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Gender differences in ultradian serum levels of NGF and BDNF correlate with psychophysical traits in healthy humans

Le differenze di genere nei livelli sierici ultradiani di NGF e BDNF correlano con i tratti psicofisici nei soggetti sani

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SUMMARY. We aimed at investigating the gender and/or ultradian pattern of serum levels of the Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF). Blood samples were collected at the 8.00, 13.00 and 20.00 hours of the day in healthy men and women, and the neurotrophins concentration was measured in the serum by ELISA. A further aim of the study was to evaluate whether or not the NGF/BDNF variations might be related to specific physiological or psychological traits as mood, feeling good and feeling rested, sexual desire and energy. Heart rate and blood pressure were also monitored at the same hours in each enrolled subject. The anxiety (STAI-T and STAI-S score) and sleeping quality were once evaluated in the morning too. We found that serum BDNF increases in men and decreases in women from morning to evening, while NGF shows a similar ultradian profile between men and women, but with higher concentrations in women. Both neurotrophins also show gender-related associations with psychophysiological variables. High NGF levels correlated with a high score for all the psychological variables in men, but with a low score in women. An inverse correlation was found between BDNF and energy and sexual desire in women, while no correlations were found in men. These data disclose that the condition of well-being (or activity/arousal status) is featured by an increasing NGF profile in men and a negative BDNF/NGF trend in women. The clinical relevance of the present data is discussed.

KEY WORDS: mood disorders, personality traits, circadian rhythm, biomarkers, chronotypes, neurotrophic factors.

RIASSUNTO. In questo studio abbiamo analizzato le differenze di genere e/o il modello ultradiano dei livelli sierici del fattore di crescita nervoso (NGF) e del fattore neurotrofico derivato dal cervello (BDNF). Campioni di sangue sono stati raccolti alle ore 8.00, 13.00 e 20.00 del giorno in uomini e donne sani e la concentrazione di neurotrofine è stata misurata nel siero mediante ELISA. Un ulteriore obiettivo dello studio è stato valutare se le variazioni di NGF/BDNF potessero essere correlate a specifici tratti fisiologici o psicologici come umore, sentirsi bene e sentirsi riposati, desiderio sessuale ed energia. Anche la frequenza cardiaca e la pressione sanguigna sono state monitorate nelle stesse ore dello studio in ciascun soggetto arruolato. Anche l'ansia (punteggio STAI-T e STAI-S) e la qualità del sonno sono stati valutati una volta al mattino. Abbiamo trovato che il BDNF sierico aumenta negli uomini e diminuisce nelle donne dalla mattina alla sera, mentre l'NGF mostra un profilo ultradiano simile tra uomini e donne, ma con concentrazioni più elevate nelle donne. Entrambe le neurotrofine mostrano anche associazioni di genere con variabili psicofisiologiche. Alti livelli di NGF erano correlati con un punteggio elevato per tutte le variabili psicologiche negli uomini, ma con un punteggio basso nelle donne. È stata trovata una correlazione inversa tra BDNF ed energia e desiderio sessuale nelle donne, mentre non sono state trovate correlazioni negli uomini. Questi dati rivelano che la condizione di benessere (o attività/stato di eccitazione) è caratterizzata da un profilo NGF crescente negli uomini e da un trend negativo per BDNF/NGF nelle donne. La discussione verte sulla rilevanza clinica dei dati presenti.

PAROLE CHIAVE: disturbi dell'umore, tratti di personalità, ritmo circadiano, biomarcatori, cronotipi, fattori neurotrofici.

INTRODUCTION

Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF) are two structurally related molecules belonging to the neurotrophins' family which have been largely described and characterized as survival, differentiative and modulatory factors in the nervous system[1-6]. Several animal and human studies also demonstrated that NGF and BDNF exert a large spectrum of actions on non-neuronal cells, including immune and endocrine cells, suggesting a neu-

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rotrophin role in the maintenance of neuroimmunoendocrine homeostasis[7-12]. In this context, the variation of peripheral and circulating NGF and BDNF might assume clinical relevance as potential markers of physiological and pathological conditions, as well as possible therapeutic factors.

