Clinical Psychology & Psychotherapy

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Journal:	*Clinical Psychology & Psychotherapy*
Manuscript ID	CPP-1929.R5
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	n/a
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Keywords:	Burnout, Heart rate variability (HRV), Brain-derived neurotrophic factor (BDNF), Therapy evaluation using biomarkers, Stress-related mental disorder

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Abstract

The increasing prevalence of stress-related disorders such as burnout urges the need for specialized treatment approaches. Programs combining psychotherapy and regenerative interventions emerge to be the most successful. However, evaluated therapy programs are scarce and usually involve subjective symptom quantification without consideration of physiologic parameters. The aim of the present exploratory, single-group study was the multimodal investigation of the effectiveness of a specialized holistic therapy program by assessing symptoms and biological markers of chronic stress. 71 in-patients (39m/32w; age 46.8 ± 9.9 years) of a specialized burnout ward with the additional diagnosis of burnout (Z73.0) in conjunction with a main diagnosis of depressive disorder (F32 or F33) according to ICD-10 were included in the study. In addition to symptomatology, the stress-responsive biomarkers heart rate variability (HRV) and serum brain-derived neurotrophic factor (BDNF) were measured in patients at admittance to and discharge from the burnout ward applying a six-week specialized treatment program. At discharge patients showed a significant reduction of symptom burden and a significant increase in serum BDNF, while HRV remained unchanged. The findings implicate that the therapy program may have beneficial effects on symptomatology and neuroplasticity of patients with burnout. As therapy was often supplemented by psychopharmacological treatment, a relevant influence of antidepressant medication especially on BDNF has to be considered.

Key Practitioner Message

- A therapeutic program specifically designed for treatment of burnout is introduced and its effectiveness explored in a pre-post single-group study involving patients with severe burnout and concomitant depressive disorder.
- In addition to the monitoring of chronic stress-associated psychological symptoms by questionnaires, the impact of therapy was also assessed using biomarkers of stress, namely brain-derived neurotrophic factor (BDNF) and heart rate variability (HRV), which deliver a more objective insight.
- The therapy program combining psychotherapy, physical exercise, regenerative interventions and, depending on the indication, psychopharmacological treatment seems to lead to symptomatic relief as well as an increase in BDNF in burnout patients

Keywords

- Stress-related mental disorder
- Burnout
- Heart rate variability (HRV)
- Brain-derived neurotrophic factor (BDNF)
- Exploratory therapy evaluation using biomarkers

Introduction

Burnout is thought to be an unspecific maladaptive reaction to long-term stress and has an increasing impact on our society, work environment, health care system and research. To date burnout is not incorporated as a diagnosis in the classification systems DSM-IV and ICD-10 , in the latter, however, it is handled as a Z-diagnosis which is a “factor influencing health status and contact with health services” accompanying main diagnoses of depressive, anxiety or adjustment disorder. There are several descriptions of burnout, one of which is the widely used definition by

Maslach and colleagues describes three symptoms as the core dimensions of burnout, namely exhaustion, depersonalization and reduced professional efficacy, which are a prolonged reaction to chronic interpersonal and emotional stress at work (Maslach & Goldberg, 1998; Maslach et al., 2001). In another concept, burnout has been described as a process of increasing exhaustion, which is paralleled by decreasing mental and physical efficiency, caused by chronic stressors perceived as not manageable in the context of performance (Ballweg et al., 2013). In this connection, performance is associated with highly demanding and exhausting situations at work or in social relationships. It is subject of inexhaustible discussion and research if burnout and major depression are identical, overlapping or different concepts (Ahola et al., 2005; Bianchi et al., 2015; Orosz et al., 2016). Burnout can be regarded as a phase in the development of depression. It has been suggested that the probability of having a depressive disorder rises with the level of burnout. Especially severe burnout seems to coincide often with major depressive disorder (Ahola et al. 2005). However, patients with severe burnout do not necessarily fulfill the criteria of depressive disorder, which leads to the conclusion that burnout and depression are related but not identical. There is broadening consensus that burnout needs specialized assessment and therapy concepts for its treatment (Ahola et al., 2005; Kakiashvili et al., 2013). Indeed, many forms of clinical burnout therapies have arisen (Meyer et al., 2016; Schwarzkopf et al., 2016), which focus on personal, stress management or coping skills and on regeneration rather than on medication, which is essential in the treatment of major depression in clinical practice. A systematic literature review found cognitive–behavioral therapy (CBT) to be reliably effective in the treatment of burnout (Korczak et al., 2012). Moreover, a qualitative assessment interviewing remitted clinical burnout patients revealed that besides individual psychotherapy sessions, body therapeutic interventions (both relaxation and activation) as well as

complementary medical approaches were regarded as the key factors to remission (Elkuch et al., 2010).

