Biopsychological stress regulation in work-related burnout: Allostatic load, hypothalamic-pituitary-adrenal axis (re)activity and neural stress processing

Kumulative Inaugural-Dissertation
zur Erlangung der Doktorwürde
der Fakultät für Humanwissenschaften
der Universität Regensburg

vorgelegt von

Christoph Bärtl

geboren am 5. Januar 1993 in Neumarkt i.d.OPf.

Die Arbeit entstand in Betreuung durch
Prof. Dr. Brigitte M. Kudielka
(Institut für Psychologie)

Regensburg
2024

Erstgutachterin: Prof. Dr. Brigitte M. Kudielka

Zweitgutachterin: Prof. Dr. Silja Bellingrath

DANKSAGUNG

Ich bedanke mich herzlich bei Prof. Dr. Brigitte M. Kudielka für die umfassende Unterstützung und Betreuung meiner Promotion. Ich danke ihr für das Vertrauen in meine Person sowie die wertvollen Erfahrungen, die sie mir im Rahmen der Promotion ermöglicht hat. Ebenfalls möchte ich mich bei Prof. Dr. Silja Bellingrath für die bereitwillige Übernahme des Zweitgutachtens bedanken.

Ich danke Prof. (apl.) Dr. Stefan Wüst für den wissenschaftlichen Austausch sowie seine Unterstützung im Rahmen des Projekts. Bei Dr. Ludwig Kreuzpointner bedanke ich mich für seine vielfältige Hilfe – insbesondere bei schwierigen Revisions-Prozessen. Außerdem danke ich Dr. Babette Stadler-Werner für ihr offenes Ohr und den emotionalen Beistand. Ich danke Heike Hochmuth und Klara Zwengauer für die organisatorische Unterstützung und die vielen angenehmen Gespräche. Zudem möchte ich mich bei Daniela Biermeier sowie Dr. Stefan Wallner für die tatkräftige Unterstützung bei den Blutentnahmen bedanken. Ein besonderer Dank gilt meinen ehemaligen Kolleg:innen Marina Giglberger, Dr. Julian Konzok, Dr. Hannah Peter und Dr. Nina Speicher sowie allen Hilfskräften des Lehrstuhls für die Unterstützung bei der Datenerhebung. Dr. Hannah Peter danke ich für ihre humorvolle Art und die vielen gemeinsamen Erlebnisse. Bei meinem ehemaligen Bürokollegen Dr. Julian Konzok bedanke ich mich für zahlreiche lustige Momente und entschuldige mich für alle Unannehmlichkeiten. Bei Marina Giglberger möchte ich mich insbesondere für ihre Hilfsbereitschaft in schwierigen Zeiten bedanken. Außerdem danke ich der Deutschen Forschungsgemeinschaft (DFG) für die Förderung des Forschungsprojekts.

Abschließend möchte ich meiner Familie danken. Meiner Schwester Dr. Susanne Bärtl für deinen unnachgiebigen Rückhalt und Zuspruch. Meinem Bruder Lukas und meiner Schwester Hannah Bärtl möchte ich dafür danken, dass ihr stets an meiner Seite seid. Mein besonderer Dank gilt Dr. Gina-Isabelle Henze, die mich mit ihrer Stärke und ihrem Mut tief beeindruckt hat. Auch in Zeiten, als dir das Leben große Hürden auferlegt hat, hast du mir stets Kraft und Zuversicht gegeben. Für deine bedingungslose Unterstützung und Liebe bin ich dir von Herzen dankbar. Schließlich möchte ich meinen Eltern für die Unterstützung und den Rückhalt auf meinem gesamten Lebensweg danken. Danke, dass ihr immer an mich geglaubt habt – auch dann, wenn ich selbst gezweifelt habe. Diese Arbeit widme ich euch als Zeichen meiner Dankbarkeit und Zuneigung.

FOREWORD

This cumulative dissertation comprises three studies investigating biopsychological stress regulation in work-related burnout with respect to allostatic load, hair cortisol concentrations as well as neural and salivary cortisol responses to acute psychosocial stress. All chapters were written specifically for this thesis with three included chapters based on already published original research articles (*Studies I*, *II*, and *III* in the Chapters 4 to 6). For *Studies I*, *II*, and *III*, Elsevier permitted the inclusion of the articles in my dissertation (inclusion of articles in full or in part in a thesis or dissertation for non-commercial purposes). The studies are currently not used or designated for use in other dissertations. The three original research articles and respective contributions of the co-authors are listed below in the order of their appearance in the present thesis.

For improved readability of the dissertation, all three studies were formatted consistently with one combined reference section at the end of the dissertation and continuous numbering of contents, figures, and tables.

All three studies were conducted within the project "*Biopsychological stress regulation in burnout*" funded by the German Research Foundation (DFG, KU1401/9-1 and KU1401/9-2) assigned to Brigitte M. Kudielka and Stefan Wüst.

CONTRIBUTIONS

Study I

Bärtl, C., Henze, G.-I., Giglberger, M., Peter, H. L., Konzok, J., Wallner, S., Kreuzpointner, L., Wüst, S., Kudielka, B. M., 2022. Higher allostatic load in work-related burnout: The Regensburg Burnout Project. *Psychoneuroendocrinology, 143*, 105853. https://doi.org/10.1016/j.psyneuen.2022.105853

Christoph Bärtl: Conceptualization, Investigation, Formal analysis, Data curation, Visualization, Project administration, Writing – original draft. **Gina-Isabelle Henze:** Visualization, Writing – review & editing. **Marina Giglberger:** Writing – review & editing. **Hannah L. Peter:** Writing – review & editing. **Julian Konzok:** Writing – review & editing. **Stefan Wallner:** Investigation, Writing – review & editing. **Ludwig Kreuzpointner:** Formal analysis, Writing – review & editing. **Stefan Wüst:** Conceptualization, Resources, Funding acquisition, Writing – review & editing. **Brigitte M. Kudielka:** Conceptualization, Resources, Supervision, Funding acquisition, Visualization, Project administration, Writing – original draft.

Study II

Bärtl, C., Kreuzpointner L., Wüst, S., Kudielka, B. M., 2023. Investigation of cross-sectional and longitudinal associations between work-related burnout and hair cortisol: The Regensburg Burnout Project. *Psychoneuroendocrinology, 149*, 106026. https://doi.org/10.1016/j.psyneuen.2023.106026

Christoph Bärtl: Conceptualization, Investigation, Formal analysis, Data curation, Visualization, Project administration, Writing – original draft. **Ludwig Kreuzpointner:** Formal analysis, Writing – review & editing. **Stefan Wüst:** Conceptualization, Resources, Funding acquisition, Writing – review & editing. **Brigitte M. Kudielka:** Conceptualization, Resources, Supervision, Funding acquisition, Visualization, Project administration, Writing – original draft.

Study III

Bärtl, C., Henze, G.-I., Peter, H. L., Giglberger, M., Bohmann, P., Speicher, N., Konzok, J., Kreuzpointner, L., Waller, L., Walter, H., Wüst, S., Kudielka, B. M., 2024. Neural and cortisol responses to acute psychosocial stress in work-related burnout: The Regensburg Burnout Project. *Psychoneuroendocrinology*, *161*, 106926. https://doi.org/10.1016/j.psyneuen.2023.106926

Christoph Bärtl: Conceptualization, Investigation, Formal Analysis, Data Curation, Visualization, Software, Project Administration, Writing – Original Draft. **Gina-Isabelle Henze:** Investigation, Formal Analysis, Visualization, Software, Supervision, Writing – Original Draft. **Hannah L. Peter:** Investigation, Writing – Review & Editing. **Marina Giglberger:** Investigation, Writing – Review & Editing. **Patricia Bohmann:** Investigation, Writing – Review & Editing. **Nina Speicher:** Investigation, Writing – Review & Editing. **Julian Konzok:** Investigation, Writing – Review & Editing. **Ludwig Kreuzpointner:** Formal Analysis, Software, Writing – Review & Editing. **Lea Waller:** Formal analysis, Software, Writing – Review & Editing. **Henrik Walter:** Formal analysis, Software, Writing – Review & Editing. **Stefan Wüst:** Conceptualization, Resources, Supervision, Funding acquisition, Writing – Review & Editing. **Brigitte M. Kudielka:** Conceptualization, Formal Analysis, Resources, Supervision, Funding acquisition, Visualization, Project Administration, Writing – Original Draft.

LIST OF CONTENTS

LIST OF ABBREVIATIONS

ACC ..... *anterior cingulate cortex*
ACTH..... *adrenocorticotropic hormone*
AL ..... *allostatic load*
ANCOVA ..... *analysis of covariance*
AV..... *actual value*
AVP..... *arginine vasopressin*
AW..... *areas of worklife model*
BAT..... *Burnout Assessment Tool*
BCSQ..... *Burnout Clinical Subtype Questionnaire*
BIA..... *bioelectrical impedance analysis*
BNST ..... *bed nucleus of the stria terminalis*
BO group..... *burnout group*
BOLD..... *blood-oxygenation-level-dependent*
CAR ..... *cortisol awakening response*
CATS ..... *cognitive activation theory of stress*
CBG ..... *corticosteroid-binding globulin*
CBI..... *Copenhagen Burnout Inventory*
CNS..... *central nervous system*
COPSOQ..... *Copenhagen Psychosocial Questionnaire*
COR ..... *conservation of resources*
CRH ..... *corticotropin releasing hormone*
DBP..... *diastolic blood pressure*
DGPPN ..... *German Association for Psychiatry, Psychotherapy and Psychosomatics*
DHEA-S..... *dehydroepiandrosterone-sulfate*
dlPFC ..... *dorsolateral prefrontal cortex*
DP ..... *depersonalization*
DSM..... *Diagnostic and Statistical Manual of Mental Disorders*
DST..... *dexamethasone suppression test*
ECV..... *explained common variance*
ED ..... *exhaustion disorder*
EDTA..... *ethylenediaminetetraacetic acid*
EE..... *emotional exhaustion*
ERI ..... *effort-reward imbalance*
ERI-Q..... *Effort-Reward Imbalance Questionnaire*
ER-ratio..... *effort-reward ratio*
FC..... *functional connectivity*
fMRI..... *functional magnetic resonance imaging*
FWE ..... *family-wise error*
GABA ..... *gamma-aminobutyric acid*
GAS..... *General Adaption Syndrome*
GLM..... *general linear model*
GM ..... *grey matter*
GR ..... *glucocorticoid receptors*
HADS..... *Hospital Anxiety and Depression Scale*
HADS-A ..... *Hospital Anxiety and Depression Scale-anxiety scale*
HADS-D ..... *Hospital Anxiety and Depression Scale-depression scale*

HbA1c ..... *glycosylated hemoglobin*
HC group ..... *healthy comparison group*
HCC ..... *hair cortisol concentrations*
HDL ..... *high-density lipoprotein*
HPA axis ..... *hypothalamic-pituitary-adrenal axis*
hsCRP ..... *high-sensitivity c-reactive protein*
ICD ..... *International Classification of Diseases*
IL-6 ..... *interleukin 6*
JSS ..... *Jenkins Sleep Scale*
LA ..... *lack of personal accomplishment*
LC-MS/MS ..... *liquid chromatography coupled with tandem mass spectrometry*
LC-NE system ..... *locus coeruleus-norepinephrine system*
MBI ..... *Maslach Burnout Inventory*
MBI-GS ..... *Maslach Burnout Inventory-General Survey*
$MBI_{weighted}$ ..... *weighted Maslach Burnout Inventory-score*
MDD ..... *major depression disorder*
MFG ..... *middle frontal gyrus*
MIST ..... *Montreal Imaging Stress Task*
mPFC ..... *medial prefrontal cortex*
MR ..... *mineralocorticoid receptors*
MRI ..... *magnetic resonance imaging*
MRS ..... *magnetic resonance spectroscopy*
NA ..... *negative affect*
OC ..... *overcommitment*
OLBI ..... *Oldenburg Burnout Inventory*
PA ..... *positive affect*
PAI-1 ..... *plasminogen activator inhibitor 1*
PANAS ..... *Positive and Negative Affect Schedule*
PNCs ..... *parvocellular neuroendocrine cells*
POMC ..... *proopiomelanocortin*
PSS ..... *Perceived Stress Scale*
PTSD ..... *post-traumatic stress disorder*
PVN ..... *paraventricular nucleus*
rANOVA ..... *repeated-measures analysis of variance*
ROI ..... *region of interest*
SAM system ..... *sympathetic-adrenal medullary system*
SBP ..... *systolic blood pressure*
SCID-I ..... *Structured Clinical Interview for DSM-IV Axis I Disorders*
SD ..... *standard deviation*
SMBM ..... *Shirom-Melamed Burnout Measure*
STG ..... *superior temporal gyrus*
SV ..... *set value*
TC/HDL ..... *total cholesterol to HDL cholesterol ratio*
TNF-α ..... *tumor necrosis factor-alpha*
TSH ..... *thyroid stimulating hormone*
TSST ..... *Trier Social Stress Test*
VBM ..... *voxel-based morphometry*
vmPFC ..... *ventromedial prefrontal cortex*
WHR ..... *waist-hip ratio*
WPC-Scale ..... *Work-Privacy-Conflicts Scale*

LIST OF FIGURES

LIST OF TABLES

0 SUMMARY

Burnout is characterized by feelings of emotional exhaustion (EE), depersonalization (DP), and reduced personal accomplishment (LA) resulting from a long-term involvement in an over-demanding workplace. However, as burnout is not listed as a mental disorder in the major classification systems, the burnout construct lacks conceptual clarity reflected by varying operationalizations across studies.

On the one hand, numerous prospective studies have consistently highlighted the adverse effects of burnout on long-term physical as well as mental health. On the other hand, convincing evidence on the underlying pathophysiology of burnout remains scarce with previous studies on biopsychological alterations in burnout revealing inconsistent results. Importantly, this inconsistency has been mainly attributed to the imprecise operationalization of burnout, potentially leading to heterogeneous study samples across studies. Therefore, the overarching goal of the present thesis was to investigate potential biopsychological alterations in burnout within a strictly specified and – with respect to pathogenesis – more homogeneous sample. In a first step, a sophisticated and theory-driven recruitment procedure was performed to obtain a burnout and a healthy comparison group (HC group). In contrast to previous studies, burnout cases were not only selected based on current burnout symptomatology, but also based on burnout-specific etiological factors. Accordingly, only individuals characterized by the presence of burnout symptomatology and chronic work stress as well as by a certain level of work-related functioning and engagement before the onset of burnout symptoms, additionally verified by peer-reports, were assigned to the burnout group (BO group). Moreover, strict exclusion criteria were applied regarding exhaustion-related physical diseases and mental disorders. Analogous, individuals with low levels of burnout, chronic work stress, and depression were assigned to the HC group. The multi-stage recruitment process is described in detail in *Study I*.

Building upon this recruitment procedure, the three studies of the thesis sought to identify biopsychological alterations in burnout with respect to allostatic load (AL), hair cortisol concentrations (HCC) as well as neural and salivary cortisol responses to acute psychosocial stress.

In *Study I*, the BO group (n = 56) was compared to the HC group (n = 65) regarding an index of AL as the model of AL was considered to depict a potential biological

pathway for the associations between burnout and negative mental and physical health outcomes. Thereby, the AL-index comprised 14 parameters: high-sensitivity c-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), fibrinogen, d-dimer, plasminogen activator inhibitor 1 (PAI-1), glycosylated hemoglobin (HbA1c), high-density lipoprotein (HDL) cholesterol, total cholesterol to HDL cholesterol ratio (TC/HDL), dehydroepiandrosterone-sulfate (DHEA-S), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist-hip ratio (WHR), and body fat percentage. In line with our hypothesis, the BO group exhibited significant higher AL-scores compared to the HC group indicating a higher cumulative physical burden in individuals suffering from burnout. Besides this group difference, overall burnout symptoms as well as the Maslach Burnout Inventory-General Survey (MBI-GS) subscales EE and DP were significantly related to higher AL. Moreover, a significant positive association between chronic work stress (measured with the effort-reward imbalance questionnaire; ERI-Q) and AL-scores was found.

Study II focused on the cross-sectional as well as longitudinal association between burnout and HCC as alterations of the hypothalamic-pituitary-adrenal (HPA) axis activity have been suggested a psychobiological correlate of burnout. Therefore, psychometric data and hair samples (1cm = 1 month) were repeatedly obtained at two appointments t1 (n = 114) and t2 (n = 100) with an interval of M = 7.20 months (SD = 1.16). In contrast to the hypothesis, the analysis revealed no cross-sectional associations between burnout and HCC at both time points. However, when the analysis was restricted to the BO group, higher degrees of burnout symptomatology were cross-sectionally associated with higher HCC at t1, but not at t2. With respect to the longitudinal analysis, burnout symptoms at t1 were significant negative predictors of HCC at t2 (i.e., higher burnout symptoms at t1 were associated with lower HCC at t2). However, the findings of *Study II* remain somewhat inconclusive as the change in burnout symptoms from t1 to t2 showed no association with the change in HCC.

Finally, in *Study III* neural responses to acute psychosocial stress were examined for the first time in burnout applying Scan*STRESS*, a psychosocial stress induction paradigm suited for functional magnetic resonance imaging (fMRI) environments presented in two runs. Besides neural responses, the BO group (n = 55) and the HC group (n = 61) were compared regarding acute salivary cortisol responses to Scan*STRESS*. In the whole study sample, stress exposure induced significant increases in salivary cortisol, heart rate, and negative affect ratings as well as activations and deactivations in distinct structures

comprising the medial prefrontal cortex (mPFC), cingulate cortex, striatum, and hippocampus. However, no differences emerged between the study groups with respect to cortisol and mean neural stress responses. Interestingly, the exploratory comparison of neural stress responses changes from the first to the second run of Scan*STRESS* indicated a burnout-specific response pattern in one cluster peaking in the left dorsal anterior cingulate (dACC). Thereby, the HC group was characterized by higher neural activation in the first compared to the second run of Scan*STRESS* reflecting decreasing activation. In contrast, the BO group exhibited a reversed pattern indicated by increasing activation (i.e., lower neural activation in the first compared to the second run of Scan*STRESS*). Together with findings from previous studies consistently revealing decreasing neural activation over stress exposure time in healthy samples, deviations from this pattern may indicate dysfunctional neural stress processing in burnout.

In conclusion, the elaborate recruitment procedure incorporating both burnout symptomatology and burnout-specific etiology represents the unique feature of the thesis' studies. Thereby, the results of our recruitment procedure confirmed the initial assumption of variability in pathogenesis among individuals exhibiting burnout symptoms. For instance, some individuals reported on burnout symptoms without experiencing chronic work stress, and vice versa. Consequently, heterogeneous subgroups of individuals with burnout symptoms may exist differing considerably in terms of etiological factors. Although the results of the respective studies were in part inconsistent, it can be concluded that also pre-clinic burnout comes along with dysregulations of distinct stress-sensitive systems. However, it was suggested that biopsychological alterations may become more evident once a certain threshold of burnout severity has been exceeded. Thus, it seems promising for future studies on biopsychological correlates of the burnout syndrome to focus on well-specified subgroups including individuals with varying burnout severity ranging from mild to clinical burnout.

CHAPTER 1

1 INTRODUCTION AND OUTLINE OF THE THESIS

"*In order to burn out a person needs to have been on fire at one time."*

This well-known quote by Pines et al. (1981, p. 4) from the early days of burnout research suggests that commitment and dedication to work are indispensable conditions for the development of job burnout. Similarly, the founding father of the burnout concept, Herbert J. Freudenberger, assumed that those individuals tend to burn-out who "work too much, too long and too intensively" (Freudenberger, 1974, p. 161).

Since then, the number of scientific publications on burnout has increased exponentially with the burnout concept sparking interest far beyond the boundaries of medical and psychological research. However, despite extensive knowledge growth in the field, the burnout construct lacks conceptual clarity (Heinemann & Heinemann, 2017; Hewitt et al., 2020). Accordingly, burnout has become more of a "catch-all label" (Bianchi & Schonfeld, 2020, p. 6), reflected by over one-hundred reported definitions and symptoms of burnout (Hillert, 2012; Rotenstein et al., 2018; Schwenk & Gold, 2018).

Importantly, the lack of consensus on burnout criteria has been considered one of the main reasons for inconsistent results across studies focusing on biopsychological corelates of burnout as convincing evidence on the pathophysiology of burnout remains scarce (Danhof-Pont et al., 2011; Nadon et al., 2022; Salvagioni et al., 2017). However, the numerous findings of adverse psychological (e.g., depression, insomnia), occupational (e.g., absenteeism, disability pension), and physical (e.g., cardiovascular diseases, type 2 diabetes) consequences of burnout emphasize the need for further investigation of its potential biopsychological correlates (Ahola & Hakanen, 2014; Bayes et al., 2021; Grossi et al., 2015; Khammissa et al., 2022; Salvagioni et al., 2017; Swider & Zimmerman, 2010).

To be more illustrative regarding the consequences of the imprecise operationalization of burnout for biopsychological burnout research, a typical study design is described first. Although the description may have some elements of exaggeration or simplification, most of the previous studies on biopsychological correlates of burnout can be summarized as follows: The current burnout symptomatology is assessed via a self-report questionnaire and varying strict exclusion criteria are applied. However, usually no further criteria like burnout-specific etiological factors or differential diagnostic criteria are applied to categorize subjects as burned-out

or healthy. In addition, one or more biological parameters are collected using different biopsychological methods. On the one hand, great progress has been made in recent decades with respect to investigated biological parameters in burnout research as the available biopsychological methods became more elaborate and complex. On the other hand, limited progress has been made regarding the measurement of burnout and classification of burnout cases, or in other words: relatively little effort has been devoted to more sophisticated and theory-driven approaches in the selection of study samples (Nadon et al., 2022).

Accordingly, previous studies regularly employed a single self-report questionnaire to assess burnout symptoms or to identify burnout cases (Bayes et al., 2021; Danhof-Pont et al., 2011; Korczak et al., 2010; Salvagioni et al., 2017). Based on the most frequent used burnout questionnaire, the presence of burnout is reflected by high levels of the core symptom exhaustion as well as depersonalization and reduced personal accomplishment (Maslach et al., 2001; Schaufeli et al., 1996). However, especially the core symptom exhaustion lacks specificity as feelings of exhaustion or fatigue are one of the most common complaints and symptoms of physical diseases and mental disorders (Kroenke & Price, 1993; von Känel, 2008). Given this lack of specificity, the application of additional criteria for identifying burnout cases seems appropriate.

In line with the mentioned quote by Freudenberger (1974), burnout symptoms are assumed to develop as a consequence of chronic work stress (Maslach et al., 2001). Consequently, the experience of enduring work stress seems to be a crucial precursor for the development of burnout. However, in most studies this prerequisite was taken for granted and not additionally verified (Bayes et al., 2021; Maslach et al., 2001). In addition, the opening quote from Pines et al. (1981) suggests that only individuals characterized by high levels of premorbid job-related motivation and dedication *can* actually develop burnout emphasizing the importance of a burnout-specific pathogenesis. Yet, the pathogenesis of burnout has hardly been considered in the selection of study samples in biopsychological burnout research so far. Moreover, the selection of eligible burnout cases has predominantly relied on self-report data, with minimal incorporation of objective information such as third-party assessments (Ahola & Hakanen, 2014; Bayes et al., 2021; Danhof-Pont et al., 2011; Korczak et al., 2010; Nadon et al., 2022).

As a result of the imprecise operationalization of burnout, potential biopsychological correlates may have been investigated in highly heterogeneous study samples,

presumably leading to the observed inconsistent findings (Danhof-Pont et al., 2011; Rothe et al., 2020). Therefore, the overarching aim of the present thesis conducted within the *Regensburg Burnout Project* was to examine potential biopsychological alterations in burnout within a strictly specified and – with respect to pathogenesis – more homogeneous sample by addressing the imprecise operationalization described above. Accordingly, a sophisticated recruitment procedure was conducted based on self- and peer-report as well as on burnout symptomatology and pathogenesis resulting in a burnout and a healthy comparison group. The recruitment procedure is described in detail in *Study I.* Subsequently, both study groups were compared regarding distinct measures of biopsychological stress regulation. In *Study I*, differences in allostatic load were examined between the burnout and the healthy comparison group. Moreover, in *Study II* cross-sectional as well as longitudinal associations between burnout and hair cortisol concentrations were investigated. Finally, in *Study III*, the burnout and the healthy comparison group were compared with respect to salivary cortisol and, for the first time, neural responses to acute psychosocial stress applying Scan*STRESS* (Henze et al., 2020; Streit et al., 2014).

Regarding the outline of the thesis, Chapter 1 provides a concise overview of the thesis' research aims and rationale. In Chapter 2, essential theoretical concepts of stress and burnout are presented. With respect to stress, the focus is on the psychobiology of stress and the biopsychological methods used in *Study I, II,* and *III.* The theoretical background of burnout is structured into three main sections: definition and assessment of burnout, the development of burnout, and the differentiation of burnout from depression and exhaustion-related conditions. Each section addresses specific aspects of burnout to provide a comprehensive understanding of the concept. Chapter 3 focuses on the primary research objectives of the thesis and provides a summary of the theoretical background, research design, and methodology of my own studies included in this dissertation. The already published manuscripts of *Study I, II* and *III* are featured in Chapters 4 to 6, respectively. Ultimately, the general discussion presented in Chapter 7 integrates the empirical findings of the thesis and addresses potential implications for future biopsychological burnout research, followed by a general conclusion.

CHAPTER 2

2 THEORETICAL BACKGROUND: STRESS AND BURNOUT

2.1 Stress

Since burnout is considered a possible consequence of stress, the first section of this chapter covers the theoretical and biopsychological background of the concept of stress. Moreover, it provides an overview of relevant biopsychological methods applied in the present thesis.

2.1.1 Theoretical background of the stress concept

While Hans Selye initially did not use the term "stress" in his popular article published in *Nature* in 1936, he is widely acknowledged as the founding father of modern stress research and discoverer of the biological stress response (Selye, 1936; Szabo et al., 2017). Initially, Selye tried to identify a new ovarian hormone in extracts of cattle ovaries and therefore injected these extracts into rats. At first, Selye assumed that he has indeed detected a new sex hormone, when he observed an orchestrated triad of morphological changes: 1) enlargement of the adrenal cortex, 2) involution of the thymus and lymph nodes and, 3) gastrointestinal ulcers. However, in further studies, Selye discovered that this morphologic triad can be elicited under numerous adverse conditions (i.e., by *diverse nocuous agents* such as heat or surgical injury) and thus became the objective index of the biologic stress response known as the *General Adaption Syndrome* (GAS) (Kagan, 2016; Kvetnansky et al., 2009; Selye, 1936, 1950, 1973; Szabo et al., 2017). The GAS develops in three stages, namely the *alarm reaction*, the *stage of resistance*, and the *stage of exhaustion*. The alarm reaction refers to the first exposure to the stressor and encompasses all non-specific reactions to stimuli to which the organism is not adequately adapted. The stage of resistance is characterized by the adaption of the organism to the stimuli after prolonged exposure. With this, most symptoms of the alarm reaction either disappear or are reversed. However, in case the organism is no longer able to maintain adaption, the stage of exhaustion occurs that finally may also result in death (Fink, 2017; Selye, 1936, 1946, 1950). In sum, Selye defined stress as the "nonspecific response of the body to any demand made upon it" (Selye, 1973, p. 692). Although Selye never gave up his idea of non-specificity, he later made a health-centered distinction between good stress (*eustress*) and harmful, damaging stress (*distress*) (Kudielka & Kirschbaum, 2001; Selye, 1976). Meanwhile, the concept of non-specificity was invalidated by numerous

empirical findings on specific reactions evoked by different stressors (Fink, 2016; Navarro-Oliveira et al., 2000; Pacák et al., 1998; Pacák & Palkovits, 2001). In addition, besides physical stressors such as heat or blood loss (Selye, 1973), psychological stressors were shown to be capable of eliciting reactions of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal medullary (SAM) system; especially situations characterized by social evaluative threat, novelty, uncertainty, unpredictability, and personal involvement (Dickerson & Kemeny, 2004; Koolhaas et al., 2011; Mason, 1968a, 1968b). As a consequence, Koolhaas et al. (2011) have recently suggested to restrict the terms 'stress' and 'stressor' to situations that can exclusively be characterized by uncontrollability and unpredictability.

While Selye focused rather on the HPA axis and glucocorticoids, Cannon (1914) introduced the popular terms of the so-called *fight-or-flight* response and *homeostasis*, concentrating on the SAM system. The concept of fight-or-flight suggests that animals respond to threats by activating the sympathetic nervous system preparing the animal for either fighting or fleeing. According to Cannon, the body reacts similarly in both *fight* and *flight* responses with epinephrine[1] release exerting various effects on different organs with the aim of maintaining or reestablishing *homeostasis* (i.e., a dynamic internal physiological equilibrium with preferred set-points). The concept of homeostasis is based on the idea that physiological parameters such as blood pressure have optimal set-points and that deviations from those set-points are counterbalanced by physiological reactions attempting to reestablish homeostatic balance. With respect to Cannon, stress can be defined as a threat to homeostasis. Later, the stimulus threatening the homeostasis was termed 'stressor'. This is followed by the 'stress response' referring to the coordinated physiological reactions attempting to maintain or reestablish homeostatic balance. Moreover, Cannon assumed that the fight-or-flight response can be evoked not only by physical (e.g., blood loss) but also by psychological threats (Cannon, 1914, 1929; Chrousos, 2009; Chrousos & Gold, 1992; Fink, 2017; Goldstein, 2013; Koolhaas et al., 2011; Kvetnansky et al., 2009; McCarty, 2016).

Later, the concept of homeostasis was criticized and thereby expanded to the concept of allostasis and allostatic load (AL) as almost every physiological activity was assumed to maintain internal balance rendering the definition of stress obsolete (Koolhaas et al.,

[1]Cannon assumed epinephrine to be the main neurotransmitter of the SAM system. Later, von Euler (1946) correctly recognized norepinephrine as the main neurotransmitter of the SAM (Kvetnansky et al., 2009).

2011; McEwen, 1998b; McEwen & Stellar, 1993; Sterling & Eyer, 1988). In short, the concept of allostasis and AL is not limited to acute stress responses but follows a broader approach including the long-term consequences of the body's effort to cope with and adapt to stress. In this regard, allostasis refers to the physiological coping to (acute) stress with the aim of "maintaining stability through change" (McEwen, 2000b, p. 174). While the processes of allostasis are adaptive in the short term to respond adequately to a potentially stressful event, allostatic processes can also have long-term costs under certain conditions referring to the price of adaption (i.e., allostatic load; McEwen, 1998b, 2018). AL can be operationalized by combining multiple physiological parameters into an index of AL (Juster & Misiak, 2023; Seeman et al., 1997). The concept of AL as well as the biopsychological method of assessing an index of AL applied in *Study I* of the present thesis are described in detail in Chapter 2.1.3.3.

Whereas the early stress concepts tended to focus mainly on the physiological nature of stress, Lazarus and Folkman (1984) presented a psychological perspective on stress by introducing their transactional stress model. According to Lazarus and Folkman (1984), cognitive appraisal processes have to be considered to understand variations in individual responses to a potentially threatening (stressful) event. First, each processed stimulus is categorized as irrelevant, benign-positive, or stressful referring to *primary appraisals*. Stressful appraisals can again be distinguished into harm/loss, threat, and challenge depending on *secondary appraisal* processes. Thereby, the individual evaluates available resources for coping with the situation and the possible consequences. In the transactional stress model, psychological stress is defined as an unfavorable person-environment relationship with the degree of the stress reaction being determined by individual perceptions and appraisals highlighting the subjective nature of stress (Lazarus, 1993; Lazarus & Folkman, 1984). However, the strong focus on subjective cognitive processes led to criticism as the stress concept by Lazarus and Folkman (1984) was considered ambiguous and circular, and therefore not suitable for direct empirical testing (Hobfoll, 1989). With the model of conservation of resources (COR), Hobfoll (1989) presented an alternative stress model and defined psychological stress "as a reaction to the environment in which there is (a) the threat of a net loss of resources, (b) the net loss of resources, or (c) a lack of resource gain following the investment of resources" (Hobfoll, 1989, p. 516). Thereby, resources refer to objects (e.g., a home), personal attributes (e.g., self-esteem), conditions (e.g., marriage), or energies (e.g.,

money, time) holding value for an individual. The value of a resource basically depends on its importance for survival of the individual (Hobfoll, 1989; Holmgreen et al., 2017).

Finally, the cognitive activation theory of stress (CATS) by Ursin and Eriksen (2004) serves as an integrating approach of the theories presented offering a more formal system with clear definitions. Within the framework of the CATS, stress is operationalized by a stimulus (called "stressor"), subjective reports of stress experience (only in humans), and a general non-specific increase in arousal including activation and the feedback of the reaction to the brain. Similarly to Lazarus and Folkman (1984), the degree of stress evoked by a stimulus is determined by individual appraisal processes taking previous experience and potential outcomes into account. The subjective reports of stress experience refer to the conscious perception of the stimuli as threatening or negative and the possible verbalization of this state as stressful. Finally, the stress response is triggered "whenever there is a discrepancy between what is expected [..] (set value; SV) and what is happening (actual value; AV)" (Ursin & Eriksen, 2004, p. 572). In line with homeostatic theories, stress occurs whenever the brain detects a discrepancy between the SV and the AV. Within the CATS, the stress response is considered a non-specific response reflected by an increase in arousal (activation) and corresponding changes in behavior. As proposed in the AL-model (McEwen, 1998b), different physiological systems are involved in the stress response with individual as well as situational variance and reciprocal relationships. The stress response is maintained until the discrepancy between the AV and SV is resolved by changing either the AV or the SV. According to the CATS, a short-lasting stress response is considered adaptive leading to coping behavior. When the expectancy regarding the coping behavior is positive, the stress response may be reduced or eliminated. However, in case of a lack of coping resources, the arousal is sustained increasing the risk of stress-related diseases (Ursin & Eriksen, 2004, 2010).

2.1.2 The physiology of stress

The HPA axis and the locus coeruleus-norepinephrine (LC-NE) system act as the two major pathways of the brain capable of influencing almost every cell during the exposure to stress (Chrousos & Gold, 1992; Habib et al., 2001). With this, the stress responses incorporate the activation of two distinct but interrelated systems (de Kloet et al., 1998; Gunnar & Quevedo, 2007). The LC-NE system located in the brain stem plays a crucial role in the immediate physiological response to stress triggering the fight-or-flight

response (Cannon, 1914) by reducing the activity of the parasympathetic nervous system and activating the sympathetic nervous system. Within milliseconds, epinephrine and norepinephrine are released throughout the brain and the body increasing alertness and vigilance as well as providing additional energy to prepare the body for either fighting or fleeing. Most of the epinephrine and approximately 30% of the norepinephrine released into the bloodstream during stress originate from the adrenal medulla, while the remaining norepinephrine is released from sympathetic nerve endings (Nostramo & Sabban, 2015). The activation of the LC-NE system results in increased arousal and vigilance through activation of core limbic structures (e.g., amygdala) as well as numerous peripheral physiological changes such as increased heart rate or blood pressure (Chrousos & Gold, 1992; Pruessner & Ali, 2015).

While this thesis primarily examines the HPA axis (re)activity in burnout, there exist numerous sites of interaction between the HPA axis and the LC-NE system as both systems are anatomically and functionally connected. For example, both systems engage in a mutually reinforcing feedback loop, where activation of one system tends to stimulate the other (Chrousos & Gold, 1992). However, despite the relevance of the LC-NE system for stress regulation in general (for an detailed overview see Nostramo & Sabban, 2015), the present chapter focuses on the HPA axis owing to the research objectives of the thesis.

The HPA axis with its end product of glucocorticoids (cortisol in most mammals including humans, corticosterone in rats, mice, and other rodents) is an essential adaptive system promoting survival as well as psychological and physiological functioning (de Kloet et al., 1998; Jankord & Herman, 2008). In coordination with other physiological systems, the HPA axis demonstrates two modes of operation. First, under basal and relatively unthreatening conditions, glucocorticoid secretion follows a circadian rhythm controlled by inputs from the nucleus suprachiasmaticus, with its highest level typically at the initiation of the waking cycle. The increased secretion of glucocorticoids during the waking phase is considered crucial for ensuring the functional balance of various physiological systems (de Kloet et al., 1998; Herman et al., 2003; Herman et al., 2016; Kalsbeek et al., 2012). Thereby, the activity of the HPA axis is pulsatile reflected by about one pulse per hour leading to phasic secretion of its hormones (de Kloet & Derijk, 2004). Under basal conditions, glucocorticoids facilitate the coordination of circadian events, including sleep / wake cycle as well as energy mobilization, and play a decisive

role in higher-order cognitive processes such as selective attention and learning (de Kloet et al., 1998; Herman et al., 2003; Herman et al., 2016; Kalsbeek et al., 2012).

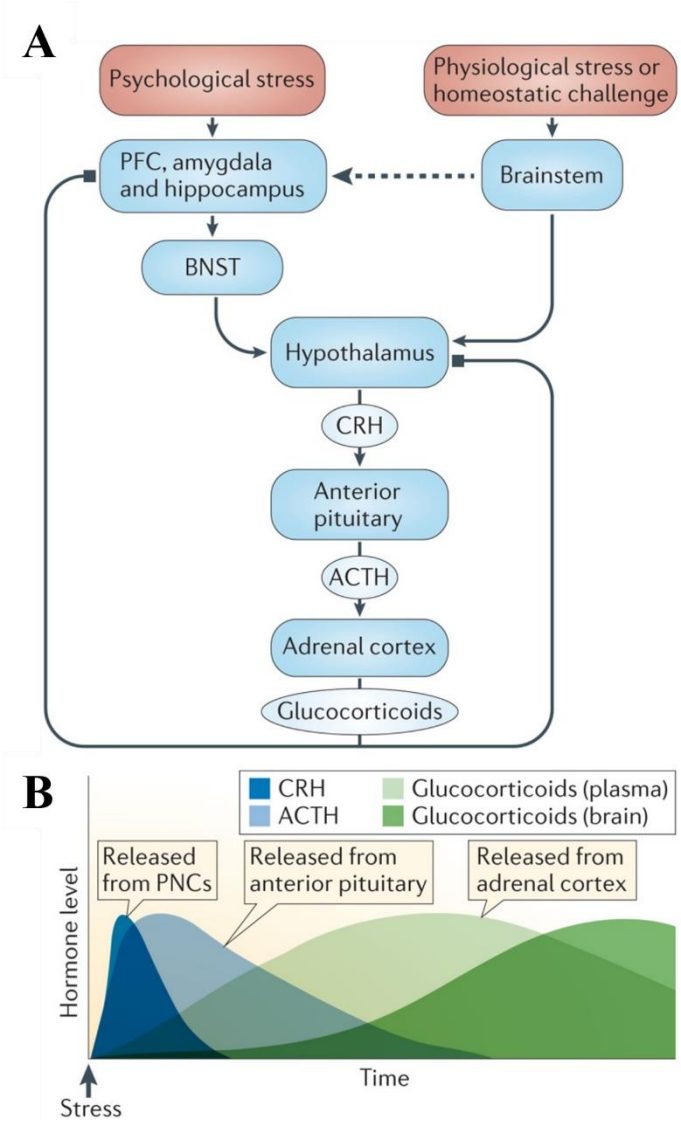
Importantly, the second mode of operation of the HPA axis and the principal topic of this chapter, is the glucocorticoid secretion under stress. The HPA axis stress response can be activated through mainly two stimulus-specific neural pathways: First, reflexively by sensory signals in response to physiological stressors (e.g., inflammatory challenges or painful stimuli) referring to *reactive* stress responses prompted by ascending peripheral signals via serotonergic or catecholaminergic projections from the brainstem or from other sensory regions to the neurons of the hypothalamic paraventricular nucleus (PVN). Secondly, psychological stressors (real, anticipated, or imagined) induce *anticipatory* HPA axis stress responses via stress-excitatory and stress-inhibitory limbic structures (de Kloet & Derijk, 2004; Herman et al., 2003; Herman et al., 2016). The distinction between reactive and anticipatory stress responses resulted from the observation that physiological stressors lead to a physiological imbalance with glucocorticoid secretion being a *direct* reaction to these conditions (= reactive stress response). In contrast, psychological stressors do not instantly induce a real physiological challenge or imbalance but may lead to an *anticipation* of a physiological challenge (= anticipatory stress response). Thus, HPA axis activation through psychological stressors requires the involvement of pre-limbic brain structures (Heck & Handa, 2019; Herman et al., 2016; Jankord & Herman, 2008). In detail, potential psychological stressors are processed in neural circuits, including the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC). These structures receive information from subcortical as well as cortical areas as well as ascending inputs from the e.g., locus coeruleus and raphe nuclei and activate the PVN mostly indirect via GABAergic neurons surrounding the PVN or located in the bed nucleus of the stria terminalis (BNST). Thereby, inputs from excitatory (amygdala) and inhibitory (hippocampus, mPFC) structures are integrated in the PVN determining the net endocrine stress response (Godoy et al., 2018; Herman et al., 2016; Joëls et al., 2012; Ulrich-Lai & Herman, 2009).

Despite different pathways, physiological and psychological stressors both stimulate hypophysiotropic neurons of the PVN initiating the release of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the PVN of the hypothalamus into the pituitary portal circulation (Gunnar & Quevedo, 2007; Herman & Cullinan, 1997; Herman et al., 2003). By binding to receptors on corticotropes in the anterior pituitary, CRH and AVP cause the release of adrenocorticotropic hormones (ACTH) from the

anterior pituitary into the hypophyseal portal system. ACTH then travels to the adrenal cortex binding on receptors in the zona fasciculata of the adrenal cortex prompting a complex biochemical cascade of synthesizing and pulsatile releasing of glucocorticoids (Godoy et al., 2018; Herman & Cullinan, 1997; Herman et al., 2003; Herman et al., 2016). Glucocorticoids exert their effects via high-affinity mineralocorticoid receptors (MR) predominantly located in the hippocampus and through ubiquitously distributed low-affinity glucocorticoid receptors (GR) (de Kloet & Derijk, 2004; Herman et al., 2016). With this, once secreted glucocorticoids can target and affect neural cells in the brain as well as nearly every tissue and cell of the body. This results in a wide range of possible glucocorticoid-related effects such as energy mobilization and gluconeogenesis promotion in the liver as well as pro- and anti-inflammatory and anti-reproductive effects (Kuo et al., 2015; Tsigos & Chrousos, 2002; Vedder, 2007). In addition, glucocorticoids have a variety of effects on the brain and thus on cognition including memory and learning as well as attention and vigilance (de Kloet, 2000; Lupien et al., 2007; McEwen, 2000b).

However, before glucocorticoids can reach and bind to (neural) target cells, fluctuating concentrations are locally regulated by different factors. First, 90 to 95% of circulating glucocorticoids are bound to its primary carrier proteins corticosteroid-binding globulin (CBG) and additionally to albumin. Thus, only the remaining 5 to 10% of unbound glucocorticoids are biologically active by diffusing and binding on receptors (Hammond, 1990; Joëls et al., 2012). Under basal conditions, CBG thereby controls bioavailability of glucocorticoids protecting tissues and the brain from potentially adverse effects of high glucocorticoid concentrations. However, bioavailability of glucocorticoids can be increased under stressful conditions, either by surpassing the CBG saturation through increased pulsatile release of glucocorticoids or by altered binding properties and expression levels. Importantly, free unbound glucocorticoids can diffuse across the blood-brain barrier owing to their small size and lipophilic nature. Once crossed the blood-brain barrier, unbound glucocorticoid level are further regulated by enzymes (i.e., 11ß-hydroxysteroid dehydrogenase enzymes; for a review see Wyrwoll et al., 2011) (Joëls et al., 2012; Keller-Wood, 2015). Figure 1 illustrates the HPA axis response to stress (A) as well as the temporal dynamics of HPA axis stress responses (B).

Figure 1
(A) Overview of the HPA axis response to psychological as well as physiological stress and (B) temporal dynamics of HPA axis stress responses



Note. Figure A: PFC = prefrontal cortex; BNST = bed nucleus of the stria terminalis; CRH = corticotropin releasing hormone; ACTH = adrenocorticotropic hormone. Figure B: CRH is released from the parvocellular neuroendocrine cells (PNCs) and activates the secretion of ACTH (peaking within 15 min after stressor onset). In turn, glucocorticoids peak usually within 20-60 min after stressor onset (Herman et al., 2016; Pruessner & Ali, 2015).
Reprinted from *Nature Reviews Neuroscience*, *35*, Bains. J., Cusulin, J., & Inoue, W., Stress-related synaptic plasticity in the hypothalamus, 377-388., https://doi.org/10.1038/nrn3881. Copyright (2015), reproduced with permission from Springer Nature (license number 5725270068661, license date 10.02.2024).

