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Review Article

Limbic brain structures and burnout—A systematic review

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ABSTRACT

More profound understanding of the relationship between the burnout and the limbic system function can provide better insight into brain structures associated with the burnout syndrome. The objective of this review is to explore all evidence of limbic brain structures associated with the burnout syndrome. In total, 13 studies were selected. Four of them applied the neuroimaging technology to investigate the sizes/volumes of the limbic brain structures of burnout patients. Six other studies were to investigate the hypothalamus-pituitary-adrenal (HPA) axis of burnout patients. Based on the results of the studies on the HPA-axis and neuroimaging of the limbic brain structures, one can see great impact of the chronic occupational stress on the limbic structures in terms of HPA dysregulation, a decrease of BDNF, impaired neurogenesis and limbic structures atrophy. It can be concluded that chronic stress inhibits the feedback control pathway in the HPA axis, causes the decrease of brain-derived neurotrophic factor (BDNF), then impaired neurogenesis and eventually neuron atrophy.

Contents

1. Introduction

The term ‘limbic system’ was introduced by Paul Broca. The cortical areas to form a ring around the brain stem, called later the ‘limbic lobe’, consisted primarily of the cingulate cortex, the temporal lobe cortex and the hippocampus [1]. Further studies discovered that our emotions, including our consciousness, are

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largely connected with these particular brain areas. The 'Papez circuit' included the hippocampus, fornix, mammillary bodies, anterior nucleus of the thalamus, anterior cingulate gyrus but not the amygdala [2]. Today, the limbic system structures include the hypothalamus, hippocampus, amygdala, and the nuclei septal. These structures are largely interconnected and have their own individual overlapping functions. These structures are responsible for our memory, emotions, emotional learning, and behavior, as well as motivation and reward [3].

Burnout is defined as an excessive stress reaction to the occupational or professional environment, composed of three major dimensions; emotional exhaustion, depersonalization and low personal accomplishment [4]. Burnout patients also reported having typical symptoms such as memory and concentration problems, insomnia, diffuse aches, physical fatigue, irritability, anxiety and a feeling of being emotionally drained. These symptoms are often known as subjective health complaints as up until now, no objective signs of illness have been found for these complaints. The burnout symptoms are symptom clusters comparable with characteristics of chronic fatigue syndrome (CFS) and post-traumatic stress disorder (PTSD) [5–7]. However, the burnout is preceded by a prolonged work-related stress. Work-related stress is defined as an occupational stress wherein emotional factors predominate. This is an important difference as work-related stress and burnout are usually assessed using different tools.

The attention should be paid to the key issues reflecting correlations between the burnout, work-related stress and biological parameters:

- the link between the burnout and work-related stress,
- the biological aspects of burnout, more specifically, the role of limbic system and HPA-axis in the development of burnout,
- the link between the burnout and CFS and PTSD.

Concerning stress, there are two major systems mediating most components of the stress response [8,9]. The first is the limbic-hypothalamic-pituitary-adrenal (LHPA) system which stimulates the adrenal cortex to release glucocorticoids such as cortisol into the blood. The second is the sympathico-adrenomedullary (SAM) system whose activation increases our heart rate and blood pressure by releasing catecholamines such as epinephrine and norepinephrine into the bloodstream.

Ten years ago, Langelaan et al. reported findings from a study on the burnout syndrome and level the salivary cortisol to determine the cortisol awakening response (CAR) and it kept many scientists thinking and talking about not because the authors provided a spectacular evidence but because they did not find any differences between the burnout patients and the healthy control [10]. Since then many studies have been carried out focusing on the aspect of the limbic system, especially regarding the hypothalamus-pituitary-adrenal (HPA) axis and the burnout in order to discover the relation link between them. Yet scientists are still facing many inconsistent and nonsignificant findings – the results from different studies were mixed but researchers were not able to provide any significant evidence to prove a relationship between the limbic system and the burnout syndrome. Soon after the Langelaan's [10] publication, Sonnentag [11] wrote an article to address this problem in discussion –why scientists could not find significant differences in the HPA axis and the burnout for several reasons: firstly, the complexity of the processes of the HPA axis and the associated problems of measuring its functioning. Secondly, due to the issues associated with the samples included in the analyses (the problem of defining cut off scores for differentiating between the burnt-out and healthy persons, and the small sample sizes of subjects). The third reason is related to the participants' work and life situation, and the last reason may come from the processes associated with hypocortisolism. Besides pointing out the reasons why scientists failed to find differences between the burnout and the healthy persons, the authors also provided some suggestions how to improve the methodology of burnout research.

