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Anxiety Disorder and BDNF: Integrative Review of the Literature

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ABSTRACT

Objective: To analyze the relationship between Brain-Derived Neurotrophic Factor (BDNF) and Anxiety Disorders (AD) and describe possible damage to the psychic functions in individuals with this disorder. Methods: this was an integrative review of the literature of articles published between 2008 and 2018, selected in the bibliographic databases of PubMed, Scielo and LILACS.

Results and Discussion: In total, 28 articles were selected, of studies conducted with humans and animals. The relationship between levels of BDNF, including polymorphism in the BDNF gene, and AD was observed to have been approached, showing that the neurotrophic hypothesis could contribute to the physiopathology of ADs, including volumetric changes in regions of the brain, comprising psychic functions in patients with AD. Furthermore, studies have shown that the BDNF levels may reflect the effect of antidepressant or neuromodulation therapy, and that exposure to stressful factors may be related to individuals with this genetic variant being more vulnerable to developing AD.

Conclusions: The data obtained in this research pointed towards an inverse relationship between BDNF levels and AD, and to the contribution of the neurotrophic hypothesis to the neurobiology of these disturbances, including damage to the psychic functions. Whereas considering that other studies to not show this relationship, further studies need to be conducted to validate a possible association. It was possible to hypothesize that BDNF, although unspecific, could be a biomarker associated with AD, and could be capable of helping with preventive actions to maintain mental health.

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Introduction

Anxiety disorders (AD) have specific criteria, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM V), and are the most prevalent psychiatric disorders [1, 2]. Their symptoms are: sweating, tremors, cold shivers, tachycardia, poor mental state, hyperventilation, in addition to difficulty with concentration, emotional instability, compromised sleep quality and difficulties with performing daily tasks [3]. They are classified into: panic attack, agoraphobia, generalized anxiety disorder (GAD), social phobia, specific phobia, separation anxiety disorder [4].

An American census conducted between 2019 and 2020, before and during the Covid19 pandemic, demonstrated that the rate of prevalence of anxiety increased three time more in this population, rising from 8.2% to 29.4%, with a discrete reduction between April and May 2020 [5]. Relative to gender, in women the prevalence was approximately double the rate in comparison with men [2, 4]. Furthermore, the World Health Organization (WHO) released its major global review of mental health around the world in 2022, showing that in 2019, an estimated 970 million people were living with some type of mental disorder, anxiety disorders (31.0%) and depressive disorders (28.9%) were the most prevalent for both genders [6].

ADs are brain disturbances in which various heterogeneous pathogenic mechanisms are expressed [7]. Their neurobiology is complex, resulting from the interaction of various psychological, environmental and biological factors. They are characterized by a variety of factors related to neuroendocrinology, neurotransmitter circuits and neuroanatomic changes, aggravated by the high degree of interconnectivity between the circuits of the limbic system, brainstem and cortical areas of the brain, which may be of environmental or genetic origin [8].

The physiopathology of anxiety disorders, on which studies have been limited to laboratory studies and experiments with animals in the last few decades, is similar to that of the psychiatric disorder most studied in the area of psychoimmunology, the major depressive disorder, of which the biological mechanisms most recently studied are: neuroinflammation and the immune kynurenine pathway [7].

Exposure to stress, one of the main risk factors for psychiatric diseases, may cause neuroinflammation and have repercussions on neurogenesis, leading to damage in brain plasticity, compromising psychic functions such as learning and memory, and inducing anxious behaviors [9, 10].

Studies have hypothesized that through the presence of inflammatory cytokines, neuroinflammation contributes to deviation of the route of production of the neurotransmitter serotonin. This begins from

its main precursor amino acid, tryptophan, by the presence of the enzyme dioxygenase, leading to the production of kynurenine, a compound that can be converted into the neurotoxic metabolite: quinolinic acid [2,3]. This quinolinic acid activates the receptors of glutamate, an excitatory neurotransmitter, stimulates its release and blocks its re-uptake by the astrocytes, contributing to it not becoming excessive within and outside of the synapse, increasing the glutamate excitotoxicity, diminishing the production of the brain derived neurotrophic factor (BDNF) [9].

