Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Review Article

Brain-derived neurotrophic factor and mental disorders

Chin-Chuen Lin [a,c], *Tiao-Lai Huang* [a,b,c,*]

[a] *Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[b] *Genomic and Proteomic Core Laboratory, Department of Medical Research, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*

[c] *College of Medicine, Chang Gung University, Taoyuan, Taiwan*


Dr. Tiao-Lai Huang

ARTICLE INFO

Article history:
Received 27 September 2019
Accepted 21 January 2020
Available online 5 May 2020

Keywords:
Bipolar disorder
Brain-derived neurotrophic factor
Epigenetics
Major depressive disorder
Proteomics
Schizophrenia

ABSTRACT

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that modulates neuroplasticity in the brain, and is one of the most widely investigated molecule in psychiatric disorders. The researches of BDNF emcompassed the advance of investigative techniques of past decades. BDNF researches ranged from protein quantilization, to RNA expression measurements, to DNA sequencing, and lately but not lastly, epigenetic studies. In this review, we will briefly address findings on BDNF protein levels, mRNA expression, Val66Met polymorphism, and epigenetic modifications, in schizophrenia, major depressive disorder (MDD), and bipolar disorder.

Overview

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that modulates neuronal survival and neuroplasticity in the brain, with important roles in the growth, survival, differentiation and repair of neurons [1]. Human BDNF gene consists of 11 exons and 9 promoters [2]. The most widely studied single nucleotide polymorphism (SNP) of BDNF gene is Val66Met polymorphism, also known as rs6265 or G196A polymorphism [3]. The biological effects of BDNF are mediated by the transmembrane tropomyosin-related kinase B (TrkB).

* *Corresponding author*. Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, 123, Ta-Pei Rd, Niao-Sung, Kaohsiung, 833, Taiwan.
E-mail address: a540520@adm.cgmh.org.tw (T.-L. Huang).
Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2020.01.001

On one hand, binding of mature BDNF to the TrkB receptor can trigger autophosphorylation of the tyrosine residue in the receptor's intracellular domain and activate downstream signaling pathways, associated with neurogenesis and neuroplasticity [4]. On the other hand, binding of pro-BDNF with p75 neurotrophin receptor mediates processes opposite to mature-BDNF, such as apoptosis, reduction in arborization, and impairment of long term potentiation [5]. Medications are also known to affect the BDNF pathway. For example, cyclosporine, an immunosuppressant associated with depression, could decrease BDNF and TrkB mRNA expressions in the hippocampus and midbrain of rats [6].

Past studies showed BDNF can cross the blood–brain barrier in both directions [7]. Animal studies have demonstrated that blood BDNF levels correlated positively with cortical BDNF levels [7,8]. Those studies have important implications in clinical research. While cerebrospinal fluid (CSF) and brain tissues are frequently studied in animal models, they become difficult to acquire in clinical samples, where peripheral samples such as serum and plasma are preferred.

BDNF has been associated with various neuropsychiatric disorders. In this review, we will briefly address findings on BDNF protein levels, mRNA expression, Val66Met polymorphism, and epigenetic modifications, in schizophrenia, major depressive disorder (MDD), and bipolar disorder.

Schizophrenia

Protein and mRNA

From serum samples of patients with schizophrenia, lower BDNF protein levels had also been reported [9]. In one of our earlier studies, we found no significant differences in serum BDNF protein levels between 126 patients with schizophrenia and 96 healthy controls, but patients with catatonic subtype had lower BDNF protein levels than patients with paranoid or residual subtype [10]. After relief of catatonia with intramuscular injections of lorazepam, patients with catatonic schizophrenia showed decreased serum BDNF levels [11]. In 34 drug-naive patients with first episode schizophrenia, significantly lower baseline BDNF protein levels were observed, as compared to healthy controls [12]. In patients with first-episode and chronic schizophrenia, lower plasma BDNF levels were observed [13]. From the plasma samples of 589 patients of schizophrenia and 254 patients with bipolar disorder, lower BDNF levels were found compared to controls; among patients, lower BDNF levels were associated with more depressive episodes, shorter time in remission, and childhood sexual abuse [14]. Those data suggested that lower peripheral BDNF levels had been relatively consistently observed in patients with schizophrenia.

Given that schizophrenia was characterized by cognitive deficits in addition to psychotic symptoms, and BDNF was involved in neuroplasticity, there were studies aiming to identify their relationships. In patients with schizophrenia, we found their serum BDNF protein levels to be negatively correlated with interpersonal communication of social function and accuracy rate of conjunction search in cognitive test [15]. In patients with first-episode and chronic schizophrenia, worse cognitive performance was noted, and BDNF correlated with several cognitive dimensions [13]. A meta-analysis also found BDNF levels to be significantly associated with several cognitive domains in patients with schizophrenia [16].

One thing worth noting is that gender difference of BDNF effect had been observed in schizophrenia. No difference in serum BDNF levels between patients with schizophrenia and body mass index (BMI) matched controls was initially reported, but when gender groups were analyzed separately, BDNF levels negatively correlated with BMI gain in females with schizophrenia, but not in males [17]. We found that male patients with schizophrenia with metabolic syndrome had higher serum BDNF levels than those without [18]. Pooling our data from the past ten years, we found BDNF levels of 224 patients with schizophrenia to be significantly lower than 390 controls, but comparable with levels of patients with MDD. The receiver operating characteristic curve analysis showed that BDNF levels had a moderate accuracy of differentiating female patients with schizophrenia from controls [19]. Another study found increased plasma BDNF levels in female patients with schizophrenia, as compared to male patients as well as female controls [20]. Among 132 Chinese patients with schizophrenia, female patients had lower BDNF levels compared to males [21]. Gender difference might affect the outcome of analyses of BDNF protein levels in patients with schizophrenia.