Importantly, glucocorticoids exert a negative feedback control on HPA axis activity preventing adverse effects of extreme glucocorticoid levels by limiting the secretion of corticotropin and ACTH from the pituitary and the secretion of CRH and AVP from the

hypothalamus. Negative feedback effects of glucocorticoids are mediated by MR and GR in the brain and the anterior pituitary with glucocorticoid mechanisms depending on receptor type and location (Gjerstad et al., 2018; Keller-Wood, 2015). Given their six- to ten-fold higher affinity, MR are extensively bound at low glucocorticoid levels and are important for controlling basal HPA axis activity. In contrast, lower affinity GR are bound only at high glucocorticoid levels mediating the majority of glucocorticoid negative feedback mechanisms under stress (Herman et al., 2016). Glucocorticoid feedback actions can be distinguished into fast nongenomic (seconds to minutes) as well as delayed genomic (hours to days) feedback effects. The main fast feedback effects of glucocorticoids are 1) nongenomic, GR-mediated effects in the hypothalamus inhibiting CRH neurons (within 3 to 5 min), 2) nongenomic MR-mediated effects in the hippocampus activating the inhibitory hippocampal circuits (within 10 min), and 3) non-genomic effects on the anterior pituitary inhibiting CRH stimulated ACTH secretion (within 10 to 20 min) (Gjerstad et al., 2018; Keller-Wood, 2015; Ulrich-Lai & Herman, 2009). In contrast, the main delayed genomic feedback effects of glucocorticoids can be summarized as follows 1) inhibition of CRH and ACTH secretion, 2) inhibition of proopiomelanocortin (POMC, i.e., an ACTH precursor molecule), CRH, and AVP gene expression, and 3) effects on the hippocampus and other (pre-)limbic brain structures including the brain stem (Dallman, 2005; Keller-Wood, 2015). The negative feedback loop is an essential mechanism of the HPA axis, as it limits the glucocorticoid-related catabolic, lipogenic, anti-reproductive, and immunosuppressive exposure of the body (Charmandari et al., 2005).

While quantitatively and temporally well-orchestrated stress responses of the HPA axis are essential for successful adaption, stress-related activation of the HPA axis can have deleterious health effects depending on the magnitude and chronicity of the stressor in terms of *too long*, *too often*, or *too intense* as well as on individual vulnerability (e.g., prenatal development and infancy). Maladaptive alterations of HPA axis activity are mainly characterized by increased or reduced basal activity and/or reactivity of the HPA axis (Chrousos, 2009). Both states of increased and decreased HPA axis activity are associated with numerous adverse psychological and physiological conditions. However, empirical findings on the direction of HPA dysregulation (i.e., increased HPA axis activity and hyperreactivity versus decreased HPA axis activity and hyporeactivity) for a particular adverse condition tend to vary across studies. Furthermore, particularly in the case of adverse mental conditions such as depression, it is often unclear, whether

alterations of HPA axis activity lead to health impairments or vice versa, or whether the relationship is best described as reciprocal (Chrousos, 2009; Zänkert et al., 2019; Zorn et al., 2017).

In sum, the HPA axis is an essential adaptive system ensuring psychological and physiological functioning under basal and stressful conditions. Nonetheless, dysregulation in this system may lead to a variety of adverse psychological and physiological conditions. McEwen (2019, p. 3) summed up the multifaced roles of glucocorticoids in his commentary entitled "*What is the confusion with cortisol?"* as follows*:* "the confusion with cortisol is that it does too many important beneficial things but can also cause problems!".

2.1.3 Biopsychological methods in stress research

The following sections provide a brief overview of biopsychological methods in stress research. Given the abundance of available methods, the focus is on the research methods applied in the studies of the thesis.

2.1.3.1 Measurement of cortisol in human stress research

In human stress research, the steroid hormone cortisol is one of the most frequently studied hormones as it can be reliably and non-invasively (except from blood) measured in various biological materials such as blood, saliva (Hellhammer et al., 2009), urine (Remer et al., 2008), hair (Stalder & Kirschbaum, 2012), and, nails (Nater et al., 2013; Phillips et al., 2021). Blood (plasma) and saliva samples reflect acutely circulating cortisol concentrations and are well-suited for measuring the course of acute cortisol responses to stress, pharmacological challenges, or the cortisol awakening response (CAR; i.e., a marked increase in cortisol secretion over the first 30-45 min after morning awakening; for details see Stalder et al., 2016). However, these real-time cortisol measures are of limited use for collecting information on long-term cortisol secretion over the past weeks or months as acute cortisol levels fluctuate substantially across the day and are affected by numerous factors (Kudielka et al., 2009; Stalder & Kirschbaum, 2012; Stalder et al., 2016; Zänkert et al., 2019). In contrast, the recent introduction of analyzing cortisol in hair made it feasible to non-invasively record extended periods of cortisol secretion. Based on the speed of scalp hair growth of approximately 1cm per month, analyzing hair cortisol concentrations (HCC) provides the opportunity to retrospectively capture extended periods of cumulative cortisol secretion (1cm = 1

month). Although, the mechanisms by which cortisol is incorporated into human hair are not fully understood, the utility and validity of HCC was demonstrated in numerous studies (Kirschbaum et al., 2009; Short et al., 2016; Stalder & Kirschbaum, 2012; Stalder et al., 2017). Consequently, HCC was suggested a promising biological marker of chronic stress (Russell et al., 2012). In the present thesis, *Study II* investigated the cross-sectional and longitudinal association between burnout and HCC, while in *Study III* salivary cortisol responses to acute psychosocial stress were examined with respect to burnout.

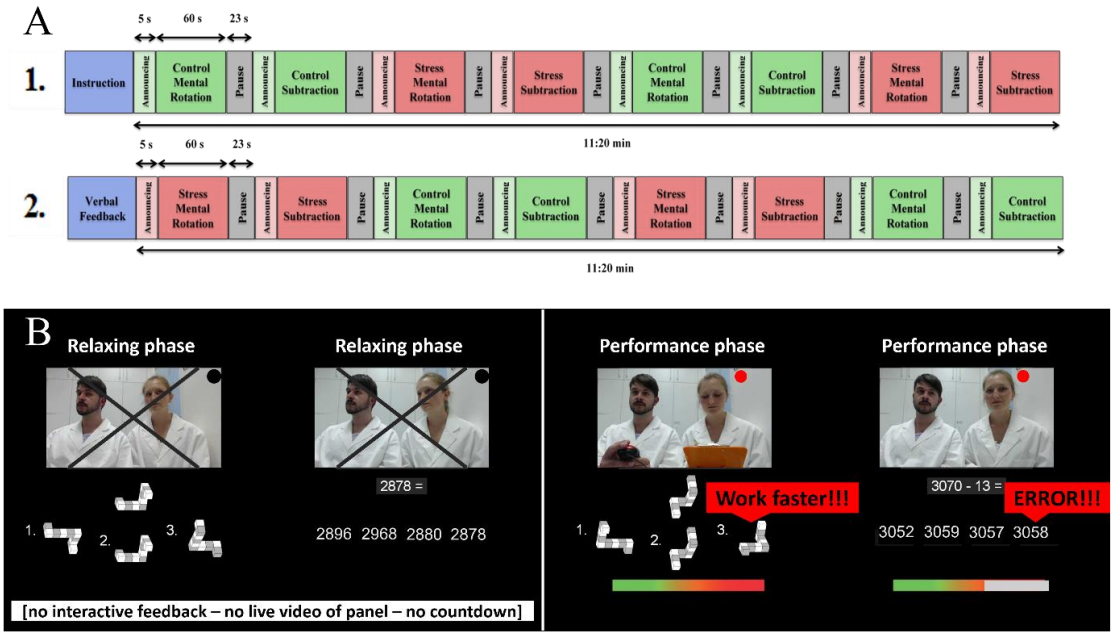
2.1.3.2 Laboratory stress paradigms

The development of laboratory stress paradigms followed the assumption that measuring HPA axis responses under challenge may be more sensitive for detecting possible HPA axis dysregulations compared to basal HPA axis activity (Zänkert et al., 2019). With respect to psychosocial stress, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993; Kirschbaum, Wüst, et al., 1992) has become the standard protocol for the experimental induction of moderate psychosocial stress in laboratory settings (Kudielka et al., 2007). In its original version, the TSST consists of a brief preparation period (original 10 min, to date usually 3 min), followed by a 5 min mock job interview and a 5 min surprise mental arithmetic task performed in front of an investigator panel (original 3 persons, to date often a gender-mixed 2 persons panel). The investigator panel evaluates the participant's performance and is instructed to behave in a standardized, unresponsive, neutral manner promoting the experience of uncontrollability and social-evaluative threat (Goodman et al., 2017; Kirschbaum et al., 1993; Kudielka et al., 2007; Labuschagne et al., 2019). For a comprehensive description of the protocol and different versions of the TSST, refer to Labuschagne et al. (2019). By incorporating the components of social-evaluative threat and uncontrollability (Dickerson & Kemeny, 2004), the TSST reliably induces two-to-threefold rises in salivary cortisol levels in about 70-80% of examined subjects. Besides increases in salivary cortisol and self-reported stress, the TSST is empirically proven to evoke significant increases in numerous stress-sensitive psychobiological parameters from the e.g., HPA and SAM axis as well as from the immune and cardiovascular system (Allen et al., 2014; Kudielka et al., 2007).

Importantly, with the advancement of bran imaging techniques it became feasible to measure not only peripheral markers of stress such as cortisol, but also neural responses of the brain to psychosocial stress. Thereby, the Montreal Imaging Stress Task (MIST)

was the first laboratory psychosocial stress protocol suited for imaging environments (Dedovic et al., 2005). Later, Streit et al. (2014) introduced Scan*STRESS* as a psychosocial stress experiment for functional magnetic resonance imaging (fMRI) environments, which was applied in *Study III* of the present thesis. While the MIST is based on the Trier Mental Challenge Test (Kirschbaum, Diedrich, et al., 1992), Scan*STRESS* follows the approach of the TSST (Henze et al., 2020; Kirschbaum et al., 1993; Streit et al., 2014). Scan*STRESS* is presented as a block design (stress condition versus control condition) consisting of two runs with a total duration of 24 min. During the stress conditions, the decisive stress elements of uncontrollability and social evaluative threat are implemented by prompting the subject to solve challenging cognitive tasks (mental rotation and serial subtraction) under time pressure while lying in the scanner. Similar to the TSST, subjects are monitored via live video by negative feedback given by the observational panel (2 persons). Between both runs, the subject receives standardized negative verbal feedback regarding the individual performance. In addition, subjects are asked to improve their performance, otherwise the data must be discharged. Conversely, during control blocks subjects have to solve less demanding tasks, i.e., figure and number matching without time pressure and observation (Henze et al., 2020; Streit et al., 2014). The experimental procedure is illustrated in Figure 8 (Chapter 6). The experimental design of Scan*STRESS* as well as an illustration of the conditions (stress and control) and tasks are presented in Figure 2.

Figure 2
(A) Experimental Design of ScanSTRESS consisting of an instruction phase, two runs and negative verbal feedback of the panel between both runs. (B) Illustration of the two different conditions (control and stress) and the two different tasks (mental rotation and subtraction)



Note. Adapted from Henze et al. (2020).

Beyond the MIST, Scan*STRESS* is one of the most used psychosocial stress paradigms for fMRI environments reliably inducing increases in salivary and blood cortisol levels, heart rate, and self-reported stress. Scan*STRESS* was further proven to evoke neural stress responses in striato-limbic clusters typically including stress-sensitive structures such as mPFC, amygdala, and hippocampus (Berretz et al., 2021; Henze et al., 2020; Noack et al., 2019; van Oort et al., 2017). For a more comprehensive description of the Scan*STRESS* protocol as well as modified versions of the paradigm refer to Henze (2021). In *Study III* of this thesis, the improved protocol of Scan*STRESS* as presented in Henze et al. (2020) was applied.

2.1.3.3 Allostatic load-index

In addition to the brief overview outlined in Chapter 2.1.1 on the theoretical background of the stress concept, this chapter specifies the assumptions of the AL-model and introduces the method of assessing and calculating an index of AL, which was applied in *Study I* of the present thesis.

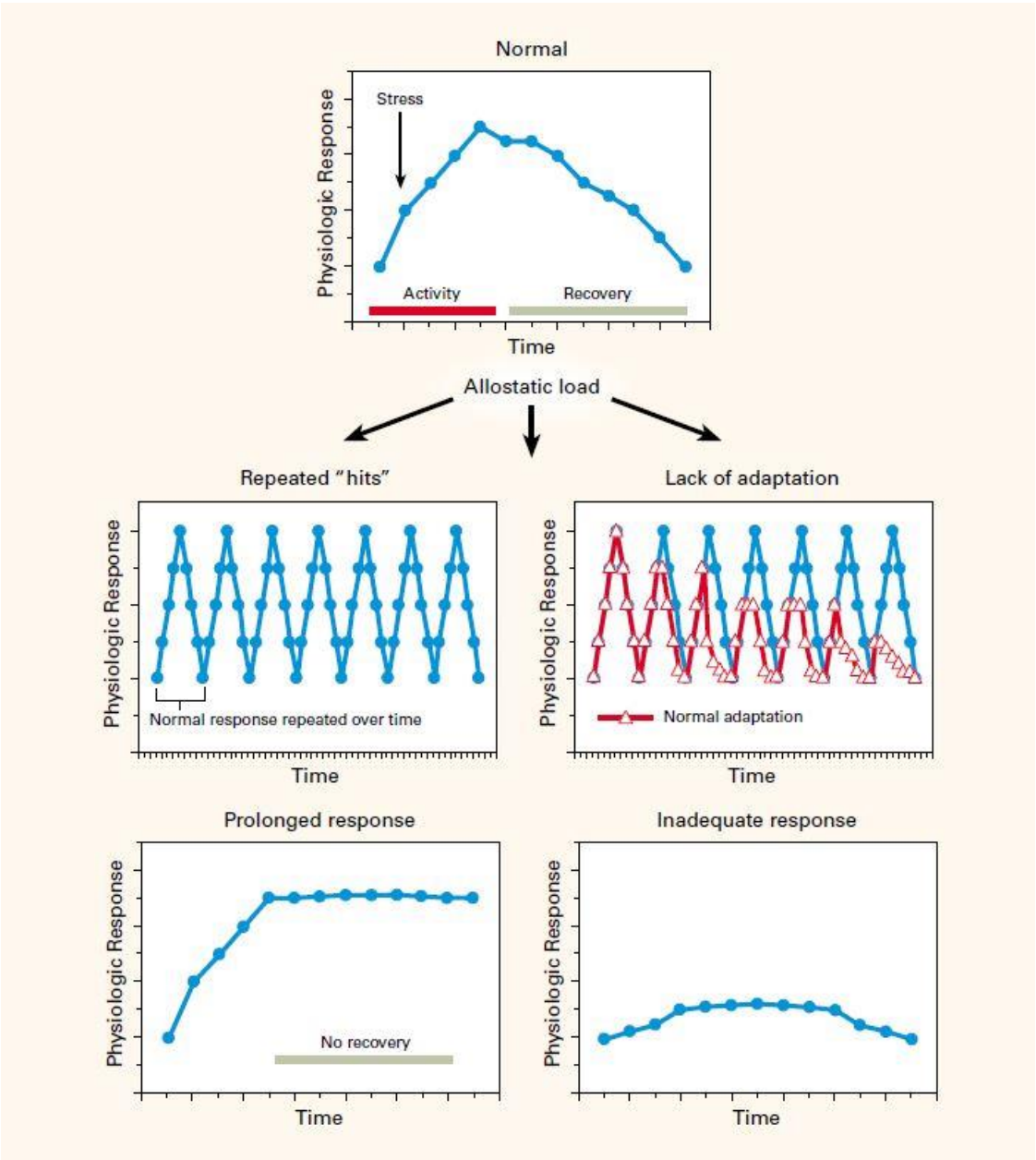
The AL-concept serves as a unifying framework for understanding the adaptive as well as adverse effects of (chronic) stress. Within the AL-model, the brain is considered the central organ of stress processing mediating the adaption to physiological and psychological challenge via different bodily systems (e.g., autonomic, neuroendocrine, immune, behavioral). The AL-model does not focus on a particular biomarker such as cortisol or one specific system such as the HPA axis. In contrast, McEwen (2016) assumed that stress responses involve numerous interacting mediators of different bodily systems, which in turn are interconnected in complex non-linear relationships. Importantly, the AL-model attempts to take this complexity into account.

Within the AL-model it is differentiated between allostasis and AL (McEwen, 2016). Sterling and Eyer (1988) introduced the term allostasis in contrast to homeostasis as the latter should refer to bodily functions being directly critical for survival such as pH, body temperature, or oxygen tension. In contrast, allostasis, refers to the active processes of maintaining stability (or homeostasis) through physiological as well as behavioral changes (McEwen, 2016; McEwen & Wingfield, 2003). Variations in blood pressure across the day depending on physical activity or catecholamine and glucocorticoid secretion for energy mobilization during stress are typical examples for processes of allostasis. Thus, the stress response described in Chapter 2.1.2 can be characterized as a basic allostatic mechanism. The so-called primary mediators of allostatic processes include, among others, hormones of the HPA axis, catecholamines, the parasympathetic system as well as pro- and anti-inflammatory cytokines (McEwen, 2000b, 2016; Sterling & Eyer, 1988). Importantly, the AL-model follows the assumption that each mediator is characterized by short-term adaptive actions promoting psychological and physiological functioning (= allostasis), but may come along with long-term adverse health effects (McEwen & Seeman, 1999). Figure 3 illustrates the deviation of four types of AL from a healthy and adaptive response to stress (McEwen, 1998a). These types of AL are repeated “hits” from multiple novel or chronic stressors, a lack of adaption to the same stressor repeatedly presented, a prolonged response characterized by a delayed shut down, and finally an inadequate response potentially leading to compensatory (hyper- or hypo-) activity of other stress-sensitive systems (McEwen & Seeman, 1999).

According to Bruce S. McEwen (1998, p. 37), AL can be defined as the “wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaption to environmental challenge”. In turn, AL can increase the risk of developing serious pathophysiological

and psychopathological conditions (i.e., allostatic overload) following a complex cause and effect cascade. Thereby, the concept of allostasis and AL provides a unifying approach incorporating different stress-sensitive systems with the aim of explaining the pathogenesis of stress-related diseases (McEwen & McEwen, 2015; McEwen & Seeman, 1999; McEwen & Wingfield, 2003).

Figure 3
Four types of allostatic load



Note. Reproduced with permission from *New England Journal of Medicine*, *338*(3), McEwen, B.S., Protective and damaging effects of stress mediators, 171-179., https://doi.org/10.1056/NEJM199801153380307. Copyright (1998) Massachusetts Medical Society.

Seeman et al. (1997) introduced an operationalization of AL by combining multiple physiological parameters into a count-based AL-index as a marker of cumulative biological risk (Seeman et al., 2001). The classical index of AL by Seeman et al. (1997) comprised the following ten parameters: systolic and diastolic blood pressure, waist-hip ratio (WHR), total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (TC/HDL), HDL cholesterol, dehydroepiandrosterone-sulfate (DHEA-S), total glycosylated hemoglobin level, as well as 12-hour urinary cortisol, norepinephrine, and epinephrine levels.

Based on the distribution of the respective study sample, quartiles are calculated for each parameter. Each parameter is then coded for each participant with either 1 if falling within the top quartile (lowest quartile for DHEA-S and HDL cholesterol, respectively) or 0 if falling below the critical quartile. Subsequently, an index of AL can be calculated for each subject by summing up the coded parameters resulting in a range of 0 to 10 for the classical AL-index comprising ten parameters. Thereby, an AL-index score of 10 represents the highest possible score indicating a high degree of "cumulative biological burden exacted on the body through attempts to adapt to life's demand" (Seeman et al., 2001, p. 4770). Since the introduction by Seeman et al. (1997), researchers have incorporated a broader range of biological parameters for measuring AL, including different neuroendocrine, blood coagulation, immune, metabolic, and cardiovascular parameters. In addition, meanwhile different algorithmic formulations and statistical approaches for calculating AL-indices were applied compared to the classical AL-index by Seeman et al. (1997). An overview and description of included parameters as well as different calculation methods is provided by Juster et al. (2010).

Beyond the theoretical significance of the AL-model in biopsychological stress research, the utility and applicability of AL-indices have been demonstrated in numerous cross-sectional and prospective studies reporting on adverse effects of AL on mental and physical health (Edes & Crews, 2017; Guidi et al., 2021; Juster et al., 2010; Juster & Misiak, 2023; Parker et al., 2022).

2.2 Burnout

The following chapter provides an overview of the burnout concept with respect to symptomatology and development of the burnout syndrome. Finally, the challenging attempt is taken to differentiate burnout from depression and other exhaustion-related constructs. Although the concept of burnout has been extended beyond the work-context

to e.g., parental burnout (for a review see Paula et al., 2021), the present chapter focuses exclusively on work-related burnout.

2.2.1 Definition and assessment of burnout

Importantly, burnout is not listed as a diagnosis neither in the *International Classification of Diseases (ICD) 11th revision* (World Health Organization, 2019) nor in the *Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th edition* (American Psychiatric Association, 2013). Consequently, the burnout concept lacks clear nosological and definable symptoms. Still, this section focuses on the main conceptualizations of burnout established over the last fifty years of burnout research since the introduction of the burnout concept in 1974 by Freudenberger.

The most prominent definition of burnout stems from the burnout pioneer Christina Maslach, which is in line with the definition provided by the ICD-11, where burnout is listed as factor influencing health status or contact with health services (World Health Organization, 2019). According to Maslach et al. (2001), burnout develops as a prolonged response to chronic work stress and can be characterized by the key dimension (emotional) exhaustion (EE; i.e., depleted emotional and physical resources) and the two dimensions of cynicism / depersonalization (DP; i.e., a negative or hostile attitude towards one's job), and inefficacy / lack of personal accomplishment (LA; i.e., a negative professional self-evaluation). The consideration of EE as the core symptom of burnout led authors to the assumption that exhaustion is the only and sufficient factor of burnout. However, according to Maslach et al. (2001) such a unidimensional approach may deny the mental distancing from work and cynical attitudes presumably as a way of coping with the work overload as well as the feelings of inefficacy experienced by affected individuals. While EE is assumed to represent the basic individual stress component of burnout resulting from long-term involvement in an over-demanding workplace, DP reflects the interpersonal and LA the self-evaluative dimension of burnout. Thereby, burnout is assumed to impair personal, social, and professional functioning in affected individuals according to the burnout concept from Maslach (Ahola, 2007; Maslach & Leiter, 2016a, 2016b; Maslach et al., 2001; Schaufeli, 2017). The three dimensions of burnout can be assessed using the Maslach Burnout Inventory (MBI) (Maslach et al., 1997), which is the most frequently used questionnaire in burnout research. To date, different versions of the MBI subsist focusing either on certain professional groups from human services (MBI-Human Services Survey), medical care (MBI-Human Services

Survey for Medical Personnel), and education (MBI-Educator Survey), or on the general population (MBI-General Survey). The MBI-General Survey (MBI-GS) was applied in the studies of the present thesis to capture the burnout symptomatology of participants (Schaufeli et al., 2020; Schaufeli et al., 2009). For the MBI-GS empirically derived cut-offs exist allowing a classification into three groups of "no burnout symptoms", "some burnout symptoms", and "serious burnout" (Kalimo et al., 2003).

Despite the dominance of the MBI in burnout research reflected by the application in approximately 90% of all empirical studies, alternative questionnaires based on different conceptualizations of burnout have been developed (Doulougeri et al., 2016; Schaufeli et al., 2020). In detail, the Shirom-Melamed Burnout Measure (SMBM) is based on the COR theory by Hobfoll (1989). Burnout is thereby defined as a combination of the respective sub-scales physical fatigue, emotional exhaustion, and cognitive weariness. In contrast to the MBI, the SMBM defines burnout exclusively as a form of energy loss on a physical, emotional, and cognitive level (Shirom, 2003; Shirom & Melamed, 2006). Similar to the SMBM, the exhaustion sub-scale of the Oldenburg Burnout Inventory (OLBI) covers physical, emotional, and cognitive aspects of exhaustion. The second sub-scale of the OLBI, called disengagement from work, is rather similar to the DP scale of the MBI (Demerouti et al., 2003). Recently Schaufeli and colleagues (2020) introduced the Burnout Assessment Tool (BAT) defining burnout as a "work-related state of exhaustion that occurs among employees, which is characterized by extreme tiredness, reduced ability to regulate cognitive and emotional processes, and mental distancing. These four core dimensions of burnout are accompanied by depressed mood as well as by non-specific psychological and psychosomatic complaints" (Schaufeli et al., 2020, p. 4). While the three core dimensions of exhaustion as well as cognitive and emotional impairment seem to be rather analogous to the dimensions of the SMBM and the OLBI, the fourth core dimension of mental distancing refers to the unwillingness to invest energy. The incorporation of three often co-occurring secondary dimensions (i.e., depressed mood, psychological distress, and psychosomatic complaints) displays a new feature in the measurement of burnout (Schaufeli et al., 2020). Another common burnout measure is the Copenhagen Burnout Inventory (CBI) consisting of the three sub-scales personal burnout, work-related burnout, and client-related burnout. The authors of the CBI proposed that burnout is not synonymous with fatigue or exhaustion but focused rather on the individual attribution of the experienced exhaustion to specific domains (i.e., personal, work, and client-related). Personal burnout

thereby refers to the general degree of physical and psychological exhaustion regardless of the attributed domain (i.e.: “How exhausted are you?”). In contrast, work-related burnout relates to the experienced physical and psychological exhaustion exclusively attributed to work. By comparing the personal burnout with the work-related burnout scale, researchers can differentiate between work-related exhaustion in the sense of burnout and exhaustion resulting from non-work factors such as health problems or family demands. In addition, the client-related burnout scale measures the exhaustion attributed to the interpersonal work with clients such as students or patients (Kristensen et al., 2005). While most burnout questionnaires were developed for quantitively measuring the degree of burnout symptomatology, the Burnout Clinical Subtype Questionnaire (BCSQ) aims at classifying different manifestations of the burnout syndrome depending on respective coping strategies and the degree of dedication to work. Thereby, three different subtypes were proposed: *frenetic*, *underchallenged*, and *worn out*. The frenetic subtype is characterized by high degrees of involvement, ambition, and motivation, while high degrees of boredom as well as a lack of personal development and concern reflect the underchallenged subtype. Finally, individuals experiencing a lack of control regarding results or recognition for efforts are assigned to the worn-out subtype (Montero-Marín & García-Campayo, 2010; Montero-Marín et al., 2011)

However, after 50 years of burnout research, consensus on the measurement and classification of burnout is still pending reflected by over one-hundred reported definitions and symptoms of burnout (Hillert, 2012; Rotenstein et al., 2018; Schwenk & Gold, 2018; Shoman et al., 2021). According to Shoman et al. (2021) the lack of harmonization with respect to definition and measurement precludes a reliable estimation of its prevalence rates. The unclear diagnostic criteria can thereby lead to both exaggeration or underestimation of the burnout prevalence with reported prevalence rates ranging substantially from 0% to 99.8% depending on the applied burnout classification and examined populations (Alkhamees et al., 2023; Bianchi et al., 2015; Claponea et al., 2022; Heinemann & Heinemann, 2017; Rotenstein et al., 2018; Shoman et al., 2021). However, even conservative studies reported on estimated prevalence rates of burnout to be around 10% and thereby typically exceeding the prevalence rates for mental disorders such as depression or anxiety disorders (Heinemann & Heinemann, 2017).

Given the conceptual ambiguity, especially the diagnosing of burnout or the dichotomous classification (burnout / no burnout) is considered challenging. As already

described, burnout is not listed as a psychiatric disorder. This is in line with the standpoint of the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). According to the DGPPN, burnout should be treated as a risk factor for the development of mental disorders and physical diseases. In case a mental disorder or physical disease develops as a consequence of burnout and chronic work stress, this should be additionally coded with the ICD-10 code of Z 73.0 (i.e., problems related to life-management difficulty). If no mental disorder or physical disease can be diagnosed while burnout symptomatology is present, only Z 73.0 should be coded (Berger et al., 2012).

With respect to diagnosis, Sweden represents a special case as the Swedish version of the ICD-10 contains the psychiatric diagnosis of "Exhaustion Disorder" (ED) reflecting clinical burnout and thereby offering clear diagnostic criteria listed in Table 1.

Table 1

Criteria of exhaustion disorder according to the Swedish National Board of Health and Welfare

A. Physical and mental symptoms of exhaustion during at least two weeks. The symptoms have developed in response to one or more identifiable stressors present for at least six months.
B. The clinical picture is dominated by markedly reduced mental energy, as manifested by reduced initiative, lack of endurance, or increased time needed for recovery after mental effort.
C. At least four of the following symptoms have been present, nearly every day, during the same two-week period: 1. Concentration difficulties or impaired memory 2. Markedly reduced capacity to tolerate demands or to work under time pressure 3. Emotional instability or irritability 4. Sleep disturbance 5. Marked fatigability or physical weakness 6. Physical symptoms such as aches and pains, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sound
D. The symptoms cause clinically significant distress or impairment in occupational, social, or other important respects.
E. The symptoms are not due to the direct physiological effect of a substance (e.g., an abuse of drug or medication) or a physical illness/injury (e.g., hypothyroidism, diabetes, infectious disease).

Note: Criteria A-E must be fulfilled to diagnose exhaustion disorder. If a patient fulfills the criteria for major depression disorder, dysthymic disorder, or general anxiety disorder, exhaustion disorder should be coded as secondary diagnosis (Grossi et al., 2015). Table adapted from Wallensten et al. (2016, p. 2).

Based on a review by Grossi et al. (2015), ED displays the most valid equivalent of clinical burnout and is estimated almost as prevalent as major depression disorder (MDD) in Sweden accounting for most cases of long-term sick leave reimbursements compared to any other single diagnosis (Lindsäter et al., 2022). In contrast to established burnout questionnaires, the diagnosis of ED also considers a specific pathogenesis by requiring one or more identifiable stressors being present for at least six months and does not focus exclusively on the presence of different symptoms. In addition, it is requested to rule out the presence of physical diseases such as hypothyroidism or diabetes potentially causing the exhaustion symptomatology. In the studies of the present thesis, participants were also selected based on etiological factors combined with strict exclusion criteria for e.g., physical diseases potentially accounting for the symptoms of exhaustion. Moreover, in contrast to most of the previous studies, third-party information were also collected as suggested by Nadon et al. (2022). The recruitment procedure of the thesis' studies is described in detail in *Study I* (Chapter 4).

2.2.2 The development of burnout

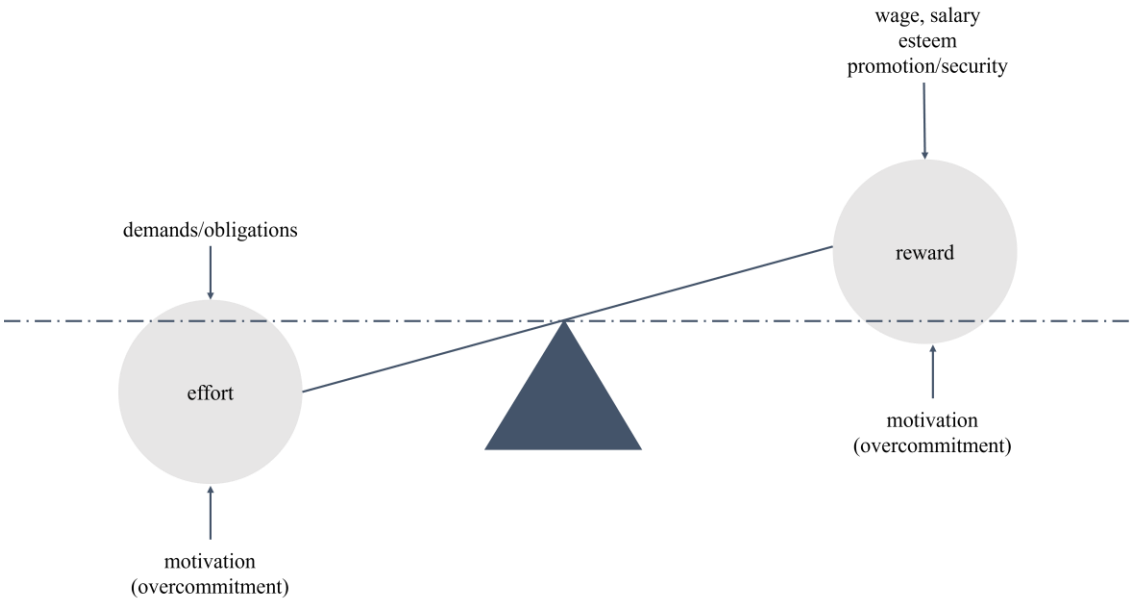
The present chapter focuses on the development of burnout. At first, the effort-reward imbalance (ERI) model of chronic work stress is presented as burnout is assumed to develop as a possible consequence of chronic work stress. In addition, the concept of "areas of worklife" (AW) is described as a burnout-specific model. In addition to etiological concepts, different phase models proposing a causal trajectory of burnout symptomatology over time exist. However, due to the lack of convincing empirical evidence, phase models will not be presented in the subsequent chapter (for an overview of phase models see Berger et al., 2012; Taris et al., 2005).

2.2.2.1 The model of effort-reward imbalance at work

The model of ERI from Siegrist (1996) was proposed as a model of psychosocial stress at work. In contrast to other concepts of chronic work stress, the ERI model emphasizes the importance of the employment contract rather than focusing on job task characteristics and is based on the fundamental principle of social reciprocity (Siegrist, 2016b). This principle reflects the expectancy of equivalence and fairness between personal effort ("give") and reward ("take") among individuals, groups or, parties representing a central feature of the ERI model. In the work context, the exchange of effort provided by the employee as well as the received reward from the employer is generally specified in the employment contract. The ERI model differentiates three basic

types of reward in the work context: salary or wage referring to financial reward, career promotion, and job security referring to status-related reward, and esteem or recognition referring to socio-emotional reward. Moreover, the employee's demands and obligations refer to effort. Thereby, a recurrent lack of reciprocity reflected by an unfavorable imbalance of high effort and low reward may lead to the experience of negative emotions and chronic work stress potentially affecting the mental and physical health of the working individual. In addition, imbalances between effort and reward are assumed to frequently occur under three distinct conditions: dependency, strategic choice, and overcommitment (OC). In case of dependency, the individual may have no alternative in the job market because of low qualification, age, or restricted mobility, and may therefore be susceptible for nonreciprocal contractual exchange and adverse working conditions. Employees can also consciously accept a reward crisis for a certain time as an anticipatory investment to improve their long-term career opportunities (i.e., strategic choice). This condition mainly occurs in early career stages and within highly competitive job markets. Above all, the absence of the expected long-term success is also considered to increase the degree of experienced chronic work stress. In addition to rather extrinsic demands, the ERI model takes the individual work-related motivation and coping characteristics into account. Individuals characterized by high levels of work-related OC are at greater risk for developing an ERI and chronic work stress. Thereby, OC is defined as a work-related motivational and coping pattern of continuously striving for high performance and sacrificing for one's job (Siegrist, 2007, 2016a, 2016b). The ERI model is illustrated in Figure 4.

Figure 4
The model of effort-reward imbalance at work



Note. Adapted from Siegrist (2016b).

Considered as one of the most influential frameworks in occupational health and stress research, the ERI model has been extensively applied and validated in numerous cross-sectional and prospective studies. Thereby, high degrees of ERI (i.e., high effort/low reward) and/or OC were associated with stress-related disorders such as cardiovascular diseases as well as mental disorders, and importantly burnout (Rugulies et al., 2017; Siegrist, 2016a; van Vegchel et al., 2005; Wahrendorf & Chandola, 2016).

The degree of ERI (i.e. the ratio between effort and reward) and OC can be measured with the effort-reward imbalance questionnaire (ERI-Q; Siegrist et al., 2004). In the studies of the present thesis, the short version of the ERI-Q (Siegrist et al., 2009) was applied to assess the degree of chronic work stress of participants. Thereby, only individuals characterized by high degrees of chronic work stress were assigned to the BO group assuring the burnout specific pathogenesis (Lehr et al., 2010).

2.2.2.2 Areas of worklife

Leiter and Maslach (2003) unified both empirical findings and different theoretical frameworks such as the ERI-model, the Job Demands-Resources Model (Bakker & Demerouti, 2007; Demerouti et al., 2001), or the demand-control model (Karasek, 1979) in their concept called "*areas of worklife"* (AW). Consequently, six key domains of risk

factors for the development of burnout were identified: workload, control, reward, community, fairness, and values. Like the ERI model, the AW model follows the assumption that person-job imbalances reflected by mismatches in those key domains promote the development of burnout. However, while the ERI model is a more general model for psychosocial stress at work focusing exclusively on effort and reward, the AW model is rather a burnout-specific model focusing on imbalances in six key domains associated with burnout. Leiter and Maslach (2003) proposed that the likelihood of burnout depends on the degree of experienced incongruence between the person and those major domains. Burnout in turn mediates the relationship between the person-job imbalances and negative outcome variables such as adverse mental and physical health, absenteeism, or reduced quality of work. Previous studies provided empirical support for the AW model as well as for the proposed mediation model (Leiter & Maslach, 2003; Maslach & Leiter, 2016a). Table 2 presents potential mismatches regarding the six key domains promoting the development of burnout (Leiter & Maslach, 2003; Maslach et al., 2001).

Table 2
Overview of potential mismatches within the six key domains of the areas of worklife model

Domain	Potential mismatches
Workload	Too many demands Lack of recovery Lack of skill
Control	Reduced capacity to influence decisions Lack of autonomy Role conflicts
Reward	Perceived unfair financial reward Lack of recognition from e.g., supervisors, colleagues, or clients Lack of intrinsic reward in terms of pleasure or satisfaction
Community	Lack of social support Lack of trust Chronic and unresolved conflicts
Fairness	Inequity of workload Inequity of salary Inappropriate evaluations and promotions
Values	Conflict between individual and organizational values Conflict between employee's career aspirations and values of the organization

2.2.3 Differentiation from depression and exhaustion-related conditions

The subsequent chapter endeavors to differentiate burnout from depression. Despite depression, an overview of other exhaustion-related constructs essential for a comprehensive differential diagnosis of burnout is provided.

The question of whether burnout represents a distinct construct or a form of depression has been a heated debate among researchers for decades (Ahola & Hakanen, 2014) as already Freudenberger stated in his inaugural article on burnout: "the person looks, acts and seems depressed" (Freudenberger, 1974, p. 161). Therefore, empirical evidence for both standpoints is presented first followed by an integrative and balanced conclusion.

According to Maslach and Leiter (2016b) empirical evidence clearly indicates that burnout is distinct from depression since burnout is classified as job-related and situation specific, while depression is assumed to be more general and context-free. In addition, findings revealing conceptual redundancy of the burnout concept were attributed to heavily exhaustion weighted burnout and depression questionnaires reflected by correlation coefficients ranging from .14 to .61 depending on used questionnaires

(Maslach & Leiter, 2016b). A recent meta-analysis reported on a mean correlation of .52 between burnout and depression indicating no conclusive overlap between both constructs (Koutsimani et al., 2019). This corresponds with a study investigating the discriminant validity of burnout measures which were shown to be capable of differentiating burnout from other mental syndromes such as anxiety or depression (Schaufeli et al., 2001). Empirical evidence for the burnout-depression distinction comes also from factor analytical studies concluding that burnout and depression are related but distinct constructs. On the one hand, symptomatology overlap is described as follows: first, the EE symptomatology seems to overlap with the depressive mood and fatigue experienced by individuals with depression. Second, individuals suffering from depression often exhibit social withdrawal, while burned out individuals tend to display a negative or hostile attitude towards their work. Third, depression encompasses elements of poor self-efficacy or learned helplessness sharing similarities with the burnout dimension of LA. Besides, Leiter and Durup (1994) emphasize the differences in the attributional patterns between burnout and depression. In burnout, the symptomatology is attributed to an over-demanding work environment, while individuals suffering from depression commonly connect negative experiences with themselves. Evidence for a different etiology comes also from a study by Bakker et al. (2000) showing that a lack of reciprocity in occupational life predicts burnout, whereas a lack of reciprocity in private life is a precursor for depression. This finding was confirmed by a mediation analysis demonstrating a direct relationship between job strain and burnout, whereas burnout mediated completely the association between job strain and depression supporting the assumption of a context-specific etiology of burnout (Ahola & Hakanen, 2007). This is also in line with the results of a recent qualitative study among individuals self-identifying as burned out (Tavella & Parker, 2020). Compared to depression, burnout symptomatology was characterized by lower levels of hopelessness, higher self-esteem, less suicidal thoughts and behavior, as well as higher functioning in different domains of life. In addition, more cognitive disturbances were assigned to burnout compared to depression confirming previous findings on cognitive malfunctions in burnout (Grossi et al., 2015; Schaufeli et al., 2020). Therefore, the authors concluded that at least from a sufferer's perspective the two constructs are distinguishable (Tavella & Parker, 2020). Further evidence supporting the distinctiveness of burnout and depression arises from the observations that burnout and depression do not regularly co-

occur (i.e., burnout can exist without depression and vice versa), especially in early stages of burnout (Ahola & Hakanen, 2014; Nadon et al., 2022).

Conversely, in particular Bianchi and colleagues argue that burnout is a manifestation of depression rendering the concept of burnout redundant. According to Schonfeld and Bianchi (2016), the overlap between burnout and depression were underestimated in previous studies due to liberal burnout cut off scores. Depending on respective cut off scores, 41-90% of individuals suffering from severe burnout met diagnosis criteria of depression. Notably, the overlap between burnout and depression increased with more conservative (i.e., higher) cut off scores for burnout (Ahola et al., 2005; Bianchi et al., 2014; Soares et al., 2007). The hypothesis of the singularity of burnout was also challenged by findings of no differences with respect to level and attribution of fatigue levels between individuals suffering from burnout compared to depression (Bianchi et al., 2013; Van Dam et al., 2015). The distinctiveness of both constructs was further questioned by the observation that the EE subscale of the MBI tends to correlate stronger with depression scores than with the other two subscales of the MBI (i.e., DP and LA) (Bianchi et al., 2015). With regard to the context-specificity of burnout, Bianchi et al. (2015) stated that "attributing a given condition or disorder to a specific domain (e.g., work) does not change the nature of this condition or disorder. Then, if the only feature that could be invoked to distinguish burnout from depression at a theoretical level was 'job-relatedness', it could be argued that burnout is an index of workplace depression" (Bianchi et al., 2015, p. 13). Given the conceptual issues regarding the burnout concept, a context-specific depression measure (i.e., the Occupational Depression Inventory) was proposed following the diagnostic criteria of MDD from the DSM-5 (Bianchi & Schonfeld, 2020).

In sum, the differentiation between burnout and depression remains challenging. However, there is at least some consensus on the context-specificity of burnout resulting from chronic work stress (Nadon et al., 2022). Moreover, it was speculated whether burnout may serve as a stage or precursor of clinical depression. However, especially findings from longitudinal studies indicate rather reciprocal associations between both conditions, with cross-sectional analyses underscoring the inter-related character but also their empirical distinctiveness (Ahola & Hakanen, 2007; Koutsimani et al., 2019; Tóth-Király et al., 2021). In conclusion, the etiology and the symptomatology of both constructs seem to differ initially, yet they tend to converge as burnout symptomatology becomes increasingly severe (Ahola et al., 2005; Bianchi et al., 2014; von Känel, 2016).

Given the described conceptual issues, a multi-stage recruitment procedure was applied in the studies of the present thesis ensuring the work-related etiology of burnout. Furthermore, individuals with a diagnosis of depression were only assigned to the burnout group (BO group) if the symptomatology was clearly attributed to work-related stress.

Despite the differentiation from depression, additional exhaustion-related constructs should be taken into account in the study of burnout as exhaustion is one of the most common symptoms of physical diseases and mental disorders (Kroenke & Price, 1993; von Känel, 2008). Table 3 gives an overview of relevant conditions potentially causing exhaustion that should be considered and excluded when investigating burnout (Korczak et al., 2010).

Table 3
Relevant conditions for the differential diagnosis of the burnout syndrome

Somatic / physical diseases	Mental disorders
Anemia	Chronic fatigue syndrome
Iron deficiency	Sleep disorders
Hypothyroidism	Neurasthenia
Diabetes	Somatization disorders
Adrenal insufficiency	Major depression disorder
Heart failure	Generalized anxiety disorder
Chronic obstructive pulmonary disease	Post-traumatic stress disorder
Renal insufficiency	Eating disorders
Lyme disease	Substance abuse (alcohol, tranquilizers)
HIV	
Tuberculosis	
Malignancy	
Lymphoma	
Leukemia	
Inflammatory systemic diseases	
Degenerative diseases of the CNS	
Obstructive sleep apnea syndrome	
Restless legs syndrome	
Medication side effects	

Note. CNS = central nervous system. Adapted and translated from Korczak et al. (2010).

Importantly, the conditions listed in Table 3 served as exclusion criteria (except depression attributed to chronic work stress) in the thesis' studies ascertained via a multi-stage recruitment procedure described in Chapter 4.

CHAPTER 3

3 RESEARCH AIMS AND STUDY OVERWIEW

Numerous prospective studies revealed adverse physical, psychological, and occupational consequences of job burnout (for a systematic review see Salvagioni et al., 2017). However, convincing evidence on the biopsychological mechanisms underlying this interplay as well as on the pathophysiological correlates of burnout remain scarce. This is reflected by inconsistent findings and heterogeneous samples across studies, presumably caused by the conceptual ambiguity of the burnout concept and the application of varying and potentially insufficiently strict criteria for identifying burnout cases (Bayes et al., 2021; Danhof-Pont et al., 2011; Grossi et al., 2015; Nadon et al., 2022; Rothe et al., 2020; Salvagioni et al., 2017).