Changes in NGF and BDNF levels in the serum and plasma are actually reported during the onset and progression of many illnesses, including neurological, psychiatric and immune diseases[8,13-16] and physiopathological conditions, such as cardiometabolic disruptions[17-19], stressful events[20,21], alcohol addiction[22-25], aging[19,26,27] and the post-partum period[28,29].

Risk factors for depressive disorders, such as age[30], gender[31], personality traits and daily habits[32,33], have also been studied in relationship with neurotrophins, strengthening the idea that changes in circulating NGF and BDNF are not a simple epiphenomenon but reflect the physiological and physiopathological status.

The modifications in serum neurotrophins concentration may further indicate the genetic or individual vulnerability for depressive disorders in healthy subjects and/or in subsyndromal conditions, like the response to traumatic and stressful experiences[34].

Recently, it has been observed that the time of blood withdrawal is also a crucial determinant for the levels of BDNF[35], and daily fluctuation of BDNF in serum or saliva has been reported in humans[33]. Only a few studies explored the changes in NGF serum concentration during the day, and/or whether the neurotrophins variations might be related to specific physiological or psychological traits, and/or gender.

Gender-related differences are observable in the clinical features of depression and co-morbidities[36], and response to psychiatric drugs and treatments[37]. In addition, the onset and the severity of symptoms, including those related to mood, as well as the efficacy of medications and treatments[38], show a circadian rhythm emphasizing the importance of the time of the day as a variable in human studies[39,40].

Based on these data and to further investigate the factors which might influence the level of circulating neurotrophins in humans, the present study was aimed at analyzing the possible correlation between the diurnal NGF and BDNF serum levels in healthy men and women taking into consideration their profile of diurnal variations of psychophysiological variables.

METHODS

Study design and subjects

The study was addressed to analyze the daily NGF and BDNF profiles in the serum of healthy men and women. The investigation was conducted at the Sapienza University of Rome and in the Unit of Psychiatry "A. Fiorini" Hospital, Terracina, by recruiting healthy post-graduate students. The study was approved by the University Hospital ethical committee and informed consent was signed by each participant, and all the study procedures were under the Helsinki Declaration of 1975, as revised in 1983, for human experimentation. All the enrolled subjects ate a normal Mediterranean diet, had body mass index within the normal values, and do not manifest nutritional-related diseases. They were not family-related, did not report any personal or familiar neurological or psychiatric diseases, neither allergic, infective nor inflammatory disorders. Recruited volunteers reported not take regular medications or drugs, not be cannabis/nicotine smokers, not have a history of alcohol/drug addiction, to not be heavy alcohol drinkers (according to the indications of the National Institute on Alcohol Abuse and Alcoholism - NIAAA) and to not have drunk alcoholic beverages in the past 42 hours. Women were included in the first week of their post-menstrual period.

Eight men (age 24±2.7 years) and twelve women (age 25±1.6 years), meeting the above inclusion criteria, underwent a psychological interview, that was repeated each time before the blood collection, in order to rate the present psychophysiological state, considering parameters like mood, feeling good, feeling rested, sexual desire and energy, using a visual analog and a verbal numeric rating scale (0-10 points), like Likert-type items. Heart rate and blood pressure were also monitored at each time point. State-Trait Anxiety Inventory (STAI)[41] was used only once at the first sampling (9:00 a.m.) to assess the state (STAI-S) and trait (STAI-T) components of anxiety. Quality and duration of sleep, including early morning awakening, poor quality sleep or non-restoring sleep, during the night before the first blood collection (9.00 a.m.), were also evaluated by using a visual analog and a verbal numeric rating scale (0-10 points).

Serum sample collection and neurotrophins measurement

The Blood was collected at 9:00, 13:00 and 20:00 hours on the same day and before the psychological interview. Approximately 10 ml of blood was drawn from the subject's antecubital vein and left a room temperature until clot forming and clear serum was obtained by centrifugation. Serum samples were stored at -70 °C until use.

NGF and BDNF concentrations in the serum were measured by using human NGF and BDNF immunoassay (R&D system, Minneapolis, USA). All the assays were performed in triplicate, following the manufacturer's instruction and using the recommended buffers, diluents and substrates. The optical density of the color reaction was read using a microtiter plate reader (Dynatech MR5000; PBI International, Dynatech International, Edgewood, NY, USA) set for 450 nm. The intra- and inter-assay coefficients of variation were below 7%. The neurotrophins concentration (expressed as pg/ml) in each sample was calculated according to a standard curve.

