

The Neurobiology of Burnout: The Hypothalamus-Pituitary-Adrenal Gland Axis and Other Findings

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Abstract

Objective: This review aimed to present an overview of neurobiological research on the etiology of burnout and to evaluate the proposed arguments.

Method: A retrospective literature review of the relevant studies conducted within the last 17 years. For this purpose a literature search was conducted via internet-based search engines, including PubMed, Science-Direct, Medline, GoogleScholar, ULAKBİM Turkish Medicine Index, and Turkish Psychiatry Index, using the key words, burnout, cortisol, the hypothalamus-pituitary-adrenal gland (HPA)-axis, stress, neurobiology, neurogenesis, BDNF, immunology, and etiology, in different combinations.

Results: The pioneering studies that focused on the relationship between burnout and dysregulation of the HPA-axis have yielded inconsistent results. Data from subsequent studies with improved designs suggest there is no HPA-axis dysregulation in burnout, but the results do not lead to more concrete interpretations. There is some evidence of impaired immunity function in burnout as compared with controls. Although there is strong evidence of a relationship between stress and impairment in hippocampal neurogenesis, there is no study of burnout in the field. Data about monoaminergic involvement in burnout, which is one of the probable pathways, is scarce.

Conclusion: In future research the essential guidelines for evaluating HPA-axis functioning (i.e. timing of collecting samples from saliva or blood and controlling for possible influencing factors on HPA-axis functioning) in patients clinically diagnosed with burnout should be taken into account, and in addition to the HPA-axis, evaluation of hippocampal neurogenesis, neurotrophins, immunity functioning, and the monoaminergic system will provide more data on the neurobiology of burnout.

Key Words: BDNF, hippocampal neurogenesis, HPA-axis, cortisol, monoaminergic system, burnout, proinflammatory response

INTRODUCTION

Burnout, which is a psychosomatic syndrome resulted of chronic work stress, is defined as detachment from the authentic meaning and goal of the job, inability to deal with individuals for whom service is provided, and psychological withdrawal from the job due to job strain and dissatisfaction (Kaçmaz, 2005). The main symptoms include loss of energy, lack of motivation, negative attitude, and withdrawal from those who are provided service. Mostly, it is seen in sectors that directly provide services to individuals and where human relations have a significant role in the management of services (health, education, and banking) (Kaçmaz, 2005).

The term burnout was first used in 1975 (Freudenberger, 1975). Maslach (1976) was the first to develop a scale (Maslach Burnout Inventory, MBI) to assess the level of burnout in individuals. The scale has been through many developmental stages and was used for screening purposes in various professional fields. In Maslach's approach, burnout is composed of 3 symptom dimensions: emotional burnout, depersonalization, and job success (Maslach and Jackson, 1986; Maslach et al., 2001).

A study in Finland reported severe and mild levels of burnout in 2.4% and 25.2% of participants, respectively, based on MBI (Honkonen et al., 2006). In Turkey, a

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study of 7255 healthcare workers revealed that general practitioners and nurses, in particular, had higher MBI emotional exhaustion and depersonalization scores compared to other groups (Ergin, 1996). In another study it was found that burnout was associated with being in the early phases of work life, having long working hours, working in shifts or working alone on workdays, and sleep habits (Aslan et al., 1996).

It is generally agreed that chronic stress in the workplace causes burnout syndrome (Maslach et al., 2001). As in other stress-related psychiatric disorders, hypothalamus-pituitary-adrenal gland (HPA)-axis functioning is expected to show variations in burnout (Kudielka et al., 2006; Sonnentag, 2006). The association of stress-related disorders (depression, post-traumatic stress disorder, fibromyalgia, and chronic fatigue syndrome) and HPA-axis function has been investigated (Heim et al., 2000; Ehlert et al., 2001; Raison and Miller, 2003); however, the results of these studies are inconsistent with respect to identifying a relationship between stress and the HPA-axis. While some studies indicate a positive relation between short- or long-term stress and cortisol levels (Melamed et al., 1999; Pruessner et al., 1999; Wüst et al., 2000), other studies report insignificant or contradictory findings (Ockenfels et al., 1995; Sluiter et al., 2003; Weibel et al., 2003). Furthermore, the relationship between job stress and cortisol levels varies with respect to other sociodemographic variables (socioeconomic status and gender) (Kunz-Ebrecht et al., 2004). In other stress-related disorders like fibromyalgia and chronic fatigue syndrome, hypocortisolism has been reported (Heim et al., 2000; Afari et al., 2003; Raison and Miller, 2003). Studies of the relationship between stress, and the immune and monoaminergic systems indicate that the two endocrine systems that are sensitive to stress are the HPA-axis and the sympathetic-adrenal-medullary (SAM) system (Cohen et al., 2007). Increased cortisol as a response to stimulation of the HPA-axis negatively affects immune system functioning. Similarly, when SAM is stimulated by stress, catecholamines increase in response to a particular stimulation. Catecholamines regulate the function of various systems (cardiovascular, respiratory, and immune systems) other than the autonomous nervous system. Extended or repetitive stimulation of the HPA-axis or SAM system increases the risk of psychiatric and physical illnesses (Cohen et al., 2007). Increased HPA-axis and SAM hormones interfere with immune system functioning, either by directly stimulating lymphatic tissues after linking to these sites or indirectly by influencing immune system cells.

