

Translational Findings on Brain-Derived Neurotrophic Factor and Anxiety: Contributions from Basic Research to Clinical Practice

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Key Words

Anxiety · Brain-derived neurotrophic factor · Humans · Mouse model · Translational research · Val⁶⁶Met polymorphism

Abstract

Background/Aims: Anxious responses are evolutionarily adaptive, but excessive fear can become disabling and lead to anxiety disorders. Translational models of anxiety might be useful sources for understanding the neurobiology of fear and anxiety and can contribute to future proposals of therapeutic intervention for the disorders studied. Brain-derived neurotrophic factor (BDNF), which is known for its importance on neuroplasticity and contextual memory, has emerged as a relevant element for emotional memory. Recent studies show that the Val⁶⁶Met BDNF polymorphism correlates with various psychiatric disorders, including anxiety, but there are several differences between experimental and clinical studies. **Methods:** In this work, we review the literature focused on the BDNF Val⁶⁶Met polymorphism and anxiety, and discuss biological findings from animal models to clinical studies. **Results:** As occurs with other psychiatric disorders, anxiety correlates with anatomical, behavioral

and physiological changes related to the BDNF polymorphism. In animal studies, it has been shown that a significant decrease in regulated secretion from both BDNF_{Val/Met} and BDNF_{Met/Met} neurons represented a significant decrease in available BDNF. **Conclusion:** These studies suggest that developing pharmacological strategies facilitating the release of BDNF from synapses or prolongation of the half-life of secreted BDNF may improve the therapeutic responses of humans expressing the BDNF polymorphism.

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Anxiety Disorders and BDNF

Anxiety is a mental state that is evoked in anticipation of a potential or imminent threat. Feeling anxiety is usually part of the human experience, but excessive or inappropriate anxiety can lead to pathological states. Anxiety is accompanied by behavioral and physiological responses, including avoidance, vigilance and arousal, which are used to protect the individual from danger. These anxiety-related responses have been observed in humans and other animals, and are part of a universal mechanism of adaptation to adverse conditions [1].

Nonpathological anxiety can be divided into two categories: the anxiety state, that would be an immediate or acute response to threat, and the anxiety trait, a more permanent feature that reflects an individual's tendency to exhibit increased anxiety responses over time. In its pathological form, anxiety can seriously interfere in daily life and can be classified into six syndromes that were described in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-R) [2]: generalized anxiety disorder, social phobia, specific phobia, panic disorder, posttraumatic stress disorder and obsessive-compulsive disorder. Although they are classified into six different syndromes, all of them have certain physiological characteristics and behaviors in common [1].

The susceptibility to psychiatric disorders such as mood disorders and anxiety disorders can be determined early in life. Mechanisms of early development can lead the organism to present a lifelong tendency to express anxiety in response to threatening stimuli. As the mechanisms of development are under both genetic and environmental control, studies in monkeys and rodents support the important role of gene-environment interactions in the etiology of anxiety [3]. Indeed, genetic variations in the promoter of the serotonin transporter gene [4], changes in the expression of the serotonin type 1B receptor [5] or a decrease in hippocampal volume [6] have been related to individuals more likely predisposed to develop anxiety disorders and depression when exposed to traumatic experiences.

Environmental effects during development are well illustrated in animals suffering from trauma in their early development, such as maternal separation [7] or malnutrition [8], thus having a tendency to develop anxiety disorders and presenting physiological changes more easily. A plausible explanation for this is that the hippocampus is more susceptible to adverse influences during the early stages of development.

Moreover, it was demonstrated that epigenetic changes may occur as a result of these insults, leading to a decrease in the synthesis of serotonin in the brain and increasing the susceptibility to anxiety [9]. Studies show that animals that are positively encouraged in the early postnatal life are less prone to anxiety and present lower levels of glucocorticoid receptors and increased levels of brain-derived neurotrophic factor (BDNF), acetylcholinesterase and synaptic markers in the cortex and hippocampus [10].

BDNF has emerged as an important factor for the understanding of memory processing in anxiety disorders and depression in humans. BDNF plays a major role in

the synaptic plasticity associated with learning and memory [11], especially in fear learning and extinction [12]. Anxiety disorders and depression have been associated with decreased levels of BDNF [13, 14] or BDNF polymorphisms [15, 16].

Effects of BDNF on Learning and Memory

BDNF was the second member of the neurotrophin family of growth factors to be described in the literature after the demonstration of its effects in promoting the survival of dorsal root ganglion cells [17].

