

Mental disorders, functional impairment, and nerve growth factor

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Abstract: Nerve growth factor (NGF) is an important member of the neurotrophin family and its alteration has been associated with psychiatric disorders. Functionality consists of the activities that an individual can perform, as well as their social participation, which is an important factor in analyzing the carrier living conditions of subjects with psychiatric suffering. Several studies have evaluated functionality in bipolar disorder; however, no studies have evaluated the functionality in other mental disorders. There are also few studies investigating the association between functionality and the biological bases of mental disorders. This study aimed to evaluate the serum NGF levels in psychiatric patients and to verify a possible association between the serum neurotrophic levels and functionality. This was a cross-sectional study with a convenient sample obtained from the Public Mental Health Service from the south of Brazil. The final sample was composed of 286 patients enrolled from July 2013 to October 2014. Data was collected using a sociodemographic questionnaire, and the diagnosis was confirmed using the Mini International Neuropsychiatric Interview (M.I.N.I) and a Functioning Assessment Short Test. The serum NGF levels were determined using the enzyme-linked immunosorbent assay method. Statistical analyses were performed using IBM SPSS Statistic 21.0 software. NGF serum levels were increased significantly in patients with obsessive-compulsive disorder compared with patients with no obsessive-compulsive disorder ($P=0.015$). An increase in serum NGF levels in generalized anxiety disorder patients was observed compared with patients with no generalized anxiety disorder ($P=0.047$). NGF was negatively associated with autonomy ($P=0.024$, $r=-0.136$), work ($P=0.040$, $r=-0.124$), and cognition ($P=0.024$, $r=-0.137$), thereby showing that changes in serum levels of NGF are associated with functionality in mental disorders.

Keywords: NGF, mental disorders, functional impairment

Introduction

Nerve growth factor (NGF) is an important member of the neurotrophin family and is produced mainly in the cortex, hippocampus, and hypothalamus. It has a role in the survival of sympathetic and some sensory and central cholinergic neurons. Additionally, NGF acts outside of the nervous system, particularly within the neuroendocrine and immune system. Previous studies have evaluated the role of altered NGF in animal and human models and found reduced levels of NGF mainly in subjects with major depression.¹⁻⁷ NGF has an important role in neuronal survival, differentiation, connectivity, and plasticity during development and adulthood, and when affected by stress, are good candidates for the transduction of the effects of adverse events to changes in brain function.^{1,8,9} Since NGFs have a relevant role in the maintenance

of neuronal homeostasis, changes in their levels have been implicated in diverse neuropsychiatric disorders.⁴ Thus, it has been recently suggested that NGF is involved in the pathophysiology of psychiatric disorders.^{2,3} In mice, NGF release was associated with an increase in behavioral stress.³ In human studies, Diniz et al⁴ found reduced levels of NGF in subjects with late-life depression. Moreover, treatment with antidepressants has restored NGF levels in both clinical and experimental studies.⁵ Recently, our group has shown that NGF and brain-derived neurotrophic factor (BDNF), but not glial cell-derived neurotrophic factor, were associated with the clinical features of major depressive disorder (MDD) in patients.¹⁰ The management of psychiatric disorders is evaluated by clinical assessments and does not consider the related biological basis of brain functions. Moreover, more useful biomarkers in the psychiatry field are needed to be explored in order to better understand mental disorders. Thus, the identification of biological parameters could improve the diagnosis and treatment of these disorders.

Functionality consists of activities that an individual can perform, as well as their social participation. Functional impairment in mental disorders is a well-known fact. Furthermore, the concept of functional impairment is complex, involving different domains of functioning and areas of life. Functionality is an important factor to evaluate the patient to understand the living conditions of psychiatric suffering.^{11,12} Several studies have evaluated functionality in bipolar disorder;^{13–19} however, to the best of our knowledge, no studies have evaluated the functionality in other mental disorders. There are also few studies investigating the association between functionality and biological bases of mental disorders. The most common mental disorders present in the general population are associated with functioning deficits, interfering with the management of one's life; however, they are not considered as biological parameters. Therefore, this study aimed to evaluate the serum NGF levels in psychiatric patients and to verify a possible association between serum NGF levels and functionality in patients from the Brazilian Public Mental Health Service.