In this review article we aimed to investigate the neurobiology of burnout, with respect to data provided in scientific resources. Understanding the etiology of burnout, which has severe psychosocial consequences, is important in terms of the emergence of new treatment approaches, experimentation with these approaches, and evaluation of available experimental treatments.

METHODS

All English and Turkish language articles published between 1990 and 2007 were searched in PubMed, Science-Direct, Medline, GoogleScholar, ULAKBİM Turkish Medicine Index, and Turkish Psychiatry Index using the keywords, burnout, HPA-axis, cortisol, stress, neurobiology, neurogenesis, BDNF, immunity and etiology, in different combinations. The reference sections of articles were also reviewed for more available resources in English. Articles about the stress-HPA-axis, stress-immune system, stress-monoaminergic system, and stress-neurogenesis relationships outside the scope of burnout syndrome were excluded from the discussion, as they were not directly related to the topic.

As a result, 25 articles related directly to the topic were found, of which 22 were original research articles with a case-control design and 3 were review articles. In 19 of the original research articles the relationship between burnout and HPA-axis function was investigated, and 2 of them were based on data from the same sample group (Ekstedt et al., 2004; Söderstrom et al., 2006). In 1 article, both HPA-axis and SAM indicators were used (De Vente et al., 2003). In another article hormonal indicators were included in the research, as well as HPA-axis indicators (Moch et al., 2003). Two other articles included immune system indicators in addition to the HPA-axis (Grossi et al., 2003; Mommersteeg et al., 2006d). In 1 article, the relationship between the serotonergic-dopaminergic system and burnout was investigated in addition to the HPA-axis (Tops et al., 2007). In 11 of 19 research articles patients with a diagnosis of burnout were compared to healthy controls or to each other, in terms of pre-treatment and post-treatment differences. In other papers, there were no healthy controls and individuals were compared based on groups determined by burnout scale scores. Two studies investigated the relationship between burnout and immune system indicators (Nakamura et al., 1999; Bargellini et al., 2000), and 1 article investigated the relationship between burnout and SAM system indicators (Zanstra et al., 2006).

Among the 3 review articles, 1 reviewed the relation-

Table 1a. Studies of HPA-axis function and its relationship to burnout that grouped participants according to burnout inventory scores for comparison.*

Evaluation of Burnout	Assessed Values	Results	Reference
SMBS (n = 111)	<ul style="list-style-type: none"> • 08:00 and 16:00 salivary cortisol levels 	<ul style="list-style-type: none"> • In both measurements, cortisol levels were higher in those with higher burnout [statistically significant only in those with chronically high burnout] 	Melamed et al., 1999
SMBS (n = 36)	<ul style="list-style-type: none"> • 08:00-10:00 pm, 1 blood sample: total cortisol; 3 years follow up 	<ul style="list-style-type: none"> • No established relationship between burnout and cortisol 	Grossi et al., 1999
MBI and TBI (n = 66)	<ul style="list-style-type: none"> • 2 consecutive days of assessment of salivary cortisol and CAR (4 samples) • Third day, after 0.5 mg DST salivary CAR (4 samples) 	<ul style="list-style-type: none"> • In all measurements, low cortisol levels were established in the high-level burnout group • Increased dexamethasone response in high-level burnout 	Pruessner et al., 1999
MBI (n = 41)	<ul style="list-style-type: none"> • Morning and evening cortisol (salivary and plasma) levels 	<ul style="list-style-type: none"> • Morning cortisol levels significantly lower in high-level burnout group compared to the low-level burnout group • Significantly higher evening cortisol levels in the high-level burnout group 	Morgan et al., 2002
SMBS (n = 63)	<ul style="list-style-type: none"> • 08:00-10:00 pm, 1 blood sample: total cortisol 	<ul style="list-style-type: none"> • No established difference in serum cortisol levels between the high- and low-level burnout groups 	Grossi et al., 2003
SMBS (n = 24)	<ul style="list-style-type: none"> • 08:00 and 16:00 salivary cortisol levels • Salivary CAR (4 samples) • Diurnal salivary cortisol cycle (5 samples) 	<ul style="list-style-type: none"> • No established difference between groups • No established difference between groups • No established difference between groups 	Ekstedt et al., 2004
MBI (n = 42)	<ul style="list-style-type: none"> • 17:00-19:00 pm salivary sample: total cortisol [Pre and post operational within group comparison] 	<ul style="list-style-type: none"> • No established difference between groups 	Galantino et al., 2005