In the past 10 years, more studies were carried out in the same area with the same focus. Despite the aforementioned attempts, it seems we have not been able to overcome those obstacles and find any significant differences in the relationship of the burnout and the limbic system structures.

The objective of this review is to explore the evidence of limbic brain structures associated with the burnout and work-related stress. This enables more profound understanding of the interrelationship between the burnout, work-related stress, brain structures, and their activation.

2. Methods

This systematic review is based on the published peer-reviewed articles. For the purpose of this systematic review, the literature search was made in two major databases (PubMed and Medline Complete) with the following keywords: 'limbic system'; 'hypothalamus'; 'hippocampus'; 'amygdala'; 'HPA'; 'burnout' and 'work-related stress'. Focus on only the studies observing burnout and limbic structures would be limited. The search period covered from 2006 to 2016 and was limited to the English language. The authors used the following inclusion and exclusion criteria:

- the inclusion criteria: the original papers published in journals and conference proceedings, peer-reviewed, the language of publication: English,
- the exclusion criteria: reviews, case studies, editorials, letters, book chapters, etc., non peer-reviewed, the language of publication: other.

The studies were evaluated by using the own quality assessment tool providing an added value and improving the quality of the review. The evaluation system:

- study design (including sampling): 0–3 pts.,
- research tools (including the use of standardized tools): 0–3 pts.,
- analysis (including used statistical and/or computational methods): 0–3 pts.

The total score: 0–9 points. The studies with higher scores were estimated to be more valuable.

3. Results

The preliminary electronic literature search resulted in the identification of total 40 studies: 34 from PubMed and 6 from Medline. All the selected studies applied Maslach Burnout Inventory (MBI) as the burnout measures, and after satisfying the inclusion criteria for this review, only total 10 studies were selected. From among of those studies, four (3 using functional magnetic resonance imaging (fMRI) and 1 using positron emission tomography (PET)) employed neuroimaging technology to investigate the differences of sizes/volumes of the limbic brain structures in the burnout patients and healthy control. Six other studies were to investigate the HPA-axis of burnout patients (Fig. 1). The detailed information of the studies (including their score) is presented in Table 1. The studies included in the analyses are heterogeneous and grouped in Table 1: firstly, some studies focus on the burnout and the others on the work-related stress.

Three of our studies [12–14] covered the cortisol studies described earlier by Danhof-Pont et al. Danhof-Pont et al. found no

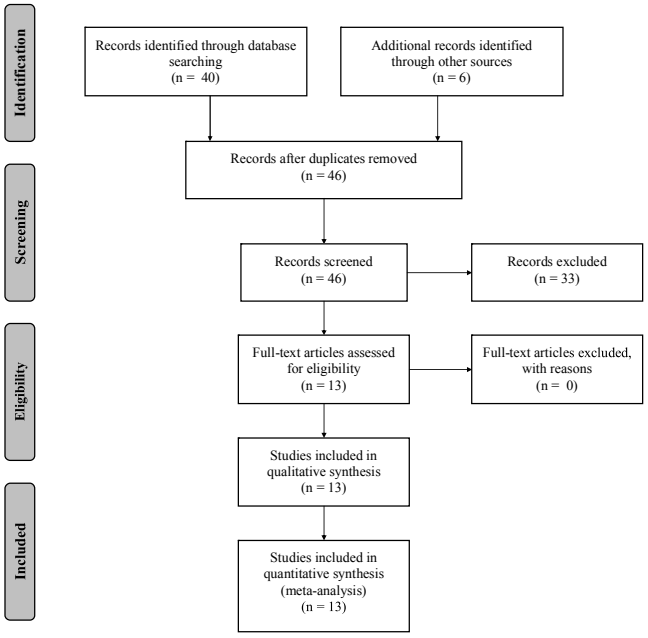

Fig. 1. PRISMA flow diagram.

