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Daily serum and salivary BDNF levels correlate with morning-evening personality type in women and are affected by light therapy

I livelli di BDNF nel siero e nella saliva correlano con la personalità mattutina-serotina nelle donne e sono modificati dalla terapia della luce

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SUMMARY. Introduction. BDNF is present in human serum and its level changes have been used as a marker of antidepressant efficacy in some psychiatric disorders. In addition, the positive effects of light therapy on major depression suggest that circadian-regulated factors should be taken into account in the management of mood disorders. The aim of the present study was to test ultradian fluctuations in serum and salivary BDNF levels and their interaction with light therapy in a sample of healthy women. **Methods.** The study included 16 young women. Psychopathological status and chronotype traits were assessed by SPAQ, BDI, STAI, TAS, and MEQ. Standard light treatment protocol was applied. Serum and saliva were collected at 8.00, 13.00 and 20.00 hrs on the same day and at the end of light therapy. **Results.** BDNF levels declined over the course of the day both in serum and saliva, and a correlation between diurnal BDNF trend and personality traits and habits characterizing the morning and evening types in healthy women was found. **Conclusions.** The present study is one of the first to show measurable BDNF in human saliva and to demonstrate its daily fluctuations in both saliva and serum of healthy young women. The correlation between diurnal changes in BDNF and the personality traits associated with body rhythms corroborates the notion that salivary BDNF may be a useful biomarker for stress-related research and different clinical investigations.

KEY WORDS:major depression, morning-evening personality type, serum BDNF, salivary BDNF, circadian rhythms, light therapy, peripheral markers.

RIASSUNTO. Introduzione. Il BDNF è presente nel siero umano e cambiamenti nei suoi livelli sono stati utilizzati come marker per la misura dell'efficacia antidepressiva in alcuni disturbi psichiatrici. Inoltre, l'effetto positivo della terapia della luce sulla depressione maggiore suggerisce che fattori regolatori dell'attività circadiana potrebbero essere presi in considerazione nel trattamento dei disturbi dell'umore. Obiettivo del presente studio è stato quello di valutare in un campione di donne sane la fluttuazione ultradiana dei livelli sierici e salivari di BDNF e la risposta di questa neurotrofina alla terapia della luce. **Metodo.** Lo studio è stato condotto su 16 giovani donne. Lo stato psicopatologico e le caratteristiche di cronotipo sono state valutate con le scale SPAQ, BDI, STAI. TAS e MEQ. È stato applicato il protocollo standard della terapia della luce. Il siero e la saliva sono stati raccolti alle ore 8.00, 13.00 e 20.00 di ciascun giorno e alla fine del trattamento. **Risultati.** I livelli di BDNF si abbassano nel corso della giornata sia nel siero sia nella saliva ed è stata riscontrata una correlazione tra il trend diurno del BDNF e le caratteristiche di personalità mattutino-serotina nelle giovani donne studiate. **Conclusioni.** Il presente studio è uno dei primi che ha dimostrato la presenza di quantità misurabili di BDNF nella saliva umana e la fluttuazione ultradiana della neurotrofina sia nella saliva sia nel siero di giovani donne. Il riscontro di una correlazione tra cambiamenti diurni del BDNF e tratti di personalità associati ai ritmi del corpo corrobora la tesi di un'implicazione del BDNF salivare come marker biologico utile per le ricerche sullo stress e per lo studio di differenti quadri clinici.

PAROLE CHIAVE: depressione maggiore, personalità mattutina-serotina, BDNF sierico, BDNF salivare, ritmi circadiani, terapia della luce, marker periferici.

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INTRODUCTION

The neurotrophin brain-derived neurotrophic factor (BDNF) is largely expressed in the central nervous system where it regulates the neuronal activity and plasticity in all life stages, from development to aging (1,2). Numerous studies support the role of BDNF in the central events concurring to mood in humans and animals (3-5), and in the mechanism of action of antidepressant and anxiolytic drugs (6,7). Accordingly, the up-regulation of brain or serum BDNF levels reported in patients and animal models after treatment with antidepressants would contribute to revert the atrophy and/or malfunctioning of central limbic structures resulting in behavioral and clinical improvement (8).