*Of 8 articles, 2 were conducted with the same sample and thus only 1 (Ekstedt et al., 2004) was placed in the table.

CAR: Cortisol awakening response; DST: Dexamethasone Suppression Test; MBI: Maslach Burnout Inventory; SMBS: Shirom-Melamed Burnout Scale; TBI: Teacher Burnout Inventory.

ship between burnout and the HPA-axis based on the findings of a single study (Sonnentag, 2006). In another, studies that investigated the relationship between the HPA-axis, and burnout and vital exhaustion were evaluated together (Kudielka et al., 2006). No clinical studies of the relationship between the HPA-axis and neurogenesis in the etiology of burnout were found. Only a review was found on this subject (Eriksson and Wallin, 2004). We recently investigated the relationship between the HPA-axis and brain-derived neurotrophic factor (BDNF) in the neurobiology of burnout (Onen Sertoz et al., 2008). In this paper only the findings related to the HPA-axis will be discussed.

RESULTS

Burnout and HPA-axis Functions

The studies we found were evaluated in 2 groups due

to methodological differences. Studies that investigated the relationship between burnout and the HPA-axis by grouping the participants as low or high scorers on self-report scales are presented in Table 1a. Studies that compared patients clinically diagnosed (based on semi-structured interviews) to healthy controls, or studies that compared patients before and after treatment are shown in Table 1b. As 2 of the 8 studies that grouped participants as low or high scorers on self-report scales were conducted with the same sample, only 1 (Ekstedt et al., 2004) is presented in Table 1a.

In the first study focusing on the association between burnout syndrome and HPA-axis function, although cortisol levels of the individuals with higher levels of burnout were higher than those with lower levels of burnout, this difference reached statistical significance only for individuals with chronically high-level burnout (Melamed et al., 1999). In a three-year follow-up study,

Table 1b. Studies that investigated HPA-axis functions and its relationship to burnout by comparing patients clinically diagnosed with semi-structured interviews to healthy controls, and by comparing within group differences before and after treatment interventions.*

Evaluation of Burnout	Assessed Values	Results	Reference
<ul style="list-style-type: none"> • MBI • Evidence-based clinical diagnosis • (n = 16/16) 	<p>[Assessed pre- and post-operationally and monthly for 4 months]</p> <ul style="list-style-type: none"> • 24-h free urine cortisol level • 08:00 pm, 1 blood sample: cortisol • 08:00 pm, 1 blood sample: DHEAs • 08:00 pm, 1 blood sample: ACTH 	<ul style="list-style-type: none"> • Low levels unchanged for 4 months in patients • No established difference between groups • No established difference between groups • No established difference between groups 	Moch et al., 2003
<ul style="list-style-type: none"> • MBI • Evidence-based clinical diagnosis • (n = 22/23) 	<ul style="list-style-type: none"> • Salivary CAR (3 samples) • 12:00 salivary cortisol • Salivary cortisol after stress test 	<ul style="list-style-type: none"> • High CAR in patients • No established difference between groups • No established difference related with the test 	DeVente et al., 2003
<ul style="list-style-type: none"> • SMBS • DSM-IV/ICD-10 conduct disorder diagnosis • (n = 22/42) 	<ul style="list-style-type: none"> • Salivary CAR (4 samples) 	<ul style="list-style-type: none"> • Higher in female patients • No established difference between male patients and controls [In males, CAR was higher in the moderate-level burnout group than in the low-level burnout group] 	Grossi et al., 2005
<ul style="list-style-type: none"> • MBI • ICD-10 work related neurasthenia diagnosis • (n = 74/35) 	<ul style="list-style-type: none"> • Salivary CAR on 2 consecutive days (3 samples) • Third day salivary CAR after 0.5 mg DST (3 samples) • Diurnal salivary cortisol cycle (3 samples) 	<ul style="list-style-type: none"> • No established difference between groups • No established difference between groups • No established difference between groups 	Mommersteeg et al., 2006a
<ul style="list-style-type: none"> • MBI • ICD-10 work related neurasthenia diagnosis • (n = 22/21) 	<ul style="list-style-type: none"> • Salivary CAR on 2 consecutive days (3 samples) • Diurnal salivary cortisol cycle (3 samples) • Post-psychotherapy salivary CAR (3 samples) 	<ul style="list-style-type: none"> • Lower levels in patients • No established difference between groups • Increased CAR after psychotherapy 	Mommersteeg et al., 2006c
<ul style="list-style-type: none"> • MBI • ICD-10 work related neurasthenia diagnosis • (n = 56/38) 	<ul style="list-style-type: none"> • Salivary CAR (3 samples) • Third day salivary ACR after 0.5 mg DST (3 samples) • Salivary DHEAs • Cortisol/DHEAs ratio 	<ul style="list-style-type: none"> • No established difference between groups • No established difference between groups • Higher DHEAs in patients • No established difference between groups 	Mommersteeg et al., 2006d

