Frontiers in Neuroendocrinology 55 (2019) 100784

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

BDNF and Cortisol integrative system – Plasticity vs. degeneration: Implications of the Val66Met polymorphism☆

Gilmara Gomes de Assis[a,b,*], Eugene V. Gasanov[c]

[a] Department of Applied Physiology, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland
[b] Lab. of Behavioral Endocrinology, Brain Institute, Federal University of Rio Grande do Norte, Natal, Brazil
[c] Laboratory of Neurodegeneration, International Institute of Molecular and Cell Biology in Warsaw, Poland

ARTICLE INFO

Keywords:
Brain-derived neurotrophic factor
Cortisol
Val66Met polymorphism
Depression
Exercise

ABSTRACT

BDNF is the neurotrophin mediating pro-neuronal survival and plasticity. Cortisol (COR), in turn, is engaged in the coordination of several processes in the brain homeostasis. Stress-responsive, both factors show an integrative role through their receptor's dynamics in neurophysiology. Furthermore, the Val66Met *BDNF* polymorphism may play a role in this mechanism. **Aim:** to investigate BDNF-COR interaction in the human neurophysiology context. **Methods:** We collected all papers containing BDNF and COR parameters or showing COR analyses in genotyped individuals in a PubMed search – full description available on PROSPERO – CRD42016050206. **Discussion:** BDNF and COR perform distinct roles in the physiology of the brain whose systems are integrated by glucocorticoid receptors dynamics. The *BDNF* polymorphism appears to have an influence on individual COR responsivity to stress. BDNF and COR play complementary roles in the nervous system where COR is a regulator of positive/negative effects. Exercise positively regulates both factors, regardless of *BDNF* polymorphism.

1. Introduction

Brain-derived neurotrophic factor (BDNF), which is the most active of the neurotrophic factors, is engaged in a variety of pro-neuroprotection processes like neurogenesis, dendritic growth and synaptogenesis (Lu et al., 2013; Sasi et al., 2017). Expressed mainly by neuronal cells, the synapse-dependent release of BDNF guarantees the maintenance and formation of neuronal networks i.e. neuroplasticity.

Similarly, cortisol (COR) as a hormone involved in the coordination of diverse processes throughout the body and the brain is a highly stress-responsive factor with a systemic impact. In response to a stimulus, the autonomic nervous system rapidly reacts via hypothalamus-pituitary-adrenal (HPA) axis causing COR secretion (Choi et al., 2018) into the bloodstream. A proper COR response is crucial for the physiological allostasis whereas high loads of COR are more likely to develop metabolic and/or brain disorders (Duman, 2002; Eiden, 2010).

A tender integration of BDNF and COR systems in the brain has recently been elucidated in experimental research (Kawashima et al., 2010; Numakawa et al., 2012). BDNF induces pro-neuroprotection signaling cascades by binding to tropomyosin receptor kinase B (TrkB), however, some of these mechanisms are indirectly affected by COR actions. It has been demonstrated that chronic exposure to dexamethasone suppresses BDNF-induced glutamate release (Numakawa et al., 2009), which has an impact on the processes of long-term memory and the development of mental illnesses (Chen et al., 2012; Panja and Bramham, 2014). More precisely, the inhibition of glucocorticoid receptors (GR) negatively affects BDNF-induced TrkB phosphorylation and its downstream signaling pathways whereas a short activation of GR is associated with the long-lasting BDNF-delivered mechanisms required for memory consolidation (Begni et al., 2016).

It is well known that high loads of COR activation of GR have a negative feedback effect on their expression. Therefore, the thesis supported by the molecular research regarding the integration of BDNF and COR systems to influence BDNF changes in the brain structure and/or functioning is reliant on GR dynamics (Gray et al., 2013).

Since this hypothesis has not been observed in clinical context and,

Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; COR, cortisol; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal gland; DXT, dexamethasone suppression test; DD, depressive disorder; BD, bipolar disorder; SZ, Schizophrenia

☆ The terms addressed for this review were systematically searched by two different Researchers in a blinded protocol. The synthesis of information and discussion was performed by a single Researcher.

* Address: Department of Applied Physiology, Mossakowski Medical Research Centre Polish Academy of Sciences, 5 Pawinskiego Street, 02-106 Warsaw, Poland.
E-mail address: ggomes@imdik.pan.pl (G.G. de Assis).

https://doi.org/10.1016/j.yfrne.2019.100784
Received 16 March 2019; Received in revised form 12 August 2019; Accepted 14 August 2019
Available online 16 August 2019

considering that the human BDNF gene (*BDNF*) presents a single nucleotide polymorphism - a G (guanosine) to A (adenosine) variation resulting in a methionine (Met) occurrence in protein 66th residue (Val66Met) - here referred to as "*BDNF*-p" in a high frequency of ~20% of population that has been investigated for possible physiopathological associations (Skibinska et al., 2018), we gathered information and collected all studies containing the data on both BDNF and COR parameters, including reports of COR analyses in *BDNF*-genotyped individuals, to discuss whether these systems integration is observable in physiology as well as in clinical or ambulatory practice.

2. Methods

In accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P, 2015), to access the available literature which includes BDNF and COR analyses we firstly carried out a double blinded and amplified search in PubMed database following the PICO strategy (P – patient/problem; I – Intervention; C – Comparison; O – Outcome) where P – designated Neurological disorders; I – Biochemical and/or genetic analyses; C – Healthy conditions; O – BDNF and COR analyses. Studies dating from 1960 to October 2016 were retrieved. A search update was performed in February 2018 and March 2018, as registered in NHS - PROSPERO platform – CRD42016050206. The following combinations of terms were used and duplicates were removed.

(brain derived neurotrophic factor) AND (Hydrocortisone)
(brain derived neurotrophic factor) AND (Glucocorticoid)
(brain derived neurotrophic factor) AND (Receptors, Glucocorticoid)
(brain derived neurotrophic factor) AND (Cortisol)
(Receptor, trkB) AND (Cortisol)
(Receptor, trkB) AND (Hydrocortisone)
(Receptor, trkB) AND (Glucocorticoid)
(Receptor, trkB) AND (Receptors, Glucocorticoid)

Retrieved papers were screened by abstract for inclusion by two researchers in a double-blinded manner. Inclusion criteria comprised human studies which involved subjects aged above 18 years, and analyzed both parameters: BDNF and COR. Reviews, Books, Commentaries, Case-studies and studies involving postmenopausal and pregnant subjects were excluded. The articles inclusion and exclusion schemes are presented in Fig. 1. After screening full texts, a complementary search was performed with the terms listed below to enclose the genetic studies referring to the *BDNF*-p that met the criteria of presenting COR data.

(bdnf val66met) AND (Cortisol)
(bdnf polymorphism) AND (Cortisol)

3. Results and discussion

BDNF and COR are two of the main factors discussed nowadays in the preventive care of mood and neurodegenerative disorders (Libro et al., 2017; Soldan et al., 2017). Together, these factors have revealed an increasing association with the physiopathology of different stress-related disorders. The description of retrieved studies according to the criteria is included in Tables 1 and 2.

With regard to the importance of each of them for the physiology of the nervous systems, we analyzed whether these systems integration, respecting its complexity and, in times, dichotomic dynamics, is a potential factor of the development of dementia and stress-related disorders. Additionally, we elucidated the role of exercise as a metabolic regulator of both factors.

3.1. BDNF and Cortisol dynamics

In accordance with extensive literature, the study by Mackin et al. (2007) reported that the levels of BDNF were diminishing in time in individuals with different psychiatric disorders, regardless of the treatment they underwent. The decrease in BDNF level is a common marker of different types of dementia where it reflects the cognitive decline (Ventriglia et al., 2013).

BDNF is mainly produced by neural cells and its expression appears in the earlier stages of embryonic development to reach the peak at the brain's maturation, around the age of 18, and persist through the adult life. An optimal BDNF production is thus as necessary for the proper development as for the brain functioning and a natural decline is expected in senescence. Whereas malfunction in BDNF systems putatively refers to nervous system disorders (Kowiański et al., 2018), a good maintenance of BDNF can be achieved by metabolic stress as demonstrated by exercise, irrespective of age, gender, or even neuropathological conditions (de Assis and de Almondes, 2017).

Contrastingly, elevated COR level is an early biomarker of the processes involved in the etiology of dementia and stress-related disorders (Ennis et al., 2017). For instance, it has been shown that BDNF and COR levels are inversely related in AD, which may suggest that the COR/BDNF ratios are a valuable marker for the clinical recognition of the dementia and advances in cognitive impairment (Curto et al., 2017).

The military veterans with post-traumatic stress disorder in the study by Blessing et al., (2017) were found to have higher levels of BDNF then military controls with comparable COR levels. It should be noticed that the two groups differed in education profiles. The condition group reported notably higher education than the control, which is a relevant factor for the enhancement of BDNF systems and cognitive reserve against neurodegeneration (Cheng, 2016).

Comparing different types of DD Otsuki et al. (2008) showed that there was no significant difference in the levels of BDNF or COR, and the HPA axis activity between the individuals with major DD, BD and healthy controls. Likewise, no association between BDNF and COR levels was identified in the patients with SZ in Ichioka et al. (2012) study, or in major DD like in Hellweg et al. (2008) study, or in alcohol-dependency in other studies by Heberlein et al., (2016), Meng et al., (2011), or even in the large sample with major DD in Ninan et al. (2014) study. The same observation referred to the individuals with Burning Mouth Syndrome in the study by De Souza et al., (2015), with BD in Chou et al. (2016) study, or with hepatitis C in the study by Kenis et al. (2011) or the large sample with Attention-Deficit/Hyperactivity Disorder reported by Vogel et al. (2017).