In patients with schizophrenia treated with atypical antipsychotics for four weeks, their serum BDNF protein levels showed no significant change after treatment; however, serum BDNF levels were increased in the subgroup receiving risperidone compared to that receiving clozapine, but the phenomenon was observed in males only, suggesting a gender difference in terms of drug effect [22]. After six weeks of olanzapine or lurasidone treatment, unmedicated patients with schizophrenia showed increase of serum BDNF levels, and the increase was more prominent with the olanzapine group [23]. After eight weeks of olanzapine treatment, fourteen drug-naive patients with first-episode schizophrenia showed no statistical significant increase of serum BDNF levels [24]. While most data suggested an increase of BDNF levels after medications, statistical significant increase was not always achieved. Different treatment durations, different drug mechanics, and even heterogenous sample populations could all contribute to the discrepancy.

Single nucleotide polymorphism (SNP)

Met/Met allele of Val66Met polymorphism was initially thought to increase the risk of schizophrenia [25]. Our investigation of Val66Met polymorphism of 132 patients with schizophrenia and 103 healthy controls found no significant difference of allele or genotype distributions between the two groups, though a significant difference was detected between patients with and without suicide history [26]. A recent updated meta-analysis of 11,480 patients with schizophrenia and 13,490 healthy controls found no association between Val66Met polymorphism with schizophrenia [27]. Yet, there could be a gender and ethnic difference in how Val66Met polymorphism affect patients with

schizophrenia. Female patients with schizophrenia with Val allele of the BDNF Val66Met polymorphism scored higher in PANSS scale and lower in cognitive tests, but no performance difference was observed in male patients [28]. When analyzing Val66Met polymorphism based on different ethnic groups, a meta-analysis found that Met/Met genotype was a risk factor of schizophrenia, and increased the risk of schizophrenia up to 9% in Asian, up to 26% in European populations, and up to 9% in people with Chinese origin [29]. In terms of antipsychotic response, a recent meta-analysis found no association between Val66Met polymorphism and treatment response [30]. The role of Val66Met polymorphism in schizophrenia might not be as robust as we initially thought, but the SNP may affect a range of clinical symptoms such as age of onset, treatment response, cognition, and brain morphology [31].

Epigenetic modifications

Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNAs can affect gene activity and expression, without changing the DNA sequence. In a genome-wide epigenomic analysis of the postmortem brains of patients with schizophrenia and bipolar disorder, no significant methylation level difference was found in BDNF gene from controls, but Val homozygotes of Val66Met SNP in exon IX had significantly higher DNA methylation in the four nearby CpG sites than Val/Met or Met/Met carriers [32]. In another study using postmortem brains of 15 patients with schizophrenia and 15 controls, analysis of a region surrounding BDNF promoter IV revealed that a single CpG site at −93 was hypomethylated in patients with schizophrenia [33].

Using DNA from blood samples of patients with schizophrenia and healthy controls, frequency of the BDNF gene methylation was highlighted as a statistically significant relationship between patients and controls regarding decreased risk of disease in comparison to unmethylated patterns [34]. In the peripheral blood cells of the patients with schizophrenia and healthy controls, patients had a higher methylation level at BDNF promoter I compared to controls, but no significant difference was detected in methylation levels of BDNF promoter IV [35].

Histone methylation is the transfer to one to three methyl groups to lysine or arginine residues of histone proteins, performed by histone methyltransferase. Mixed-lineage leukemia 1 (MLL1) is a histone 3 lysine-specific methyltransferase which could affect BDNF histone modifications. We found increased levels of blood MLL1 mRNA and BDNF exon IV promoter H3K4me3 in patients with schizophrenia as compared to healthy controls [36]. In the follow-up study evaluating clozapine treatment effect, we found higher H3K9me2 levels in patients with schizophrenia, but found no difference in MLL1 mRNA levels, H3K9me2 levels, and H3K27me3 levels between patients with clozapine treatment and non-clozapine treatment [37].

The most well-studied noncoding RNAs are microRNA (miRNA), which are 21–23 nucleotides long and can inhibit the translation of messenger RNA (mRNA), regulating protein expression via post-transcriptional gene silencing. A large number of miRNAs had been investigated in schizophrenia. For example, miR-183 levels in the whole blood samples were significantly decreased in the patients with tumor alone than the patients with comorbid tumor and schizophrenia [38]. The study design and investigated targets often vary widely among epigenetic studies, thus it has not been hard to find an unified conclusion. Nevertheless, as more data accumulate, we might be able to utilize those findings better in diagnosis, treatment, and prognosis.

Major depressive disorder (MDD)

Protein and mRNA

Similar to schizophrenia, BDNF is also one of the most well studied molecule in MDD. Lower serum BDNF protein levels had been observed in patients with MDD. In our recent study, patients with MDD had a lower serum BDNF protein and mRNA levels than the healthy controls [39]. Compared to healthy controls, serum BDNF levels were lower in patients with MDD [40]. Plasma BDNF levels were significantly lower in patients with MDD and those with attempted suicide [41]. We also noted a gender difference of BDNF effect in MDD. At baseline, only female patients with MDD had significantly lower serum BDNF protein levels than controls, but no significant difference was found between male patients and controls [42]. Drug naive patients with first episode MDD had lower BDNF protein levels than healthy controls [43]. Pooling our data from the past ten years, we found BDNF levels of 224 patients with schizophrenia to be significantly lower than 390 controls, but comparable with levels of 273 patients with MDD. The receiver operating characteristic curve analysis showed that BDNF levels had a moderate accuracy of differentiating male patients with MDD from controls [19]. Generally, lower BDNF protein and mRNA levels were observed in patients with MDD.