burnout was found to decrease as working conditions improved, while cortisol levels were found to increase; however, the relationship between morning cortisol levels and burnout was not established (Grossi et al. 1999). In another study, cortisol-awakening response (CAR) measured on 3 consecutive working days was lower in individuals with higher levels of burnout compared to individuals with lower levels of burnout. Before measurement on the third day dexamethasone was administered and an increase in suppression response was obtained in individuals with higher levels of burnout (Pruessner et

al., 1999). In another study morning salivary cortisol levels were found to be significantly lower in individuals with higher levels of burnout than in individuals with lower levels of burnout, and evening salivary cortisol levels were significantly higher in high burnout group (Morgan et al., 2002).

Grossi et al. (2003) compared female employees with respect to immune, metabolic, and endocrine function parameters and reported that women with higher levels of burnout had higher job stress and less social support in the workplace; however, the study showed that al-

Table Ib. Continued.

Evaluation of Burnout	Assessed Values	Results	Reference
<ul style="list-style-type: none"> • MBI and UWES • ICD-10 work related neurasthenia diagnosis • (n = 29/33/26) 	<ul style="list-style-type: none"> • Salivary CAR on 2 consecutive days (3 samples) • Third day salivary CAR after 0.5 mg DST (3 samples) • Salivary CAR (3 samples) [Weekend] • Salivary DHEAs on all days • Cortisol/DHEAS ratio 	<ul style="list-style-type: none"> • No established difference between groups • Higher suppression in the group with job adaptation • No established difference between groups; lower than weekends • No established difference between groups • No established difference between groups 	Langelaan et al., 2006
<ul style="list-style-type: none"> • MBI and UWES • ICD-10 work related neurasthenia diagnosis • (n = 42) 2-week follow up 	<ul style="list-style-type: none"> • Salivary CAR on two consecutive days (3 samples) • Third day salivary CAR after 0.5 mg DST (3 samples) • Salivary DHEAS measured on 2 consecutive days • Cortisol/DHEAs ratio 	<ul style="list-style-type: none"> • [In the individuals with high-level burnout and the ones that rest less at sleep] • Lower CAR • Stronger suppression after DST • Higher DHEAs • Lower Cortisol/DHEAs 	Sonnenschein et al. 2007
<ul style="list-style-type: none"> • MBI • Clinical diagnosis method not mentioned • (n = 9/9) 	<ul style="list-style-type: none"> • 08:00-10:00 pm, 1 blood sample: total cortisol • 08:00-10:00 pm, 1 blood sample: ACTH 	<ul style="list-style-type: none"> • No established difference between groups • No established difference between groups 	Tops et al. 2007
<ul style="list-style-type: none"> • MBI • ICD-10 work related neurasthenia diagnosis • (n = 37/34) 	<ul style="list-style-type: none"> • 08:00 pm, 1 blood sample: total cortisol • Serum cortisol after 1 mg DST 	<ul style="list-style-type: none"> • No established difference between groups • No established difference between groups 	Onen Sertoz et al. 2007

*Of 10 articles, 2 (Mommersteeg et al., 2006a, 2006b) were conducted with the same sample and thus only 1 (Mommersteeg et al. 2006a) was placed in the table.