The assessment of clinical burnout symptoms and the evaluation of therapeutic effects are mainly based on self-report questionnaires (Elkuch et al., 2010; Meyer et al., 2016; Schwarzkopf et al., 2016). Although convenient to assess current symptomatology, questionnaires mirror subjective evaluation and may miss some aspects of the condition (Suzuki et al., 2014). Indeed, multimodal approaches for evaluation are proposed, which not only rely on symptom change or reduction, but also involve biological parameters which may complement the results of the questionnaires (Buchkremer & Klingberg, 2001). As stress is a fundamental biological concept, biomarkers that reflect the severity of mental stress may be especially desirable to measure in burnout. Although there is a body of literature investigating biological stress parameters in burnout (Danhof-Pont et al., 2011; Juster et al., 2011), to the best of our knowledge there are only few studies involving them for therapy evaluation (Mommersteeg et al., 2006a; Mommersteeg et al., 2006b). A convenient stress-responsive biomarker is brain-derived neurotrophic factor (BDNF), a brain-wide distributed protein with functions in neuronal development, survival and differentiation of the central nervous system (Waterhouse & Xu, 2009). BDNF is involved in adult neurogenesis in the hippocampus and has been suggested to be a driving regulator of synaptic plasticity (Figurov et al., 1996). It has been first found in animal experiments that chronic stress can decrease BDNF (Smith et al., 1995). Analogously, recent human studies have shown that occupational stress (Okuno et al., 2011) and burnout (Onen Sertoz et al., 2008) are correlated with reduced BDNF levels. Furthermore, there is a large body of evidence that major depressive disorder (MDD), which is also regarded as a stress-related disorder (Tennant, 2002), is associated with decreased BDNF levels (Karege et al., 2002; Shimizu et al., 2003). Antidepressant treatment has consistently been shown to restore reduced BDNF levels in depressed patients (Brunoni et al.,

2008). It is ambiguous, if the normalization of BDNF is achieved by a specific antidepressant class such as selective serotonin reuptake inhibitors (SSRIs) (Gonul et al., 2005; Molendijk et al., 2011) and if BDNF restoration is paralleled by symptomatic relief (Brunoni et al., 2008; Molendijk et al., 2011).

Another reliable biomarker of stress and a candidate measure to support therapy evaluation is heart rate variability (HRV), which is considered to mirror neurovegetative regulation capacities of the autonomic nervous system. HRV parameters are calculated either from the variability of the intervals between two heartbeats in an electrocardiogram or by the quantification of specific frequency components (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HRV can reflect regulatory processes involved in emotional, cognitive, and psychosocial activities (Kotov & Revina, 2012) and have been reported to be decreased in stressful work conditions (Loerbroks et al., 2010). In burnout, HRV may be basically reduced (de Vente et al., 2015; Lennartsson et al., 2016). Specifically, the time domain HRV measure RMSSD (root mean square of successive differences in the interbeat intervals), which is supposed to reflect parasympathetic activity, has been found to be lower in clinical burnout patients compared to non-clinical burnout and healthy controls (Lennartsson et al., 2016). Moreover, HRV has consistently been reported to be decreased in MDD patients (Gorman & Sloan, 2000).

The effects of antidepressant treatment on HRV are diverse and medication class may have a significant impact. In clinical burnout there was no significant difference in HRV between patients using antidepressant medication and antidepressant-free patients (Lennartsson et al., 2016). SSRIs have not been found to affect HRV in MDD patients (Kemp et al., 2010; van Zyl et al., 2008), although contradicting observations exist (O'Regan et al., 2015). Other classes of antidepressants, particularly tricyclics have been shown to lead to a significant decline in HRV,

especially in parasympathetic measures (O'Regan et al., 2015; van Zyl et al., 2008). Thus, antidepressants have no beneficial effect on HRV, but rather leave it unaffected in the best case. A common modulator of BDNF and HRV seem to be insomnia and poor quality of sleep which are symptoms concomitant with both burnout and depression. It has been proposed that sleep quality is linked to BDNF levels rather than the disorders per se (Giese et al., 2013; Giese et al., 2014b). Analogously, recent work proposed that lowered parasympathetic activity may be associated with elevated depressiveness only if it is correlated with diminished sleep quality (Werner et al., 2016).