BDNF is an abundant neurotrophin in the brain, and among its other functions, it is responsible for cerebral plasticity and neurogenesis - the process whereby the neurons are generated from progenitors for integration into the neuronal network-[11].

Further to the neurobiology of ADs, the increase in activity in regions of the brain that process emotion, in patients who have anxiety disorder, this may result from glutamate excess [8]. On diminishing the levels of BDNF, this excess may in turn affect the integrity of the neuronal system, by compromising brain neurogenesis [10].

According to the WHO, approximately half of the cases of AD are diagnosed, 1/3 receive medication treatment, 1/5 (20.6%) seek the help of health services, so that 23.2% receive no treatment whatsoever. Of the others, 30.8% receive medication treatment only, 19.6% receive psychological treatment only, and 26.5 were treated with medication and psychotherapy [4]. At least 1/3 of the patients with anxiety disorders do not respond to pharmacological treatment, and as yet there is no explanation for justifying the reason why some patients respond well, and others do not [12].

Regarding treatment, when compared with medication therapy, physical exercise is considered an alternative for anxiety disorders. Not only does it cost less and have fewer adverse side effects, but it may be associated with the rise in BDNF levels [13]. A research with lifestyle intervention (diet, physical exercise, and change in behavior), showed considerable benefits in cases of moderate to severe anxiety [14].

Methodology

This was an integrative review of the literature, with articles being selected among scientific publications in the Virtual Library on Health ("Biblioteca Virtual em Saúde (BVS)") and Pubmed. The inclusion criteria were as follows; 1) publications in the electronic databases of: PubMed, Scielo and LILACS, between 2008 and 2018, using the following descriptors: Anxiety disorders (transtornos da ansiedade) and BDNF. Analysis were performed in two stages, according to the PRISMA Flow Diagram, Fig.

1. In the first stage, the exclusion criteria were: 1) text written in a language other than English and Portuguese, 2) did not approach the subject of anxiety disorders (AD) and BDNF, including polymorphisms related to the BDNF gene. The exclusion criteria applied in the second stage were: 1) articles with an approach to the relationship between BDNF, including polymorphisms related to the BDNF gene, and AD, in accordance with the diagnosis of DSM V, 2) review articles and 3) absence of consensus among all the researchers about the selection of the article.

Results and Discussion

Initially, 698 articles in English were selected, in the period from 2000 to 2018. These went through two stages of analysis, according to the Flow Diagram PRISMA, Fig 01. Initially, 10 duplicated articles were removed. At this stage, the articles were divided among the researchers, who made their selections independently. After applying the exclusion criteria, 101 articles remained for analysis. After this, in the first stage of exclusion, the following were removed: review articles, those that did not approach the relations between levels of BDNF and TA, including polymorphism, and those with absence of consensus about the relations between BDNF and AD among all the researchers, who had analyzed them independently, after having read the complete text. In cases in which there was disagreement, the researchers decided on exclusion of the article. The 28 final articles generated data for filling out Tables 01, 02 and 03. Due to the type of study design chosen, there was no need to approach ethical aspects.

Table 1: Results of the integrative review of the literature of studies with humans