BDNF is well known for its effects on the synaptic plasticity necessary for learning and memory, and new studies have shown that the differential activation and the role of different cascades activated by BDNF in neuronal survival depend on the cell type and the involvement of pathological or physiological stimuli. Through the activation of different signaling pathways, BDNF induces rapid effects on synaptic transmission and membrane excitability, acting at both pre- and postsynaptic sites [18].

The role of BDNF in learning and memory was established by investigations in *in vivo* models. Increased hippocampal BDNF levels have been correlated with better performance in the Morris water maze [19], and improved performance was observed in hippocampal BDNF knockout animals in the object recognition test [20] and in fear conditioning [21] tests.

These data indicate that the regulation of BDNF activity might correlate with hippocampal-dependent learning. Consistent with these studies, it has been demonstrated that the highest levels of BDNF expression are found in the neocortex, hippocampus, striatum, cerebellum, amygdala and prelimbic cortex [21–24], all key areas for cognitive processing.

These studies suggest that BDNF has an essential role in the consolidation of short- and long-term memories (LTM), which has been shown by a wide range of behavioral testing protocols in wild-type animals [25].

In particular, BDNF/tyrosine kinase (Trk) B signaling through the mitogen-activated protein kinase pathway has been associated with enhanced excitatory synaptic transmission *in vivo*, as well as with hippocampus-dependent behavior. This provides strong evidence for the notion that intracellular signaling cascades involved in synaptic plasticity are induced by environmental interactions and influence behavioral learning [25].

There are two critical periods for LTM formation in which BDNF is required: one 1–4 h after information en-

coding, and this is critical for LTM lasting for 1–2 days, whereas the other occurs 12 h after memory formation and is important for persistence of LTM 7 days later. Extinction of previously acquired memories is a new form of learning and a potential target of BDNF-mediated plasticity. It has been shown that extinction of conditioned fear is accompanied by a significant increase in BDNF gene expression, particularly the transcription mediated by BDNF promoters I and III in the prefrontal cortex and amygdala [26]. Moreover, extinction of fear-potentiated startle was impaired in mice with a site-specific knockout of the BDNF gene in the dorsal hippocampus through targeted injections of a Cre recombinase lentivirus in adult mice floxed at the BDNF locus [27].

Long-term potentiation (LTP) is the most studied form of synaptic plasticity and is considered to be a cellular correlate of learning and memory. It is defined as a sustained increase in synaptic strength induced by activity. The induction of LTP is associated with activation of a large number of signaling cascades, including those activated by BDNF. At low concentrations, BDNF activates neurons in the hippocampus, cortex and cerebellum. Neurotrophin-induced depolarization resulting in the activation of sodium conductance was reversibly blocked by K-252a, a protein kinase blocker, which preferentially binds to Trk receptors [28]. These data demonstrate that neurotrophins elicit a very rapid excitatory action, placing them among the most potent endogenous neuro-excitants in the mammalian central nervous system. In addition, other studies have shown that BDNF not only acts as a modulator of ion channels, but can also directly and rapidly gate Na⁺ channels, thereby assigning BDNF the property of a classical excitatory neurotransmitter [29]. This was a remarkable finding, as before then, only classical neurotransmitters were believed to exert rapid effects on the membrane potential of neurons. Substantial evidence has indicated that BDNF can cause an immediate and robust induction of LTP in the dentate gyrus [30] and in CA1 cells [31].

BDNF can modulate fast excitatory transmission by increasing the number of vesicles docked at the active zone of the synapse, or postsynaptically by altering the activation kinetics of N-methyl-D-aspartate receptors and increasing the expression of 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptors [18].

BDNF and glutamate interact to regulate developmental and adult neuroplasticity. Glutamate stimulates the production of BDNF, which, in turn, modifies neuronal glutamate sensitivity, Ca²⁺ homeostasis and plasticity [32]. BDNF also modulates inhibitory synapses, a process that occurs by the activation of TrkB receptors. Taken to-

gether, all this provides evidence for the concept that activity-dependent inhibitory synaptogenesis signaling occurs via the TrkB receptor and that continuous extracellular supply of BDNF is important for the proper formation and functional maturation of glutamatergic and GABAergic synapses [33].

Thus, BDNF plays an important role in the control and regulation of the balance between the activity of excitatory and inhibitory synapses to maintain the proper functioning of neural networks. In contrast to these rapid effects on synaptic transmission and membrane excitability, BDNF also mediates slower cellular events. It is well established that, like other neurotrophins, BDNF promotes the growth, differentiation, target innervation and survival of neurons during development in the central and peripheral nervous system [25, 34].