Antidepressant treatment has also been shown to increase BDNF levels [44]. A meta-analysis also reported similar findings [45]. In our recent study, we also found that BDNF protein and mRNA levels significantly increased after four weeks of antidepressant treatment [46]. Baseline plasma BDNF to leptin ratio was lower in patients with MDD, but in antidepressant responders the ratio was higher than non-responders [47]. After twelve weeks of antidepressant treatment, plasma BDNF increased significantly [41]. There may also be a gender difference in terms of BDNF and antidepressant. After antidepressant treatment, BDNF levels increased significantly, but only female responders had significantly increased changes in serum BDNF protein levels [42]. Antidepressant treatment appears to increase BDNF levels in patients with MDD.

Down regulation of the TrkB signaling pathway has been suggested as one of the underlying mechanisms of MDD [48]. Patients with MDD had significantly higher TrkB levels than healthy controls [49]. Similarly, significantly higher TrkB protein levels were found in obese patients with MDD as compared to non-obese patients with MDD [50]. The other component of BDNF pathway could be susceptible to the disease process, and a holistic evaluation of the entire pathway may be needed in the future.

SNP

The relationships between BDNF Val66Met polymorphism and MDD also have been extensively studied, but the results were not entirely consistent, as a meta-analysis in 2010 found no association between Val66Met polymorphism and depression, but sex-stratified analyses revealed that Met increased risk for depression in men, but not in women, hinting at a gender difference of Val66Met effect on depression [51]. Another meta-analysis found no association between Val66Met polymorphism with MDD [52], but later studies found Val66Met polymorphism moderate life stress in depression [53,54]. The findings on Val66Met polymorphism and DNA methylation levels were limited and were mostly inconsistent. Three SNPs, including Val66Met, could modulate the association between late-life depression and BDNF exon I promoter methylation levels [55]. In a study investigating patients with MDD and bipolar disorder, no significant genotype–methylation interactions were found with Val66Met polymorphism [56]. We did not find any significant difference on Val66Met methylation levels in patients with MDD [39]. A recent study found that Val66Met polymorphism was associated with less antidepressant-induced insomnia [57]. A recent prospective study found Val66Met polymorphism to have no correlation with suicide ideation or treatment response [41]. Val66Met showed no influence on serum BDNF levels and BDNF methylation levels in patients with MDD [40]. Using machine learning, Val66Met polymorphism along with several other SNPs of various genes could predict antidepressant response [58,59]. Similar to schizophrenia, the evidences of Val66Met polymorphism having a strong association with MDD appear weak, though the particular polymorphism could modulate other associated symptoms such as life stress. Furthermore, advances in deep learning might detect previously subtle effect of SNPs.

Epigenetic modifications

DNA methylation studies were the most frequently investigated epigenetic studies of BDNF gene, and BDNF exon I and IV promoters were the most studied. Among 29 differentially methylated CpG sites out of 35 studied sites in BDNF exon I between patients with MDD and healthy controls, no significant difference was detected in methylation levels in BDNF exon IV [60]. D'Addario et al. reported higher methylation of BDNF exon I promoter and lower BDNF gene expression in patients with MDD [61]. In a study of both patients with MDD and bipolar disorder, patients with MDD had higher BDNF exon I promoter methylation levels than patients with bipolar disorder and healthy controls [56]. Their follow-up study found higher BDNF exon I promoter methylation levels in both patients with MDD and patients with bipolar II disorder, but not in patients with bipolar I disorder; when analysis was performed based on the mood state instead of diagnosis, the study reported higher methylation levels among patients in depressive state, than those of manic/mixed states [62]. In geriatric patients with MDD, DNA methylation levels of both BDNF promoters I and IV were associated with depression at baseline, and chronic late-life depression [55]. Three SNPs, including Val66Met polymorphism, were found to modify the association between depression and BDNF promoter I methylation level [55]. BDNF exon IV promoter methylation levels were not associated with memory performance [63]. A recent study reported increased BDNF methylation levels were detected in patients with MDD [40]. We recently found that patients with MDD had a significantly higher methylation level at CpG site 217 and lower methylation levels at CpG site 327 and CpG site 362 in BDNF exon IX than the healthy controls, along with lower BDNF protein and mRNA levels [39].

Associations between BDNF methylation levels and psychiatric medications were reported. Patients treated with both mood stabilizers and antidepressants had lower BDNF exon I promoter methylation levels than those treated with just antidepressants [61]. Lack of methylation of CpG site −87 of BDNF exon IV promoter was associated with poor treatment response in patients with MDD [64]. However, in the follow-up study, the predictor function of CpG-87 of BDNF exon IV promoter was not replicated, but in a subgroup of patients with severe depression, patients with hypermethylation at CpG-87 had significantly higher remission rates than patients without a methylation [65]. In patients after acute coronary syndrome, increased BDNF methylation was associated with the finding that escitalopram was more effective than placebo for treating depressive disorder, and this effect leads to prevent persistent depressive disorder [66]. In our study, antidepressant responders had higher methylation levels at CpG site 24 and CpG site 324 of BDNF exon IX than non-responders [39].