ACTH: Adrenocorticotropin hormone; CAR: Cortisol awakening response; DHEAs: Dehydroepiandrosterone-sulphate; DST: Dexamethasone Suppression Test; MBI: Maslach Burnout Inventory; SMBS: Shirom-Melamed Burnout Scale; UWES: Utrecht Work Engagement Scale.

though women with higher levels of burnout were more depressed and anxious, they had similar serum cortisol levels as women with lower levels of burnout. Ekstedt et al. (2004) investigated the relationships between burnout, and CAR and sleep properties. They reported no differences between the groups with higher and lower levels of burnout, in terms of CAR and diurnal cortisol levels (salivary); however, it was reported that cortisol measured in the morning was the best predictor of night awakenings. In another study that was based on the same data, in the group with higher levels of burnout, CAR was higher during the week than the weekends (Söderstrom et al., 2006). The group with higher levels of burnout reported more fatigue and lower levels of mental activity. Furthermore, night awakenings on the previous day of measurements was shown to be related to the level of increase in cortisol levels through the following day and with earlier peaking of cortisol levels on work days. Because night awakenings were shown to be related to

increases in daily cortisol levels and changes observed in individuals with burnout were not reversed with short-term separation from stress (resting at weekends), it was suggested by the researchers that this condition could be related to burnout (Söderstrom et al., 2006).

In a study in which the cortisol levels of participants were compared before and after 8 weeks of cognitive behavioral therapy designed specifically for burnout, no differences were found between baseline and post treatment measurements (Galantino et al., 2005).

Findings from studies that compared HPA-axis function in individuals diagnosed with burnout to a control group are inconsistent (Table Ib). In a study in which female patients were compared to age-matched controls with respect to measurements at baseline, once a month, and after the administration of 4 months of stress management training, it was shown that only urine free cortisol levels were significantly lower, and this difference

did not change at the end of training program despite psychological and clinical improvement (Moch et al. 2003). De Vente et al. (2003) reported that in individuals diagnosed with burnout, morning cortisol levels were higher, and daily distribution and post-stress test cortisol levels were not different when compared to the controls. In these 2 studies, burnout was diagnosed with unstructured interviews and diagnoses were based on symptom and functional levels of the individuals.

The study by Grossi et al. (2005) was the first to question the clinical significance of the diagnosis of burnout. In that study the diagnoses of individuals reporting high levels of burnout syndrome were based on a classification system for the first time and adjustment disorder was questioned with respect to DSM-IV (APA, 1994). Individuals with comorbid depression and additional psychiatric illness were excluded. Patients diagnosed with burnout ($n = 22$) were compared, in terms of CAR, to employees that reported moderate ($n = 20$) and low ($n = 22$) levels of burnout. The authors reported that female patients with clinically diagnosed burnout had higher CAR levels than women reporting lower levels of burnout. For males, while there were no differences between the patient group and men reporting moderate levels of burnout, cortisol levels of males reporting moderate levels of burnout were higher than in those reporting lower levels of burnout (Grossi et al., 2005).

Mommersteeg et al. (2006a) highlighted the methodological limitations in the literature concerning the pathophysiology of burnout syndrome and they used a semi-structured interview for the first time. Participants were diagnosed with respect to ICD-10 criteria for work-related neurasthenia (F.48) (WHO, 1992) and all participants were administered a structured clinical interview (First et al. 1997) for diagnosing DSM-IV Axis I disorders. They reported that 95% of individuals diagnosed with burnout syndrome had a diagnosis of undifferentiated somatoform disorder, according to DSM-IV. In that study it was reported that there were no differences between individuals that had clinically significant levels of burnout and healthy controls in terms of HPA-axis functions (Mommersteeg et al., 2006a). The same research team included patients from the previous study (Mommersteeg et al., 2006a) with a diagnosis of burnout in a cognitive-behavioral treatment program to reduce the risk factors that cause burnout and the continuation of these complaints. HPA-axis functions in the participants were evaluated with similar methods as were used in the previous study at pre-treatment ($n = 74$), at 8.5 months of treatment ($n = 62$), and at the

end of a follow-up period with a mean of 6.3 months ($n = 55$) (Mommersteeg et al., 2006b). Although burnout symptoms were observed to have obviously reduced at the time of the evaluation performed after 8.5 months, at 6.3 months symptom levels were the same as during the previous evaluation. Cortisol levels after awakening and after DST were not different at pre-treatment, post-treatment, or follow-up evaluations (Mommersteeg et al., 2006b).