In serum, BDNF is present in large amounts, and although the source of circulating BDNF and its relationship with brain neurotrophin activity is still unclear, there is evidence that serum BDNF changes can serve as a marker of therapeutic efficacy in some psychiatric disorders (e.g., depression) (9) as well as to define personality traits and vulnerability for depression in healthy human subjects (10). These data suggest that changes in peripheral BDNF concentration are not a simple epiphenomenon but they may reflect the central neurotransmission state and/or neuronal plasticity (11). Further, the findings that serum BDNF levels correlate with habitual (12) or trained physical activity (13) and a related healthy lifestyle in men and women (14) underline the physiological value of BDNF storage and release in the peripheral system.

In this context, it is worth noting that the effects of antidepressants or the efficacy of physical therapy, such as light therapy, are often associated with patient chronotype or the day time of administration (15), indicating the high level of importance of circadian-regulated factors in the management of mood disorders.

While there are studies describing the circadian variation of BDNF expression in different brain areas of animal models (16,17), only few information about the possible daily fluctuations in serum neurotrophin is available (18).

Several clinical indicators of mood disorders, schizophrenia and stress (i.e. cortisol) (19), melatonin (20,21), serotonin (22), and nerve growth factor (NGF) (23) show a daily rhythm in bodily fluids – including serum and saliva – and are altered in circadian levels in psychopathological conditions and after pharmacological or light therapy.

To further validate the use of BDNF as a biomarker for behavior, mood and therapy, the present study is focused on the assessment of daily fluctuation of serum and salivary BDNF in a sample of young healthy women screened for morning-evening personality and seasonal mood changes. In addition, the effects of light therapy on daily BDNF trend in serum and saliva were also investigated.

MATERIALS AND METHODS

Study design, subjects and inclusion criteria

The study included 16 young female students (mean age 21±0.5 years) from the University of L'Aquila with the aim to analyze daily serum and salivary BDNF levels in correlation with personality traits, and to evaluate the effects of light therapy. The study was approved by the intramural ethic committee, and all participants, who received a complete description of the study, accepted the experimental procedures.

None of the subjects were family-related, nor did they report any personal or familial neurological or psychiatric disease, allergy or inflammation. They were not taking regular medications and were non-smokers. Women in the first week of their post-menstrual period were included.

Psychopathological signs and chronotype were assessed by Seasonal Pattern Assessment Questionnaire (SPAQ) (24), Beck Depression Inventory (BDI) (25), State-Trait Anxiety Inventory (STAI) (26), Toronto Alexithymia Scale (TAS) (27), and Morningness-Eveningness Questionnaire (MEQ) (28).

Light therapy protocol

Standard light therapy protocol was applied using Samalux 600 (Samarit, Switzerland) and 10,000-lux for 30 min on habitual awakening for 5 consecutive days per week, and the treatment lasted 3 weeks. The experiment started within the first week of the post-menstrual period. The samples of serum and saliva were collected before (baseline) and at the end of light therapy.

Serum and saliva sample collection

The samples of serum and saliva were collected at 8.00, 13.00 and 20.00 hrs on the same day as described below. At the time of sample collection, all subjects had fasted and were not under the effect of theine or caffeine.

Approximately 10 ml of blood was drawn from the subject's antecubital vein and left at room temperature until forming a clot, and clear serum was obtained by centrifugation. The sample of saliva was collected via passive drool in plastic tube followed by centrifugation at 10,000 rpm for 10 min. Serum and saliva samples were stored at -70°C until use.

BDNF measurement

Serum and salivary BDNF levels were assayed using the Quantikine Human BDNF immunoassay (R&D Sys-

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tem, Minneapolis, Minnesota, USA). All assays were performed in duplicate following the manufacturer's instructions as to using the recommended buffers, diluents and substrates. The optical density of the color reaction was read using a microtiter plate reader set at 450 nm. The intra- and inter-assay coefficients of variation were below 7%. BDNF concentration (in pg/ml) in each sample was calculated according to a standard curve. Data are expressed as means ± SD.