Several miRNAs had been known to affect the expression of BDNF in depression. Depressive patients had an inverse relationship between the serum BDNF levels and the miR-132/miR-182 levels [67]. Increased miR-132 levels in patients with MDD were reported, and miR-132 levels significantly correlated with visual memory [68]. We found serum miR-30e, miR-132, miR-185, and miR-212 levels were increased in patients with MDD at baseline compared to healthy controls [46].

miRNAs associated with BDNF could also affect treatment response. miR-30b, miR-132, and miR-212 levels differed significantly between paroxetine-sensitive and non-sensitive cell lines [69]. After twelve weeks of escitalopram treatment in ten patients with MDD, levels of 26 miRNAs were statistically increased [70]. We found that antidepressant treatment increased serum miR-183 and miR-212 levels in patients with MDD [71]. Data on treatment response had still been scarce, however, especially among clinical populations.

As in schizophrenia, epigenetic investigations of BDNF in MDD utilize a wide variety of study methods and samples, so the current findings could not be deciphered with a simple, clear message. Further studies will be needed.

Bipolar disorder

Protein and mRNA

Bipolar disorder features three distinct mood states: manic, depressive, and euthymic states. Peripheral BDNF protein levels and their relationship with various mood states of bipolar disorder had been studied in the past [45,72], but not all studies were consistent [73].

A meta-analysis showed that BDNF levels were decreased in patients with either depressive or manic episodes, but no significant differences were found between euthymic patients and controls [45]. Another meta-analysis reported similar findings [72]. We initially found no significant differences in serum BDNF protein levels between patients with bipolar mania and healthy controls [73]. However, in a more recent study, we did find that patients with bipolar mania had decreased BDNF protein levels compared to healthy controls [74]. Pooling our data from the past twenty years, we compared 83 patients with bipolar disorder with 222 controls matched with age, sex, and BMI and found that patients had significantly lower BDNF protein levels. Furthermore, the receiver operating characteristic curve analysis showed that BDNF levels showed a moderate accuracy of differentiating patients with bipolar disorder from healthy controls [75]. Another recent study reported lower plasma BDNF levels were found in patients with bipolar disorder [14]. Lower serum BDNF levels were observed in bipolar patients of euthymic and manic states, and BDNF levels were associated with executive functioning and verbal memory [76].

Most studies concerning BDNF mRNA and bipolar disorder utilized postmortem brains. Lower BDNF mRNA levels were found in bipolar group than control group [77,78]. The patients with bipolar disorder from aforementioned studies included patients in both manic and depressive episode. In patients with only bipolar mania, we found lower BDNF mRNA levels than did the controls [74]. In another study, we simultaneously showed that patients with bipolar mania exhibited lower BDNF protein and mRNA levels than did the healthy controls [79].

A meta-analysis found an increase in BDNF levels following the treatment for acute mania [72]. After about two months of treatment, the initially decreased BDNF levels of acute manic patients showed a sharp increase after medications [80]. After eight weeks of treatment, pediatric bipolar patients had significantly higher BDNF mRNA levels [81]. In contrast, our earlier work found no significant change in serum BDNF protein levels after four weeks of treatment with mood stabilizers [73], and our follow-up study found no significant change in BDNF protein and mRNA levels after four weeks of treatment [74]. Given that antipsychotics were frequently prescribed during manic phase, antipsychotics may have different effect on BDNF protein and mRNA levels. After a sixteen week follow-up, extended-release quetiapine increases BDNF levels with time in those with a depressive episode, but decreases BDNF levels with time in those with a manic/mixed episode [82]. The frequent co-prescription of antipsychotics in addition to mood stabilizer to treat acute manic patients could affect BDNF protein and mRNA levels in unexpected directions. Those data also suggest that BDNF levels could be affected by the disease state of bipolar disorder.

SNP

Early findings suggested a significant association bewteen BDNF Val66Met polymorphism and bipolar disorder [83], but recent meta-analysis indicated otherwise [84,85]. When different ethnic groups were taken into consideration, Val66Met polymorphism was significantly associated with bipolar disorder in Europeans, but not in Asians [86]. A meta-analysis investigating Val66Met polymorphism's effects on cognitive functions of patients with bipolar disorder found that adult Val carriers were associated with better executive functions, verbal learning, and verbal memory, and Met carriers might negatively module the association between childhood trauma and cognitive performances, as well as structural abnormalities in cognitive cerebral structures [87]. As previously mentioned, there were gender and ethnic differences in BDNF's effect in various psychiatric disorders. More data will be needed to clarify the role of Val66Met polymorphism in bipolar disorder.

Epigenetic modifications

In the postmortem brains of 35 patients with schizophrenia and 35 patients with bipolar disorder, Val homozygotes of Val66Met polymorphism had significantly higher DNA methylation levels across the exonic region profiled with pyrosequencing [32]. In the postmortem brains of ten patients with bipolar disorder, global DNA hypermethylation and BDNF CpG hypermethylation were found [88]. In BDNF exon I, higher degree of methylation of BDNF and lower mRNA level were found in the blood of patients with bipolar II diorder, but not of patients with bipolar I disorder [89]. That study also found that patients treated with both mood stabilizers and antidepressants had increased methylation levels than the patients treated with mood stabilizers alone, and that treatment with lithium or valproate was associated with significant decrease of methylation compared to other drugs. In BDNF promoters III and V in the leukocytes of 50 patients of bipolar I disorder and 50 age and sex matched controls, five CpG sites out of 36 CpG sites showed significantly increased methylation levels [90]. In BDNF exon I, higher methylation levels were found in the blood of patients with MDD than in either bipolar disorder or control group, and higher methylation levels were associated with antidepressant treatment [56]. In a follow-up of D'Addario et al.'s work focusing on BDNF exon I using peripheral blood samples, higher methylation was found again in patients with bipolar II diosrder as compared to patients with bipolar I disorder or major depressive disorder, and higher methylation levels was found in patients with depressed state as compared to patients with manic or mixed state [62]. That study continued to find that treatment with lithium or valproate was associated with lower methylation levels in BDNF exon I. Overall, the investigated regions of BDNF methylation could vary widely between the studies, making direct comparisons challenging, not to mention the methodological and analytical differences [91]. We found that patients with bipolar mania had a higher degree of methylation at CpG site 217 and lower degree of methylation at CpG site 391 than did the healthy controls in BDNF exon IX, but no difference was detected at Val66Met polymorphisms [79]. We also found that serum BDNF protein level correlated significantly with the degree of methylation at CpG site 348, and that BDNF mRNA level correlated significantly with degree of methylation at CpG sites 134, 177, and 217.