In the adult brain, BDNF promotes the growth of dendrites through the activation of TrkB receptors [35], prevents apoptosis of cells in the hippocampus and cerebellum [36, 37], positively regulates hippocampal neurogenesis in the subgranular zone of the dentate gyrus [11, 38] and maintains dendritic spines in cortical neurons [39].

The BDNF gene contains four differentially regulated promoters that generate four distinct mRNA transcripts, each containing a unique noncoding 5'-exon and a common 3'-coding exon. The diverse BDNF promoters and 5'-exons exert different functions during the consolidation of learning. The selective increase in BDNF transcripts containing exons I and III was verified in the amygdala 2 h following fear conditioning, while mRNA levels of BDNF exons II and IV remained unchanged. These results provided the first evidence of differential splicing and/or differential BDNF promoter usage in response to a behaviorally relevant learning paradigm [40].

Thus, BDNF can activate various signaling pathways that may act to regulate the necessary effects for synaptic plasticity and memory formation. The pathway to be selectively activated is triggered by biological responses that are dependent on the expression levels of BDNF and TrkB receptors, the temporal pattern of BDNF stimulation, the form of BDNF that is released and whether the signaling is activated pre- or postsynaptically.

There are many feedback systems that control BDNF activity. Besides being able to increase its own transcription through a mechanism mediated by CREB [41], for example, BDNF can also enhance the expression of TrkB receptor on the surface [42]. Moreover, it can regulate its own release [43, 44]. These properties are likely to contribute to the strengthening and stabilization of synaptic connections.

However, prolonged exposure to BDNF induces a negative feedback loop, exhausting TrkB receptors on the neuronal surface, resulting in receptor long-term desensitization to BDNF [45].

BDNF Polymorphism in Humans

The confirmation of the importance of the regulated traffic of BDNF for cognitive function comes from a functional single nucleotide polymorphism (SNP) identified in the human BDNF gene, the Val⁶⁶Met [46]. This SNP is the substitution of methionine for valine at position 66 in the BDNF precursor (pro-BDNF). This BDNF SNP exists in human populations with an allele frequency of 20–30% (BDNF_{Val/Met}), but homozygosity for the Met allele (BDNF_{Met/Met}) is rare in the general population, comprising only 4% of people in Caucasian populations [47]. However, there are significant ethnic differences in the BDNF Val⁶⁶Met polymorphism. In the Korean population, for example, the most frequent genotype was found to be BDNF_{Val/Met} and they display a similar distribution of Met and Val alleles [48]. The BDNF polymorphism may provide a valuable tool to understand how BDNF is associated with anatomical and behavioral phenotypes in humans and how genetic variations interfere in the development of neuropsychiatric disorders.

Morphological studies showed that in healthy human subjects, the met allele is linked with diminished levels of hippocampal N-acetyl aspartate, a putative marker of neuronal integrity and synaptic abundance [46, 49], but is not associated with changes in the serotonergic system [50]. In brain structure investigations, a reduction in the volume of the hippocampal formation has been observed [51]. In addition, volume reductions in gray matter in the cerebral neocortex of healthy Met allele carriers were found to be associated with a decreased volume of the dorsolateral prefrontal cortex, as well as of subcortical regions such as the caudate nucleus [52] and amygdala in healthy aged subjects [53].

In relation to behavioral studies, the Met group exhibited deficits in episodic memory [46], reduced hippocampal activity during both encoding and retrieval processes, as shown by blood oxygenation level-dependent functional MRI responses in the posterior hippocampal formation [54], as well as impaired extinction learning [15]. Furthermore, healthy subjects with the BDNF_{Val/Met} genotype showed lower mean performance IQ in the Object Assembly subtest [55]. Moreover, the BDNF polymorphism attenuated the cognitive benefits

of exercise in recognition memory in healthy, sedentary young adults [56].