The aim of the present study was to explore the effectiveness of a specialized burnout therapy program conceived for in-patient treatment. The therapy program "SymBalance" builds on a concept of burnout that it arises from an imbalance between external demands and individual resources, which takes place in three dimensions (Ballweg et al., 2013). The objective dimension refers to an imbalance between individual resources and the effective demands at work or personal life. The subjective dimension comprises the subjective perception of the relation between resources and demands, whereas the existential dimension indicates the extent to which an imbalance is considered as relevant for one's own identity. The SymBalance therapy program included treatments for an imbalance in all the three dimensions. Deficits in the objective dimension can be treated through training programs in a group therapy setting and impairments in the subjective dimension by means of selected forms of cognitive behavioral therapy. The existential dimension is treated by a philosophically informed evaluation of the individual's life plans. The therapeutic interventions are supplemented by a regeneration program that meets the needs for relief and relaxation, and, if indicated, by psychopharmacological medication in order to support the therapeutic process. For the study, patients' clinical symptoms were assessed by

self-rating questionnaires at admittance and discharge, and BDNF and HRV were measured to complement the subjective data.

Moreover, psychopharmacological pretreatment, class of medication before and during hospitalization, and sleep quality were explored as potential modulating factors of the biomarkers. As men and women have been reported to show biological and psychological differences in stress response (de Vente et al., 2015; Kudielka & Kirschbaum, 2005), gender differences were assessed for all measured variables at admittance as well as for the changes in symptomatology and biomarkers over the period of hospitalization.

Materials and Methods

Participants

Seventy-one patients (39m/32w, average age 46.8 ± 9.9 years) from the burnout ward at the Centre of Stress Related Illnesses at the Sanatorium Kilchberg, Zurich, Switzerland, were included in the study. The burnout ward is specialized for patients with a disease development in the context of performance, which was assessed in a preliminary diagnostic interview by experienced psychotherapists determining the external and subjective factors as well as the progression and severity of stress burden. All included patients had the additional diagnosis of burnout (Z73.0: problems related to life-management difficulty: burnout) according to ICD-10 criteria (World Health Organization, 1992) coupled to the main diagnoses of single episode (F32) or recurrent (F33) depressive disorder. Severe burnout increases the probability of a concomitant depressive disorder (Ahola et al., 2005), what explains that the majority of the in-patients of the burnout ward also fulfilled the diagnostic criteria for depression. The assignment to the burnout ward and treatment, respectively, was based on the etiopathogenesis of the symptoms, i.e. their

development in the specific context of performance (Ballweg et al., 2013). During the data acquisition period from July 2013 to August 2015 totally 127 patients were admitted to the burnout ward. At admittance, patients were asked to voluntarily participate in an effectiveness study in order to evaluate the specialized therapy program of the center. Reasons for non-participation and exclusion, respectively, were lack of motivation in taking part in the study or conditions preventing the patients from attending certain therapies or filling in the questionnaires, such as physical impairments or insufficient knowledge of German language. Moreover, patients with F-diagnoses other than depressive disorders were excluded from the analyses, in order to have a more homogeneous group of patients. Most patients (63.4%) had a higher education (university or university of applied sciences), 25.4 % obtained an apprenticeship and 8.4 % reported to have finished education after compulsory school. As terms of employment, 40.8% of the patients reported to hold a management position, 47.9% were employees, 5.6% were self-employed. The majority (71.8%) received full, 15.5% part-time and 12.7% no salary at admittance. Personal and clinical characteristics, data about duration of sick leave, psychiatric or psychological outpatient treatment as well as medication were collected from the medical histories and are shown in Table 1 and 2. This study had a single-group, two-time point repeated measures design without controlled interventions and was approved by the ethical committee of Zurich, Switzerland, which is in agreement with the latest Declaration of Helsinki.