Statistical analysis

According to methods previously described[42,43], the statistical analysis of the psychophysical traits and neurotrophins daily profile was conducted by using a two-way ANOVA, with time and sex being the between-subject factors. Post hoc comparisons within logical sets of means were performed using the Tukey's test, the use of which is permissible or even recommended also in the absence of significant main or interaction effects in the ANOVA, in order to minimize frequency errors of both types 1 and 2 following the indications given by Wilcox[44]. All data are presented as the mean ± s.e. The significance level was set at $p<0.05$. The correlations between the levels of serum neurotrophins in men and women and the psychophysical traits were determined by using the Pearson's correlation coefficient (with BDNF and NGF values as independent variables). Again, the significance level was set at $p<0.05$.

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RESULTS

Gender differences of psychophysiological traits

Based on the clinical assessment, the subjects did not present pre-symptomatic, subclinical or pathological signs of anxiety, as evaluated using STAI. No gender differences were found by comparing the men and women STAI-T scores (M 43±1.0; W 43.5±0.8 means ± s.e.; F(1,18)=0.123; p=0.72), while the STAI-S score in women at the 9:00 a.m was significantly higher than in men (M 16.7±0.2; W 20,5±1.2 means ± s.e.; F(1,18)=6.21; p<0.023).

No sleeping disturbances were reported by participants but women show a higher score average for sleeping - which indicates the duration and quality of sleep – when compared to men (M 4.562±0.3; W 6.83±0.3 means ± s.e.; F(1,18)=24.72; p<0.001).

Both genders reported normal mood, feelings, and activity levels but differences between sexes in the scoring average and/or daily trend for some rated psychophysical traits were found. The descriptive data and ANOVA results are shown in Table 1.

In general, men show a similar average score for mood, feeling good and energy at the three daily points examined, while in women the scoring average for these parameters is higher in the morning and decrease at the night. Only the sexual desire shows a significant morning score reduction in women when compared to men.

The cardiac parameters reveal gender-related differences: the cardiac frequency and the systolic blood pressure tend to decrease from morning to night in women and to increase in men. No gender differences were observed in measuring the diastolic blood pressure.

Table 1. Diurnal trend of psychophysiological traits in men and women.

	MEN	WOMAN	ANOVA Analysis
Mood			
09:00 h	4.18±0.32	4.66±0.44	Sex $F_{(1,54)}$=0.05 p=0.81
13:00 h	4.56±0.45	4.58±0.41	Time $F_{(1,54)}$=1.34 p=0.26
20:00 h	4.31±0.24	3.58±0.29	Sex*Time $F_{(2,54)}$=1.17 p=0.31
Feeling good			
09:00 h	4.18±0.23	4.87±0.46	Sex $F_{(1,54)}$=0.10 p=0.74
13:00 h	4.25±0.28	4.79±0.47	Time $F_{(1,54)}$=0.10 p=0.90
20:00 h	4.81±0.25	3.92±0.40	Sex*Time $F_{(2,54)}$=2.19 p=0.12
Feeling rested			
09:00 h	4.37±0.25	4.85±0.33	Sex $F_{(1,54)}$=2.18 p=0.14
13:00 h	3.57±0.24	4.50±0.36	Time $F_{(1,54)}$=3.34 p=0.04
20:00 h	3.62±0.25	3.83±0.36	Sex*Time $F_{(2,54)}$=1.43 p=0.24
Energy			
09:00 h	4.50±0.40	4.21±0.27	Sex $F_{(1,54)}$=2.46 p=0.12
13:00 h	4.25±0.42	4.17±0.38	Time $F_{(1,54)}$=0.08 p=0.92
20:00 h	4.48±0.44	3.62±0.42	Sex*Time $F_{(2,54)}$=.1.04 p=0.35
Sexual desire			
09:00 h	4.93±0.24	3.42±0.45	Sex $F_{(1,54)}$=7.34 p=0.01
13:00 h	4.68±0.37	4.34±0.52	Time $F_{(1,54)}$=0.29 p=0.74
20:00 h	4.93±0.30	3.88±0.41	Sex*Time $F_{(2,54)}$=0.88 p=0.41
Systolic blood pressure			
09:00 h	117±1.60	115±1.94	Sex $F_{(1,54)}$=4.44 p=0.04
13:00 h	109±2.90	109±2.26	Time $F_{(1,54)}$=4.27 p<0.01
20:00 h	117±3.50	106±2.22	Sex*Time $F_{(2,54)}$=2.72 p=0.07
Diastolic blood pressure			
09:00 h	72.5±1.63	71.6±2.07	Sex $F_{(1,54)}$=0.39
13:00 h	67.4±1.63	66.6±2.24	Time $F_{(1,54)}$=1.86 p=0.16
20:00 h	70.6±3.91	68.3±2.84	Sex*Time $F_{(2,54)}$=3.51 p=0.94
Heart rate			
09:00 h	74.1±3.80	86.0±2.54	Sex $F_{(1,54)}$=7.31 p<0.01
13:00 h	68.0±3.16	80.5±3.16	Time $F_{(1,54)}$=1.82 p=0.17
20:00 h	80.6±3.67	77.8±2.62	Sex*Time $F_{(2,54)}$=3.51 p=0.03