Conclusion

The researches of BDNF summarized the advance of investigative techniques of past decades. We moved from protein quantilization, to RNA expression measurements, to DNA sequencing, and lately, epigenetic studies. While BDNF had been demonstrated to be differentially expressed in many psychiatric disorders, BDNF alone could not explain everything. That leads to another line of study techniques that look for differentially expressed molecules between diseased populations and healthy controls, such as proteomics and metabolomics.

Utilizing metaolomics and proteomics of medicinal plants used in sleep disorders, BDNF activity positively correlated with the isolated proteins and metabolites [92]. Proteomic approach was also utilized to identified BDNF regulated proteins in patients undergoing cochlear implantation [93]. We had also utilized proteomic investigations on psychiatric disorders, such as schizophrenia [94], MDD [95–97], catatonia [98], and medication effects, such as risperidone [99], antidepressants [100]. Those investigations provide a different approach which would complement our understanding of the BDNF pathway.

BDNF is relatively well studied in the major psychiatric disorders, but its protein level alone could not explain everything. Advancing investigative techniques give us new insights into how BDNF behave in disease presentations as well as treatment responses. While the heterogenous nature of epigenetic studies make drawing a simple conclusion challenging, they nevertheless pave the way to a better understanding of this particular molecule, and hopefully, human brains.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the clinical research grants No. CMRPG8D1471, CMRPG8D1472, CMRPG8E0351, CMRPG8F1461, CMRPG8F1462, and CMRPG8G1161 from Kaohsiung Chang Gung Memorial Hospital in Taiwan.

REFERENCES

[1] Lewin GR, Barde YA. Physiology of the neurotrophins. Annu Rev Neurosci 1996;19:289–317.
[2] Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics 2007;90:397–406.
[3] Tsai SJ. Critical issues in BDNF Val66Met genetic studies of neuropsychiatric disorders. Front Mol Neurosci 2018;11:156.
[4] Nagappan G, Lu B. Activity-dependent modulation of the BDNF receptor TrkB: mechanisms and implications. Trends Neurosci 2005;28:464–71.
[5] Hing B, Sathyaputri L, Potash JB. A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. Am J Med Genet Part B, Neuropsychiatric genetics : Off Publ Int Soci Psychiatr Genet 2018;177:143–67.
[6] Chen CC, Hsu LW, Huang LT, Huang TL. Chronic administration of cyclosporine A changes expression of BDNF and TrkB in rat hippocampus and midbrain. Neurochem Res 2010;35:1098–104.
[7] Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci Lett 2002;328:261–4.
[8] Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2011;14:347–53.
[9] Cui H, Jin Y, Wang J, Weng X, Li C. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia: a systematic review. Shanghai Arch Psychiatry 2012;24:250–61.
[10] Huang TL, Lee CT. Associations between serum brain-derived neurotrophic factor levels and clinical phenotypes in schizophrenia patients. J Psychiatr Res 2006;40:664–8.
[11] Huang TL, Hung YY. Lorazepam reduces the serum brain-derived neurotrophic factor level in schizophrenia patients with catatonia. Progress in neuro-psychopharmacology & biological psychiatry 2009;33:158–9.
[12] Chiou YJ, Huang TL. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naive first-episode schizophrenia: effects of antipsychotics. World J Biol Psychiatr : Off J World Fed Soci Biol Psychiat 2017;18:382–91.
[13] Yang Y, Liu Y, Wang G, Hei G, Wang X, Li R, et al. Brain-derived neurotrophic factor is associated with cognitive impairments in first-episode and chronic schizophrenia. Psychiatr Res 2019;273:528–36.
[14] Aas M, Dieset I, Morch R, Steen NE, Hope S, Reponen EJ, et al. Reduced brain-derived neurotrophic factor is associated with childhood trauma experiences and number of depressive episodes in severe mental disorders. Schizophr Res 2019;205:45–50.
[15] Lin IM, Lin HL, Huang TL. BDNF, social cognition and social function in patients with schizophrenia. Taiwan J Psychiatry 2017;31:80–9.
[16] Bora E. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med 2019;49:1971–9.
[17] Zhang XY, Tan YL, Zhou DF, Cao LY, Wu GY, Xu Q, et al. Serum BDNF levels and weight gain in schizophrenic patients on long-term treatment with antipsychotics. J Psychiatr Res 2007;41:997–1004.
[18] Lin CC, Hung YY, Tsai MC, Huang TL. Increased serum brain-derived neurotrophic factor in male schizophrenic patients with metabolic syndrome. Medicine (Baltim) 2017;96:e7089.
[19] Chiou YJ, Huang TL. Accuracy of brain-derived neurotrophic factor levels for differentiating between Taiwanese patients with major depressive disorder or schizophrenia and healthy controls. PloS One 2019;14:e0212373.
[20] Weickert CS, Lee CH, Lenroot RK, Bruggemann J, Galletly C, Liu D, et al. Increased plasma Brain-Derived Neurotrophic Factor (BDNF) levels in females with schizophrenia. Schizophr Res 2019;209:212–7.
[21] Yang F, Wang K, Du X, Deng H, Wu HE, Yin G, et al. Sex difference in the association of body mass index and BDNF levels in Chinese patients with chronic schizophrenia. Psychopharmacology 2019;236:753–62.