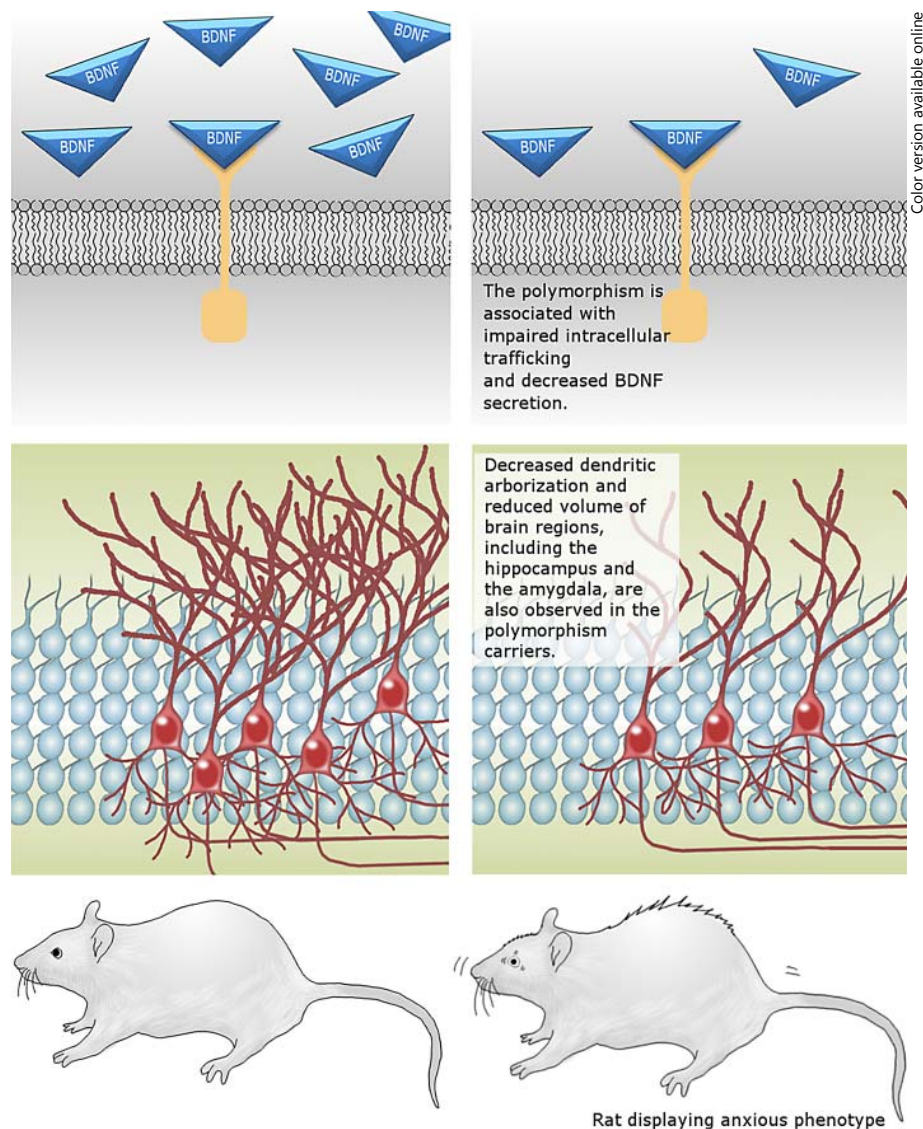
The BDNF polymorphism has been associated with several neuropsychiatric disorders, such as Alzheimer's disease [57–59], schizophrenia [60, 61], attention-deficit hyperactivity disorder [62], bipolar disorder [63], suicide pathogenesis [64], Parkinson's disease [65], risk for affective disorder [66], drug abuse [67, 68] and depression [69]. In general, correlations are made between the pathology and the morphological and behavioral features of the BDNF polymorphism carriers. However, there are also studies that found no relationship between the disease and the BDNF_{Val/Met} or BDNF_{Met/Met} genotype, suggesting that the BDNF polymorphism may not be considered a predictor but a genetic risk factor for the development or worsening of some diseases.

BDNF_{Met} Knockin Mice

The first study examining the trafficking of BDNF_{Met} showed that when it is expressed in hippocampal neurons, less BDNF_{Met} is secreted in an activity-dependent manner [46]. Subsequently, Chen et al. [70] demonstrated that the Met substitution in the BDNF prodomain impaired intracellular trafficking and regulated secretion of BDNF in primary cortical neurons, and that the coexpression of BDNF_{Val} and BDNF_{Met} heterodimers resulted in less efficient BDNF trafficking into the regulated secretory pathway in neurons. The molecular mechanism underlying defective BDNF_{Met} function appeared to be attributable not to the form of BDNF secreted but more simply to the amount of BDNF released in an activity-dependent manner.

