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ORIGINAL ARTICLE

Effects of cognitive-behavioral therapy on neurotrophic factors in patients with major depressive disorder

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Objective: To correlate neurotrophic factors – brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and beta-nerve growth factor (beta-NGF) – and severity of depressive symptoms in patients diagnosed with major depressive disorder (MDD) undergoing cognitive-behavioral therapy (CBT).
Methods: In this quasi-experimental study, participants were selected by convenience and received 16 sessions of CBT. The outcomes of interest were severity of depressive symptoms and changes in neurotrophic factor levels after CBT. The differences between variables before and after treatment (deltas) were analyzed.
Results: Patients had significant changes in symptom severity after treatment. No significant associations were found between Beck Depression Inventory II (BDI-II) scores and any independent variable. No correlations were observed between BDNF or GDNF levels and BDI scores before or after treatment, although there was a trend toward significant differences in beta-NGF levels.
Conclusion: BDNF, beta-NGF, and GDNF were not influenced by the effects of CBT on depressive symptoms.

Keywords: Blood; neurotrophic factor; major depressive disorder; cognitive-behavioral therapy

Introduction

Several interventions have proven efficient for the treatment of major depressive disorder (MDD).[1] Among these, cognitive-behavioral therapy (CBT) is particularly relevant, due to its short duration and low relapse rate.[2,3] Methods for measurement of therapeutic results in psychiatry include self-report scales and psychometric tests. In addition, efforts are underway to identify biological measures that could be used in the diagnosis or follow-up of mental disorders.[4] Intracellular pathways and neurotransmitter systems have been involved in the pathogenesis of depression.[5] Information about biomarkers and brain metabolism obtained before and after psychotherapy could help clinicians decide the best treatment, by providing outcome measures that are possibly not influenced by the limits of patient self-reports.[4] In this sense, the possibility of correlations between depressive symptoms and peripheral changes, such as neurotrophic factors, appears as an important hypothesis. Changes to depressive thoughts effected by CBT might also change the biochemical function of the mood disorder.[6]

Neurotrophic factors can modulate the impact of depression on patients' lives, and even their response to treatment with antidepressant medication at different levels. Modulation of their synthesis, secretion, and signaling determines the result of their action.[7] A systematic review addressed the influence of neurotrophic factors on synaptic plasticity and their changes in patients with MDD.[8] Much research has been conducted to determine the association of brain-derived neurotrophic factor (BDNF) with depression; in fact, BDNF was the neurotrophic factor most widely investigated in the last decade. In mammals, it is responsible for regulating axonal growth and synaptic plasticity in neuronal networks involved in depressive behaviors, among other functions.[9] Beta-nerve growth factor (beta-NGF) is a neurotrophic factor structurally related to BDNF. Its signaling is widespread and plays an important role in the development and preservation of sensory and sympathetic systems.[10] The glial cell line-derived neurotrophic factor (GDNF) influences the maintenance of serotonergic neurons and glial cells, as well as regulates, dopaminergic, noradrenergic, and GABAergic routes.[9] Specifically, this factor is responsible for promoting the uptake of dopamine and the survival and morphological differentiation of neurons,[10] effects which may influence the clinical manifestations of MDD. Research has shown that levels of these factors in peripheral blood are reduced in patients with depressive disorders.[9]

CBT is a psychotherapeutic modality based on effecting behavioral changes through cognitive aspects.[2] The association between CBT and changes in the immune system has been investigated, but knowledge of the biological processes involved in the effects of this therapy is still limited.[11] Research findings suggest that the brain responds to environmental influences through alteration of gene expression; that psychotherapy has specific measurable effects on the brain; and that implicit memory

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may be modified by psychotherapeutic interventions.[12] In short, psychotherapeutic interventions have a neurobiological effect in addition to their "psychological" impact.[12]

Nevertheless, major gaps remain in the scientific literature regarding this topic. Some studies have tested for correlation between severity of depressive symptoms and levels of neurotrophic factors, mainly in patients undergoing pharmacological treatment; reduced BDNF serum levels have been described in untreated patients with MDD,[13] and these levels have been reported to increase with antidepressant pharmacotherapy.[7,14] Regarding the effects of psychotherapy, however, there is very little information. One study designed to investigate the effect of CBT on the pro-inflammatory cytokine interleukin (IL)-6 levels showed that CBT decreased both depressive symptoms and IL-6 levels in a group of women experiencing their first depressive episode.[11]

