Psychoneuroendocrinology 109 (2019) 104415

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Growth factors and neurotrophins in patients with stress-related exhaustion disorder

Anna Sjörs Dahlman[a,b,*], Kaj Blennow[c,d], Henrik Zetterberg[c,d,e,f], Kristina Glise[a], Ingibjörg H. Jonsdottir[a,g]

[a] The Institute of Stress Medicine, Region Västra Götaland, Gothenburg, Sweden
[b] The Swedish National Road and Transport Research Institute, Gothenburg, Sweden
[c] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Sweden
[d] Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
[e] Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom
[f] UK Dementia Research Institute at UCL, London, United Kingdom
[g] Department of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

ARTICLE INFO

Keywords:
Burnout
Stress
Neurotrophic model
Exhaustion
Growth factor
Neurotrophin

ABSTRACT

Growth factors, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), and neurotrophic factors, including brain-derived neurotophic factor (BDNF), have attracted attention in studies of the biological effects of long-term stress exposure due to their neuroprotective roles.

This study investigated whether circulating levels of EGF, VEGF and BDNF were altered in individuals with stress-related exhaustion disorder. Forty patients diagnosed with exhaustion disorder and 40 healthy subjects (50% women) provided fasting blood samples for analysis of EGF, VEGF, and BDNF in plasma.

We found significantly lower levels of EGF, VEGF, and BDNF in patients with ED compared to healthy controls. This pattern was seen in both male and female patients. Given the important roles of BDNF and VEGF for brain plasticity and neurogenesis, decreased levels after long-term stress exposure could indicate increased risk of neuronal damage and cognitive impairments in this patient group.

1. Introduction

Large efforts have been made in recent years to elucidate the biological effects of long-term stress exposure, with the goal to better understand, prevent and treat stress-related conditions such as burnout and exhaustion. Several biological mechanisms have been shown to be affected by prolonged psychosocial stress and among these are important adaptive responses that serve to protect the body's organs from changes in the cellular environment that might arise due to stress (McEwen, 2007).

Various organ systems have been suggested to be affected by chronic stress, including the nervous system, the immune system and endocrine axis, but the literature is inconsistent regarding the link between the exposure to chronic psychosocial stress and the biological consequences (Allen et al., 2017; Jonsdottir and Sjörs Dahlman, 2019). Frequently studied physiological mechanisms associated with chronic stress include the autonomic nervous system and neuroendocrine reactions, mainly the HPA axis and cortisol (Danhof-Pont et al., 2011; Jonsdottir and Sjörs Dahlman, 2019).

Other molecules and systems that are of value to study in relation to the adaptive responses to stress are various growth factors involved in repairing and stimulating the growth of nerves and vessels and preventing programmed cell death (Galvez-Contreras et al., 2016). One of the factors that has attracted interest is vascular endothelial growth factor (VEGF), which is a growth factor associated with neovascularization (Gora-Kupilas and Josko, 2005). VEGF also has neuroprotective roles as it promotes neurogenesis, neuronal patterning, neuroprotection and glial growth (Rosenstein et al., 2010). Since VEGF has been identified as a potentially important factor in the pathophysiology of stress-related disorders studies of both rodents and humans have attempted to delineate its precise role (Clark-Raymond and Halaris, 2013; Sharma et al., 2016). VEGF has been demonstrated to play a role in hippocampal neurogenesis and response to stress, as well as in exerting neuroprotective effects and influencing synaptic transmission (Clark-Raymond and Halaris, 2013). Moreover, epidermal growth factor (EGF) has also emerged as potential component in the pathophysiology of

* Corresponding author at: Institute of Stress Medicine, Carl Skottsbergs gata 22 B, 413 19 Göteborg, Sweden.
E-mail address: anna.sjors@vgregion.se (A. Sjörs Dahlman).

https://doi.org/10.1016/j.psyneuen.2019.104415
Received 3 May 2019; Received in revised form 23 July 2019; Accepted 19 August 2019

stress-related disorders. However, studies of plausible deviations in the levels of these growth factors in patients with stress-related conditions have been inconclusive, showing both increased and unchanged VEGF and EGF levels in women with stress-related exhaustion (Jonsdottir et al., 2009; Wallensten et al., 2016; Åsberg et al., 2009). No studies have reported on EGF and VEGF in male patients.