	Author, year	Design	N	Results	Conclusions
1	ANDREATTA, M., et al 2018.	Case-Contro l	65.	In the experiment with humans, with prior genotype analysis, in a virtual environment with predictable shock stimulus (CTX+), another without shock stimulus (CTX), and one with unpredictable stimulus (G-CTX), considered a mixture between the two previous types, the responses were analyzed. CTX+ was classified as being more excitant, anxiogenic and caused potentiated responses.	The BDNF polymorphism did not affect... ...contextual learning and its generalization at a verbal level. Individuals with Met are characterized by rapid discriminative contextual learning and a tendency towards generalizing anxiety responses to ambiguous contexts. This learning may be related to the reduction in functionality of the hippocampus, and the risk of individuals with Met developing anxiety disorders. "
2.	CARLINO, D., et al. 2015.	Cross-sectio nal	672.	There was no significant correlation between the levels and severity of AD, reduction in neurotrophic activity (serum level of BDNF) or associated genetic polymorphism. There was evidence of a significant reduction in serum BDNF in women with GAD, and in men with Specific Phobias. There were indications of low heritability and absence of any impact of Val66Met polymorphism in the circulating concentrations of BDNF.	BDNF is not a general biomarker of anxiety, but the serum levels of BDNF were specifically correlated to gender with the subtypes of Anxiety Disorders.

3	3. JAMAL, M.; VAN DER DOES, W.; and PENNINX, B. W. J. H. 2015.	Cross-sectional	1271.	Among individuals with BDNF Val carrier patients, those who were nicotine dependent smokers had more severe symptoms of depression than the other three groups (smokers not dependent on nicotine, and non-smokers) who also had the polymorphism.	The study suggested that genetic differences maybe crucial for the worst behavioral results in nicotine users, and that BDNF Val (66) polymorphism carrier patients could benefit their mental health to a greater extent by quitting smoking.
4	KONISHI, Y., et al. 2014.	Cross-sectional	252.	In the Group with Early Onset of Panic Disorder (<30 years), the State-Trait Anxiety Inventory (STAI) Score was higher in carriers of the BDNF Met/Met polymorphism and tended to be lower in those with Val/Val or Val/Met. The high score was also found in the Val/Val genotype of the control group (healthy individuals).	The genotype BDNF Met/Met could increase the characteristics of anxiety in early onset Panic Disorder.
5	CHAGNON, Y. C., et al. 2015.	Cross-sectional	43.	The higher [level of] DNA methylation of BDNF was observed in individuals with anxiety/depression in comparison with individuals in the Control Group. The difference was greater for BDNF genotype CT rs626 carriers, compared with those with genotype CC.	The results suggested that DNA methylation interaction with the Single Nucleotide Variants (SNVs) in BDNF are associated with the occurrence of anxiety / depression in elderly women.
6	MUELLER, S. C., et al. 2013.	Cross-sectional	39.	The dorsal anterior cingulate cortex (dACC), hippocampus, amygdala and insula, main brain structures related to Anxiety Disorder (AD) were found to have differentiated volumes in Groups of adolescents with AD. These changes vary according to the BDNF genotype.;	The volume of some structures, specifically the dorsal portion of the dorsal-lateral cortex and insula undergo modulation by BDNF-Val polymorphism. This reinforces the neurotrophic hypothesis of the physiopathology of AD. These structures may be more sensitive to the action of BDNF in adolescence, so that the risk for development of AD may be identified.
7	TOCCHETTO, A., et al. 2011.	Case-Control	240.	In analysis of the BDNF gene, by means of saliva samples of children and adolescents with and without Anxiety Disorder (AD), a considerable association was found of being an Met allele carrier of BDNF, with greater chance of anxiety disorders.	The Val/Met genotype represents an independent risk factor for AD in childhood and adolescence, reinforcing the neurotrophic hypothesis of the physiopathology of AD, which ratifies the hypothesis that BDNF may be related to the development of early onset AD.
8	LAU, J. Y. F., et al. 2010.	Case-Control	58.	In the investigation of association between the BDNF genotype and the amygdala-hippocampal responses to emotional stimuli in adolescents with AD and/or major depressive disorder in comparison with healthy adolescents (Control Group). Evidence was shown of greater activations in the regions of the amygdala and anterior hippocampus in a higher number of patients with AD.	In the comparison between cases and controls, there was greater activation of brain structures such as the amygdala and hippocampus in response to expressions in the cases of Met variant carriers. This activation is modulated by BDNF. Lower levels of BDNF were associated with the expression of symptoms during the period of adolescence, and also played a role in the long term effects, which culminated in AD.
9	ENOCH, M., et al. 2008.	Cross-sectional	249.	Individuals with anxiety comorbidity had a higher proportion of alleles COMT Met158 and BDNF Met66 (P = 0,009), and a higher level of neuroticism to avoid damage, (P<0.0005) than all the other groups.	There may be two vulnerability factors for AD with different genetic susceptibility: (a) increased attention and better memory of work with slightly elevated anxiety neuroticism and (b) lower level of attention and working memory with higher level of anxiety - neuroticism. This refinement of the anxiety phenotype may have implications for therapeutic interventions.
10	MONTAG , C et al. 2008.	Experimental	37.	The 66Met variant carriers showed a stronger activation of the amygdala in the right hemisphere in response to emotional stimuli in comparison with that to neutral stimuli.	The results of this study added to the growing literature, showing that the BDNF 66Met polymorphism, which is associated with greater intensity of anxious manifestations.