Although functionally integrated, BDNF and COR have distinct mechanisms of expression and secretion. BDNF is synthesized by cells and accumulated to be locally released after a stimulus whereas COR is fully produced by the adrenal glands after HPA axis activation and spontaneously released in the bloodstream wherefrom it reaches basically all tissues. In the brain, COR binds to widely spread GRs and activates the promoter regions of about 1%–2% of genome (Godoy et al., 2018) and BDNF interacts with TrkB in neighboring neurons regulating their synaptic proteome and survival (Leal et al., 2014). Whereas this review results confirm that COR is a biomarker of stress-related disorders, BDNF fails to be as indicative of mood disorders as it does of neurodegenerative processes (Allen et al., 2013; Damasceno et al., 2015).

BDNF and COR exhibited corresponding, though independent, circadian rhythms with peaks in the morning followed by a progressive decrease during the day (Begliuomini et al., 2008), which proved to be unaffected by sleep disorders in the study by Panaree et al. (2011). However, in the women suffering from functional hypothalamic amenorrhea, a stress disorder characterized by a downregulation of the hypothalamic-pituitary axis with inhibition of gonadotropin-releasing hormones, in the study by Drakopoulos et al. (2015), the levels of BDNF

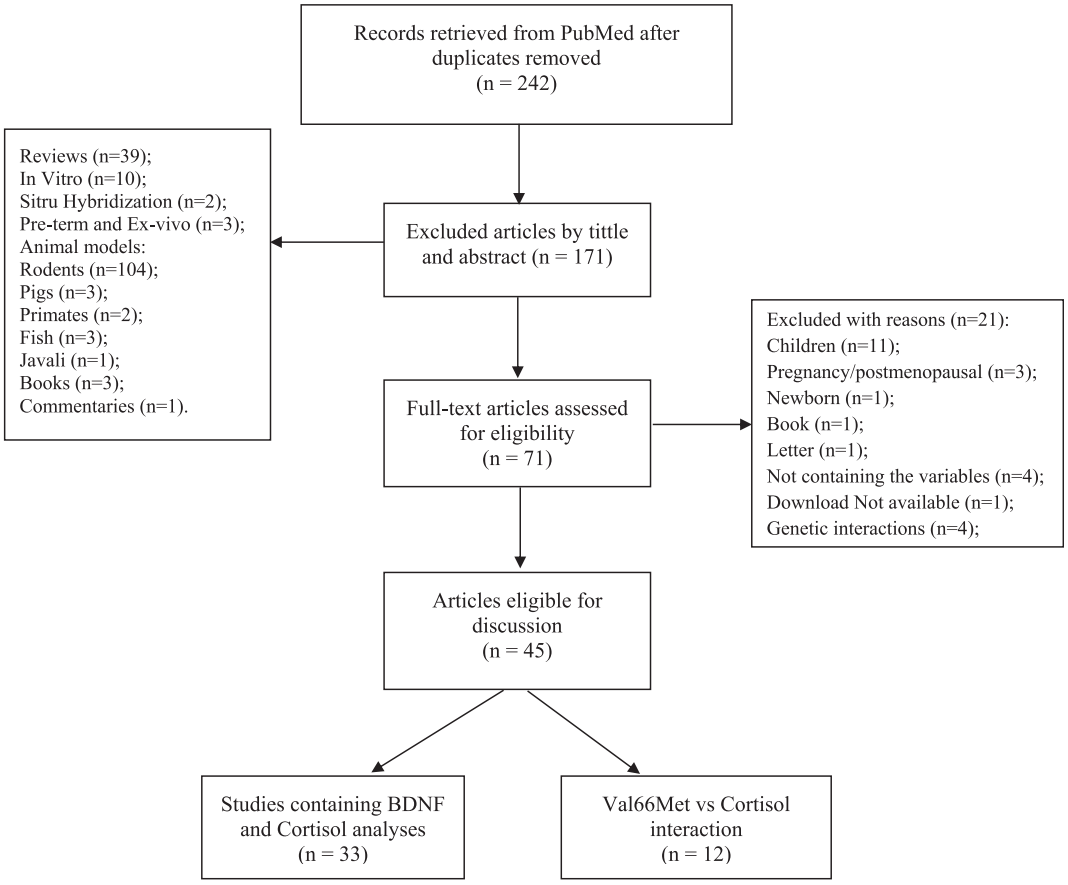

Fig. 1. PRISMA research flow chart.

were lower in the whole circadian cycle compared to eumenorrheic controls while their COR levels were elevated. Such phenomena can be attributed to a variation in estrogen levels characteristic of the condition.

Sex-differences, more specifically, the contributions of gonadal hormones and sex chromosomes, shall be considered as a biological variable when discussing dynamics of both BDNF and COR factors in the physiology of nervous system (Bale and Epperson, 2017). Stress-related increase in COR has been linked with a higher risk of early pregnancy loss (Nepomnaschy et al., 2006) and some specific levels of COR have been demonstrated to be necessary for a balanced gonadal function and fertility (Barel et al., 2017; Goikoetxea et al., 2017). Estrogen, in turn, can modulate BDNF expression by several mechanisms. For instance, the basal transcription and stress-response expression of *BDNF* have shown a gender-dependent region- specific variation patterns in the brain, regardless of the blood BDNF levels (Wei et al., 2017). BDNF levels in the female subjects of the aforementioned study were not correlated with any of the other measured factors, except for estrogen during the follicular phase in the eumenorrheic group.

It must be pointed out that due to its protein structure, BDNF is not able to cross lipid membranes and does not act in an endocrine manner (Pardridge et al., 1994), therefore, the blood concentrations and stress-response variations in BDNF are more likely to have their source in immune cells and/or endothelial tissue (Brunelli et al., 2012). Furthermore, blood BDNF profiles are strongly affected by metabolic factors such as exercise, starvation and fitness, which has already been investigated focusing mainly on males (Boström et al., 2012; De Assis et al., 2018).

As in vast available literature, the studies highlighting COR roles in this review mostly referred to psychiatric and/or mood disorders which are not necessarily associated with neurodegeneration (Veltman et al., 2018). Except for a BDNF reduction in the predominantly female sample with burnout syndrome of Onen Sertoz et al. (2008), and the renal patients undergoing hemodialysis from Zoladz et al. (2012) study, no other patterns of BDNF profiles were found across the conditions in the studied samples.

3.2. The role of BDNF Val66Met polymorphism

The site of BDNF-p encodes the pro-BDNF domain which contains information for the neurotrophin processing and secretion (Anastasia et al., 2013; Uegaki et al., 2017). It has been demonstrated that, when inserted in animal models, the Met variant of pro-BDNF is not as efficiently targeted into the regulated system of secretion as the Val variant, which implies the BDNF activity-dependent release (Waqas and Ji, 2017). However, these studies are not conclusive regarding the human specificity of BDNF-p and limitations in its assessment. Differences in blood BDNF profiles have not been associated with the polymorphism (Toh et al., 2018), though the influence of BDNF-p on psychobiologic and stress-related disorders has been widely investigated (Dincheva et al., 2012; Notaras et al., 2016; Zhao et al., 2017).

Met carriers have higher levels of COR (Schüle et al. (2006) suggesting a negative relation between BDNF-p and HPA axis activity. In Met-carrier twins of Vinberg et al. (2009) cohort, the COR levels were elevated, specifically in those classified at a high risk of affective disorders. Blood BDNF in these individuals was also elevated, which can reinforce the argument that the BDNF-p may not be a determining factor for the development of disease conditions. Contrastingly, COR appears to have some impact on the carriers of the BDNF-p for the etiology of stress disorders. One might suggest that the elevated BDNF in such individuals could actually imply a protective role (Hosang et al., 2010, 2014).

Table 1
Studies reporting BDNF and Cortisol analyses.