Methods

Participants

This was a cross-sectional study with a convenient sample obtained from the Public Mental Health Service (Bage, Brazil). Subjects were 19 years of age or above, of either sex, and in their first psychiatry and/or psychological care. The total sample was composed of 286 subjects who participated between July 2013 and October 2014. The project was

approved by the ethical committee of the Catholic University of Pelotas (16429713.9.0000.5339), and all subjects signed an informed consent.

Data collection

For data collection, a sociodemographic questionnaire was used to obtain information, such as age, education, economic status, and marital status. The economic classification was performed using the criteria of the Brazilian Association of Research Companies, which is based on the accumulation of material goods and education of the household head. This classification fits people into Classes A, B, C, D, or E from the scores achieved, in which the letter "A" refers to the highest socioeconomic status and "E" refers to the lowest.²⁰ There were no participants belonging to the Class E in this sample. Body mass index (BMI) was calculated by using the following formula: weight (kg)/height (m²). Participants were asked about current psychiatric medication use. The diagnosis was conducted by trained psychologists of the Mental Health Service using the structured diagnostic interview – Mini International Neuropsychiatric Interview, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition diagnostic criteria.²¹ The mental disorders evaluated were major depression, bipolar disorder, obsessive-compulsive disorder (OCD), panic disorder, generalized anxiety disorder (GAD), and schizophrenia. Moreover, suicide risk was evaluated. To measure the individual functionality, we used the Functioning Assessment Short Test (FAST). FAST is a 24-item interview designed to assess the damaged areas of everyday functioning, which included the objective evaluation of six specific areas of functionality: autonomy, work, cognition, interpersonal skills, finance, and leisure.¹⁶ Scores were determined by the sum of items, ranging from 0 (indicating no problems) to 3 (indicating a severe limitation) over a period of 15 days prior to the application of the scale.¹³ Therefore, the higher the scores, the higher the functional impairment. Comorbidity was calculated through diagnosis groups: anxiety disorder (GAD, OCD, and panic disorder [PD]), mood disorder (major depression and bipolar disorder), and psychotic disorders (schizophrenia and presence of psychotic symptoms) and after the sum of each group separated.

Biochemical analyses

For the biochemical analyses, 10 mL of blood were drawn from each subject by venipuncture into an anticoagulant-free vacuum tube at baseline and postintervention. All venous blood samples were taken in the morning (between 9 am and 11 am). The blood was at room temperature for 30 minutes

for coagulation, after which the blood was immediately centrifuged at $4000\times g$ for 10 minutes, and serum was kept frozen at -80°C until analysis. Serum NGF levels were measured using a commercial immunoassay kit (DuoSet ELISA Development, R&D Systems, Inc., Minneapolis, MN, USA). Serum NGF levels were expressed in pg/mL. The kits have a minimum detectable dose of 9.46 pg/mL for NGF. NGF levels ranged from 7.39 to 198.37 pg/mL, with values below 9.46 pg/mL considered as the reference number ($n=12$).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistic 21.0 (IBM Corporation, Armonk, NY, USA) software. Sociodemographic characteristics and serum NGF levels are shown by the absolute and relative frequencies, mean \pm standard deviation, or by the median and interquartile range (IQR). The serum levels of NGF had non-Gaussian distributions. To verify the association between sociodemographic and clinical characteristics and NGF serum levels, the Mann–Whitney U test, Kruskal–Wallis test, and Spearman correlation were used. Differences between FAST scale and diagnosis groups were analyzed using Student t -test for independent sample and Pearson's correlation. A multivariate linear regression was performed to verify the relation between NGF levels and functioning. NGF outliers were considered in the analyses. The results with $P\leq 0.05$ were considered statistically significant.