11	MOREIRA, F. P., et al. 2015.	Cross-sectional	816.	The study showed a significant association between the Met and GAD allele. The serum levels of BDNF, however, did not diverge according to the diagnosis or distribution of the genotype. There were differences in the serum levels of BDNF in patients with GAD, according to the allele, with the allele Met being associated with higher levels of BDNF in comparison with Val/Val, after adjustment of variables.	The study suggested that BDNF could be characterized as a biological marker associated with AD, to the extent to which it could be involved in the neurobiology of GAD; and considering the association of the allele Met as a risk factor for the occurrence of disease.
12	ERNST, C et al. 2012.	Case-Control	67 255	Five individuals with deletions that covered to entire BDNF gene were identified in the study. This genic region was not changed in the control individuals or in cases diagnosed as being without developmental abnormalities.	Hemizygosis (exclusion of alleles) from the BDNF region contributes to variable psychiatric phenotypes, including those at the AD, behavioral and mood levels.
13	UGUZ, F., et al. 2013.	Cross-sectional	44	Newborns, children of healthy mothers, showed approximately two times more concentration of BDNF in comparison with children of mothers who had GAD. The duration of GAD during pregnancy was the only variable that correlated with the levels of BDNF in the umbilical cord.	The duration of maternal GAD has a significant effect on the reduction of fetal BDNF levels, while the severity of anxious symptoms did not interfere.
14	WANG, Y., et al. 2015.	Case-Control	355	Patients who had GAD or Compulsive Obsessive Disorder (COD) had significantly reduced plasma levels of BDNF, when compared with healthy control patients.	BDNF was involved in the physiopathology of mental disorders, not only in COD, but also in GAD. The patients with COD and GAD showed lower plasma levels of BDNF in comparison with healthy controls.
15	BALL , S. et al. 2013.	Randomized Clinical Trial	210	Patients who had GAD were treated with Duloxetine, whereas those treated with placebo obtained a significant mean increase in the BDNF levels from the beginning to end of the trial.	Treatment with Duloxetine increased the plasma levels of BDNF in patients with GAD. The studies suggested that the increase in BDNF reflected an effect of the antidepressant therapy. In spite of the increase in BDNF representing a normalization reflex of the physiopathology of the disease, the mechanisms of BDNF alone, could not be pointed out as being responsible for the therapeutic response.
16	VANDERMEE, M. R. J., 2018.	Cohort	476	This study showed that individuals with at least one allele met had better stability of behavioral inhibition at the age from 3 to 6 than individuals without the met variant.	The BDNF Val66Met single nucleotide polymorphism (SNP) was associated with reduced stability of behavioral inhibition from 3 to 6 years of age .
17	LU, R., et al, 2018.	Clinical Trial	35	The overall score on the HAM-A scale post-treatment with bilateral low-frequency repetitive transcranial magnetic stimulation on the dorsolateral prefrontal cortex for GAD, was significantly reduced when compared with the pre-treatment score. This suggested a significant reduction in the anxious symptoms, and significant increase in the serum concentrations of BDNF and 5-HT. The results showed a positive correlation between the increase in BDNF concentration with an increase in 5-HT concentration, and negative correlation between the serum concentrations of BDNF and 5-HT in relation to the score on the HAM-A scale.	The results suggested that the potential therapeutic mechanisms of bilateral low-frequency repetitive transcranial magnetic stimulation on the dorsolateral prefrontal cortex for GAD, at least partly, involved the interaction of BDNF and 5-HT in the brain.
18	MONTAG , C et al. 2010.	Cross-sectional Study	610	Patients who were homozygous for the BDNF 66Met Allele showed a significantly increased Temperament and Character Inventory (TCI) score for the facets related to the anxious personality in the construct of Harm Avoidance: Anticipatory worry and fear of uncertainty, when compared with allele Val66 carriers.	The impact of the BDNF Val66Met variant may represent a link to predisposition for developing GAD, and must, therefore, selectively influence specific facets of anxious behavior.