Author	Title	Methods	Main outcomes
(Rojas Vega et al., 2006)	Acute BDNF and COR response to low intensity exercise and following ramp incremental exercise to exhaustion in humans	Eight healthy physically active males (age: 24.6 ± 1.3 years) underwent a GXT in a cycloergometer consisting of: 10-min warm-up plus 2 min at 2 W·kg − 1 body weight followed by + 25 W every 30 s to exhaustion. Blood samples were collected after the warm-up, at exhaustion, and at 3-, 6-, 10- and 15-min post-GXT.	Subjects showed an increase in BDNF levels during the exercise and returned to baseline within 15 min. COR increase was delayed appearing from min 10th to 15th after the exercise. BDNF and COR levels did not change during warm-up.
(Mackin et al., 2007)	Changes in BDNF Following Treatment with Mifepristone in Bipolar Disorder and Schizophrenia	20 depressive patients with BD (age: 48.6 ± 10.8 year; F:1) and 20 patients with SZ (42.1 ± 10.3; F:2) were engaged in a crossover study with adjunctive mifepristone or placebo treatment for 7 days and 14 days' washout each arm. Blood samples for BDNF and COR analyses were collected at baseline, immediately after treatments, and at 14 days' follow-up. BDNF was also measured in 14 healthy controls.	Patients had BDNF levels diminishing in time during the whole study period. COR levels after 7 days of mifepristone treatment were higher than in all other time points, but lower than the 14-day follow-up. A negative correlation between COR and BDNF was found after treatment in SZ, but not in BD.
(Otsuki et al., 2008)	Altered expression of neurotrophic factors in patients with major depression.	60 patients with major DD (age: 55.3 ± 3.5 years; F:35) and 42 patients with BD (age: 54.9 ± 3.5 years; F: 35) plus healthy controls were assessed for blood BDNF and COR and a DST.	BDNF and/or COR parameters showed no difference between control and conditions.
(Rojas Vega et al., 2008)	Impact of exercise on neuroplasticity-related proteins in spinal cord injured humans	11 male paraplegic elite athletes (age: 40.6 ± 6.3 years) tested for GXT were engaged into a 10-min warm-up plus a time trial over the typical marathon distance on their own handbike with venous blood samples collected at rest, immediately after the warm-up and Marathon.	The warm-up in test b increased BDNF levels that returned to baseline before the end of Marathon. Contrastingly, COR levels did not change after the warm-up and were elevated at the end of Marathon.
(Hellweg et al., 2008)	Serum concentrations of nerve growth factor and BDNF in depressed patients before and after antidepressant treatment.	40 patients with major DD (age: 50.7 ± 14.4 years; F:31) divided in two treatment groups with amitriptyline or paroxetine for 36 days. 21 patients in randomized double-blind with placebo-controlled wash-out condition, and 19 under open conditions. Blood samples were collected from day 1 and day 35. Salivary COR was measured on days − 6 to − 1 and again from day 30 to 35.	Subjects COR and BDNF were not different between the groups before treatment. Amitriptyline, but not Paroxetine, led to an increase in BDNF levels. BDNF and COR levels were not associated in these patients.
(Begliuomini et al., 2008)	Plasma BDNF daily variations in men: correlation with COR circadian rhythm	34 young healthy males (age: 25.6 ± 3.2 years) had blood samples collected for BDNF and COR analyses at every 4 h in 5 time-points during 24 h: 08:00 h fasting, at 1200, 1600, 2000, and 2400 h.	A BDNF peak was found early in the morning with a progressive decrease during the day and lowest concentration at midnight. A COR peak was also detected early in the morning with a progressive decrease during the day, in particular at 16:00. A trend for a correspondence between BDNF and COR circadian decreases was observed.
(Onen Sertoz et al., 2008)	The role of BDNF and HPA axis in the neurobiology of burnout syndrome	37 subjects with burnout syndrome (age: 31.67 ± 4.74 years; F:30) and 35 controls (age: 31.65 ± 7.60 years; F:30) had blood collected for COR and BDNF analyses at 08:00 h in the morning, then received an oral dose of 1 mg dexamethasone at 23:00 h, and had blood collected again at 08:00 h the next morning for the analysis of HPA axis activity.	No differences were found in HPA-axis function. Burnout group had lower levels of BDNF comparing to healthy controls.There was no relationship between levels of COR and BDNF.
(Gustafsson et al., 2009)	The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major DD	18 patients with major DD (age: 33.5 ± 14 years; F:9) and 18 healthy controls were submitted to a GXT with blood samples collected at rest, at sub-maximal and maximal workloads, and 30- and 60-min follow-up.The subjects were given 1 mg of dexamethasone orally at 22:00 h on the same day of exercise test with blood collected 7 h before, and the following day at 08:00 h and 15:00 h for a DXT.	Patients and controls showed no difference in BDNF dynamics during the exercise task. A progressive BDNF increase following exercise intensity was observed only in males, while it was increased only after maximal workload in all other groups. There was no correlation between BNDF and COR parameters. Baseline COR was lower in patients than in controls. No difference was observed between condition and control to DST.
(Panaree et al., 2011)	Effects of obstructive sleep apnea on serum BDNF protein, COR, and lipid levels	39 patients with obstructive sleep apnea (age: 47.2 ± 1.6 years; F:15) and 24 controls (age: 32.3 ± 2.4 years; F:0) had their blood collected at 8:00 for determination of BDNF, COR analyses.	There was no difference between BDNF and COR parameters of patients with or without obstructive sleep apnea. BDNF and COR levels were independent in both groups.
(Goekint et al., 2011)	Influence of citalopram and environmental temperature on exercise-induced changes in BDNF	11 male athletes (age: 23.3 ± 5.1 years) performed 4 cycleergometric trials: under citalopram (20 mg in 12 h) or placebo treatment; under environmental temperature of 18∘C or 30 °C. Blood samples were collected at rest, immediately after trails, and 15-min follow up in all conditions.	Basal levels of BDNF were lower in citalopram conditions, while COR was increased. Exercise-induced increase in BDNF followed the pattern of individual core temperature. BDNF and COR levels peaks were reached at 30 °C environment.
(Meng et al., 2011)		14 alcohol-dependent males (age: 29.6 ± 10.3 years) and 10 controls (37.5 ± 11.9 years) performed The	The stressor event showed an effect of time in both COR and BDNF increases.

(*continued on next page*)

Table 1 (*continued*)

Author	Title	Methods	Main outcomes
	Serum NPY and BNDF response to a behavioral stressor in alcohol-dependent and healthy control participants	Trier Social Stress Test followed by an arithmetic task with blood samples collected at 2 time-points both before and after.	There was no relationship between basal and the delta peak of BDNF or COR concentrations in either group.
(Miodownik et al., 2011)	Serum Levels of BDNF and COR to Sulfate of Dehydroepiandrosterone Molar Ratio Associated with Clinical Response to L-Theanine as Augmentation of Antipsychotic Therapy in SZ and Schizoaffective Disorder Patients	40 inpatients with SZ and Schizoaffective disorder (are: 32.3 ± 10.2 years; F:9) randomized to receive L-theanine or placebo had blood samples collected for BNDF and COR analyses; before therapy, then after 2, 4, 6, and 8 weeks.	Changes in the levels of BDNF and COR were significantly associated with the positive effects of L-theanine. BDNF was suggested as one of the markers for the assessment of clinical response.
(Kenis et al., 2011)	Depressive symptoms following interferon-a therapy: mediated by immune-induced reductions in BDNF?	17 patients with hepatitis C and depressive symptoms (age: 42 ± 7.4 years; F:4) had blood samples collected for BDNF analysis before and at 1, 2, 4, 8, 12 and 24 weeks of Interferon-a treatment. Salivary COR was collected on the day prior to each of the seven blood sampling.	BDNF levels gradually decreased during treatment. There was no association between BDNF and COR (either awakening or average).
(Ichioka et al., 2012)	Triiodothyronine may be possibly associated with better cognitive function and less extrapyramidal symptoms in chronic SZ	93 inpatients with SZ (age: 68.0 ± 8.8 years; F:71), undergoing antipsychotics, were evaluated for COR and BDNF levels among other factors.	BDNF and COR levels showed no association in these patients.
(Zoladz et al., 2012)	Hemodialysis Decreases Serum Brain-Derived Neurotrophic Factor Concentration in Humans	20 male renal patients (age: 69.8 ± 2.9 years) undergoing maintenance hemodialysis for 15–71 months, had blood samples collected before and during one dialysis session after 1-day-free of hemodialysis. Healthy males (age: 69.1 ± 2.0 years) had blood samples collected in morning fasting state as a control.	Basal BDNF levels were lower in the study than in control group. BDNF levels were significantly lower at the end of dialysis session. COR levels also decreased after dialysis. There was no correlation between the changes in BDNF or COR.
(Wu et al., 2014)	Modulatory effects of aromatherapy massage intervention on electroencephalogram, psychological assessments, salivary COR and plasma brain-derived neurotrophic factor.	25 female individuals (age: 34 to 48 years) were signed to either an aromatherapy massage program: 2 × 40 min per week for 4 weeks, or control. Blood samples were collected at the same time point a day before and after the aromatherapy program. Saliva samples were collected immediately before and after one time-bout aromatherapy massage treatment.	BDNF levels were increased after the massage program. COR levels changed neither after the aromatherapy massage program nor in controls.
(Strollo et al., 2014)	Changes in Stress Hormones and Metabolism During a 105-Day Simulated Mars Mission	6 healthy males (age: 32.7 ± 5.9 years) had COR and plasma BDNF monitored during the 105-d Mars mission simulation. Blood samples were collected before, at week 2.5, 5, 10, 15, and after confinement (+1 week).	BDNF levels were increased at week 5 and 10 then returned to baseline values. COR levels were increased at any confinement time-point, reaching a significant level after week 2.5 and 15, and normalizing 1 week after the end of confinement.
(Whiteman et al., 2014)	Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults	63 healthy young individuals (age: 20.5 ± 2.1 years; F: 39) were submitted to a GXT gathered with a cognitive task and had blood samples collected for descriptive analyses.	While BDNF levels positively predicted the cognitive performance, COR levels were a negative predictor. There was a positive correlation between the BDNF changes and the fitness conditions predicting the cognitive performance.
(Ninan et al., 2014)	BDNF, interleukin-6, and salivary COR levels in depressed patients treated with desvenlafaxine	285 outpatients (age: 43.2 ± 11.7 years; F:188) and 142 outpatients (age: 41.6 ± 12.6 years; F: 93) with major DD respectively signed for 12 weeks of desvenlafaxine or placebo treatments had blood samples collected for BDNF analysis, and Saliva for COR determinations collected at baseline and at weeks 4, 6, 8, and 12 (or at early discontinuation).	Patients undergoing desvenlafaxine treatment did not show any relation between BDNF and COR levels. BDNF showed greater increases in patients with more severe vs less severe depressive conditions. The treatment reduced patient's scales of depression, but neither BDNF nor COR predicted treatment response.
(Schmidt-Kassow et al., 2014)	Treadmill walking during vocabulary encoding improves verbal long-term memory	18 (age: 22.8 ± 2.6 years; F: 9) and 31 (age: 21.7 ± 2.7 years; F: 16) young healthy individuals took part in 2 identical experiments with either blood samples for BDNF analysis or Saliva collected for COR analysis. The protocol refers to a learning task (memorizing foreign words) while walking or sitting. Samples were collected at rest and immediately after two activities (walking and sitting).	Basal levels of BDNF higher in Male than females. No effects were found for BDNF. The better cognitive performances were associated with a lesser decrease in COR levels.
(De Souza et al., 2015)	The Association of Openness Personality Trait with Stress-Related Salivary Biomarkers in Burning Mouth Syndrome	30 individuals with Burning Mouth Syndrome (age: 62.13 ± 12.74 years; F: 29) and 32 controls (age: 61.59 ± 12.84 years; F: 31) had salivary BDNF and COR analyzed in a cross-sectional study.	BDNF and COR levels were not different between the study and the control groups.
(Yu et al., 2015)	Chronic Supplementation of Curcumin Enhances the Efficacy of Antidepressants in Major DD	100 male adults undergoing major DD divided in 50 (age: 44.14 ± 8.02 years) curcumin treatment for 6 weeks and 50 (45.22 ± 7.68 years) placebo. Saliva and blood samples were collected for descriptive analyses.	Long-term treatment with curcumin increased BDNF levels in comparison to placebo. Subjects treated with curcumin had COR concentrations decreased in comparison to placebo.
(Drakopoulos et al., 2015)	Diurnal Variation of Plasma Brain-Derived Neurotrophic Factor Levels in Women with Functional Hypothalamic Amenorrhea	36 females with functional hypothalamic amenorrhea (age: 26.5 ± 4.7 years) and 30 controls (age: 24.6 ± 3.5 years) had blood collected for BDNF and	Circadian variations in BDNF levels were lower in amenorrheic than in eumenorrheic women (in the follicular phase).