In addition, the possible role of neurotrophic factors in stress-related mood disorders has been hypothesized in the context of the neurotrophic model, which postulates that stress can lead to decreased level of neurotrophins, including brain-derived neurotophic factor (BDNF), nerve growth factor (NGF), and neurotrophin 3 (NT-3) (Duman and Monteggia, 2006). The model suggests that stress-related decline in neurotrophins may cause atrophy of some limbic structures that control mood, resulting in symptoms of depression, and that antidepressant treatment can reverse this atrophy and restore physiological levels of neurotrophins. So far, little direct evidence of BDNF deficits in humans with stress-related disorders is available, but emerging evidence using animal models suggests the possible involvement of neurotrophic factors in depression (Numakawa et al., 2013). Several clinical studies have also shown that BDNF levels are associated with depression response; supporting the notion that depression improvement is associated with neuroplastic changes (Lopes et al., 2008). Although the focus in previous studies has mainly been on depression, most animal models of depression are based on stress paradigms and may therefore also be of relevance for other stress-related conditions, such as burnout and exhaustion (Eriksson and Wallin, 2004). One study suggested that serum BDNF levels could be used as a biological marker of psychological job stress in healthy workers as they found a negative correlation between serum BDNF levels and scores for the stress items in the Stress and Arousal Check List et al. (Mitoma et al., 2008). A recent study reported associations between burnout symptoms and low serum BDNF in healthy subjects (He et al., 2017). Low serum BDNF has also been found in employees with clinical burnout (Onen Sertoz et al., 2008).

The aim of this study was to investigate whether levels of EGF, VEGF and BDNF in the blood differed between individuals with stress-related exhaustion disorder and healthy controls. As previous studies on this topic predominantly have included female participants, possible differences between men and women were tested. In addition, we aimed to investigate whether EGF, VEGF, and BDNF levels were related to symptom duration and severity in the patient group. The overall objective is to increase knowledge about the pathophysiology of stress-related mental illness.

2. Materials and methods

2.1. Study population

This study includes 40 clinical burnout patients (20 men and 20 women) referred to an outpatient clinic at the Institute of Stress Medicine, Gothenburg, Sweden. All patients fulfilled the diagnostic criteria for Exhaustion Disorder (ED) as previously described by Jonsdottir et al. (2009) and had a maximal duration of sick leave of six months. The ED diagnosis was used since there are no diagnostic criteria for burnout and ED is considered to be comparable to clinical burnout (Grossi et al., 2015). Comorbidity of depression and/or anxiety was screened for by using the one-page Primary Care Evaluation of Mental Disorders questionnaire (Spitzer et al., 1994). This was followed up by a physician who set anxiety and/or depression diagnosis according to the DSM IV criteria using a structured interview form (American Psychiatric Association, 2000). Two patients had comorbid depression, eight had anxiety, 29 patients had both depression and anxiety, and one patient did not have comorbid depression or anxiety. Patients using antidepressant medication were excluded from this study, since it has been shown that antidepressants can increase the levels of BDNF (Bjorkholm and Monteggia, 2016).

Healthy controls (20 men and 20 women) were recruited from ongoing studies at the clinic. The primary inclusion criteria were: self-reported good health, no use of medication with systemic effects, age 25–50, and body mass index (BMI) between 18.5 and 30 kg/m2. None of the controls fulfilled diagnostic criteria for ED.

The participants underwent a screening test, including anthropometric measurements and blood samples to assess the following exclusion criteria: systemic disease (such as thyroid disorder, hypertension, or diabetes), psychiatric disease (except for depression, anxiety, and exhaustion for the patients), current infection, pregnancy, breast-feeding, medication with substances having systemic effects, vitamin B12 deficiency, and over-consumption of alcohol.

Self-reported physical activity was assessed with a question developed by Saltin and Grimby (Grimby et al., 2015). The participants reported the level that best corresponded to their physical activity during the last three months: 1) mostly sedentary; 2) light physical activity at least two hours a week; 3) moderate physical activity at least two hours a week; 4) intense physical activity at least five hours a week.

The study was approved by the Regional Ethical Review Board in Gothenburg (439-05) and was conducted in accordance with the Declaration of Helsinki. All participants included in the study gave written informed consent.