Results

The sample demographic and clinical characteristics according to NGF levels are presented in Table 1. We recruited 276 subjects with a mean \pm standard deviation age of 38.79 ± 12.98 years, of which 75.3% were female, 57.1% belonged to C and D socioeconomic classes, 53.8% were married, and the mean BMI was 26.43 kg/m^2 ($\pm 5.15\text{ kg/m}^2$). Regarding clinical characteristics, 30.4% ($n=84$) were using psychiatric medication; the prevalence of depression was 53.3% ($n=147$), bipolar disorder 18.8% ($n=52$), suicide risk 55.8% ($n=154$), schizophrenia 11.6% ($n=32$), OCD 24.7% ($n=67$), GAD 12.3% ($n=33$), and panic disorder 26.4% ($n=73$). The mean age of onset of the disease was 27.28 (± 12.37) years, and the mean duration of the disease was 10.46 years (± 10.93 years). The median NGF levels in the total sample was 21.81 pg/mL (15.72–32.28 pg/mL). The total mean of the FAST score was 31.05 (± 16.83). Serum NGF levels were increased significantly in OCD patients compared with patients with no OCD: 24.25 pg/mL (IQR = 18.31–34.58) and 21.25 pg/mL (IQR = 18.31–34.58) ($P=0.017$), respectively. We also observed an increase in serum NGF levels in GAD patients compared with patients

Table 1 Sample distribution and median (IQR) of serum NGF levels according to demographic and clinical characteristics

Variables	Total sample, n (%)	Serum NGF levels (pg/mL)	P-values
Sex ^a			0.411
Female	207 (75.3)	21.78 (15.52–33.16)	
Male	68 (24.7)	21.93 (16.80–27.42)	
Marital status ^b			0.088
Single	87 (31.9)	24.85 (16.76–32.77)	
Married	147 (53.8)	19.72 (13.70–32.09)	
Separated	28 (10.3)	22.60 (16.56–33.51)	
Widower	11 (4.0)	28.50 (20.19–32.52)	
Socioeconomic levels ^a			0.216
A + B	117 (42.9)	22.83 (16.1233.74)	
C + D	156 (57.1)	20.54 (15.15–30.81)	
Age (years), mean (\pm SD) ^c	38.79 (± 12.98)	$r = -0.014$	0.812
BMI (kg/m^2), mean (\pm SD) ^c	26.43 (± 5.15)	$r = -0.050$	0.416
Psychiatric medication use	84 (30.4)	20.79 (16.06–20.33)	0.414
Major depression ^a			0.453
No	129 (46.7)	22.38 (16.10–33.22)	
Yes	147 (53.3)	20.69 (15.03–30.25)	
Bipolar disorders ^a			0.608
No	224 (81.2)	21.69 (15.91–32.65)	
Yes	52 (18.8)	22.88 (13.85–30.45)	
Suicide risk ^a			0.435
No/low	122 (44.2)	22.56 (16.55–33.35)	
Moderate/severe	154 (55.8)	24.25 (18.31–34.58)	
OCD ^a			0.017
No	209 (75.7)	21.25 (14.26–32.11)	
Yes		24.25 (18.31–34.58)	
Panic disorders ^a			0.230
No	203 (73.6)	22.38 (16.00–32.52)	
Yes	73 (26.4)	19.36 (14.48–31.34)	
GAD ^a			0.037
No	236 (87.7)	22.25 (15.97–32.40)	
Yes	33 (12.3)	17.81 (13.43–23.54)	
Schizophrenia ^a			0.855
No	244 (88.4)	22.25 (15.54–32.50)	
Yes	32 (11.6)	18.54 (17.04–29.55)	
Age of onset of disease (years), mean (\pm SD)	27.28 (± 12.37)	$r = -0.103$	0.146
Duration of disease comorbidity (years), mean (\pm SD)	10.46 (± 10.93)	$r = -0.033$	0.648
Anxiety + mood ^a	113 (39.8)	19.68 (14.79–29.70)	0.355
Anxiety + psychotic ^a	42 (15.6)	19.04 (16.12–29.37)	0.701
Mood + psychotic ^a	56 (20.3)	19.04 (14.40–29.45)	0.401
FAST score mean (\pm SD)	31.05 (± 16.83)	$r = -0.155$	0.011
Total	276 (100.0)	21.81 (15.72–32.28)	—

Notes: ^aMann–Whitney U test. ^bKruskal–Wallis test. ^cSpearman correlation. "—" = no data.

Abbreviations: IQR, interquartile range; NGF, nerve growth factor; BMI, body mass index; OCD, obsessive–compulsive disorder; GAD, generalized anxiety disorder; FAST, Functioning Assessment Short Test.

with no GAD: 22.25 pg/mL (IQR =15.97–32.40) and 17.81 pg/mL (IQR =13.43–23.54) ($P=0.047$), respectively.