(*continued on next page*)

Table 1 (*continued*)

Author	Title	Methods	Main outcomes
		COR analyses at 8: 00, 12: 00, 16: 00, 20: 00, and 24: 00 h on the same day.	Levels of BDNF and COR were correlated to the morning COR in amenorrheic woman.
(Corrêa et al., 2015)	Psychophysiological correlates of cognitive deficits in family caregivers of patients with Alzheimer Disease	17 family caregivers of patients with AD (age: 64.83 ± 3.64 years; F: 13) and 18 controls (age: 58.29 ± 3.16 years; F: 14) had blood samples collected for BDNF analysis and Saliva collected at 8 a.m. and 10p.m. for COR and dehydroepiandrosterone levels determination.	BDNF levels were lower in the caregivers. There was no relation between BDNF and COR levels or COR/DHEA ratios. COR and DHEA levels were higher at 8:00 h than at 10:00 h in all groups. Caregivers had higher levels of COR than controls. A stress effect was observed in the COR increase in caregivers; whilst there was a stress effect on BDNF decrease.
(Chou et al., 2016)	Neither COR nor brain-derived neurotrophic factor is associated with serotonin transporter in bipolar disorder	28 patients with BD (age: 36.6 ± 8.1 years; F: 9) and 28 controls (age: 36.6 ± 7.9 years; F: 9) underwent a tomography while blood samples were collected for BDNF and COR analysis.	BDNF and COR levels did not differ between patients and controls.
(Naveen et al., 2016)	Serum COR and BDNF in patients with major depression —effect of yoga	54 drug-naive DD patients were divided into 16 (age: 33.18 ± 7.11 years; F: 7) only on antidepressants, 19 (age: 34.11 ± 10.75 years; F: 8) on antidepressants + Yoga, or 19 (35.89 ± 7.85 years; F: 7) only in Yoga therapy. Blood samples were collected for BDNF and COR analyses at baseline and at 12 weeks follow-up.	Patients in yoga/antidepressant group presented lower levels of BDNF. Patients in yoga groups showed a decrease in COR levels while those in the antidepressant group showed COR increase. There was a negative correlation between changes in COR and BDNF, more prominently in the yoga-only group.
(Heberlein et al., 2016)	Association of testosterone and BDNF serum levels with craving during alcohol withdrawal	99 alcohol-dependent males admitted for detoxification (age: 42.22 ± 7.83 years) and 17 controls (age: 44.41 ± 9.63) had blood samples collected once a day on day 1, 7, and 14 of an alcohol withdrawal period, between 8 and 10 a.m.	There was no association between alcohol concentrations and BDNF or COR levels in the study group. Both BDNF and COR levels decreased with alcohol withdrawal.
(Hötting et al., 2015)	The Effects of Acute Physical Exercise on Memory, Peripheral BDNF, and COR in Young Adults	81 young healthy individuals (age: 22 ± 2.36 years; F: 40) had to memorize a list of German-Polish vocabulary 20 min before exercising for 30 min at either high, or low intensity, or before a relaxing phase. Blood samples and Saliva were collected for BDNF and COR analyses at baseline, after intervention, and at 24 h follow-up.	BDNF levels were increased only after the high-intensity exercise. Larger increases in COR levels were found after the high-intensity exercise comparing to other groups.
(Ma et al., 2016)	The correlation between perceived social support, COR and BDNF levels in healthy women	72 community individuals (age: 35.71 ± 13.15 years; F: 44) engaged in a Routine Support subscale of Support Function questionnaire had blood samples collected for BDNF and COR analyses, and a DST.	There was a positive correlation between BDNF levels and the DST rates in females.
(Neves et al., 2017)	Different levels of brain-derived neurotrophic factor and COR in healthy heavy smokers	35 healthy adult males divided into light smokers (age: 37.43 7.55 years), heavy smokers (age: 34.43 ± 5.35 years) and controls (age: 31.83 ± 4.97 years) had blood samples and Saliva collected for BDNF and COR analyses at awakening, 30 min after awakening, at 10:00 and 12:00 a.m. plus at 5:00 and 10:00p.m.	Heavy, but not light smokers, presented higher levels of BDNF compared to controls. Heavy smokers presented lower COR levels at 10:00p.m. than controls.
(Vogel et al., 2017)	Attention-deficit/hyperactivity disorder symptoms and stress-related biomarkers.	Data from 2307 individuals (age: 42.2 ± 13.1 years; F:1530) from the Netherlands Study of Depression and Anxiety (NESDA) were cross-sectioned for the analyses of Attention deficit/hyperactivity disorder and different biological markers including HPA axis activity, COR and BDNF.	No associations were observed for BDNF and COR parameters.
(Blessing et al., 2017)	Biological predictors of insulin resistance associated with posttraumatic stress disorder in young military veterans	166 male military veterans 83 (age: 33.0 ± 7.7 years) with posttraumatic stress disorder and 83 (age: 32.5 ± 8.0 years) controls had blood samples collected in the fasting morning for biochemical analyses in a cross-sectional study.	COR levels did not differ between the study group and controls. BDNF levels were higher in the study subjects. BDNF levels were positively correlated with the stress disorder, while COR showed the opposite.
(Curto et al., 2017)	Increased Total Urinary COR (tUC) and Serum Brain-derived Neurotrophic Factor (BDNF) Ratio in Alzheimer Disease (AD)-affected Patients	18 drug-naive patients with AD (age: 80.1 ± 7.90 years; F: 11) and 22 controls (age: 74.1 ± 14.5 years; F: 12) had urinary COR assessed from 8 a.m. to 8 a.m. on the subsequent day. Blood samples for BDNF analyses were collected between 10 and 12 a.m. of day 1.	COR levels were higher in patients, while BDNF levels were lower. The COR/BDNF ratio was higher in patients than controls. There was a negative correlation between COR levels and the COR/BDNF ratio, but not in patients. Cognition performances were negatively correlated with COR/BDNF ratio both in patients and controls.

Table 2
BDNF polymorphism and Cortisol.

