol 3-kinase/protein kinase B). The activation of the signaling pathways by BDNF leads to a variety of cellular effects. These effects include promoting the survival and growth of neurons, enhancing synaptic strength and plasticity, regulating gene expression, and modulating neurotransmitter release[11].

## Results

### *Major Depressive Disorder*

Major depressive disorder (MDD) is characterized by a number of symptoms, including loss of pleasure, decreased energy, fatigue, trouble focusing or concentrating, trouble sleeping, and feelings of emptiness[1]. MDD is suspected to be polygenic and complex in cause. About 40-50 percent of depression cases are shown to have some genetic basis[12]. Further, depression is associated with atrophy of neurons and reduced synaptic connectivity in the hippocampus and prefrontal cortex[13]. Several studies have demonstrated that reduced serum BDNF (which does not contain clotting factors) levels correlate with depression[14]. This is likely due to BDNF's role in neurogenesis and synaptic plasticity changing the function of the brain, thus resulting in behavioral manifestations. Research has suggested that the Val66Met polymorphism in the BDNF gene makes one more susceptible to developing MDD, with some studies estimating the raised likelihood to be twofold[15]. Further, BDNF levels of patients with a depressive disorder who had attempted suicide or experienced suicidal ideation were found to be significantly lower than comparison participants[16].

Researchers have also recommended that BDNF be used as a marker for antidepressant response in the treatment of MDD. This is particularly important, as many patients do not experience improvement in symptoms and are considered to have treatment-resistant depression (TRD)[17]. Some have debated this, reporting that intensive TRD treatments have no correlation with peripheral BDNF levels (the levels of serum/blood BDNF in the peripheral blood), nor does peripheral BDNF correlate with antidepressant response[18]. However, others have contradicted this, providing evidence that BDNF may play a role in the antisuicidal effects of low dose ketamine infusion, a common treatment for TRD[19]. Therefore, BDNF could potentially be used as a biomarker to indicate presence of depression in patients with depression or to predict response to potential treatments.

### *Bipolar Disorder*

Bipolar disorder is a mood disorder characterized by episodes of mania, hypomania and depression. Mania involves prolonged feelings of euphoria, restlessness, and/or talkativeness. Additionally, there are two types of bipolar disorder that are relevant to this analysis: Bipolar 1 and Bipolar 2. Bipolar 1 is categorized by episodes of mania, hypomania, and depression, while Bipolar 2 is categorized by the absence of mania. Hypomania and mania are similar, but mania is more severe and long-lasting than hypomania[1]. Bipolar disorder can often have several comorbidities, such as anxiety, depression, OCD, addiction, and psychosis. Bipolar disorder can be highly difficult to diagnose, as there are no available biomarkers[20]. Additionally, Bipolar disorder

is estimated to be 62 percent heritable[21]. Although, research has concluded that genes such as those involved in serotonergic transmission and neuroplasticity are altered by childhood trauma.

Studies show that BDNF levels are decreased during both stages of mania and depression in bipolar disorder, but others have suggested that lowered plasma BDNF is a better indicator of disease activity (the overall severity of the condition) rather than the stage of the disorder (regarding episodes of depression, mania, or hypomania)[22]. Lithium, a medication commonly used to treat bipolar disorder, has been shown to raise BDNF in hippocampal neurons[23]. Thus, through plasma testing, BDNF can be regarded as a potential biomarker for diagnosing both types of bipolar disorder because patients with both types of bipolar disorders typically have low levels of BDNF.

### *Borderline Personality Disorder*

According to the DSM-5, borderline personality disorder (BPD) is marked by a pervasive pattern of instability in relationships, self-image, emotions, and impulsivity. Due to the similarities of BPD with mood disorders, it can often be difficult to diagnose. Comorbidity of BPD with anxiety disorders, substance use disorders, and depression is common. 1 Further, BPD has been found to be about 46% heritable[24].