potential biomarkers for the burnout due to the incomparability of studies. They emphasized the need for a wider dimensional and longitudinal approach in future studies [15].

3.1. Hypothalamus-pituitary-adrenal axis and burnout studies

Langelaan et al. [10] examined the differences in the functioning of the hypothalamus-pituitary-adrenal (HPA) axis in 29 burnouts, 33 work-engaged, and 26 healthy reference managers in a large Dutch telecommunication company. The burnout and work-engaged subjects were identified with Maslach Burnout Inventory and the Utrecht Work Engagement Scale respectively. The salivary cortisol was sampled on the three consecutive workdays and one non-workday to determine the cortisol awakening response. Salivary dehydroepiandrosterone-sulfate (DHEAS), a cortisol-counterbalancing product of the HPA axis, was measured on these days 1 h after the managers woke up. The dexamethasone suppression test was used to investigate the feedback sensitivity of the HPA axis. The results indicated that the morning cortisol levels were higher on the workdays than on the non-workday but this effect was observed in all groups. The burnout, work-engaged and reference groups showed little or no significant differences in the cortisol and DHEAS levels, the slope of the cortisol awakening response and the cortisol: DHEAS ratio. The authors concluded the burnout and work-engaged subjects only differ marginally in the HPA-axis functioning; no significant differences are found between three groups.

Sonnenschien et al. [16] studied the association between the energy depletion in the clinical burnout and the indicators of HPA-axis functioning in a reliable and in-depth way through the electronic diary method; experience sampling method (ESM) symptom assessments. 42 clinically burnout patients completed the exhaustion subscale of the Maslach burnout inventory and kept an electronic diary for 2 weeks to assess the momentary exhaustion and daily recovery through sleep. On 3 consecutive weekdays within the diary period, saliva was sampled to determine the CAR, level of dehydroepiandrosterone-sulphate (DHEAS) on the first 2 weekdays, and to conduct the dexamethasone suppression test (DST) on the third weekday. The results showed a significant relationship between the endocrine values and general symptoms severity as assessed with the diary. The authors found the burnout subjects with the higher general severity of exhaustion and poor recovery through sleep in the diary displayed lower cortisol levels, higher DHEAS levels, and consequently, a smaller cortisol/DHEAS ratio as well as a stronger suppression of cortisol after DST. These findings are the signs of hypoactive HPA-axis and this added another strong support to the hypothesis that severity of burnout symptoms is associated with HPA-axis functioning.

Sertoz et al. [17] investigated the role of BDNF and HPA axes in the neurobiology of burnout. In this study, 37 clinically diagnosed burnout participants were compared with 35 healthy controls in terms of the brain-derived neurotrophic factor (BDNF), HPA axis, burnout symptoms, depression, anxiety and psychosomatic complaints. Basal serum cortisol, sBDNF, and cortisol level after 1 mg of DST were sampled. The authors found no significant differences in terms of HPA axis functions but lowered sBDNF level in the burnout group (88.66 ± 18.15 pg/ml) was observed the healthy controls (102.18 ± 20.92 pg/ml) and the difference was statistically significant ($p = 0.005$). The logistic Regression Analysis revealed that emotional exhaustion ($p = 0.05$), depersonalization ($p = 0.005$) and depression ($p = 0.025$) were significantly associated with the burnout. The sBDNF levels correlated negatively with the emotional exhaustion ($r = -0.268$, $p = 0.026$), depersonalization ($r = -0.333$, $p = 0.005$) and correlated positively with the competence ($r = 0.293$, $p = 0.015$) sub-scales of burnout inventory. However, there were no significant relationships between the cortisol levels and the sBDNF levels ($r = 0.80$, $p = 0.51$), depression, anxiety, psychosomatic complaints and burnout inventory. The authors concluded that low BDNF might contribute to the neurobiology of burnout syndrome and it seems to be associated with the burnout symptoms including altered mood and cognitive functions.