Author	Title	Methods	Main outcomes
(Schüle et al., 2006)	BDNF Val66Met polymorphism and dexamethasone/CRH test results in depressed patients.	187 inpatients with major DD and depressive BD (age: 47.63 ± 0.97; F: 101) were genotyped for *BDNF* and performed a DST.	The HPA axis hormones had different patterns of increase between genotypes with higher adrenocorticotropic hormone concentrations in the Met/Met compared to Val/Val homozygotes and a trend for the same when comparing to Val/Met heterozygous. In female, the Met-homozygotes yielded higher COR concentrations in comparison to Val-carriers.
(Shalev et al., 2009)	BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions	97 young adults (age: 25.29 ± 3.6; F: 51) took part in a social stress task with repeated measurement of COR.	There was a gender effect on the *BDNF* genotype influence on COR responsivity to stress. In male, Val-homozygotes had greater COR arousal than Met-carriers. A trend for the opposite was observed in female.
(Vinberg et al., 2009)	The BDNF Val66Met polymorphism: Relation to familiar risk of affective disorder, BDNF levels and salivary cortisol	205 twins (age: 45.2 ± 13.4; F: 150) classified at Low-risk and High-risk for affective disorders were genotyped for *BDNF* had blood samples collected for BDNF analysis. Saliva was collected 15 min after awakening and 12 h later at evening for two consecutive days.	The twins at High-risk for disorder carrying the Met allele presented higher evening COR levels. Twins at High-risk carrying the met allele also presented higher levels of BDNF.
(Alexander et al., 2010)	The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress	100 healthy males (age: 23.79 ± 2.7 years) genotyped for *BDNF* participated in a stress paradigm and had Saliva collected for COR analysis at 6 time points: baseline, after anticipation (+15 min), after speech (+25 min) and + 50, +75, and + 100 min.	Baseline levels of COR did not differ between genotypes. There was an attenuation in the patterns of COR secretion response in Met-carriers compared to Val homozygotes. Met-carriers showed smaller perceived stress and reactivity to a stressor compared to Val homozygotes subjects.
(Colzato et al., 2011)	BDNF Val66Met polymorphism is associated with higher anticipatory COR stress response, anxiety, and alcohol consumption in healthy adults	98 healthy adults (age: 22.2 ± 2.6 years; F: 54) genotyped for *BDNF* participated in a physical test immediately after an anxiety test and had Saliva collected for COR analysis 15 min prior to the task, and 15- and 30-min follow-up.	The levels of COR rose in time during the stress. Met-carriers had higher COR response to stress compared to Val-homozygotes. Met-carriers reached higher scores on social anxiety than Val-homozygotes.
(Tsuru et al., 2014)	Association of BDNF Val66Met polymorphism with HPA and SAM axis reactivity to psychological and physical stress	226 healthy volunteers with no history of mental illness (age: 24.9 ± 4.3; F: 88 years) genotyped for *BDNF* underwent both a social (TSST) and a physical (Electrical stimulation) stress test with repeated measurements of salivary COR.	In Male, Met-homozygous had stronger COR responses than Val-carriers. In female, Met-homozygous showed a trend for stronger COR responses to stress than Val-carriers. There was no change in COR levels in response to the physical stress.
(Armbruster et al., 2016)	BDNF val66met genotype shows distinct associations with the acoustic startle reflex and the cortisol stress response in young adults and children	3 samples with 127 (age: 24.14 ± 3.47 years; F: 56), 104 (age: 22.65 ± 3.58 years; F: 55), and 116 (age: 23.82 ± 2.58 years; F: 59) individuals genotyped for *BDNF* were summarized in this study. Subjects underwent a Startle reaction test - a single 50 ms burst of white noise (95 dB SPL with an instantaneous rise time) gathered with a visual attention stimulus and a TSST protocol.	Male yielded larger COR responses than female. Met-carriers exhibited higher COR responses than Val-homozygotes. Reversed patters of COR response were found for the psychological and physical stress paradigms.
(Li-Tempel et al., 2016)	Polymorphisms of genes related to the HPA axis influence the cortisol awakening response as well as self-perceived stress	217 healthy males (age: 23 ± 2.8 years; F: 115) genotyped for *BDNF* had awakening saliva samples collected at 0, +15, +30, +45 and + 60 min in two consecutive weekdays for COR analyses.	No effect of *BDNF*-p was observed in COR levels.
(Jiang et al., 2017)	BDNF Val66Met polymorphism interacts with gender to influence cortisol responses to mental stress	156 individuals (age: 34 ± 7.2 years; F: 69) genotyped for *BDNF* were recruited to a study designed to examine the effects of genetic, behavioral and environmental mechanisms through a mental stress protocol including four tasks and four rest periods. Blood samples were collected immediately before, after each task and the rest.	A gender vs genotype interaction was found on the COR AUC over the mental stress protocol. In female, the adjusted mean COR AUC was higher in Val-homozygotes than in Met carriers.
(Keyan and Bryant, 2017)	Role of BDNF val66met polymorphism in modulating exercised-induced emotional memories	62 healthy individuals randomly signed for exercise 31 (age: 20.84 ± 3.28 years; F:20) and control 31 (age: 20.90 ± 2.76 years; F: 22) condition for either 10-min of intense exercise or slow walking before immediate exposition to positive and negative images. Saliva samples were collected for COR analyses and genotyping.	Interaction between the Val-homozygotes and COR response was found in intense exercise condition. Higher exercise intensity provoked increases in COR, as well as better memory recall scores compared to lower intensity. The Val allele presence and COR response predicted better recall memory in intense exercise condition.
(Sharpley et al., 2018)	Comparing a genetic and a psychological factor as correlates of anxiety, depression, and chronic stress in men with prostate cancer	93 prostate cancer patients (age: 67.9 ± 6.37 years) genotyped for *BDNF* addressed a Questionnaire inventory about anxiety, depression and psychological resilience, and had saliva collected for COR analysis.	The Met-carriers showed higher COR levels than Va-homozygotes.
(Young et al., 2018)	The interaction of BDNF Val66Met, PTSD, and child abuse on psychophysiological reactivity and HPA axis function in a sample of Gulf War Veterans	226 Military veterans from a cross-sectional study of the effects of Gulf War deployment on the brain (age: 44.83 ± 9.53; F: 30) were genotyped for BDNF and submitted to both a fear potentiated acoustic Startle paradigm and a DST.	The *BDNF*-p did not predict COR suppression response to DST. Met-carriers diagnosed with posttraumatic stress disorder exhibited greater COR suppression compared to Val-homozygotes.

(*continued on next page*)

Table 2 (*continued*)

Author	Title	Methods	Main outcomes
			The *BDNF*-p association with HPA axis dysfunction, showed that Met-carriers exhibited greater psychophysiological response magnitude, especially for those with posttraumatic stress disorder with this latter also showing greater COR suppression.

When analyzing our findings, it was possible to observe a consistence in the COR responsivity to stress in Met-carriers with higher COR peaks reported by Colzato et al. (2011), and by Armbruster et al. (2016), who recorded precise 50/50% distribution by sex.

Regarding a possible sex-influence as evidenced in animal models (Marrocco et al., 2018), in the male individuals of Shalev et al. (2009) study, Val-homozygotes yielded greater COR response than Met-carriers, while a trend for the opposite was observed in females. Similarly, the males in Alexander et al. (2010) study also showed a higher COR responsivity to stress in Val-homozygotes then Met-carriers. Alternatively, Val-homozygous females in the large sample of Jiang et al. (2017) study displayed higher COR responses than those carrying the BDNF-p while no significant differences were showed by males, even though the number of males was higher. Finally, in the study by Tsuru et al. (2014), where the number of males was about 2-fold higher and the outcomes were not speared by sex, greater COR responses were observed in Met-carriers (the summarized data are presented in Table 3).

When observing homeostatic parameters, most of the studies reported no association between the BDNF-p and COR levels (Li-Tempel et al. (2016); Vinberg et al. (2009); and Young et al. (2018)). However, in some studies, Met-carriers appeared to have elevated COR (Schüle et al., 2006; Sharpley et al., 2018). Curiously enough, greater COR suppression was observed in the Met-carriers in Young et al. (2018) study, without excluding the hypothesis of a BNDF-p influence on COR responsivity.

Table 3
Cortisol levels in BDNF polymorphism and gender.

(N)	Val-Homozygotes	Met allelic	Authors
Studies' findings in COR responsivity			
Female (54)	Lower	Higher	(Colzato et al., 2011)
Male (44)			
Female (170)	Lower	Higher	(Armbruster et al., 2016)
Male (170)			
Studies' findings in COR responsivity spared by Gender			
Female (54)	Higher	Lower	(Jiang et al., 2017)
Male (77)	–	–	
Female (51)	–	–	(Shalev et al., 2009)
Male (46)	Higher	Lower	
Female (0)	–	–	(Alexander et al., 2010)
Male (100)	Higher	Lower	
Female (88)	Lower	Higher	(Tsuru et al., 2014)
Male (138)	Lower	Higher	
Studies' findings in Morning COR			
Female (115)	No difference	No difference	(Li-Tempel et al., 2016)
Male (102)			healthy
Female (234)	No difference	No difference	(Vinberg et al., 2009)
Male (102)			
Female (30)	No difference	No difference	(Young et al., 2018)
Male (196)			
Studies' findings in Morning COR spared by Gender			
Female (101)	Lower	Higher	(Schüle et al., 2006)
Male (86)	–	–	
Female (0)	–	–	(Sharpley et al., 2018)
Male (95)	Lower	Higher	
Studies' findings in COR suppression			
Female (30)	Smaller	Greater	(Young et al., 2018)
Male (196)			
Studies' findings in COR suppression spared by Gender			
Female (101)	Greater	Smaller	(Schüle et al., 2006)
Male (86)	Smaller	Greater	
Exercise effects on COR (and BDNF) levels			
Female (20)	Increase	Increase	(Keyan and Bryant, 2017)
Male (42)			

All the individuals in the study by Keyan and Bryant, (2017) performing moderate- to high- (but not low-) intensity exercise had proportional increases in COR which were associated with gains in cognition, regardless of the genotype. In Armbruster et al. (2016) study, it was possible to differentiate patterns of COR response by the type of stress: psychological and physical. Consequently, it was revealed that Met-carriers did not only yield higher COR responses to stressors but they also showed reduced COR response to physical stress.

Physical stress, such as exercise, is well known to increase both COR and BDNF levels, in this case, generating positive changes. During a physical stress, BDNF expression is initiated after peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) release in the cell, due to the accumulation of reactive oxygen species and catabolism by-products, whereas the COR hormone is secreted by adrenal glands into the bloodstream in a long-lasting manner and cleared by cellular uptake and clearance mechanisms, mediating the proteomic adjustments required for the different tissues which includes an attenuation in COR reactivity to stress (Anderson and Wideman, 2017; Mücke et al., 2018).

This effect was observed in the study by Whiteman et al. (2014), where increases in individuals' BDNF after a short-term high-intensity exercise were negatively correlated to COR. By contrast, in Schmidt-Kassow et al. (2014) study the subjects who performed a low-intensity long-term exercise did not achieve changes in BDNF levels. Furthermore, in Naveen et al. (2016) study, the individuals with DD practicing Yoga, which is considered a type of low-intensity exercise, did show elevated BDNF to be negatively correlated to COR levels, which, in that case, was due to a greater reduction in COR levels.

4. Final considerations

It is plausible that the BDNF-p has an influence on the COR responsivity to stress, thereby implying a Met-allele role in BDNF and COR integrative system. BDNF and COR undoubtedly play distinct and complementary roles in the physiology of the nervous system in which COR proves to be the regulator of positive as well as negative effects.

In general, the data is not sufficiently conclusive to affirm a sex-interference in COR dynamics between genotypes. However, to further understand the underlying mechanisms, future clinical and experimental studies should include samples comparable by the Met allele frequency and age and pay special attention to the female estrous cycle which can modulate both BDNF and COR dynamics.

Acknowledgements

We are thankful to Prof. Joanna Leszczyńska for the great support in the language writing and to Prof. Andrzej Ziemba, the Head of the Department of Applied Physiology at Mossakowski Medical Research Centre – Polish Academy of Sciences for the financial support necessary for this publication. This research was supported by grant 2016/21/B/NZ3/00354 from the National Science Center (Krakow, Poland).