BDNF methylation has been found to be higher in saliva of BPD patients than those without BPD, and levels of methylation decreased after a 12-week psychotherapeutic intervention[25]. This is because methylation of the BDNF gene results in suppression of transcription. Although, the exact process by which demethylation occurs is unknown, but in this instance it occurred due to a neurobiological alteration as a result of psychotherapies aimed to treat BPD. Another study suggested similar results through the use of similar methodology. However, this study concluded that levels of DNA methylation were independent of serum or plasma BDNF levels. Further, it was concluded that childhood mistreatment and environmental factors strongly influence the development of BPD[26]. Current studies suggest that determining the methylation statuses on DNA sequences is a possible method of detecting BPD, as BPD patients often have elevated BDNF levels, which could be diagnostically indicative of BPD. However, further studies should still be conducted to further analyze BDNF methylation as a biomarker for BPD. Nonetheless, if established as a biomarker, BDNF could act as an objective difference between bipolar disorder and BPD, which would greatly benefit the field of psychiatry by limiting misdiagnoses.

### *Schizophrenia and Psychosis*

Schizophrenia is a disorder that affects about 1% of the population[27]. Schizophrenia is characterized by episodes of psychosis, distinct periods in which symptoms such as delusions, hallucinations, and thought disorder are present, without insight to their pathologic nature. Psychotic episodes can vary in length, from a few days to weeks long, and can result in severe functional impairment[1]. One study estimated that schizophrenia is about 79% heritable, suggesting that there is a strong genetic component to the disorder[28].

Serum BDNF levels correlate with disease progression in the early stages of psychosis[29]. Although the Val66Met polymorphism has not been found to be responsible as a pathogenic factor of schizophrenia, it has been found to affect the age of onset, brain morphology, cognition, symptomatology, and therapeutic responsiveness[30]. Others have shown a correlation between suicide attempts and the Val66Met polymorphism[31], which may explain why schizophrenia is often comorbid with depression, as the negative symptoms overlap in both illnesses. Among patients with schizophrenia, lower BDNF levels are associated with more severe depressive symptomatology[32]. Therefore, whether as a biomarker for schizophrenia or comorbid schizophrenia and depression, BDNF could be utilized as a biomarker for since decreased BDNF levels due to the Val66Met polymorphism correspond with schizophrenia's symptomatology.

| Levels of BDNF | Neuropsychiatric Disorder |
|---|---|
| Decreased | Depression |
| Decreased | Bipolar Disorder |
| Elevated | Borderline Personality Disorder |
| Decreased | Schizophrenia |

**Table 1** Summary of Levels of BDNF Corresponding with Neuropsychiatric Conditions

## Discussion

### *General Limitations of BDNF as a Biomarker*

BDNF testing faces several significant gaps and limitations that hinder its widespread clinical application. First, the lack of standardized testing methods and assays across different laboratories introduces variability and challenges in result interpretation[33]. This regards testing DNA methylation of the BDNF gene versus measuring serum or peripheral blood levels. Additionally, BDNF is not exclusive to the brain, and peripheral measurements (measurements of serum blood that are not specific to one organ) may not always reflect central nervous system levels accurately, limiting its clinical relevance[34]. The dynamic nature of BDNF levels, influenced by factors like stress, sleep, medication use, and physical activity, further complicates the establishment of reliable baseline levels and can hinder its diagnostic potential[34]. These limitations collectively highlight the need for further research and standardization to harness the full

potential of BDNF as a diagnostic and therapeutic biomarker. Through establishing consistent standardized testing methods and conducting further studies to establish both baselines and abnormal levels of BDNF in many samples, each with different demographics (for age, sex, medication use, and physical activity levels), these limitations of BDNF as a biomarker should be corrected, thus allowing BDNF to be used as an objective biomarker in neuropsychiatry. More research is also needed to explore the molecular mechanisms that underlie variation in serum BDNF levels.