[22] Chen CC, Huang TL. Effects of antipsychotics on the serum BDNF levels in schizophrenia. Psychiatr Res 2011;189:327–30.
[23] Jena M, Ranjan R, Mishra BR, Mishra A, Nath S, Sahu P, et al. Effect of lurasidone vs olanzapine on neurotrophic biomarkers in unmedicated schizophrenia: a randomized controlled trial. J Psychiatr Res 2019;112:1–6.
[24] Hatziagelaki E, Tsiavou A, Gerasimou C, Vavougios GD, Spathis A, Laskos E, et al. Effects of olanzapine on cytokine profile and brain-derived neurotrophic factor in drug-naive subjects with first-episode psychosis. Exp Ther Med 2019;17:3071–6.
[25] Gratacos M, Gonzalez JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biol Psychiatr 2007;61:911–22.
[26] Huang TL, Lee CT. Associations between brain-derived neurotrophic factor G196A gene polymorphism and clinical phenotypes in schizophrenia patients. Chang Gung Med J 2007;30:408–13.
[27] Zhao X, Huang Y, Chen K, Li D, Han C, Kan Q. The brain-derived neurotrophic factor Val66Met polymorphism is not associated with schizophrenia: an updated meta-analysis of 11,480 schizophrenia cases and 13,490 controls. Psychiatr Res 2015;225:217–20.
[28] Kim SW, Lee JY, Kang HJ, Kim SY, Bae KY, Kim JM, et al. Gender-specific associations of the brain-derived neurotrophic factor Val66Met polymorphism with neurocognitive and clinical features in schizophrenia. Clin Psychopharmacol Neurosci 2016;14:270–8.
[29] Kheirollahi M, Kazemi E, Ashouri S. Brain-derived neurotrophic factor gene Val66Met polymorphism and risk of schizophrenia: a meta-analysis of case-control studies. Cell Mol Neurobiol 2016;36:1–10.
[30] Huang E, Hettige NC, Zai G, Tomasi J, Huang J, Zai CC, et al. BDNF Val66Met polymorphism and clinical response to antipsychotic treatment in schizophrenia and schizoaffective disorder patients: a meta-analysis. Pharmacogenomics J 2019;19:269–76.
[31] Notaras M, Hill R, van den Buuse M. A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. Neurosci Biobehav Rev 2015;51:15–30.
[32] Mill J, Tang T, Kaminsky Z, Khare T, Yazdanpanah S, Bouchard L, et al. Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. Am J Hum Genet 2008;82:696–711.
[33] Keller S, Errico F, Zarrilli F, Florio E, Punzo D, Mansueto S, et al. DNA methylation state of BDNF gene is not altered in prefrontal cortex and striatum of schizophrenia subjects. Psychiatr Res 2014;220:1147–50.
[34] Kordi-Tamandani DM, Sahranavard R, Torkamanzehi A. DNA methylation and expression profiles of the brain-derived neurotrophic factor (BDNF) and dopamine transporter (DAT1) genes in patients with schizophrenia. Mol Biol Rep 2012;39:10889–93.
[35] Ikegame T, Bundo M, Murata Y, Kasai K, Kato T, Iwamoto K. DNA methylation of the BDNF gene and its relevance to psychiatric disorders. J Hum Genet 2013;58:434–8.
[36] Huang TL, Lin CC, Chen RF, Lee CT. Higher blood MLL1 mRNA and BDNF promoter IV on histone H3K4me3 levels in patients with schizophrenia. Psychiatr Res 2016;243:207–9.
[37] Hsieh MT, Lin CC, Huang TL. Increased brain-derived neurotrophic factor exon IV histone 3 lysine 9 dimethylation in patients with schizophrenia. Taiwan J Psychiatry 2019;33:99–104.
[38] Rizos E, Siafakas N, Katsantoni E, Skourti E, Salpeas V, Rizos I, et al. Let-7, mir-98 and mir-183 as biomarkers for cancer and schizophrenia [corrected]. PloS One 2015;10:e0123522.
[39] Hsieh MT, Lin CC, Lee CT, Huang TL. Abnormal brain-derived neurotrophic factor exon IX promoter methylation, protein, and mRNA levels in patients with major depressive disorder. J Clin Med 2019;8:568.
[40] Schroter K, Brum M, Brunkhorst-Kanaan N, Tole F, Ziegler C, Domschke K, et al. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatr Clin Neurosci 2020;270:169–81.
[41] Ai M, Wang J, Chen J, Wang W, Xu X, Gan Y, et al. Plasma brain-derived neurotrophic factor (BDNF) concentration and the BDNF Val66Met polymorphism in suicide: a prospective study in patients with depressive disorder. Pharmgenomics Pers Med 2019;12:97–106.
[42] Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J Psychiatr Res 2008;42:521–5.
[43] Chiou YJ, Huang TL. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naive first-episode major depressive disorder: effects of antidepressants. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2017;20:213–8.
[44] Martinotti G, Pettorruso M, De Berardis D, Varasano PA, Lucidi Pressanti G, De Remigis V, et al. Agomelatine increases BDNF serum levels in depressed patients in correlation with the improvement of depressive symptoms. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2016;19:pyw003.
[45] Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. J Affect Disord 2015;174C:432–40.
[46] Lin CC, Lee CT, Sun M-H, Huang TL. Increased levels of miR-30e, miR-132, miR-185, and miR-212 at baseline and increased brain-derived neurotrophic factor protein and mRNA levels after treatment in patients with major depressive disorder. Neuropsychiatry 2017;7:920–6.
[47] An JH, Jang EH, Kim AY, Fava M, Mischoulon D, Papakostas GI, et al. Ratio of plasma BDNF to leptin levels are associated with treatment response in major depressive disorder but not in panic disorder: a 12-week follow-up study. J Affect Disord 2019;259:349–54.
[48] Tsai SJ. Down-regulation of the Trk-B signal pathway: the possible pathogenesis of major depression. Med Hypotheses 2004;62:215–8.
[49] Hung YY, Lin CJ, Huang TL. Higher serum tropomyosin-related kinase B protein level in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 2010;34:610–2.
[50] Lin CC, Huang TL. Increased serum tropomyosin-related kinase B protein level in obese major depressive patients. Taiwan J Psychiatry 2010;24:301–6.
[51] Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vasquez A, Buitelaar JK, et al. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Mol Psychiatr 2010;15:260–71.
[52] Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, et al. No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. Am J Med