Significant p *values in the ANOVA are reported in bold.*

Ultradian serum NGF and BDNF levels in men and women

The serum NGF content measured in men and women at 9.00 a.m., 1.00 and 8.00 p.m. is shown in graph A of Figure 1. A significant gender effect was revealed by two-tailed ANOVA (F(1,54)=12.79 p<0.001), but no gender*time interaction was found. The post-hoc analysis reveals that NGF levels in men are significantly higher at 8.00 pm (p=0.01), while no differences were found in women by comparing the NGF levels at the diverse daytime. The NGF levels in women are significantly higher than in men in all the 3-time points examined (see legend of Figure 1 for data description).

As for BDNF, a significant gender effect (F(1,54)=6.98 p=0.011) and a gender*time interaction (F(2,54)=2.96 p=0.05) were found for diurnal BDNF serum levels (Figure 1B).

Neurotrophins and psychophysiological traits

The correlations between the levels of serum NGF and BDNF in men and women and their psychophysiological traits, determined by using the Pearson's coefficient, are shown in Tables 2 and 3 respectively.

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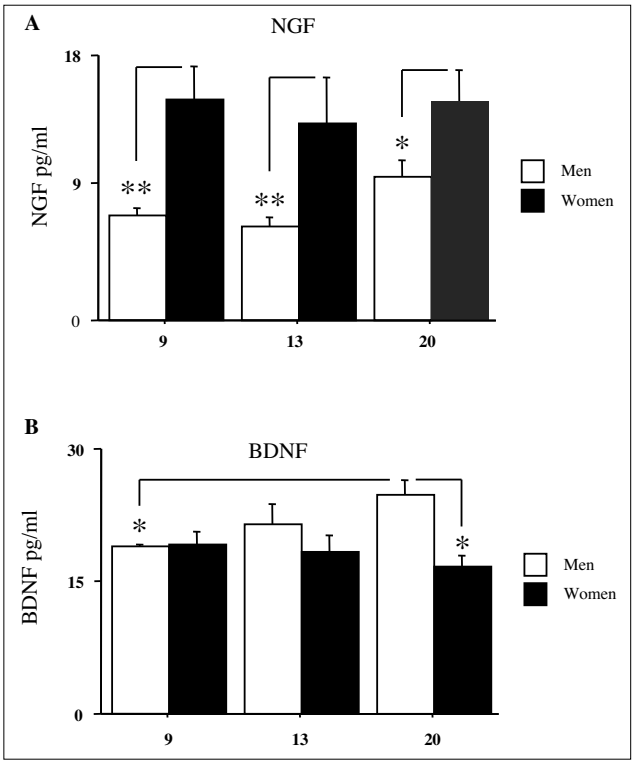

Figure 1. The graphs show the serum levels of NGF (A) and BDNF (B) in men and women at different hours of the day. The values are expressed as means ± s.e. Asterisks indicate significant differences in post-hocs between groups (*p<0.05; **p<0.01).

Table 2. Correlation between psychophysiological characteristics and serum NGF levels.