Statistical analysis

Statistical analysis was performed using the SuperANOVA package for Macintosh (Abacus Concepts Inc., Berkeley, CA, USA). The ANOVA for repeated measures was used to analyze BDNF daily trends in saliva and serum and the effects of light therapy. The relationship between salivary and serum BDNF and MEQ, TAS, BDI and STAI scores was determined using the Pearson correlation coefficient and multiple regression (with BDNF values as independent variable). A P-value of <0.05 was considered statistically significant.

RESULTS

The study sample was, in general, in good psychological and mood conditions, with no pre-symptomatic or pathological signs of anxiety and depression (STAI score 43±9; BDI score 5±2; TAS score 47±5), or seasonal changes in mood and behavior. The MEQ scored the subjects as morning (scored as 3), inter-media (scored as 2) and night personality types (scored as 1). No sleep discomfort was reported.

BDNF in serum and saliva and its correlation with the female chronotype

Serum and salivary BDNF levels of the young women included in the present study are shown in **Figure 1** as revealed by the ANOVA analysis for repeated measures. A significant similar BDNF daily trend was detected in the two body fluids, although regression analysis showed no significant correlation between serum and salivary BDNF levels.

Multiple regression analysis also showed that serum (**Figure 2**) and salivary (**Figure 3**) BDNF levels were significantly but differently correlated with the MEQ score. For example, in evening type subjects (low MEQ score), serum BDNF levels increased from morning to evening, whereas salivary BDNF levels followed an opposite trend.

No correlations between serum/salivary BDNF levels and STAI, TAS or BDI scores were found.

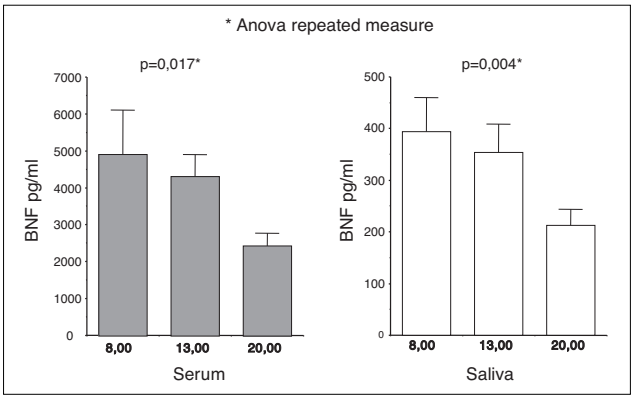

Figure 1. Daily BDNF levels in serum and saliva of healthy young women.

Effects of light therapy on serum and salivary BDNF levels

After 3 weeks of light therapy, serum and saliva samples were collected at different time points. As shown in **Figures 4** and **5**, treatment affected both serum and salivary BDNF daily trends. However, while BDNF serum levels were dramatically increased at all the time points examined, no similar effects were found in the saliva. Actually, a significant decrease was found by comparing basal and post-treatment BDNF levels in the saliva taken at 8.00 and 13.00 hrs, but not at 20.00 hrs.

BDNF changes induced by light therapy did not affect the STAI or BDI scores, and no sleep discomfort was reported by the subjects.

DISCUSSION

Given the difficulty of studying BDNF levels in the human brain directly, the discovery of measurable amounts of BDNF in serum and plasma has been of great help to explore the role of this neurotrophin in neurological and psychiatric diseases. To the best of our knowledge, the present study is one of the first showing the presence of measurable amounts of BDNF in human saliva and to demonstrate a daily fluctuation in both the saliva and serum of young healthy women. Although diurnal variation (29) as well as age and gender differences (30) have been previously observed for salivary NGF levels – the BDNF-family-related neurotrophin –, no studies have previously addressed similar issues concerning BDNF in human saliva.