19	PALLANTI, S., et al. 2014.	Case-Control	24	PCR Analysis showed that the BDNF measures were elevated in the lymphocytes of patients with GAD, when compared with those of healthy controls. The levels of BDNF RNAm expression were significantly increased in patients with GAD, when compared with healthy controls.	There was a considerable increase in the BDNF levels in patients with GAD, when compared with healthy controls.
20	SHARPLEY, C. F., et al. 2018.	Case-Control	93	Patients with BDNF Val66Met polymorphism had significantly higher concentrations of salivary cortisol than patients without the allele Met.	Psychological resilience was inversely associated with anxiety and depression, emphasizing the value of the psychological factor in patients with prostate cancer, who could be more vulnerable to the development of anxiety and depression. Patients who had the allele met of the BDNF Val66Met polymorphism were at greater risk for the development of ypercortisolemia as a result of their stressful experiences, than patients who did not have this allele.
21	MOLENDIJK, M. L., et al. 2012.	Case-Control	775	Patients with anxiety disorder, in general, didn't show significantly different concentrations of BDNF, when compared with controls. Patients of the female sex, with anxiety disorder, showed lower serum concentrations of BDNF than controls of the female sex, and male sex patients. There was no difference in the serum concentrations of BDNF between the different types of anxiety, and there was no association between severity, chronic anxiety or major depressive disturbance and the levels of serum concentration. Age at onset of symptoms showed positive relation to the serum concentration of BDNF in the univariate analysis.	Due to the results, it appears to be improbable that BDNF is involved in the physiopathology of AD per se. The specific finding of gender, sowing low levels of BDNF only in women with anxiety disorder, may suggest that BDNF is related to the physiopathology of anxiety only in women, and not in men.

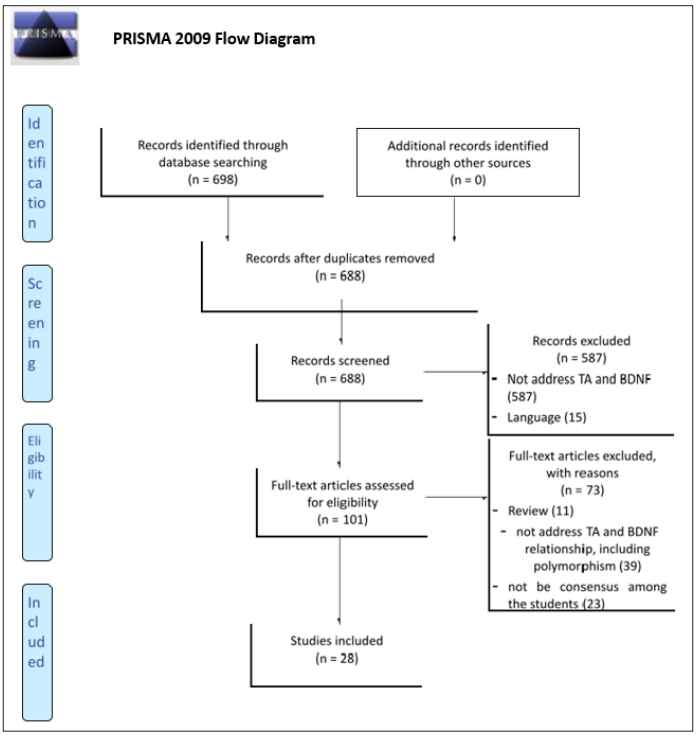
Table 2: Results of integrative review of the literature in studies with animals