Genet Part B, Neuropsychiatric genetics : Off Publ Int Soc Psychiatr Genet 2013;162B:61–70.
[53] Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med 2014;12:7.
[54] Zhao M, Chen L, Yang J, Han D, Fang D, Qiu X, et al. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene-environment interaction. J Affect Disord 2018;227:226–35.
[55] Januar V, Ancelin ML, Ritchie K, Saffery R, Ryan J. BDNF promoter methylation and genetic variation in late-life depression. Transl Psychiatry 2015;5:e619.
[56] Carlberg L, Scheibelreiter J, Hassler MR, Schloegelhofer M, Schmoeger M, Ludwig B, et al. Brain-derived neurotrophic factor (BDNF)-epigenetic regulation in unipolar and bipolar affective disorder. J Affect Disord 2014;168:399–406.
[57] Badamasi IM, Lye MS, Ibrahim N, Stanslas J. Genetic endophenotypes for insomnia of major depressive disorder and treatment-induced insomnia. J Neural Transm 2019;126:711–22.
[58] Bartova L, Dold M, Kautzky A, Fabbri C, Spies M, Serretti A, et al. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. World J Biol Psychiatr 2019;20:427–48.
[59] Kautzky A, Baldinger P, Souery D, Montgomery S, Mendlewicz J, Zohar J, et al. The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression. Eur Neuropsychopharmacol : J Eu Coll Neuropsychopharmacol 2015;25:441–53.
[60] Fuchikami M, Morinobu S, Segawa M, Okamoto Y, Yamawaki S, Ozaki N, et al. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. PloS One 2011;6:e23881.
[61] D'Addario C, Dell'Osso B, Galimberti D, Palazzo MC, Benatti B, Di Francesco A, et al. Epigenetic modulation of BDNF gene in patients with major depressive disorder. Biol Psychiatr 2013;73:e6–7.
[62] Dell'Osso B, D'Addario C, Carlotta Palazzo M, Benatti B, Camuri G, Galimberti D, et al. Epigenetic modulation of BDNF gene: differences in DNA methylation between unipolar and bipolar patients. J Affect Disord 2014;166:330–3.
[63] Engelmann J, Wagner S, Wollschlager D, Kaaden S, Schlicht KF, Dreimuller N, et al. Higher BDNF plasma levels are associated with a normalization of memory dysfunctions during an antidepressant treatment. Eur Arch Psychiatr Clin Neurosci 2019;270:183–93.
[64] Tadic A, Muller-Engling L, Schlicht KF, Kotsiari A, Dreimuller N, Kleimann A, et al. Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. Mol Psychiatr 2014;19:281–3.
[65] Lieb K, Dreimuller N, Wagner S, Schlicht K, Falter T, Neyazi A, et al. BDNF plasma levels and BDNF exon IV promoter methylation as predictors for antidepressant treatment response. Front Psychiatr 2018;9:511.
[66] Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, et al. BDNF methylation and depressive disorder in acute coronary syndrome: the K-DEPACS and EsDEPACS studies. Psychoneuroendocrinology 2015;62:159–65.
[67] Li YJ, Xu M, Gao ZH, Wang YQ, Yue Z, Zhang YX, et al. Alterations of serum levels of BDNF-related miRNAs in patients with depression. PloS One 2013;8:e63648.
[68] Liu Y, Yang X, Zhao L, Zhang J, Li T, Ma X. Increased miR-132 level is associated with visual memory dysfunction in patients with depression. Neuropsychiatric Dis Treat 2016;12:2905–11.
[69] Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, Shomron N, Rehavi M, et al. Genome-wide miRNA expression profiling of human lymphoblastoid cell lines identifies tentative SSRI antidepressant response biomarkers. Pharmacogenomics 2012;13:1129–39.
[70] Bocchio-Chiavetto L, Maffioletti E, Bettinsoli P, Giovannini C, Bignotti S, Tardito D, et al. Blood microRNA changes in depressed patients during antidepressant treatment. Eur Neuropsychopharmacol 2013;23:602–11.
[71] Lin CC, Tsai MC, Lee CT, Sun MH, Huang TL. Antidepressant treatment increased serum miR-183 and miR-212 levels in patients with major depressive disorder. Psychiatr Res 2018;270:232–7.
[72] Fernandes BS, Gama CS, Cereser KM, Yatham LN, Fries GR, Colpo G, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res 2011;45:995–1004.
[73] Huang TL, Hung YY, Lee CT, Chen RF. Serum protein levels of brain-derived neurotrophic factor and tropomyosin-related kinase B in bipolar disorder: effects of mood stabilizers. Neuropsychobiology 2012;65:65–9.
[74] Lin CC, Lee CT, Lo YT, Huang TL. Brain-derived neurotrophic factor protein and mRNA levels in patients with bipolar mania - a preliminary study. Biomed J 2016;39:272–6.
[75] Chiou YJ, Huang TL. Brain-derived neurotrophic factor (BDNF) and bipolar disorder. Psychiatr Res 2019;274:395–9.
[76] Mora E, Portella MJ, Pinol-Ripoll G, Lopez R, Cuadras D, Forcada I, et al. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. Eur Psychiatr 2019;60:97–107.
[77] Kim HW, Rapoport SI, Rao JS. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol Dis 2010;37:596–603.
[78] Pillai A. Decreased expression of Sprouty2 in the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder: a correlation with BDNF expression. PloS One 2008;3:e1784.
[79] Lin CC, Hung YY, Huang TL. Associations between DNA methylation of promoter exon IX, serum protein and mRNA levels of brain-derived neurotrophic factor in patients with bipolar mania. Neuropsychiatry 2018;8:224–31.
[80] Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett 2009;452:111–3.
[81] Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. J Am Acad Child Adolesc Psychiatr 2008;47:1077–85.
[82] Grande I, Kapczinski F, Stertz L, Colpo GD, Kunz M, Cereser KM, et al. Peripheral brain-derived neurotrophic factor changes along treatment with extended release quetiapine during acute mood episodes: an open-label trial in drug-free patients with bipolar disorder. J Psychiatr Res 2012;46:1511–4.
[83] Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 2002;71:651–5.