References

Alexander, N., Osinsky, R., Schmitz, A., Mueller, E., Kuepper, Y., Hennig, J., 2010. The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. Psychoneuroendocrinology 35, 949–953. https://doi.org/10.1016/j.psyneuen.2009.12.008.

Allen, S.J., Watson, J.J., Shoemark, D.K., Barua, N.U., Patel, N.K., 2013. GDNF, NGF and BDNF as therapeutic options for neurodegeneration. Pharmacol. Ther. 138, 155–175. https://doi.org/10.1016/j.pharmthera.2013.01.004.

Anastasia, A., Deinhardt, K., Chao, M.V., Will, N.E., Irmady, K., Lee, F.S., Hempstead, B.L., Bracken, C., Chao, M.V., Anastasia, A., Deinhardt, K., Hempstead, B.L., Irmady, K., Bracken, C., Lee, F.S., 2013. Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. Nat. Commun. 4, 1–12. https://doi.org/10.1038/ncomms3490.

Anderson, T., Wideman, L., 2017. Exercise and the cortisol awakening response: a systematic review. Sport. Med. - Open. https://doi.org/10.1186/s40798-017-0102-3.

Armbruster, D., Müller-Alcazar, A., Strobel, A., Lesch, K.-P.P., Kirschbaum, C., Brocke, B., 2016. BDNF val66met genotype shows distinct associations with the acoustic startle reflex and the cortisol stress response in young adults and children. Psychoneuroendocrinology 66, 39–46. https://doi.org/10.1016/j.psyneuen.2015.12.020.

Bale, T.L., Epperson, C.N., 2017. Sex as a biological variable: who, what, when, why, and how. Neuropsychopharmacology. https://doi.org/10.1038/npp.2016.215.

Barel, E., Shahrabani, S., Tzischinsky, O., 2017. Sex hormone/cortisol ratios differentially modulate risk-taking in men and women. Evol. Psychol. 15. https://doi.org/10.1177/1474704917697333.

Begliuomini, S., Lenzi, E., Ninni, F., Casarosa, E., Merlini, S., Pluchino, N., Valentino, V., Luisi, S., Luisi, M., Genazzani, A.R., 2008. Plasma brain-derived neurotrophic factor daily variations in men: correlation with cortisol circadian rhythm. J. Endocrinol. 197, 429–435. https://doi.org/10.1677/joe-07-0376.

Begni, V., Riva, M.A., Cattaneo, A., 2016. Cellular and molecular mechanisms of the brain-derived neurotrophic factor in physiological and pathological conditions. Clin. Sci. 131, 123–138. https://doi.org/10.1042/cs20160009.

Blessing, E.M., Reus, V., Mellon, S.H., Wolkowitz, O.M., Flory, J.D., Bierer, L., Lindqvist, D., Dhabhar, F., Li, M., Qian, M., Abu-Amara, D., Galatzer-Levy, I., Yehuda, R., Marmar, C.R., 2017. Biological predictors of insulin resistance associated with posttraumatic stress disorder in young military veterans. Psychoneuroendocrinology 82, 91–97. https://doi.org/10.1016/j.psyneuen.2017.04.016.

Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Boström, E.A., Choi, J.H., Long, J.Z., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1a dependent myokine that derives browning of white fat and thermogenesis. Nature 481, 463–468. https://doi.org/10.1038/nature10777.A.

Brunelli, A., Dimauro, I., Sgrò, P., Emerenziani, G. Pietro, Magi, F., Baldari, C., Guidetti, L., Di Luigi, L., Parisi, P., Caporossi, D., 2012. Acute exercise modulates BDNF and pro-BDNF protein content in immune cells. Med. Sci. Sports Exerc. 44, 1871–1880. https://doi.org/10.1249/MSS.0b013e31825ab69b.

Chen, D.Y., Bambah-Mukku, D., Pollonini, G., Alberini, C.M., 2012. Glucocorticoid receptors recruit the CaMKIIα-BDNF-CREB pathways to mediate memory consolidation. Nat. Neurosci. 15, 1707–1714. https://doi.org/10.1038/nn.3266.

Cheng, S.T., 2016. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. Curr. Psychiatry Rep. 18, 85. https://doi.org/10.1007/s11920-016-0721-2.

Choi, K.W., Na, E.J., Fava, M., Mischoulon, D., Cho, H., Jeon, H.J., 2018. Increased adrenocorticotropic hormone (ACTH) levels predict severity of depression after six months of follow-up in outpatients with major depressive disorder. Psychiatry Res. 270, 246–252. https://doi.org/10.1016/j.psychres.2018.09.047.

Chou, Y.H., Lirng, J.F., Hsieh, W.C., Chiu, Y.C., Tu, Y.A., Wang, S.J., 2016. Neither cortisol nor brain-derived neurotrophic factor is associated with serotonin transporter in bipolar disorder. Eur. Neuropsychopharmacol. 26, 280–287. https://doi.org/10.1016/j.euroneuro.2015.12.011.

Colzato, L.S., Van der Does, A.J.W., Kouwenhoven, C., Elzinga, B.M., Hommel, B., 2011. BDNF Val66Met polymorphism is associated with higher anticipatory cortisol stress response, anxiety, and alcohol consumption in healthy adults. Psychoneuroendocrinology 36, 1562–1569. https://doi.org/10.1016/j.psyneuen.2011.04.010.

Corrêa, M.S., Vedovelli, K., Giacobbo, B.L., de Souza, C.E.B., Ferrari, P., de Lima Argimon, I.I., Walz, J.C., Kapczinski, F., Bromberg, E., 2015. Psychophysiological correlates of cognitive deficits in family caregivers of patients with Alzheimer Disease. Neuroscience 286 (10), 371–382. https://doi.org/10.1016/j.neuroscience.2014.11.052.

Curto, M., Martocchia, A., Ferracuti, S., Comite, F., Scaccianoce, S., Girardi, P., Nicoletti, F., Falaschi, P., 2017. Increased Total Urinary Cortisol (tUC) and serum Brain-derived Neurotrophic Factor (BDNF) Ratio in Alzheimer Disease (AD)-affected patients. Alzheimer Dis. Assoc. Disord. 31, 173–176. https://doi.org/10.1097/WAD.0000000000000156.

Damasceno, A., Damasceno, B.P., Cendes, F., Moraes, A.S., Farias, A., Santos, L.M.B. Dos, 2015. Serum BDNF levels are not reliable correlates of neurodegeneration in MS patients. Mult. Scler. Relat. Disord. 4, 65–66. https://doi.org/10.1016/j.msard.2014.11.003.

de Assis, G.G., de Almondes, K.M., 2017. Exercise-dependent BDNF as a modulatory factor for the executive processing of individuals in course of cognitive decline. A systematic review. Front. Psychol. 8, 1–8. https://doi.org/10.3389/fpsyg.2017.00584.

De Assis, G.G., Gasanov, E.V., de Sousa, M.B.C., Kozacz, A., Murawska-Cialowicz, E., 2018. Brain derived neutrophic factor, a link of aerobic metabolism to neuroplasticity. J. Physiol. Pharmacol. 69, 351–359. https://doi.org/10.26402/jpp.2018.3.12.

De Souza, F.T.A., Kummer, A., Silva, M.L.V., Amaral, T.M.P., Abdo, E.N., Abreu, M.H.N.G., Silva, T.A., Teixeira, A.L., 2015. The association of openness personality trait with stress-related salivary biomarkers in burning mouth syndrome. NeuroImmunoModulation 22, 250–255. https://doi.org/10.1159/000367714.

Dincheva, I., Glatt, C.E., Lee, F.S., 2012. Impact of the BDNF Val66Met polymorphism on cognition: Implications for behavioral genetics. Neuroscientist 18, 439–451. https://doi.org/10.1177/1073858411431646.

Drakopoulos, P., Casarosa, E., Bucci, F., Piccinino, M., Wenger, J.-M.M., Nappi, R.E., Polyzos, N., Genazzani, A.R., Pluchino, N., 2015. Diurnal variation of plasma brain-derived neurotrophic factor levels in women with functional hypothalamic amenorrhea. Neuroendocrinology 101, 256–262. https://doi.org/10.1159/000381456.

Duman, R.S., 2002. Pathophysiology of depression: The concept of synaptic plasticity. Eur. Psychiatry 17, 306–310. https://doi.org/10.1016/S0924-9338(02)00654-5.

Eiden, L.E., 2010. Commentary on chapters “clinical and developmental aspects” and “stress responses of the adrenal medulla”. Cell. Mol. Neurobiol. 1371–1375. https://doi.org/10.1007/s10571-010-9607-8.

Ennis, G.E., An, Y., Resnick, S.M., Ferrucci, L., O’Brien, R.J., Moffat, S.D., 2017. Long-term cortisol measures predict Alzheimer disease risk. Neurology 88, 371–378. https://doi.org/10.1212/WNL.0000000000003537.

Godoy, L.D., Rossignoli, M.T., Delfino-Pereira, P., Garcia-Cairasco, N., de Lima Umeoka, E.H., 2018. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front. Behav. Neurosci. 12, 1–23. https://doi.org/10.3389/fnbeh.2018.00127.

Goekint, M., Roelands, B., Heyman, E., Njemini, R., Meeusen, R., 2011. Influence of citalopram and environmental temperature on exercise-induced changes in BDNF. Neurosci. Lett. 494 (2), 150–154. https://doi.org/10.1016/j.neulet.2011.03.001.

Goikoetxea, A., Todd, E.V., Gemmell, N.J., 2017. Stress and sex: does cortisol mediate sex change in fish? Reproduction 154, R149–R160. https://doi.org/10.1530/rep-17-0408.