Österberg et al. [18] studied the cognitive performance in patients with the burnout, as regards to the flexibility of the hypothalamic-pituitary-adrenal (HPA) axis. 65 burnout patients and 65 healthy controls were given six neuropsychological tests and self-rating scale for cognitive problems. The diurnal salivary cortisol was measured in the burnout and 174 external reference group, including a dexamethasone suppression test (DST) in the burnout. Compared with the referents, the burnout group underperformed in a cognitive speed test (Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol), but not in any other test of sustained attention, episodic memory, or vocabulary. The burnout cases had considerably more subjective cognitive problems, ratings were unrelated to the test performance. Compared with the referent, burnout cases had similar morning salivary cortisol levels and similar awakening response, but lower evening cortisol. Among the burnout cases, lower diurnal cortisol variability was related to slower performance in several tests. The DST response showed no consistent relationship with any cognitive parameter. Hence, despite considerable subjective cognitive problems, the burnout group showed only a partial, mild deviation in cognitive performance. The authors found no significant differences between the burnout subjects and the reference group.

As a useful compartmental study – Wolfram et al. [20] examined responses using two pharmacological stimulation tests in 53 healthy teachers (31 females, 22 males; average age: 49.3 years; age range: 30–64 years): 1, the low-dose adrenocorticotrophic hormone (ACTH1-24, Synacthen) test was used to assess adrenal cortex sensitivity and 2, the combined dexamethasone −corticotropin-releasing hormone (DEX-CRH) test to examine pituitary and adrenal cortex reactivity. Blood saliva samples were collected at −1, +15, +30, +45, +60, +90, + 120 min. The emotional exhaustion (EE), the core dimension of the burnout, was measured

Table 1
Studies included in the review.