2.2. Symptom assessment

Symptom duration was assessed with a question about time elapsed since the onset of ED symptoms. The response alternatives were <1 year, 1–2 years, 3–5 years, and >5 years. Burnout symptoms were assessed with the 18-item version of the Shirom Melamed Burnout Questionnaire (Lundgren-Nilsson et al., 2012). Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983).

2.3. Blood sampling

All subjects had blood drawn from an antecubital vein by a research nurse between 7:30 and 10:00 after fasting since 22:00 the day before. The participants were instructed to abstain from hard physical exercise for 24 h prior to the blood sampling. The samples were collected in pre-chilled 9 mL EDTA tubes and centrifuged at 4 °C, 1835*g* for 15 min. Plasma was aliquoted into 1–1.5 mL volumes and stored at −80 °C until assayed.

2.4. Biochemical analysis

Plasma EGF, total BDNF and VEGF concentrations were measured using commercially available Quantikine enzyme-linked immunosorbent assays from R&D Systems (Minneapolis, MN). The assays were performed by board-certified laboratory technicians who were blinded to clinical data. Intra- and inter-assay coefficients of variation were below 10%.

2.5. Statistical analysis

All outcome variables were tested for normality by the Shapiro-Wilk test. Logarithmic transformations were performed on non-normally distributed variables. Chi-square tests and *t*-tests were used to compare background characteristics between patients and controls. To investigate differences between patients and controls in EGF, VEGF and BDNF, a two-way multivariate analysis of variance (MANOVA) was performed with EGF, VEGF and BDNF as the dependent variables and group (patient or control) and sex (male or female) as the fixed factors. This was followed by univariate ANOVA for each analyte. Age, body mass index (BMI), waist to hip ratio (WHR), and physical activity were considered potential confounders. These were included as covariates in analyses of covariance (ANCOVA) if applicable.

In the patient group, we investigated whether BDNF, VEGF, and

Table 1
Mean (SD) of background data in patients and controls.

	Patients	Controls	Test statistic	p
Sex (♀/♂)	20/20	20/20		
Age	39 (10)	40 (8)	t = 0.4	0.677
BMI (kg/m^2)	24.6 (3.3)	23.6 (2.5)	t = 1.5	0.137
WHR	0.87 (0.07)	0.86 (0.06)	t = 0.6	0.574
Physical activity			Chi^2 = 14.9	0.002
Sedentary	17.5%	5.1%		
Light	65.0%	38.5%		
Moderate	17.5%	43.6%		
Vigorous	6.3%	12.8%		

BMI = body mass index, WHR = waist to hip ratio.

EGF were related to ED symptoms by performing Spearman rank correlation analyses with self-reports of symptom duration and severity of depressive, anxiety, and burnout symptoms.

For all tests, the level of significance was set at $p < 0.05$, two-tailed. Analyses were conducted with IBM SPSS v22.

3. Results

The patients and controls were similar regarding age and body composition, whereas self-reported physical activity differed between groups (Table 1). The patients were generally less physically active than the healthy individuals.

3.1. Patients vs. controls

EGF, VEGF, and BDNF were not normally distributed and all analyses of variance below were performed using ln-transformed data. The MANOVA showed a significant difference between patients and controls ($F(3,74) = 12.9$, $p < 0.001$, Wilk's lambda = 0.657, $\eta^2 = 0.343$) and significant effect of sex ($F(3,74) = 6.4$, $p = 0.001$, Wilk's lambda = 0.795, $\eta^2 = 0.205$). The group*sex interaction was not significant ($F(3,74) = 0.6$, $p = 0.597$, Wilk's lambda = 0.975), indicating that the difference between patients and controls in EGF, VEGF and BDNF was present in both men and women. In detail, EGF, VEGF, and BDNF were all significantly lower in patients than controls (see Table 2, Fig. 1). VEGF levels were significantly higher in men than women, whereas EGF and BDNF did not differ between men and women. The potential confounders, age, BMI, WHR, and physical activity level were entered one-by-one as well as together in the model but controlling for these factors did not change the results. As physical activity differed significantly between groups, results from the MANCOVA controlling for physical activity is presented in Table 3.

3.2. Symptom duration and symptom severity

Within the patient group, no significant correlation was seen between symptom duration and EGF, VEGF and BDNF (Table 3). Anxiety symptoms were moderately correlated to EGF, VEGF and BDNF, whereas no correlation was seen with symptoms of burnout and depression (Table 4).