A meta-analysis found that serum and plasma BDNF levels were decreased in acute MDD and bipolar disorder, whereas in euthymia, these levels did not differ from those of control subjects. Antidepressive treatment increased serum BDNF levels in MDD responders and remitters significantly more than in nonresponders.[15] GDNF levels have been described to increase when depressive symptoms are remitted or absent.[16] As for beta-NGF, a study of MDD patients showed that levels reduced after antidepressant pharmacotherapy, following the reduction of depressive symptoms; however, results were inconsistent, with patients in the same study that were interviewed for less time showing no significant differences in beta-NGF levels compared with controls.[17] In another study, beta-NGF levels were significantly reduced in depressed patients compared with healthy elderly controls.[18]

Within this context, we aimed to correlate BDNF, GDNF, and beta-NGF levels with severity of depressive symptoms in patients diagnosed with a current episode of MDD and undergoing CBT.

Methods

This is a quasi-experimental study nested in a randomized clinical trial (RCT) designed to evaluate the efficacy of two brief psychotherapeutic modalities for MDD: CBT and psychodynamic psychotherapy. All subjects between the ages of 18 and 60 who sought treatment at the mental health service where the study was conducted and were diagnosed with current MDD were invited to participate in the RCT. Once MDD diagnosis had been established by the Mini International Neuropsychiatric Interview Plus (MINI-Plus),[19] the names of participants were placed in an envelope and drawn out by a single-blinded investigator, alongside slips of paper listing each of the two intervention models, which had been placed in another envelope. Patients were thus randomly allocated to either treatment. In this nested study, we will focus solely on the CBT arm.

Patients who had cognitive limitations precluding comprehension of the instruments (as determined during the diagnostic interview) were excluded, as were those who refused blood sample collection, those diagnosed with bipolar disorder, those with psychotic symptoms, those who had taken antidepressants in the preceding 3 months, those allocated to the other model of intervention during randomization, and those diagnosed with moderate to severe suicide risk at any moment during intervention.

This study was approved by the ethics committee. The CBT protocol followed the Beck model. It consisted of establishing therapeutic alliance, providing psychoeducation about the treatment model and the disorder, applying cognitive or behavioral techniques, and doing relapse prevention.[20] All patients attended 16 sessions lasting 50 minutes each, once weekly, with psychologists or psychology students. We investigated longitudinal associations between depression scores on the Beck Depression Inventory II (BDI-II) and serum levels of the neurotrophic factors of interest. Before, during, and after treatment (on sessions one, 10, and 16), blood was collected and the BDI-II was administered simultaneously. The before-and-after differences (deltas) in neurotrophic factor levels and BDI-II scores, calculated by subtracting the initial (baseline) measure from the final measure, were considered for analysis.

Clinical and demographic data

We collected sociodemographic and clinical information from all participants at baseline. Socioeconomic class was categorized in accordance with the Brazilian Association of Research Companies (ABEP) classification. Regarding clinical history, participants were asked about the presence of any of the following diseases: arthritis, bronchitis, cancer, cirrhosis, diabetes, heart disease, tendonitis, tuberculosis, and "others." Given the prevalence of spinal conditions and hypertension, we considered them in separate categories; other conditions were pooled for analysis.

Blood collection and assays

Peripheral blood samples (15 mL) were collected by venipuncture and stored at -80°C until the time of analysis. BDNF, GDNF, and beta-NGF levels were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits (DuoSet ELISA Development, R&D Systems, Inc., USA). Briefly, streptavidin-HRP conjugate was added to detection antibodies against each neurotrophic factor; specimens were analyzed in a microplate reader (SpectraMax 190, Molecular Devices). Samples were run in triplicate to prevent false-positive or false-negative results, and the analyst was blinded.

Beck Depression Inventory-II (BDI-II)

The BDI-II has been validated in Brazil.[21] It is a self-report instrument consisting of 21 questions about depressive symptoms. The final score ranges for 0 to 63, and can be used to classify symptoms as indicative of minimal, mild, moderate, or severe depression. To reduce the risk of error, this questionnaire was administered on a tablet PC.