Procedure

After giving their written informed consent, patients were additionally screened with a structured diagnostic interview (MINI-SCID) according to DSM-IV criteria for a global report of diagnoses. Patients underwent identical measurements at admittance (pre) and shortly before leaving the

hospital (post). These comprised various questionnaires assessing burnout, depression and sleep, a 24-h electrocardiogram (ECG) recording for HRV and the collection of a blood sample for BDNF extraction. Demographic and clinical data were collected from the electronic clinic information system and are shown in Table 1. All patients were treated by experienced therapists according to the SymBalance therapy concept (Ballweg et al., 2013). The intensive therapy program was designed for six weeks and contained weekly three individual cognitive-behavioral psychotherapy sessions. The individual therapy was complemented by weekly eight hours of group therapy (emotional competences (3h), mindfulness (0.5h), communication skills (1.5h), stress management (1.5h) and philosophy (1.5h)), six hours of body therapies, two hours of guided physical exercise and three hours of regenerative interventions as Shiatsu and massages (Table 4). If indicated, psychotherapy was supported by psychopharmacological treatment.

Measurements

Symptomatology

- Maslach Burnout Inventory

In order to assess the severity of burnout, subjects were asked to complete the validated German version of the Maslach Burnout Inventory (Maslach et al., 1996). The MBI consists of 21 items with questions to the dimensions of emotional exhaustion (EE), depersonalization (DP) and personal efficacy (PE) to which can be responded on a Likert-type scale with seven response options, scored between 0 (‘never’) and 6 (‘always’). The scores of the different burnout dimensions were submitted separately for analyses as recommended by Maslach and colleagues (Maslach et al., 1996).

- Beck Depression Inventory

The Beck Depression Inventory (BDI) is a self-report measure of depressive symptoms and includes 21 reliable and well-validated items (Beck, 1995). Each item has a score range of 0–3, with a possible total score of 63. A score of 0–12 reflects no depression, 13–19 light depression and 20–28 moderate depression and a sum higher than 29 means severe depression.

- The Insomnia Severity Index

The German translation of the Insomnia Severity Index (ISI) (Bastien et al., 2001; Morin, 1993) was administered to assess subjective sleep quality and the nature, severity, and impact of insomnia, where applicable. The ISI has seven items which can be rated on a 5-points scale ranging from 0 (= not at all) to 4 (= very much). A sum score between 0 to 7 has no clinical relevance, 8 to 14 indicate sub-threshold insomnia, 15 to 21 can be interpreted as moderate clinical insomnia and a sum score higher than 22 represents severe clinical insomnia.

Biomarkers

- BDNF

Together with the routine blood withdrawal performed at admittance and discharge, an additional blood sample was collected in a serum vacutainer (6ml) per subject and time point. As serum BDNF concentration follows a circadian rhythm and has been shown to decline over the course of a day (Giese et al., 2014a), blood was withdrawn in the morning between 8.00 and 11.30 am. After 60 min of clotting time at room temperature, serum was obtained by centrifugation at 1300xg for 10 minutes. Aliquots (3 to 4 per person and blood withdrawal) were frozen immediately to –23° C then rearranged to -80°C for long-term storage until assaying. BDNF serum level was analyzed in the Neurobiology Laboratory for Brain Aging and Mental Health of

the University of Basel with an enzyme-linked immunoabsorbent assay (ELISA) (Promega BDNF Emax®, Madison, Wis.). Samples were appropriately diluted (1:100) and detection of total soluble BDNF was carried out in an antibody sandwich format following the manufacturer's protocol. The absorbance was measured within 30 minutes in a microplate reader at 450nm to determine BDNF concentrations according to the standard curve. All assays were performed in a blinded fashion, carried out in duplicates and means of concentration were calculated.

- HRV

For HRV measurements a 24-hours electrocardiogram (ECG) was recorded using a portable ECG monitoring device (eMotion Faros 180°, Mega Electronics Ltd, Kuopio, Finland). The data sampling rate was set at 500 Hz. Patients were instructed to keep an activity diary during the measurement period. For the present study, the sleep time period was extracted as it was a consistent activity on the patients' individual daily schedules. Of the self-reported sleep time period, data of 10 minutes from the beginning and the end of indicated sleep were omitted in order to prevent misinterpretations due to mismatches between the actual and the reported sleep time. Furthermore, sleep time was verified on the basis of noticeable changes within the high frequency band of the power spectrum density graph – 0.15-0.40 Hz, indicating parasympathetic activity - and the accelerator signal produced by the HRV scanner software (BioSign GmbH, Ottenhofen, Germany). HRV data were analyzed using the Kubios HRV software version 2.1 (Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland, Kuopio, Finland). The root mean square of successive differences (RMSSD) was used for further analyses. The RMSSD reflects the beat-to-beat variance in the heart rate and is the primary time domain measure used to estimate parasympathetic activity

reflected in HRV (Shaffer & Ginsberg, 2017). Data were controlled for length of sleep time period and body mass index (BMI).