4. Discussion

We found markedly lower levels of EGF, VEGF, and BDNF in patients with stress-related exhaustion disorder compared to healthy controls. This was seen in both male and female patients. Symptoms of anxiety, measured with the HAD scale, were positively related to EGF, VEGF, and BDNF in the patient group whereas symptom of depression was not correlated to any of the biological markers measured in this study.

In contrast to our results, one study found that VEGF and EGF were significantly higher in women with ED compared to healthy women (Åsberg et al., 2009). Some indications of a dose-response relationship between stress exposure and VEGF and EGF levels were reported. However, the dose-response relationship was only found in a non-clinical population with occupational stress, not in ED patients. They also proposed diagnostic cut-off values for VEGF and EGF in plasma. We previously presented data on a similar patient group and used the same analytic method but did not find increased plasma levels of VEGF or EGF in women with ED compared to healthy controls (Jonsdottir et al., 2009). In that study, VEGF was measured using two different methods and a 3.7-fold mean difference was found between methods. Based on these large discrepancies between various analytical techniques, we argued against the use of cut-offs for screening or diagnostic purposes in ED. Another study performed a two-year follow-up study on plasma levels of VEGF and EGF in women with ED and found significantly higher plasma levels of VEGF and EGF in patients compared to healthy controls at baseline (Wallensten et al., 2016). VEGF and EGF decreased significantly among the patients during follow-up but were still significantly higher in patients 12 months and 24 months after inclusion compared to baseline data from healthy controls. These studies only included female participants and either patients on antidepressant medication were included or did not report antidepressant use, which could partly explain the contrasting results.

Low BDNF has previously been reported in both clinical and non-clinical burnout populations. We thus confirm that BDNF might be a pathogenic factor involved in burnout. Onen Sertoz et al. (2008) studied BDNF levels among hospital employees (81% female). Clinical burnout cases were identified through a semi-structured clinical interview and burnout syndrome diagnosis was based on the ICD-10 criteria for work-related neurasthenia. The burnout group had significantly lower serum BDNF than the healthy control group. Relationships between BDNF levels and burnout symptoms measured with the Maslach Burnout Inventory (MBI) and its sub-scales were also investigated. They found a negative relationship between serum BDNF levels and total MBI score and EE and DP sub-scale scores and a positive relationship with the PA sub-scale. In a recent study, the relationship between burnout, serum BDNF levels and cognition was investigated in healthy subjects (83% female) working in a hospital (He et al., 2017). Burnout subjects were defined as participants scoring in the highest tertile of the MBI sub-scales EE or DP or the lowest tertile of the PA sub-scale. The study showed that serum BDNF levels were significantly lower in burnout than non-burnout subjects. Furthermore, burnout subjects scored lower on immediate memory, attention, and total cognitive functioning. BDNF levels were negatively associated with burnout symptoms measured using the MBI total and its sub-scale scores, but positively associated with immediate memory, attention and total cognitive

Table 2
Geometric mean (CI) of EGF, VEGF and BDNF in patients and controls and between-subjects effects from the ANOVA.

	Patients	Controls	Group			Sex			Group*Sex		
	Mean (CI)	Mean (CI)	F	p	η^2	F	p	η^2	F	p	η^2
EGF (pg/mL)	18.6 (14.1; 24.5)	44.8 (36.3; 55.4)	26.2	<0.001	0.257	1.3	0.255	n.a.	0.0	0.984	n.a.
VEGF (pg/mL)	39.9 (31.8; 50.0)	70.0 (54.2; 90.3)	12.9	0.001	0.145	14.2	<0.001	0.157	0.9	0.355	n.a.
BDNF (pg/mL)	819.1 (597.4; 1123.1)	2666.1 (2143.0; 3316.8)	38.0	<0.001	0.333	0.6	0.430	n.a.	0.9	0.887	n.a.