Gray, J.D.D., Milner, T.A.A., McEwen, B.S.S., 2013. Dynamic plasticity: The role of glucocorticoids, brain-derived neurotrophic factor and other trophic factors. Neuroscience 239, 214–227. https://doi.org/10.1016/j.neuroscience.2012.08.034.

Gustafsson, L., Lira, C.M., Johansson, J., Wisen, A., Wohlfart, B., Ekman, R., Westrin, A., 2009. The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder. Psychiat. Res. 169 (3), 244–248. https://doi.org/10.1016/j.psychres.2008.06.030.

Heberlein, A., Lenz, B., Opfermann, B., Gröschl, M., Janke, E., Stange, K., Groh, A., Kornhuber, J., Frieling, H., Bleich, S., Hillemacher, T., 2016. Association of testosterone and BDNF serum levels with craving during alcohol withdrawal. Alcohol 54, 67–72. https://doi.org/10.1016/j.alcohol.2016.06.004.

Hellweg, R., Ziegenhorn, A., Heuser, I., Deuschle, M., 2008. Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry 41, 66–71. https://doi.org/10.1055/s-2007-1004594.

Hosang, G.M., Shiles, C., Tansey, K.E., McGuffin, P., Uher, R., 2014. Interaction between stress and the BDNF Val66Met polymorphism in depression: A systematic review and meta-analysis. BMC Med. 12, 1–11. https://doi.org/10.1186/1741-7015-12-7.

Hosang, G.M., Uher, R., Keers, R., Cohen-Woods, S., Craig, I., Korszun, A., Perry, J., Tozzi, F., Muglia, P., McGuffin, P., Farmer, A.E., 2010. Stressful life events and the brain-derived neurotrophic factor gene in bipolar disorder. J. Affect. Disord. 125, 345–349. https://doi.org/10.1016/j.jad.2010.01.071.

Hötting, K., Schickert, N., Kaiser, J., Röder, B., Schmidt-Kassow, M., 2015. The effects of acute physical exercise on memory, peripheral BDNF, and cortisol in young adults. Neur. Plast. 2016 (2016), 1–12. https://doi.org/10.1155/2016/6860573.

Ichioka, S., Terao, T., Hoaki, N., Matsushita, T., Hoaki, T., 2012. Triiodothyronine may be possibly associated with better cognitive function and less extrapyramidal symptoms in chronic schizophrenia. Prog. Neuro-Psychopharmacology Biol. Psychiatry 39, 170–174. https://doi.org/10.1016/j.pnpbp.2012.06.008.

Jiang, R., Babyak, M.A., Brummett, B.H., Hauser, E.R., Shah, S.H., Becker, R.C., Siegler, I.C., Singh, A., Haynes, C., Chryst-Ladd, M., Craig, D.M., Williams, R.B., 2017. Brain-derived neurotrophic factor rs6265 (Val66Met) polymorphism is associated with disease severity and incidence of cardiovascular events in a patient cohort. Am. Heart J. 190, 40–45. https://doi.org/10.1016/j.ahj.2017.05.002.

Kawashima, H., Numakawa, T., Kumamaru, E., Adachi, N., Mizuno, H., Ninomiya, M., Kunugi, H., Hashido, K., 2010. Glucocorticoid attenuates brain-derived neurotrophic factor-dependent upregulation of glutamate receptors via the suppression of microRNA-132 expression. Neuroscience 165, 1301–1311. https://doi.org/10.1016/j.neuroscience.2009.11.057.

Kenis, G., Prickaerts, J., Van Os, J., Koek, G.H., Robaeys, G., Steinbusch, H.W.M., Wichers, M., 2011. Depressive symptoms following interferon- therapy: Mediated by immune-induced reductions in brain-derived neurotrophic factor? Int. J. Neuropsychopharmacol. 14, 247–253. https://doi.org/10.1017/S1461145710000830.

Keyan, D., Bryant, R.A., 2017. Role of BDNF val66met polymorphism in modulating exercised-induced emotional memories. Psychoneuroendocrinology 77, 150–157. https://doi.org/10.1016/j.psyneuen.2016.12.013.

Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., Moryś, J., 2018. BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. Cell. Mol. Neurobiol. 38, 579–593. https://doi.org/10.1007/s10571-017-0510-4.

Leal, G., Comprido, D., Duarte, C.B., 2014. BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2013.04.005.

Li-Tempel, T., Larra, M.F., Winnikes, U., Tempel, T., DeRijk, R.H., Schulz, A., Schächinger, H., Meyer, J., Schote, A.B., 2016. Polymorphisms of genes related to the hypothalamic-pituitary-adrenal axis influence the cortisol awakening response as well as self-perceived stress. Biol. Psychol. 119, 112–121. https://doi.org/10.1016/j.biopsycho.2016.07.010.

Libro, R., Bramanti, P., Mazzon, E., 2017. Endogenous glucocorticoids: Role in the etiopathogenesis of Alzheimer’s disease. Neuro Endocrinol. Lett. 38, 1–12.

Lu, B., Nagappan, G., Guan, X., Nathan, P.J., Wren, P., 2013. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat. Rev. Neurosci. 14, 401–416. https://doi.org/10.1038/nrn3505.

Ma, D.Y., Chang, W.H., Chi, M.H., Tsai, H.C., Yang, Y.K., Chen, P.S., 2016. The correlation