Statistical Analyses

In order to evaluate changes during the treatment with the therapy program, symptomatic and biological parameters collected at admittance and discharge were compared using paired-sample T-test or Wilcoxon signed rank test, if data were not normally distributed. To explore the influence of psychopharmacological pretreatment on the biomarkers, a one-way analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test in case of not normally distributed data, respectively, was performed comparing the biomarkers at admittance between the pretreatment groups “no medication (n=23)”, “SSRI (n=19)” and “other ADs (other antidepressants, e.g. tricyclic, tetracyclic, serotonin–norepinephrine reuptake inhibitors or melatonergic antidepressants; n=16)”. The number of patients pre-treated with other kinds of psychotropic drugs was too small to form additional groups.

The impact of medication as part of the in-patient treatment was investigated using the Kruskal-Wallis test with the categorical variable of medication class at discharge as between-subject factor and the difference scores of the measured biomarkers as dependent variables. In order to explore group differences, the Dunn- Bonferroni post hoc test was used.

Because of small group sizes in some medication categories, the groups “no medication” (n=8), “SSRI” (n=16), “AD and AP” (antidepressant and antipsychotic medication; n=22), and “other AD” (n=11) were formed. Patients with other kinds of medication such as benzodiazepines or phytopharmaceuticals were excluded from this analysis. Medication class at discharge was considered for analysis, because medication was introduced or changed, respectively, soon after

admittance and maintained until discharge. The influence of sleep quality on biomarkers was investigated in regression analyses with the ISI difference score as predictor and the difference scores of the biomarkers as dependent variables. In order to investigate gender differences, all variables measured at admittance as well as their difference scores were submitted to Mann-Whitney U-Tests with gender as the grouping variable. Analyses were performed using SPSS 24 (IBM SPSS Statistics).

Results

The study parameters at admittance and discharge, and the pre- post comparisons are presented in Table 3. Several partial dropout cases occurred: three patients did not return the questionnaires at discharge but their physiologic and demographic data were available and included into the analyses. There were incomplete or missing HRV measurements of 21 patients because of recording or data failures. Biomarkers and symptoms at admittance as well as their difference scores did not differ between genders.

Pre-post comparisons

Patients showed a highly significant increase in serum BDNF from admittance to discharge. In contrast, there was no change in the parasympathetic measure of HRV (RMSSD) during sleep over the study period. The BDI sum score, the ISI and the MBI scales of emotional exhaustion and depersonalization decreased significantly from pre to post. Concurrently, there was a significant increase in the personal efficacy score of the MBI.

Influencing factors

- Medication

Concerning antidepressant pretreatment, there was no effect of pretreatment group (no medication, SSRI, other AD) either on the BDNF serum level (X^2=.51, p=.77), or on RMSSD (F(2, 43)=.25, p=.78) at admittance.

There was a significant effect of medication class at discharge on the BDNF difference score (X^2=8.1, p<.05). The subsequently performed post hoc test revealed that the increase in BDNF serum level was significantly higher in the "SSRI" group compared to the "no medication" group (z=-2.3, p<.05) and to the "AD and AP" group (z=-2.2, p<.05) (Figure 1). There was no effect of medication class at discharge on the RMSSD difference score (X^2=1.75, p=.63).

- Sleep quality

The regression analyses revealed no influence of change in sleep quality either on the BDNF (R^2=.02; F (1,68) =1.58, p=0.21) or on the RMSSD difference scores (R^2=.01; F (1,47) =.65, p=0.42).

Discussion

The aim of the present study was to explore the effectiveness of a specialized holistic therapeutic concept on symptoms and biological markers of chronic stress in clinical burnout patients. The main results of this explorative work are on the one hand the significant reduction of symptoms associated with burnout and depression, and on the other, the significant increase in serum BDNF. These outcomes implicate that the multimodal therapy program is promising in the treatment of burnout. Whereas pretreatment with antidepressants has been found to have no

influence on the biomarkers, treatment with SSRIs as part of the therapy program has been shown to have an enhancing effect on BDNF increase. Another relevant finding is the unchanged HRV during sleep over the period of hospitalization. Moreover, improvement in sleep quality shows no influence on the pre to post change in BDNF or HRV.