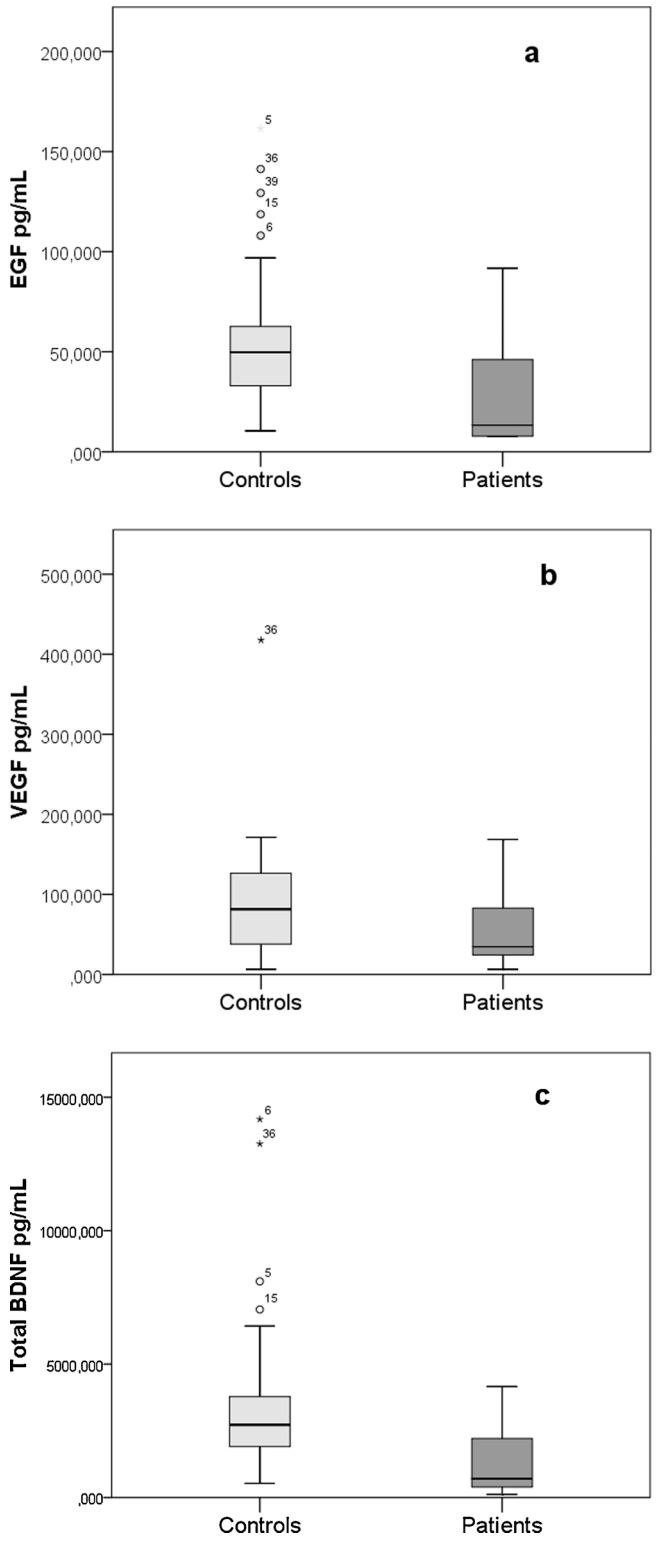

Fig. 1. Box plots of a) EGF, b) VEGF, and d) BDNF in patients and controls.

functioning score. A mediation analysis showed that BDNF had a mediating effect in the relation between burnout and cognitive impairments. The authors hypothesized that chronic stress could result in inadequate brain plasticity by lowering of hippocampal neurogenesis via decreasing BDNF levels. This is in line with a previous study proposing that the failure of adult hippocampal neurogenesis provides the biological and cellular basis of altered brain plasticity in burnout, and that burnout is the result of inadequate brain plasticity caused by stress-induced lowering of neurogenesis (Eriksson and Wallin, 2004).

Circulating BDNF has been shown to be related to memory and general cognitive function in healthy adults (Gunstad et al., 2008; Komulainen et al., 2008) Thus, the results of our study are in line with the view that neurotrophic factors plausibly play a role in stress-related exhaustion and that decreased rather than increased levels of both BDNF and VEGF would be expected based on theoretical models of chronic stress and findings from animal studies (Molteni et al., 2016; Numakawa et al., 2013; Taliaz et al., 2011; Zaletel et al., 2017). Furthermore, cognitive impairments and cognitive fatigue while performing cognitive tasks are pronounced in patients with stress-related exhaustion (Grossi et al., 2015; Krabbe et al., 2017) and the role of the decreased level of BDNF and VEGF in relation to these impairments needs to be further explored (Lu et al., 2014).