In another study by the same research team in which they used another sample to compare HPA-axis functions of patients diagnosed with burnout to healthy controls before and after psychotherapy, individuals with burnout had lower CAR at baseline. Additionally, after a 14-week cognitive-behavioral treatment specifically targeting burnout, morning cortisol levels that had been low in burnout patients increased and complaints significantly decreased; however, there was no significant relationship between subjective complaints and changes in cortisol levels (Mommersteeg et al., 2006c).

In a study focusing on the functioning of the immune and endocrine systems, which was conducted by the same team with different samples, DHEAs levels were higher in individuals diagnosed with burnout than in controls; however, there was no significant difference with respect to CAR, post-DST CAR, and cortisol DHEAs ratios (Mommersteeg et al., 2006d). In another study in which similar parameters were investigated it was found that when managers with burnout, managers with good job adjustment, and healthy controls working at the same place were compared, CAR was higher in all 3 groups during the work week than during weekends; however, there were no significant differences with respect to HPA-axis functions (Langelaan et al., 2006). Likewise, a significant difference was not found between individuals with clinically diagnosed burnout and controls with respect to serum basal cortisol levels and ACTH (Tops et al., 2007).

In a study that investigated whether or not there is a fluctuating relationship between cortisol levels and burnout symptoms, patients diagnosed with burnout recorded their daily symptoms in an electronic diary for 2 weeks (Sonnenschein et al., 2007). Despite the significant relationship between burnout symptoms evaluated momentarily and endocrine measurements (CAR, DHEAs, and post-DST cortisol), the same relationship was not established for symptoms evaluated retrospectively. The researchers established that severe symptoms of burnout were related to low morning cortisol levels,

high DHEAs levels, low cortisol/DHEA ratios, and post-DST suppression of cortisol release (Sonnenschein et al., 2007). In a study that we conducted there were no significant differences observed between morning cortisol levels and morning cortisol levels after administration of 1 mg of DST (Onen Sertoz et al., 2007).

Stress Response in Burnout Syndrome and Alternative Pathways for Symptoms

In the last decade the quantity of data about the effect of the HPA-axis on hippocampal neurogenesis has increased. It was suggested that a decrease in hippocampal neurogenesis might be related to depression and anxiety disorders (Cameron and Gould, 1994; Duman et al., 2000; Kempermann and Kronenberg, 2003). In animal experiments it was shown that hippocampal neuronal formation decreased in response to chronic stress (Gould et al., 1998). Suppression of hippocampal neurogenesis in response to chronic stress is suggested to be mediated by HPA-axis activation (Cameron and Gould, 1994) and that this mediation is one of the possible pathways for stress-related disorders like depression and other neuropsychiatric illnesses (Sapolsky, 2000). Considering HPA-axis mediated change, some researchers think there is a common pathway for depression, fibromyalgia, chronic fatigue syndrome, and burnout (Ehlert et al., 2001). Some of the emotional and physical symptoms of burnout may be related to an increase in HPA-axis activation in response to chronic job stress and increased suppression of hippocampal neurogenesis by glucocorticoids (McEwen, 2001). Nonetheless, present studies on the HPA-axis are far from proving there is an increase in glucocorticoids or a difference in HPA-axis functions in study and control groups.

On the other hand, some symptoms that are attributed to glucocorticoids may be related to proinflammatory cytokines. It is known that cytokines cause a syndrome known as 'illness behavior' (Kent et al., 1992). The symptoms of this syndrome, including anhedonia, anorexia, malaise, sleep disturbances, and cognitive function disorders, are common symptoms in various stress-related conditions (Raison and Miller, 2003). At the same time it is generally agreed that chronic stress may cause impairment in immune response and may increase the risk of inflammatory disorders (Kiecolt-Glaser et al., 2002). It may also be expected that in burnout, which is a condition related to chronic job stress, immune function may decrease. One study reported that burnout was related to an increase in the frequency of diseases like cold, flu-like syndrome, and gastroenteritis (Mohren et al., 2003).

In 2 studies that investigated the relationship between immune functions and burnout symptoms, a decrease in number and activity of lymphocytes was reported in participants that had severe burnout, although this was not found to be related to emotional exhaustion as a core symptom of burnout (Nakamura et al., 1999; Bargellini et al., 2000). A study that investigated the indicators of the immune system in burnout reported an increase in TNF- α (Grossi et al., 2003) and another study (the only study conducted with a clinically diagnosed patient group) reported an increase in IL-10 release in monocytes, but for TNF- α no difference between patients and controls was found (Mommersteeg et al., 2006d).