The present findings that patients medicated with SSRIs exhibited the strongest increase in serum BDNF are in line with the results of Molendijk and colleagues (Molendijk et al., 2011), who found that an increase in BDNF was confined to the use of SSRIs and not visible with other classes of antidepressants. This outcome can be attributed to the elevated extra-synaptic levels of serotonin, which is known to stimulate BDNF gene expression (Martinowich & Lu, 2008). However, a meta-analysis reported significant BDNF level increases as an effect of antidepressant treatment irrespective of drug class (Brunoni et al., 2008). It is not possible to adequately evaluate the influence of antidepressant pretreatment on serum BDNF, as the initial BDNF values before out-patient treatment are not known. As medication was added or changed during hospitalization, i.e. SSRIs were started or ceased after admittance, pretreatment may not have great relevance for the pre to post change in serum BDNF anyhow.

There are also other interventions within the therapy program that may have contributed to the BDNF increase during hospitalization. Physical exercise has been repeatedly found to increase serum BDNF (Ferris et al., 2007). As the present therapy program contained various body activating approaches, these may have probably promoted the observed increase in serum BDNF. Indeed, in a recent study it could be shown that in MDD patients the addition of exercise to treatment as usual, consisting of psychotherapy plus antidepressant medication, had a boosting effect on BDNF increase after six weeks (Kerling et al., 2017). Thus, it seems to be a combination of psychotherapy, exercise and SSRIs that promotes significant BDNF increase after a relatively short intervention time.

Sleep quality has been proposed to be a potent modulator of BDNF levels as well (Giese et al., 2013; Giese et al., 2014b). However, the present data did not reveal any relationships between alleviation of insomnia and BDNF increase. This is not necessarily opposite to the literature as the cited studies reporting modulatory effects of insomnia on BDNF included individuals without symptoms of burnout or depression (Giese et al., 2013; Giese et al., 2014b).

Concerning HRV, there was no change in the parasympathetic tone despite symptomatic relief. The lack of a change in parasympathetic activity from pre to post therapy might indicate that neurovegetative adaptations to health interventions, e.g. psychotherapy, restorative physical exercise or regenerative therapies require longer periods than 6 to 8 weeks to manifest. Consistent with the present results, another study found no change in sleep RMSSD after several weeks of successful CBT (Carney et al., 2000). However, the outcome may also be explained by the relatively high parasympathetic tone measured in the present patient group. Compared to HRV data of similar investigations, the present RMSSD values are in the range of the values of non-clinical burnout patients (Lennartsson et al., 2016) or even healthy subjects (Carney et al., 2000; de Vente et al., 2015). Consequently, the potential for further increase in basal parasympathetic tone may have been limited. In the current case, measuring parasympathetic reactivity, e.g. quantifying the extent and duration of change in parasympathetic activity in response to regenerative or physically/emotionally arousing interventions may have delivered more conclusive insights.

Although measured during sleep, no relationship between sleep quality and HRV was yielded. Similarly, a recent study (Werner et al., 2015) reported that measures of sleep quality were rather associated to parasympathetic activity during wakefulness than during sleep. Indeed, sleep quality has been proposed to have more a moderating role in the relationship between HRV and depression than a direct impact on HRV (Werner et al., 2016).

Eventually, HRV did not differ between patients in different medication groups, indicating that medication might not have affected the outcome. There are further studies also providing evidence against an effect of antidepressants on HRV (Kemp et al., 2010; Lennartsson et al., 2016). In their review analyzing potential beneficial effects of antidepressant treatment on HRV, Kemp and colleagues summarized that antidepressants ameliorate depressive symptoms but not HRV and referred to the hypothesis that depression, i.e. affective illnesses in general, may have residual neurophysiological effects (Kemp et al., 2010).

The present therapy evaluation was performed as a naturalistic study in a specialized burnout ward, and was affected by some limitations. The study was entailed to apply a one stranded design without a control group. A reasonable control condition could have been to measure symptoms and biomarkers in the patients before their admittance to the burnout ward, i.e. during their waiting period. However, such a design would have been affected by many uncontrollable factors and differences, such as duration of waiting or the use and kind of treatment. Moreover, patients without pretreatment could not have been included.

With regard to HRV, alternative approaches may be applied to detect possible neurovegetative changes in the course of stress recovery. Future studies are suggested to integrate standardized conditions such as paced breathing or stress tests to measure parasympathetic reactivity as well as a more longitudinal study design including several follow-up measurements after symptomatic improvement in order to monitor changes in parasympathetic tone. Furthermore, the quantification of the patients' activity level, e.g. by actimetry or pedometers, would allow the incorporation of the individual therapy schedules into HRV analysis and provide more conclusive insights. Also the investigation of BDNF would profit from additional recording of movement signals, as physical activity is known to be - besides SSRIs - a modulator of BDNF.