Several reports have documented BDNF concentrations in human serum and plasma but provided dif-

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Anova table: MEQ score vs BDNF serum levels (3 indipendent variables)

	DF	Sum of Squares	Mean Square	F-Value	P-Value
Regression	3	5,495	1,832	14,599	,0003
Residual	12	1,505	,125		
Total	15	7,000			

Table of regression coefficients

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1,247	,542	1,247	2,299	,0403
8.00	2,237E-4	4,688E-5	,747	4,772	,0005
13.00	8,743E-5	1,291E-4	,253	,677	,5111
20.00	-1,397E-4	6,964E-5	-,720	-2,006	,0679

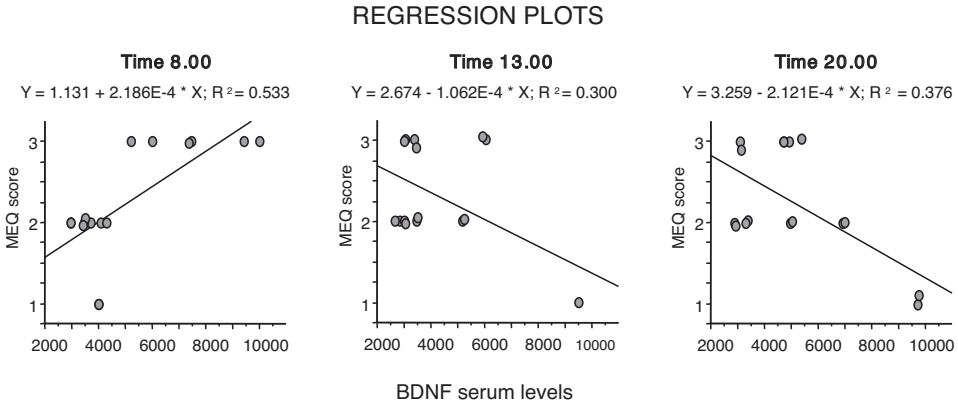

Figure 2. Serum BDNF levels are significantly correlated with the MEQ score and increase from morning to evening in evening type subjects (low MEQ score).

ferent and/or conflicting results. Daily variations of BDNF have been demonstrated in male plasma (31), whereas no changes were found in female plasma or in the serum of both sexes (32). Pluchino et al. (33) have recently shown that BDNF diurnal variation appears to be influenced by ovarian function and associated with cortisol variations. However, other studies failed to confirm a menstrual cycle-dependent variation of BDNF (34) or a correlation between BDNF and cortisol in human serum (35).

In addition, since BDNF changes in humans correlate with age, physical activity, energy balance, and life habits – including smoking and drinking – (12,14,34, 36), and are affected by stress (4,37), differences in results can also derive from heterogeneous sampling conditions.

In our study, different variables were considered in selecting the sample group. For example, all participants were young female students (mean age 21±0.5 years) with comparable levels of activity, non-smokers and nor habitual alcoholic drinkers, and without reported allergy or inflammation. In addition, at the beginning of the experiments they were in their estrogenic phase without signs of seasonality or depression.

In this experimental condition, we were able to detect daily BDNF changes in both serum and saliva and to demonstrate a correlation between diurnal BDNF trends and personality traits and habits characterizing the morning and evening types in healthy women.

In accordance with observed BDNF daily trends in male and female plasma (31,33), the decline of serum and salivary BDNF levels during the course of the day might indicate a correspondence between BDNF and the activity/arousal status in healthy conditions.

This hypothesis is supported by the findings that BDNF daily trends correlate with the MEQ score, so that, for example, at 8.00 hrs, in parallel with the alertness levels (38), the morningness and eveningness

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Anova table: MEQ score vs saliva BDNF levels (3 indipendent variables)

	DF	Sum of Squares	Mean Square	F-Value	P-Value
Regression	3	4,945	1,648	17,179	,0002
Residual	11	1,055	,096		
Total	14	6,000			

Table of regression coefficients

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1,504	,378	1,504	3,980	,0022
8.00	-,005	,001	-,878	-5,143	,0003
13.00	,002	,001	,415	2,403	,0350
20.00	,008	,001	,812	5,924	<,0001