	MEN		WOMEN	
	Person's *r*	p-value	Person's *r*	p-value
Mood	0.465*	0.022	-0.461**	0.005
Feeling good	0.803***	<.001	-0.370*	0.026
Energy	0.671***	<0.001	-0.335*	0.046
Feeling rested	-0.234	0.271	-0.088	0.609
Sexual desire	0.659***	<0.001	-0.057*	0.032
Cardiac frequency	0.788***	<0.001	-0.040	0.816
Systolic blood pressure	0.614**	0.001	0.004	0.982
Diastolic blood pressure	0.232	0.113	-0.207	0.225

**p<0.05, **p<0.01, ***p<0.001*

Mood, feeling good, energy and sexual desire correlate with diurnal NGF serum levels in positive and negative manners in men and women respectively. The cardiac frequency and systolic blood pressure were also positively correlated with NGF in men, while no correlation was found in women (Table 3).

Table 3. Correlation between psychophysiological characteristics and serum BDNF levels.

	MEN		WOMEN	
	Person's *r*	p-value	Person's *r*	p-value
Mood	-0.135	0.528	-0.098	0.570
Feeling good	-0.219	0.304	-0.048	0.782
Energy	-0.309	0.142	-0.562***	<0.001
Feeling rested	-0.146	0.497	-0.246	0.148
Sexual desire	-0.126	0.558	-0.026**	0.010
Cardiac frequency	0.124	0.564	0.226	0.184
Systolic blood pressure	0.163	0.447	0.153	0.372
Diastolic blood pressure	-0.040	0.853	-0.052	0.762

**p<0.05, **p<0.01, ***p<0.001*

In men, no psychophysiological variable correlates with BDNF serum levels, while in women-only the energy and sexual desire resulted negatively associated with BDNF (Table 3).

DISCUSSION

Based on previous observations showing that serum NGF and BDNF variate during the daytime[33,40], the present study was aimed at investigating whether in healthy humans the ultradian neurotrophins profile might reflect gender differences, and correlate with psychophysiological characteristics associated with mood.

We found that serum NGF and BDNF levels at different hours of the day are gender-related. An opposite morning to evening course for BDNF is observable in men and women serum, while the NGF levels increase at night in men, but not in women, and are higher in women than in men at all the day-time points analyzed.

To the best of our knowledge, only one clinical study reported the gender difference and the existence of an ultradian NGF variation in healthy subjects, but not in schizophrenic patients[45] indicating that the alteration of normal NGF rhythm might be an indicator of mental disorders.

More studies explored the gender-related changes and/or BDNF rhythm in humans. For instance, Piccinni et al.[46] found no diurnal variation in plasma BDNF of women in the follicular or luteal phases of the menstrual cycle. A study by Pluchino et al.[47] reported that BDNF and cortisol plasma levels decrease during the day in both normally menstruating and post-menopausal women, reaching significant levels at 20.00 hours. A decreasing BDNF level from 9:00 to 20:00 hours was found in the men plasma[48], while other studies[49,50] showed a plasma BDNF decrease only at 13.00 hour in men, but no variations in women. These results are partly consistent with other studies[33] showing that in women the BDNF content in the serum is lowered from 9.00 to 20.00 hours, while it is increasing in men.

The discrepancies between the BDNF serum profile detected by us and that found in other studies might be due to

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the use of plasma instead of serum-like in our experimental conditions. Differently from plasma, serum BDNF reflects the pool of BDNF stored in platelets[51,52], explaining the higher BDNF concentration found in the serum than in plasma. In addition, BDNF stored in platelets is probably derived from both the circulating plasma pool and from resident cells in the brain or other organs, thus it might also reflect the gender differences present in brain neurotrophins expression[52,53], or their release and uptake[51].

Notwithstanding, the possible differences between the study protocols, the common results that NGF and BDNF serum levels are different in men and women pointed out the significance of gender as a variable when analyzing circulating neurotrophins. Further, our present findings showing that serum NGF and BDNF are differently susceptible to changes at a different hour of the day in men and women underline the importance of the daytime of blood withdrawal during sampling. Last but not least, the observations that the neurotrophins levels are correlated with psychophysical variables in a gender-related manner support the psychophysiological value of neurotrophins variations in the serum.