Therefore, the overarching aim of the present thesis was to examine potential biopsychological alterations in burnout comparing a conceptually strictly specified group of individuals suffering from burnout (BO group) to a healthy comparison group (HC group). To address the imprecise operationalization described in the previous chapter, burnout cases were selected based on current burnout symptomatology as well as on pathogenesis reflected by the experience of chronic work stress. With respect to etiological factors, it was further ensured that participants of the BO group displayed a certain level of work-related functioning and motivational pattern before the onset of burnout symptoms (i.e., self-rated job performance, job resiliency, job motivation, and job commitment on a medium to high level), additionally verified by peer-report. Moreover, strict exclusion criteria were applied with respect to exhaustion-related physical diseases and mental disorders. The aim of this multi-stage recruitment procedure was to obtain a – with respect to pathogenesis - more homogeneous subsample of individuals suffering burnout out of the heterogeneous group of individuals exhibiting burnout symptoms. The multi-stage recruitment procedure is described in detail in *Study I*. Building upon this recruitment procedure, the respective studies of the thesis sought to identify biopsychological correlates of the burnout syndrome with respect to AL, HCC, as well as neural and salivary cortisol responses to acute psychosocial stress.

In *Study I*, the BO and the HC group were compared regarding an index of AL as the AL-model was considered to depict a biological pathway for the association between the experience of chronic stress and negative physical and mental health outcomes. However, previous studies on the association between burnout and AL revealed inconsistent results, probably due to the heterogeneity of investigated samples (Bayes et

al., 2021; Danhof-Pont et al., 2011). Based on our sophisticated recruitment procedure potentially leading to a more homogeneous study sample as well as empirical findings and theoretical considerations, we expected to find higher AL in the BO group compared to the HC group.

Since burnout is assumed to develop from chronic work stress, sustained activation of the HPA axis leading to HPA axis dysregulations has been proposed as a psychobiological pathway for the development of burnout symptoms (Bayes et al., 2021; Rohleder, 2018). While in most previous studies measures of short-term HPA axis (re)activity were applied yielding mixed results, the investigation of long-term integrated HCC was suggested a more promising marker for chronic stress conditions such as burnout. However, first studies on HCC in burnout were based only on cross-sectional data and showed again an inconsistent results pattern mainly attributed to the imprecise operationalization of burnout (Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020). Therefore, the aim of *Study II* was to investigate cross-sectional as well as longitudinal associations between burnout and HCC within our strictly specified sample. Thereby, we hypothesized positive cross-sectional and longitudinal associations between burnout and HCC indicating hypercortisolism in burnout.

While studies on the pathophysiology of burnout have pre-dominantly focused on peripheral markers of stress, no previous study has yet investigated neural responses to acute psychosocial stress in burnout. Therefore, in *Study III* we investigated – for the first time – differences in neural responses to acute psychosocial stress between individuals suffering from burnout (BO group) and healthy controls (HC group) applying Scan*STRESS* (Henze et al., 2020; Streit et al., 2014). In addition to neural responses, acute salivary cortisol responses to Scan*STRESS* were compared between both study groups. Based on a rather limited and inconsistent empirical evidence (Rothe et al., 2020), we hypothesized reduced salivary cortisol responses in the BO group compared to the HC group indicating a burnout-related cortisol hyporeactivity. In contrast, no directional or structure-specific hypothesis were made with respect to neural stress responses as *Study III* was the first fMRI study investigating neural stress responses in burnout.

CHAPTER 4

4 STUDY I: HIGHER ALLOSTATIC LOAD IN WORK-RELATED BURNOUT: THE REGENSBURG BURNOUT PROJECT

4.1 Abstract

Background: Burnout and chronic work stress have been linked to various negative health outcomes. While the mechanisms underlying this interplay are still unclear, the allostatic load (AL) model was suggested to demonstrate a possible biological pathway. However, previous studies provided divergent results regarding the association between burnout and AL, probably also due to the heterogeneity of selected samples. Therefore, the aim of the present study was to examine differences in AL between a conceptually strictly specified group of individuals suffering from burnout (BO group) and a healthy comparison group (HC group).

Methods: After a multi-stage recruitment procedure with strict inclusion criteria based on burnout symptomatology and pathogenesis, the BO group (n = 56) was compared to the HC group (n = 65) regarding an index of AL. The AL-index included 14 parameters: high-sensitivity c-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), fibrinogen, d-dimer, plasminogen activator inhibitor 1 (PAI-1), glycosylated hemoglobin (HbA1c), high-density lipoprotein (HDL) cholesterol, total cholesterol to HDL cholesterol ratio (TC/HDL), dehydroepiandrosterone-sulfate (DHEA-S), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist-hip ratio (WHR), and body fat percentage.

Results: The BO group showed significantly higher AL-scores in comparison to the HC group. This effect remained significant after adjusting for sex, age, and smoking status. Additionally, burnout symptoms (assessed with the Maslach Burnout Inventory; MBI), MBI-subscales emotional exhaustion and depersonalization as well as chronic work stress (assessed with the effort-reward imbalance questionnaire) were significantly associated with higher AL-scores.

Conclusions: Consistent with our hypothesis, we detected higher AL-scores in the BO compared to the HC group, indicating a greater cumulative physiological burden in individuals suffering from burnout. Given the high heterogeneity in individuals experiencing burnout symptoms, future studies may focus on well-specified subgroups,

when examining the association between burnout and psychophysiological dysregulations.

4.2 Introduction

Burnout symptoms potentially arise as a consequence of chronic work stress and the symptom complex encompasses emotional, cognitive, behavioral, and physical responses to chronic stress (Bayes et al., 2021; Maslach et al., 2001). According to the most widely used definition by Maslach et al. (2001), burnout comprises the three core symptoms emotional exhaustion (EE), depersonalization (DP), and lack of personal accomplishment (LA). Although burnout has been shown to be associated with various adverse effects on mental as well as physical health (Bayes et al., 2021; Salvagioni et al., 2017), the burnout syndrome is not recognized as a medical diagnosis according to the International Classification of Diseases (ICD-11) and is listed merely as a "factor influencing health status or contact with health services" (World Health Organization, 2019). In more detail, burnout was linked to, e.g., higher all-cause mortality (Ahola et al., 2010) and musculoskeletal pain (Melamed, 2009), greater risk for type-2 diabetes (Melamed, Shirom, Toker, & Shapira, 2006) and cardiovascular disease (Melamed, Shirom, Toker, Berliner, et al., 2006; Toker et al., 2012) as well as the development of psychiatric disorders (Ahola et al., 2005). Especially the strong symptom overlap with depression led to an ongoing debate about whether burnout is a distinct construct which can also be a precipitating factor for depression (e.g., Koutsimani et al., 2019; Maslach & Leiter, 2016b) or whether burnout should be considered as a depressive condition (e.g., Bianchi et al., 2015; Bianchi et al., 2021). In terms of medical diagnosis, Grossi et al. (2015) suggested that exhaustion disorder would be the most valid diagnosis for clinical burnout, but also work-related neurasthenia, undifferentiated somatoform disorder, adjustment disorder, or major depression have been used as diagnosis for clinical burnout in previous research (see also Jonsdottir & Sjörs Dahlman, 2019).

Previous studies examining the pathophysiology of burnout have focused on the hypothalamic-pituitary-adrenocortical (HPA) axis, in particular cortisol. However, these studies yielded mixed results with reports of increased as well as decreased HPA axis (re)activity or no HPA axis alterations in individuals with burnout symptoms (Kudielka et al., 2006; Rothe et al., 2020). Beyond cortisol, other studies have investigated the association between burnout and single biomarkers reflecting e.g., the functioning of the immune system and the autonomic nervous system, but to date, no reliable physiological changes related to burnout have been identified (Bayes et al., 2021; Jonsdottir & Sjörs Dahlman, 2019). Another approach to explain the association between symptoms of

burnout and various health impairments is the allostatic load (AL)-model by McEwen and Stellar (1993) which serves as a possible mechanistic pathway. AL refers to the 'wear and tear' of the body and a change in the operating range of various physiological systems resulting from the experience of repeated or chronic stress. Theoretically, the AL-model assumes that short-term alterations in the activity of physiological systems are adaptive to respond adequately to acute stress (i.e., allostasis), whereas too excessive, inappropriate, and/or long-term stress responses may exert a negative impact and finally increase disease risk, i.e., allostatic overload (McEwen & Stellar, 1993; Seeman et al., 1997). Derived from their empirical work, Seeman et al. (1997) introduced a count-based index of AL initially comprising the following 10 biomarkers: 12-h urinary cortisol, epinephrine, and norepinephrine; serum dehydroepiandrosterone-sulfate (DHEA-S); total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (TC/HDL), HDL cholesterol; glycosylated hemoglobin (HbA1C); systolic (SBP) and diastolic blood pressure (DBP); and waist-hip ratio (WHR). For each biomarker, quartiles based on the sample's distribution were calculated, with the highest quartile defined as risk (except for DHEA-S and HDL cholesterol where the lowest quartile referred to risk). Biomarkers were either coded with 1 or 0, if falling within or below the risk-quartile, respectively, and summed up. Thus, the AL-index as introduced by Seeman et al. (1997) can range between 0 and 10. Since then, the classical AL-index has been extended and modified including additional biomarkers (e.g., inflammation, blood coagulation) as well as alternative formulations (Juster et al., 2010). To date, the utility of this multisystemic approach could be empirically proven in various research fields by, e.g., showing that elevated AL-indices were associated with both adverse mental and physical health (Edes & Crews, 2017; Guidi et al., 2021; Juster et al., 2010).

Meanwhile, at least some studies have investigated the relationship between burnout and AL. However, available data show very divergent results with positive (Bellingrath et al., 2009; Hintsa et al., 2016; Juster, Sindi, et al., 2011), no (Langelaan et al., 2007; Sjörs et al., 2013; Viljoen & Claassen, 2017) or even negative (Traunmüller et al., 2018) associations. These discrepancies can probably be attributed to the methodological diversity of available studies as well as the heterogeneity of selected samples. Besides the differences in terms of sample sizes, measured AL-parameters, or applied exclusion criteria, in particular, the lack of consensus on how to identify burnout cases, may have led to inconsistencies. In this respect, it was suggested earlier that burnout should not be considered as a homogeneous entity across studies (Danhof-Pont et al., 2011). Thus, it

seems promising to define conceptually strictly specified groups suffering from burnout based on etiological considerations (see below).

Most of the previous studies used a single questionnaire to capture burnout symptoms or to identify burnout cases (Bayes et al., 2021; Danhof-Pont et al., 2011), thus focusing exclusively on current burnout symptomatology. However, burnout symptoms are assumed to be a consequence of chronic work stress, implying that respective individuals have experienced chronic work stress before the onset of burnout symptoms (Maslach et al., 2001). Therefore, it stands to reason to assess burnout symptoms in conjunction with indicators of chronic work stress and to identify burnout cases based on both, current symptomatology as well as burnout pathogenesis (i.e., the experience of foregoing chronic work stress). With respect to pathogenesis, previous studies did not explicitly examine whether individuals suffering from burnout had been able to adequately cope with their job demands before the onset of symptoms. Since the term burnout connotes that burned-out individuals had shown at least satisfactory work performance and had been resilient, motivated, and committed in the working context until symptom onset, acknowledging these variables may help to obtain a more homogeneous sample suffering from burnout.

Therefore, the overarching aim of the Regensburg Burnout Project was to examine potential alterations in biopsychological stress regulation in a conceptually strictly specified group of individuals suffering from the burnout syndrome (BO group) compared to a healthy comparison group (HC group). Thus, in the course of the present project, burnout cases were defined based on current burnout symptoms as well as pathogenesis. Additionally, volunteers were only assigned to the BO group if their job performance, resiliency, motivation, and commitment had been on a medium to high level preceding the onset of burnout symptoms, verified by work-related self- and peer-ratings. In sum, in this first study of the Regensburg Burnout Project, we investigated differences in an index of AL between the BO and the HC group. Thus, the present study aims to further elucidate the association between burnout and negative health outcomes. Based on both, empirical findings as well as the theoretical framework of the AL-model, we hypothesized higher AL-scores in the BO compared to the HC group.

4.3 Material and methods

4.3.1 Project overview

The present analysis was the first part of a larger study, namely the Regensburg Burnout Project (for overview see Figure 5A). To test for general eligibility, we initially performed a multi-stage recruitment procedure (see Figure 5B and 5C). Then, at a first lab appointment, AL-parameters were gained (reported here). At a second lab appointment, participants were exposed to the Scan*STRESS* paradigm (to be reported elsewhere), which is a psychosocial stress paradigm for fMRI environments (Henze et al., 2020; Streit et al., 2014). Approximately six months thereafter, a follow-up measurement was performed analogous to the first lab appointment.

4.3.2 Participants

Potential study participants were approached via flyers and social media internet platforms as well as newspaper announcements in the region of Regensburg (Bavaria, Germany). Initially, a total of 1022 volunteers completed an online assessment, including sociodemographic, work- and health-related variables, the Maslach Burnout Inventory-General Survey (MBI-GS; Schaufeli et al., 1996), the short version of the Effort-Reward Imbalance Questionnaire (ERI-Q; Siegrist et al., 2009), and the Hospital Anxiety and Depression Scale (HADS; Herrmann-Lingen et al., 2011). For the present analysis, an *a-priori* power analysis resulted in a required total sample size of $n = 128$ (sample sizes for each group $n = 64$) to achieve a test power of 80% to detect at least moderate effect sizes ($d = 0.50$).

In a first step of the recruitment procedure, scores of the MBI-GS, ERI-Q, and HADS-depression Scale (HADS-D) were scrutinized. Volunteers tentatively qualified for the BO group if they reached mild to severe weighted MBI-GS scores (mild: 1.5-3.49; severe: 3.5-6.0; Kalimo et al., 2003) as well as increased ERI values (ER-ratio ≥ .715 Lehr et al., 2010). Analogous, the HC group was open for subjects scoring low on burnout (weighted MBI-score < 1.5), ERI (ER-ratio < .715) as well as depression (HADS-D ≤ 7). Due to the symptom overlap with depression, increased HADS-D scores (>7) did not lead to exclusion of participants qualifying for the BO group. Secondly, to account for burnout pathogenesis, we additionally ensured that volunteers assigned to the BO group indicated that their job performance, job resiliency, job motivation, and job commitment had been on a medium to high level before the onset of burnout symptoms.

In a third step, it was ascertained that all subjects currently worked at least part-time (i.e., 20 hours/week). In a fourth step, health- and MRI-related exclusion criteria (e.g., metal parts inside the body, wearing a pacemaker, pregnancy) were checked. Past or acute mental disorders (e.g., psychosis, PTSD), medication with corticosteroids, psychotropic (e.g., antidepressant medication) or anticoagulant medication, current use of illegal drugs, a diagnosis of fibromyalgia, chronic-fatigue syndrome, or encephalomyelitis, endocrine, immunological, and heart diseases, or cancer served as further exclusion criteria for the whole sample. In a fifth step, the work-related self-evaluation (see step 2) had to be confirmed by peer-report (see Section 4.3.4.2 and Table 5 for further information). In a sixth step, this was followed by an interview including the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; Wittchen et al., 1997) as well as a final check of health- and MRI-related exclusion criteria. Due to the symptom overlap and recognition of burnout as a risk state for mental and somatic diseases, diagnoses such as adjustment disorder or mild depressive episode did not lead to exclusion of participants qualifying for the BO group if clearly identified as a consequence of chronic work stress. However, only one male subject of the BO group had a diagnosis of a mild depressive episode. In contrast, individuals who had received a psychiatric diagnosis before the beginning of their employment or who developed symptoms of exhaustion as a result of prior somatic illness were not eligible.

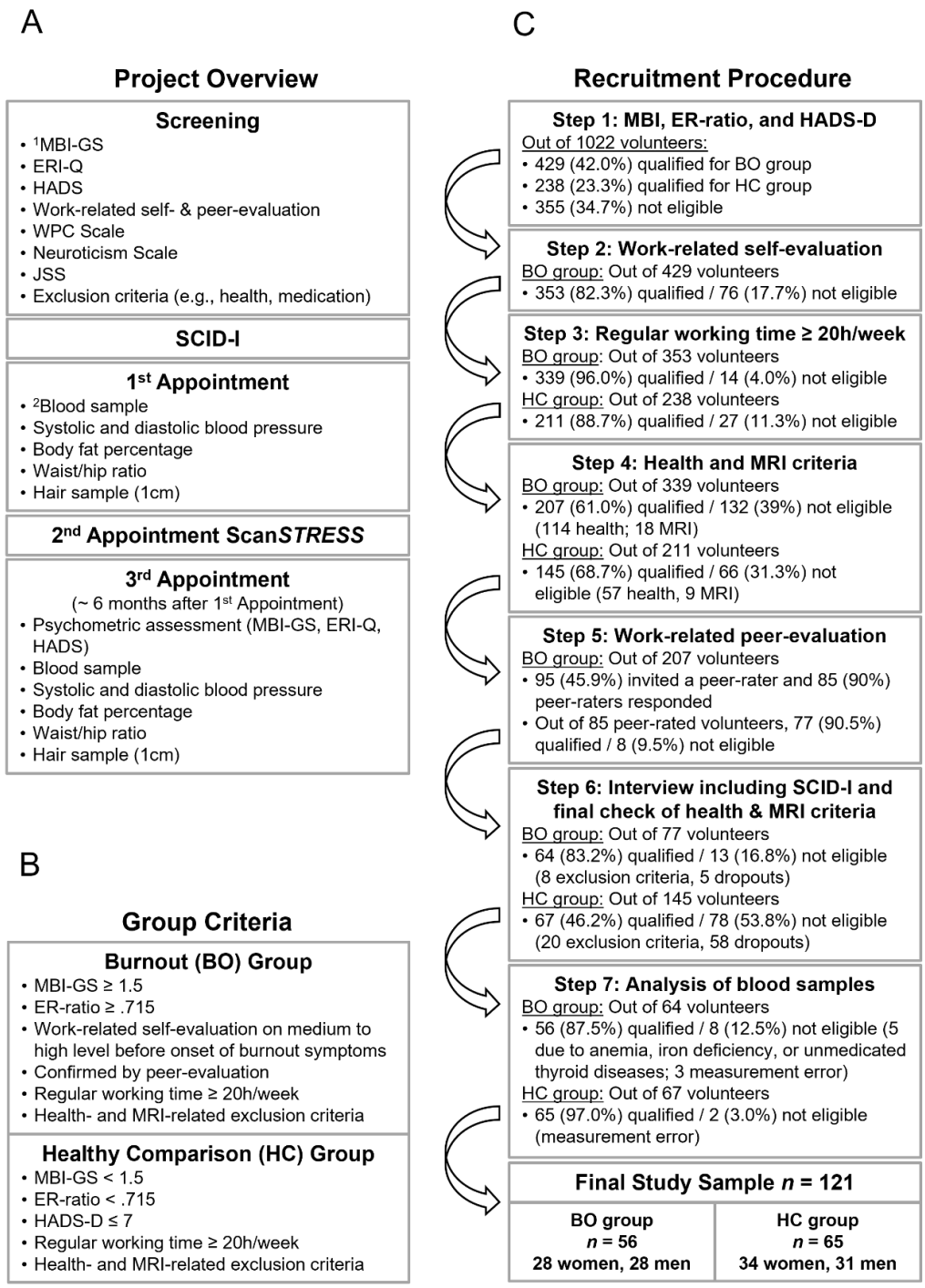
Only those volunteers, who were classified as eligible after the sixth step, were invited to the first appointment (see Figure 5A). In a last seventh step, participants of the BO group with anemia, iron deficiency, and unmedicated thyroid diseases as indicated by hemoglobin, serum ferritin, and thyroid stimulating hormone (TSH) concentrations were excluded from data analysis using clinical cut-offs because these conditions may cause symptoms of exhaustion (n = 5) (von Känel, 2008, 2016). Additionally, 5 subjects (3 from BO group, 2 from HC group) could not be included in the final study sample owing to measurement errors in single parameters, thus calculation of AL-indices was not feasible in these individuals. Figure 5B summarizes the inclusion criteria of the present study; Figure 5C illustrates the whole recruitment procedure and the number of eligible subjects at each step.

This recruitment procedure rendered a final study sample of 121 currently employed participants with 56 subjects (28 women, 28 men) assigned to the BO group and 65 subjects (34 women, 31 men) to the HC group. All participants provided written

informed consent and received a monetary compensation. The study was approved by the local ethics committee of the University of Regensburg.

Figure 5

The Regensburg Burnout Project: project overview (A), grouping criteria (B), and recruitment procedure (C)



Note. [1]MBI-GS = Maslach Burnout Inventory-General Survey; ERI-Q = Effort-Reward Imbalance Questionnaire; ER-ratio = Effort-Reward ratio; HADS = Hospital Anxiety and Depression Scale; HADS-D = HADS-Depression Subscale; WPC-Scale = Work-Privacy-Conflicts Scale; JSS = Jenkins Sleep Scale; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders. [2]The following parameters were measured within blood samples: high sensitivity c-reactive protein, tumor necrosis factor-alpha, interleukin 6, fibrinogen, d-dimer, plasminogen activator inhibitor 1, glycosylated hemoglobin, high-density lipoprotein cholesterol, total cholesterol, dehydroepiandrosterone-sulfate, serum ferritin, thyroid stimulating hormone, and a hemogram.

4.3.3 Procedure

At the first lab appointment, AL-parameters were measured (see Figure 5A) at the Institute of Clinical Chemistry and Laboratory Medicine of the University Hospital Regensburg. Blood samples were drawn from overnight-fasting participants. SBP and DBP were recorded after 10 min of rest in seated position and calculated as the average of two consecutive measurements. Body fat percentage was measured in lying position after a 10 min rest period using bioelectrical impedance analysis (BIA; Nutri Plus, Data Input GmbH, Darmstadt, Germany). WHR was calculated based on waist circumference (narrowest point between ribs and iliac crest) and hip circumference (widest point between hips). AL-biomarkers sampling took place between 8:00 and 10:00 am with an average duration of 45 minutes. In addition, if feasible, hair samples (1cm) were collected as part of the longitudinal project.

4.3.4 Psychological assessment

The psychometric assessment consisted of self-report data and peer-ratings (see Figure 5A).

4.3.4.1 Psychological self-assessment

A screening questionnaire covered sociodemographic (e.g., sex, age, education), work- (e.g., working hours per week), and health-related variables (e.g., past or acute diseases, smoking status). Furthermore, the psychometric assessment comprised the following questionnaires:

Maslach Burnout Inventory-General Survey (MBI-GS). Burnout symptomatology was assessed with a German version of the 16-items MBI-GS (Schaufeli et al., 1996) including the three subscales emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (inverted, i.e., lack of personal accomplishment (LA)). The MBI-GS measures the frequency of burnout symptoms on a 7-point Likert scale ranging from never (=0) to daily (=6). For the present study, the weighted MBI-score ($MBI_{weighted}$) following Kalimo et al. (2003) was calculated ($MBI_{weighted}$ = 0.4 x EE + 0.3 x DP + 0.3 x LA) with EE, as the core symptom, receiving a higher weighting. According to Kalimo et al. (2003), $MBI_{weighted}$-scores can be categorized into “no burnout risk” (scores 0-1.49; i.e., burnout symptoms a few times per year or never), “some burnout symptoms” (scores 1.5-3.49; i.e., burnout symptoms a few times per month or nearly

weekly) and “serious burnout symptoms” (scores 3.50-6.0; i.e., burnout symptoms several times per week or daily).

Effort-Reward Imbalance Questionnaire (ERI-Q). Chronic work stress was assessed using the German short-version of the ERI-Q (Siegrist et al., 2004; Siegrist et al., 2009). Effort and reward had to be rated on 5-point Likert scales ranging from 1 (“no”) to 5 (“yes, and I am very stressed”) as in the original form by Siegrist et al. (2009). The ER-ratio of the scales Effort (3 items) and Reward (7 items) was calculated according to the formula given by the authors in order to capture ERI (Siegrist et al., 2009). According to Lehr et al. (2010), the optimal cut-off point for the ER-ratio is .715. The personality trait overcommitment (OC) was assessed by the 6-item Overcommitment Scale of the ERI-Q.

Hospital Anxiety and Depression Scale (HADS). The German version of the HADS was used to assess symptoms of anxiety (HADS-A) and depression (HADS-D; Herrmann-Lingen et al., 2011). Both subscales comprise 7 items and are coded on a 4-point Likert scale ranging from 0 (“not at all”) to 3 (“mostly”). Sum scores ≤ 7 indicate no symptoms of anxiety/depression, while sum scores ≥ 8 reflect mild (scores 8-10), severe (scores 11-14), and very severe symptomatology (scores 15-21).

Work-related self-evaluation. First, all participants estimated their present job performance (3 items inquiring about quality, efficiency, and general job performance), job resiliency (1 item), and job motivation (2 items inquiring about motivation and engagement) on a 7-point Likert scale ranging from “well below average” (=1) to “well above average” (=7) as applied earlier in Feuerhahn et al. (2012). Job commitment was assessed by the respective 3-items scale of the Copenhagen Psychosocial Questionnaire (COPSOQ; Nübling et al., 2006). Finally, workload (3 items inquiring about quantitative, qualitative, and emotional workload; 1=”very low” to 5=”very high”) was assessed. The English translations of the items for the work-related self-evaluation are provided in the Supplemental Table 11.

Second, only if participants stated that they were currently suffering from exhaustion or burnout symptoms, they were once again asked to rate their job performance, resiliency, motivation, commitment, and workload before the onset of first burnout symptoms.

Work-Privacy-Conflicts Scale (WPC Scale). We used the Work-Privacy-Conflicts Scale (5 items) of the German version of the COPSOQ to measure conflicts regarding private life deriving from work (Nübling et al., 2006).

Neuroticism Scale. Neuroticism was measured with the 12-item Neuroticism Scale of the German version of the NEO-Five-Factor-Inventory (Borkenau & Ostendorf, 2008).

Jenkins Sleep Scale (JSS). Sleep quality and sleep disturbances were inquired with the 4-items JSS by Jenkins et al. (1988).

4.3.4.2 Work-related peer-evaluation

If participants qualified for the BO group based on their self-reports, they were requested to provide email addresses of at least one or a maximum of two potential peer-evaluators. Eligible peer-evaluators were either partners/friends/family members (= private-peers) or colleagues/co-workers/supervisors (= work-peers). The peer-questionnaires were directly sent to peer-evaluators. Owing to privacy and to achieve unbiased ratings, peer-evaluators only received a date as reference (e.g., January 2018) but were neither informed about the specific meaning of the date (i.e., reflecting the onset of burnout symptoms of the target person) nor the target person's group assignment (BO versus HC group). In addition to questions regarding the relationship with the target person (i.e., duration and quality of acquaintanceship), peer-evaluators were required to rate the target person's job performance, resiliency, motivation, commitment, and workload (see above) for two different time points (i.e., before burnout symptom onset (reference date) and present). For peer-evaluation, a 'don't know' option was additionally offered in case the peer-evaluator was not able to rate a specific item. However, peer-evaluators were requested to use this option only as an exception.

4.3.5 Allostatic load

Analogous to previous studies (Juster et al., 2010), the present AL-index was composed of 14 parameters representing immune, blood coagulation, metabolic, neuroendocrine, and cardiovascular system functioning, namely: high-sensitivity c-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), fibrinogen, d-dimer, plasminogen activator inhibitor 1 (PAI-1), HbA1c, HDL cholesterol, TC/HDL, DHEA-S, SBP, DBP, WHR, and body fat percentage. All single AL-parameters were selected

beforehand based on the current state of AL-research and no selection had been taken place post-hoc (i.e., no exclusion of single parameters).

Overnight-fasting blood samples were collected by a physician using serum, EDTA, and citrate Monovettes (Sarstedt, Nümbrecht, Germany) amounting to 30 mL of venous blood. All samples were directly analyzed on site or frozen at -20°C for later analysis by the Institute of Clinical Chemistry and Laboratory Medicine. All samples were processed according to standard laboratory procedures (for details see Table 10 in the Appendix).

Once biomarkers were obtained from the total study sample, sex-specific quartiles of each biomarker were calculated based on the distribution of the HC group. With this, values within the highest quartile reflect increased risk; except for HDL and DHEA-S where the lowest quartile refers to higher risk. Empirically derived cut-off values of the respective biomarkers are presented in Table 6. For each participant, biomarkers were coded with either "no-risk" (=0) or "risk" (=1) and an index of AL was calculated by summing up all parameters reflecting risk. Consequently, AL-indices could range between 0 to 14 with higher values indicating greater cumulative physiological burden.

4.3.6 Statistical analysis

The study groups (BO versus HC) were compared regarding demographic, health-, and work-related variables as well as psychometric characteristics using unpaired *t*-tests and chi-square tests, respectively. Paired *t*-tests were used to investigate differences in self- and peer-evaluations regarding present job performance, resiliency, motivation, commitment, and workload of the BO group compared to the reference time point before onset of burnout symptoms.

In order to explore differences in AL-scores between the BO and HC group, an unpaired *t*-test was computed with the AL-index as dependent variable. Subsequently, we performed a univariate analysis of covariance (ANCOVA) with group (BO versus HC group) and sex (women, men) as between-subjects factors and age as continuous covariate to account for possible confounding sex- and age-specific effects.

Although smoking was not considered as an exclusion criterion, the ANCOVA was rerun after exclusion of smokers (remaining n = 98) to control for potential negative health-related effects due to smoking. In addition, exploratory partial correlations controlling for age were computed to measure associations between questionnaire scores (MBI, ER-ratio) and the AL-index.

Data were analyzed with IBM SPSS Statistics version 28 (IBM, Corp., Armonk, NY). Despite clear unidirectional hypotheses, significance was defined by a threshold of $\alpha = .05$ (two-tailed).

4.4 Results

4.4.1 Study sample

Descriptive comparisons of demographic, health-, and work-related as well as psychometric characteristics of the study groups are presented in Table 4.

Table 4

Demographic, health-, and work-related as well as psychological characteristics of the burnout (BO) and healthy comparison (HC) group

	BO group (n = 56)	HC group (n = 65)
Sex (%)	28 females (50.0)	34 females (52.3)
Age (*SD*)	41.96 (10.35)	40.60 (10.56)
Smoking, *n* (%)	9 (16.1)	14 (21.5)
Body-mass-index (*SD*)	26.87 (4.08)	25.76 (4.86)
Highest education, *n* (%)		
Secondary school (5 years)	2 (3.6)	4 (6.2)
Secondary school (6 years)	18 (32.1)	22 (33.8)
Highschool	36 (64.3)	39 (60.0)
Highest professional qualification, *n* (%)		
Apprenticeship	26 (46.4)	32 (49.2)
University degree	26 (42.9)	28 (43.1)
Doctoral degree	6 (10.7)	5 (7.7)
Work schedule		
Shiftwork, *n* (%)	6 (10.7)	7 (10.8)
Official working hours/week (*SD*)	37.28 (11.19)	35.49 (7.56)
Irregular hours/week (*SD*)	6.49 (5.41)	5.44 (9.99)
Total working hours/week (*SD*)	43.77 (10.73)	40.93 (11.76)
Work experience in years (*SD*)	21.06 (10.66)	19.41 (11.43)
MBI-GS		
$MBI_{weighted}$ (*SD*)	2.84 (0.88)	0.83 (0.35)***
EE (*SD*)	3.71 (1.29)	0.88 (0.59)***
DP (*SD*)	2.79 (1.37)	0.58 (0.61)***
LA (*SD*)	1.72 (1.08)	1.01 (0.83)***
ERI-Q		
ER-ratio (*SD*)	1.16 (0.39)	0.50 (0.14)***
Effort (*SD*)	11.59 (1.97)	6.74 (1.97)***
Reward (*SD*)	24.79 (5.62)	31.88 (2.40)***
Overcommitment (*SD*)	2.97 (0.54)	1.94 (0.58)***
HADS		
HADS-A (*SD*)	9.83 (4.08)	3.55 (2.52)***
HADS-D (*SD*)	8.71 (3.92)	2.65 (1.65)***
Work-Privacy Conflicts Scale (*SD*)	16.02 (4.06)	8.75 (3.64)***
Neuroticism Scale (*SD*)	2.07 (0.61)	0.99 (0.58)***
JSS (*SD*)	9.11 (3.92)	4.89 (3.57)***

Note. ***$p \leq .001$. MBI-GS = Maslach Burnout Inventory-General Survey; $MBI_{weighted}$ = weighted MBI-GS score; EE = Emotional Exhaustion; DP = Depersonalization; LA = Lack of Personal Accomplishment; ERI-Q = Effort-Reward Imbalance Questionnaire; HADS-A = Hospital Anxiety and Depression Scale – Anxiety Scale; HADS-D = Hospital Anxiety and Depression Scale – Depression Scale; JSS = Jenkins Sleep Scale.

First, chi-square tests confirmed an equal distribution across study groups for the following variables: sex, smoking, highest education, highest professional qualification, and shiftwork ($ps \geq .45$). Further, chronological age was comparable between the BO and HC group ($p = .48$). Also, the body-mass-index was comparable between groups ($p = .18$). On a descriptive level, participants of the BO group reported to work slightly more (irregular) hours per week than HC group-members, however, this effect was

nonsignificant (*p*s ≥ .17). Compared to the HC group, individuals in the BO group rated their present job performance, resiliency, motivation, and commitment significantly lower (*p*s ≤ .01). In respect to present workload, only a trend towards higher values in the BO group compared to the HC group was detected (*p* = .09). Furthermore, according to both self- and peer-evaluation, participants of the BO group (target persons) showed a significant decline in their present job performance, resiliency, motivation, and commitment compared to the reference time point before onset of burnout symptoms (*p*s ≤ .05), whereas the reported workload remained relatively stable (*p*s ≥ .32). Results of these self- as well as peer-evaluations are illustrated in Table 5. Finally, comparing ratings of the self- and peer-evaluation revealed that the peer-ratings of target persons were, at least in part, higher than the respective self-evaluations (see supplementary Tables 12-13).

Table 5

Self-evaluation of the burnout (BO) and healthy comparison (HC) group and peer-evaluation of the BO group

	Self-evaluation		Peer-evaluation of target person	
	BO group (n = 56)	HC group (n = 65)	Private-peers (n = 53)	Work-peers (n = 40)
Acquaintanceship				
Duration of acquaintanceship with target person in years (*SD*)			17.33 (12.30)	10.19 (8.43)
Quality of acquaintanceship with target person (1= "very little" to 6 = "very well") (*SD*)			5.75 (0.59)	4.98 (0.85)
Work-related evaluation				
Job performance				
Present (*SD*)	5.03 (1.11)	5.51 (0.72)*	5.75 (0.97)	5.55 (1.02)
Before (*SD*)	5.83 (0.72)**		6.09 (0.80)*	6.00 (0.67)**
Job resiliency				
Present (*SD*)	4.36 (1.75)	5.60 (1.21)**	4.60 (1.68)	4.80 (1.42)
Before (*SD*)	6.07 (0.76)**		5.81 (1.19)***	5.79 (1.24)***
Job motivation				
Present (*SD*)	4.29 (1.32)	5.52 (0.86)**	5.02 (1.39)	5.15 (1.57)
Before (*SD*)	6.10 (0.74)**		6.03 (0.88)***	6.10 (0.99)***
Job commitment				
Present (*SD*)	2.98 (0.80)	4.03 (0.52)**	3.38 (0.97)	3.40 (0.98)
Before (*SD*)	4.06 (0.53)**		4.05 (0.64)***	4.03 (0.71)**
Workload				
Present (*SD*)	4.08 (0.64)	3.88 (0.60)	4.35 (0.53)	4.33 (0.59)
Before (*SD*)	4.04 (0.62)		4.33 (0.59)	4.12 (0.56)

Note. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$. *p*-values in the rows 'before' indicate results of paired *t*-tests (present vs. before). *p*-values in the row 'present' indicate results of unpaired *t*-tests (BO group vs. HC group).

In accordance with the study design, participants of the BO group reported significantly more burnout symptoms and higher work-related stress ($MBI_{weighted}$ M = 2.84, SD = 0.88; ER-ratio M = 1.16, SD = 0.39) than the participants of the HC group ($MBI_{weighted}$ M = 0.83, SD = 0.35; ER-ratio M = 0.50, SD = 0.14; all $ps \leq .001$). Based on the categorization established by Kalimo et al. (2003), 41 participants of the BO group showed "some burnout symptoms" ($MBI_{weighted}$ = 1.50-3.49) while 15 participants reported "severe burnout symptoms" ($MBI_{weighted}$ = 3.50-6.00). In addition, significant group differences

(BO group > HC group) emerged for each MBI-subscale (EE, DP, and LA), ER-ratio, OC, HADS-A and HADS-D, the WPC Scale, the Neuroticism Scale, as well as the JSS, as presented in Table 4. For intercorrelations between the questionnaire scores see supplementary Table 14.

4.4.2 Allostatic load

The sex-specific distribution of the 14 AL-parameters and the respective sex-specific cut-off values are illustrated in Table 6. Correlations between the AL-index and single AL-parameters are displayed in the Appendix (Table 17).

Table 6
Distribution of allostatic load parameters and respective sex-specific cut-off values

	Women (n = 62)			Men (n = 59)		
	Mean	*SD*	Cut-off	Mean	*SD*	Cut-off
hsCRP (mg/l)	1.96	2.60	> 2.13	1.17	1.10	> 1.60
TNF-α (pg/ml)	5.38	1.27	> 5.88	5.91	1.34	> 6.90
IL-6 (pg/ml)	2.30	1.22	> 2.50	2.36	1.86	> 2.50
Fibrinogen (mg/dl)	326.26	75.29	> 388.43	276.34	57.37	> 306.20
D-dimer (mg/l)	0.34	0.16	> 0.35	0.28	0.14	> 0.29
PAI-1 (U/ml)	2.28	0.76	> 2.00	2.69	1.29	> 2.10
HbA1c (mmol/mol)	33.77	3.12	> 35.64	34.40	2.94	> 36.10
TC/HDL (mg/dl)	3.05	0.97	> 3.33	4.21	1.26	> 5.06
SBP (mm Hg)	115.14	14.21	> 123.88	124.17	13.53	> 127.00
DBP (mm Hg)	73.66	9.04	> 78.75	75.11	8.72	> 80.50
WHR (cm)	0.77	0.06	> 0.79	0.86	0.06	> 0.90
Body fat percentage (%)	31.31	6.78	> 35.28	21.52	5.75	> 24.90
DHEA-S (mg/l)	1.61	1.06	< 0.88	2.36	0.99	< 1.72
HDL (mg/dl)	70.63	17.64	< 62.13	53.90	13.74	< 46.00

Note. hsCRP = high-sensitivity c-reactive protein; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; HbA1c = glycosylated hemoglobin; TC/HDL = total cholesterol to high-density lipoprotein cholesterol ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist-hip ratio; DHEA-S = dehydroepiandrosterone-sulfate; HDL = high-density lipoprotein cholesterol.

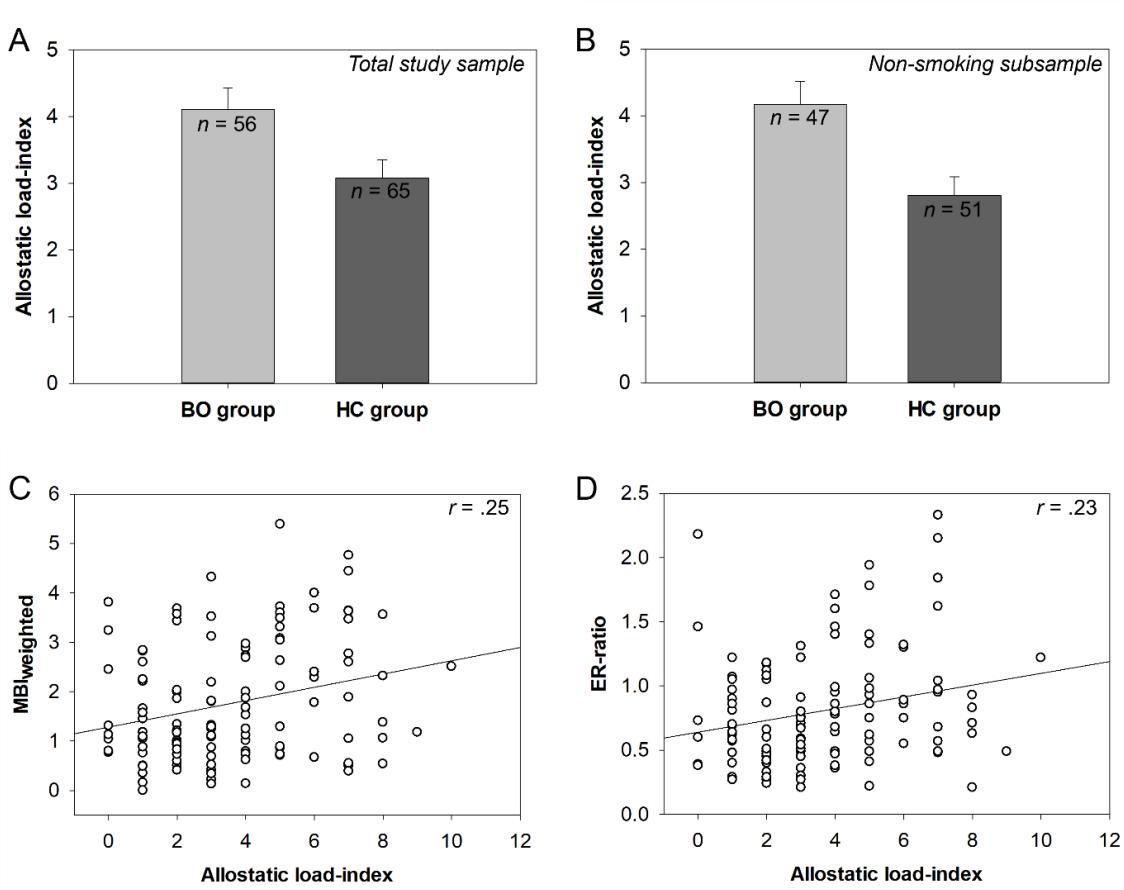
The mean AL-score for the whole sample (n = 121) was M = 3.55 (SD = 2.34); AL-indices ranged from 0 to 10. As hypothesized, an unpaired t-test revealed significantly higher AL-scores for the BO group (M = 4.11, SD = 2.37) compared to the HC group (M = 3.08, SD = 2.22, t (119) = 2.46, p = .02, d = 0.45). A subsequent ANCOVA controlling for sex and age also yielded a significant main effect group, confirming higher AL-scores in the BO group ($F_{1, 116}$ = 5.41, p = .02, η^2 = .05). Furthermore, age was significantly associated with AL-scores ($F_{1, 116}$ = 4.60, p = .03, η^2 = .04) while the main effect of sex as well as interaction effect group x sex did not reach significance (ps ≥ .53). Given the absence of sex differences, no further sex-specific group analyses were conducted. In the

subsample consisting of non-smokers (BO group n = 47; HC group n = 51), the group difference became even more apparent with higher AL-scores in the BO group (M = 4.17, SD = 2.36) compared to the HC group (M = 2.80, SD = 1.99; $F_{1, 93}$ = 8.70, p = .004, η^2 = .09). The main effect age remained significant in the non-smoking subsample ($F_{1, 93}$ = 4.19, p = .04, η^2 = .04), whereas the main effect sex as well as the interaction effect group x sex stayed non-significant (ps ≥ .60). Figure 6 illustrates the mean differences in AL-scores between both groups in the whole sample (Figure 6A) as well as in the non-smoking subsample (Figure 6B).

4.4.3 Exploratory analysis

Burnout symptoms as assessed by the weighted MBI-score were significantly correlated with greater AL-scores (r(118) = .25, p = .007). Among the three MBI-subscales, DP showed the strongest correlation with AL-scores (r(118) = .24, p = .008). The subscale EE also showed a significant correlation with AL-scores (r(118) = .20, p = .03), whereas this relationship rendered non-significant for LA (r(118) = .17, p = .07). In addition, higher ERI was significantly related to higher AL-scores (r(118) = .23, p = .01). Figure 6C-D shows scatterplots of the correlations between the AL-index and weighted MBI-score as well as ER-ratio.

Figure 6
Significant mean differences in allostatic load-scores between the burnout (BO) and healthy comparison (HC) group in the whole sample (A) as well as in the non-smoking subsample (B) and scatterplots of significant correlations between the allostatic load-index and $MBI_{weighted}$ (C)



Note. Error bars represent standard error of mean. $MBI_{weighted}$ = weighted Maslach Burnout Inventory-General Survey score; ER-ratio = Effort-Reward ratio.

When controlling for age and depression symptoms (HADS-D), the partial correlation between AL-indices and $MBI_{weighted}$ (r = .17, p = .07) was only somewhat reduced. However, the correlation no longer reached the level of significance, possibly owing to the high intercorrelations between $MBI_{weighted}$ and HADS-D (r = .79, $p \leq .001$; see supplementary Table 14). Partial correlations (controlling for age) between log-transformed single AL-parameters and $MBI_{weighted}$ as well as ER-ratio are presented in supplementary Table 15.

4.5 Discussion

The aim of the present study was to explore if there were differences in AL between a conceptually strictly specified group of otherwise healthy individuals from the working

population suffering from the burnout syndrome (BO group) compared to a healthy comparison group (HC group). In line with our main hypothesis, we found higher AL-scores in our BO group compared to the HC group, reflecting a higher cumulative physical burden in individuals suffering from burnout. The finding remained significant after adjusting for age and became even more apparent in the subgroup of non-smokers. This effect was already observed by Bellingrath et al. (2009). Furthermore, $MBI_{weighted}$, the MBI-subscales EE and DP as well as chronic work stress indicated by the ER-ratio, were significantly associated with higher AL-scores. In contrast, the MBI-subscale LA was not significantly related to AL.