Other than stress there are several factors that affect hippocampal neurogenesis including physical activity, antidepressant medication, hypoglycemia, hypoxia, and neurotrophic factors (Warner-Schmidt and Duman, 2006). Neurotrophic factors either stimulate the reproduction of stem cells or mediate the reproduction process in the hippocampus while also having a regulatory function on the plasticity of neuronal networks (Huang and Reichardt, 2001). The relationship between BDNF and stress was evaluated both in animal studies and stress-related psychiatric disorders (Duman and Monteggia, 2006). Other studies reported that both serum and plasma BDNF levels of depressive patients are lower (Shimizu et al., 2003; Gonul et al., 2005; Lee et al., 2007), and that serum BDNF levels increase in response to antidepressant treatment (Gonul et al., 2005). On the other hand, it was shown that stress decreases hippocampal BDNF gene expression (Smith et al., 1995) and this decrease may be prevented by antidepressant treatment (Tsankova et al., 2006).

The use of antidepressants for stress-related disorders and burnout, suggests a relationship between a reduction in burnout symptoms and the effect of this treatment on the level of decrease in BDNF (Duman et al., 2000). Eriksson and Wallin (2004) suggested that hippocampal neurogenesis may be important in the neurobiology of burnout, and that a reduction in hippocampal neurogenesis and the subsequent disruption of brain plasticity in response to stress may have a role in burnout. They base their hypothesis on two findings: (1) The reduction of neuronal formation in the adult hippocampus in response to stress, which is mediated by the HPA-axis because the hippocampus is the primary region for the formation of feedback stimuli in glucocorticoid release; (2) The use of antidepressant medication in the treatment of patients diagnosed with burnout, the use of antidepressants in depression treatment, the finding that

antidepressants cause structural changes (volume change by triggering neurogenesis), and the finding that both depression and burnout symptoms overlap all point to the fact that these two conditions may be linked with HPA-axis dysregulation. In accordance with their hypothesis, they proposed that stress decreases neuronal formation through the HPA-axis and consequently hippocampal function and negative feedback mechanisms in glucocorticoid release might be impaired, resulting in inadequate coping with stress (Eriksson and Wallin, 2004).

On the other hand, symptoms like fatigue, malaise, somatic pain, and burning sensations in burnout have similar properties as fatigue, exhaustion, and decreased bodily energy in depression. In depression, the relationship between emotional symptoms and the serotonergic system, and the relationship between physical symptoms and the noradrenergic system are emphasized (Malhi et al., 2005). There are some published reports of decreased or increased serotonergic activity and increased serotonergic sensitivity in chronic fatigue syndrome (Cleare et al., 1995). Additionally, there are some findings concerning the noradrenergic system in burnout, although they are limited. In a case-control study in which SAM system function was investigated, mean heart rate was higher in the patient group than in healthy controls while resting, but both groups' blood pressure was similar (De Vente et al., 2003). In a study that compared clinically diagnosed burnout patients ($n = 39$) with controls ($n = 40$) in terms of sympathetic vagal efficacy, it was reported that sympathetic vagal efficacy patterns were different between the groups after long-term work overload. While the control group showed greater improvement after mental and performance-based tests, sympathetic suppression was observed in the burnout group after the tests (Zanstra et al., 2006).

A recent study reported that in burnout cases basal prolactin levels show distributions at higher or lower extreme values than those of the control group (Tops et al. 2007). In that study researchers administered 35 mg of cortisol and placebo to participants. It was established that in the burnout group and in those with higher attachment scores, cortisol treatment reduced prolactin levels. Researchers proposed that patients with higher prolactin levels also have decreased dopaminergic activity. After cortisol treatment the physical energy of these cases increased, while fatigue and high prolactin levels decreased. They proposed that the response to cortisol treatment was mediated by dopaminergic activity, especially via D2 receptors. On the other hand, the group

with lower prolactin levels did not respond to cortisol and had lower attachment scores, more severe anxiety, and negative mood. The researchers proposed that decreased serotonergic activity was responsible for lower prolactin levels and that there was an association between lower serotonergic activity, burnout, depression, and antidepressant treatment (Tops et al., 2007). There are some findings that support this association, as selective serotonin reuptake inhibitors were also shown to increase basal prolactin levels (Cowen and Sargent, 1997). On the other hand, another mediator responsible for lower prolactin levels may be reduced noradrenergic activity (Cowen and Sargent, 1997). Reboxetine, a selective noradrenalin reuptake inhibitor, is known to stimulate both prolactin and cortisol release (Schule et al., 2004). By taking these findings into account, Tops et al. (2007) proposed that there may be subgroups that have low serotonergic and low dopaminergic functions in burnout, and that the group with lower dopaminergic function may benefit from cortisol replacement therapy. Nonetheless, in a study in which serum growth hormone and prolactin levels were compared between healthy controls and burnouts, no difference between the groups was established (Moch et al., 2003).