Study (Year) Score [pts.]	Main aim(s)	Particpants	Instruments/tools used	Main results
Langelaan et al. [10] Score: 7	Is there a relationship in the functioning of the hypothalamic-pituitary-adrenal (HPA) in patients with burnout and healthy?	Burnout Participants: burned-out (n = 29) work-engaged (n = 33) healthy (n = 26)	Maslach Burnout Inventory-General Survey Utrecht Work Engagement Scale	Burned-out managers only differ marginally in HPA-axis functioning.
Sonnenschien et al. [16] Score: 5	Is there a relationship between HPA-axis functioning and burnout symptoms?	Clinically burned-out participants (n = 42)	Exhaustion subscale of the Maslach Burnout Inventory	Severity of burnout symptoms is associated with HPA-axis functioning.
Onen Sertoz et al. [17] Score: 7	To investigate the role of BDNF and HPA axis in the neurobiology of burnout.	Participants with clinically diagnosed burnout (n = 37) Healthy controls (n = 35)	Maslach Burnout Inventory (MBI)	Low BDNF can contribute to the neurobiology of burnout syndrome and it seems to be associated with burnout symptoms (altered mood, cognitive functions).
Österberg et al. [18] Score: 7	If level of diurnal salivary cortisol is related to cognitive function in patients with burnout?	Clinical cases with work stress-induced burnout (n = 65) Healthy patients (n = 65) External reference group (n = 174)	six neuropsychological tests self-rating scale for cognitive problems	Cortisol level varies across groups.
Oosterholt et al. [19] Score: 7	Relationship between burnout and cortisol levels	Burnout patient group (n = 32), Non-clinical burnout group (n = 29), Healthy control group (n = 30)	Maslach Burnout Inventory (MBI)	Lowered cortisol in both clinical and non-clinical burnout.
Mommersteeg et al. [12] Score: 7	Endocrine and ex vivo immune function of severe cases of burnout.	Patients with burnout of different institutions: - study group (n = 56) - control group (n = 38), female	MBI (Dutch version) DSM-IV	Higher DHEAS levels in burnout group
Mommersteeg et al. [13] Score: 6	Changes of HPA-axis hormone cortisol after awakening and during the day.	Burnout patients: - study group (n = 22) - control group (n = 21)	MBI (Dutch version)	Lowered cortisol after awakening in burnout group
Tops et al. [14] Score: 5	Role of low cortisol, dopamine and/or serotonin in burnout and detachment.	Burnout patients premenopausal, less than 4 weeks of absence from work: - study group (n = 9), female - control group (n = 9), female	MBI (Dutch version)	High prolactin burnout subjects tended to show cortisol-induced decreased prolactin.
Jovanovic et al. [5] Score: 6	Stress activates the limbic circuits, causing specific changes of the 5-HT(1A) receptor.	Work-related stress Participants: chronically stressed (n = 16), non-stressed (n = 16)	battery of neuropsychological tests	Impaired top-down regulation of stress stimuli identifies potential targets for early treatment.
Blix et al. [6] Score: 7	Comparative MRI studies of cerebral gray matter (GM) and white matter (WM) volumes between patients with chronic occupation-related stress and healthy controls.	Participants with diagnosed severe stress and F43, ICD-10 (n = 30) Healthy reference group (n = 63)	Maslach Stress-Burnout Inventory – General Survey (MBI-GS)	Partial result, need for further research.
Savic et al. [7] Score: 7	Whether and how chronic occupational stress is associated with cerebral changes.	Subjects reporting symptoms of chronic occupational stress (n = 40) Controls (n = 40)	Maslach Burnout Inventory (MBI)	Occupational stress is associated with cortical thinning and selective changes of subcortical volumes.
Wolfram et al. [20] Score: 4	If altered hypothalamus-pituitary-adrenal (HPA) axis regulation is a possible biological pathway underlying the link between stress and disease?	Chronically work-stressed teachers (n = 53) .	Maslach Burnout Inventory (MBI)	Altered HPA axis regulation in chronically work-stressed teachers, with differential patterns of hyper- and hyporeactivity depending on individual stress condition and the tested functional level of the HPA axis.

Table 1 (*Continued*)

Study (Year) Score [pts.]	Main aim(s)	Particpants	Instruments/tools used	Main results
Golkar et al. [21]	Whether chronic occupational stress can be associated with a functional uncoupling of the limbic networks and an impaired modulation of emotional stress	Patients with chronic occupational stress (n = 70)	Maslach Stress-Burnout Inventory – General Survey (MBI-GS)	In subjects suffering from chronic occupational stress, the functional couplings within the emotion- and stress-processing limbic networks is altered. I is associated with reduced ability to down-regulate the response to emotional stress.
Score: 7		healthy control group (n = 40)		

with Maslach Burnout Inventory, Overcommitment (OC) was assessed according to the Siegrist's effort −reward-imbalance model. The writers found a significant association between the EE and higher plasma cortisol profiles after Synacthen (p = 0.045). By contrast, OC was significantly associated with the attenuated ACTH (p = 0.045), plasma cortisol (p = 0.005) and salivary cortisol (p = 0.023) concentrations following DEX-CRH. The results of the study support the notion altered HPA-axis regulation in chronically work-stressed teachers, with differential patterns of hyperactivity and hyporeactivity depending on the individual stress condition and the tested functional level of the HPA axis.