Gender and circadian rhythmicity are important determinants of biomarkers for disease insurgence and severity, including mood disturbances. Recently, we proposed a role for NGF and BDNF as chronomarkers of mood disorders based on the evidence that the daily rhythm of serum neurotrophins are altered in psychiatric patients and following antidepressant or mood-stabilizing therapies[40].

We also speculated about the serum neurotrophins levels correlate with the morning–evening dimensions, and are influenced by light in healthy humans[54]. Associations between the eveningness dimension and the Depression and Night Eating Syndrome[54,55] have been reported at pre-morbidity age, and modifications in appetite, sleep and energy profile are indicated as an index of vulnerability to the onset of adult depressive disorders[56-58], emphasizing the importance of alterations of biological rhythms for the psychiatric patient personalized treatment and follow-up[59].

In this context, our present findings that NGF and BDNF profiles in healthy subjects are associated with specific psychophysiological traits in a gender-related manner support the idea the variations of one or both neurotrophins in the serum might have a clinical value by describing physiological (well-being condition) and/or sub-syndromic status. In line with this, we found that mood, feeling good, energy and sexual desire are oppositely correlated with NGF so that high NGF levels are associated with high scores for all the psychological variables in men, and with a low score in women. In addition, in men the heart rate and the systolic pressure correlate with NGF suggesting that the condition of well-being (or activity/arousal status) is featured by an increasing NGF profile in men. At variance, in women the well-being condition is featured by a negative NGF trend, and the optimum timing occurs during the daylight when also the neurotrophins level is high.

Quite interestingly, only energy and sexual desire are negatively correlated with BDNF in women, while no correlation was found in men, indicating that BDNF variations in healthy subjects – which do not manifest subclinical or pathological signs of anxiety – might not reflect the mood or good feelings.

Adan et al.[60,61] found a diurnal pattern of positive activation for alertness and vigor (energy), as well as for mood in men, similar to that reported for evening types. The same authors showed an opposite pattern in women, like a morning type personality, and speculate that the circadian pattern of women is more dependent on environmental synchronizers, thus justifying the gender-related incidence of seasonal mood disorders. Thus, our observations on the NGF and BDNF gender-related trends in the serum and their relationship with the psychophysical variables might corroborate indirectly our previous data on the association between neurotrophins and chrono-type[33] and suggest that gender and time might be important determinants in studies investigating serum neurotrophins changes in humans.

In this view, the gender-related NGF and BDNF ultradian profiles might be useful for a better understanding of the different susceptibility to develop mood disorders between genders, as well as to identify more effective treatments relative to gender and/or chronotypes. Specifically, we propose that alterations in NGF or BDNF might have a different impact on men's and women's abilities to cope with environmental changes or stressors, and therefore represent a gender-related risk factor for developing clinical anxiety or depression. Studies on the association between NGF and BDNF gene polymorphism and depression support this hypothesis. Indeed, a non-synonymous NGF (beta subunit) gene polymorphism (rs6330, c.104C >T, p.Ala35Val), which affects NGF intracellular processing and secretion[62], confers susceptibility to anxiety-related personality traits[63], and reduces the cardiac vagal modulation in men but not in women[64]. Similarly, the BDNF Val66Met polymorphism, which characterizes anxiety- and depression-related personality traits[65] and is connected with changes in BDNF trafficking and secretion[66], plays subtle roles in cortisol responses to mental stress only in women.

In conclusion, the present study shows gender-related NGF and BDNF levels in the serum, and a correlation between NGF, BDNF and psychophysical variables in healthy and no depressed individuals, suggesting the NGF evening type profile and BDNF morning type profile as conditions of health and well-being in men and women, respectively. The findings might offer new insights into the physiological value of neurotrophins in the human serum and their possible use as markers of vulnerability to pathological conditions.

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Author contributions: A.I. and G.B. were responsible for the clinical study concept and design. A.I., and P.T. were responsible for the neurotrophic study design. M.F. and F.P were responsible for the statistical analysis. A.I., P.T., F.P. and M.F. were responsible for manuscript preparation. P.R. and E.F. were responsible for running experiments. A.G., A.P., A.Q., G.R., P.R. and E.F. were responsible for recruiting the subjects and collecting clinical data and performing the clinical rating. All authors critically reviewed content and approved final version for publication.

Competing interests: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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