Finally, it has to be taken into account that the present study population encompasses a particular group of patients with a high socioeconomic status and good social integration what may question the generalizability of the results. While a higher socioeconomic status may reduce stress in terms of existential worries, it has been found that burnout is more prevalent in managerial and intellectual jobs, i.e. higher socioeconomic positions (van der Molen et al., 2018). Thus, it can be hypothesized that while a higher socioeconomic status itself may be protective, the personal traits promoting it (e.g. high performance motivation) may increase the vulnerability for burnout. In what way this combination of factors influences the therapeutic process and outcome could be subject of further investigations.

In summary it can be stated that this study is a data driven explorative analysis of the effectiveness of a therapeutic concept specialized on the stress-related disorder burnout. Despite the given limitations based on the naturalistic study design, the results provided by the questionnaires and biomarkers of stress suggest that the multimodal therapy program combining psychotherapy, physical exercise, regenerative interventions and supplementary psychopharmacological treatment may lead to improvements in patients' subjective report of symptoms and neuroplasticity. Further studies involving a suitable control condition and applying a more standardized setting are needed to provide stronger evidence for the effectiveness of the therapy program and the contribution of antidepressant treatment to the measured effects.

Acknowledgements

We want to thank all patients who found time and effort during their hospitalization to take part in the study and the staff of the Centre of Stress Related Illnesses for integrating study tasks in their daily work. Special thanks go to Pietro Ballinari for his extremely valuable statistical advice and

support, to Karla Lagler, Kurt Gassmann and Fides Meier for their indispensable logistic help concerning BDNF handling and to Sophie Fritsche for the careful data management.

Conflicts of interest

None of the authors has conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Figure 1

Box plot depiction of the Kruskal-Wallis Test with the BDNF difference score (post-pre) as the dependent variable and medication class at discharge as between-subject factor. The difference score was significantly higher in the SSRI group compared to the no medication and the AD and AP group.

SSRI selective serotonin reuptake inhibitor; AD antidepressant; AP antipsychotic; ○ outlier

Table 1: Personal and treatment characteristics

Age (years)	46.8 ± 9.9 (26-67)
BMI (kg/m^2) (n=63)	25.5 ± 4.7 (16.5-40.4)
Days of hospitalization	46.2 ± 9.8 (24-80)
Outpatient treatment (n)*	33
- duration (weeks)	34.4 ± 49.1 (3-208)
Sick leave (n)	37
- duration (weeks)	10.2 ± 13.6 (0.5-57)

Data shown as mean ± SD (range); BMI body mass index; * information of three patients is missing

Table 2: Details about medication at admission and discharge, and duration of pretreatment

	Admittance (pre)	Discharge (post)
Psychopharmacological medication		
- none	23	8
- SSRI	19	16
- SNRI	3	2
- Tricyclic	3	7
- other AD	10	2
- Antipsychotics	1	5
- AD + AP	2	22
- other	9	9
- missing information	1	-
Cardiovascular medication		
- anti-hypertensive	8	8
Duration of pretreatment	Weeks	
- SSRI (n*=16)	11.4 ± 15.0 (1-57)	
- SNRI	6.7 ± 7.2 (2-15)	
- Tricyclic	17.7 ± 11.7 (9.5-26)	
- other AD (n*=8)	23.5 ± 32.9 (2-78)	
- Antipsychotics	82	
- AD + AP	6 ± 4.2 (3-9)	

Data shown as mean ± SD (range); SSRI selective serotonin reuptake inhibitor; SNRI selective serotonin noradrenalin reuptake inhibitor; AD antidepressant; AP antipsychotic: * information is missing from three patients treated with SSRIs and two treated with other ADs

Table 3: Symptomatology and biomarkers at admission and discharge, and their change from pre to post