Statistical analysis

Data were collected using Open Data Kit Collect 1.1.7 and analyzed in SPSS version 10. To verify significant correlation between serum levels of each neurotrophic

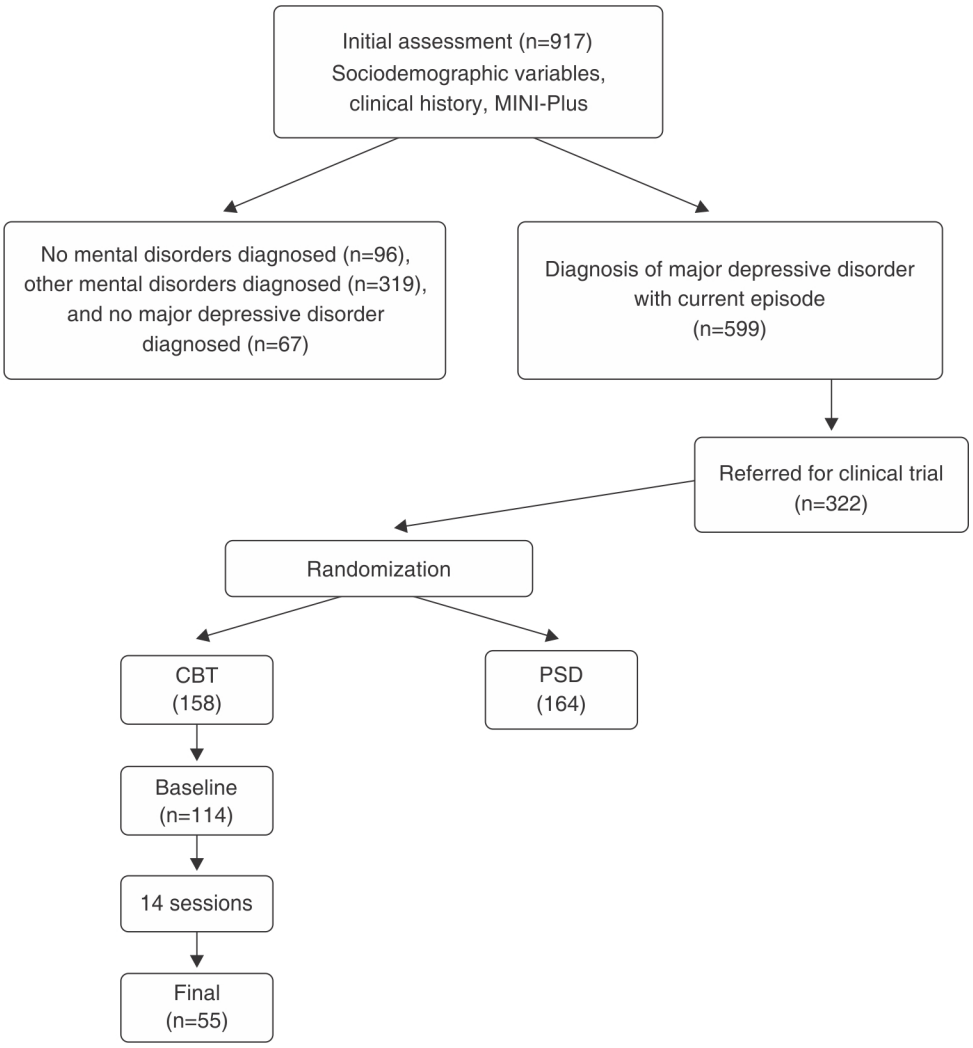

Figure 1 Flow chart of participant selection process and losses to follow-up during a randomized clinical trial of psychotherapeutic modalities for major depressive disorder (MDD). CBT = cognitive-behavioral therapy; MINI-Plus = Mini International Neuropsychiatric Interview Plus; PSD = psychodynamic therapy.

factor and a reduction in severity of depressive symptoms, a Pearson correlation coefficient of 0.30 between the tested variables before and after treatment was estimated. The sample size needed to test for this association was established as 85 participants.[22]

For multivariate analysis, a linear regression model was constructed to verify correlations between delta beta-NGF and delta BDI-II scores, mediated by any independent variable. Variables were considered at the same level: current psychopharmacotherapy, hypertension, spinal disease, current occupation (employment or study), and skin color. Although less than 10% of participants were on psychopharmaceuticals, the decision was made to maintain this variable for regression analysis because of its importance to the results of BDI-II scores after treatment.