	Author, year	Design	N	Results	Conclusions
1	JANKE, K. L., et al. 2015.	experimental	15	There's indirect relationship between AD and BDNF. The changes inherent to BDNF system have a repercussion on facilitated associative learning.	Not only was it observed that the reduction in BDNF in the hippocampus of rodents was related to the acquisition of associative learning, but also that the administration of BDNF in the hippocampus of rats contributed to its occurrence.
2	MIAO, Z., et al. 2017.	Prospective Cohort	45	Pregnant female rats, submitted to stress, showed anxious behaviors in propitious tests. In the amygdala of these same females, increased levels of BDNF were found.	The stress caused by witnessing the social defeat of their partners in pregnant female rats may induce anxious behavior up to 3 weeks postpartum. This finding could be correlated to changes in BDNF expression in the hippocampus, medial prefrontal cortex and amygdala of these rats.
3	KUMARI, A., et al. 2016.	Prospective Cohort	45	Social isolation caused anxious behavior in female rats. Significantly increased BDNF expression in the cerebral cortex of isolated female rats was observed, when compared with controls.	The anxious behavior caused by social isolation may be mediated by the expression of BDNF.
4	BAHI, A., 2016.	Prospective Cohort	40	Rats submitted to neonatal isolation as a model of stress showed an increase in miR124a expression, accompanied by suppression of the BDNF RNAm levels in the hippocampus. These findings were accompanied by reduction in social interaction and increase in anxious behavior, when compared with control	Ectopic expression of miR124a showed efficacy in reducing the social interaction in rats exposed to neonatal isolation. A robust effect of miR124a on anxious behavior was also seen. It was demonstrated that miR124a directly inhibited the expression of BDNF RNAm. These results indicated that in the hippocampus miR124a plays a critical role in the autism spectrum disorder and it could consequently be hypothesized that miR124a could participate in autism induced by stress and anxious behaviors caused by neonatal isolation by means of regulating the expression of BDNF RNAm.

5	BIRD, C. W., et al 2018.	Prospective Cohort	Total n was not informed and varied in each experime nt performed	Early exposure to vaporized ethanol interacted with the BDNF polymorphism to reduce the volume of the hippocampus. But this effect was not static and disappeared as the animal aged. There were no significant changes relative to anxiety.	Genetic variants of BDNF modulate the effect of development in the presence of exposure to ethanol. The findings showed that the interaction between genes and the environment play a determinant role in the behavioral phenotype in individuals with Fetal Alcohol Spectrum Disorder.

Table 3: Results of integrative review of the literature in studies with animals and humans

	Author, year	Design	N	Results	Conclusions
1	MOLLE, R. D., et al. 2012.	experimental 129	Adolescents, 17 rats	The plasma levels of BDNF in rats demonstrated that early exposure to stress (risk factor for AD), had repercussion on a change in the relationship between mother and pups, and indicated higher levels of BDNF in adult life, in comparison with another group, without exposure.	In addition to the relations of serum levels of BDNF with early stress in rats, similar associations were found in a sample of adolescent human beings, particularly in BDNF Met carriers. Furthermore, maternal overprotection and control behaviors in the human sample, appeared to be related to increased peripheral layers of BDNF an AD in the adult stage.
2	McGregor, N.W., et al. 2018.	Prospective Cohort (rats)/ Case- control (humans)	52 rats 286 humans	The rats exposed to stressful situations, maternal separation, contention and combinations of the two showed significant depressive and anxious behaviors, when compared with unexposed rats. There was association between the diagnosis of anxiety disorder in humans who had: MMP9 (rs3918242) and BDNF (rs6265 e rs10835210) polymorphisms, indicating the vulnerability of individuals with these genetic variants.	The association between BDNF polymorphisms and diagnosis of anxiety disorder in humans, emphasizes the fundamental role of BDNF as moderator of ADs.