Oosterholt et al. [19] carried out a study on the relationship between the burnout and cortisol levels by adopting a newer design to overcome important limitations of earlier studies. Their main objective of the study was to improve the understanding of biological underpinnings of the burnout and to develop the knowledge about the relationship between the burnout and cortisol. They compared the burnout symptoms, physical and psychological complaints, and cortisol levels in three groups; the clinical burnout patient group (32 subjects), the non-clinical burnout group (29 subjects) and the healthy controls (30 subjects). The salivary cortisol was collected six times a day during two consecutive non-workdays in order to examine a broad range of cortisol indices including different measures of the CAR and several day-curve measures. The results showed the clinical burnout group reported more burnout symptoms as well as physical and psychological complaints than the non-clinical burnout group which in turn, reported more burnout symptoms as well as physical and psychological complaints than the healthy control group. The authors found that until 30 min after awakening, the CAR of both the clinical and non-clinical burnout groups was lower compared with the healthy control one. Furthermore, there was some evidence that the decline of cortisol during the day was smaller in the non-clinical burnout group than in the healthy control group.

3.2. Neuroimaging on burnout studies

Jovanovic et al. [5] carried out a PET study on 16 chronically stressed subjects who had the average stress-burnout score >3.0 in the Maslach Stress-Burnout Inventory-General Survey (MBI-GS) and 16 non-stressed subjects. The limbic function was tested by measuring the cerebral blood flow during rest and when using an odor activation paradigm. The 5-HT1A receptor binding potential (BP) was investigated by using PET images acquired with an ECAT exact HR 47 scanner and with bolus injection. Radioactivity in the brain was measured in a series of 15 consecutive frames of 63 min, of which the nine first frames were acquired over 15 min. The stressed subjects showed a functional disconnection between the amygdala and the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) and an impaired odor activation of the ACC. They also displayed a reduced 5-HT1A receptor BP in the ACC, the insular-cortex, and the hippocampus. Their performance in attention, odor discrimination, and semantic memory tasks was impaired and correlated with the BP-values in the respective region. The degree of reported stress was inversely correlated with the activation of ACC, and the 5-HT1A receptor BP in amygdala and hippocampus. According to the findings from this study, enduring everyday psychosocial stress seems to be associated with the limbic reduction of 5-HT1A receptor binding and functional disintegration of ACC/mPFC. These changes support the notion of an impaired top-down regulation of stress stimuli and identify potential targets for early treatment.

Blix et al. [6] carried out comparative MRI studies of cerebral gray matter (GM) and white matter (WM) volumes between the patients with chronic occupation-related stress and the healthy controls. The study also included an analysis of the structural volumes of the hippocampus, caudate and putamen but not amygdala, the structures known to be susceptible to neurotoxic changes. 30 (23 females and 7 males) right-handed, non-smoking patients, who had been diagnosed as having had a 'reaction to severe stress and an adjustment disorder' according to the International Classification of Disease (ICD-10), were recruited. The subjects were also required to have an average stress-burnout score >3.0 on the Maslach Stress-Burnout Inventory-General Survey (MBI-GS). While 68 healthy, right-handed, non-smoking volunteers (53 females and 15 males) with no history of chronic stress or any heredity mental disorders were used as the control group. The results of the study showed that the burnout (chronic occupation stress) subjects exhibited a significant reduction in the GM volumes of the ACC and the dorsolateral prefrontal cortex. Furthermore, their caudate and putamen volumes were reduced and those correlated inversely to the degree of perceived stress. The results gave a clear indication of a morphological involvement of the frontostriatal circuits in the stress subjects. The findings of morphological changes, particularly GM atrophy in these regions confirm the previous conclusion that the patients who report classic symptoms of occupational stress have a medical condition that requires careful and precise diagnosis and treatment.