Results

Overall, 322 patients with current MDD were eligible for inclusion in this RCT. Among these, 158 were recruited for the CBT model, and 114 were present at the first session for enrollment in this study. However, over the course of treatment, 59 participants were lost due to emergence of exclusion criteria or failure to attend the sessions properly. Among these patients, 13 were excluded due to impossibility of blood collection or analysis (Figure 1). Thus, the final sample consisted of 42 patients who began and completed the intervention. The characteristics of this sample are listed in Table 1.

For analysis of BDNF levels, blood was drawn from 42 patients. For GDNF and NGF levels, blood samples from the initial and final time points were only available for 40 patients.

For bivariate analysis, ANOVA with Bonferroni correction was used to establish differences between the groups of deltas (Table 2).

Associations of delta BDNF, delta GDNF, and delta beta-NGF with some independent variables are shown in Table 3. Regarding delta BDI-II scores, no significant

associations were found between higher scores and any of the independent variables.

Discussion

Similar results were observed in other studies, despite some methodological differences. An intervention study found no difference in BDNF levels between patients treated with antidepressants for 3 vs. 8 weeks.[13] In another study, no correlations were found between depression scores and serum levels of BDNF at baseline or on longitudinal analysis; at baseline, serum levels did not predict depression scores after 12 weeks of treatment.[23]

Regarding GDNF, one study reported significantly reduced levels in patients with unipolar and bipolar depression as compared with healthy controls. These patients were in partial remission of mood episodes (but still had depressive symptoms) and untreated.[24] Conversely, another study found no significant differences in GDNF levels between depressive patients after 8 weeks of antidepressant treatment and healthy controls.[16]

Another investigation found significantly lower baseline beta-NGF levels among depressed patients compared to healthy controls. However, the difference was not significant in patients who responded to duloxetine after 6 weeks of treatment, while it was significant in those who did not respond early (with a 50% reduction in depression scores). During duloxetine treatment, beta-NGF levels further decreased in association with clinical response, ultimately reaching significantly lower values.[17]

In contrast, the present study found a trend toward statistically significant association between higher delta beta-NGF and BDI-II scores. We also found a significant difference between pre-treatment and post-treatment beta-NGF levels; multivariable analysis revealed an increase in these levels with psychotherapy and reduction of symptoms ($p = 0.122$). This result could represent a lower neurotrophic set point that might reflect some impairment in MDD.

A previous study with rats highlighted modulation of endogenous beta-NGF levels as a potential therapeutic target for the management of inflammatory diseases.[25] This finding from animal models could explain our finding of an association between delta beta-NGF and presence of spinal diseases (which might represent inflammatory diseases).

In a systematic review and meta-analysis, peripheral beta-NGF protein levels were found to be significantly lower in patients with MDD than in healthy controls. However, a possible publication bias was detected for this association. No significant differences in peripheral beta-NGF before vs. after treatment were found in patients who received electroconvulsive therapy, specific antidepressants, or unspecific antidepressants (clinical treatment, possibly psychotherapy), indicating a possible influence of factors yet to be proved.[26] However, the cited literature enrolled samples with a profile different from that of our study, largely focusing on outpatients undergoing

Table 1 Characteristics of patients who completed cognitive-behavioral therapy for major depressive disorder (n=42)

Variable	n (%)
Gender	
Male	7 (16.6)
Female	35 (83.3)
Age	
19-29 years	18 (42.8)
30-59 years	24 (57.1)
Skin color	
White	32 (76.1)
Nonwhite	10 (23.8)
Years of schooling	
$\leqslant 8$	13 (30.9)
$\geqslant 9$	29 (69.0)
Socioeconomic class	
C, D, E	23 (54.7)
A, B	19 (45.2)
Currently employed and/or studying	
No	14 (33.3)
Yes	28 (66.6)
Major organic disease	
No	31 (73.8)
Yes	11 (26.1)
Spinal disease	
No	30 (71.4)
Yes	12 (28.5)
Hypertension	
No	29 (69.0)
Yes	13 (30.9)
Current psychopharmacotherapy (any)	
No	38 (90.4)
Yes	4 (9.5)