The decreased regulated secretion of BDNF may explain the behavioral deficits observed in humans heterozygous for the relatively common Met polymorphism, since the majority of BDNF is released from the regulated secretory pathway in neurons.

To better understand the molecular mechanisms related to this BDNF polymorphism, Chen et al. [71] generated a variant BDNF mouse (BDNF_{Met/Met}). This BDNF_{Met/Met} model reproduces the phenotypic hallmarks of humans although comparable levels of BDNF are observed in brain lysates in BDNF_{Val/Met} and BDNF_{Met/Met} mice and wild-type controls. Moreover, no difference was found in constitutive secretion from either BDNF_{Val/Met} or BDNF_{Met/Met} neurons. However, a significant decrease in regulated secretion from both BDNF_{Val/Met} and BDNF_{Met/Met} neurons represented a significant decrease in available BDNF.



Color version available online

Fig. 1. The BDNF polymorphism is associated with different neural features. Although no difference was found in constitutive secretion from neurons of either BDNF_{Val/Met} (right panel) or BDNF_{Met/Met} (left panel) mice, a significant decrease in regulated secretion from both BDNF_{Val/Met} and BDNF_{Met/Met} neurons represented a significant decrease in available BDNF. A significant decrease in hippocampal volume and in dendritic arborization complexity in the dentate gyrus was also observed. Accordingly, both BDNF_{Val/Met} and BDNF_{Met/Met} mice showed significantly less context-dependent memory and exploratory behavior in tests that selectively assess hippocampal and amygdala-dependent learning.

A significant decrease in hippocampal volume and in dendritic arborization complexity in the dentate gyrus was also observed. Finally, in tests that selectively assess hippocampal and amygdala-dependent learning, BDNF_{Val/Met} and BDNF_{Met/Met} mice showed significantly less context-dependent memory and exploratory behavior (fig. 1).

Correlation between the BDNF Polymorphism and Anxiety

As occurs with other psychiatric disorders, anxiety correlates with anatomical changes related to the BDNF polymorphism, such as reduction in the volume of the

hippocampal formation [72], impaired survival of newly born cells and LTP in the dentate gyrus [73] and dysfunctions in the medial prefrontal cortex, as well as in amygdaloid and midbrain central gray [74]. In addition, the BDNF polymorphism is believed to be associated with responsiveness of the hypothalamic-pituitary-adrenal axis to psychological stress characterized by individual differences in stress regulation and possibly genetic vulnerability to stress-related disorders [75–78].

In animal models, behavioral tests showed that the anxious phenotype of BDNF_{Met/Met} mice relates to decreased exploratory behavior, as demonstrated by a reduction in the number of entries and in the percentage of time spent in the center of the open field arena, and a sig-

Table 1. The BDNF polymorphism in different anxiety disorders and populations

Reference	Disorder	Association	Sample	Comments
Lam et al. [82], 2004	PD	No	103 patients	Analyzed genotype or allele in the Chinese population.
Shimizu et al. [83], 2005	PD	No	109 patients	Analyzed genotype or allele in the Japanese population.
Wendland et al. [84], 2007	OCD	No	295 patients	The gene variants were no significantly associated with comorbid anxiety disorders.
Katerberg et al. [85], 2009	OCD	Yes	419 patients	In women with OCD, the BDNF _{Met/Met} genotype was associated with later age of onset and a trend for a negative family history, whereas the BDNF _{Val/Val} genotype was associated with a trend for lower Yale-Brown Obsessive Compulsive Scale severity scores.
da Rocha et al. [86], 2011	OCD	Yes	122 patients	Met allele carriers showed impairment in decisions made under ambiguous conditions possibly related to the dysfunctions of the orbitofrontal cortices that are associated with OCD.
Fullana et al. [87], 2012	OCD	Yes	106 patients	Genetic variation in BDNF was associated with treatment response in exposure-based cognitive behavior therapy.
Zhang et al. [88], 2006	PTSD	No	96 patients	The negative results for PTSD could be due to low statistical power.
Valente et al. [89], 2011	PTSD	No	65 patients and 34 victims of urban violence	There was no statistically significant difference between the BDNF _{Val/Met} and serotonin transporter polymorphism and traumatic phenotype.
Wichers et al. [90], 2008	Social stress	Yes	446 healthy subjects	Healthy heterozygous BDNF _{Met} carriers exhibited an increased stress-induced negative affect response to social stress.
Xie et al. [91], 2011	Phobic disorders	Yes	120 patients and 267 healthy subjects	A significant association between phobic disorders and BDNF haplotype was proposed in the Han Chinese population.
Jiang et al. [92], 2005	Anxiety	Yes	153 Met allele carriers	Genotyping was performed in US Caucasian, American Indian and African American populations. The Met 66 allele was associated with increased harm avoidance and was most abundant in individuals with both anxiety disorders and major depression.
Gatt et al. [93], 2009	Anxiety	Yes	374 subjects	European BDNF _{Met} carriers exposed to greater early-life stress presented smaller hippocampal and amygdala volumes, heart rate elevations, decline in working memory, elevated neuroticism and higher depression and anxiety.
Tocchetto et al. [94], 2011	Anxiety	Yes	228 subjects	An association between carrying one copy of the Met allele and higher chance of anxiety disorders in children and adolescents was proposed.
Hünnerkopf et al. [95], 2007	Anxiety traits	Yes	272 subjects	There was a significant dopamine transporter gene variation-dependent association between neuroticism and the BDNF _{Val/Met} polymorphism in healthy volunteers of German ethnicity.
Arias et al. [96], 2012	Anxiety traits	Yes	553 individuals	There was a significant gene-gene interaction on harm avoidance between the serotonin transporter gene and the BDNF _{Val/Met} polymorphism.