between perceived social support, cortisol and brain derived neurotrophic factor levels in healthy women. Psychiat. Res. 239, 149–153. https://doi.org/10.1016/j.psychres.2016.03.019.
Mackin, P., Gallagher, P., Watson, S., Young, A., Ferrier, I.N., 2007. Changes in brain-derived neurotrophic factor following treatment with mifepristone in bipolar disorder and schizophrenia. Aust. N. Z. J. Psychiatry 41, 321–326. https://doi.org/10.1080/00048670701213211.
Marrocco, J., Einhorn, N.R., Petty, G.H., Li, H., Dubey, N., Hoffman, J., Berman, K.F., Goldman, D., Lee, F.S., Schmidt, P.J., McEwen, B.S., 2018. Epigenetic intersection of BDNF Val66Met genotype with premenstrual dysphoric disorder transcriptome in a cross-species model of estradiol add-back. Mol. Psychiatry 1. https://doi.org/10.1038/s41380-018-0274-3.
Meng, D., Wu, T., Rao, U., North, C.S., Xiao, H., Javors, M.A., Adinoff, B., 2011. Serum NPY and BNDF response to a behavioral stressor in alcohol-dependent and healthy control participants. Psychopharmacology 218, 59–67. https://doi.org/10.1007/s00213-011-2414-1.
Miodownik, C., Maayan, R., Ratner, Y., Lerner, V., Pintov, L., Mar, M., Weizman, A., Ritsner, M.S., 2011. Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to l-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Clin. Neuropharm. 34 (4), 155–160. https://doi.org/10.1097/WNF.0b013e318220d8c6.
Mücke, M., Ludyga, S., Colledge, F., Gerber, M., 2018. Influence of regular physical activity and fitness on stress reactivity as measured with the trier social stress test protocol: a systematic review. Sport. Med. 48, 2607–2622. https://doi.org/10.1007/s40279-018-0979-0.
Naveen, G.H., Varambally, S., Thirthalli, J., Rao, M., Christopher, R., Gangadhar, B.N., 2016. Serum cortisol and BDNF in patients with major depression—effect of yoga. Int. Rev. Psychiatry 28, 273–278. https://doi.org/10.1080/09540261.2016.1175419.
Nepomnaschy, P.A., Welch, K.B., McConnell, D.S., Low, B.S., Strassmann, B.I., England, B.G., 2006. Cortisol levels and very early pregnancy loss in humans. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.0511183103.
Neves, C.D.C., Lacerda, A.C.R., Lima, L.P., Lage, V.K.S., Balthazar, C.H., Leite, H.R., Mendonca, V.A., 2017. Different levels of brain-derived neurotrophic factor and cortisol in healthy heavy smokers. Brazi. J. Med. Biol. Res. 50 (12), e6424. https://doi.org/10.1590/1414-431X20176424.
Ninan, P.T., Shelton, R.C., Bao, W., Guico-Pabia, C.J., 2014. BDNF, interleukin-6, and salivary cortisol levels in depressed patients treated with desvenlafaxine. Prog. Neuro-Psychopharmacology Biol. Psychiatry 48, 86–91. https://doi.org/10.1016/j.pnpbp.2013.09.016.
Notaras, M., Hill, R.A., van den Buuse, M., 2016. Dissecting a genomic role of BDNF in schizophrenia and psychosis. J. Clin. Psychiatry 77, e1029–e1031. https://doi.org/10.4088/JCP.15com10536.
Numakawa, T., Adachi, N., Richards, M., Chiba, S., Kunugi, H., 2012. The influence of glucocorticoids on neuronal survival and synaptic function. Biomol. Concepts 3, 495–504. https://doi.org/10.1515/bmc-2012-0012.
Numakawa, T., Kumamaru, E., Adachi, N., Yagasaki, Y., Izumi, A., Kunugi, H., 2009. Glucocorticoid receptor interaction with TrkB promotes BDNF-triggered PLC- signaling for glutamate release via a glutamate transporter. Proc. Natl. Acad. Sci. 106, 647–652. https://doi.org/10.1073/pnas.0800888106.
Onen Sertoz, O., Tolga Binbay, I., Koylu, E., Noyan, A., Yıldırım, E., Elbi Mete, H., Yildirim, E., Elbi Mete, H., 2008. The role of BDNF and HPA axis in the neurobiology of burnout syndrome. Prog. Neuro-Psychopharmacology Biol. Psychiatry 32, 1459–1465. https://doi.org/10.1016/j.pnpbp.2008.05.001.
Otsuki, K., Uchida, S., Watanuki, T., Wakabayashi, Y., Fujimoto, M., Matsubara, T., Funato, H., Watanabe, Y., 2008. Altered expression of neurotrophic factors in patients with major depression. J. Psychiatr. Res. 42, 1145–1153. https://doi.org/10.1016/j.jpsychires.2008.01.010.
Panaree, B., Chantana, M., Wasana, S., Chairat, N., 2011. Effects of obstructive sleep apnea on serum brain-derived neurotrophic factor protein, cortisol, and lipid levels. Sleep Breath 15, 649–656. https://doi.org/10.1007/s11325-010-0415-7.
Panja, D., Bramham, C.R., 2014. BDNF mechanisms in late LTP formation: A synthesis and breakdown. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2013.06.024.
Pardridge, W.M., Kang, Y.S., Buciak, J.L., 1994. Transport of human recombinant brain-derived neurotrophic factor (BDNF) through the rat blood-brain barrier in vivo using vector-mediated peptide drug delivery. Pharm. Res. 11, 738–746.
Rojas Vega, S., Strüder, H.K., Wahrmann, V.B., Schmidt, A., Bloch, W., Hollmann, W., 2006. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res. 1121 (1), 59–65. https://doi.org/10.1016/j.brainres.2006.08.105.
Rojas Vega, S., Abel, T., Lindschulten, R., Hollmann, W., Bloch, W., Strüder, H.K., 2008. Impact of exercise on neuroplasticity-related proteins in spinal cord injured humans. Neuroscience 153 (4), 1064–1070. https://doi.org/10.1016/j.neuroscience.2008.03.037.
Sasi, M., Vignoli, B., Canossa, M., Blum, R., Manju, S., Vignoli, B., Canossa, M., Blum, R., 2017. Neurobiology of local and intercellular BDNF signaling. Pflugers Arch. Eur. J. Physiol. 469, 1–18. https://doi.org/10.1007/s00424-017-1964-4.
Schmidt-Kassow, M., Zink, N., Mock, J., Thiel, C., Vogt, L., Abel, C., Kaiser, J., 2014. Treadmill walking during vocabulary encoding improves verbal long-term memory. Behav. Brain Funct. 10, 24. https://doi.org/10.1186/1744-9081-10-24.
Schüle, C., Zill, P., Baghai, T.C., Eser, D., Zwanzger, P., Wenig, N., Rupprecht, R., Bondy, B., 2006. Brain-derived neurotrophic factor Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. Psychoneuroendocrinology 31, 1019–1025. https://doi.org/10.1016/j.psyneuen.2006.06.002.
Shalev, I., Lerer, E., Israel, S., Uzefovsky, F., Gritsenko, I., Mankuta, D., Ebstein, R.P., Kaitz, M., 2009. BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. Psychoneuroendocrinology 34, 382–388. https://doi.org/10.1016/j.psyneuen.2008.09.017.
Sharpley, C.F., Christie, D.R.H., Bitsika, V., Andronicos, N.M., Agnew, L.L., Richards, T.M., McMillan, M.E., 2018. Comparing a genetic and a psychological factor as correlates of anxiety, depression, and chronic stress in men with prostate cancer. Support. Care Cancer 26, 3195–3200. https://doi.org/10.1007/s00520-018-4183-4.
Skibinska, M., Groszewska, A., Kapelski, P., Rajewska-Rager, A., Pawlak, J., Dmitrzak-Weglarz, M., Szczepankiewicz, A., Twarowska-Hauser, J., 2018. Val66Met functional polymorphism and serum protein level of brain-derived neurotrophic factor (BDNF) in acute episode of schizophrenia and depression. Pharmacol. Rep. 70, 55–59. https://doi.org/10.1016/j.pharep.2017.08.002.
Soldan, A., Pettigrew, C., Cai, Q., Wang, J., Wang, M.-C., Moghekar, A., Miller, M.I., Albert, M., 2017. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. Neurobiol. Aging 60, 164–172. https://doi.org/10.1016/j.neurobiolaging.2017.09.002.
Strollo, F., Vassilieva, G., Ruscica, M., Masini, M., Santucci, D., Borgia, L., Magni, P., Celotti, F., Nikiporuc, I., 2014. Changes in stress hormones and metabolism during a 105-day simulated Mars mission. Aviat. Space Environ. Med. 85 (8), 793–797. https://doi.org/10.3357/ASEM.3907.2014.
Toh, Y.L., Ng, T., Tan, M., Tan, A., Chan, A., 2018. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: A systematic review. Brain Behav. 8, 1009. https://doi.org/10.1002/brb3.1009.
Tsuru, J., Tanaka, Y., Ishitobi, Y., Maruyama, Y., Inoue, A., Kawano, A., Ikeda, R., Ando, T., Oshita, H., Aizawa, S., Masuda, K., Higuma, H., Kanehisa, M., Ninomiya, T., Akiyosh, J., 2014. Association of BDNF Val66Met polymorphism with HPA and SAM axis reactivity to psychological and physical stress. Neuropsychiatr. Dis. Treat. 10, 2123–2133. https://doi.org/10.2147/NDT.S68629.
Uegaki, K., Kumanogoh, H., Mizui, T., Hirokawa, T., Ishikawa, Y., Kojima, M., 2017. BDNF binds its pro-peptide with high affinity and the common val66met polymorphism attenuates the interaction. Int. J. Mol. Sci. 18, 1042. https://doi.org/10.3390/ijms18051042.
Veltman, E.M., Lamers, F., Comijs, H.C., Stek, M.L., van der Mast, R.C., Rhebergen, D., 2018. Inflammatory markers and cortisol parameters across depressive subtypes in an older cohort. J. Affect. Disord. https://doi.org/10.1016/j.jad.2018.02.080.
Ventriglia, M., Zanardini, R., Bonomini, C., Zanetti, O., Volpe, D., Pasqualetti, P., Gennarelli, M., Bocchio-Chiavetto, L., 2013. Serum brain-derived neurotrophic factor levels in different neurological diseases. 901082. Biomed Res. Int. 2013. https://doi.org/10.1155/2013/901082.
Vinberg, M., Trajkovska, V., Bennike, B., Knorr, U., Knudsen, G.M., Kessing, L.V., 2009. The BDNF Val66Met polymorphism: Relation to familiar risk of affective disorder, BDNF levels and salivary cortisol. Psychoneuroendocrinology 34, 1380–1389. https://doi.org/10.1016/j.psyneuen.2009.04.014.
Vogel, S.W.N., Bijlenga, D., Verduijn, J., Bron, T.I., Beekman, A.T.F., Kooij, J.J.S., Penninx, B.W.J.H., 2017. Attention-deficit/hyperactivity disorder symptoms and stress-related biomarkers. Psychoneuroendocrinology 79, 31–39. https://doi.org/10.1016/j.psyneuen.2017.02.009.
Waqas, A., Ji, J., 2017. Thermal management of conventional PV panel using PCM with movable shutters – A numerical study. Sol. Energy 158, 797–807. https://doi.org/10.1016/j.solener.2017.10.050.
Wei, Y.C., Wang, S.R., Xu, X.H., 2017. Sex differences in brain-derived neurotrophic factor signaling: Functions and implications. J. Neurosci. Res. https://doi.org/10.1002/jnr.23897.
Whiteman, A.S., Young, D.E., He, X., Chen, T.C., Wagenaar, R.C., Stern, C.E., Schon, K., 2014. Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults. Behav. Brain Res. 259, 302–312. https://doi.org/10.1016/j.bbr.2013.11.023.
Wu, J.J., Cui, Y., Yang, Y.S., Kang, M.S., Jung, S.C., Park, H.K., Yeun, H.Y., Jang, W.J., Lee, S., Kwak, Y.S., Eun, S.Y., 2014. Modulatory effects of aromatherapy massage intervention on electroencephalogram, psychological assessments, salivary cortisol and plasma brain-derived neurotrophic factor. Complement. Ther. Med. 22 (3), 456–462. https://doi.org/10.1016/j.ctim.2014.04.001.
Young, D.A., Neylan, T.C., O'Donovan, A., Metzler, T., Richards, A., Ross, J.A., Inslicht, S.S., 2018. The interaction of BDNF Val66Met, PTSD, and child abuse on psychophysiological reactivity and HPA axis function in a sample of Gulf War Veterans. J. Affect. Disord. 235, 52–60. https://doi.org/10.1016/j.jad.2018.04.004.
Yu, J.J., Pei, L.B., Zhang, Y., Wen, Z.Y., Yang, J.L., 2015. Chronic Supplementation of Curcumin Enhances the Efficacy of Antidepressants in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. J. Clin. Psychopharmacol. 35 (4), 406–410. https://doi.org/10.1097/JCP.0000000000000352.
Zhao, M., Chen, L., Yang, J., Han, D., Fang, D., Qiu, X., Yang, X., Qiao, Z., Ma, J., Wang, L., Jiang, S., Song, X., Zhou, J., Zhang, J., Chen, M., Qi, D., Yang, Y., Pan, H., 2017. BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. J. Affect. Disord. 227, 226–235. https://doi.org/10.1016/j.jad.2017.10.024.
Zoladz, J.A., Śmigielski, M.M., Majerczak, J., Nowak, L.R., Zapart-Bukowska, J., Smoleń ski, O., Kulpa, J., Duda, K., Drzewińska, J., Bartosz, G., Nowak, Ł.R., Zapart-Bukowska, J., Smoleński, O., Kulpa, J., Duda, K., Drzewińska, J., Bartosz, G., 2012. Hemodialysis decreases serum brain-derived neurotrophic factor concentration in humans. Neurochem. Res. 37, 2715–2724. https://doi.org/10.1007/s11064-012-0862-6.
PRISMA-P, 4:1.