Table 2 shows the functioning scores according to clinical characteristics. FAST scores were significantly increased in all the disorders and there was a trend toward significance for GAD ($P=0.062$). No correlation was observed between the FAST score and age of onset and duration of disease. Sex, age, marital status, and BMI were not associated with OCD and GAD (data not shown).

Table 2 Functioning scores according to clinical characteristics

Psychiatric disorders	FAST	Statistics	
	Mean (\pm SD)	t	P-values
Major depression			<0.001
No	27.11 (\pm 16.52)	-3.68	
Yes	34.52 (\pm 16.39)		
Bipolar disorders			0.014
No	29.83 (\pm 16.98)	-2.47	
Yes	36.23 (\pm 15.27)		
Suicide risk			0.003
No/low	25.42 (\pm 16.31)	-3.05	
Moderate/severe	33.17 (\pm 15.21)		
OCD			0.001
No	29.09 (\pm 16.85)	-3.41	
Yes	37.06 (\pm 15.39)		
Panic disorder			0.016
No	29.56 (\pm 16.95)	-2.42	
Yes	35.12 (\pm 15.91)		
GAD			0.062
No	30.27 (\pm 16.94)	-1.88	
Yes	36.12 (\pm 15.26)		
Schizophrenia			0.026
No	30.24 (\pm 16.63)	-2.23	
Yes	37.47 (\pm 17.30)		
Age of onset of any disease	$r=-0.016$	—	0.825
Duration of disease comorbidity	$r=-0.005$	—	0.945
Anxiety + mood	37.84 (\pm 16.28)	-6.01	<0.001
Anxiety + psychotic	38.88 (\pm 16.47)	-3.33	0.001
Mood + psychotic	38.68 (\pm 16.88)	-3.82	<0.001
Total	31.05 (16.83)	—	—

Note: "—" = no data.

Abbreviations: FAST, Functioning Assessment Short Test; OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder.

Table 3 Multivariate linear regression of the relation between NGF and functioning scores and domains

FAST score	Unadjusted NGF serum levels (pg/mL)		Adjusted NGF serum levels (pg/mL) ^a	
	B	P-values	B	P-values
Total FAST	-0.20 (-0.38; -0.17)	0.032	-0.21 (-0.40; -0.02)	0.035
Autonomy	-1.16 (-2.05; -0.28)	0.011	-1.20 (-2.12; -0.28)	0.011
Work	-0.58 (-1.24; 0.08)	0.083	-0.62 (-1.32; 0.04)	0.084
Cognition	-0.65 (-1.39; 0.09)	0.083	-0.65 (-1.41; 0.12)	0.096
Finance	-0.92 (-2.25; 0.42)	0.177	-0.96 (-2.34; 0.41)	0.170
Interpersonal skills	-0.39 (-1.04; 0.27)	0.248	—	—
Leisure	-0.48 (-1.87; 0.92)	0.504	—	—

Notes: ^aAdjusted for OCD and GAD. "—" = no data.

Abbreviations: NGF, nerve growth factor; FAST, Functioning Assessment Short Test; OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder.

A multivariate linear regression was calculated to predict serum NGF levels based on FAST total score and domains. After adjustments for GAD and OCD, participant's NGF levels decreased: -0.21 pg/mL for each increase in the FAST total score ($P=0.035$) and -1.20 pg/mL for the autonomy domain for each increase in the FAST total score ($P=0.011$). A trend toward significance was observed in the work ($P=0.084$) and cognition domain ($P=0.096$; Table 3).

Discussion

In this study, OCD and GAD were associated with serum NGF levels, and higher functional impairment was observed in all mental disorders. After adjustments, we found a negative association in the total scores of the FAST and NGF, as well as autonomy domain and NGF. Epidemiological studies in Brazil show a degree of functional impairment of psychiatric patients. Upon analyzing the domains, "work and income", we found that 35% had never worked and 55% do not have their own income.^{22,23} The occupational dysfunction is not only bad per se but also has been reported as a predictor of relapse.²⁴