Table 2 Mean (standard deviation) BDI-II scores and levels of neurotrophic factors in patients who completed cognitive-behavioral therapy for major depressive disorder (n=42)

	Pre-treatment	Post-treatment	Delta	p-value
BDI-II	32.26 (11.38)	17.023 (14.55)*	15.238 (13.10)	0.000
BDNF	1.387 (0.26)	1.329 (0.30)*	0.057 (0.35)	0.294
GDNF	0.946 (0.19)	1.003 (0.24)*	-0.057 (0.24)	0.154
Beta-NGF	1.215 (0.18)	1.295 (0.18)*	-0.062 (0.19)	0.051

BDI-II = Beck Depression Inventory II; BDNF = brain-derived neurotrophic factor; GDNF = glial cell line-derived neurotrophic factor; beta-NGF = beta-nerve growth factor; SD = standard deviation.
*$p < 0.05$.

Table 3 Results of ANOVA with Bonferroni correction to assess differences in neurotrophic levels according to independent variables

Independent variable	BDNF	GDNF	Beta-NGF
Nonwhite	prob > $F_{0.34}$, p = 0.000	prob > $F_{0.71}$, p = 0.007	
⩾ 9 years of formal education		prob > $F_{0.55}$, p = 0.47	
Employed or studying			
Yes	prob > $F_{0.64}$, p = 0.185		
No	prob > $F_{0.20}$, p = 0.003		
Hypertension			
Yes	prob > $F_{0.42}$, p = 0.010		prob > $F_{0.48}$, p = 0.000
No		prob > $F_{0.89}$, p = 0.037	
Diabetes			prob > $F_{0.19}$, p = 0.029
Spinal disease			prob > $F_{0.58}$, p = 0.053
Any psychopharmacotherapy			prob > $F_{0.77}$, p = 0.037

BDNF = brain-derived neurotrophic factor; GDNF = glial cell line-derived neurotrophic factor; beta-NGF = beta-nerve growth factor.

psychotherapy, and few were conducted from a biological perspective.

Individual alterations in a complex signaling network, which includes the hypothalamic-pituitary-adrenal axis, the production of neurotrophic and other growth factors, and the production of proinflammatory cytokines, are able to induce major mood changes. Furthermore, all of these factors modulate neurogenesis in brain regions involved in MDD, and are interconnected in their functionalities, so that an initial alteration in one factor can induce abnormalities in others.[8] It is also known that beta-NGF, unlike BDNF and GDNF, plays direct roles in the endocrine and immune systems.[26] Recent studies found that beta-NGF is associated with the response to stress, a factor associated with MDD development.[26]

The present study aimed to contribute to a better understanding of neurotrophic factors and their potential associations with MDD. We expected to find improvements in depressive symptoms and changes in neurotrophic factor levels over the course of psychotherapeutic treatment. However, no significant association was found between neurotrophic factors in peripheral blood and BDI-II scores. The results of this study can help further our understanding of neurobiological changes in major depression and serve as valuable inputs for clinical practice in mental health.

Although we did not find any changes in neurotrophic factor levels in association with the effects of psychotherapy, our findings are still important. At least, identifying whether neurochemical changes occur in association with psychotherapeutic treatment can demonstrate the influence of mental processes on cerebral plasticity at different levels. These biological bases before and after treatment can help define the optimal modality for each case and patient. Our findings also provide evidence regarding the use of outcome measures unaffected by the limitations of self-reporting.[4] The results of this study show that, although MDD causes biological and neurochemical changes, levels of BDNF, beta-NGF, and GDNF in peripheral blood are not influenced by the effects of psychotherapy in reducing symptoms of depression.

This study had some limitations. We did not know the pre-treatment duration of participants' MDD episodes or of their changes in neurotrophic factor levels; if the onset of depression was recent, the body may not have had enough time to respond with biological or neurochemical changes. It is also possible that, after experiencing reductions in symptoms, patients were not given enough time to readapt and reestablish brain function.

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Disclosure

The authors report no conflicts of interest.

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