Savic et al. [7] carried out a study to investigate structural changes in the brain in relation to the occupational stress. The study compared the cortical thickness and the subcortical volumes in 40 burnout patients and 40 controls. The degree of stress was measured with Maslach Burnout Inventory (MBI). In the burnout patients, there was a significant thinning of the medial frontal cortex. When investigating the correlation between the age and the cortical thickness, the thinning effect of age was more pronounced in the burnout patients in the frontal cortex. Furthermore, the results also showed that their amygdala volumes were bilaterally increased ($P = 0.020$ and $P = 0.003$), whereas their caudate volumes were reduced ($P = 0.040$) and accompanied by impaired fine motor function. The burnout patients correlated positively with the amygdala volumes ($r = 0.44$, $P = 0.04$; $r = 0.43$, $P = 0.04$). The study showed the burnout was found to be associated with cortical thinning as well as with selective changes of subcortical volumes, with behavioral correlates. The findings of

this study support the hypothesis that stress-related excitotoxicity might be an underlying mechanism and that the described condition is a stress-related illness.

Golkar et al. [21] carried out a study to test two specific hypotheses: (1) That subjects suffering from occupational stress have an impaired ability to modulate stressful emotions; and (2) That subjects show altered amygdala functional connectivity. 40 subjects with the occupational burnout with and having the average stress-burnout score of $\geq$3.0 on the Maslach Burnout Inventory, along with 70 healthy controls were investigated using the cognitive emotion regulation task as well as the resting state fMRI. The participants' ability to up-regulate, down-regulate, and maintain emotions was evaluated by recording their acoustic startle response while viewing neutral and negative loaded images. Functional connectivity was calculated from the amygdala seed regions; the seed region analysis is based on calculating the cross-correlation coefficients of the time series in the particular seed region of interest (ROI) will all other voxels in the brain which reveals the strength of the functional connectivity with respect to this brain region. The results showed that the burnout subjects were less capable of down-regulating negative emotions but had normal acoustic responses when asked to up-regulate or maintain them and when no regulation was required. The functional connectivity was significantly weaker in the burnout group as was the amygdala connectivity with the dorsolateral prefrontal cortex (DLPFC) and the motor cortex whereas connectivity from the amygdala to the cerebellum and the insular cortex was stronger. In the burnout subjects, the functional couplings within the emotion- and stress-processing limbic networks seem to be altered and associated with reduced ability to down-regulate the response to emotional stress, providing a biological substrate for a further facilitation of the stress condition.

4. Discussion

It is advisory to be aware that there is a clear distinction between the terms "burnout" and "work-related stress" as far as Instruments/tools are used. The aforementioned fact constitutes the additional basis for discussion which should be concluded concerning work-related stress and what is specific for the studies observing burnout.

This review indicates a significant relationship linked directly between the limbic system and the burnout syndrome. Based on the results from the studies on the HPA-axis and neuroimaging ones on the limbic brain structures, it can be seen that the chronic occupational stress has a great impact on the limbic structures, in terms of HPA dysregulation, BDNF decrease, impair neurogenesis, limbic structures atrophy.

The results from 4 studies [16–19] show that the burnout subjects hav an abnormal activity of HPA; either hypo or hypercortisolism depends on the stage of the HPA dysregulation. The results showed that the HPA dysregulation in the burnout subjects is caused by the chronic stress to the limbic system, especially to the amygdala and the hippocampus. The amygdala and the hippocampus normally inhibit hypothalamic activity but stress blocks this feedback pathway and leads to stimulation of hypothalamic releasing hormone such as the 'stress peptide' corticotropin-releasing hormone (CRH). Increased CRH promotes pituitary ACTH release that itself stimulates the release of glucocorticoids from the adrenal cortex. By influencing the gene transcription and altering the electrical activity of excitable cells, these steroid hormones are potent modulators of cell physiology and behavior [22,23]. The action is not restricted to the peripheral organs but due to their high lipophilicity, they cross the blood-brain barrier and have an impact on many brain structures, especially the limbic system that expresses high numbers of corticosteroid receptors [24].

In the study carried out by Sertoz [17], the authors found a significantly lower level of BDNF in the burnout group. BDNF sustains the viability of brain neurons but under stress, the gene for BDNF can be repressed. Stress can lower 5HT levels and largely increase, then chronically deplete both norepinephrine and dopamine. These monoamine neurotransmitter changes together with deficient amounts of BDNF can lead to atrophy and possible apoptosis of vulnerable neurons in the hippocampus and other brain structures such as prefrontal cortex [19]. Neurons from the hippocampus and the amygdala normally suppress the HPA axis so if stress causes hippocampus and amygdala atrophy with a loss of their inhibitory input to the hypothalamus, this could lead to overactivity of the HPA axis.