### *BDNF as a Single Specific Biomarker*

Despite correlations between BDNF and certain conditions, causality remains difficult to establish due to the complex interplay of biological and environmental factors[35]. Moreover, the complex regulation of BDNF by multiple genetic and environmental factors makes it difficult to establish its precise role in various neurological and psychiatric disorders[36]. There is also considerable overlap among the studies reviewed in terms of the directionality of BDNF relationships with disorders. For example, decreased BDNF levels are observed in MDD, BD, and BPD, so it is crucial to explore ways to aid in differentiation of these disorders, which often present quite similarly in clinical practice. Accurate diagnosis is essential to ensure proper management and appropriate treatment approaches. This is a drawback faced not only by BDNF however, as all biomarkers must be established before being clinically utilized. However, once established, biomarkers have few limitations when used in clinical practice, and are more helpful than harmful.

BDNF's altered levels can still contribute to ruling out certain disorders and preventing misdiagnosis. BDNF's potential in predicting the onset of psychotic episodes in patients with BD and BPD can be invaluable for timely intervention and prevent misdiagnosis with a primary psychotic disorder (e.g., schizophrenia). Monitoring BDNF levels may help identify individuals at higher risk for BD and BPD, allowing for preemptive measures to reduce symptom severity[37]. BDNF may also be useful as a transdiagnostic tool, as it has demonstrated associations with long-term effects of adverse experiences on brain function[38], which is seen across disorders. Understanding this relationship can guide targeted interventions for individuals exposed to adversity during their developmental years, regardless of their presenting diagnosis.

### *Gaps and Limitations of Studies Reviewed*

Generally, all studies that were reviewed had the same three limitations: small sample sizes, heterogeneity in study samples, and different forms of BDNF testing. Methods of testing BDNF ranged from serum BDNF testing, to testing the BDNF in peripheral tissue, to testing the amount of methylated DNA in the BDNF gene. Direct and controlled comparison of these methods against one another have been limited, and therefore it is difficult to know exactly how this impacted researchers' findings. Future clinical trials should be conducted with larger sample sizes and more similar BDNF testing methods in order to counter these two problems. Additionally, heterogeneity of the studies reviewed is an important limitation because it makes forming conclusions about BDNF more difficult, as drawing conclusions from diverse samples is difficult when the dynamic nature of BDNF may skew the results. Heterogeneity (an important confounder between the levels of BDNF and one's neuropsychiatric condition) can be addressed in larger-scaled clinical trials through testing people of similar age groups, sexes, and physical activity levels[39].

For this paper, Google Scholar provided many papers from PubMed and ResearchGate. In Google Scholar, the following keywords were inputted to achieve favorable search results: brain-derived neurotrophic factor, psychiatry, diagnosis, biomarker. The main criterion for studies selected was being from a peer-reviewed journal. However, the RDoC article was the one exception to this rule, as it was from the National Institute of Mental Health's website. Additionally, the dates of the studies were not taken into account because for general context, some information about the signaling pathways of BDNF were known 20-30 years ago. Further, all of the studies from the varying year ranges faced the same limitations, and all generally yielded similar results, respective to the disorder(s) that they focused on. From these sources, rather than extracting raw data, the conclusions of the papers, specifically the correlation of BDNF to a disorder or its symptoms, to synthesize the argument that BDNF can be a potentially clinically utilized tool.

## Conclusions

In conclusion, despite BDNF being altered in various neuropsychiatric conditions such as depressive disorders, bipolar disorder, borderline personality disorder, and schizophrenia, its potential relevance as a biomarker lies in its theoretical ability to aid in differential diagnosis, predict the onset of severe episodes, elucidate the impact of life experiences on symptoms, and enhance neuroplasticity to support effective treatment strategies. BDNF has potential clinical utility in aiding the objectivity of neuropsychiatric diagnosis, so through further studying its neurobiology and through establishing both standardized testing and consistent baselines in repeated trials for different neuropsychiatric conditions, diagnostic neuropsychiatry could be improved.

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