[84] Gonzalez-Castro TB, Nicolini H, Lanzagorta N, Lopez-Narvaez L, Genis A, Pool Garcia S, et al. The role of brain-derived neurotrophic factor (BDNF) Val66Met genetic polymorphism in bipolar disorder: a case-control study, comorbidities, and meta-analysis of 16,786 subjects. Bipolar Disord 2015;17:27–38.
[85] Wang Z, Li Z, Gao K, Fang Y. Association between brain-derived neurotrophic factor genetic polymorphism Val66Met and susceptibility to bipolar disorder: a meta-analysis. BMC Psychiatr 2014;14:366.
[86] Li M, Chang H, Xiao X. BDNF Val66Met polymorphism and bipolar disorder in European populations: a risk association in case-control, family-based and GWAS studies. Neurosci Biobehav Rev 2016;68:218–33.
[87] Mandolini GM, Lazzaretti M, Pigoni A, Delvecchio G, Soares JC, Brambilla P. The impact of BDNF Val66Met polymorphism on cognition in Bipolar Disorder: a review: special Section on "Translational and Neuroscience Studies in Affective Disorders" Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. J Affect Disord 2019;243:552–8.
[88] Rao JS, Keleshian VL, Klein S, Rapoport SI. Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. Transl Psychiatry 2012;2:e132.
[89] D'Addario C, Dell'Osso B, Palazzo MC, Benatti B, Lietti L, Cattaneo E, et al. Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. Neuropsychopharmacol : Off Publ Am Coll Neuropsychopharmacol 2012;37:1647–55.
[90] Strauss JS, Khare T, De Luca V, Jeremian R, Kennedy JL, Vincent JB, et al. Quantitative leukocyte BDNF promoter methylation analysis in bipolar disorder. Int J Bipolar Disord 2013;1:28.
[91] Mitchelmore C, Gede L. Brain Derived Neurotrophic Factor: epigenetic regulation in psychiatric disorders. Brain Res 2014;1586:162–72.
[92] Gonulalan EM, Nemutlu E, Bayazeid O, Kocak E, Yalcin FN, Demirezer LO. Metabolomics and proteomics profiles of some medicinal plants and correlation with BDNF activity. Phytomedicine 2019 (in press).
[93] de Vries I, Schmitt H, Lenarz T, Prenzler N, Alvi S, Staecker H, et al. Detection of BDNF-related proteins in human perilymph in patients with hearing loss. Front Neurosci 2019;13:214.
[94] Huang TL, Lo LH, Shiea J, Su H. Rapid and simple analysis of disease-associated biomarkers of Taiwanese patients with schizophrenia using matrix-assisted laser desorption ionization mass spectrometry. Clin Chim Acta 2017;473:75–81.
[95] Huang TL, Sung ML, Chen TY. 2D-DIGE proteome analysis on the platelet proteins of patients with major depression. Proteome Sci 2014;12:1.
[96] Huang TL, Cho YT, Su H, Shiea J. Principle component analysis combined with matrix-assisted laser desorption ionization mass spectrometry for rapid diagnosing the sera of patients with major depression. Clin Chim Acta 2013;424:175–81.
[97] Lo LH, Huang TL, Shiea J. Acid hydrolysis followed by matrix-assisted laser desorption/ionization mass spectrometry for the rapid diagnosis of serum protein biomarkers in patients with major depression. Rapid Commun Mass Spectrom 2009;23:589–98.
[98] Huang TL, Lo LH, Lin CC, Hung YY. Proteome analysis of catatonia. Neuropsychiatry 2017;7:942–51.
[99] Lo LH, Shiea J, Huang TL. Rapid detection of alteration of serum IgG in patients with schizophrenia after risperidone treatment by matrix-assisted laser desorption ionization/time-of-flight mass spectrometry. Rapid Commun Mass Spectrom 2016;30:2645–9.
[100] Huang TL, Lo LH. Proteomics approach for biomarker research in major depression: antidepressant effects. Curr Drug Metabol 2018;19:502–12.