REGRESSION PLOTS

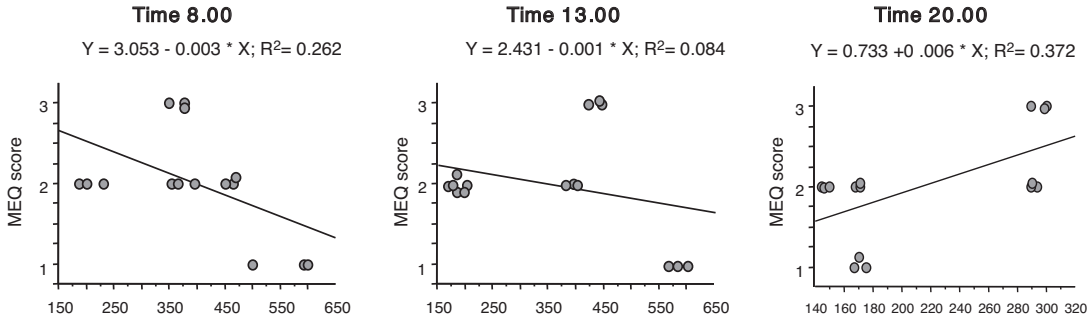

Figure 3. Salivary BDNF levels are significantly correlated with the MEQ score and decrease from morning to evening in evening type subjects (low MEQ score).

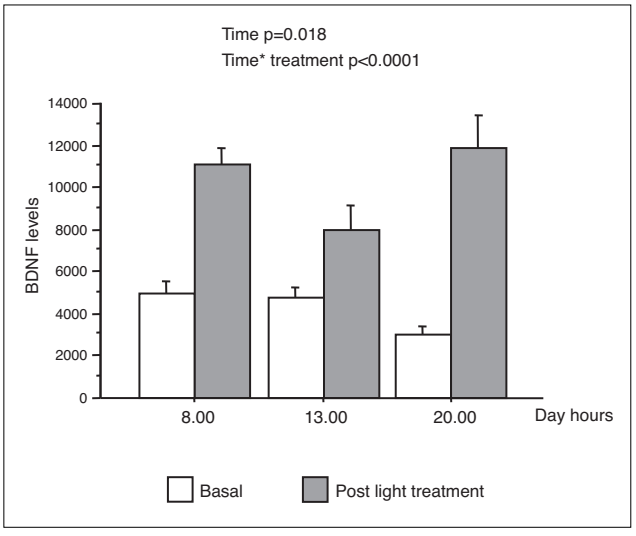

Figure 4. Serum BDNF levels are significantly increased after light therapy at all the time points examined.

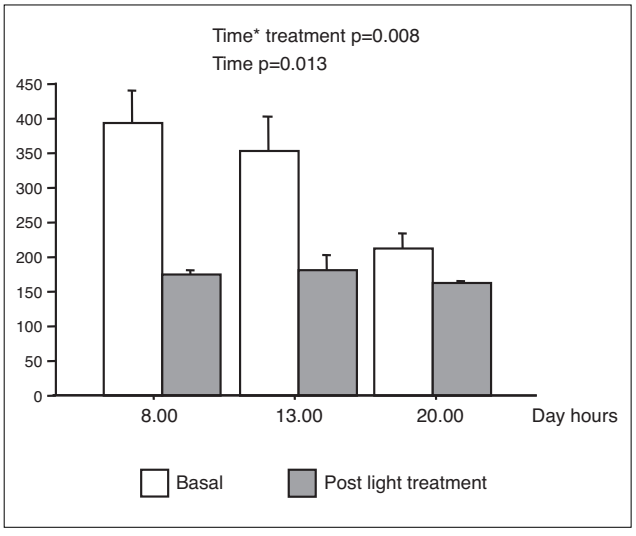

Figure 5. Salivary BDNF levels are significantly decreased after light therapy at 8.00 and 13.00 hrs, but not at 20.00 hrs.

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types are characterized by high and low serum BDNF, respectively. Given that biological, genetic and environmental factors contribute to the morningness and eveningess personality (39) a unidirectional explanation for the relationship between BDNF and chronotype is improbable. However, it is worth noting that, compared to the morningness type, eveningness persons have low cortisol levels in serum and saliva in the morning (40), and increased cardiac activity and response to stress in the afternoon with respect to the morning (41) suggesting a different pattern in sympathetic-adrenal system activity and response. Chronotype also influences depressive symptomatology, including sleep disturbances, in healthy persons (42) and correlate with symptom severity in psychiatric patients (43,44).