4.5.1 Higher allostatic load-index in the burnout group

Overall, the results of the present study are consistent with earlier findings from Bellingrath et al. (2009), Juster, Sindi, et al. (2011), and Hintsa et al. (2016). However, a comparable number of studies subsists reporting no significant associations between burnout and AL (Langelaan et al., 2007; Sjörs et al., 2013; Viljoen & Claassen, 2017) or diverse findings (i.e., lower AL-scores in clinically-diagnosed burnout inpatients compared to healthy controls but no correlation with burnout scores; Traunmüller et al., 2018). The present study design allowed us to compare two discrete groups regarding AL, whereas most previous studies applied a correlational approach or grouped study participants *post-hoc* based on their burnout levels or AL-scores (Bellingrath et al., 2009; Hintsa et al., 2016; Juster, Sindi, et al., 2011). By following this approach with two well-specified groups the present results provide further evidence for the assumption, that the burnout syndrome is associated with increased risk for health impairments as indicated by higher AL. Higher AL was repeatedly linked to poorer health outcomes (Guidi et al., 2021; Juster et al., 2010) suggesting that individuals suffering from burnout are at greater risk for the development of various diseases, even if their single AL-parameters are still in the nonclinical range. Although we only found small to medium effect sizes for group differences in AL-scores as well as for the correlations between indicators of burnout (MBI-scores) or chronic work stress (ER-ratio) and AL-scores, it should be kept in mind that, in the present study, these effects were stronger than age-related increases in AL-scores. Importantly, none of the single AL-parameters was significantly related to burnout symptoms, which is a common finding in burnout and AL research (e.g., Bellingrath et al., 2009; Seeman et al., 1997).

Importantly, only a small proportion of our BO group (*n* = 15; 26.8%) showed "severe burnout symptoms" according to the categorization by Kalimo et al. (2003), which may be due to the strict inclusion criteria (e.g., no sick leave, no antidepressant medication). It is well-known from prospective studies that the more severe the burnout symptomatology, the greater the risk for sickness absence (Borritz et al., 2010; Hallsten et al., 2011) and use of psychotropic or antidepressant drugs (Leiter et al., 2013; Madsen et al., 2015). To date, two studies examined the association between burnout and AL in clinical patient populations (Sjörs et al., 2013; Traunmüller et al., 2018). In the study by Sjörs et al. (2013) AL-scores did not differ between patients and controls whereas Traunmüller et al. (2018) reported on – surprisingly – higher AL-scores in the control group compared to the inpatient group. However, the study by Traunmüller et al. (2018) did not include an appropriate control group as MBI-scores were comparably high between the patient and the control group. Additionally, in contrast to the present BO group, the clinical samples were characterized by a high proportion of individuals being on (long-term) sick leave and antidepressant medication, which may explain (at least in part) the divergent findings. Another, though speculative, explanation for these divergent findings might be that the association between burnout and allostatic load may depend on the duration and/or severity of burnout symptoms (see also below). Especially regarding the HPA axis it was suggested by Miller et al. (2007) that HPA axis activity might be elevated at the onset but might be reduced when the stressor persists, reflecting inappropriate stress responses. This could also be valid for AL-scores including parameters from different stress-sensitive systems.

One major issue in burnout research addresses the differentiation of burnout from (clinical) depression (Bianchi et al., 2015; Parker & Tavella, 2021). In the present study, burnout symptoms were no longer significantly related to AL-scores when controlling for depression symptoms which is in line with previous reports by Bellingrath et al. (2009) and Hintsa et al. (2016). This finding is not surprising, acknowledging the large overlap between symptoms of burnout and depression (Ahola et al., 2005). To date, relatively little evidence has been found suggesting that burnout is reflected by a different underlying pathophysiology than depression (Orosz et al., 2017; Rothe et al., 2020). In addition, higher AL was also shown to be associated with depression symptoms (e.g., Gillespie et al., 2019; Honkalampi et al., 2021; Juster et al., 2010). Though, it should be of note that our inclusion criteria for the respective groups (see Figure 5B) may have led to an overestimation of the overlap between burnout and depression symptoms in the

present study, since volunteers with high HADS-D scores were not eligible for the comparison group. Nevertheless, even given the high intercorrelations between burnout and depression scores in the present sample, the association between burnout and AL-scores was only somewhat reduced if controlling for depression symptoms.

4.5.2 Limitations

Finally, important limitations have to be acknowledged. In the present study, urine samples were not feasible which would have allowed the measurement of the primary mediators urinary cortisol, epinephrine, and norepinephrine. However, besides DHEA-S, the present index of AL included two other primary mediators (i.e., IL-6 and TNF- α) that are also involved in the acute adaption to stress (McEwen, 2003, 2008). Furthermore, the present AL-index comprised additional parameters reflecting immunological, metabolic, and blood coagulation processes, following the recommendation by the original authors (Seeman et al., 2001; Seeman et al., 1997). Thus, one important consequence of the specific operationalization of our AL-index is its limited comparability with the initial AL-index as introduced by Seeman et al. (1997). It should also be of note, that AL-indices lack the discriminative value of a clinical tool as increased allostatic load is not a burnout-specific condition (Guidi et al., 2021; Juster et al., 2010).

In addition, it has been suggested that there may be complex temporal dynamic relationships between burnout and AL-parameters, possibly depending on the severity and duration of burnout symptoms. This has, for example, been shown for HPA axis (re)activity (Rohleder, 2018; Rothe et al., 2020). Also, associations between psychological stress and immune parameters were reported to depend on the type and the duration of the stressor (Segerstrom & Miller, 2004). With this, individual AL-parameters might be upregulated in some individuals and downregulated in others depending on the duration as well as the severity of burnout symptoms. Consequently, a cross-sectionally measured AL-index, which simply sums up the risk across all parameters as expressed in one number, is not capable of identifying such potentially complex associations. This could be another explanation for the inconsistent directionality of the correlations between burnout symptoms and single AL-parameters.

Furthermore, the present cross-sectional design does not permit conclusions about the temporal sequence of burnout and AL. Given the above mentioned temporally dynamic relationship between burnout symptoms and biological dysregulation, it will be

of high interest to investigate associations between burnout and AL in longitudinal analyses. However, this issue will be addressed in the future longitudinal course of the Regensburg Burnout Project (see Figure 5A).

Another limitation concerns the sample size of the present study. While the power was high enough for investigating AL-differences between the two study groups, the given sample size did not allow for investigating burnout-related differences in single AL-parameters in more detail. Therefore, large cohort studies are needed to further investigate the psychobiological causes and consequences of burnout.

Furthermore, our recruitment strategy followed the assumption that burnout is primarily caused by chronic work stress. However, one cannot rule out an impact of stress from the private sector on the development of burnout symptoms. In this vein, recent studies suggested that burnout symptoms can also occur in other domains (de Beer & Bianchi, 2017; Kristensen et al., 2005) such as parenthood (e.g., Mikolajczak & Roskam, 2020) or family caregiving (e.g., Alves et al., 2019). Therefore, it seems promising to consider also non-occupational strains in future burnout research (Bianchi, 2016). However, in the present study the BO and HC groups did not differ significantly regarding possible private-related stressors (see extended study sample description in the Appendix). Also, taking these variables into account did reveal the same results (i.e., higher Al-indices in the BO compared to the HC group).

Finally, for the recruitment procedure we used the $MBI_{weighted}$-score as a global burnout syndrome indicator as introduced by Kalimo et al. (2003). While the $MBI_{weighted}$-score seems to be well suited for the differentiation of burned out and non-burned out individuals (see discriminant analysis in the Appendix), the MBI-GS appears not to be unidimensional (de Beer & Bianchi, 2017; see also the results of the bifactor analysis of the present data set in the Appendix). Thus, the subsequent correlation between $MBI_{weighted}$ and the AL-index should be interpreted with some caution.

4.6 Conclusion

In line with our hypothesis, we detected higher AL-scores in a conceptually strictly specified group of individuals from the working population suffering from the burnout syndrome compared to a healthy comparison group. These findings provide further evidence that conditions such as burnout and chronic work stress may, even if not extreme, lead to the ‘wear and tear’ of the body and alterations in the operating range of

various stress-sensitive physiological systems. However, as AL-indices are not suitable as a clinical tool, large prospective cohort studies focusing also on single potential biomarkers of burnout are needed to further elucidate the pathophysiology of burnout. Finally, given the high heterogeneity in individuals suffering from burnout symptoms, it seems promising for future studies, to focus on well-specified subgroups as applied in the present study, when examining the association between the burnout syndrome and psychophysiological dysregulations.

CHAPTER 5

5 STUDY II: INVESTIGATION OF CROSS-SECTIONAL AND LONGITUDINAL ASSOCIATIONS BETWEEN WORK-RELATED BURNOUT AND HAIR CORTISOL: THE REGENSBURG BURNOUT PROJECT

5.1 Abstract

Background: Burnout is characterized by feelings of exhaustion, depersonalization as well as reduced personal accomplishment and is linked to various negative health effects. Previous studies on biological correlates of burnout have focused on the hypothalamic-pituitary-adrenal (HPA) axis. However, especially studies on hair cortisol concentrations (HCC) were often based on cross-sectional data and yielded inconsistent results, probably due to the heterogeneity of the selected samples. Accordingly, the aim of the present study was to investigate cross-sectional as well as longitudinal associations between burnout and HCC within a sample consisting of a strictly specified group of individuals suffering from burnout (BO group) and a healthy comparison group (HC group).

Methods: After a multi-stage recruitment procedure based on burnout symptoms and pathogenesis, eligible subjects (out of an initial sample of 1022 volunteers) were assigned either to a BO (n = 55) or HC group (n = 59), as described in detail in Bärtl et al. (2022). Burnout symptoms as well as HCC (1cm hair samples) were measured repeatedly at two sampling time points t1 (n = 114) and t2 (n = 100) with an interval of M = 7.20 months (SD = 1.16) between assessments.

Results: In the total study sample, no cross-sectional associations between burnout and HCC were found either at t1 or at t2. When the analysis was restricted to the BO group, HCC was positively related to burnout symptomatology at t1 but not t2. In the longitudinal analysis, burnout symptoms at t1 were significant negative predictors of HCC at t2. However, the change in HCC from t1 to t2 was not associated with the change in burnout symptoms.

Conclusions: In the present study, we investigated the association between HCC and burnout in a strictly defined sample of subjects suffering from burnout and healthy controls. Our findings mainly do not support our hypotheses. At least, the positive association between HCC and burnout symptoms only within the BO group supports the

idea that HPA axis alterations in burnout might only become apparent once a certain threshold of burnout symptomatology has been exceeded, while the longitudinal data provide some empirical evidence for the potential long-term development of hypocortisolism in burnout. However, respective results remain relatively inconclusive.

5.2 Introduction

Burnout is defined as a prolonged response to chronic work stress which is characterized by feelings of emotional exhaustion (EE), depersonalization (DP), and lack of personal accomplishment (PA) (Maslach et al., 2001). While convincing evidence shows that burnout has adverse effects on mental as well as physical health, the underlying mechanisms of how burnout can increase disease risk are still unclear. As burnout symptoms develop under conditions of chronic work stress, psychobiological burnout research has focused, amongst others, on the hypothalamic-pituitary-adrenal (HPA) axis and particularly on cortisol to elucidate the link between burnout and negative health outcomes (Jonsdottir & Sjörs Dahlman, 2019). However, studies on HPA axis alterations in burnout revealed mixed results regarding the cortisol awakening response, diurnal cortisol levels as well as cortisol responses to pharmacological challenge tests or acute psychosocial stress. While Jonsdottir and Sjörs Dahlman (2019) called the usefulness of these short-term cortisol measurements as an indicator of chronic stress into question, the measurement of long-term integrated hair cortisol concentration (HCC) seems to be a promising marker for chronic stress exposure such as burnout (Rothe et al., 2020). Based on theoretical considerations as well as studies investigating chronic stress in general, burnout symptoms were expected to be associated with *hypocortisolism* (Rohleder, 2018). However, previous studies on burnout and HCC have shown either no (Deng et al., 2021; Marcil et al., 2022; Wekenborg et al., 2019) or positive associations indicating *hypercortisolism* (Ibar et al., 2021; Penz et al., 2018; Wang et al., 2019; Wendsche et al., 2020). In the only longitudinal study so far by Wendsche et al. (2020), a positive nonlinear (i.e., exponential) association between burnout and HCC was found; however, only burnout symptoms were measured repeatedly. These divergent findings can probably be attributed in large part to the lack of conclusive criteria on how to identify burnout cases resulting in highly heterogeneous study samples (Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020).

Therefore, the aim of the present study was to examine both, cross-sectional and longitudinal associations in HCC within a sample consisting of a strictly specified group of individuals suffering from burnout and a healthy comparison group. Based on empirical findings, we hypothesized positive cross-sectional and longitudinal associations between burnout and HCC. In addition, we investigated whether the change in burnout symptoms across time was associated with the change in HCC. Based on

previous findings indicating nonlinear relationships (Wendsche et al., 2020; Penz et al., 2018), we further exploratively investigated the association between burnout and HCC exclusively within the burnout group.

5.3 Materials and methods

5.3.1 Participants

The present analysis was part of a larger study, namely the Regensburg Burnout Project (Bärtl et al., 2022). After screening an initial sample of 1022 volunteers, a total of 116 subjects either suffering from burnout (BO group) or serving as healthy comparisons (HC group) qualified for study participation after passing an extensive multi-stage recruitment procedure with strict inclusion criteria based on burnout symptomatology and pathogenesis, additionally verified by peer-ratings (described in great detail in Bärtl et al., 2022). The assignment of eligible volunteers to the BO and HC group was based on this multi-stage recruitment procedure and took place before the first appointment (t1). Inclusion criteria for the BO group were mild to severe burnout symptoms (Kalimo et al., 2003), the experience of foregoing chronic work stress, a work-related evaluation reassuring at least medium to high levels of self- and peer-rated job performance, resiliency, motivation, and commitment before the onset of burnout symptoms as well as a regular working time ≥ 20 h/week. Participants of the HC group were required to score low on burnout, chronic work stress as well as depression and to regularly work ≥ 20 h/week. General health- and work-related exclusion criteria (including a clinical diagnostic interview as well as the analysis of a blood sample) are described in Bärtl et al. (2022). In addition, a hair length of at least 1cm was required. The remaining 906 volunteers were not eligible as they did not fulfill the strict inclusion criteria for either study group as checked step-by-step in the multi-stage recruitment procedure (Bärtl et al., 2022). Accordingly, no further data (e.g., HCC) were collected from these volunteers.

All participants provided written informed consent and received a monetary compensation. The study was approved by the local ethics committee of the University of Regensburg.

5.3.2 Procedure

A screening questionnaire covered sociodemographic, work- and health-related variables, chronic work stress as well as burnout and depression symptomatology. At the first appointment (t1), biomarker sampling took place between 8:00 and 10:00 a.m. with

an average duration of 45 minutes. In addition to hair sampling, allostatic load parameters were gained (Bärtl et al., 2022). Analogously, hair samples as well as psychometric data were repeatedly obtained approximately seven months after the first appointment (t2; *M* = 7.20 months; *SD* = 1.16). Additionally, the psychometric assessment at t2 covered questions regarding health- and job-related changes compared to t1 (see Supplemental Table 19).

5.3.3 Self-report measures

Maslach Burnout Inventory-General Survey (MBI-GS). Burnout symptomatology was assessed with a German version of the 16-items MBI-GS (Schaufeli et al., 1996). For the present study, the weighted MBI-score from Kalimo et al. (2003) was used.

Checklist hair characteristics. Number of hair washes/week, natural hair color, and hair treatment (tint, coloration, permanent wave) were inquired by an in-house questionnaire.

5.3.4 Hair cortisol

At both time points, hair samples were obtained as close as possible to the scalp from the posterior vertex region. HCC was measured from the 1cm segment most proximal to the scalp reflecting the integrated cortisol secretion over the last month (Stalder et al., 2017) and determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) following the protocol by Gao et al. (2013).

5.3.5 Hair cortisol and statistical analysis

HCC was log-transformed to approximate a normal distribution. Participants with log-transformed HCC ± 3 standard deviations from the mean were excluded (t1 *n* = 2; t2 *n* = 1) resulting in a final study sample of *n* = 114 for t1 and *n* = 100 for t2. Cross-sectional (t1 and t2) and longitudinal associations between burnout and HCC were analyzed using multiple regressions. Each model was adjusted for the possible confounders sex, hormonal contraception, age, number of hair washes/week, hair treatment (tint, coloration, permanent wave), and body-mass-index (Stalder et al., 2017) representing the baseline model.

Cross-sectional associations at t1 were examined by adding MBI-weighted$_{t1}$ to the baseline model with HCC$_{t1}$ as dependent variable. Cross-sectional associations at t2 were

examined adding MBI-weighted$_{t2}$ to the baseline model with HCC$_{t2}$ as dependent variable.

Longitudinal associations were investigated by adding MBI-weighted$_{t1}$ to the baseline model with HCC$_{t2}$ as dependent variable, additionally controlling for HCC$_{t1}$. To test for potential reverse causation, the inverse association between burnout and HCC was investigated by entering HCC$_{t1}$ into the baseline model with MBI-weighted$_{t2}$ being the dependent variable, additionally controlling for MBI-weighted$_{t1}$. Furthermore, we conducted separate correlational analysis between the change in burnout symptoms (MBI-weighted$_{delta}$ = MBI-weighted$_{t2}$ – MBI-weighted$_{t1}$) and the change in HCC (HCC$_{delta}$ = HCC$_{t2}$ – HCC$_{t1}$).

Data were analyzed with IBM SPSS Statistics version 28 (IBM, Corp., Armonk, NY) and significance was defined by a threshold of $\alpha = .05$ (two-tailed).

5.4 Results

Demographic, health- and hair-related as well as psychometric characteristics of the study groups for t1 and t2 are presented in Table 7. MBI-weighted at t1 and t2 was significantly correlated ($r = .76$, $p < .001$) as was HCC ($r = .65$, $p < .001$).

Table 7
Demographic, health-, and hair-related as well as psychological characteristics of the burnout (BO) and healthy comparison (HC) group for both measurement time points

	t1		**t2**	
	BO group (*n* = 55)	HC group (*n* = 59)	Assigned to BO group at t1 (*n* = 51)	Assigned to HC group at t1 (*n* = 49)
Sex (%)	29 women (52.7)	34 women (57.6)	26 women (51.0)	29 women (59.2)
Hormonal contraception, *n* (%)	6 (10.9)	7 (11.9)	6 (11.8)	6 (12.2)
Age (*SD*), yrs.	42.25 (10.21)	41.24 (10.92)	41.31 (10.11)	41.88 (11.36)
Smokers, *n* (%)	8 (14.5)	13 (20.3)	8 (15.7)	10 (20.4)
Body-mass-index (*SD*)	26.75 (3.91)	26.18 (5.14)	26.99 (3.85)	24.76 (3.51)
HCC (*SD*)	0.67 (0.27)	0.68 (0.26)	0.53 (0.30)	0.65 (0.27)
Hair characteristics				
Hair washes/week (*SD*)	4.57 (1.87)	5.51 (2.01)	4.63 (1.92)	4.65 (2.12)
Tint, *n* (%)	9 (16.4)	8 (13.6)	6 (11.8)	5 (10.2)
Coloration, *n* (%)	10 (18.2)	12 (20.3)	8 (15.7)	12 (24.5)
Permanent wave, *n* (%)	1 (1.8)	1 (1.7)	0 (0.0)	1 (2.0)
MBI-GS				
Weighted MBI-score (*SD*)	2.83 (0.87)	0.83 (0.34)	2.49 (1.04)	0.97 (0.60)
EE (*SD*)	3.77 (1.31)	0.90 (0.59)	3.22 (1.47)	1.27 (0.95)
DP (*SD*)	2.75 (1.35)	0.59 (0.59)	2.29 (1.47)	0.64 (0.66)
LA (*SD*)	1.66 (1.08)	0.97 (0.80)	1.72 (1.19)	0.90 (0.73)

Note. HCC = log-transformed hair cortisol concentrations (pg/mg); MBI-GS = Maslach Burnout Inventory-General Survey; EE = Emotional Exhaustion; DP = Depersonalization; LA = Lack of Personal Accomplishment.

The dropout rate from t1 to t2 (no-shows, hair length < 1cm) was about 7.3% for the BO group (n = 4) and 16.9% for the HC group (n = 10). Dropout analyses did not reveal any indication of systematic dropout, except higher mean body-mass-index in the dropped-out participants (see Supplemental Table 20). Between t1 and t2, three participants of the BO group sought treatment (2x psychotherapy, 1x antidepressant medication) and two participants changed their employers.

5.4.1 Analysis of the association between burnout and hair cortisol

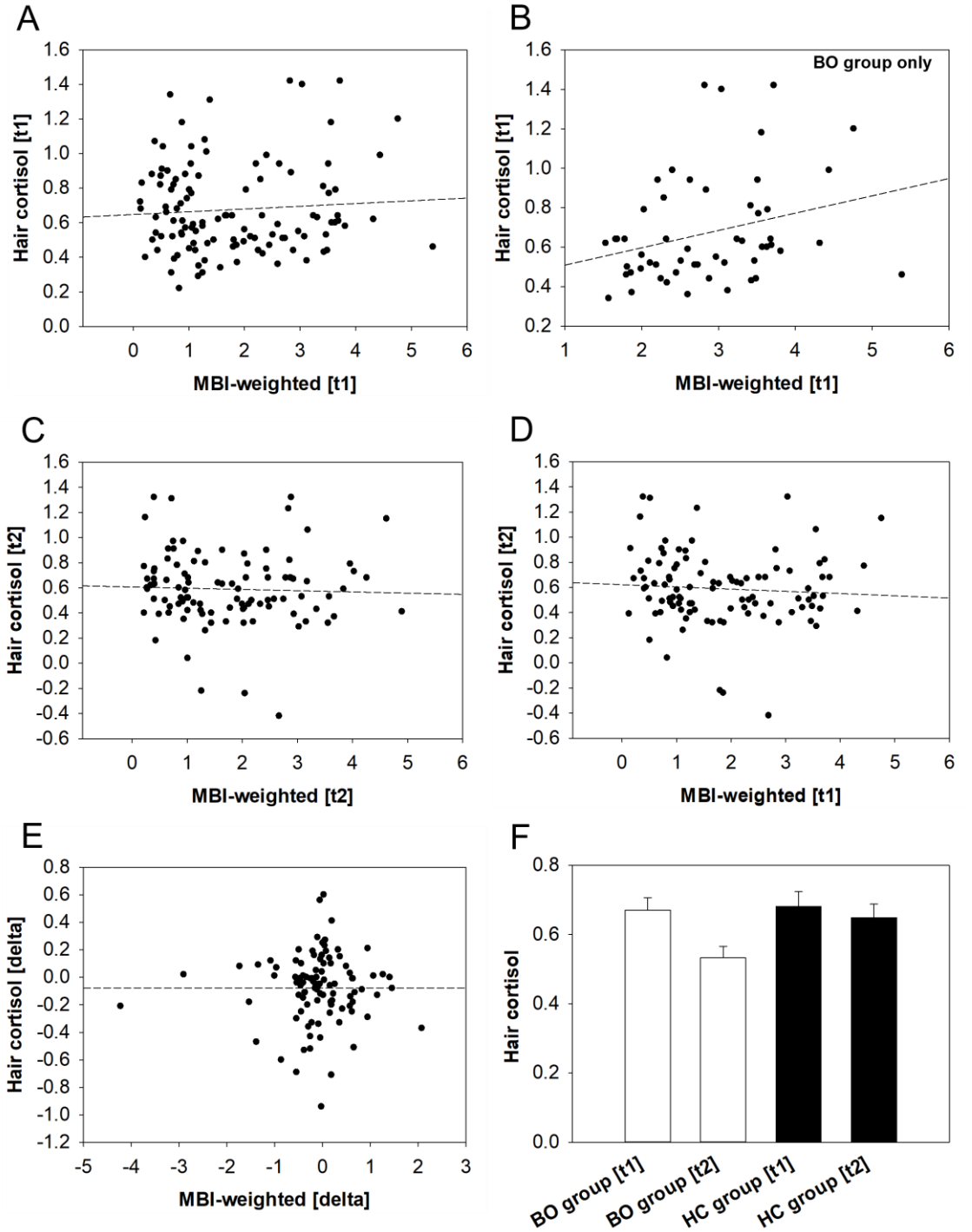
Contrary to our hypothesis, multiple regressions in the total study sample revealed no significant cross-sectional associations either at t1 (MBI-weighted$_{t1}$ ß = .07) or at t2 (MBI-weighted$_{t2}$ ß = -.05). Exploratory analyses within the BO group revealed a significant positive association between MBI-weighted and HCC at t1 (ß = .36, p = .033) but not at t2 (ß = .17).

In respect to longitudinal associations, MBI-weighted$_{t1}$ (ß = -.18, p = .045) was a significant negative predictor of HCC$_{t2}$ in the total sample indicating that higher MBI-weighted scores at t1 predicted lower HCC at t2. In the analysis restricted to the BO group, MBI-weighted$_{t1}$ was no significant predictor of HCC$_{t2}$ (ß = .05). After excluding the participants from the analysis (total sample) who received treatment or changed their employers (n = 5) between t1 and t2, only a trend towards a negative association remained (ß = -.15, p = .109). To further investigate the longitudinal association, MBI-weighted$_{delta}$ was correlated with HCC$_{delta}$; this correlation rendered non-significant within the whole sample (r = .02) as well as the BO subgroup (r = .04). Finally, in terms of reverse causation, HCC$_{t1}$ was no significant predictor of MBI-weighted$_{t2}$, neither in the total sample (ß = .07) nor in the BO group (ß = -.01).

Figures 7A-F show scatterplots of the association between burnout and HCC as well as mean HCC scores of both groups. In Supplemental Tables 21-28 fit indices as well as ß-values are provided for each analysis.

Figure 7

Scatterplots of the cross-sectional (A–C) and longitudinal (D–E) associations between burnout (MBI-weighted) and log-transformed hair cortisol concentrations (pg/mg) in the total study sample (A, C–E) and the BO group only (B) as well as mean log-transformed hair cortisol concentrations (pg/mg) of the burnout and healthy comparison group (F)



Note. Error bars represent standard error of mean. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; BO group = burnout group; HC group = healthy comparison group.

5.5 Discussion

In the present study, we investigated cross-sectional and longitudinal associations between burnout and HCC in a study sample consisting of a strictly specified group of individuals suffering from burnout and a healthy comparison group. Contrary to our hypothesis, no cross-sectional associations between burnout and HCC were found at either measurement time point indicating no specific HPA axis alterations in individuals suffering from burnout. While this finding is in line with the results obtained by Wekenborg et al. (2019), Deng et al. (2021), and Marcil et al. (2022), a comparable number of studies exists reporting significant positive associations between burnout and HCC (Ibar et al., 2021; Penz et al., 2018; Wang et al., 2019; Wendsche et al., 2020). However, in two of these studies (Penz et al., 2018; Wendsche et al., 2020) only nonlinear associations were found and, additionally, in a study by Lennartsson et al. (2015) only patients with more severe burnout symptoms exhibited lower salivary cortisol responses to acute psychosocial stress. Together with our finding of a positive association between burnout symptoms and HCC at t1 exclusively in the BO group, this again supports the idea that HPA axis alterations only become apparent once a certain threshold of burnout symptomatology has been exceeded. Interestingly, Stalder et al. (2017) concluded that the 'lack of psychoneuroendocrine covariance' in HCC stress research should be addressed by investigating samples suffering from more severe stress conditions as moderate stress might only have minor effects on HCC. In this vein, it should be of note that in our sample, we only included non-clinical and otherwise healthy subjects with a regular working schedule of ≥ 20 h/week. In addition, the association between burnout and HCC may not only depend on the severity but also on the duration of burnout symptoms suggesting that HCC might be elevated in some individuals with burnout symptoms and reduced in others depending on both, the severity and duration of burnout (Rohleder, 2018), due to idiosyncratic progression of HPA axis dysregulations across individuals.

The longitudinal analysis showed that burnout symptomatology at t1 significantly predicted HCC at t2. Interestingly, the decrease in HCC from t1 to t2 was restricted to the BO group, while HCC of the healthy group remained stable (see Figure 7F). This finding is in line with the longitudinal study by Penz et al. (2019) who also reported on a negative association between the degree of chronic work stress and HCC. In contrast, another recent study provides no evidence for a longitudinal association between HCC

and psychological distress conditions such as depressive symptomatology (Walther et al., 2023). One might speculate that the present finding speaks for a time-dependent development of hypocortisolism in burnout (Rohleder, 2018). If so, the decrease in HCC from t1 to t2 should probably be attributable to the change in burnout symptomatology from t1 to t2, but this is not the case. Also, it seems somewhat surprising that this effect was only observed in the longitudinal and not in the cross-sectional analysis. In this vein, *post-hoc* inspection of the association between the retrospectively assessed duration of burnout symptoms already before t1 and HCC also did not indicate any kind of (non)linear association (see Supplemental Figures 17-18). After exclusion of participants who meanwhile started treatment or changed their employers, the *post-hoc* analysis of the association between burnout symptomatology at t1 and HCC at t2 rendered non-significant. Thus, our subsidiary analyses regarding this effect (i.e., burnout symptomatology at t1 being a negative predictor of HCC at t2) are inconclusive and partly challenge the validity of this finding. Finally, it is well-known from laboratory studies on acute stress that timing is essential when investigating psychoendocrine covariance (Schlotz et al., 2008). For example, Het et al. (2012) have shown that acute cortisol stress responses may have lagged mood-buffering effects, illustrating that associations between psychological and cortisol stress responses may become apparent when taking lagged effects into account. However, if or how such effects may also apply to longterm stress remains completely unclear.

Finally, important limitations must be addressed. As stated above, HPA axis alterations might only become evident when a certain threshold of burnout severity is exceeded. As the BO group contained relatively few participants with “severe burnout symptoms” (n = 14) (Kalimo et al., 2003), probably due to the strict inclusion criteria (e.g., no antidepressant medication, no sick-leave), this might be an explanation for the given cross-sectional results. Another limitation relates to the strict division of the sample into a BO and HC group at t1 (Bärtl et al., 2022), as group membership cannot be assumed to be stable over time, and application of the inclusion criteria was not feasible at t2. In addition, the present study was limited to HCC as a marker of long-term cortisol accumulation. Therefore, we cannot draw any conclusions about possible changes of short-term HPA axis functionality (e.g., acute stress responses) or potential alterations on different functional levels of the HPA axis (e.g., hypothalamus, pituitary gland, adrenal cortex, molecular level) in burnout.

On the other hand, the study design and the recruitment procedure are a major strength of the present study. While previous studies followed a correlational approach or grouped participants *post-hoc* based on burnout symptomatology or HCC (Ibar et al., 2021; Penz et al., 2018), the present study sample consisted of two distinct groups with varying burnout levels. Importantly, to the best of our knowledge this is the first longitudinal study, in which both, burnout and HCC were measured repeatedly.

In sum, we investigated HCC in a strictly defined sample of 55 subjects suffering from burnout and 59 healthy controls derived from the Regensburg Burnout Project. While our cross-sectional results appear to support the idea that HPA axis alterations in terms of elevated HCC in burnout might only become apparent once a certain threshold of burnout severity has been exceeded, the longitudinal data show some empirical evidence for the potential long-term development of hypocortisolism in burnout. However, the results of the present study remain somewhat inconclusive. With this, our results point to the need for future longitudinal studies in combination with larger study samples with varying burnout symptoms, longer observational periods, and more measurement time points to further elucidate the association between burnout and HCC.

CHAPTER 6

6 STUDY III: NEURAL AND CORTISOL RESPONSES TO ACUTE PSYCHOSOCIAL STRESS IN WORK-RELATED BURNOUT: THE REGENSBURG BURNOUT PROJECT

6.1 Abstract

Background: While several attempts have been made to elucidate the pathophysiology of burnout, neural stress responses have not yet been investigated. Therefore, the aim of this study was to examine salivary cortisol and - for the first time - neural responses to acute psychosocial stress within a strictly specified sample consisting of individuals suffering from burnout (BO group) and a healthy comparison group (HC group).

Methods: After a multi-stage recruitment procedure based on burnout symptomatology and pathogenesis, 55 individuals suffering from burnout (25 women) and 61 individuals serving as HC group (31 women) out of an initial sample of 1022 volunteers were exposed to acute psychosocial stress during functional magnetic resonance imaging (fMRI) applying Scan*STRESS*.

Results: No differences were found between the BO and the HC group with respect to cortisol and mean neural stress responses. However, an exploratory comparison of neural stress responses of the first and second run of Scan*STRESS* (exposure-time effect) revealed group-specific response patterns in one cluster peaking in the left dorsal anterior cingulate cortex (dACC). While the neural activation of the HC group was higher in the first compared to the second run of Scan*STRESS* (i.e., decreasing activation), this pattern was reversed in the BO group (i.e., increasing activation).

Conclusions: Our analysis mainly did not provide evidence for altered acute cortisol and mean neural stress responses in burnout. However, the BO group was characterized by a limited capacity to show decreasing activation over stress exposure-time and exhibited instead increasing activation. Importantly, this group difference manifested in the left dACC which is both involved in neural stress processing and affected in individuals suffering from burnout. Given the present results, it seems promising to further examining temporal dynamics of neural stress responses in (sub-) clinical conditions such as burnout.

6.2 Introduction

The burnout syndrome results from chronic work stress that has not been dealt with successfully and relates to feelings of emotional exhaustion (EE), depersonalization (DP), and lack of personal accomplishment (LA) (Maslach et al., 2001; World Health Organization, 2019). Although burnout is incorporated as an occupational phenomenon and not listed as a mental disorder in the *International Classification of Diseases Eleventh Revision* (World Health Organization, 2019), convincing evidence from prospective studies shows that burnout is associated with various negative physical (e.g., cardiovascular diseases), psychological (e.g., insomnia), as well as occupational (e.g., absenteeism) consequences (Salvagioni et al., 2017). However, the mechanisms underlying this interplay are still unknown, although several attempts have been made to identify a pathophysiological signature of burnout (Bayes et al., 2021; Jonsdottir & Sjörs Dahlman, 2019). Since burnout arises from chronic stress, a large body of research has focused on the hypothalamic-pituitary-adrenal (HPA) axis as a key component of the acute stress reaction (Jonsdottir & Sjörs Dahlman, 2019). With this, it was assumed that HPA axis (re)activity may be reduced in burnout owing to repeated or chronic adaptions to stress (Danhof-Pont et al., 2011; Kudielka et al., 2006; Rohleder, 2018).

However, only a few studies on burnout have investigated cortisol responses to acute psychosocial stress applying the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or modified versions of the protocol (Rothe et al., 2020). In detail, Wekenborg et al. (2019) and de Vente et al. (2003) found no alterations of cortisol reactivity in burnout, while in other studies reduced cortisol responses emerged only in subgroups consisting of men (de Vente et al., 2015) or of individuals with more severe burnout symptomatology (Jönsson et al., 2015; Lennartsson et al., 2015). Moreover, in studies applying the dexamethasone suppression test (DST), a similar picture emerged indicating either an increased cortisol suppression or no altered cortisol suppression in burnout (Rothe et al., 2020). In addition, studies on chronic stress conditions revealed that cortisol secretion is elevated at stressor onset but will decrease with longer duration of stress experience (Miller et al., 2007; Rohleder, 2018).

Given the mixed findings of either reduced or no altered cortisol reactivity in burnout, it is likely that the lack of clear criteria for identifying burnout cases may have contributed to heterogeneous study samples generating those divergent results (Bayes et

al., 2021; Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020). Therefore, the first objective of the present study was to investigate potential differences regarding cortisol responses to acute psychosocial stress comparing a strictly specified group of individuals suffering from burnout (BO group) with a healthy comparison group (HC group) (Bärtl et al., 2022).

While it seems reasonable that the focus has long been on peripheral markers of HPA axis or autonomic system (re)activity, in the meanwhile, at least some studies exist examining burnout-related changes in the brain (Bayes et al., 2021; Jonsdottir & Sjörs Dahlman, 2019). Most of these studies used methods such as voxel-based morphometry (VBM) and/or extracted cortical thickness, or volume measures of (sub)cortical brain structures. With respect to VBM, reduced grey matter (GM) volumes in the ventromedial prefrontal cortex (vmPFC), dorsolateral PFC (dlPFC), insula, thalamus, and anterior cingulate cortex (ACC) were associated with chronic work stress and burnout symptoms (Abe et al., 2022; Blix et al., 2013). In contrast, Rydmark et al. (2006) found no altered GM volumes in patients with job stress-induced depression compared to healthy matched controls. Regarding cortical thickness, a thinning of the (m)PFC and left superior temporal gyrus (STG) was present in individuals suffering from chronic work stress and burnout (Savic, 2015; Savic et al., 2018). In addition, reduced nucleus caudatus and putamen volumes as well as enlarged amygdala but not hippocampal volumes were found in individuals experiencing chronic work stress or burnout symptoms (Blix et al., 2013; Sandström et al., 2011; Savic, 2015; Savic et al., 2018). Moreover, data on functional connectivity (FC) in individuals suffering from chronic work stress and burnout point to an altered FC of structures including, among others, hippocampus, amygdala, ACC, and (m)PFC (Golkar et al., 2014; Jovanovic et al., 2011; Shang et al., 2022). Interestingly, data obtained with magnetic resonance spectroscopy (MRS) also indicated the specific role of prefrontal regions and the ACC as burnout-related structures (Savic, 2020). Beyond that, Durning et al. (2013) reported on associations between burnout scores and task-based blood-oxygenation-level-dependent (BOLD) signals in e.g., the right dlPFC and posterior cingulate cortex (PCC) during clinical reasoning in internal medicine residents. The involvement of frontal as well as striatal regions in burnout was further supported by the findings of Gavelin et al. (2017) who examined the association between burnout symptoms and neural activation during a working memory task.

In sum, previous studies on burnout-related brain changes point to various alterations of striato-limbic structures. Importantly, these structures have been repeatedly shown to

play a key role in acute neural stress processing in healthy individuals (Berretz et al., 2021; Henze et al., 2020). However, neural responses to acute psychosocial stress in individuals suffering from burnout have not yet been investigated.

Therefore, the second aim of the present study was to examine neural stress responses using the Scan*STRESS* paradigm (Henze et al., 2020; Streit et al., 2014) in individuals suffering from burnout compared to healthy controls. Interestingly, in a recent study of our own group, we observed an increasing deactivation of limbic structures over psychosocial stress exposure-time (the so-called *exposure-time effect*) in young healthy adults. Based on this, we speculated if differences in this shift could possibly be a relevant marker of an altered central stress processing in e.g., chronic stress conditions such as burnout (Henze et al., 2020). First evidence for this assumption comes from a study examining neural stress responses in patients with first episode major depression disorder (MDD), as female patients did not exhibit increasing deactivation of pre-limbic structures (e.g., amygdala, medial orbital frontal cortex) over stress exposure-time (Dong et al., 2022). Given the considerable symptom overlap between burnout and depression (Koutsimani et al., 2019), it seems promising to investigate whether individuals with burnout symptoms can also be characterized by a limited capacity to show increasing deactivation over stress exposure-time. Hence, the present study further aimed at exploring if study groups may differ with respect to the exposure-time effect.

In sum, findings on cortisol reactivity in burnout have been inconclusive with a tendency towards reduced cortisol responses. As it was suggested that heterogeneous study samples may have contributed to those divergent results (Bayes et al., 2021; Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020), we expected to find lower salivary cortisol responses to acute psychosocial stress in a more strictly specified group of individuals suffering from burnout (BO group) compared to a HC group. Regarding neural responses we did not postulate directional or structure-specific differences and followed a whole-brain approach with subsequent peak-based region of interest (ROI) analysis as the present study was the first examining neural stress responses in burnout. Finally, we investigated differences between study groups with respect to the exposure-time effect on an exploratory level and have therefore also applied non-parametric tests using Randomise (Winkler et al., 2014).

6.3 Material and methods

6.3.1 Participants

The present study was conducted as part of the Regensburg Burnout Project (Bärtl et al., 2022). The study protocol was not pre-registered. An a priori analysis of sample size was performed using the software GPower3 by Faul et al. (2007). Based on an estimated effect size of $f = 0.17$ for salivary cortisol responses to acute stress (as empirically derived from Bellingrath & Kudielka, 2008), a nominal significance level of $\alpha = .05$, a test power of $1-\beta = .80$, applying a between group design (2 groups) with repeated measurements (10 saliva samples), we pre-calculated a required sample size of $N = 30$. An additional power analysis resulted in a total sample size of $N = 80$ participants given $\alpha = .05$ and a test power of 80% to detect at least small effect sizes of $f = 0.10$ according to Cohen (1988).

We screened an initial sample of 1022 volunteers. A total of 116 participants qualified to take part in the functional magnetic resonance imaging (fMRI) experiment with 55 participants (30 women) assigned to the burnout group (BO group) and 61 participants (31 women) to the healthy comparison group (HC group).

Eligibility of participants was ascertained by an extensive multi-stage recruitment procedure with strict inclusion criteria based on burnout symptomatology and pathogenesis, additionally verified by peer-ratings (described in detail in Bärtl et al., 2022). In more detail, inclusion criteria for the BO group were mild to serious burnout symptoms determined by the Maslach Burnout Inventory-General Survey (Kalimo et al., 2003; Schaufeli et al., 1996) and the experience of foregoing chronic work stress as indicated by effort-reward imbalance (Bärtl et al., 2022; Siegrist et al., 2009). Additionally, participants assigned to the BO group must have demonstrated at least medium to high levels of self- and peer-rated job performance, resiliency, motivation, and commitment before the onset of burnout symptoms (= work-related self- and peer-evaluation). Only individuals who reported low levels of burnout, chronic work stress, as well as depression were included in the HC group (Bärtl et al., 2022). General MRI- (e.g., wearing a pacemaker, pregnancy), health- (e.g., physical diseases, anticoagulant or psychopharmacological treatment, medication with corticosteroids) as well as work-related (e.g., long-term sick-leave, working time < 20h/week) exclusion criteria are described in detail in Bärtl et al. (2022). The inclusion criteria for the respective study groups are summarized in Table 8.

Table 8
Inclusion criteria of the burnout and the healthy comparison group

Burnout Group	Healthy Comparison Group
○ Burnout: MBI-GS score ≥ 1.50 ○ Work stress: ER-ratio ≥ 0.715 ○ Work-related self- and peer-evaluation on a medium to high level before the onset of burnout symptoms ○ Regular working time ≥ 20h/week	○ Burnout: MBI-GS score < 1.50 ○ Work stress: ER-ratio < 0.715 ○ Depression: HADS-D ≤ 7 ○ Regular working time ≥ 20h/week

Note. MBI-GS = Maslach-Burnout Inventory-General Survey; ER-ratio = Effort-Reward ratio calculated from the Effort-Reward Imbalance Questionnaire; HADS-D = Hospital Anxiety and Depression Scale – Depression Scale.

All participants provided written informed consent and received a monetary compensation. The study was approved by the local ethics committee of the University of Regensburg.

6.3.2 General procedure

A screening questionnaire covered sociodemographic, work- and health-related variables, chronic work stress as well as burnout and depression symptomatology. At a first appointment allostatic load parameters and hair samples were gained (Bärtl et al., 2022).

After the first appointment, the MRI-experiment (i.e., Scan*STRESS*) took place on a separate weekday between 11:30 a.m. and 07:00 p.m. and lasted 3h 20min. Pre-menopausal women not using hormonal contraceptives were tested during the luteal phase of the menstrual cycle, as confirmed by urine ovulation test kits (gabmed GmbH, Köln, Germany). After arriving at the laboratory, participants first watched a neutral movie as part of a pro-longed relaxation phase (45min duration). Additionally, 45min prior to stress onset, 75g glucose mixed with 200ml of herbal tea was administered to facilitate cortisol reactivity (Henze et al., 2020; Zänkert et al., 2020). A brief training session of the Scan*STRESS* control blocks was performed during the relaxation phase. In the subsequent one-hour MRI examination, the Scan*STRESS* paradigm as well as resting state and anatomical measurements were applied. After the MRI session, participants remained in the laboratory for additional 45min to fill out questionnaires. At the end of the experimental session participants were debriefed (Henze et al., 2020).

Approximately seven months after the first appointment, psychometric data as well as hair samples and allostatic load parameters were collected again (Bärtl et al., 2023).

6.3.3 Self-report measures

A detailed description of the screening and psychometric assessment conducted in the Regensburg Burnout Project can be found in Bärtl et al. (2022).

Maslach Burnout Inventory-General Survey (MBI-GS). Burnout symptomatology was assessed with a German version of the 16-items MBI-GS (Schaufeli et al., 1996) consisting of the three subscales emotional exhaustion (EE), depersonalization (DP), and lack of personal accomplishment (LA). For the present study, the weighted MBI-score was calculated according to the formula given by Kalimo et al. (2003): $MBI_{weighted} = 0.4 \times EE + 0.3 \times DP + 0.3 \times LA$. Based on $MBI_{weighted}$ scores individuals can be characterized by having "no burnout risk" (scores: 0-1.49), "some burnout symptoms" (scores 1.5-3.49), or "serious burnout symptoms" (scores 3.50-6.0).

Effort-Reward Imbalance Questionnaire (ERI-Q). The short version of the ERI-Q with the subscales effort and reward was used to capture the degree of chronic work stress. ER-ratio was calculated according to the formula given by the authors (Siegrist et al., 2009).

Hospital Anxiety and Depression Scale (HADS). Anxiety (HADS-A) as well as depression (HADS-D) symptomatology was assessed with the German version of the HADS (Herrmann-Lingen et al., 2011).