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The neurotrophic hypothesis is applicable, particularly to depression, however, the relationship of BDNF with AD has been approached in up to date researches, both in rodents and human beings. In addition to having similar physiopathological characteristics, ADs and depression share a genetic base in various subtypes, therefore, contributing to the emergence of studies about the neurotrophic hypothesis for the physiopathology of AD [15].

According to CARLINO, BDNF is not a biomarker of anxiety, but its serum levels have been found to be reduced to a greater extent in women with generalized anxiety disorder, than in men, and have been specifically correlated with gender. In a case-control study, conducted with 775 persons, the results did not confirm the hypothesis that the serum concentration of BDNF would be reduced in patients with anxiety disorder, when compared with controls, suggesting that it was improbable that BDNF would be involved in the physiopathology of Ads [16]. The specific finding of gender, showing low levels of BDNF only in women with anxiety disorder may suggest that BDNF was related with the physiopathology of anxiety, only in women, not in men. The findings also suggested that there was no relationship between the levels of BDNF and severity of the anxiety [17].

Changes in the BDNF levels may be related to the reduction in functionality of the hippocampus, pointing towards the risk of developing anxiety disorders, as well greater severity of depressive and anxious symptoms in patients dependent on nicotine, worse conditions of anxiety in individuals with early onset panic disorders, and the occurrence of anxiety in elderly women [18-21]. One case-control study showed that the BDNF levels were elevated in the lymphocytes of patients with GAD, and so were the levels of BDNF RNAm expression, when compared with those of healthy controls [22].

Evaluation of the plasma levels of BDNF, in a research with 129 adolescents and 17 rats, demonstrated that exposure to early stress was a risk factor for AD, and had repercussions on higher levels of BDNF in adult life, in comparison with the other group, without exposure to stress. Moreover, maternal overprotection and control behaviors in the human sample, appeared to be related to increased peripheral levels of BDNF and AD in the adult stage [23].

In addition to the serum levels of BDNF, studies have evaluated the correlation between levels of BDNF polymorphism and AD. One study with this objective comparing cases of GAD with healthy controls, showed that there was no significant difference in frequency of BDNF polymorphisms in cases with GAD, in spite of the plasma levels of BDNF being significantly reduced in these cases [24]. According to MONTAG et al. The BDNF polymorphism may suggest a predisposition to developing GAD, in addition to selectively influencing specific facets of anxious behavior [25]. Individuals with anxiety comorbidity had a higher proportion of BDNF polymorphisms, and higher level of neuroticism for avoiding damage than all the other groups [26].

A cross-sectional study showed that BDNF polymorphism was also associated with greater trait anxiety and reduction in stability of behavioral inhibition from 3 to 6 years of age, seen in another study [27,28]. In an experimental prospective cohort study with rats, association was demonstrated between early exposure to vaporized ethanol, BDNF polymorphism and reduction in volume of some regions of the hippocampus [29].

In an experimental study and another with humans, it was observed that rats exposed to stressful situations: maternal separation, contention and combinations of the two conditions, showed significant depressive and anxious behaviors, when compared with controls. There was association between anxiety disorder and BDNF polymorphisms, which could indicate the psychic vulnerability of individuals with this genetic variant. This discovery, in conjunction with the association between BDNF polymorphisms and anxiety disorder, emphasized the role of BDNF in this pathology [30].