DISCUSSION

The results of the studies we reviewed that investigated the relationship between burnout syndrome and HPA-axis function are inconsistent. In prior burnout studies, participants were selected from among relatively healthy individuals based on the scores of self-report burnout questionnaires and later they were not evaluated for burnout symptoms at the clinical level. Moreover, sample sizes were small and no healthy controls were used in most of the studies. In later years research designs were strengthened by using larger sample sizes, individuals with clinically diagnosed burnout syndrome, and measuring CAR, which better reflects HPA-axis function. Nonetheless, in most of the studies possible confounding factors (smoking, alcohol consumption, taking medication, gender) that may have affected HPA-axis function were not controlled.

When taken together, among all the studies that investigated HPA-axis function and burnout, 3 support an increase in HPA-axis functions in burnout (Melamed et al., 1999; Grossi et al., 2005; Söderstrom et al., 2006), 5 support a decrease in HPA-axis functions (Pruessner et al., 1999, Morgan et al., 2002; Moch et al., 2003, Mommersteeg et al., 2006c; Sonnenschein et al., 2007), and 11 did not support a significant relationship (see

Table Ia and b). As a result of our literature search, among all of the articles that investigated the relationship between HPA-axis functions and burnout, we consider 3 of them (Momersteeg et al., 2006a, Langelaan et al., 2006; Sonnenschein et al., 2007) to be superior in terms of both sample size and research design. In the first 2 studies, HPA-axis functions in burnout were not found to be different than in healthy controls. In the other study, when burnout symptoms were assessed with momentarily measurements, HPA-axis functions in those diagnosed with burnout and in healthy participants were different (Sonnenschein et al., 2007). Although this finding provides a new insight into the field, we think that it must be repeated. On the other hand, none of the studies that evaluated HPA-axis function investigated corticotrophin-releasing hormone (CRH), which regulates HPA-axis function at a higher order; however, a decrease in the release of higher order regulators may lead to a differentiation of cortisol functions. This condition was shown in stress-related disorders with symptoms similar to those of burnout, like atypical depression (Geraciotti et al., 1997), fibromyalgia (Torpy et al., 2000), and chronic fatigue syndrome (Scott et al., 1998). Consequently, when the relationship between burnout and HPA-axis function are evaluated, current study findings may be assumed to not demonstrate a significant relationship.

Conversely, it would not be adequate to investigate only HPA-axis function in burnout. Four studies investigated burnout and inflammatory response, and the findings were compared with controls in only one of them. Although current research findings point to decreased immune system function in burnout, it is not possible to reach conclusive results due to the low number of controlled studies. On the other hand, 3 studies investigated burnout and its relationship to the serotonergic-noradrenergic-dopaminergic system; but only 1 investigated the noradrenergic system, 1 investigated only sympathetic vagal activity, and 1 investigated only the

dopaminergic-serotonergic system. Although the findings showed differences in the serotonergic-noradrenergic-dopaminergic system between those with burnout and controls, the findings lack generalizability due to the limited number of studies in this field. Consequently, based on current knowledge one could argue for a primary role of functional impairment in the occurrence of burnout symptoms, which includes HPA-axis function, the immune system, or the serotonergic-adrenergic-dopaminergic system.

In burnout, emotional and physical symptoms occur in response to chronic stress and further progress in relevant literature is required to explore these processes. Firstly, individual characteristics in response to stress should be evaluated. Specifically, scales that assess personality dimensions based on the underlying biology may be more informative. Although some studies have investigated this relationship in depressive patients (Cloninger et al., 1993), it has not been investigated in patients with burnout syndrome. Secondly, neuronal development and neurotrophins are candidates for a more direct contribution to the neurobiology of burnout. Thirdly, more studies of the monoaminergic system's role in burnout that also play a role in depression need to be performed. Along with this, systematic work concerning the treatment of burnout would provide additional information. Fourthly, the inflammatory cytokines and CRH, which have been studied in disorders like chronic fatigue syndrome and fibromyalgia should be studied in a case-control design in burnout. Providing that burnout is prominent in branches of industry that provide human services and that cognitive judgment (decision making, retrospective analysis) has an important role in the provision of these services, the impact of psychosocial stressors on the brain and the impact of moral cognition (Moll et al. 2005) on human relations should be examined as well.

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