6.3.4 Scan*STRESS*

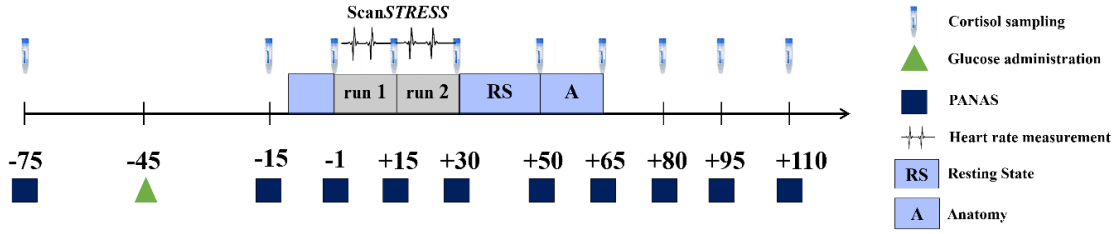
The Scan*STRESS* paradigm was applied to compare both cortisol and neural responses to acute psychosocial stress between the BO and HC group. Scan*STRESS* is a psychosocial stress experiment for fMRI environments consisting of two runs with a total duration of 24min and is conceived as a block design with the two conditions stress and control. During the stress conditions, participants are required to perform challenging mental arithmetic and rotation tasks under time pressure while being monitored by a negative feedback-giving observational panel. During control conditions, less demanding tasks are presented (i.e., figure and number matching) without time pressure and observation taking place. Between the two runs, participants receive verbal negative feedback by the observational panel about their individual performance and an urgent

request to improve their performance in the second run. For a more detailed description of the protocol see Henze et al. (2020).

Saliva samples using Cortisol Salivettes® (Sarstedt, Nümbrecht, Germany) as well as mood ratings (Positive and Negative Affect Schedule (PANAS); Watson et al., 1988) were collected at ten time points: -75, -15, -1min before the start of Scan*STRESS* and +15, +30, +50, +65, +80, +95, and +110min thereafter. In addition, during Scan*STRESS*, heart rate was recorded with an MRI-compatible finger oximeter (Model 7500 FO; Nonin Medical, Plymouth, MN). The experimental procedure is illustrated in Figure 8.

Figure 8

Experimental procedure including the repeated collection of cortisol samples, heart rate measurements, and affect ratings (PANAS) during ScanSTRESS



Note. Adapted from Henze (2021)

6.3.5 Biochemical analysis of salivary cortisol

Cortisol saliva samples were stored at -20°C until analysis and then assayed in duplicate using a time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA) at the biochemical laboratory at the University of Trier. The inter- and intra-assay coefficients of variation were below 10%. Six of the 1160 cortisol samples were missing data. Two cortisol values were replaced by linear regression estimates of respective neighboring values while two participants were excluded from cortisol analysis due to critical missing values around peak time, respectively.

6.3.6 Statistical analysis of salivary cortisol, heart rate and psychological data

Salivary cortisol values were log-transformed to approximate a normal distribution. As a manipulation check, cortisol, heart rate, and psychological stress responses of the total study sample were analyzed using repeated-measures analyses of variance (rANOVA) with the within-subjects factor Time (respective measurement time points) on cortisol (nmol/l), heart rate (beats/min) and positive and negative affect (PANAS) test scores. Cortisol increases were calculated based on raw cortisol data and defined by the

difference between the individual cortisol peak of samples +30, +50, or +65 and the pre-stress sample -1. Additionally, participants were descriptively grouped into responders and non-responders following the 1.5-nmol/l criterion by Miller et al. (2013).

Differences between the BO and the HC group regarding cortisol responses were investigated by computing rANOVA with group (BO group / HC group) as between subjects-factor and Time as within-subjects factors (respective measurement time points), controlling for sex / menstrual cycle condition (men, women using hormonal contraceptives, women in luteal phase, postmenopausal women) and age (Kudielka et al., 2009). In addition, groups were compared regarding differences in cortisol increase using univariate analyses of variance, controlling for sex / menstrual cycle condition and age. We further exploratively conducted rANOVA with cortisol measurements as within-subjects factor and $MBI_{weighted}$-scores as covariate exclusively within the BO group as previous studies indicated nonlinear associations between burnout and HPA axis activity (i.e., burnout-related HPA axis alterations might only become evident once a certain threshold of burnout severity has been exceeded) (Bärtl et al., 2023; Penz et al., 2018; Wendsche et al., 2020). Moreover, rANOVAs with group as between-subjects factor and Time as within-subjects factors (respective measurement time points) were performed on heart rate (beats/min), and positive and negative affect (PANAS) test score.

Data were analyzed with IBM SPSS Statistics version 28 (IBM, Corp., Armonk, NY); significance was defined by a threshold of $\alpha = .05$ (two-tailed). Greenhouse-Geisser corrections were applied where appropriate; only adjusted results are reported.

6.3.7 fMRI acquisition and data analysis

fMRI data acquisition and analysis followed the procedure presented in Henze et al. (2020). Briefly, participants were scanned in a Siemens MAGNETOM Prisma 3T MRI scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil (for acquisition parameters see Supplemental Tables 29-30). Skull stripping of the anatomical images was performed using SynthSeg (Billot et al., 2023) with robust performance in terms of changes in contrast and resolution. Further preprocessing was carried out using fMRIPrep and freesurfer implemented in HALFpipe (Waller et al., 2022). For the anatomical data, additional preprocessing includes tissue segmentation and spatial normalization. For the functional images, preprocessing encloses motion correction, susceptibility distortion correction, coregistration, and spatial normalization. In addition, HALFpipe performs spatial smoothing (6mm), grand mean scaling,

independent component analyses-based denoising, and temporal filtering to remove low-frequency drift (Gaussian high-pass filter: 125s). Based on motion parameters (mean frame-wise displacement > 0.5), we finally excluded n = 10 participants (5 participants per group) from the task-based analyses resulting in a final study sample for fMRI analyses of N = 106.

Data analysis was conducted using FSL (FMRIB Software Library, Oxford, United Kingdom) tool FEAT version 6.0. The z (Gaussianized t/F) statistic images were thresholded nonparametrically using clusters determined by $z > 3.1$. For each participant, general linear models (GLMs) were computed including regressors for control and stress conditions and the respective announcement phase. GLMs were calculated separately for each run (first level, $z > 3.1$) and mean responses were obtained by a fixed-effects analysis (second level, $z > 3.1$). Neural response differences between the BO and HC group were investigated by a between-subjects group analysis (mixed effects, $z > 3.1$) on a third level. An additional GLM with run as regressor (after the first level) was carried out to investigate differences between both groups regarding the exposure-time effect (Henze et al., 2020). For condition- (stress > control, control > stress) and group-specific effects, family-wise error (FWE; $p < .025$, two-tailed combined test, FWE < .05) correction was performed over the whole brain at a threshold of $z > 3.1$. This threshold was lowered to $z > 2.3$ in order to explore possible group differences with respect to the exposure-time effect and general neural stress responses. In addition, fsl's tool Randomise was applied to further test our results on a non-parametric basis (n = 5000 iterations).

Group differences regarding the exposure-time effect were further explored (for illustrative reasons) within one *post-hoc* ROI analysis. First, a binary 5mm spherical mask (see Figure 13C) around the local activation peak (49 62 58) in the left dorsal ACC (dACC) was generated using fslmaths (MNI coordinates: -8 -2 44). Subsequently, run-specific mean ß-values (extracted from first-level analysis; $z > 3.1$) of the contrast stress > control were extracted via featquery for each participant. The mean ß-values were exported to SPSS and a *post-hoc* rANOVA was performed with mean ß-values of the first and second run of Scan*STRESS* as within-subjects factor (left dACC run 1 / dACC run 2) and group (BO group / HC group) as between-subjects factor. In addition, potential interaction effects group x run x sex were exploratively analyzed as it was suggested that burnout-related brain changes are more pronounced in women (Savic et al., 2018).

6.4 Results

6.4.1 Study sample

Demographic, health-related, as well as psychological characteristics of the study groups are presented in Table 9.

Table 9
Demographic, health-related, as well as psychological characteristics of the burnout (BO) and healthy comparison (HC) group, and results of chi-square tests as well as unpaired t-tests

	Burnout group (n = 55)	Healthy comparison group (n = 61)			
			χ^2	*df*	*p*-value
Men (%)	30 (54.5)	30 (49.2)	0.33	1	.56
Women using hormonal contraception (%)	7 (12.7)	6 (9.8)	0.24	1	.62
Women in luteal phase (%)	14 (25.5)	11 (18.0)	0.94	1	.33
Postmenopausal women (%)	4 (7.3)	14 (23.0)	5.42	1	.02
Smokers, *n* (%)	8 (14.5)	13 (20.3)	0.46	1	.50
			t	*df*	*p*-value
Age (*SD*), yrs.	41.20 (10.29)	41.28 (11.16)	-0.04	114	.97
MBI-GS					
Weighted MBI-score (*SD*)	2.79 (0.82)	0.83 (0.35)	16.39	70.98	.001
EE (*SD*)	3.68 (1.27)	0.88 (0.60)	14.94	75.09	.001
DP (*SD*)	2.78 (1.34)	0.59 (0.62)	11.08	74.31	.001
LA (*SD*)	1.60 (1.00)	1.00 (0.82)	3.50	104.74	.001
ERI-Q					
ER-ratio (*SD*)	1.16 (0.41)	0.50 (0.15)	11.51	66.52	.001
Effort (*SD*)	11.58 (2.04)	6.72 (2.00)	12.93	114	.001
Reward (*SD*)	24.77 (5.68)	31.76 (2.41)	-8.79	71.22	.001
Overcommitment (*SD*)	3.00 (0.53)	1.92 (0.61)	10.21	114	.001
HADS					
HADS-A	9.65 (4.01)	3.54 (2.47)	9.75	88.01	.001
HADS-D	8.45 (3.89)	2.61 (1.66)	10.33	71.37	.001

Note. MBI-GS = Maslach Burnout Inventory-General Survey; EE = Emotional Exhaustion; DP = Depersonalization; LA = Lack of Personal Accomplishment; ERI-Q = Effort-Reward Imbalance Questionnaire; HADS-A = Hospital Anxiety and Depression Scale – Anxiety Score; HADS-D = Hospital Anxiety and Depression Scale – Depression Score.

While the HC group consisted of a significant higher number of postmenopausal women ($\chi^2(1, N = 116) = 5.42$; $p = .02$), a chi-square test revealed no significant differences between study groups regarding the overall distribution of the sex / menstrual cycle condition variable ($\chi^2(3, N = 116) = 5.70$; $p = .13$).

6.4.2 Cortisol, heart rate, and psychological stress responses

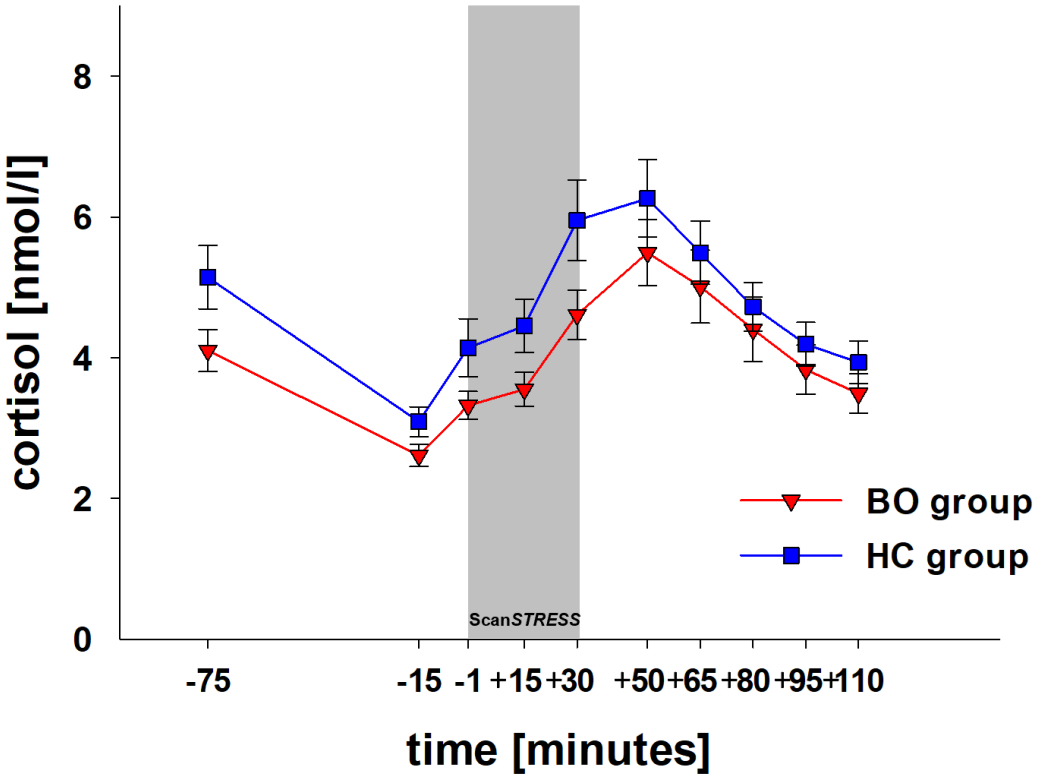
In the total sample (N = 114) a significant rise of salivary cortisol in response to acute psychosocial stress induction was observed ($F_{2.87, 324.51}$ = 29.64, $p \leq .001$, η_p^2 = .21); the cortisol responder-rate was 57%. In addition, negative affect (NA) ratings increased and positive affect (PA) ratings decreased significantly in the whole sample (NA: $F_{3.78, 431.29}$ = 69.93, $p \leq .001$, η_p^2 = .38; PA: $F_{5.31, 605.62}$ = 19.98, $p \leq .001$, η_p^2 = .15). Mean heart rates were significantly higher during stress compared to control blocks in the first ($F_{2.42, 247.10}$ = 63.23, $p \leq .001$, η_p^2 = .38) as well as second run ($F_{1.87, 194.33}$ = 84.33, $p \leq .001$, η_p^2 = .45) of Scan*STRESS*, indicating that Scan*STRESS* resulted in a successful stress induction in the total sample.

However, contrary to our hypothesis, no differences were found regarding cortisol responses between the BO and HC group ($F_{2.88, 302.07}$ = 0.33, p = .79) as illustrated in Figure 9. Also, the analysis restricted to the BO group including $MBI_{weighted}$-scores as covariate revealed only a non-significant trend for a negative association between cortisol responses and burnout symptoms ($F_{2.80, 131.69}$ = 2.37, p = .07). In addition, no differences emerged between the BO and the HC group with respect to cortisol increase (BO group M = 2.71nmol/l, SD = 3.48; HC group M = 3.23nmol/l, SD = 3.91; $F_{1, 105}$ = 0.17, p = .68). Beyond that, no interaction effect group x time point was observed with respect to mean heart rate responses (run 1: $F_{3.43, 346.63}$ = 1.53, p = .20; run 2: $F_{2.72, 280.54}$ = 1.25, p = .29), PA ($F_{5.30, 599.26}$ = 1.54, p = .17), and NA ($F_{3.78, 427.35}$ = 0.57, p = .68).

Only the main effect group indicated generally reduced PA ($F_{1, 113}$ = 12.38, $p \leq .001$, η_p^2 = .10) and higher NA ($F_{1, 113}$ = 12.51, $p \leq .001$, η_p^2 = .10) in the BO compared to the HC group. Figures 9-11 show the cortisol, heart rate, and psychological responses of the respective study groups.

Figure 9

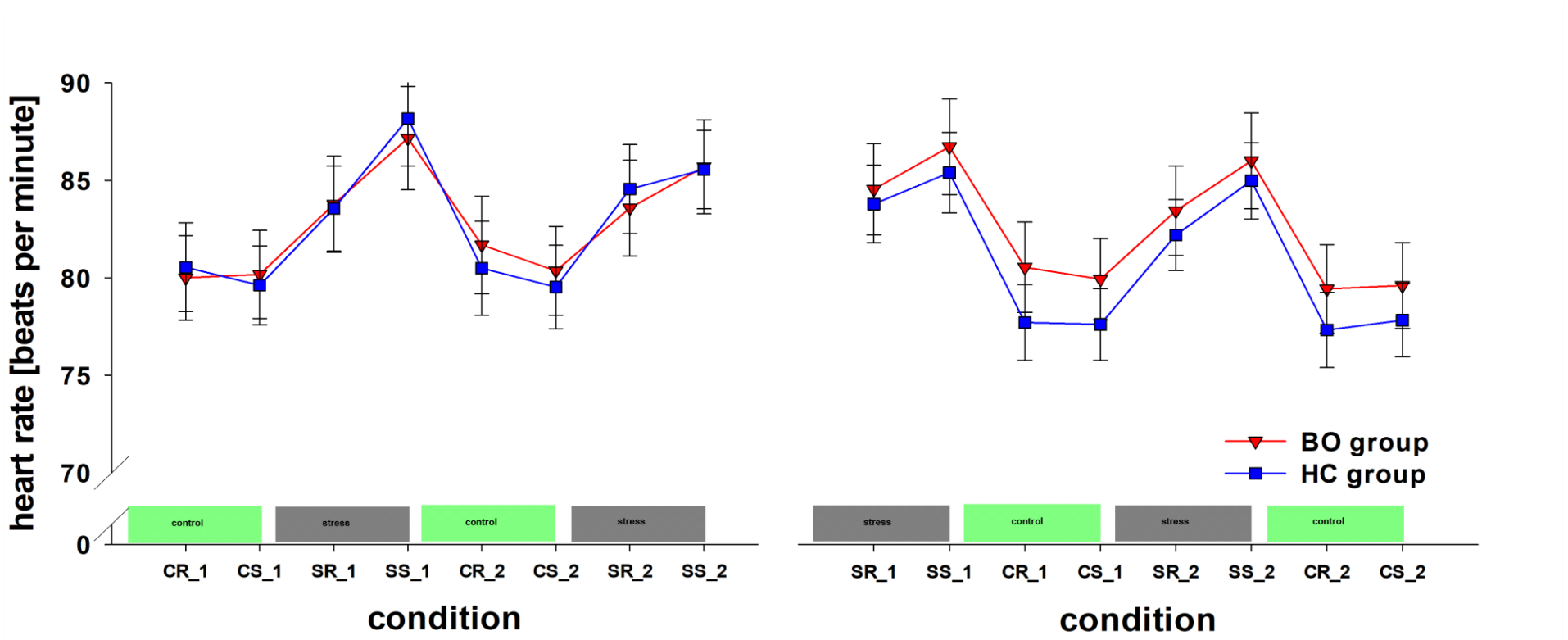
Salivary cortisol responses (raw data shown for illustrative purposes) to ScanSTRESS of the burnout and healthy comparison group



Note. Error bars represent standard error of mean. BO group = burnout group; HC group = healthy comparison group.

Figure 10

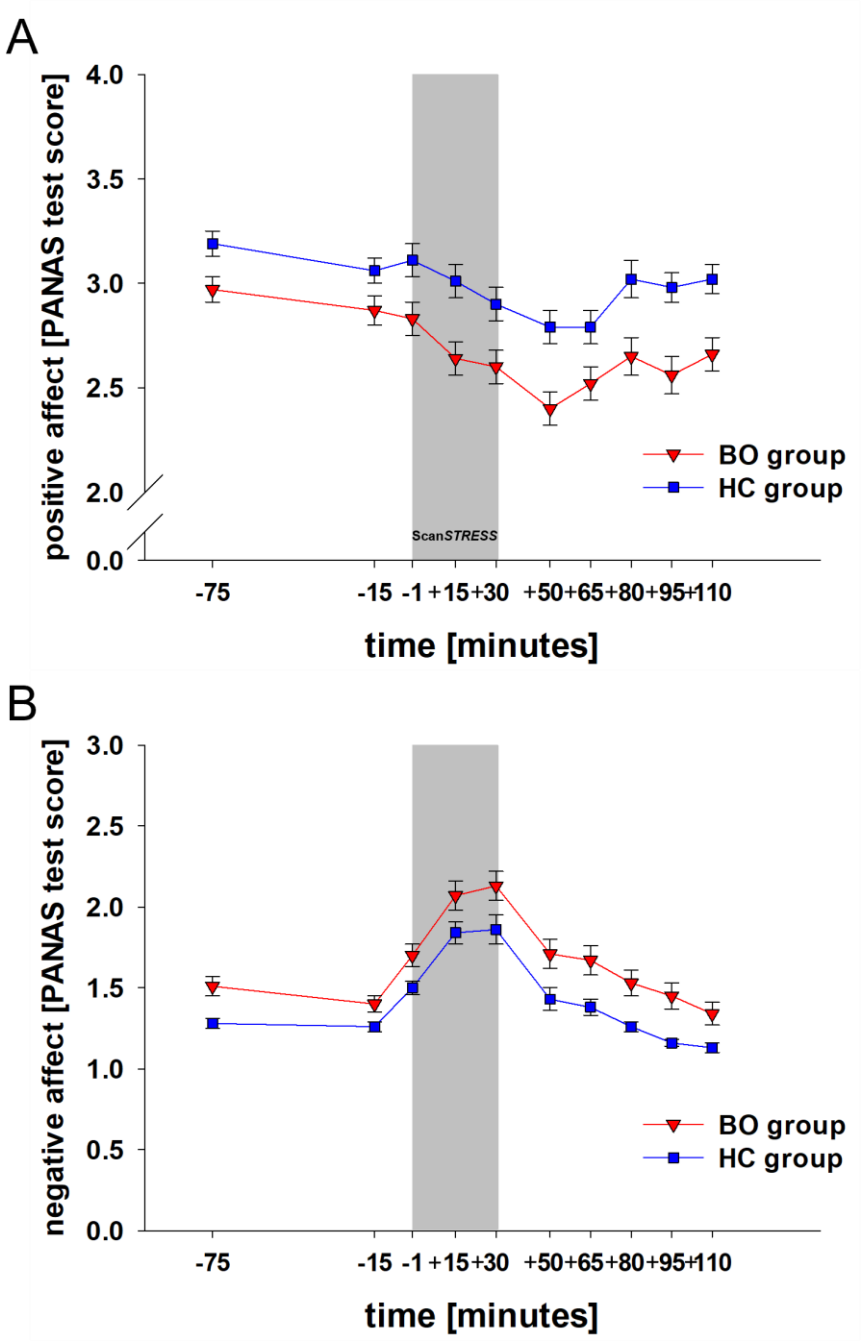
Mean heart rate of the burnout and healthy comparison group for each control and stress block over the two runs of ScanSTRESS



Note. Error bars represent standard error of mean. BO group = burnout group; HC group = healthy comparison group; CR = control rotation; CS = control subtraction; SR = stress rotation; SS = stress subtraction.

Figure 11

(A) Positive and (B) Negative Affect Schedule scores of the burnout and healthy comparison group throughout the experimental procedure of ScanSTRESS



Note. Error bars represent standard error of mean. BO group = burnout group; HC group = healthy comparison group; PANAS = Positive and Negative Affect Schedule.

6.4.3 Neural responses to acute psychosocial stress

First, data on motion during the fMRI experiment taken from motion correction using MCFLIRT (Jenkinson et al., 2002) indicated no group (BO vs. HC group) nor run (run 1 vs. run 2) differences in mean or relative displacements (all *ps* ≥ .18). For run 1, absolute

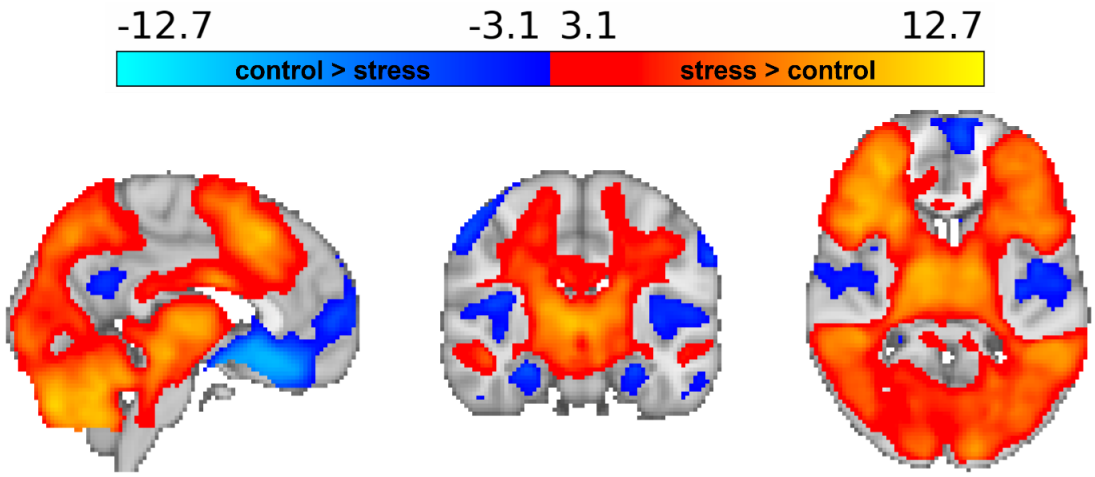
mean displacement was *M* = 0.56mm (*SD* = 0.35mm) and relative mean displacement was *M* = 0.07mm (*SD* = 0.03). For run 2, absolute mean displacement was *M* = 0.54mm (*SD* = 0.33) and relative mean displacement was *M* = 0.07mm (*SD* = 0.03).

The whole-brain analysis (Figure 12) for the total sample (irrespective of the variable group) revealed typical activations (stress > control) and deactivations (control > stress) in different clusters including structures such as the mPFC, cingulate cortex, insula, thalamus, striatum, and hippocampus ($z > 3.1$; FWE-correction $p < .025$, two-tailed combined test FWE-corrected < .05; peak voxels are reported separately in Supplemental Table 31).

However, no response differences emerged between study groups, indicating that overall neural responses did not differ between the BO and HC group under stress and control conditions. To control for possible confounding effects of age and individual error rates during the stress blocks of Scan*STRESS*, both variables were added separately as covariates of no interest into the group-level whole brain analyses ($z > 3.1$). These analyses did not evoke changes in the condition effects (stress > control; control > stress) of the total sample, nor did they enable the detection of group differences (BO vs. HC group). In addition, error rates did not differ between the BO (*M* = 38%, *SD* = 8.05) and the HC group (*M* = 37%, *SD* = 9.36; *p* = .75).

Figure 12

Activations (red to yellow) and deactivations (blue) in response to psychosocial stress induction of the total sample contrasting stress and control blocks (i.e., activations) and vice versa (i.e., deactivations)



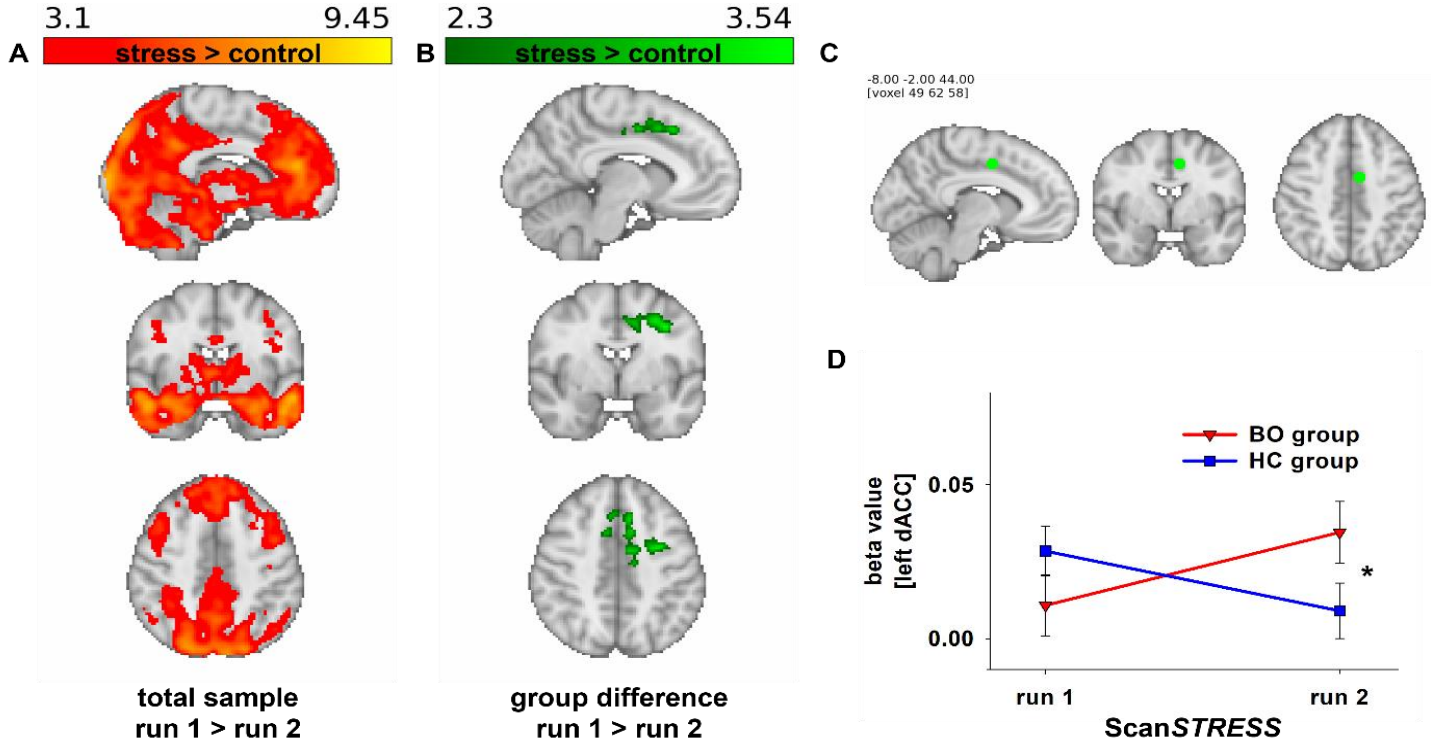
6.4.4 Exposure-time effect

Whole brain analysis (stress > control; $z > 3.1$ FWE-correction $p < .05$) regarding the exposure-time effect, i.e., investigating whether (group-specific) response differences exist between the first and second run of Scan*STRESS*, revealed a distributed network for the total sample (see Figure 13A). This network included, e.g., mPFC, cingulate cortex, insula, thalamus, striatum, hippocampus, and amygdala; all structures exhibited higher activations in the first compared to the second run of Scan*STRESS* (see Supplemental Table 32 for peak voxels).

With respect to a possible group difference (BO vs. HC, see Figure 13B) in the exposure-time effect, we detected a cluster involving the left dACC (114 voxels) as well as the left middle frontal gyrus (MFG, 102 voxels) at an exploratory threshold of $z > 2.3$ (see Supplemental Table 33 for peak voxels). In these regions, participants of the HC group showed higher activations in the first run compared to the second run of Scan*STRESS* while participants of the BO group showed the reversed pattern, i.e., lower activations in the first run compared to the second run. The illustrative *post-hoc* ROI analysis for the left dACC (see Figure 13C) further supported this finding, describing a significant group (BO versus HC group) x run (run 1 versus run 2) interaction ($F_{1, 103} = 7.86$, $p < .01$, $\eta_p^2 = .07$). Moreover, our analysis revealed no interaction effect of group x run x sex ($F_{1, 101} = 0.60$, $p = .44$). Figures 13A-D show the group differences regarding the exposure-time effect. In addition, the whole-brain analyses for the exposure-time effect were also tested non-parametrically using Randomise ($n = 5000$ iterations). While the results for the total sample did not change ($z_{max} = 3.54$), the group difference between BO and HC group rendered non-significant.

Figure 13

(A) Exposure-time effect of the total sample in a pre-limbic cluster. (B) Differences between the burnout (BO) and healthy comparison (HC) group regarding the exposure-time effect. (C) Illustration of the post-hoc region of interest analysis with respect to the left dorsal anterior cingulate cortex (dACC). (D) Group-specific mean ß-values of neural activation during the first and second run of ScanSTRESS in the left dACC



Note. (A) Main effect run for the main task effect stress > control of the total study sample for structures that showed higher neural responses in run 1 versus run 2 (red to yellow). (B) Results of the between-subjects group analysis (BO versus HC group) with run as regressor (run 1 versus run 2) indicating group differences in left dACC and MFG (run 1 > run 2 green to light green). (C) Given are the MNI coordinates as well as the voxel coordinates in square brackets. (D) *$p \leq .01$; error bars represent standard error of mean; BO group = burnout group; HC group = healthy comparison group.

6.5 Discussion

In the present study, we investigated cortisol and neural responses to acute psychosocial stress within a strictly specified sample consisting of individuals suffering from burnout and a healthy comparison group. Contrary to our hypothesis, salivary cortisol responses did not differ between groups indicating no HPA axis hyporeactivity in burnout. When the analysis was restricted to the BO group, a non-significant trend towards a negative association between burnout symptoms and cortisol responses was observed (i.e., higher levels of burnout symptoms were descriptively related to lower cortisol responses).

Based on neural, cortisol, heart rate as well as psychological data, Scan*STRESS* led to a successful stress induction in the total sample. However, this has not manifested itself in group-specific mean neural response patterns. Accordingly, no significant cluster emerged responding differently to stress versus control blocks or vice versa, between study groups. Interestingly, group-specific response patterns in the left dACC emerged when investigating the so-called exposure-time effect (Henze et al., 2020).

6.5.1 Cortisol responses to acute psychosocial stress

The first objective was to examine if otherwise healthy individuals suffering from burnout can be characterized by reduced cortisol responses to acute psychosocial stress. It was suspected that previous studies might have revealed inconsistent results due to small sample sizes and/or heterogeneity within study samples (Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020). Thus, we conducted an elaborate recruitment process consisting of multiple stages, self- and peer-report applying strict inclusion criteria based on burnout symptomatology and pathogenesis. With this, we aimed at achieving a more homogeneous study sample, especially with respect to burnout pathogenesis (Bärtl et al., 2022). Furthermore, our recruitment strategy guaranteed that eligible cases showed no co-morbidities and were still working. To the best of our knowledge, the present study features the largest sample size among studies that have examined acute salivary cortisol responses to stress in burnout (Rothe et al., 2020). However, our data does not support the hypothesis that an altered HPA axis stress reactivity develops in sub-clinical burnout (e.g., no sick leave, no antidepressant medication). Accordingly, previous studies did also not detect any significant associations including individuals with varying degrees of burnout severity (de Vente et al., 2003; de Vente et al., 2015; Jönsson et al., 2015; Lennartsson et al., 2015; Wekenborg et al., 2019). In contrast, reduced cortisol stress responses have only been observed in certain subgroups with severe burnout symptoms

indicating that HPA axis alterations might only become evident in more severe and/or clinical cases (Jönsson et al., 2015; Lennartsson et al., 2015). In accordance with these findings, a non-significant trend towards a negative association between burnout symptoms and salivary cortisol responses was found when the analysis was restricted to the BO group. Additional support for this assumption is provided by studies on hair cortisol suggesting that the association between burnout and hair cortisol is probably best described as nonlinear (Bärtl et al., 2023; Penz et al., 2018; Wendsche et al., 2020). It can thus be speculated that significant associations would have emerged in a sample including more severe burnout cases as in the present sample only 14 participants were characterized by serious burnout symptoms (Kalimo et al., 2003). Moreover, the BO group consisted of only non-clinical and otherwise healthy participants with a working schedule of ≥ 20h/week indicating a relatively high level of psychological and physical functioning. Thus, based on the allostatic load model, the cumulative 'wear and tear' exposed on the HPA axis, resulting from repeated adaptions to chronic stress, may not have been severe enough to induce an allostatic state characterized by an inadequate cortisol response. Inconsistent empirical findings on cortisol reactivity in burnout have often been attributed to heterogeneous study samples (Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020). Based on the present as well as previous findings (Jönsson et al., 2015; Lennartsson et al., 2015), we suggest that HPA axis dysregulation may only manifest in samples experiencing clinical and more severe burnout. Consequently, future studies should consider incorporating different burnout subgroups, encompassing individuals both within and outside the clinical range. However, in the Regensburg Burnout Project we refrained from including patients as a patient-based approach may have impaired the comparability with healthy controls, such as differences in sick leave and working time, psychopharmacological treatment, or comorbidities.

Another potential restriction refers to the heterogeneity within and between study groups in terms of sex / menstrual cycle condition since both were demonstrated to affect HPA axis reactivity possibly impeding the detection of significant effects (Kudielka et al., 2009). Furthermore, Scan*STRESS* follows a block design with frequent alternations of stress and control blocks possibly resulting in attenuated HPA axis responses. Thus, psychosocial stress experiments without such interruptions and alternations (e.g., the TSST) might be more capable to elicit robust HPA axis stress responses (Henze et al., 2020; Kirschbaum et al., 1993), facilitating the investigation of potential group

differences. With this, the simultaneous investigation of HPA axis and neural stress responses comes at the cost of somewhat attenuated cortisol responses.

In the present study, we administered 75g glucose prior to stress onset to facilitate cortisol reactivity and to minimize confounding effects owing to interindividual differences in energy availability (Kudielka et al., 2009; Zänkert et al., 2019). Though, we cannot rule out the possibility of an interfering effect of glucose administration as cortisol hyporeactivity in burnout might have remained undetected owing to a potential stimulatory effect of glucose (Zänkert et al., 2020). However, no evidence exists that glucose administration has varying effects on cortisol responses depending on study populations (e.g., BO vs. HC group).

6.5.2 Neural responses to acute psychosocial stress

No differences in mean neural stress responses over both runs of Scan*STRESS* were found between the BO and HC group. While previous fMRI studies indicated altered neural stress responses in clinical samples (e.g., Ming et al., 2017), this may not be the case in individuals suffering from sub-clinical conditions such as burnout. Thus, it might be speculated if the burnout symptomatology of the BO group may not have been severe enough to manifest at the acute neural level. It may be that a potential group difference manifests itself only after a stressful situation has been experienced, i.e., in the aftermath of acute stress. Therefore, investigating whether connectivity differences exist between the BO and HC groups after Scan*STRESS* will be very promising.

Other reasons for not observing a group difference could be that, compared to prior fMRI studies on psychosocial stress, the present sample featured relatively high heterogeneity with respect to age, ranging from 22 to 62 years. Although, our *post-hoc* analysis controlling for age did not reveal an interfering effect, it remains conceivable that this variable, in combination with fluctuations in gonadal hormones might have influenced neural stress processing (Chung et al., 2016), as our sample varied somewhat in respect to sex and menstrual cycle condition. Indeed, this again highlights the need for large - healthy as well as (pre-) clinical - samples considering these types of possible confounders as well as their interactive impact on distinct stress activation systems (Henze et al., 2023).

Notably, the expected neural response pattern in pre-limbic structures such as mPFC, cingulate cortex, insula, thalamus, striatum, and hippocampus emerged when contrasting

stress and control blocks in the total sample (Berretz et al., 2021; Noack et al., 2019). Accordingly, a successful stress induction can be assumed, confirmed with respect to all studied stress activation systems (neural, cortisol, heart rate, and affect responses).

6.5.3 Exposure-time effect

The total sample showed stronger neural activations during the first compared to the second run of Scan*STRESS* (= exposure-time effect) in a pre-limbic cluster replicating our previous finding (Henze et al., 2020). Together with the present study, the exposure-time effect has now been observed within almost identical brain structures in three independent samples (Henze et al., 2020; Streit et al., 2014). This supports the idea that this effect may be a robust and replicable phenomenon across studies, samples, and psychosocial stress paradigms for scanner environments, as it was also found within the healthy sample in the study by Dong et al. (2022) implementing the Montreal Imaging Stress Task.

Remarkably, the BO group differed from the HC group regarding the exposure-time effect. The HC group showed higher activations in the first compared to the second run, while the BO group displayed an inverse exposure-time effect in a cluster comprising the left dACC and MFG. More precisely, the HC group merely showed decreasing activation rather than increasing deactivation, as the beta values (see Figure 13D) for the left dACC were always positive; however, both terms express a decrease in beta values in the contrast stress > control and can therefore be used synonymously. Importantly, activations increased in the BO group, indicating a differential exposure-time effect between the two study groups for the left dACC. This is in line with our preliminary hypothesis and supports the finding of Dong et al. (2022) in patients with first episode MDD. Hence, the present results suggest that also pre-clinic conditions, such as burnout, might be associated with altered neural responses over stress exposure-time. As healthy samples consistently showed a pattern of increasing neural deactivation, respectively decreasing neural activation, it can be speculated if this represents an adaptive mechanism (Henze et al., 2020). Consequently, deviations from this pattern may indicate dysfunctional neural stress processing. In this vein, a study by Sinha et al. (2016) points to the importance of temporal dynamics (“neuroflexibility”) of the neural stress response regarding adaptive coping in real life.

Although in some earlier studies burnout- and MDD-related brain changes appeared to be more pronounced in women (Dong et al., 2022; Savic et al., 2018), we did not detect

any interactions between group and sex within *post-hoc* analyses. This suggests that temporal dynamics of neural stress processing may be altered in both, women and men suffering from burnout. Moreover, in our previous study we also found no evidence for sex differences regarding the exposure-time effect in healthy individuals (Henze et al., 2021).

Importantly, the BO and HC group exhibited this difference primarily in a structure that has been consistently shown to be both, involved in neural stress processing and affected in individuals suffering from burnout (Bayes et al., 2021; Berretz et al., 2021). This raises the idea that the (left) dACC may play a decisive role in the development and/or symptomatology of burnout. Moreover, the differences observed between our study groups in the left MFG emphasize again the involvement of prefrontal structures in the pathophysiology of burnout (Blix et al., 2013; Durning et al., 2013; Gavelin et al., 2017; Golkar et al., 2014; Jovanovic et al., 2011; Savic, 2015, 2020; Savic et al., 2018). Notably, glutamate levels in the mPFC/ACC were found to be elevated in patients with stress-related exhaustion. It has been proposed that glutamatergic excitotoxicity damages the mPFC/ACC attenuating the inhibitory feedback mechanism from the mPFC/ACC on the amygdala. This, in turn, may cause hyperactivity of the amygdala in burnout (Savic, 2020). While our data indeed suggest an involvement of frontal regions and parts of the cingulum (i.e., dACC), we did not observe any burnout-related alterations of amygdala activity during stress. Moreover, with respect to the cingulate cortex, previous studies often focused on the ACC (Abe et al., 2022; Blix et al., 2013; Golkar et al., 2014; Jovanovic et al., 2011; Savic, 2020), while our whole-brain analysis rather suggests alterations in the dorsal part possibly extending to posterior substructures as well. Remarkably, neural activity of the PCC during stress or clinical reasoning was also shown to be affected in individuals with sub-clinical depression and burnout (Dedovic et al., 2014; Durning et al., 2013). It therefore seems promising to investigate cingulate substructures more closely in future studies.

Although our whole-brain effects for group differences in the exposure-time effect rendered non-significant after non-parametric test via Randomise, this does not necessarily invalidate our results or diminish their potential relevance. Rather, it may suggest that the group differences occurred only in parts of certain structures, as indicated by the respective voxel numbers. This suggests that it might be beneficial to examine areas in a more substructured way. Notwithstanding, our results should be considered preliminary and require further investigation beyond the present exploratory scope.

6.6 Conclusions

In sum, we investigated salivary cortisol and - for the first time - neural responses to acute psychosocial stress in burnout. Our results mainly did not support our hypotheses regarding altered cortisol and neural stress responses in individuals suffering from burnout. However, group differences were evident with respect to the exposure-time effect in the left dACC as reflected by a limited capacity of the BO group to show decreasing activation over stress exposure-time. In view of the present results, it seems promising to further examine temporal dynamics of neural stress responses in burnout. Importantly, future studies are needed to determine, if and if yes, how useful potential deviations from the exposure-time effect are in predicting clinical outcomes or forecasting the course of chronic stress experience.

CHAPTER 7

7 GENERAL DISCUSSION

The final Chapter of the thesis serves as a general discussion and integration of the findings presented in *Studies I, II,* and *III* and addresses potential implications for future biopsychological burnout research, followed by final conclusions. As the results of the thesis' studies have been thoroughly discussed in the respective Chapters 4 to 6, the following section aims to provide a broader discussion of the study design and the implications of the findings for future burnout research.

7.1 Summary of main findings

It was the overarching aim of the Regensburg Burnout Project to obtain a – with respect to pathogenesis – more homogeneous sample out of the heterogeneous group of individuals exhibiting burnout symptoms. Thereby, strict inclusion and exclusion criteria for the respective study groups (i.e., BO and HC group) were applied within a multi-stage recruitment procedure described in *Study I* (Bärtl et al., 2022). After screening an initial sample of 1022 volunteers, this multi-stage recruitment procedure rendered final sample sizes for the respective studies ranging from 100 participants to 121 participants (*Study I* n = 121; *Study II* n_{t1} = 114 and n_{t2} = 100; *Study III* n = 116) emphasizing the importance of a sophisticated recruitment strategy in burnout research (see discussion below). Importantly, despite the differences in burnout symptomatology and chronic work stress levels between the BO and HC group, our analysis revealed an equal distribution of potential confounders across both study groups, including, among others, sex, age, smoking status, body-mass-index, and total working hours per week (Bärtl et al., 2022). Building upon this recruitment procedure, a multimethodological as well as cross-sectional and longitudinal approach was followed, comparing the BO and the HC group regarding an index of AL (Bärtl et al., 2022), HCC (Bärtl et al., 2023), as well as neural and salivary cortisol responses to acute psychosocial stress (Bärtl et al., 2024), with the aim of identifying biopsychological dysregulations in burnout.