Concerning the neurobiology of AD, the volume of some structures, specifically the dorsal portion of the dorsal-lateral cortex and insula, undergo modulation by the BDNF polymorphism, which is distinctly observed when anxious adolescents are compared with healthy individuals, reinforcing the neurotrophic hypothesis of the physiopathology of AD. The modulation of these regions by BDNF suggests that these structures could have greater sensitivity to the action of BDNF in adolescence, and could present risk for AD [31].

An experimental study with 15 rodents demonstrated association between AD and BDNF levels, with repercussions on facilitated associative learning. In this study, not only was the reduction of BDNF in the hippocampus of rodents observed to be related to the acquisition of associative learning, but also that the administration of BDNF in the hippocampus of rats contributed to its occurrence [32].In a prospective cohort with 45 pregnant female rats, submitted to stress (witnessing the social defeat of their partners), they showed anxious behaviors up to three weeks postpartum. This could be related to changes in BDNF expression in the hippocampus, prefrontal medial cortex and amygdala, with the expression being reduced in the hippocampus, and increased in the amygdala [33].

Furthermore, in a prospective cohort with 45 isolated female rats, significantly increased BDNF expression in the cerebral cortex was shown, when compared with the control, in addition to anxious behavior [34].

From this perspective, studies have pointed out that the Val/Met genotype represented an independent risk factor for AD in childhood and adolescence, reinforcing the hypothesis that BDNF has neurobiological characteristics that have influence in the genesis of anxiety [35]. Furthermore, LAU et al [15], in a study comparing healthy adolescents with individuals with AD, considered the activation of brain structures such as the amygdala and hippocampus, as findings in BDNF polymorphism carriers, also considering that the activation was modulated by BDNF. Therefore, it was concluded that lower levels of BDNF were associated with the expression of AD symptoms during adolescence, possibly also playing a role in the long term effects on individuals.

A case-control study with 93 participants, showed that BDNF polymorphism carrier patients with prostate cancer, were at greater risk for hypercortisolism secondary to stressful experiences than patients who did not have the allele, data that could be important for preventing GAD in men with prostate cancer [36]. Further to the relationship between stress and BDNF, in an experimental prospective cohort, autism induced by stress and anxious behaviors caused by neonatal isolation could be hypothesized, by means of regulating the expression of BDNF RNAm [37].

According to the studies described above, when considering that both plasma levels of BDNF and BDNF polymorphism could be altered in AD, it would be plausible to question whether both, although unspecific, could be biomarkers of AD. A population based cross-sectional study has suggested that BDNF could be characterized as a biologic marker associated with AD, to the extent to which it may be involved in the neurobiology of GAD, and considering the association of the BDNF polymorphism as risk factor for the occurrence of the disease [38]. A research conducted with pregnant women with GAD, showed reduced serum levels of BDNF when compared with healthy women, which explained the reduced fetal levels of BDNF in the umbilical cord. The duration of maternal GAD showed a significant effect on the reduction of fetal BDNF levels, however, without association with the severity of the anxious symptoms [39].

In spite of the increase in BDNF representing a reflection of normalization of the physiopathology of the disease, the mechanisms of BDNF, isolated, could not be pointed out as being responsible for the response to antidepressants. However, considering that a study with Duloxetine increased the plasma levels of BDNF in patients with GAD, this suggests that the increase in the levels of BDNF reflected the effect of the medication therapy [40].

Regarding neuromodulation treatment for GAD, with rTMS (bilateral low-frequency transcranial repetitive magnetic stimulation) on the dorsolateral prefrontal cortex, at least partially involves the interaction of BDNF and 5-HT in the brain [41].

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Conclusion

The studies were observed to point towards the relationship between levels of BDNF and AD, with change in the levels of this neurotrophin in both humans and animals. However, further studies are necessary to present evidence of this association which, if proved, could contribute to action of prevention of AD in the services of mental health care, from primary prevention, including improvements in lifestyle, through to secondary prevention, with early diagnosis, considering the possibility of validating the use of BDNF as a possible, although unspecific, biomarker for mental health.

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