NGF has a significant role in neurite outgrowth, thereby promoting neuronal integrity.^{25,26} Furthermore, NGF supported the activity-dependent neuronal plasticity underlying cognitive processes, such as learning and memory, thereby having an important role in anxiety, emotions, and behavioral changes.²⁷⁻³¹ A wide variety of studies show that reduced serum levels for the neurotrophic factors are associated with reduced neuronal complexity and impaired learning, and many of these effects can be restored with increased neurotrophic factor levels.³²⁻³⁶ According to this perspective, studies have speculated a significant role of NGF and BDNF levels in complex social interactions, which shows that higher levels of these neurotrophic levels are associated with more aggression and reduced social interactions, while decreased NGF and BDNF levels are associated with socially submissive behaviors and increased social bonding.³⁷

In a psychosocial stress model, agonistic encounters induce NGF release, and the circulating levels of this protein reflect the number of aggressive episodes and hierarchical status.³⁸ Moreover, similar results were found in humans.²⁷ Interestingly, the serum NGF levels precede the increase of cortisol and adrenocorticotrophic hormone, thereby suggesting, as a sort of early alert mechanism, that these levels are associated with a homeostatic adaptation. In subjects with chronic stress, such as withdrawal in alcoholics and being a caregiver, there was an association between stress and elevated peripheral NGF.³ Regarding psychiatric disorders, in animal models of depression, changes in NGF levels in rats have been observed.³⁹ In a recent clinical study, reduced NGF levels were found in bipolar disorder patients during manic episodes, in schizophrenia patients with impaired cognitive performance, and in unmedicated patients in first psychosis episode.⁴⁰

Our results agree with a previous study that NGF levels increase in OCD, and the authors found a statistically significant positive correlation between both NGF levels and the symptoms severity. Fontenelle et al⁴¹ suggested two hypotheses: 1) increased NGF levels could represent a coping response involved in preparing the organism to face a highly stressful situation or 2) OCD washing may be associated with some sort of cholinergic dysfunction, since the highest brain levels of NGF are found in targets for basal forebrain cholinergic neurons. We suppose that this increase is according to some cholinergic dysfunction since the patients involved in this study are patients in serious state of mental health and many of them do not use medicines. GAD patients presented an increase in NGF levels compared to non-GAD patients. A previous study by Jockers-Scherübl et al⁴² did not observe differences between GAD patients and healthy subjects. However, our sample have no control group to compare with mental disorders. Moreover, we cannot discard a possible highly stressful situation together with the NGF changes in the other group as a bias in these results.

Banerjee et al¹ and Dwivedi⁴³ found that NGF levels in the hippocampus and serum of suicide victims decreased considerably. We found no association between suicide risk and NGF levels; one possible explanation might be the characteristics of our sample, in which almost no one was taking any medication and probably was seeking attendance for the first time. However, treatment with antidepressants and electroconvulsive therapy increased NGF levels in both clinical and experimental studies.^{44,45} The psychopathology that was more prevalent included MDD, and the pathogenesis

of these disorders is related to the regulation of multiple neurotrophic factors and associated NGF levels decreased in the early stages.⁴⁶ These results together corroborate that NGF is effective in the pathophysiology of schizophrenia.² Recently, our group has reported an increase in NGF in some other mental disorders, such as MDD, suicide risk, and alcohol abuse disorder,⁷ thereby presupposing a relevant role of NGF in mental disorders. In this way, our results agree with previous literature data. Furthermore, these changes in serum NGF levels are associated with functionality in mental disorders.

Limitations

The limitations of this study are related to the control group, which was not diagnosed, and heterogeneity of the sample in relation to the stages of disorders. The design of the cross-sectional study limits the established causal relation between clinical characteristics and neurotrophin. Peripheral NGF levels do not represent the central environment fully, but changes in the circulant NGF can reflect the central nervous system. Moreover, the correlation between peripheral and central NGF levels would have interaction in some specific situations; however, more studies are necessary for a better understanding of this field.⁴⁷

Conclusion

Understanding the physiological changes related to mental disorders can provide a better understanding of the genesis and mechanisms involved in the progression of these conditions. In this work, we observed an association between functionality and serum levels of NGF in patients from a Public Mental Health Service suggesting a relevant role of NGF in GAD and OCD and its association in functionality.

Acknowledgments

This study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes; 23038.001671/2012-16), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ), and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS; 10/0055-0) Brazil.

Disclosure

The authors report no conflicts of interest in this work.

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