7.1.1 Study I

In the first study of the thesis (Bärtl et al., 2022), the BO group (n = 56) and the HC group (n = 65) were compared regarding an index of AL. The AL-index included 14 parameters reflecting immune, blood coagulation, metabolic, neuroendocrine, and cardiovascular system functioning, namely: hsCRP, TNF-α, IL-6, fibrinogen, d-dimer, PAI-1, HbA1c, HDL cholesterol, TC/HDL, DHEA-S, SBP, DBP, WHR, and body fat percentage. In line

with our hypothesis, the BO group exhibited significantly higher AL-scores compared to the HC group. After adjusting for age, the finding remained significant and was even more evident in the subgroup of non-smokers. In addition, correlational analyses revealed positive associations of AL-scores with levels of burnout (i.e., $MBI_{weighted}$, EE, DP) and chronic work stress (i.e., ER-ratio) confirming previous findings from Bellingrath et al. (2009), Juster, Sindi, et al. (2011), and Hintsa et al. (2016). In contrast, the MBI-subscale LA showed only a non-significant trend towards a positive association with AL-scores. Although the BO group only included non-clinical and otherwise healthy working individuals suffering from burnout, effect sizes of burnout-related increases in AL were stronger than age-related effects on AL. In contrast to our findings, a comparable number of previous studies indicated either no (Langelaan et al., 2007; Sjörs et al., 2013; Viljoen & Claassen, 2017) or an opposite association pattern (Traunmüller et al., 2018) between burnout and AL, presumably due to methodological differences between studies. For example, two of these studies (Sjörs et al., 2013; Traunmüller et al., 2018) focused on clinical samples, predominantly composed of individuals being on sick leave or receiving antidepressant medication. In case of burnout, sick leave may be analogous to a removal of the stressor, potentially reducing allostatic processes and thus AL-indices in the sense of a physiological recovery, even if the burnout symptomatology persists on the subjective psychological level (Traunmüller et al., 2018). In addition, there has been considerable variation with respect to the parameters used for measuring AL across studies (e.g., Bellingrath et al., 2009; Traunmüller et al., 2018). Hence, it can be concluded that the AL-index from *Study I* seems to be well-suited for identifying stress-related interindividual differences. Notably, none of the single AL-parameters was significantly associated with burnout symptoms, which is a frequently observed finding in burnout and AL-research emphasizing the utility and sensitivity of this multi-systemic approach for the detection of individuals at risk (Bellingrath et al., 2009; Edes & Crews, 2017; Juster et al., 2010; Seeman et al., 1997). In sum, our results indicate a higher cumulative physical burden and a shift in the operating range of various stress-sensitive systems in individuals suffering from burnout, potentially accounting for the increased risk of long-term health impairments in burnout (Bärtl et al., 2022; Bayes et al., 2021; Guidi et al., 2021).

7.1.2 Study II

In *Study II* of the thesis (Bärtl et al., 2023), cross-sectional and longitudinal associations between burnout and HCC were examined as stress-related dysregulations of the HPA

axis activity have been considered a biopsychological correlate of the burnout syndrome (Jonsdottir & Sjörs Dahlman, 2019; Rothe et al., 2020). Although HCC was initially regarded as a highly promising marker of chronic stress and burnout (Jonsdottir & Sjörs Dahlman, 2019), first studies yielded, again, inconsistent findings of either no (Deng et al., 2021; Marcil et al., 2022; Wekenborg et al., 2019) or positive associations indicating burnout-related hypercortisolism (Ibar et al., 2021; Penz et al., 2018; Wang et al., 2019; Wendsche et al., 2020). Therefore, the rationale for *Study II* was to investigate whether burnout-related dysregulations of long-term HPA axis activity could be identified within a more strictly specified study sample in combination with a longitudinal approach. Accordingly, burnout symptomatology as well as HCC (1cm hair samples = 1 month) were obtained at two time points t1 (n = 114; BO group n = 55; HC group n = 59) and t2 (n = 100; BO group n = 51; HC group n = 49) with an interval of approximately seven months between assessments. However, contrary to our hypotheses no significant cross-sectional associations were evident at t1 or at t2. Based on previous findings indicating a non-linear relationship between burnout and HCC (Penz et al., 2018; Wendsche et al., 2020), exploratory analyses were conducted exclusively within the BO group revealing a significant positive cross-sectional association between burnout symptomatology and HCC at t1, but not at t2 and thus, providing at least some evidence for burnout-related *hypercortisolism*. On the one hand, this result is consistent with the findings of Penz et al. (2018) and Wendsche et al. (2020) reinforcing the assumption that dysregulations of the HPA axis activity may only manifest once a certain threshold of burnout severity has been surpassed. On the other hand, the longitudinal analysis demonstrated an opposite effect as burnout symptomatology at t1 was a negative predictor of HCC at t2 pointing to the long-term development of *hypocortisolism* in burnout. However, the additional analyses on this effect were equivocal as the decrease in HCC from t1 to t2 was not associated with the change in burnout symptomatology from t1 to t2. Moreover, it seemed somewhat surprising that this effect was only evident in the longitudinal but not in the cross-sectional analysis at t2. Consequently, the cross-sectional as well as the longitudinal results of *Study II* (Bärtl et al., 2023) remain inconclusive emphasizing the need for future studies.

7.1.3 Study III

Finally, in *Study III* (Bärtl et al., 2024) differences in salivary cortisol and – for the first time – neural responses to acute psychosocial stress were investigated between the BO and the HC group. Therefore, in this fMRI study, 116 participants (BO group n = 55; HC

group *n* = 61) were exposed to Scan*STRESS*. In the total sample, a significant rise of salivary cortisol in response to acute psychosocial stress was observed with a cortisol-responder rate of 57% (Miller et al., 2013). Moreover, negative affect ratings increased, while positive affect ratings decreased during Scan*STRESS*. Mean heart rate responses were significantly higher during stress compared to control blocks in both runs of Scan*STRESS*. On a neural level, the whole-brain analysis in the total sample revealed typical activations (stress > control) and deactivations (control > stress) in different clusters including the mPFC, cingulate cortex, and hippocampus (Berretz et al., 2021; Henze et al., 2020). Consequently, it can be assumed that Scan*STRESS* led to a successful stress induction in the total sample as indicated by salivary cortisol, affect, mean heart rate, and neural responses. Moreover, the whole-brain analysis examining the exposure-time effect (i.e., comparison of the neural responses from the first to the second run of Scan*STRESS*) in the total sample revealed a distributed network of stress-sensitive structures (e.g., mPFC, hippocampus, and amygdala) confirming the previous finding of higher neural activation in the first compared to the second run of Scan*STRESS*, as first reported by Henze et al. (2020).

With respect to the group analyses (BO vs. HC group), no difference emerged between the BO and HC group regarding salivary cortisol responses to acute psychosocial stress. Accordingly, our results did not provide evidence for the hypothesis of an altered HPA axis stress reactivity in sub-clinical burnout. The rationale for *Study III* was that heterogeneous study samples accounted for the inconsistent results pattern observed in previous studies (Rothe et al., 2020) and that burnout-related dysregulations of HPA axis reactivity might become apparent in a more homogeneous sample. In contrast, our finding supports the hypothesis that the HPA axis reactivity may remain unaffected until a critical threshold of burnout severity has been exceeded, as altered cortisol stress responses have predominantly been observed in subgroups with severe burnout symptomatology (Jönsson et al., 2015; Lennartsson et al., 2015; Rothe et al., 2020). Further evidence for this assumption stems from the exploratory analysis within the BO group rendering a non-significant trend towards a negative association between burnout symptoms and salivary cortisol responses.

Moreover, the analysis of mean neural stress responses over both runs of Scan*STRESS* revealed no differences between the BO and the HC group. In contrast, the group analysis of the exposure-time effect indicated burnout-related alterations of neural responses over stress exposure time in a cluster comprising the left dACC and MFG.

While the HC group exhibited higher neural activation (i.e., stress > control) in the first compared to the second run of Scan*STRESS* (i.e., decreasing activation), the BO group was characterized by a reversed pattern of increasing activation (i.e., higher neural activation in the second compared to the first run). Together with *Study III*, the pattern of increasing deactivation (respectively decreasing activation) over stress exposure time has now been consistently found in four independent healthy samples applying either Scan*STRESS* (Bärtl et al., 2024; Henze et al., 2020; Streit et al., 2014) or the MIST (Dong et al., 2022). While in *Study III* burnout was associated with a limited capacity to show decreasing activation over stress exposure time in a cluster peaking in the left dACC, Dong et al. (2022) reported on a failure to deactivate pre-limbic structures in unmedicated women diagnosed with first-episode MDD. Thus, it can be speculated that the exposure-time effect represents an adaptive mechanism in healthy individuals. Thereby, deviations from this pattern may potentially indicate maladaptive neural stress processing in (pre-)clinical conditions such as burnout or depression (Dong et al., 2022; Henze et al., 2020). In conclusion, the results of *Study III* further underscore the involvement of the ACC and prefrontal regions in the pathophysiology of burnout (e.g., Blix et al., 2013; Jovanovic et al., 2011; Savic et al., 2018).

7.2 Implications of the findings and future directions in biopsychological burnout research

As the recruitment procedure was the unique feature of the Regensburg Burnout Project, potential implications for future burnout research as well as limitations of the study design and the recruitment procedure are discussed first.

Strengths of the study design and the recruitment procedure:

According to Heinemann and Heinemann (2017), most previous studies have not addressed the imprecise operationalization of burnout leading to the assumption that "current burnout research uncritically reproduces the blurry idea of burnout again and again, and in doing so, just reinforces it" (Heinemann & Heinemann, 2017, p. 9). Thereby, the imprecise operationalization and measurement of burnout was considered to impede the entire scientific investigation of the construct and, in particular, the investigation of its underlying pathophysiology (Bayes et al., 2021; Danhof-Pont et al., 2011; Heinemann & Heinemann, 2017).

Importantly, our sophisticated recruitment was conceptualized with the aim of addressing the major limitations and challenges regarding the operationalization of the burnout syndrome. With respect to future burnout studies, Hewitt et al. (2020) emphasized the importance of providing a rationale for the applied burnout criteria. Moreover, in accordance with the aforementioned quote by Heinemann and Heinemann (2017), it was recommended to address the conceptual and measurement issues by applying innovative approaches instead of relying on previous measurement methods (i.e., the application of a single burnout questionnaire lacking specificity) (Bayes et al., 2021; Nadon et al., 2022). Hence, our sophisticated and theory-driven recruitment approach can be regarded as a highly promising attempt to improve the assessment of burnout in general. In detail, the results of our recruitment procedure (see Figure 5C) indicated that only about 12% of the initially screened volunteers (n = 1022) fulfilled our inclusion criteria und thus, took part in the first appointment (*Study I*). Thereby, our initial assumption of variability in pathogenesis among individuals exhibiting burnout symptoms was confirmed as, for instance, some individuals reported on burnout symptoms without experiencing increased levels of chronic work stress, and vice versa. Moreover, the heterogeneity in etiological factors was further supported by the results of the self- and peer-evaluation regarding the job-related performance, resiliency, motivation, and commitment before the onset of burnout symptoms. Thereby, a considerable number of volunteers was excluded based on the work-related self- or peer-evaluation indicating etiological variability among individuals exhibiting burnout symptoms. Thus, the presence of a certain premorbid work-related functioning and the experience of chronic work stress do not seem to be a prerequisite for the occurrence of burnout symptoms. In this regard, a recent study revealed that only a minority of individuals reporting on burnout symptoms attributed their burnout symptomatology to work-related stress (Bianchi et al., 2024). Consequently, the presence of chronic work stress may be verified in future studies before individuals are classified as burnout cases, since also in the ICD-11 burnout is defined as a syndrome arising from chronic work stress (World Health Organization, 2019). Importantly, the prospective relationship between chronic work stress and burnout has been confirmed in previous prospective studies (e.g., Hadžibajramović et al., 2019; Nuebling et al., 2022), apart from a recent inconsistent finding (Shoman et al., 2023).

In addition, by the incorporation of third-party information, our studies are among the few addressing the limitation of burnout research predominantly relying on self-report data (Ahola & Hakanen, 2014; Feuerhahn et al., 2012; Feuerhahn et al., 2013;

Nadon et al., 2022). Thereby, 9.5% of the volunteers were excluded as their work-related self-evaluation was not confirmed by peer-ratings indicating at least some discrepancies between self- and peer-evaluation. However, in terms of feasibility, it must be noted that only 45.9% of the initially eligible volunteers invited a peer-rater leading to a substantial dropout rate at this stage of the recruitment procedure, possibly due to privacy concerns. While third-party information may serve as a source of more objective data, it should be carefully evaluated in future studies whether and how third-party information can be collected without significantly increasing the dropout rate. Finally, our thoroughly review of health-related exclusion criteria emphasize the importance of a comprehensive differential diagnosis of burnout as a considerable number of volunteers, initially eligible for the BO group, were excluded based on e.g., the SCID-I (Wittchen et al., 1997) or blood analysis (see step 4, 6, and 7 in Figure 5C, respectively; Bärtl et al., 2022). Consequently, future burnout research may also benefit from thoroughly considering exhaustion-related conditions as exclusion criteria in accordance with the recommendations regarding the differential diagnosis of the burnout syndrome (Korczak et al., 2010; von Känel, 2008). In sum, it can be concluded that our recruitment strategy addressed important limitations of previous (biopsychological) burnout research, probably leading to a more homogeneous sample, particularly in terms of etiological factors (Bayes et al., 2021; Danhof-Pont et al., 2011; Heinemann & Heinemann, 2017; Nadon et al., 2022). Therefore, the results of our multi-stage recruitment procedure may encourage to apply more sophisticated study sampling methods in the future as well, presumably leading to more homogeneous samples and consistent findings on the biopsychological correlates of the burnout syndrome.

Limitations of the study design and the recruitment procedure:

While our recruitment strategy has notable strengths, it is important to note that our recruitment strategy and the resulting study samples come with various limitations, valid for all three included studies (Bärtl et al., 2022; Bärtl et al., 2024; Bärtl et al., 2023). One major limitation refers to the small proportion of severe burnout cases within the BO group (Kalimo et al., 2003). Presumably, this was mainly caused by the strict exclusion criteria regarding sick leave, mental disorders, as well as use of psychotropic medication. On the one hand, we refrained from the inclusion of clinical burnout cases being on sick leave or undergoing psychopharmacological treatment as it could have affected the comparability with healthy controls in terms of current workload or potential pharmacological effects on the examined biomarkers. For instance, cortisol reactivity

was shown to be reduced during antidepressant treatment (Thakore et al., 1997). On the other hand, especially regarding HPA axis (re)activity, it has been proposed that dysregulations may only be apparent in individuals exhibiting more severe or clinical burnout symptomatology (Bärtl et al., 2024; Bärtl et al., 2023; Jönsson et al., 2015; Lennartsson et al., 2015; Penz et al., 2018; Wendsche et al., 2020). Consequently, based on our findings, future studies may benefit from incorporating an additional third group of individuals with clinical burnout to clarify the unresolved questions regarding HPA axis dysregulations in burnout. Thereby, clinical burnout could be operationalized by applying the diagnostic criteria for ED (see Table 1) included in the Swedish version of the ICD-10 as ED is considered the most valid equivalent of clinical burnout (Grossi et al., 2015; Lindsäter et al., 2022; Wallensten et al., 2016). In the meanwhile, questionnaires such as the 'Karolinska Exhaustion Disorder Scale' (Besèr et al., 2014; Saboonchi et al., 2013) or the 'Self-Rating for Stress-Related Exhaustion Disorder' (Glise et al., 2010) are available offering cut-off scores for diagnosing ED. In addition, as outlined in Section 2.2.1, the diagnosis of ED may be superior compared to established burnout questionnaires. First, diagnosis of ED considers a specific pathogenesis by requiring one or more identifiable stressors to be present for at least six months, rather than merely focusing on the presence of different symptoms. Second, unlike the MBI, diagnosis of ED includes a time criterion of two weeks (i.e., physical and mental symptoms of exhaustion being present nearly every day during the last two weeks). Third, diagnosing ED requires to rule out the presence of a physical disease potentially accounting for the symptomatology (Lindsäter et al., 2022; Nadon et al., 2022). Therefore, it seems promising to employ those criteria or questionnaires also outside Sweden for "diagnosing" clinical burnout. This is also supported by the observation that biopsychological studies applying ED-criteria have rendered a more consistent results pattern on e.g., brain alterations compared to studies using standard burnout questionnaires (e.g., Bärtl et al., 2024; Bayes et al., 2021; Jovanovic et al., 2011; Savic, 2015; Savic, 2020; Savic et al., 2018). However, future studies are needed to determine whether a clearer understanding regarding the pathophysiology of burnout, especially concerning HPA axis alterations, might emerge by including individuals with varying symptom severity ranging from mild to clinical burnout. Moreover, another approach for the measurement of clinical burnout is the operationalization of burnout as a context-specific depression, following the diagnostic criteria of MDD from the DSM-5. Given the nosological ambiguity of the burnout concept and its symptom overlap with

depression, Bianchi and Schonfeld (2020) recently introduced the ‘Occupational Depression Inventory’ for measuring work-attributed depression symptomatology as a potential replacement for burnout questionnaires. However, as the distinctiveness between burnout and depression remains an unresolved question (see Section 2.2.3) it seems uncertain whether the operationalization of burnout as a context-specific form of depression is appropriate (e.g., Koutsimani et al., 2019; Maslach & Leiter, 2016b; Schonfeld & Bianchi, 2016). Nevertheless, with the introduction of the Occupational Depression Inventory, Bianchi and Schonfeld (2020) provide at least clear diagnostic criteria, potentially stimulating improvements in the conceptualization and measurement of burnout.

In the Regensburg Burnout Project, we aimed at obtaining a more homogeneous sample with respect to etiological factors (e.g., Bayes et al., 2021; Danhof-Pont et al., 2011). As a consequence of the applied inclusion criteria, our findings are limited to this – with respect to pathogenesis – homogeneous sample. Thereby, our BO group may represent only a subgroup from the heterogeneous population of individuals exhibiting burnout symptoms. Notably, we focused on individuals showing medium to high levels of work-related functioning and dedication before the onset of burnout symptoms. However, recent evidence indicated that ‘being on fire’ (i.e., high work-related engagement and dedication) may rather act as a protective factor against the development of burnout symptoms, challenging the initial and basic assumptions of the burnout concept (Freudenberger, 1974; Hakanen & Bakker, 2017; Hakanen et al., 2018; Maslach et al., 2001; Pines et al., 1981). In this regard, Montero-Marín and García-Campayo (2010) suggested the presence of distinct subtypes of burnout depending on coping strategies and the degree of dedication to work (i.e., frenetic, under-challenged, and worn-out subtype; see Section 2.2.1). Hence, our inclusion criteria (e.g., regarding work-related functioning before the onset of burnout symptomatology) probably resulted in participants characterized by either the frenetic subtype (e.g., high work-related dedication and motivation) or the worn-out subtype (e.g., lack of recognition for efforts). In contrast, the underchallenged subtype (e.g., lack of challenges, boredom) may have been underrepresented in our sample (Montero-Marín & García-Campayo, 2010; Montero-Marín et al., 2011). In addition to this approach (Montero-Marín & García-Campayo, 2010), Leiter and Maslach (2016) have identified five different burnout profiles applying latent profile analysis: burnout (high on all three MBI-subscales), engagement (low on all three MBI-subscales), overextended (high on EE only),

disengaged (high on DP only), and ineffective (high on LA only). In this respect, it is of particular interest that also different pathophysiological signatures of burnout have been proposed based on the observation that burned-out individuals tended to exhibit an extreme distribution of physiological parameters (e.g., lower or higher levels of plasma prolactin compared to controls after receiving 35mg of hydrocortisone). Thus, it seems promising to explore whether distinct pathophysiological signatures of burnout exist, possibly depending on the respective burnout subtype or profile (Leiter & Maslach, 2016; Montero-Marín & García-Campayo, 2010; Tops et al., 2007; Traunmüller et al., 2019).

Moreover, while the participants of the BO group were characterized by an overlapping etiology, there was substantially heterogeneity regarding other variables. The participants of the thesis' studies worked in a variety of different professions as there were no occupation-specific inclusion criteria. While this enhances the generalizability of our findings, it may also have contributed to heterogeneity within our sample. In this regard, Metzler and Bellingrath (2017) reported that certain types of psychosocial work stress were more prevalent in blue- versus white-collar workers, and vice versa. This is also consistent with the finding of a different distribution of job demands between blue- and white-collar workers (Schreuder et al., 2008). Therefore, in addition to the consideration of etiological factors, future studies may focus on individuals from specific professions to obtain more homogeneous samples with respect to numerous potential confounding variables (e.g., education, socioeconomic status, or predominant job demands) as applied, for instance, in the Trier Teacher Stress Study (e.g., Bellingrath & Kudielka, 2008; Bellingrath et al., 2008; Bellingrath et al., 2009; von Känel et al., 2008). Hence, it can be speculated that our studies may have yielded more consistent findings if we had focused exclusively on participants from a single professional group (e.g., teachers, physicians).

To conclude, our study design with its strict inclusion criteria can be regarded as a promising approach addressing key limitations of previous burnout research (e.g., Bayes et al., 2021). Future (biopsychological) burnout research may strongly benefit from (expert) consensus guidelines regarding the operationalization and diagnostic criteria of the burnout syndrome (Doulougeri et al., 2016), potentially taking etiological factors and differential diagnosis criteria into account. Beyond the limitations described above, the multimethodological as well as the cross-sectional and longitudinal investigation of the association between burnout and distinct biopsychological measures of stress within an identical sample, can be regarded as a notable strength of the thesis' studies (Bärtl et al.,

2022; Bärtl et al., 2024; Bärtl et al., 2023). Following this approach, we were able to identify various indications of biopsychological dysregulations in burnout. In the last section of this chapter, study-specific implications as well as limitations are discussed separately for *Study I*, *II*, and *III*.

Study I:

First, in *Study I* (Bärtl et al., 2022) the BO group was characterized by higher AL compared to the HC group indicating a greater cumulative physiological burden in work-related burnout (McEwen & Seeman, 1999). Importantly, increased levels of AL were empirically proven to predict numerous adverse outcomes, including poorer mental (e.g., depression) and physical health (e.g., cardiovascular diseases, disabilities, mortality, type 2 diabetes) (Edes & Crews, 2017; Guidi et al., 2021). In the same vein, burnout has been repeatedly linked to a pattern of adverse mental (e.g., depression) and physical health consequences (e.g., cardiovascular diseases, disability pensions, mortality, type 2 diabetes) in prospective studies. These findings led to the hypothesis that the AL-model may depict a potential biological pathway through which burnout and chronic work stress can increase the risk for negative health outcomes (Bayes et al., 2021; Salvagioni et al., 2017). However, it is important to note that the causality and directionality between burnout and AL is uncertain; more precisely, whether burnout and chronic work stress lead to higher AL-indices or vice versa, or if the relationship is best described as reciprocal (Bayes et al., 2021). For instance, in a study by Juster, Marin, et al. (2011) higher AL predicted higher depression symptomatology three years later providing some empirical evidence for reverse causation. Given the low incidence rates of severe adverse health outcomes such as cardiovascular diseases, prospective studies with large sample sizes and long observational periods are needed to clarify the temporal sequence between burnout, AL, and additional adverse health outcomes as it may have important implications for prevention and treatment strategies. Despite this, our results indicate that otherwise healthy individuals suffering from burnout were characterized by an unfavorable shift in the operating range of various stress-sensitive systems, presumably increasing the risk of developing additional health problems (Guidi et al., 2021). Moreover, the lack of significant associations between burnout symptomatology and single AL-parameters in *Study I* (Bärtl et al., 2022) emphasizes again the sensitivity and utility of a composite measure integrating biomarkers of different stress-sensitive systems compared to focusing on single biomarkers (e.g., DHEA-S, IL-6) or systems (e.g., cardiovascular, immune) (Juster et al., 2010; Seeman et al., 1997). Thereby, the

AL-model may also provide a possible explanation for the inconsistent findings on the underlying pathophysiology of the burnout syndrome as McEwen (1998b) proposed that numerous mediators of different bodily systems involved in physiological stress processing are interconnected in complex non-linear relationships. In other words, the fluctuations in any one parameter induce interindividual compensatory mechanisms in other parameters. Thereby, one parameter may be upregulated in some individuals while being downregulated in others, depending on numerous factors (e.g., individual vulnerability, duration and intensity of the stressor). However, given the complexity of these interactions, delineating the time-courses of burnout-related dysregulations of single biomarkers remains challenging, even in longitudinal studies (Juster et al., 2010; McEwen, 2000a, 2008).

One major limitation of *Study I* refers to the different operationalization of the AL-index compared to the classical AL-index introduced by Seeman et al. (1997) as urine sampling was not feasible. Consequently, our AL-index lacks comparability with the initial AL-index as it did not incorporate the primary mediators urinary cortisol, epinephrine, and norepinephrine. While the inclusion of additional parameters was recommended by the original authors (McEwen & Seeman, 1999; Seeman et al., 2001), the differences between studies on burnout and AL with respect to included AL-parameter impede the comparability of the respective findings. Hence, it is unclear, whether the inconsistent findings on the association between burnout and AL can be attributed to the variability of included parameters or to the heterogeneity of the respective samples (Bellingrath et al., 2009; Hintsa et al., 2016; Juster, Sindi, et al., 2011; Langelaan et al., 2007; Sjörs et al., 2013; Traunmüller et al., 2018; Viljoen & Claassen, 2017). Consequently, it seems reasonable for future studies to include the original ten parameters (plus additional parameters if required) facilitating comparability between studies. One general limitation in AL-research refers to the calculation of the AL-index being based on the distribution of the respective study sample, thus additionally impeding the comparability between studies as well as the practical application in healthcare settings (Carbone et al., 2022). Therefore, Juster, Sindi, et al. (2011) introduced a clinical AL-index based on risk-quartiles of clinical reference ranges. However, following this approach would have led to ceiling- and floor-effects of different AL-parameters in the present sample. For example, the World Health Organization (2011) defines abdominal obesity based on WHR scores of ≥ 0.90cm for men and ≥ 0.85cm for women. Thereby, following the approach by Juster, Sindi, et al. (2011) would have resulted in extremely

low cut-off values for WHR (i.e., WHR values of ≥ 0.68cm for men and ≥ 0.64cm for women being defined as risk[2]), and consequently all participants (n = 121) would have fallen within the risk-quartile of WHR. Hence, multidisciplinary collaboration is needed to define normative risk reference ranges for different biomarkers based on large population-based samples, potentially advancing the research on AL as well as the practical application in healthcare settings (Bizik et al., 2013; Juster & Misiak, 2023). With respect to the latter, the identification of individuals at risk reflected by increased AL-scores seems reasonable, given the numerous potential adverse effects of increased AL (Guidi et al., 2021). In this regard, first attempts have been made to integrate AL-indices into the clinical practice with the aim of screening for comorbidities (e.g., obesity, hypertension) and monitoring the effects of pharmacological and psychosocial treatments in severe mental disorders (i.e., schizophrenia and bipolar disorder). Thereby, the implementation of AL-indices in clinical settings has been considered a powerful screening tool providing important implications for the prevention, treatment, and rehabilitation of (severe) mental disorders (Bizik et al., 2013). Given the routine assessment of frequently used AL-parameters (e.g., total cholesterol) in typical blood tests performed in regular health care or occupational health examinations, monitoring of burnout symptomatology and norm-based AL-indices seems both feasible and promising for identifying workers at risk and for providing individual prevention and treatment strategies. Notably, in the meanwhile, numerous prevention and treatment strategies for individuals suffering from burnout are available. These strategies include, among others, change of work patterns (e.g., reducing work time), improvement of coping skills, or relaxation skills (Edú-Valsania et al., 2022; Hakanen & Bakker, 2017; Maslach & Leiter, 2016b). In this respect, it could be of particular interest to examine if initially elevated AL-scores may decrease after successful treatment of the (clinical) burnout symptomatology.

Study II:

Second, in *Study II* (Bärtl et al., 2023) we investigated whether individuals suffering from burnout are characterized by altered HCC. Thereby, our analysis revealed no cross-sectional associations between burnout symptoms and HCC at both time points t1 and t2 in the total sample, but the exploratory analysis within the BO group provided at least some evidence for burnout-related *hypercortisolism*. In contrast, the analysis of the

[2] Calculation of the highest quartile for men (0.90 x 0.75 = 0.68) and women (0.85 x 0.75 = 0.64).

longitudinal data yielded an opposite effect pattern as burnout symptomatology at t1 was a negative predictor of HCC at t2 indicating the development of *hypocortisolism*. However, the change in HCC from t1 to t2 was not attributable to the change in burnout symptoms between measurement time points challenging the validity of this finding. While HCC was considered a promising biomarker of chronic stress conditions such as burnout (Russell et al., 2012), our study as well as previous investigations on burnout and HCC revealed an inconsistent results pattern (Rothe et al., 2020). Based on the cross-sectional data available, there seems to be the most empirical evidence for hypercortisolism in burnout, probably manifesting only in more severe burnout cases (Ibar et al., 2021; Penz et al., 2018; Rothe et al., 2020; Wang et al., 2019; Wendsche et al., 2020). In the meanwhile, a second longitudinal study exists measuring both burnout and HCC repeatedly. In the prospective cohort study by Kaltenegger et al. (2024), burnout and HCC were captured at three time points with follow-up intervals of six months, respectively. In this study, no significant (prospective) associations between burnout and HCC were found. The authors attributed this non-finding primarily to the overall low burnout symptomatology within the examined sample (Kaltenegger et al., 2024). As outlined above, future studies including an additional group of clinical burnout cases are necessary to test the hypothesis that HPA axis alterations may only become apparent after surpassing a certain threshold of burnout symptomatology. Beyond this, additional limitations must be addressed: In a meta-analysis, stress-exposed groups were characterized by 22%-elevated HCC, primarily driven by groups experiencing ongoing chronic stress. In contrast, no associations with mood disorders (e.g., depression) were found (Stalder et al., 2016). Thus, it can be speculated that the frequency as well as the intensity of acute stress experience during the sampling period (e.g., 1cm = 1 month) may have stronger effects on HCC than rather long-lasting adverse conditions such as burnout or depression. In this regard, it is important to note that exhibiting increased MBI- as well as ER-ratio-scores does not necessarily imply that the participants of the BO group were indeed experiencing more frequent and severe (work) stress during the HCC sampling period compared to the HC group. In addition, reporting higher levels of burnout and chronic work stress does not permit conclusions about overall stressor frequency and intensity. In our study, we did not validate or monitor the degree of the participants' overall stress experience during the one-month HCC sampling period. Thereby, future studies on burnout and HCC may apply additional questionnaires capturing the degree of overall stress experience during the respective sampling period.

For example, in our study, the Perceived Stress Scale (PSS) would have been a suitable questionnaire capturing the overall perceived stress during the last month (Cohen et al., 1983; Klein et al., 2016). Notably, Stalder et al. (2017) emphasized to consider distinct stressor categories (e.g., work-related vs. caregiving stress) in future studies on HCC. In this regard, Brianda et al. (2020) reported on elevated HCC in individuals suffering from parental burnout (i.e., exhaustion as a consequence of parental stress), after controlling for work-related burnout symptomatology (Mikolajczak & Roskam, 2018). Moreover, other chronic stress conditions (e.g., caregiving of relatives) have also been linked to altered HCC (Stalder et al., 2014) emphasizing the need to thoroughly consider additional stressors (e.g., parenting, caregiving) when investigating the relationship between work-related burnout and HCC. Importantly, Stalder et al. (2017, p. 270) referred to the inconsistent empirical evidence between self-reported stress and HCC as "another example for a lack of psychoendocrine covariance" and, thus, recommended the application of more advanced stress assessment methods such as ecological momentary assessment, also known as ambulatory assessment (AA) or experienced sampling method. This is supported by a study investigating the association between burnout and endocrine functioning (i.e., CAR, DHEA-S, and DST) using an electronic symptom diary to capture momentary burnout symptomatology. Thereby, participants were prompted to indicate their momentary level of exhaustion (i.e., "right now I feel exhausted") at two fixed time points (morning and evening) as well as at five randomly occurring time points per day for a two-week period. In line with the suggestions by Stalder et al. (2017), the authors reported on significant associations of endocrine functioning with momentary burnout symptom severity, but not with the retrospectively assessed MBI-scores. In detail, higher momentary exhaustion levels were related to a reduced CAR, higher levels of DHEA-S, as well as stronger suppression of cortisol after the DST (Sonnenschein et al., 2007). Given the advantages in terms of reliability and ecological validity (Trull & Ebner-Priemer, 2014), AA can be regarded a highly promising approach to elucidate the link between burnout and long-term HPA axis activity in future studies. For instance, in the prospective-longitudinal LawStress project, perceived stress in daily life was repeatedly measured using AA in law students experiencing a long-lasting stress period (i.e., preparation for the first state examination) and a control group (i.e., law students in earlier semesters not preparing for the first state examination). Subsequently, associations between daily life stress and e.g., the CAR or neural responses to psychosocial stress were investigated (Giglberger et al., 2023; Giglberger et al., 2022).

The adoption of such quasi-experimental longitudinal designs in combination with AA may represent a promising future direction in biopsychological burnout research. Notably, in *Study II* both burnout symptomatology as well as HCC remained relatively stable between both measurement time points impeding the identification of longitudinal effects. Interestingly, in a recent study, the implementation of digital transformation processes in hospitals was linked to stress-enhancing effects in physicians (Wekenborg et al., 2024). Therefore, the implementation of such digital transformation or restructuring processes (Kieselbach et al., 2010) may contribute to greater intra- and inter-individual variability of burnout symptomatology and HCC over time. Quasi-experimental AA studies monitoring burnout symptomatology and measures of HPA axis activity before, during, and after such organizational change processes (e.g., digital transformation or restructuring processes) may therefore be a promising approach, potentially facilitating the detection of (complex) temporal dynamic associations between burnout and HPA axis activity.

Moreover, a general limitation of HCC must be addressed as the mechanisms of how cortisol is integrated into hair are not fully understood. According to Stalder and Kirschbaum (2012), different mechanisms were proposed including passive diffusion from blood, sweat, sebum, external sources, or locally produced cortisol. While numerous studies supported the reliability and validity of HCC as a long-term retrospective calendar of cortisol secretion (Stalder & Kirschbaum, 2012; Stalder et al., 2017), a recent experimental animal study (rat model) challenged this assumption to some extent (Colding-Jørgensen et al., 2023). Thereby, adrenalectomized rats with no adrenal glucocorticoid production received high doses of corticosterone for seven days, while hair glucocorticoid concentrations (HGC) were measured before, during, and after corticosterone treatment. HGC increased rapidly after the first injection (i.e., after three hours) and reached their highest level on the seventh day of treatment. Surprisingly, the authors observed a significant decline in HGC after treatment (from day 8 to day 14 to day 26) indicating substantial elimination of glucocorticoids out of the hair. Hence, the authors concluded that HGC may rather be a measure of recent or ongoing stress than a measure of glucocorticoid secretion over the past weeks or months. In this regard, basic (psychoneuro-)endocrine research seems necessary to elucidate the mechanisms of glucocorticoid integration into hair and, importantly, whether this finding from an animal model is transferable to humans (Colding-Jørgensen et al., 2023).

Study III:

Finally, in *Study III* (Bärtl et al., 2024) we examined salivary cortisol and neural responses to acute psychosocial stress applying Scan*STRESS* (Henze et al., 2020; Streit et al., 2014). Thereby, no differences emerged between the BO and the HC group with respect to salivary cortisol responses. Based on our results as well as previous studies, it can be concluded that cortisol responses to stress may remain unaffected in subclinical burnout (e.g., Lennartsson et al., 2015; Penz et al., 2018; Wendsche et al., 2020). The observation of a (albeit non-significant) trend towards a negative association between burnout symptomatology and salivary cortisol responses within the BO group again supports the idea of a non-linear relationship between burnout and HPA axis (re)activity. As already discussed above, future studies including an additional third group of individuals with clinical burnout are needed to clarify whether alterations of HPA axis stress reactivity may become evident in more severe burnout cases. Moreover, our study sample lacked homogeneity regarding potential confounders of HPA axis responses to stress (e.g., sex / menstrual cycle condition, age, smoking). Given the typically modest effect sizes in the field of psychoneuroendocrine stress research, the variability in terms of potential confounders within our sample may have impeded the identification of burnout-related alterations of cortisol responses to stress (Kudielka et al., 2009; Zänkert et al., 2019). While the overarching aim of the Regensburg Burnout Project was to obtain a more homogeneous sample in terms of etiological factors, future studies may also apply strict exclusion criteria with respect to potential confounders of HPA axis responses to stress (e.g., intake of OC or smoking as exclusion criteria). In addition, the frequent interruptions and alternations between stress and control blocks during Scan*STRESS* were considered to induce reduced HPA axis responses compared to standard psychosocial stress induction paradigms such as the TSST (Henze et al., 2020; Kirschbaum et al., 1993). However, in previous studies, the application of the TSST did also not reveal consistent results regarding burnout-related alterations of HPA axis reactivity (Princip et al., 2024; Rothe et al., 2020).

While our findings from *Study II* and *III* did not indicate consistent evidence for an altered HPA axis (re)activity, we cannot draw any conclusions about potential burnout-related alterations on different functional levels of the HPA axis (i.e., hypothalamus, pituitary gland, adrenal cortex). Interestingly, available studies on HPA axis feedback sensitivity applying the DST yielded either non-significant findings or findings of increased HPA axis sensitivity (i.e., stronger cortisol suppression after dexamethasone

administration) in burnout. In contrast, no study exists reporting on reduced HPA axis feedback sensitivity in burnout leading to the assumption that there is at least some evidence for an altered HPA axis functionality in terms of increased feedback sensitivity, presumably owing to GR hypersensitivity in burnout (Bellingrath et al., 2008; Menke et al., 2014; Pruessner et al., 1999; Rothe et al., 2020; Sonnenschein et al., 2007). To the best of my knowledge, only one study has applied a low-dowse $ACTH_{1\text{-}24}$ (Synacthen®) or the combined dexamethasone-CRH test (i.e., dexamethasone administration followed by CRH administration) to investigate burnout-related HPA axis dysfunctions. Thereby, higher burnout symptomatology (EE) was associated with higher plasma cortisol profiles after Synacthen indicating increased sensitivity of the adrenal cortex (Wolfram et al., 2013). Although the procedures of pharmacological challenge tests have some disadvantages in terms of feasibility (e.g., invasive, complexity of the protocols, ethical considerations) and ecological validity, application of e.g., the dexamethasone-CRH test as the most sensitive pharmacological challenge test in future studies may contribute to a clearer understanding of burnout-related HPA axis dysfunctions (Heuser et al., 1994; Ising et al., 2005; Rothe et al., 2020; Watson et al., 2006).

The second aim of *Study III* (Bärtl et al., 2024) was the investigation of neural responses to acute psychosocial stress. However, we did not find differences in mean neural stress responses (i.e., over both runs of Scan*STRESS*) between the BO and HC group. Most of the previous studies on burnout-related changes in the brain applied methods such as structural MRI (e.g., VBM, cortical thickness, volume measures of brain structures) or resting-state FC (i.e., the measurement of the correlation between spontaneous neural activity under rest of different brain structures; van den Heuvel & Hulshoff Pol, 2010). While both structural MRI and FC studies indicated numerous alterations in stress-sensitive brain structures (e.g., thinning of the mPFC, enlarged amygdala volumes), this does not imply that these rather stable structural and FC alterations necessarily manifest themselves in altered neural stress responses (e.g., Savic et al., 2018; Shang et al., 2022). Thereby, the interpretation of our finding on mean neural stress responses is inherently challenging as our study was the first examining neural stress responses in burnout. One tentative speculation refers – again – to the small proportion of severe burnout cases within our sample. This is supported by two studies examining neural responses to psychosocial stress in patients with MDD indicating altered neural stress responses in striato-limbic regions compared to healthy controls (Dong et al., 2022; Ming et al., 2017). Moreover, Dedovic et al. (2014) reported on neural

stress response differences between individuals with subclinical depression and healthy controls in e.g., the thalamus and the right posterior cingulate cortex. In addition, mean depression scores were positively associated with neural stress responses in the right subgenual ACC. Considering the substantial symptom overlap between burnout and (subclinical) depression (Koutsimani et al., 2019), it is somewhat unexpected that, in contrast to Dedovic et al. (2014), we did not observe associations between burnout and mean neural stress responses. However, our study sample exhibited substantial variability in terms of age (mean age = 41.20 years *SD* = 10.29), education, and menstrual cycle condition compared to the study sample of Dedovic et al. (2014) including only young college students (mean age = 21.9 years, *SD* = 2.5). Although evidence on potential confounders of neural stress responses is scarce, it is reasonable to speculate that the variability regarding potential confounders within our sample may have considerably increased the – in technical terms – 'signal to noise ratio', thereby hampering the detection of true effects. For instance, neuroimaging studies have revealed that the menstrual cycle phase (e.g., luteal vs. follicular phase) affects neural activity during (non-)psychosocial stress (e.g., watching of aversive stimuli) and emotion regulation (e.g., Chung et al., 2016; Derntl et al., 2024; Derntl et al., 2008; Ossewaarde et al., 2010). Thus, in future studies, potential confounders should thoroughly be considered, especially concerning menstrual cycle as burnout-related brain changes appeared to be more pronounced in women (Savic et al., 2018). However, as our study was the first examining neural stress responses in burnout, it can preliminarily be assumed that individuals with subclinical burnout do not exhibit altered mean neural responses to acute psychosocial stress. In contrast, our subsequent analysis of the exposure-time effect (i.e., comparing the neural responses from the first to the second run of Scan*STRESS*) revealed burnout-related alterations of neural responses over stress exposure time in a cluster including the left dACC and MFG. In detail, the BO group exhibited higher neural activation (stress > control) in the second compared to the first run, while the HC group displayed a reversed pattern. Notably, structural and functional alterations of the ACC as a key region of neural stress processing were repeatedly linked to burnout in previous studies (e.g., Blix et al., 2013; Golkar et al., 2014; Jovanovic et al., 2011). Interestingly, the dACC was shown to play a decisive role in emotion regulation (Etkin et al., 2015). Hence, it can tentatively be speculated that the impaired capability of downregulating neural responses over stress exposure time may reflect a neural correlate of the observed maladaptive emotion regulation (i.e., impaired down-

regulation of negative emotions) and coping strategies in individuals suffering from burnout (e.g., Bing et al., 2022; Jackson-Koku & Grime, 2019; Maslach & Leiter, 2016b). Moreover, our finding with respect to the MFG again points to an involvement of prefrontal structures in the pathophysiology of burnout (Bayes et al., 2021). Based on a MRS study, it was proposed that attenuated feedback from the ACC and the mPFC amplifies hyperactivity of the amygdala and its glutamatergic excitotoxic projections, potentially accounting for the observed brain alterations in burnout and ED. In this regard, MRS seems to be a promising method for future studies to further elucidate whether burnout is associated with altered metabolite concentrations (e.g., glutamate, GABA) in distinct brain structures as it may provide important implications for treatment (Savic, 2020).

Increasing neural deactivation (respectively decreasing activation) of almost identical brain structures over stress exposure time has now been consistently observed in four independent healthy samples (Bärtl et al., 2024; Dong et al., 2022; Henze et al., 2020; Streit et al., 2014). Thus, this time-course of neural stress responses may reflect an adaptive mechanism of the brain to cope with ongoing psychosocial stress. Remarkably, our BO group as well as patients with MDD exhibited deviations from this neural response pattern in stress-sensitive structures, presumably indicating maladaptive neural stress processing. However, given the cross-sectional nature of the data, we cannot draw any conclusions about whether deviations from the exposure-time effect reflect consequences of burnout and chronic stress, or whether they represent a stable predisposition in terms of increased vulnerability for adverse mental health conditions such as burnout and depression. Given the limited evidence of two studies reporting on deviations from the exposure-time effect in adverse mental conditions, additional studies are needed to replicate these findings. With respect to future directions in biopsychological stress research, it would be of particular interest whether deviations from the exposure-time effect may serve as predictors or correlates of other stress-related adverse conditions and mental disorders as well.

7.3 Final conclusions

In the present thesis, a sophisticated and theory-driven recruitment procedure was conducted addressing major limitations regarding the imprecise operationalization of the burnout syndrome. Building upon this multi-stage recruitment procedure, a multimethodological as well as cross-sectional and longitudinal approach was followed to identify potential pathophysiological correlates of burnout. Thereby, the recruitment procedure, combined with the application of different methods from biopsychological stress research within an identical study sample, represents a unique feature in the field of biopsychological burnout research. Although the results of the included studies were in part inconsistent, we were able to identify various indications of biopsychological dysregulations in burnout. First, the BO group was characterized by increased AL indicating a higher cumulative physical burden in individuals suffering from burnout compared to healthy controls. Second, with respect to HCC, our results were inconclusive providing some cross-sectional evidence for hypercortisolism in more severe burnout cases, while our longitudinal data indicated rather the opposite (i.e., hypocortisolism). Based on our findings on HPA axis (re)activity from *Study II* and *III*, it can preliminary be assumed that the HPA axis may remain unaffected in subclinical burnout but may become dysregulated in more severe burnout cases. Third, while we did not observe altered mean neural stress responses, the BO group was characterized by a different pattern of neural responses over stress exposure-time.

Fifty years after the introduction of the concept, the lack of consensus on the definition and criteria of burnout still represents a major obstacle to (biopsychological) burnout research. Above all, establishing (expert) consensus guidelines on the operationalization and measurement of burnout appears to be a pivotal aspect for making significant progress in the future research on the pathophysiology of the burnout syndrome. A clearer understanding of the pathophysiological mechanisms may ultimately facilitate the development of more effective prevention and treatment strategies for affected individuals. In this respect, I am convinced that biopsychological stress research, as conducted in the present thesis, can contribute important implications to achieve these overarching aims in the future.