PD = Panic disorder; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder.

nificant decrease in the number of entries and in the percentage of time spent in the open arms of the elevated plus maze [71]. Administration of fluoxetine, an antidepressant for which one postulated mechanism of action involves increasing BDNF levels, the BDNF_{Met/Met} mice showed decreased anxiety-related behaviors in the open field and in the novelty-induced hypophagia tests. The authors report that only the homozygous mice exhibited anxiety, and that although a correlation between this animal model and heterozygous individuals cannot be made, it can be suggested that genetic, as well as environmental influences, might be required for this SNP to influence psychiatric pathology [71, 75].

A strong correlation between polymorphisms and anxiety has been proposed based on similar changes demonstrated in extinction learning in both mice and humans. These studies measured brain activity during the extinction of a previously conditioned stimulus memory, and Met allele carriers showed weaker extinction rates. Imaging data showed significantly less ventromedial prefrontal cortex (vmPFC) activity and greater amygdala activity during extinction in Met allele carriers in comparison with non-Met allele carriers. These findings indicate that cortical regions previously shown to be essential for extinction (vmPFC) in both rodents and humans are hyporesponsive in Met allele carriers in relation to non-Met allele carriers. Moreover, Met allele carriers showed continued recruitment of the amygdala, a brain structure expected to display diminished activity during the extinction trials of the experiment. A significant decrease in vmPFC volume in BDNF_{Met/Met} mice was shown, and no significant differences in taste discrimination in the BDNF_{Met/Met} mice compared to wild-type mice were found, with no observable impairments in acquisition or retention of conditioned taste aversion [15, 79].

Neurophysiological data that show impaired extinction learning have also been implicated in anxiety disorders, including phobias and posttraumatic stress disorders [80]. However, clinical studies conducted so far are still controversial, and have not conclusively demonstrated the association between the polymorphism for BDNF and anxiety, as can be noticed in table 1.

The differences in the results on anxiety between the BDNF_{Met} animal model and clinical studies may be due to: (1) mice were subjected to conflict tests to elicit the increased anxiety-related behavior, whereas human studies relied on questionnaires; (2) the anxiety-related phenotype was only present in homozygous mice for the Met allele, which suggested that association studies that focused primarily on heterozygous humans for the Met allele may

not detect the correlation found by Chen et al. [81]; (3) genotyping difficulties in humans; (4) small sample size, which leads to decreased statistical power; (5) clinical heterogeneity, and finally (6) significant ethnic differences.

Prospects in BDNF Polymorphism Research for Anxiety Treatment

The BDNF polymorphism research in animals and humans represents a powerful tool for understanding the involvement of BDNF on the pathogenesis of anxiety disorders. In this respect, it is worth noting the observation made by many authors that the BDNF genotype along with clinical observations, such as those identified by neuroimaging techniques, may be useful as biomarkers to provide guidance for more customized therapeutic directions or predict the patients' responsiveness to treatment. However, more clinical studies must be performed on the basis of the observations reported in this work. Studies on animal models suggest that developing pharmacological strategies facilitating the release of BDNF from synapses or prolongation of the half-life of secreted BDNF may improve the therapeutic responses of humans expressing the BDNF polymorphism.

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