Several studies investigated the effects of stress and glucocorticoids on the hippocampal function in laboratory animals and in humans [25–27]. It suggests that glucocorticoids cause a hippocampal neuronal loss [28] and later studies reformulated the 'glucocorticoid cascade concept of stress and hippocampal damage'. Loss of CA3 (cornu amonis) neurons under extreme and/or prolonged stress or extremely high concentrations of glucocorticoids can possibly be mediated through apoptosis.

The findings from the neuroimaging studies [5,6,7,21] indicate a relationship between the disturbances of the activity of the LHPA system with both structural alterations and volumetric reduction of the hippocampal and amygdala formation. The plus several cross-sectional studies demonstrated that both hyperactivity of the LHPA system with elevated levels of circulating cortisol and hypoactivity of the low glucocorticoid plasma levels are accompanied by hippocampal atrophy [28–32]. The hippocampus atrophy was also shown to be reversible in the patients with Cushing's disease upon normalization of glucocorticoid levels [33]. Fortunately, this reduction in volumes and sizes of limbic structures is reversible. Papers showed that treatment with antidepressant and pharmacological blockage of the corticosteroid stress response prevented the stress-induced atrophy [34,35].

This review leads us to the hypothesis about the pathophysiology of burnout syndrome, and eventually, a new light can be shed on the development of a new set of criteria to diagnose the burnout syndrome.

The complex analysis includes not only correlation analysis and clinical data interpretation, but also such complicated measurements as structural volumetry and voxel-based morphometry. Several methodological limitations need for further comments:

- a small number of neuroimaging and BDNF studies related to burnout and work-related stress,
- a small sample, partially limited by homogenous groups requirement,
- in the studies in which the subjects with burnout are compared with only healthy controls, it is impossible to know the specificity of the differences found between the two groups,
- different approaches chosen in the neuroimaging studies,
- undetermined correlation (e.g. the relation between the stress duration and morphological brain changes),
- unstandardized or unsystematized (neuro)psychological data.

The aforementioned limitations can be overcome owing to the combined methodology and careful recruitment of both the study and control groups.

The main directions for further studies are larger series and consecutive investigations before and after treatment coupled with parallel mapping of cognitive and motor functions. Moreover, the key issue constitutes the identification of clinical relevance for the burnout and work-related stress biomarkers and

standardization of assessment procedures for everyday clinical practice purposes despite possible great intra-individual and inter-individual varieties.

The limbic system and burnout are related in many ways. The burnout and work-related stresses are not homogeneous entities. The overview of the current concepts and research is presented. An interesting and not fully explained question is whether the burnout presence is related to the quicker development of musculoskeletal disorders, even in such 'static' professions as computer scientists or clerks. On the other hand, the problem is how physical exercises can reduce the aforementioned risk? The issues concerning the burnout risk factors and prevention strategies are still open. The summarized available literature does not provide the ultimate answer – there is need to carry on research and discuss its potential impact on clinical practice.

5. Conclusions

To sum up it can be concluded that according to the evidence-based medicine paradigm there is too strong concern about significant relationship linked directly between the limbic system and the burnout syndrome. For the time being no ultimate relationship between any of these biomarkers (including HP-axis markers) and burnout is found. The findings of the review indicate that burnout induces changes in the neuroendocrine pathways especially in the HPA axis and alterations in size and volume of brain structures and morphology of neurons. This takes place in limbic brain structures affected by the stress-activated system. Chronic stress inhibits the feedback control pathway in the HPA axis, can decrease BDNF, then impair neurogenesis and eventually leads to neuron atrophy.

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Conflict of interests

The authors declare no conflict of interests.

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