	Admittance (pre)	Discharge (post)	Pre-post statistics
BDNF (ng/ml)	29.3±7.5 (5.7-51.5)	34.4±8.7 (15.2-66.8)	Z=-4.90, p<.001
HRV (n=50)			
- RMSSD [ms]	40.1±20.0.7 (6.3-115.8)	35.6±14.7 (12.2-73.6)	Z=-1.54, p=.124
Sleep time* [h]	8.4±1.4 (5.6-11.4)	8.2±1.4 (3.7-10.7)	t(49)=0.70 p=.484
BDI	24.1±7.8 (3-41)	9.0±7.6 (0-34)	Z=-7.01, p<.001
MBI			
- EE	4.8±0.7 (3-5.9)	3.8±1.0 (1.7-5.7)	t(67)=9.04, p<.001
- DP	2.8±0.9 (1-5)	2.5±0.8 (1-4.2)	t(67)=3.60, p<.001
- PE	4.5±0.5 (2.3-5.9)	4.8±0.5 (3.3-5.9)	t(67)=-4.73, p<.001
ISI	15.1±6.5 (0-26)	6.5±5.0 (0-23)	Z=-6.93, p<.001

Data shown as mean ± SD (range); BDNF brain-derived neurotrophic factor; HRV heart rate variability; RMSSD root mean square of successive differences; BDI Beck depressions inventory; MBI Maslach Burnout Inventory (EE emotional exhaustion, DP depersonalization, PE personal efficacy); ISI insomnia severity index; * sleep time as indicated in the patients' activity protocol during 24h HRV measurement.

Table 4: Detailed composition of the therapy program

Intervention	Therapy units/ week
Individual cognitive-behavioral psychotherapy	3
Group therapies	8

(emotional competences, communication skills, stress management, mindfulness, philosophy)	
Activating body therapies (e.g. Yoga, Qi Gong, physical exercise, movement therapy)	8
Regenerative individual therapies (Massage, Shiatsu, physiotherapy, ear acupuncture)	4
Resource activating therapies (music, art)	2-4
Job Coaching	If required

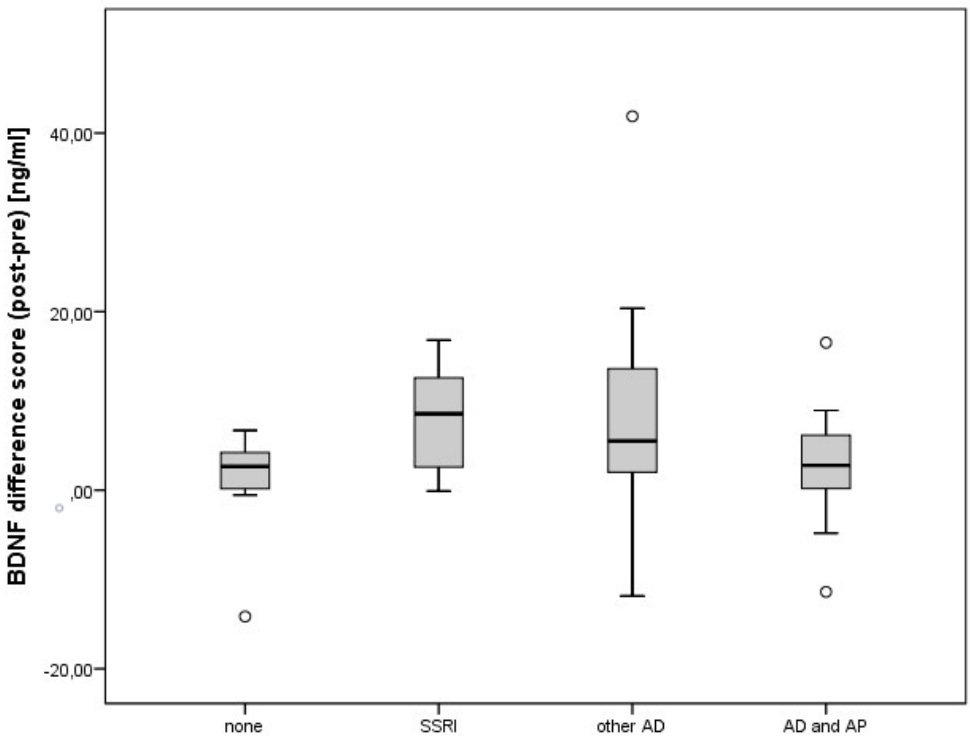

Figure 1
Box plot depiction of the Kruskal-Wallis Test with the BDNF difference score (post-pre) as the dependent variable and medication class at discharge as between-subject factor. The difference score was significantly higher in the SSRI group compared to the no medication and the AD and AP group.
SSRI selective serotonin reuptake inhibitor; AD antidepressant; AP antipsychotic; ○ outlier

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