8 REFERENCES

Abe, K., Tei, S., Takahashi, H., & Fujino, J. (2022). Structural brain correlates of burnout severity in medical professionals: A voxel-based morphometric study. *Neuroscience Letters*, *772*, 136484. https://doi.org/10.1016/j.neulet.2022.136484

Ahola, K. (2007). Occupational burnout and health. *People and Work Research Reports*, *81*.

Ahola, K., & Hakanen, J. (2007). Job strain, burnout, and depressive symptoms: A prospective study among dentists. *Journal of Affective Disorders*, *104*(1), 103-110. https://doi.org/10.1016/j.jad.2007.03.004

Ahola, K., & Hakanen, J. (2014). Burnout and health. In M. P. Leiter, A. B. Bakker, & C. Maslach (Eds.), *Burnout at work: A psychological perspective* (pp. 10-31). London: Psychology Press. https://psycnet.apa.org/doi/10.4324/978131589416

Ahola, K., Honkonen, T., Isometsä, E., Kalimo, R., Nykyri, E., Aromaa, A., & Lönnqvist, J. (2005). The relationship between job-related burnout and depressive disorders—results from the Finnish Health 2000 Study. *Journal of Affective Disorders*, *88*(1), 55-62. https://doi.org/10.1016/j.jad.2005.06.004

Ahola, K., Väänänen, A., Koskinen, A., Kouvonen, A., & Shirom, A. (2010). Burnout as a predictor of all-cause mortality among industrial employees: A 10-year prospective register-linkage study. *Journal of Psychosomatic Research*, *69*(1), 51-57. https://doi.org/10.1016/j.jpsychores.2010.01.002

Alkhamees, A. A., Aljohani, M. S., Kalani, S., Ali, A. M., Almatham, F., Alwabili, A., Alsughier, N. A., & Rutledge, T. (2023). Physician's burnout during the COVID-19 pandemic: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, *20*(5), 4598. https://doi.org/10.3390/ijerph20054598

Allen, A. P., Kennedy, P. J., Cryan, J. F., Dinan, T. G., & Clarke, G. (2014). Biological and psychological markers of stress in humans: Focus on the Trier Social Stress Test. *Neuroscience & Biobehavioral Reviews*, *38*, 94-124. https://doi.org/10.1016/j.neubiorev.2013.11.005

Alves, L. A.-O. X., Monteiro, D. Q., Bento, S. R., Hayashi, V. D., Pelegrini, L. N. C., & Vale, F. A. C. (2019). Burnout syndrome in informal caregivers of older adults with dementia: A systematic review. *Dementia & Neuropsychologia*, *13*(4), 415-421. https://doi.org/10.1590/1980-57642018dn13-040008

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5 ed.). Washington, DC.

Bains, J. S., Cusulin, J. I. W., & Inoue, W. (2015). Stress-related synaptic plasticity in the hypothalamus. *Nature Reviews Neuroscience*, *16*(7), 377-388. https://doi.org/10.1038/nrn3881

Bakker, A. B., & Demerouti, E. (2007). The job demands-resources model: State of the art. *Journal of Managerial Psychology*, *22*(3), 309-328. https://doi.org/10.1108/02683940710733115

Bakker, A. B., Schaufeli, W. B., Demerouti, E., Janssen, P. P. M., Van Der Hulst, R., & Brouwer, J. (2000). Using equity theory to examine the difference between burnout and depression. *Anxiety, Stress, & Coping*, *13*(3), 247-268. https://doi.org/10.1080/10615800008549265

Bärtl, C., Henze, G.-I., Giglberger, M., Peter, H. L., Konzok, J., Wallner, S., Kreuzpointner, L., Wüst, S., & Kudielka, B. M. (2022). Higher allostatic load in work-related burnout: The Regensburg Burnout Project. *Psychoneuroendocrinology*, *143*, 105853. https://doi.org/10.1016/j.psyneuen.2022.105853

Bärtl, C., Henze, G.-I., Peter, H. L., Giglberger, M., Bohmann, P., Speicher, N., Konzok, J., Kreuzpointner, L., Waller, L., Walter, H., Wüst, S., & Kudielka, B. M. (2024). Neural and cortisol responses to acute psychosocial stress in work-related burnout: The Regensburg Burnout Project. *Psychoneuroendocrinology*, *161*, 106926. https://doi.org/10.1016/j.psyneuen.2023.106926

Bärtl, C., Kreuzpointner, L., Wüst, S., & Kudielka, B. M. (2023). Investigation of cross-sectional and longitudinal associations between work-related burnout and hair cortisol: The Regensburg Burnout Project. *Psychoneuroendocrinology*, 106026. https://doi.org/10.1016/j.psyneuen.2023.106026

Bayes, A., Tavella, G., & Parker, G. (2021). The biology of burnout: Causes and consequences. *The World Journal of Biological Psychiatry*, *22*(9), 686-698. https://doi.org/10.1080/15622975.2021.1907713

Bellingrath, S., & Kudielka, B. M. (2008). Effort-reward-imbalance and overcommitment are associated with hypothalamus–pituitary–adrenal (HPA) axis responses to acute psychosocial stress in healthy working schoolteachers. *Psychoneuroendocrinology*, *33*(10), 1335-1343. https://doi.org/10.1016/j.psyneuen.2008.07.008

Bellingrath, S., Weigl, T., & Kudielka, B. M. (2008). Cortisol dysregulation in school teachers in relation to burnout, vital exhaustion, and effort–reward-imbalance. *Biological Psychology*, *78*(1), 104-113. https://doi.org/10.1016/j.biopsycho.2008.01.006

Bellingrath, S., Weigl, T., & Kudielka, B. M. (2009). Chronic work stress and exhaustion is associated with higher allostastic load in female school teachers. *Stress*, *12*(1), 37-48. https://doi.org/10.1080/10253890802042041

Berger, M., Linden, M., Schramm, E., Hillert, A., Voderholzer, U., & Maier, W. (2012). *Positionspapier der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN) zum Thema Burnout.* Berlin: Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN).

Berretz, G., Packheiser, J., Kumsta, R., Wolf, O. T., & Ocklenburg, S. (2021). The brain under stress—A systematic review and activation likelihood estimation meta-analysis of changes in BOLD signal associated with acute stress exposure. *Neuroscience & Biobehavioral Reviews*, *124*, 89-99. https://doi.org/10.1016/j.neubiorev.2021.01.001

Besèr, A., Sorjonen, K., Wahlberg, K., Peterson, U., Nygren, Å., & Åsberg, M. (2014). Construction and evaluation of a self rating scale for stress-induced exhaustion disorder, the Karolinska Exhaustion Disorder Scale. *Scandinavian Journal of Psychology*, *55*(1), 72-82. https://doi.org/10.1111/sjop.12088

Bianchi, R. (2016). Occupational and non-occupational strains should be concomitantly considered in research on burnout, organizational commitment, and turnover

intention. *International Journal of Nursing Studies*, *53*, 403-404. https://doi.org/10.1016/j.ijnurstu.2015.10.005

Bianchi, R., Boffy, C., Hingray, C., Truchot, D., & Laurent, E. (2013). Comparative symptomatology of burnout and depression. *Journal of Health Psychology*, *18*(6), 782-787. https://doi.org/10.1177/1359105313481079

Bianchi, R., Lindsäter, E., Vollan, T. E., Tesaker, R., Mathisen, H. H., Øyangen, S. H., Ek, B., Bø, U. W., Eilertsen, E. S., Hauglie-Hanssen, T., Hunvik, J. S., Rasul, M. H., & Schonfeld, I. S. (2024). Most people do not attribute their burnout symptoms to work. *Journal of Psychosomatic Research*, *187*, 111962. https://doi.org/10.1016/j.jpsychores.2024.111962

Bianchi, R., & Schonfeld, I. S. (2020). The Occupational Depression Inventory: A new tool for clinicians and epidemiologists. *Journal of Psychosomatic Research*, *138*, 110249. https://doi.org/10.1016/j.jpsychores.2020.110249

Bianchi, R., Schonfeld, I. S., & Laurent, E. (2014). Is burnout a depressive disorder? A reexamination with special focus on atypical depression. *International Journal of Stress Management*, *21*(4), 307-324. https://doi.org/10.1037/a0037906

Bianchi, R., Schonfeld, I. S., & Laurent, E. (2015). Burnout-depression overlap: A review. *Clinical Psychology Review*, *36*, 28-41. https://doi.org/10.1016/j.cpr.2015.01.004

Bianchi, R., Verkuilen, J., Schonfeld, I. S., Hakanen, J. J., Jansson-Fröjmark, M., Manzano-García, G., Laurent, E., & Meier, L. L. (2021). Is burnout a depressive condition? A 14-sample meta-analytic and bifactor analytic study. *Clinical Psychological Science*, *9*(4), 579-597. https://doi.org/10.1177/2167702620979597

Billot, B., Greve, D. N., Puonti, O., Thielscher, A., Van Leemput, K., Fischl, B., Dalca, A. V., & Iglesias, J. E. (2023). SynthSeg: Segmentation of brain MRI scans of any contrast and resolution without retraining. *Medical Image Analysis*, *86*, 102789. https://doi.org/10.1016/j.media.2023.102789

Bing, H., Sadjadi, B., Afzali, M., & Fathi, J. (2022). Self-efficacy and emotion regulation as predictors of teacher burnout among english as a foreign language teachers: A

structural equation modeling approach. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.900417

Bizik, G., Picard, M., Nijjar, R., Tourjman, V., McEwen, B. S., Lupien, S. J., & Juster, R.-P. (2013). Allostatic load as a tool for monitoring physiological dysregulations and comorbidities in patients with severe mental illnesses. *Harvard Review of Psychiatry*, *21*(6), 296-313. https://doi.org/10.1097/hrp.0000000000000012

Blix, E., Perski, A., Berglund, H., & Savic, I. (2013). Long-term occupational stress is associated with regional reductions in brain tissue volumes. *PLOS ONE*, *8*(6), e64065. https://doi.org/10.1371/journal.pone.0064065

Borkenau, P., & Ostendorf, F. (2008). *NEO-Fünf-Faktoren-Inventar nach Costa und McCrae*. Göttingen: Hogrefe.

Borritz, M., Christensen, K. B., Bültmann, U., Rugulies, R., Lund, T., Andersen, I., Villadsen, E., Diderichsen, F., & Kristensen, T. S. (2010). Impact of burnout and psychosocial work characteristics on future long-term sickness absence. Prospective results of the Danish PUMA study among human service workers. *Journal of Occupational and Environmental Medicine*, *52*(10), 964-970. https://doi.org/10.1097/JOM.0b013e3181f12f95

Brianda, M. E., Roskam, I., & Mikolajczak, M. (2020). Hair cortisol concentration as a biomarker of parental burnout. *Psychoneuroendocrinology*, *117*, 104681. https://doi.org/10.1016/j.psyneuen.2020.104681

Cannon, W. B. (1914). The interrelations of emotions as suggested by recent physiological researches. *The American Journal of Psychology*, *25*(2), 256-282. https://doi.org/10.2307/1413414

Cannon, W. B. (1929). Organization for physiological homeostasis. *Physiological Reviews*, *9*(3), 399-431. https://doi.org/10.1152/physrev.1929.9.3.399

Carbone, J. T., Clift, J., & Alexander, N. (2022). Measuring allostatic load: Approaches and limitations to algorithm creation. *Journal of Psychosomatic Research*, *163*, 111050. https://doi.org/10.1016/j.jpsychores.2022.111050

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology*, *67*(1), 259-284. https://doi.org/10.1146/annurev.physiol.67.040403.120816

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374-381. https://doi.org/10.1038/nrendo.2009.106

Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. *JAMA*, *267*(9), 1244-1252. https://doi.org/10.1001/jama.1992.03480090092034

Chung, K. C., Peisen, F., Kogler, L., Radke, S., Turetsky, B., Freiherr, J., & Derntl, B. (2016). The influence of menstrual cycle and androstadienone on female stress reactions: An fMRI study. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00044

Claponea, R. M., Pop, L. M., Iorga, M., & Iurcov, R. (2022). Symptoms of burnout syndrome among physicians during the outbreak of COVID-19 pandemic—A systematic literature review. *Healthcare*, *10*(6), 979. https://doi.org/10.3390/healthcare10060979

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2 ed.). Hillsdale, NJ: Erlbaum.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*(4), 385-396. https://doi.org/10.2307/2136404

Colding-Jørgensen, P., Hestehave, S., Abelson, K. S. P., & Kalliokoski, O. (2023). Hair glucocorticoids are not a historical marker of stress – Exploring the time-scale of corticosterone incorporation into hairs in a rat model. *General and Comparative Endocrinology*, *341*, 114335. https://doi.org/10.1016/j.ygcen.2023.114335

Dallman, M. F. (2005). Fast glucocorticoid actions on brain: Back to the future. *Frontiers in Neuroendocrinology*, *26*(3), 103-108. https://doi.org/10.1016/j.yfrne.2005.08.001

Danhof-Pont, M. B., van Veen, T., & Zitman, F. G. (2011). Biomarkers in burnout: A systematic review. *Journal of Psychosomatic Research*, *70*(6), 505-524. https://doi.org/10.1016/j.jpsychores.2010.10.012

de Beer, L. T., & Bianchi, R. (2017). Confirmatory factor analysis of the Maslach Burnout Inventory. *European Journal of Psychological Assessment*, *35*(2), 217-224. https://doi.org/10.1027/1015-5759/a000392

de Kloet, E. R. (2000). Stress in the brain. *European Journal of Pharmacology*, *405*(1), 187-198. https://doi.org/10.1016/S0014-2999(00)00552-5

de Kloet, E. R., & Derijk, R. (2004). Signaling pathways in brain involved in predisposition and pathogenesis of stress-related disease: Genetic and kinetic factors affecting the MR/GR balance. *Annals of the New York Academy of Sciences*, *1032*(1), 14-34. https://doi.org/10.1196/annals.1314.003

de Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joëls, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews*, *19*(3), 269-301. https://doi.org/10.1210/edrv.19.3.0331

de Vente, W., Olff, M., Van Amsterdam, J. G. C., Kamphuis, J. H., & Emmelkamp, P. M. G. (2003). Physiological differences between burnout patients and healthy controls: blood pressure, heart rate, and cortisol responses. *Occupational and Environmental Medicine*, *60*, i54-i61. https://doi.org/10.1136/oem.60.suppl_1.i54

de Vente, W., van Amsterdam, J. G. C., Olff, M., Kamphuis, J. H., & Emmelkamp, P. M. G. (2015). Burnout is associated with reduced parasympathetic activity and reduced HPA axis responsiveness, predominantly in males. *BioMed Research International*, *2015*, 431725. https://doi.org/10.1155/2015/431725

Dedovic, K., Duchesne, A., Engert, V., Lue, S. D., Andrews, J., Efanov, S. I., Beaudry, T., & Pruessner, J. C. (2014). Psychological, endocrine and neural responses to social evaluation in subclinical depression. *Social Cognitive and Affective Neuroscience*, *9*(10), 1632-1644. https://doi.org/10.1093/scan/nst151

Dedovic, K., Renwick, R., Khalili Mahani, N., Engert, V., Lupien, S. J., & Pruessner, J. C. (2005). The Montreal Imaging Stress Task: Using functional imaging to

investigate the effects of perceiving and processing psychosocial stress in the human brain. *Journal of Psychiatry & Neuroscience, 30*(5), 319-325.

Demerouti, E., Bakker, A. B., Nachreiner, F., & Schaufeli, W. B. (2001). The job demands-resources model of burnout. *Journal of Applied Psychology, 86*(3), 499-512. https://doi.org/10.1037/0021-9010.86.3.499

Demerouti, E., Demerouti, E., Bakker, A. B., Vardakou, I., & Kantas, A. (2003). The convergent validity of two burnout instruments. *European Journal of Psychological Assessment, 19*(1), 12-23. https://doi.org/10.1027//1015-5759.19.1.12

Deng, H., Zhuo, Y., Qi, X., Wu, H., Liu, Y., Li, J., & Jin, C. (2021). The role of personal biological resource in the job demands-control-support model: Evidence from stress reactivity. *Frontiers in Psychology, 12*. https://doi.org/10.3389/fpsyg.2021.658180

Derntl, B., Eber, C. H., Kogler, L., Rehbein, E., Sundstöm-Poromaa, I., & Morawetz, C. (2024). Estradiol modulates changes in effective connectivity in emotion regulation networks. *Psychoneuroendocrinology, 167*, 107103. https://doi.org/10.1016/j.psyneuen.2024.107103

Derntl, B., Windischberger, C., Robinson, S., Lamplmayr, E., Kryspin-Exner, I., Gur, R. C., Moser, E., & Habel, U. (2008). Facial emotion recognition and amygdala activation are associated with menstrual cycle phase. *Psychoneuroendocrinology, 33*(8), 1031-1040. https://doi.org/10.1016/j.psyneuen.2008.04.014

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*(3), 355-391. https://doi.org/10.1037/0033-2909.130.3.355

Dong, D., Ironside, M., Belleau, E. L., Sun, X., Cheng, C., Xiong, G., Nickerson, L. D., Wang, X., Yao, S., & Pizzagalli, D. A. (2022). Sex-specific neural responses to acute psychosocial stress in depression. *Translational Psychiatry, 12*(1), 2. https://doi.org/10.1038/s41398-021-01768-y

Doulougeri, K., Georganta, K., & Montgomery, A. (2016). "Diagnosing" burnout among healthcare professionals: Can we find consensus? *Cogent Medicine, 3*(1), 1. https://doi.org/10.1080/2331205X.2016.1237605

Durning, S., Costanzo, M., Artino, A., Dyrbye, L., Beckman, T., Schuwirth, L., Holmboe, E., Roy, M., Wittich, C., Lipner, R., & van der Vleuten, C. (2013). Functional neuroimaging correlates of burnout among internal medicine residents and faculty members. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00131

Edes, A. N., & Crews, D. E. (2017). Allostatic load and biological anthropology. *American Journal of Physical Anthropology*, *162*(S63), e23146. https://doi.org/10.1002/ajpa.23146

Edú-Valsania, S., Laguía, A., & Moriano, J. A. (2022). Burnout: A review of theory and measurement. *International Journal of Environmental Research and Public Health, 19*(3), 1780. https://doi.org/10.3390/ijerph19031780

Etkin, A., Büchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews Neuroscience, 16*(11), 693-700. https://doi.org/10.1038/nrn4044

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175-191. https://doi.org/10.3758/BF03193146

Feuerhahn, N., Kühnel, J., & Kudielka, B. M. (2012). Interaction effects of effort–reward imbalance and overcommitment on emotional exhaustion and job performance. *International Journal of Stress Management*, *19*(2), 105-131. https://doi.org/10.1037/a0028338

Feuerhahn, N., Stamov-Roßnagel, C., Wolfram, M., Bellingrath, S., & Kudielka, B. M. (2013). Emotional exhaustion and cognitive performance in apparently healthy teachers: A longitudinal multi-source study. *Stress and Health*, *29*(4), 297-306. https://doi.org/10.1002/smi.2467

Fink, G. (2016). Stress, definitions, mechanisms, and effects outlined: Lessons from anxiety. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 3-11). San Diego: Academic Press. https://doi.org/10.1016/B978-0-12-800951-2.00001-7

Fink, G. (2017). Stress: Concepts, definition and history. In *Reference Module in Neuroscience and Biobehavioral Psychology* (pp. 1-9). Elsevier. https://doi.org/10.1016/b978-0-12-809324-5.02208-2

Freudenberger, H. J. (1974). Staff burn-out. *Journal of Social Issues*, *30*(1), 159-165. https://doi.org/10.1111/j.1540-4560.1974.tb00706.x

Gao, W., Stalder, T., Foley, P., Rauh, M., Deng, H., & Kirschbaum, C. (2013). Quantitative analysis of steroid hormones in human hair using a column-switching LC–APCI–MS/MS assay. *Journal of Chromatography B*, *928*, 1-8. https://doi.org/10.1016/j.jchromb.2013.03.008

Gavelin, H. M., Neely, A. S., Andersson, M., Eskilsson, T., Järvholm, L. S., & Boraxbekk, C.-J. (2017). Neural activation in stress-related exhaustion: Cross-sectional observations and interventional effects. *Psychiatry Research: Neuroimaging*, *269*, 17-25. https://doi.org/10.1016/j.pscychresns.2017.08.008

Giglberger, M., Peter, H. L., Henze, G.-I., Kraus, E., Bärtl, C., Konzok, J., Kreuzpointner, L., Kirsch, P., Kudielka, B. M., & Wüst, S. (2023). Neural responses to acute stress predict chronic stress perception in daily life over 13 months. *Scientific Reports*, *13*(1), 19990. https://doi.org/10.1038/s41598-023-46631-w

Giglberger, M., Peter, H. L., Kraus, E., Kreuzpointner, L., Zänkert, S., Henze, G.-I., Bärtl, C., Konzok, J., Kirsch, P., Rietschel, M., Kudielka, B. M., & Wüst, S. (2022). Daily life stress and the cortisol awakening response over a 13-months stress period – Findings from the LawSTRESS project. *Psychoneuroendocrinology*, *141*, 105771. https://doi.org/10.1016/j.psyneuen.2022.105771

Gillespie, S. L., Anderson, C. M., Zhao, S., Tan, Y., Kline, D., Brock, G., Odei, J., O'Brien, E., Sims, M., Lazarus, S. A., Hood, D. B., Williams, K. P., & Joseph, J. J. (2019). Allostatic load in the association of depressive symptoms with incident coronary heart disease: The Jackson Heart Study. *Psychoneuroendocrinology*, *109*, 104369. https://doi.org/10.1016/j.psyneuen.2019.06.020

Gjerstad, J. K., Lightman, S. L., & Spiga, F. (2018). Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. *Stress*, *21*(5), 403-416. https://doi.org/10.1080/10253890.2018.1470238

Glise, K., Hadzibajramovic, E., Jonsdottir, I. H., & Ahlborg, G. (2010). Self-reported exhaustion: A possible indicator of reduced work ability and increased risk of sickness absence among human service workers. *International Archives of Occupational and Environmental Health*, *83*(5), 511-520. https://doi.org/10.1007/s00420-009-0490-x

Godoy, L. D., Rossignoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & de Lima Umeoka, E. H. (2018). A comprehensive overview on stress neurobiology: Basic concepts and clinical implications. *Frontiers in Behavioral Neuroscience*, *12*. https://doi.org/10.3389/fnbeh.2018.00127

Goldstein, D. S. (2013). Differential responses of components of the autonomic nervous system. In R. M. Buijs & D. F. Swaab (Eds.), *Handbook of Clinical Neurology* (Vol. 117, pp. 13-22). Elsevier. https://doi.org/10.1016/B978-0-444-53491-0.00002-X

Golkar, A., Johansson, E., Kasahara, M., Osika, W., Perski, A., & Savic, I. (2014). The influence of work-related chronic stress on the regulation of emotion and on functional connectivity in the brain. *PLOS ONE*, *9*(9), e104550. https://doi.org/10.1371/journal.pone.0104550

Goodman, W. K., Janson, J., & Wolf, J. M. (2017). Meta-analytical assessment of the effects of protocol variations on cortisol responses to the Trier Social Stress Test. *Psychoneuroendocrinology*, *80*, 26-35. https://doi.org/10.1016/j.psyneuen.2017.02.030

Grossi, G., Perski, A., Osika, W., & Savic, I. (2015). Stress-related exhaustion disorder – clinical manifestation of burnout? A review of assessment methods, sleep impairments, cognitive disturbances, and neuro-biological and physiological changes in clinical burnout. *Scandinavian Journal of Psychology*, *56*(6), 626-636. https://doi.org/10.1111/sjop.12251

Guidi, J., Lucente, M., Sonino, N., & Fava, G. A. (2021). Allostatic load and its impact on health: A systematic review. *Psychotherapy and Psychosomatics*, *90*(1), 11-27. https://doi.org/10.1159/000510696

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*(1), 145-173. https://doi.org/10.1146/annurev.psych.58.110405.085605

Habib, K. E., Gold, P. W., & Chrousos, G. P. (2001). Neuroendocrinology of stress. *Endocrinology and Metabolism Clinics of North America*, *30*(3), 695-728. https://doi.org/10.1016/S0889-8529(05)70208-5

Hadžibajramović, E., Ahlborg, G., & Grimby-Ekman, A. (2019). Concurrent and lagged effects of psychosocial job stressors on symptoms of burnout. *International Archives of Occupational and Environmental Health*, *92*(7), 1013-1021. https://doi.org/10.1007/s00420-019-01437-0

Hakanen, J. J., & Bakker, A. B. (2017). Born and bred to burn out: A life-course view and reflections on job burnout. *Journal of Occupational Health Psychology*, *22*(3), 354-364. https://doi.org/10.1037/ocp0000053

Hakanen, J. J., Peeters, M. C. W., & Schaufeli, W. B. (2018). Different types of employee well-being across time and their relationships with job crafting. *Journal of Occupational Health Psychology*, *23*(2), 289-301. https://doi.org/10.1037/ocp0000081

Hallsten, L., Voss, M., Stark, S., & Josephson, M. (2011). Job burnout and job wornout as risk factors for long-term sickness absence. *Work*, *38*, 181-192. https://doi.org/10.3233/WOR-2011-1120

Hammond, G. L. (1990). Molecular properties of corticosteroid binding globulin and the sex-steroid binding proteins. *Endocrine Reviews*, *11*(1), 65-79. https://doi.org/10.1210/edrv-11-1-65

Heck, A. L., & Handa, R. J. (2019). Sex differences in the hypothalamic–pituitary–adrenal axis' response to stress: An important role for gonadal hormones. *Neuropsychopharmacology*, *44*(1), 45-58. https://doi.org/10.1038/s41386-018-0167-9

Heinemann, L. V., & Heinemann, T. (2017). Burnout research: Emergence and scientific investigation of a contested diagnosis. *SAGE Open*, *7*(1). https://doi.org/10.1177/2158244017697154

Hellhammer, D. H., Wüst, S., & Kudielka, B. M. (2009). Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*, *34*(2), 163-171. https://doi.org/10.1016/j.psyneuen.2008.10.026

Henze, G.-I. (2021). *Stress regulation in the brain: Association with cortisol release, modulation by exposure time, and gender differences.* Inaugural Dissertation. University of Regensburg. Regensburg.

Henze, G.-I., Konzok, J., Kreuzpointner, L., Bärtl, C., Giglberger, M., Peter, H., Streit, F., Kudielka, B. M., Kirsch, P., & Wüst, S. (2021). Sex-specific interaction between cortisol and striato-limbic responses to psychosocial stress. *Social Cognitive and Affective Neuroscience*, *16*, 972-984. https://doi.org/10.1093/scan/nsab062

Henze, G.-I., Konzok, J., Kreuzpointner, L., Bärtl, C., Peter, H., Giglberger, M., Streit, F., Kudielka, B. M., Kirsch, P., & Wüst, S. (2020). Increasing deactivation of limbic structures over psychosocial stress exposure time. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(7), 697-704. https://doi.org/10.1016/j.bpsc.2020.04.002

Henze, G.-I., Konzok, J., Kudielka, B. M., Wüst, S., Nichols, T. E., & Kreuzpointner, L. (2023). Associations between cortisol stress responses and limbic volume and thickness in young adults: An exploratory study. *European Journal of Neuroscience*, *59*(9), 3962-3980. https://doi.org/10.1111/ejn.16161

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: Central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in Neurosciences*, *20*(2), 78-84. https://doi.org/10.1016/S0166-2236(96)10069-2

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, *24*(3), 151-180. https://doi.org/10.1016/j.yfrne.2003.07.001

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). Regulation of the hypothalamic-pituitary-

adrenocortical stress response. In R. Terjung (Ed.), *Comprehensive Physiology* (pp. 603-621). https://doi.org/10.1002/cphy.c150015

Herrmann-Lingen, C., Buss, U., & Snaith, R. P. (2011). *Hospital Anxiety and Depression Scale - Deutsche Version* (4th ed.). Bern: Huber.

Het, S., Schoofs, D., Rohleder, N., & Wolf, O. T. (2012). Stress-induced cortisol level elevations are associated with reduced negative affect after stress: Indications for a mood-buffering cortisol effect. *Psychosomatic Medicine*, *74*(1), 23-32. https://doi.org/10.1097/PSY.0b013e31823a4a25

Heuser, I., Yassouridis, A., & Holsboer, F. (1994). The combined dexamethasone/CRH test: A refined laboratory test for psychiatric disorders. *Journal of Psychiatric Research*, *28*(4), 341-356. https://doi.org/10.1016/0022-3956(94)90017-5

Hewitt, D. B., Ellis, R. J., Hu, Y.-Y., Cheung, E. O., Moskowitz, J. T., Agarwal, G., & Bilimoria, K. Y. (2020). Evaluating the association of multiple burnout definitions and thresholds with prevalence and outcomes. *JAMA Surgery*, *155*(11), 1043-1049. https://doi.org/10.1001/jamasurg.2020.3351

Hillert, A. (2012). Burnout: Eine zeitgemäße psychische Störung? *Psych up2date*, *6*(6), 361-361. https://doi.org/10.1055/s-0032-1305103

Hintsa, T., Elovainio, M., Jokela, M., Ahola, K., Virtanen, M., & Pirkola, S. (2016). Is there an independent association between burnout and increased allostatic load? Testing the contribution of psychological distress and depression. *Journal of Health Psychology*, *21*(8), 1576-1586. https://doi.org/10.1177/1359105314559619

Hobfoll, S. E. (1989). Conservation of resources: A new attempt at conceptualizing stress. *American Psychologist*, *44*(3), 513-524. https://doi.org/10.1037/0003-066X.44.3.513

Holmgreen, L., Tirone, V., Gerhart, J., & Hobfoll, S. E. (2017). Conservation of resources theory. In C. L. Cooper & J. C. Quick (Eds.), *The Handbook of Stress and Health* (pp. 443-457). Chicester, UK: Wiley-Blackwell. https://doi.org/10.1002/9781118993811.ch27

Honkalampi, K., Virtanen, M., Hintsa, T., Ruusunen, A., Mäntyselkä, P., Ali-Sisto, T., Kärkkäinen, O., Koivumaa-Honkanen, H., Valkonen-Korhonen, M., Panayiotou, G., & Lehto, S. M. (2021). Comparison of the level of allostatic load between patients with major depression and the general population. *Journal of Psychosomatic Research*, *143*, 110389. https://doi.org/10.1016/j.jpsychores.2021.110389

Ibar, C., Fortuna, F., Gonzalez, D., Jamardo, J., Jacobsen, D., Pugliese, L., Giraudo, L., Ceres, V., Mendoza, C., Repetto, E. M., Reboredo, G., Iglesias, S., Azzara, S., Berg, G., Zopatti, D., & Fabre, B. (2021). Evaluation of stress, burnout and hair cortisol levels in health workers at a university hospital during COVID-19 pandemic. *Psychoneuroendocrinology*, *128*, 105213. https://doi.org/10.1016/j.psyneuen.2021.105213

Ising, M., Künzel, H. E., Binder, E. B., Nickel, T., Modell, S., & Holsboer, F. (2005). The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(6), 1085-1093. https://doi.org/10.1016/j.pnpbp.2005.03.014

Jackson-Koku, G., & Grime, P. (2019). Emotion regulation and burnout in doctors: A systematic review. *Occupational Medicine*, *69*(1), 9-21. https://doi.org/10.1093/occmed/kqz004

Jankord, R., & Herman, J. P. (2008). Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Annals of the New York Academy of Sciences*, *1148*(1), 64-73. https://doi.org/10.1196/annals.1410.012

Jenkins, C. D., Stanton, B.-A., Niemcryk, S. J., & Rose, R. M. (1988). A scale for the estimation of sleep problems in clinical research. *Journal of Clinical Epidemiology*, *41*(4), 313-321. https://doi.org/10.1016/0895-4356(88)90138-2

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825-841. https://doi.org/10.1006/nimg.2002.1132

Joëls, M., Sarabdjitsingh, A. R., & Karst, H. (2012). Unraveling the time domains of corticosteroid hormone influences on brain activity: Rapid, slow, and chronic

modes. *Pharmacological Reviews*, *64*(4), 901-938. https://doi.org/10.1124/pr.112.005892

Jonsdottir, I. H., & Sjörs Dahlman, A. (2019). Endocrine and immunological aspects of burnout: A narrative review. *European Journal of Endocrinology*, *180*(3), 147-158. https://doi.org/10.1530/EJE-18-0741

Jönsson, P., Österberg, K., Wallergård, M., Hansen, Å. M., Garde, A. H., Johansson, G., & Karlson, B. (2015). Exhaustion-related changes in cardiovascular and cortisol reactivity to acute psychosocial stress. *Physiology & Behavior*, *151*, 327-337. https://doi.org/10.1016/j.physbeh.2015.07.020

Jovanovic, H., Perski, A., Berglund, H., & Savic, I. (2011). Chronic stress is linked to 5-HT1A receptor changes and functional disintegration of the limbic networks. *NeuroImage*, *55*(3), 1178-1188. https://doi.org/10.1016/j.neuroimage.2010.12.060

Juster, R.-P., Marin, M.-F., Sindi, S., Nair, N. P. V., Ng, Y. K., Pruessner, J. C., & Lupien, S. J. (2011). Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. *Physiology & Behavior*, *104*(2), 360-364. https://doi.org/10.1016/j.physbeh.2011.02.027

Juster, R.-P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2-16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Juster, R.-P., & Misiak, B. (2023). Advancing the allostatic load model: From theory to therapy. *Psychoneuroendocrinology*, *154*, 106289. https://doi.org/10.1016/j.psyneuen.2023.106289

Juster, R.-P., Sindi, S., Marin, M. F., Perna, A., Hashemi, A., Pruessner, J. C., & Lupien, S. J. (2011). A clinical allostatic load index is associated with burnout symptoms and hypocortisolemic profiles in healthy workers. *Psychoneuroendocrinology*, *36*(6), 797-805. https://doi.org/10.1016/j.psyneuen.2010.11.001

Kagan, J. (2016). An overly permissive extension. *Perspectives on Psychological Science*, *11*(4), 442-450. https://doi.org/10.1177/1745691616635593

Kalimo, R., Pahkin, K., Mutanen, P., & Toppinen-Tanner, S. (2003). Staying well or burning out at work: Work characteristics and personal resources as long-term predictors. *Work & Stress*, *17*(2), 109-122. https://doi.org/10.1080/0267837031000149919

Kalsbeek, A., van der Spek, R., Lei, J., Endert, E., Buijs, R. M., & Fliers, E. (2012). Circadian rhythms in the hypothalamo–pituitary–adrenal (HPA) axis. *Molecular and Cellular Endocrinology*, *349*(1), 20-29. https://doi.org/10.1016/j.mce.2011.06.042

Kaltenegger, H. C., Marques, M. D., Becker, L., Rohleder, N., Nowak, D., Wright, B. J., & Weigl, M. (2024). Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation. *Brain, Behavior, and Immunity*, *117*, 320-329. https://doi.org/10.1016/j.bbi.2024.01.222

Karasek, R. A. (1979). Job demands, job decision latitude, and mental strain: Implications for job redesign. *Administrative Science Quarterly*, *24*(2), 285-308. https://doi.org/10.2307/2392498

Keller-Wood, M. (2015). Hypothalamic-pituitary-adrenal axis—feedback control. *Comprehensive Physiology*, *5*, 1161-1182. https://doi.org/10.1002/cphy.c140065

Khammissa, R. A. G., Nemutandani, S., Feller, G., Lemmer, J., & Feller, L. A.-O. (2022). Burnout phenomenon: Neurophysiological factors, clinical features, and aspects of management. *Journal of International Medical Research*, *50*(9), 1-13. https://doi.org/10.1177/03000605221106428

Kieselbach, T., Triomphe, C. E., Armgarth, E., Bagnara, S., Elo, A.-L., Jefferys, S., Joling, C., Kuhn, K., Nielsen, K., Popma, J., Rogovsky, N., Sahler, B., Thomson, G., & Widerszal-Bazyl, M. (2010). *Health in Restructuring (HIRES). Recommendations, National Responses and Policy Issues in the EU* (Vol. 2). Augsburg: Rainer Hampp Verlag.

Kirschbaum, C., Diedrich, O., Gehrke, J., Wüst, S., & Hellhammer, D. (1992). Cortisol and behavior: The “Trier Mental Challenge Test” (TMCT) — First evaluation of a new psychological stress test. In A. Ehlers, W. Fiegenbaum, I. Florin, & J. Margraf

(Eds.), *Perspectives and Promises of Clinical Psychology* (pp. 67-78). Boston, MA: Springer US. https://doi.org/10.1007/978-1-4899-3674-5_7

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – A tool for Investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1-2), 76-81. https://doi.org/10.1159/000119004

Kirschbaum, C., Tietze, A., Skoluda, N., & Dettenborn, L. (2009). Hair as a retrospective calendar of cortisol production—Increased cortisol incorporation into hair in the third trimester of pregnancy. *Psychoneuroendocrinology*, *34*(1), 32-37. https://doi.org/10.1016/j.psyneuen.2008.08.024

Kirschbaum, C., Wüst, S., & Hellhammer, D. (1992). Consistent sex differences in cortisol responses to psychological stress. *Psychosomatic Medicine*, *54*(6). https://doi.org/10.1097/00006842-199211000-00004

Klein, E. M., Brähler, E., Dreier, M., Reinecke, L., Müller, K. W., Schmutzer, G., Wölfling, K., & Beutel, M. E. (2016). The German version of the Perceived Stress Scale – Psychometric characteristics in a representative German community sample. *BMC Psychiatry*, *16*(1), 159. https://doi.org/10.1186/s12888-016-0875-9

Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wöhr, M., & Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1291-1301. https://doi.org/10.1016/j.neubiorev.2011.02.003

Korczak, D., Huber, B., & Kister, C. (2010). Differential diagnostic of the burnout syndrome. *GMS Health Innovation and Technologies*, *6*, Doc09. https://doi.org/10.3205/hta000087

Koutsimani, P., Montgomery, A., & Georganta, K. (2019). The relationship between burnout, depression, and anxiety: A systematic review and meta-analysis. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.00284

Kristensen, T. S., Borritz, M., Villadsen, E., & Christensen, K. B. (2005). The Copenhagen Burnout Inventory: A new tool for the assessment of burnout. *Work & Stress*, *19*(3), 192-207. https://doi.org/10.1080/02678370500297720

Kroenke, K., & Price, R. K. (1993). Symptoms in the community: Prevalence, classification, and psychiatric comorbidity. *Archives of Internal Medicine*, *153*(21), 2474-2480. https://doi.org/10.1001/archinte.1993.00410210102011

Kudielka, B. M., Bellingrath, S., & Hellhammer, D. H. (2006). Cortisol in burnout and vital exhaustion: An overview. *Giornale Italiano di Medicina del Lavoro ed Ergonomia*, *28*(1), 34-42. http://europepmc.org/abstract/MED/19031555

Kudielka, B. M., Hellhammer, D. H., & Kirschbaum, C. (2007). Ten years of research with the Trier Social Stress Test--revisited. In E. Harmon-Jones & P. Winkielman (Eds.), *Social Neuroscience: Integrating Biological and Psychological Explanations of Social Behavior*. (pp. 56-83). New York, NY, US: The Guilford Press.

Kudielka, B. M., Hellhammer, D. H., & Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology*, *34*(1), 2-18. https://doi.org/10.1016/j.psyneuen.2008.10.004

Kudielka, B. M., & Kirschbaum, C. (2001). Stress and health research. In N. J. Smelser & P. B. Baltes (Eds.), *International Encyclopedia of the Social & Behavioral Sciences* (pp. 15170-15175). Oxford: Pergamon. https://doi.org/10.1016/B0-08-043076-7/03818-3

Kuo, T., McQueen, A., Chen, T.-C., & Wang, J.-C. (2015). Regulation of glucose homeostasis by glucocorticoids. In J.-C. Wang & C. Harris (Eds.), *Glucocorticoid Signaling: From Molecules to Mice to Man* (pp. 99-126). New York: Springer. https://doi.org/10.1007/978-1-4939-2895-8_5

Kvetnansky, R., Sabban, E. L., & Palkovits, M. (2009). Catecholaminergic systems in stress: Structural and molecular genetic approaches. *Physiological Reviews*, *89*(2), 535-606. https://doi.org/10.1152/physrev.00042.2006

Labuschagne, I., Grace, C., Rendell, P., Terrett, G., & Heinrichs, M. (2019). An introductory guide to conducting the Trier Social Stress Test. *Neuroscience & Biobehavioral Reviews*, *107*, 686-695. https://doi.org/10.1016/j.neubiorev.2019.09.032

Langelaan, S., Bakker, A. B., Schaufeli, W., B., van Rhenen, W., & van Doornen, L. J. P. (2007). Is burnout related to allostatic load? *International Journal of Behavioral Medicine*, *14*(4), 213-221. https://doi.org/10.1007/BF03002995

Lazarus, R. S. (1993). From psychological stress to the emotions: A history of changing outlooks. *Annual Review of Psychology*, *44*(1), 1-22. https://doi.org/10.1146/annurev.ps.44.020193.000245

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. New York: Springer.

Lehr, D., Koch, S., & Hillert, A. (2010). Where is (im)balance? Necessity and construction of evaluated cut-off points for effort-reward imbalance and overcommitment. *Journal of Occupational and Organizational Psychology*, *83*, 251-261. https://doi.org/10.1348/096317909X406772

Leiter, M. P., & Durup, J. (1994). The discriminant validity of burnout and depression: A confirmatory factor analytic study. *Anxiety, Stress, & Coping*, *7*(4), 357-373. https://doi.org/10.1080/10615809408249357

Leiter, M. P., Hakanen, J. J., Ahola, K., Toppinen-Tanner, S., Koskinen, A., & Väänänen, A. (2013). Organizational predictors and health consequences of changes in burnout: A 12-year cohort study. *Journal of Organizational Behavior*, *34*(7), 959-973. https://doi.org/10.1002/job.1830

Leiter, M. P., & Maslach, C. (2003). Areas of worklife: A structured approach to organizational predictors of job burnout. In P. L. Perrewe & D. C. Ganster (Eds.), *Emotional and Physiological Processes and Positive Intervention Strategies* (pp. 91-134). Leeds: Emerald Group Publishing Limited. https://doi.org/10.1016/S1479-3555(03)03003-8

Leiter, M. P., & Maslach, C. (2016). Latent burnout profiles: A new approach to understanding the burnout experience. *Burnout Research*, *3*(4), 89-100. https://doi.org/10.1016/j.burn.2016.09.001

Lennartsson, A.-K., Sjörs, A., Währborg, P., Ljung, T., & Jonsdottir, I. H. (2015). Burnout and hypocortisolism – A matter of severity? A study on ACTH and cortisol

responses to acute psychosocial stress. *Frontiers in Psychiatry*, *6*. https://doi.org/10.3389/fpsyt.2015.00008

Lindsäter, E., Svärdman, F., Wallert, J., Ivanova, E., Söderholm, A., Fondberg, R., Nilsonne, G., Cervenka, S., Lekander, M., & Rück, C. (2022). Exhaustion disorder: Scoping review of research on a recently introduced stress-related diagnosis. *British Journal of Psychiatry Open*, *8*(5), e159. https://doi.org/10.1192/bjo.2022.559

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209-237. https://doi.org/10.1016/j.bandc.2007.02.007

Madsen, I. E. H., Lange, T., Borritz, M., & Rugulies, R. (2015). Burnout as a risk factor for antidepressant treatment – A repeated measures time-to-event analysis of 2936 Danish human service workers. *Journal of Psychiatric Research*, *65*, 47-52. https://doi.org/10.1016/j.jpsychires.2015.04.004

Marcil, M.-J., Cyr, S., Marin, M.-F., Rosa, C., Tardif, J.-C., Guay, S., Guertin, M.-C., Genest, C., Forest, J., Lavoie, P., Labrosse, M., Vadeboncoeur, A., Selcer, S., Ducharme, S., & Brouillette, J. (2022). Hair cortisol change at COVID-19 pandemic onset predicts burnout among health personnel. *Psychoneuroendocrinology*, *138*, 105645. https://doi.org/10.1016/j.psyneuen.2021.105645

Maslach, C., Jackson, S. E., & Leiter, M. P. (1997). Maslach Burnout Inventory: Third edition. In C. P. Zalaquett & R. J. Wood (Eds.), *Evaluating Stress: A Book of Resources* (pp. 191-218). Lanham,: Scarecrow Education.

Maslach, C., & Leiter, M. P. (2016a). Burnout. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior.* (pp. 351-357). San Diego: Academic Press.

Maslach, C., & Leiter, M. P. (2016b). Understanding the burnout experience: Recent research and its implications for psychiatry. *World Psychiatry*, *15*(2), 103-111. https://doi.org/10.1002/wps.20311

Maslach, C., Schaufeli, W. B., & Leiter, M. P. (2001). Job burnout. *Annual Review of Psychology*, *52*, 397-422. https://doi.org/10.1146/annurev.psych.52.1.397

Mason, J. W. (1968a). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosomatic Medicine*, *30*(5), 576-607. https://journals.lww.com/psychosomaticmedicine/fulltext/1968/09000/a_review_of_psychoendocrine_research_on_the.20.aspx

Mason, J. W. (1968b). A review of psychoendocrine research on the sympathetic adrenal medullary system. *Psychosomatic Medicine*, *30*(5, Pt. 2), 631-653. https://doi.org/10.1097/00006842-196809000-00022

McCarty, R. (2016). The fight-or-flight response: A cornerstone of stress research. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 33-37). San Diego: Academic Press. https://doi.org/10.1016/B978-0-12-800951-2.00004-2

McEwen, B. S. (1998a). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, *338*(3), 171-179. https://doi.org/10.1056/NEJM199801153380307

McEwen, B. S. (1998b). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33-44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S. (2000a). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108-124. https://doi.org/10.1016/S0893-133X(99)00129-3

McEwen, B. S. (2000b). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research Interactive*, *886*(1), 172-189. https://doi.org/10.1016/S0006-8993(00)02950-4

McEwen, B. S. (2003). Interacting mediators of allostasis and allostatic load: Towards an understanding of resilience in aging. *Metabolism - Clinical and Experimental*, *52*, 10-16. https://doi.org/10.1016/S0026-0495(03)00295-6

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*, *583*(2), 174-185. https://doi.org/10.1016/j.ejphar.2007.11.071

McEwen, B. S. (2016). Central role of the brain in stress and adaptation: Allostasis, biological embedding, and cumulative change. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior.* (pp. 39-55). San Diego: Academic Press.