Prospective studies have reported that midlife work-related stress and psychosocial stressors are associated with an increased risk for dementia or Alzheimer's disease (Johansson et al., 2010; Sindi et al., 2017). It should be investigated whether clinical burnout patients with low BDNF and VEGF represent a group of patients with increased vulnerability to such long-term negative consequences. Being able to find patients at risk for long-term cognitive impairments or dementia, and thereby recognizing specific treatment needs, would be clinically valuable.

As neither BDNF, VEGF nor EGF were correlated symptom severity (burnout and depressive symptoms) it is plausible that the circulating growth factors are not primarily related to current symptoms, but rather to accumulated long-term stress exposure. The lack of association between depressive symptoms and BDNF is similar to what has been found in major depressive disorder (Molendijk et al., 2014). Meta-analyses have shown that circulating BDNF is lower and VEGF is higher in depression (Carvalho et al., 2015; Molendijk et al., 2014) whereas the role of EGF in depression is less explored. It has also been suggested that BDNF is one of the main targets of antidepressants, but not the sole mediator of depression (Martinowich et al., 2007).

The positive relationship between anxiety and EGF, VEGF, and BDNF found here might seem counter-intuitive. As pointed out in the review by Bandelow et al. (2017), neurotrophic factors seem to play a different role in anxiety disorders compared with mood disorders. For example, almost twice as high levels of plasma BDNF was found in non-depressed patients with generalized anxiety disorder compared to matched healthy controls (Pallanti et al., 2014). Thus, the pattern regarding anxiety disorders seems more uncertain than for depressive disorders (Suliman et al., 2013). One speculative explanation for the pattern seen in this study could be that anxiety and burnout counteract each other. The burnout group as a whole is characterized by low levels of these markers but in a sub-group with more anxiety symptoms, the levels approach those of healthy controls.

4.1. Limitations

The measurements of EGF, VEGF and BDNF were made in plasma samples and may therefore not be representative of the levels in other body fluids, such as CSF. The source of peripheral BDNF and its relationship to BDNF in the brain remain unknown. BDNF can cross the blood-brain barrier and plasma BDNF are correlated with brain BDNF levels (Pan et al., 1998; Pillai et al., 2010).

One might argue that allowing comorbid anxiety and depression in the study population could affect the outcome. However, a clinical burnout or ED diagnosis with a comorbid depressive or anxiety disorder is common (Glise et al., 2012; Oosterholt et al., 2016). Thus, excluding patients with a comorbid disorder results in a study population that is no longer representative of the whole patient population, which might limit the generalizability of the results.

Table 3
Results from the MANCOVA and ANCOVA:s controlling for physical activity.

	Group			Sex			Group*Sex		
	F	p	η^2	F	p	η^2	F	p	η^2
Multivariate	11.6	< 0.001	0.326	6.7	< 0.001	0.218	0.8	0.519	n.a.
EGF (pg/mL)	20.7	< 0.001	0.219	1.3	0.266	n.a.	0.0	0.985	n.a
VEGF (pg/mL)	13.5	< 0.001	0.154	14.6	< 0.001	0.164	1.1	0.308	n.a.
BDNF (pg/mL)	32.4	< 0.001	0.304	0.6	0.429	n.a.	0.0	0.904	n.a.

Table 4
Spearman correlation analyses within the patient group.

	Symptom duration		Burnout		Depression		Anxiety	
	rho	p	rho	p	rho	p	Rho	p
EGF (pg/mL)	−0.150	0.355	−0.020	0.905	0.139	0.400	0.331	0.039
VEGF (pg/mL)	−0.063	0.697	0.118	0.469	0.238	0.145	0.367	0.022
BDNF (ng/mL)	−0.065	0.690	−0.025	0.878	0.145	0.378	0.339	0.035

5. Conclusions

In conclusion, reduced BDNF and VEGF due to long-term stress exposure might increase vulnerability to neuronal damage, which may, in turn, be associated with symptoms such as cognitive impairments seen in stress-related exhaustion and burnout. The role of EGF in the pathogenesis of stress-related disorders is unclear.

Funding

This work was supported by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement [ALFGBG-431391]. The funding source was not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of Competing Interest

None.

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