As largely documented, variations of circulating BDNF levels are considered predictive of depression vulnerability and severity, as well as of therapeutic efficacy (9,45). In this perspective, a diurnal rhythm in serum and salivary BDNF and its correlation with the morningness-eveningness dimensions underline the importance of considering the time of the day as a sampling variable in studies that assess the role of neurotrophins in stress and mood disorders, as also recently suggested by Bus et al. (36).

In addition, the findings of a similar daily BDNF trend in serum and saliva but of an opposite correlation with the MEQ score and response to light therapy led us to speculate that, although the average serum and salivary BDNF levels indicate a general tendency of peripheral BDNF to decline during the nocturnal hours, BDNF release in serum and saliva may be affected by different regulatory mechanisms and/or reflect the diverse neuroendocrine components associated with chronotype, resulting in a different response to light therapy performed in the morning.

Although peripheral factors – including clotting processes in platelets (46,47) – can contribute to variations of circulating neurotrophin levels, several findings suggest that serum BDNF may reflect central nervous system activity. Peripheral BDNF may mediate the response to stress through activation of peripheral tissues (48). In addition, the pituitary gland produces and releases BDNF into the bloodstream thus contributing to BDNF elevation in the serum following stress (49). Nonetheless, an effect of peripheral BDNF on the central nervous system cannot be excluded since peripheral and central BDNF levels are closely related (50) and a correlation between serum BDNF levels and an in vivo marker of cortical integrity has recently been shown (34,51). In addition, the ability of BDNF to cross the blood-brain barrier has been demonstrated (52). Studies on humans and animals demonstrated that salivary neurotrophin production is also stimulated by stress and regulated by hormones (53). However, increased neurotrophin synthesis in salivary glands is observable following mastication and secretagogue agents (30), indicating a correlation with the saliva flow rate and the involvement of the autonomic nervous system. In particular, experiments using selective adrenergic receptor blockers demonstrated that nerve stimulation elicits NGF in the saliva through the activation of alpha-adrenergic receptors (54) suggesting the contribution of the sympathetic rather than the parasympathetic nervous system.

Since saliva secretion and composition are stimulated by the activation of adrenergic receptors by the release of norepinephrine at nerve endings (55), it is likely that the BDNF trend in the saliva is mainly influenced by the different state of activation of the sympathetic nervous system and/or the levels of circulating catecholamines. Therefore, while serum BDNF levels appear centrally regulated and/or dependent on the hormonal status, the BDNF profile in the saliva of morning/evening person types may reflect adrenergic system activity at different hours of the day.

The involvement of the adrenergic system in the regulation of salivary BDNF might also enlighten our findings that light therapy differently affects BDNF levels in the saliva and serum. Indeed, light stimuli acting through the retinal-hypothalamic pathway inhibit the neural activity of sympathetic afferents to the salivary glands while stimulating those to adrenal glands, which in turn secondary can affect saliva secretion through the release of catecholamines. Desensitization of adrenergic receptors by circulating catecholamines and the subsequent reduction in saliva secretion occur in constant dark or light conditions following immobilization stress in rats (56), indicating that environmental stimuli can modify the homeostatic control of salivary gland activity. Light also influences the salivary flow rate and composition in humans, and reduced salivation and mouth dryness ares associated with medication, depression, anxiety, and stress (57).

Therefore, it is likely that the mechanisms regulating salivary gland secretion in stress-like conditions may also occur following prolonged light therapy, thus inducing a decrease and an increase in salivary and serum BDNF levels, respectively, as observed in our study.

CONCLUSIONS

Although further studies with a larger sample size are warranted to validate this hypothesis, evidence sup-

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porting that treatment with antidepressants – which are known to normalize serum BDNF levels in depressed patients – is associated with a decrease in saliva flow rate (58) could indirectly support this notion.

In conclusion, our study demonstrates a correlation between the fluctuation of circulating BDNF and the personality traits associated with body rhythms, corroborating the notion of BDNF involvement in the regulation of human behaviors and suggesting that salivary BDNF may be a useful biomarker for stress-related research and human clinical investigations. In addition, the possible dissociation between serum and salivary BDNF daily trends may offer an advantage for evaluating the impact of different antidepressant drugs or physical therapies on the autonomic nervous system.

Acknowledgments

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