McEwen, B. S. (2018). Redefining neuroendocrinology: Epigenetics of brain-body communication over the life course. *Frontiers in Neuroendocrinology*, *49*, 8-30. https://doi.org/10.1016/j.yfrne.2017.11.001

McEwen, B. S. (2019). What is the confusion with cortisol? *Chronic Stress*, *3*. https://doi.org/10.1177/2470547019833647

McEwen, B. S., & McEwen, C. A. (2015). Social, psychological, and physiological reactions to stress. In R. A. Scott & S. M. Kosslyn (Eds.), *Emerging Trends in the Social and Behavioral Sciences* (pp. 1-15). John Wiley and Sons. https://doi.org/10.1002/9781118900772.etrds0311

McEwen, B. S., & Seeman, T. E. (1999). Protective and damaging effects of mediators of stress: Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896*(1), 30-47. https://doi.org/10.1111/j.1749-6632.1999.tb08103.x

McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine*, *153*(18), 2093-2101. https://doi.org/10.1001/archinte.1993.00410180039004

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*(1), 2-15. https://doi.org/10.1016/S0018-506X(02)00024-7

Melamed, S. (2009). Burnout and risk of regional musculoskeletal pain—A prospective study of apparently healthy employed adults. *Stress and Health: Journal of the International Society for the Investigation of Stress*, *25*(4), 313-321. https://doi.org/10.1002/smi.1265

Melamed, S., Shirom, A., Toker, S., Berliner, S., & Shapira, I. (2006). Burnout and risk of cardiovascular disease: evidence, possible causal paths, and promising research directions. *Psychological Bulletin*, *132*(3), 327-353. https://doi.org/10.1037/0033-2909.132.3.327

Melamed, S., Shirom, A., Toker, S., & Shapira, I. (2006). Burnout and risk of type 2 diabetes: A prospective study of apparently healthy employed persons. *Psychosomatic Medicine*, *68*(6), 863-869. https://doi.org/10.1097/01.psy.0000242860.24009.f0

Menke, A., Arloth, J., Gerber, M., Rex-Haffner, M., Uhr, M., Holsboer, F., Binder, E. B., Holsboer-Trachsler, E., & Beck, J. (2014). Dexamethasone stimulated gene expression in peripheral blood indicates glucocorticoid-receptor hypersensitivity in job-related exhaustion. *Psychoneuroendocrinology*, *44*, 35-46. https://doi.org/10.1016/j.psyneuen.2014.02.013

Metzler, Y. A., & Bellingrath, S. (2017). Psychosocial hazard analysis in a heterogeneous workforce: Determinants of work stress in blue- and white-collar workers of the European steel industry. *Frontiers in Public Health*, *5*. https://doi.org/10.3389/fpubh.2017.00210

Mikolajczak, M., & Roskam, I. (2018). A theoretical and clinical framework for parental burnout: The balance between risks and resources. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.00886

Mikolajczak, M., & Roskam, I. (2020). Parental burnout: Moving the focus from children to parents. *New Directions for Child and Adolescent Development*, 7-13. https://doi.org/10.1002/cad.20376

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*(1), 25-45. https://doi.org/10.1037/0033-2909.133.1.25

Miller, R., Plessow, F., Kirschbaum, C., & Stalder, T. (2013). Classification criteria for distinguishing cortisol responders from nonresponders to psychosocial stress: Evaluation of salivary cortisol pulse detection in panel designs. *Psychosomatic Medicine*, *75*(9), 832-840. https://doi.org/10.1097/PSY.0000000000000002

Ming, Q., Zhong, X., Zhang, X., Pu, W., Dong, D., Jiang, Y., Gao, Y., Wang, X., Detre, J. A., Yao, S., & Rao, H. (2017). State-independent and dependent neural responses to psychosocial stress in current and remitted depression. *American Journal of Psychiatry*, *174*(10), 971-979. https://doi.org/10.1176/appi.ajp.2017.16080974

Montero-Marín, J., & García-Campayo, J. (2010). A newer and broader definition of burnout: Validation of the "Burnout Clinical Subtype Questionnaire (BCSQ-36)". *BMC Public Health*, *10*(1), 302. https://doi.org/10.1186/1471-2458-10-302

Montero-Marín, J., Skapinakis, P., Araya, R., Gili, M., & García-Campayo, J. (2011). Towards a brief definition of burnout syndrome by subtypes: Development of the "Burnout Clinical Subtypes Questionnaire" (BCSQ-12). *Health and Quality of Life Outcomes*, *9*(1), 74. https://doi.org/10.1186/1477-7525-9-74

Nadon, L., De Beer, L. T., & Morin, A. J. S. (2022). Should burnout be conceptualized as a mental disorder? *Behavioral Sciences*, *12*(3), 82. https://doi.org/10.3390/bs12030082

Nater, U. M., Skoluda, N., & Strahler, J. (2013). Biomarkers of stress in behavioural medicine. *Current Opinion in Psychiatry*, *26*(5), 440-445. https://doi.org/10.1097/YCO.0b013e328363b4ed

Navarro-Oliveira, C. M., Vassilieff, V. S., & Cordellini, S. (2000). The sympathetic adrenomedullary system, but not the hypothalamic–pituitary–adrenal axis, participates in aorta adaptive response to stress: nitric oxide involvement. *Autonomic Neuroscience*, *83*(3), 140-147. https://doi.org/10.1016/S1566-0702(00)00157-0

Noack, H., Nolte, L., Nieratschker, V., Habel, U., & Derntl, B. (2019). Imaging stress: An overview of stress induction methods in the MR scanner. *Journal of Neural Transmission*, *126*(9), 1187-1202. https://doi.org/10.1007/s00702-018-01965-y

Nostramo, R., & Sabban, E. L. (2015). Stress and sympathoadrenomedullary mechanisms. In J. Russel & M. Shipston (Eds.), *Neuroendocrinology of Stress* (pp. 95-120). Chicester: John Wiley & Sons. https://doi.org/10.1002/9781118921692.ch5

Nübling, M., Stößel, U., Hasselhorn, H. M., Michaelis, M., & Hofmann, F. (2006). Measuring psychological stress and strain at work - evaluation of the COPSOQ Questionnaire in Germany. *GMS Psycho-Social-Medicine*, *3*, Doc05. http://www.ncbi.nlm.nih.gov/pubmed/19742072

Nuebling, M., Hegewald, J., Starke, K. R., Lincke, H.-J., Jankowiak, S., Liebers, F., Latza, U., Letzel, S., Riechmann-Wolf, M., Gianicolo, E., Beutel, M., Pfeiffer, N.,

Lackner, K., Münzel, T., Wild, P. S., & Seidler, A. (2022). The Gutenberg health study: A five-year prospective analysis of psychosocial working conditions using COPSOQ (Copenhagen psychosocial questionnaire) and ERI (effort-reward imbalance). *BMC Public Health*, *22*(1), 24. https://doi.org/10.1186/s12889-021-12240-3

Orosz, A., Federspiel, A., Haisch, S., Seeher, C., Dierks, T., & Cattapan, K. (2017). A biological perspective on differences and similarities between burnout and depression. *Neuroscience & Biobehavioral Reviews*, *73*, 112-122. https://doi.org/10.1016/j.neubiorev.2016.12.005

Ossewaarde, L., Hermans, E. J., van Wingen, G. A., Kooijman, S. C., Johansson, I.-M., Bäckström, T., & Fernández, G. (2010). Neural mechanisms underlying changes in stress-sensitivity across the menstrual cycle. *Psychoneuroendocrinology*, *35*(1), 47-55. https://doi.org/10.1016/j.psyneuen.2009.08.011

Pacák, K., Palkovits, M., Yadid, G., Kvetnansky, R., Kopin, I. J., & Goldstein, D. S. (1998). Heterogeneous neurochemical responses to different stressors: A test of Selye's doctrine of nonspecificity. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *275*(4), 1247-1255. https://doi.org/10.1152/ajpregu.1998.275.4.R1247

Pacák, K., & Palkovits, M. s. (2001). Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. *Endocrine Reviews*, *22*(4), 502-548. https://doi.org/10.1210/edrv.22.4.0436

Parker, G., & Tavella, G. (2021). Distinguishing burnout from clinical depression: A theoretical differentiation template. *Journal of Affective Disorders*, *281*, 168-173. https://doi.org/10.1016/j.jad.2020.12.022

Parker, H. W., Abreu, A. M., Sullivan, M. C., & Vadiveloo, M. K. (2022). Allostatic load and mortality: A systematic review and meta-analysis. *American Journal of Preventive Medicine*, *63*(1), 131-140. https://doi.org/10.1016/j.amepre.2022.02.003

Paula, A. J., Condeles, P. C., Moreno, A. L., Ferreira, M. B. G., Fonseca, L. M. M., & Ruiz, M. T. (2021). Parental burnout: A scoping review. *Revista Brasileira de Enfermagem*, *75*(3), e20210203. https://doi.org/10.1590/0034-7167-2021-0203

Penz, M., Siegrist, J., Wekenborg, M. K., Rothe, N., Walther, A., & Kirschbaum, C. (2019). Effort-reward imbalance at work is associated with hair cortisol concentrations: Prospective evidence from the Dresden Burnout Study. *Psychoneuroendocrinology*, *109*, 104399. https://doi.org/10.1016/j.psyneuen.2019.104399

Penz, M., Stalder, T., Miller, R., Ludwig, V. M., Kanthak, M. K., & Kirschbaum, C. (2018). Hair cortisol as a biological marker for burnout symptomatology. *Psychoneuroendocrinology*, *87*, 218-221. https://doi.org/10.1016/j.psyneuen.2017.07.485

Phillips, R., Kraeuter, A.-K., McDermott, B., Lupien, S., & Sarnyai, Z. (2021). Human nail cortisol as a retrospective biomarker of chronic stress: A systematic review. *Psychoneuroendocrinology*, *123*, 104903. https://doi.org/10.1016/j.psyneuen.2020.104903

Pines, A. M., Aronson, E., & Kafry, D. (1981). *Burnout: From Tedium to Personal Growth*. New York: Free Press.

Princip, M., Zuccarella-Hackl, C., Holzgang, S. A., Sivakumar, S., Kuenburg, A., Pazhenkottil, A. P., Vieito, D. G., & von Känel, R. (2024). Cortisol reactivity to acute psychosocial stress in physician burnout. *Journal of Psychosomatic Research*, *181*, 111759. https://doi.org/10.1016/j.jpsychores.2024.111759

Pruessner, J. C., & Ali, N. (2015). Neuroendocrine mechanisms of stress regulation in humans. In J. Russel & M. Shipston (Eds.), *Neuroendocrinology of Stress* (pp. 121-142). Chicester: John Wiley & Sons. https://doi.org/10.1002/9781118921692.ch6

Pruessner, J. C., Hellhammer, D. H., & Kirschbaum, C. (1999). Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic Medicine*, *61*(2), 197-204.

Remer, T., Maser-Gluth, C., & Wudy, A. S. (2008). Glucocorticoid measurements in health and disease - Metabolic implications and the potential of 24-h urine analyses. *Mini-Reviews in Medicinal Chemistry*, *8*(2), 153-170. http://doi.org/10.2174/138955708783498096

Revelle, W. (2021). *psych: Procedures for psychological, psychometric, and personality research* https://CRAN.R-project.org/package=psych Version = 2.1.9

Rodriguez, A., Reise, S. P., & Haviland, M. G. (2016). Evaluating bifactor models: Calculating and interpreting statistical indices. *Psychological Methods*, *21*(2), 137-150. https://doi.org/10.1037/met0000045

Rohleder, N. (2018). Burnout, hair cortisol, and timing: Hyper- or hypocortisolism? *Psychoneuroendocrinology*, *87*, 215-217. https://doi.org/10.1016/j.psyneuen.2017.10.008

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, *48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Rotenstein, L. S., Torre, M., Ramos, M. A., Rosales, R. C., Guille, C., Sen, S., & Mata, D. A. (2018). Prevalence of burnout among physicians: A systematic review. *JAMA*, *320*(11), 1131-1150. https://doi.org/10.1001/jama.2018.12777

Rothe, N., Steffen, J., Penz, M., Kirschbaum, C., & Walther, A. (2020). Examination of peripheral basal and reactive cortisol levels in major depressive disorder and the burnout syndrome: A systematic review. *Neuroscience & Biobehavioral Reviews*, *114*, 232-270. https://doi.org/10.1016/j.neubiorev.2020.02.024

Rugulies, R., Aust, B., & Madsen, I. E. H. (2017). Effort–reward imbalance at work and risk of depressive disorders. A systematic review and meta-analysis of prospective cohort studies. *Scandinavian Journal of Work, Environment & Health*, *43*(4), 294-306. https://doi.org/10.5271/sjweh.3632

Russell, E., Koren, G., Rieder, M., & Van Uum, S. (2012). Hair cortisol as a biological marker of chronic stress: Current status, future directions and unanswered questions. *Psychoneuroendocrinology*, *37*(5), 589-601. https://doi.org/10.1016/j.psyneuen.2011.09.009

Rydmark, I., Wahlberg, K., Ghatan, P. H., Modell, S., Nygren, Å., Ingvar, M., Åsberg, M., & Heilig, M. (2006). Neuroendocrine, cognitive and structural imaging characteristics of women on longterm sickleave with job stress-induced depression. *Biological Psychiatry*, *60*(8), 867-873. https://doi.org/10.1016/j.biopsych.2006.04.029

Saboonchi, F., Perski, A., & Grossi, G. (2013). Validation of Karolinska Exhaustion Scale: Psychometric properties of a measure of exhaustion syndrome. *Scandinavian Journal of Caring Sciences*, *27*(4), 1010-1017. https://doi.org/10.1111/j.1471-6712.2012.01089.x

Salvagioni, D. A. J., Melanda, F. N., Mesas, A. E., González, A. D., Gabani, F. L., & Andrade, S. M. d. (2017). Physical, psychological and occupational consequences of job burnout: a systematic review of prospective studies. *PLOS ONE*, *12*(10), e0185781. https://doi.org/10.1371/journal.pone.0185781

Sandström, A., Peterson, J., SandstrÖM, E., Lundberg, M., Nystrom, I.-L. R., Nyberg, L., & Olsson, T. (2011). Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. *Scandinavian Journal of Psychology*, *52*(1), 71-82. https://doi.org/10.1111/j.1467-9450.2010.00844.x

Savic, I. (2015). Structural changes of the brain in relation to occupational stress. *Cerebral Cortex*, *25*(6), 1554-1564. https://doi.org/10.1093/cercor/bht348

Savic, I. (2020). MRS shows regionally increased glutamate levels among patients with exhaustion syndrome due to occupational stress. *Cerebral Cortex*, *30*(6), 3759-3770. https://doi.org/10.1093/cercor/bhz340

Savic, I., Perski, A., & Osika, W. (2018). MRI shows that exhaustion syndrome due to chronic occupational stress is associated with partially reversible cerebral changes. *Cerebral Cortex*, *28*(3), 894-906. https://doi.org/10.1093/cercor/bhw413

Schaufeli, W. B. (2017). Burnout: A short socio-cultural history. In S. Neckel, A. Schaffner, & G. Wagner (Eds.), *Burnout, Fatigue, Exhaustion: An Interdisciplinary Perspective on a Modern Affliction.* (pp. 105-127). Cham: Palgrave Macmillan. https://doi.org/10.1007/978-3-319-52887-8_5

Schaufeli, W. B., Bakker, A. B., Hoogduin, K., Schaap, C., & Kladler, A. (2001). On the clinical validity of the maslach burnout inventory and the burnout measure. *Psychology & Health*, *16*(5), 565-582. https://doi.org/10.1080/08870440108405527

Schaufeli, W. B., Desart, S., & De Witte, H. (2020). Burnout Assessment Tool (BAT)—Development, validity, and reliability. *International Journal of Environmental Research and Public Health*, *17*(24), 9495. https://doi.org/10.3390/ijerph17249495

Schaufeli, W. B., Leiter, M. P., & Maslach, C. (2009). Burnout: 35 years of research and practice. *The Career Development International*, *14*(3), 204-220. https://doi.org/10.1108/13620430910966406

Schaufeli, W. B., Leiter, M. P., Maslach, C., & Jackson, S. E. (1996). The MBI-General Survey. In C. Maslach, S. E. Jackson, & M. P. Leiter (Eds.), *Maslach Burnout Inventory Manual* (third ed.). Palo Alto: Consulting Psychologists Press.

Schlotz, W., Kumsta, R., Layes, I., Entringer, S., Jones, A., & Wüst, S. (2008). Covariance between psychological and endocrine responses to pharmacological challenge and psychosocial stress: A question of timing. *Psychosomatic Medicine*, *70*(7), 787-796. https://doi.org/10.1097/PSY.0b013e3181810658

Schonfeld, I. S., & Bianchi, R. (2016). Burnout and depression: Two entities or one? *Journal of Clinical Psychology*, *72*(1), 22-37. https://doi.org/10.1002/jclp.22229

Schreuder, K. J., Roelen, C. A. M., Koopmans, P. C., & Groothoff, J. W. (2008). Job demands and health complaints in white and blue collar workers. *Work*, *31*(4), 425-432.

Schwenk, T. L., & Gold, K. J. (2018). Physician burnout—A serious symptom, but of what? *JAMA*, *320*(11), 1109-1110. https://doi.org/10.1001/jama.2018.11703

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences*, *98*(8), 4770. https://doi.org/10.1073/pnas.081072698

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation - Allostatic load and its health consequences. MacArthur studies of successful aging. *Archives of Internal Medicine*, *157*(19), 2259-2268. https://doi.org/10.1001/archinte.1997.00440400111013

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130*(4), 601-630. https://doi.org/10.1037/0033-2909.130.4.601

Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature*, *138*, 32. https://doi.org/10.1038/138032a0

Selye, H. (1946). The general adaption syndrome and the diseases of adaption. *The Journal of Clinical Endocrinology & Metabolism*, *6*(2), 117-230. https://doi.org/10.1210/jcem-6-2-117

Selye, H. (1950). Stress and the general adaptation syndrome. *British Medical Journal*, *1*, 1383-1392. https://doi.org/10.1136/bmj.1.4667.1383.

Selye, H. (1973). The evolution of the stress concept. *American Scientist*, *61*(6), 692-699.

Selye, H. (1976). Stress without distress. In G. Serban (Ed.), *Psychopathology of Human Adaptation* (pp. 137-146). Boston: Springer. https://doi.org/10.1007/978-1-4684-2238-2_9

Shang, Y., Yang, Y., Zheng, G., Zhao, Z., Wang, Y., Yang, L., Han, L., Yao, Z., & Hu, B. (2022). Aberrant functional network topology and effective connectivity in burnout syndrome. *Clinical Neurophysiology*, *138*, 163-172. https://doi.org/10.1016/j.clinph.2022.03.014

Shirom, A. (2003). Job-related burnout: A review. In J. C. Quick & L. E. Tetrick (Eds.), *Handbook of Occupational Health Psychology*. (pp. 245-264). Washington, DC: American Psychological Association. https://doi.org/10.1037/10474-012

Shirom, A., & Melamed, S. (2006). A comparison of the construct validity of two burnout measures in two groups of professionals. *International Journal of Stress Management*, *13*(2), 176-200. https://doi.org/10.1037/1072-5245.13.2.176

Shoman, Y., Marca, S. C., Bianchi, R., Godderis, L., van der Molen, H. F., & Guseva Canu, I. (2021). Psychometric properties of burnout measures: A systematic review. *Epidemiology and Psychiatric Sciences*, *30*, e8. https://doi.org/10.1017/S2045796020001134

Shoman, Y., Ranjbar, S., Strippoli, M.-P., von Känel, R., Preisig, M., & Guseva Canu, I. (2023). Relationship between effort-reward imbalance, over-commitment and occupational burnout in the general population: A prospective cohort study. *International Journal of Public Health*, *68*. https://doi.org/10.3389/ijph.2023.1606160

Short, S. J., Stalder, T., Marceau, K., Entringer, S., Moog, N. K., Shirtcliff, E. A., Wadhwa, P. D., & Buss, C. (2016). Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. *Psychoneuroendocrinology*, *71*, 12-18. https://doi.org/10.1016/j.psyneuen.2016.05.007

Siegrist, J. (1996). Adverse health effects of high-effort/low-reward conditions. *Journal of Occupational Health Psychology*, *1*(1), 27-41. https://doi.org/10.1037//1076-8998.1.1.27

Siegrist, J. (2007). Effort–reward imbalance model. In G. Fink (Ed.), *Encyclopedia of Stress* (2 ed., pp. 893-896). New York: Academic Press. https://doi.org/10.1016/B978-012373947-6.00482-7

Siegrist, J. (2016a). Effort-reward imbalance model. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 81-86). San Diego: Academic Press. https://doi.org/10.1016/B978-0-12-800951-2.00009-1

Siegrist, J. (2016b). A theoretical model in the context of economic globalization. In J. Siegrist & M. Wahrendorf (Eds.), *Work Stress and Health in a Globalized Economy: The Model of Effort-Reward Imbalance.* (pp. 3-19). Cham: Springer. https://doi.org/10.1007/978-3-319-32937-6_1

Siegrist, J., Starke, D., Chandola, T., Godin, I., Marmot, M., Niedhammer, I., & Peter, R. (2004). The measurement of effort–reward imbalance at work: European comparisons. *Social Science & Medicine*, *58*(8), 1483-1499. https://doi.org/10.1016/S0277-9536(03)00351-4

Siegrist, J., Wege, N., Pühlhofer, F., & Wahrendorf, M. (2009). A short generic measure of work stress in the era of globalization: Effort–reward imbalance. *International*

Archives of Occupational and Environmental Health, *82*(8), 1005. https://doi.org/10.1007/s00420-008-0384-3

Sinha, R., Lacadie, C. M., Constable, R. T., & Seo, D. (2016). Dynamic neural activity during stress signals resilient coping. *Proceedings of the National Academy of Sciences*, *113*(31), 8837-8842. https://doi.org/10.1073/pnas.1600965113

Sjörs, A., Jansson, P. A., Eriksson, J. W., & Jonsdottir, I. H. (2013). Increased insulin secretion and decreased glucose concentrations, but not allostatic load, are associated with stress-related exhaustion in a clinical patient population. *Stress*, *16*(1), 24-33. https://doi.org/10.3109/10253890.2012.688082

Soares, J. J. F., Grossi, G., & Sundin, Ö. (2007). Burnout among women: Associations with demographic/socio-economic, work, life-style and health factors. *Archives of Women's Mental Health*, *10*(2), 61-71. https://doi.org/10.1007/s00737-007-0170-3

Soetaert, K. (2021). *plot3D: Plotting multi-dimensional data. R package* URL https://CRAN.R-project.org/package=plot3D Version = 1.4.

Sonnenschein, M., Mommersteeg, P. M. C., Houtveen, J. H., Sorbi, M. J., Schaufeli, W. B., & van Doornen, L. J. P. (2007). Exhaustion and endocrine functioning in clinical burnout: An in-depth study using the experience sampling method. *Biological Psychology*, *75*(2), 176-184. https://doi.org/10.1016/j.biopsycho.2007.02.001

Stalder, T., & Kirschbaum, C. (2012). Analysis of cortisol in hair – State of the art and future directions. *Brain, Behavior, and Immunity*, *26*(7), 1019-1029. https://doi.org/10.1016/j.bbi.2012.02.002

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wüst, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D. H., Miller, R., Wetherell, M. A., Lupien, S. J., & Clow, A. (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology*, *63*, 414-432. https://doi.org/10.1016/j.psyneuen.2015.10.010

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Kirschbaum, C., & Miller, R. (2017). Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. *Psychoneuroendocrinology*, *77*, 261-274. https://doi.org/10.1016/j.psyneuen.2016.12.017

Stalder, T., Tietze, A., Steudte, S., Alexander, N., Dettenborn, L., & Kirschbaum, C. (2014). Elevated hair cortisol levels in chronically stressed dementia caregivers. *Psychoneuroendocrinology*, *47*, 26-30. https://doi.org/10.1016/j.psyneuen.2014.04.021

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher & J. Reason (Eds.), *Handbook of of Life Stress, Cognition and Health* (pp. 629-650). Chichester: John Wiley & Sons.

Streit, F., Haddad, L., Paul, T., Frank, J., Schäfer, A., Nikitopoulos, J., Akdeniz, C., Lederbogen, F., Treutlein, J., Witt, S., Meyer-Lindenberg, A., Rietschel, M., Kirsch, P., & Wüst, S. (2014). A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala. *Stress*, *17*(4), 352-361. https://doi.org/10.3109/10253890.2014.921903

Swider, B. W., & Zimmerman, R. D. (2010). Born to burnout: A meta-analytic path model of personality, job burnout, and work outcomes. *Journal of Vocational Behavior*, *76*(3), 487-506. https://doi.org/10.1016/j.jvb.2010.01.003

Szabo, S., Yoshida, M., Filakovszky, J., & Juhasz, G. (2017). "Stress" is 80 years old: From Hans Selye original paper in 1936 to recent advances in GI Ulceration. *Current Pharmaceutical Design*, *23*(27), 4029-4041. http://dx.doi.org/10.2174/1381612823666170622110046

Taris, T. W., Le Blanc, P. M., Schaufeli, W. B., & Schreurs, P. J. G. (2005). Are there causal relationships between the dimensions of the Maslach Burnout Inventory? A review and two longitudinal tests. *Work & Stress*, *19*(3), 238-255. https://doi.org/10.1080/02678370500270453

Tavella, G., & Parker, G. (2020). Distinguishing burnout from depression: An exploratory qualitative study. *Psychiatry Research*, *291*, 113212. https://doi.org/10.1016/j.psychres.2020.113212

Thakore, J. H., Barnes, C., Joyce, J., Medbak, S., & Dinan, T. G. (1997). Effects of antidepressant treatment on corticotropin-induced cortisol responses in patients with melancholic depression. *Psychiatry Research*, *73*(1), 27-32. https://doi.org/10.1016/S0165-1781(97)00106-6

Toker, S., Melamed, S., Berliner, S., Zeltser, D., & Shapira, I. (2012). Burnout and risk of coronary heart disease: A prospective study of 8838 employees. *Psychosomatic Medicine*, *74*(8), 840-847. https://doi.org/10.1097/psy.0b013e31826c3174

Tops, M., Boksem, M. A. S., Wijers, A. A., van Duinen, H., Den Boer, J. A., Meijman, T. F., & Korf, J. (2007). The psychobiology of burnout: Are there two different syndromes? *Neuropsychobiology*, *55*(3-4), 143-150. https://doi.org/10.1159/000106056

Tóth-Király, I., Morin, A. J. S., & Salmela-Aro, K. (2021). Reciprocal associations between burnout and depression: An 8-year longitudinal study. *Applied Psychology*, *70*(4), 1691-1727. https://doi.org/10.1111/apps.12295

Traunmüller, C., Gaisbachgrabner, K., Lackner, H. K., & Schwerdtfeger, A. R. (2018). Burnout of the mind—Burnout of the body? *Journal of Psychophysiology*, *32*(1), 30-42. https://doi.org/10.1027/0269-8803/a000182

Traunmüller, C., Stefitz, R., Gaisbachgrabner, K., Hofmann, P., Roessler, A., & Schwerdtfeger, A. R. (2019). Psychophysiological concomitants of burnout: Evidence for different subtypes. *Journal of Psychosomatic Research*, *118*, 41-48. https://doi.org/10.1016/j.jpsychores.2019.01.009

Trull, T. J., & Ebner-Priemer, U. (2014). The role of ambulatory assessment in psychological science. *Current Directions in Psychological Science, 23*(6), 466-470. https://doi.org/10.1177/0963721414550706

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*(4), 865-871. https://doi.org/10.1016/S0022-3999(02)00429-4

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, *10*(6), 397-409. https://doi.org/10.1038/nrn2647

Ursin, H., & Eriksen, H. R. (2004). The cognitive activation theory of stress. *Psychoneuroendocrinology*, *29*(5), 567-592. https://doi.org/10.1016/S0306-4530(03)00091-X

Ursin, H., & Eriksen, H. R. (2010). Cognitive activation theory of stress (CATS). *Neuroscience & Biobehavioral Reviews*, *34*(6), 877-881. https://doi.org/10.1016/j.neubiorev.2009.03.001

Van Dam, A., Keijsers, G., Verbraak, M., Eling, P., & Becker, E. (2015). Level and appraisal of fatigue are not specific in burnout. *Clinical Psychology & Psychotherapy*, *22*(2), 133-141. https://doi.org/10.1002/cpp.1869

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, *20*(8), 519-534. https://doi.org/10.1016/j.euroneuro.2010.03.008

van Oort, J., Tendolkar, I., Hermans, E. J., Mulders, P. C., Beckmann, C. F., Schene, A. H., Fernández, G., & van Eijndhoven, P. F. (2017). How the brain connects in response to acute stress: A review at the human brain systems level. *Neuroscience and Biobehavioral Reviews*, *83*, 281-297. https://doi.org/10.1016/j.neubiorev.2017.10.015

van Vegchel, N., de Jonge, J., Bosma, H., & Schaufeli, W. B. (2005). Reviewing the effort–reward imbalance model: Drawing up the balance of 45 empirical studies. *Social Science & Medicine*, *60*(5), 1117-1131. https://doi.org/10.1016/j.socscimed.2004.06.043

Vedder, H. (2007). Physiology of the hypothalamic–pituitary–adrenocortical axis. In A. del Rey, G. P. Chrousos, & H. O. Besedovksy (Eds.), *NeuroImmune Biology* (Vol. 7, pp. 17-31). Elsevier. https://doi.org/10.1016/S1567-7443(07)00202-5

Venables, W. N., & Ripley, B. D. (2002). *Modern Applied Statistics with S* (4 ed.). New York: Springer. https://doi.org/10.1007/978-0-387-21706-2

Viljoen, M., & Claassen, N. (2017). Cynicism as subscale of burnout. *Work*, *56*, 499-503. https://doi.org/10.3233/WOR-172518

von Euler, U. S. (1946). A specific sympathomimetic ergone in adrenergic nerve fibres (sympathin) and its relations to adrenaline and nor-adrenaline. *Acta Physiologica Scandinavica*, *12*(1), 73-97. https://doi.org/10.1111/j.1748-1716.1946.tb00368.x

von Känel, R. (2008). Das Burnout-Syndrom: Eine medizinische Perspektive. *Praxis*, *97*(9), 477-487. https://doi.org/10.1024/1661-8157.97.9.477

von Känel, R. (2016). Was der Klinikarzt vom Burnout-Syndrom wissen sollte. *Klinikarzt*, *45*(1), 26–32. https://doi.org/10.1055/s-0041-111192

von Känel, R., Bellingrath, S., & Kudielka, B. M. (2008). Association between burnout and circulating levels of pro- and anti-inflammatory cytokines in schoolteachers. *Journal of Psychosomatic Research*, *65*(1), 51-59. https://doi.org/10.1016/j.jpsychores.2008.02.007

Wahrendorf, M., & Chandola, T. (2016). A life course perspective on work stress and health. In J. Siegrist & M. Wahrendorf (Eds.), *Work Stress and Health in a Globalized Economy: The Model of Effort-Reward Imbalance* (pp. 43-66). Cham: Springer. https://doi.org/10.1007/978-3-319-32937-6_3

Wallensten, J., Åsberg, M., Nygren, Å., Szulkin, R., Wallén, H., Mobarrez, F., & Nager, A. (2016). Possible biomarkers of chronic stress induced exhaustion - A longitudinal study. *PLOS ONE*, *11*(5), e0153924. https://doi.org/10.1371/journal.pone.0153924

Waller, L., Erk, S., Pozzi, E., Toenders, Y. J., Haswell, C. C., Büttner, M., Thompson, P. M., Schmaal, L., Morey, R. A., Walter, H., & Veer, I. M. (2022). ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data. *Human Brain Mapping*, *43*(9), 2727-2742. https://doi.org/10.1002/hbm.25829

Walther, A., Kirschbaum, C., Wehrli, S., Rothe, N., Penz, M., Wekenborg, M. K., & Gao, W. (2023). Depressive symptoms are negatively associated with hair N-arachidonoylethanolamine (anandamide) levels: A cross-lagged panel analysis of four annual assessment waves examining hair endocannabinoids and cortisol. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *121*, 110658. https://doi.org/10.1016/j.pnpbp.2022.110658

Wang, C., Dai, J., & Li, J. (2019). Mediating effects of hair cortisol on the mutual association of job burnout and insomnia: A retrospective exploratory study. *Journal of Psychiatric Research*, *117*, 62-67. https://doi.org/10.1016/j.jpsychires.2019.07.001

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*, 1063-1070. https://doi.org/10.1037/0022-3514.54.6.1063

Watson, S., Gallagher, P., Smith, M. S., Ferrier, I. N., & Young, A. H. (2006). The dex/CRH test—Is it better than the DST? *Psychoneuroendocrinology*, *31*(7), 889-894. https://doi.org/10.1016/j.psyneuen.2006.03.001

Wekenborg, M. K., Förster, K., Schweden, F., Weidemann, R., Bechtolsheim, F. v., Kirschbaum, C., Weitz, J., & Ditzen, B. (2024). Differences in physicians' ratings of work stressors and resources associated with digital transformation: Cross-sectional study. *Journal of Medical Internet Research*, *26*, e49581. https://doi.org/10.2196/49581

Wekenborg, M. K., von Dawans, B., Hill, L. K., Thayer, J. F., Penz, M., & Kirschbaum, C. (2019). Examining reactivity patterns in burnout and other indicators of chronic stress. *Psychoneuroendocrinology*, *106*, 195-205. https://doi.org/10.1016/j.psyneuen.2019.04.002

Wendsche, J., Ihle, A., Wegge, J., Penz, M. S., Kirschbaum, C., & Kliegel, M. (2020). Prospective associations between burnout symptomatology and hair cortisol. *International Archives of Occupational and Environmental Health*, *93*(6), 779-788. https://doi.org/10.1007/s00420-020-01528-3

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381-397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Wittchen, H.-U., Zaudig, M., & Fydrich, T. (1997). *SKID: Strukturiertes Klinisches Interview für DSM-IV. Achse I und II.* Göttingen: Hogrefe.

Wolfram, M., Bellingrath, S., Feuerhahn, N., & Kudielka, B. M. (2013). Emotional exhaustion and overcommitment to work are differentially associated with hypothalamus–pituitary–adrenal (HPA) axis responses to a low-dose ACTH1–24 (Synacthen) and dexamethasone–CRH test in healthy school teachers. *Stress*, *16*(1), 54-64. https://doi.org/10.3109/10253890.2012.683465

World Health Organization. (2011). *Waist Circumference and Waist-Hip Ratio : Report of a WHO Expert Consultation*. Geneva: World Health Organization. Retrieved from https://iris.who.int/handle/10665/44583

World Health Organization. (2019). *International Statistical Classification of Diseases and Related Health Problems (11 ed.)*. Retrieved from https://icd.who.int/browse/2024-01/mms/en.

Wyrwoll, C. S., Holmes, M. C., & Seckl, J. R. (2011). 11β-Hydroxysteroid dehydrogenases and the brain: From zero to hero, a decade of progress. *Frontiers in Neuroendocrinology*, *32*(3), 265-286. https://doi.org/10.1016/j.yfrne.2010.12.001

Zänkert, S., Bellingrath, S., Wüst, S., & Kudielka, B. M. (2019). HPA axis responses to psychological challenge linking stress and disease: What do we know on sources of intra- and interindividual variability? *Psychoneuroendocrinology*, *105*, 86-97. https://doi.org/10.1016/j.psyneuen.2018.10.027

Zänkert, S., Kudielka, B. M., & Wüst, S. (2020). Effect of sugar administration on cortisol responses to acute psychosocial stress. *Psychoneuroendocrinology*, *115*, 104607. https://doi.org/10.1016/j.psyneuen.2020.104607

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *77*, 25-36. https://doi.org/10.1016/j.psyneuen.2016.11.036

9 APPENDIX

Table 10
Biochemical analysis of blood samples

Analyte	Material	Method	Device	Intra-assay Variation (CV)	Inter-assay Variation (CV)
hsCRP	Serum	Nephelometry	Siemens Attelica Neph 630 and BN Prospec	≤ 4.6%	≤ 4.0%
TNF-α	Serum	CLIA	Siemens Immulite 1000	≤ 2.0%	≤ 1.4%
IL-6	Serum	ECLIA	Roche cobas e801	≤ 1.5%	≤ 3.2%
Fibrinogen	Citrate	Coagulometry	Siemens BCS XP	≤ 5.0%	≤ 7.6%
D-Dimer	Citrate	Coagulometry	Siemens BCS XP	≤ 1.4%	≤ 5.3%
PAI-1	Citrate	Chromogenic Assay	Siemens BCS XP	≤ 4.0%	≤ 6.0%
HbA1c	EDTA	Turbidimetry	Roche cobas c503	≤ 0.7%	≤ 0.9%
Cholesterol	Serum	Photometry	Roche cobas c503	≤ 0.5%	≤ 5.6%
DHEA-S	Serum	CLIA	Siemens Immulite 1000	≤ 7.4%	≤ 9.1%
HDL cholesterol	Serum	Photometry	Roche cobas c503	≤ 0.6%	≤ 2.4%
Ferritin	Serum	ECLIA	Roche cobas e801	≤ 1.7%	≤ 3.3%
Hemogram	EDTA	Impedance/flow cytometry	Sysmex XE-5000	Not applicable	
TSH	Serum	ECLIA	Roche cobas e801	≤ 1.4%	≤ 4.6%

Note. hsCRP = high-sensitivity c-reactive protein; TNF-α = tumor necrosis factor alpha; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; HbA1c = glycosylated hemoglobin; DHEA-S = dehydroepiandrosterone-sulfate; HDL cholesterol = high-density lipoprotein cholesterol; TSH = thyroid stimulating hormone. All CV values (except for hsCRP and PAI-1) represent worst case values determined in the in-house verification of the assay characteristics. hsCRP and PAI-1 values were taken from manufacturers' datasheets.

Table 11

English translation of the work-related self-evaluation variables

Work-related self-evaluation variables	Rating-scale
Job performance*	1 (“well below average”) to 7 (“well above average”)***
The quality of my work is/was…	
The efficiency of my work is/was…	
Overall, my work performance is/was…	
Job resiliency	1 (“well below average”) to 7 (“well above average”)***
My professional resiliency is/was…	
Job motivation	1 (“well below average”) to 7 (“well above average”)***
My work motivation is/was…	
My work dedication is/was…	
Job commitment**	1 (“never/hardly ever“), 2 (“seldom“), 3 (“sometimes“), 4 (“often“), 5 “always“)
At my work, I am/had been full of energy.	
I am/had been enthusiastic about my job.	
I am/had been immersed in my work.	
Workload	1 (“very low“) to 5 (“very high”)
The quantitative amount of my work is/was…	
The demands regarding the quality of my work are/were…	
The emotional demands of my work are/were…	

Note. *Job performance scale originates from Feuerhahn et al., (2012). **Job commitment scale originates from the Copenhagen Psychosocial Questionnaire (COPSOQ; Nübling et al., 2006). ***For response options 2-6 no explanatory text was presented. Work-related evaluation variables that referred to the time before burnout symptom onset were queried in the past tense with regard to the reference time point (=burnout symptom onset; e.g., “The quality of my work was…”). The respective item for the work-related peer-evaluation reads “The quality of the person’s work is/was…”.

Table 12

Paired t-tests contrasting the work-related ratings of the self-evaluation (burnout group) and the peer-evaluation of private peers (n = 53)

	Burnout group	Private-peers
Job performance		
Present (*SD*)	5.10 (1.08)	5.75 (0.97)***
Before (*SD*)	5.86 (0.71)	6.09 (0.80)
Job resiliency		
Present (*SD*)	4.38 (1.76)	4.60 (1.68)
Before (*SD*)	6.08 (0.78)	5.81 (1.19)
Job motivation		
Present (*SD*)	4.26 (1.34)	5.02 (1.39)***
Before (*SD*)	6.10 (0.74)	6.03 (0.88)
Job commitment		
Present (*SD*)	2.97 (0.80)	3.38 (0.97)**
Before (*SD*)	4.08 (0.53)	4.05 (0.64)
Workload		
Present (*SD*)	4.06 (0.66)	4.35 (0.53)**
Before (*SD*)	4.05 (0.64)	4.33 (0.59)*

Note. ***$p \leq .001$; **$p \leq .01$; *$p \leq .05$.

Table 13

Paired t-tests contrasting the work-related ratings of the self-evaluation (burnout group) and the peer-evaluation of work-peers (n = 40)

	Burnout group	Work-peers
Job performance		
Present (*SD*)	5.00 (1.19)	5.55 (1.02)*
Before (*SD*)	5.86 (0.71)	6.09 (0.80)
Job resiliency		
Present (*SD*)	4.43 (1.72)	4.80 (1.42)
Before (*SD*)	6.08 (0.74)	5.79 (1.24)
Job motivation		
Present (*SD*)	4.35 (1.28)	5.15 (1.57)**
Before (*SD*)	6.08 (0.69)	6.10 (0.99)
Job commitment		
Present (*SD*)	2.95 (0.81)	3.40 (0.98)**
Before (*SD*)	4.02 (0.57)	4.03 (0.71)
Workload		
Present (*SD*)	4.20 (0.52)	4.23 (0.69)
Before (*SD*)	4.07 (0.61)	4.12 (0.56)

Note. ***$p \leq .001$; **$p \leq .01$; *$p \leq .05$.

Table 14

Intercorrelations between $MBI_{weighted}$, EE, DP, LA, ER-ratio, OC, HADS-D, HADS-A, WPC Scale, Neuroticism Scale, JSS, and work-related self-evaluation (job performance, job resiliency, job motivation, job commitment, workload)

	$MBI_{weighted}$	EE	DP	LA	ER-ratio	OC	HADS-D	HADS-A	WPC Scale	Neuroticism Scale	JSS	Job performance	Job resiliency	Job motivation	Job commitment
EE	.91***														
DP	.88***	.70***													
LA	.59***	.27**	.39***												
ER-ratio	.79***	.80***	.67***	.32***											
OC	.66***	.73***	.51***	.20*	.69***										
HADS-D	.79***	.77***	.64***	.39***	.66***	.55***									
HADS-A	.70***	.75***	.52***	.30***	.67***	.68***	.76***								
WPC Scale	.70***	.78***	.56***	.16	.73***	.73***	.66***	.72***							
Neuroticism	.67***	.70***	.55***	.29***	.65***	.62***	.62***	.72***	.54***						
JSS	.54***	.57***	.42***	.19*	.53***	.51***	.55***	.55***	.50***	.52***					
Job performance	-.35***	-.23**	-.30***	-.41***	-.20*	-.13	-.30***	-.22*	-.13	-.27**	-.11				
Job resiliency	-.44***	-.38**	-.38***	-.29***	-.37***	-.24**	-.42***	-.38***	-.23*	-.39***	-.18*	.57***			
Job motivation	-.61***	-.50***	-.59***	-.42***	-.48***	-.21*	-.49***	-.33***	-.30***	-.38***	-.24**	.53***	.62***		
Job commitment	-.75***	-.61***	-.74***	-.48***	-.55***	-.34***	-.63***	-.40***	-.47***	-.45***	-.33***	.43***	.48***	.70***	
Workload	.08	.23*	-.02	-.19*	.20*	.39***	.07	.24**	.28**	.19*	.16	.09	.09	.22*	.21*

Note. *$p \leq .05$ **$p \leq .01$ ***$p \leq .001$. $MBI_{weighted}$ = weighted Maslach Burnout Inventory-General Survey score; EE = Emotional Exhaustion, DP = Depersonalization; LA = Lack of Personal Accomplishment, ER-ratio = Effort-Reward ratio; OC = Overcommitment; HADS-D = Hospital Anxiety and Depression Scale – Depression Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety Scale; WPC Scale = Work-Privacy-Conflicts Scale; JSS = Jenkins Sleep Scale.

Table 15

Partial correlations between log-transformed single AL-parameters, $MBI_{weighted}$, and ER-ratio controlling for age

	$MBI_{weighted}$	ER-ratio
hsCRP	.03	.04
TNF-α	.08	.07
IL-6	.05	.05
Fibrinogen	-.06	-.01
D-dimer	.15	.10
PAI-1	.17	.18*
HbA1c	.06	.12
HDL	-.13	-.08
TC/HDL	.09	.07
DHEA-S	-.06	-.04
SBP	.11	.10
DBP	.09	.05
WHR	.05	.04
Body fat percentage	.10	.11

Note. *$p \leq .05$. MBIweighted = weighted Maslach Burnout Inventory-General Survey score; ER-ratio = Effort-Reward ratio; hsCRP = high-sensitivity c-reactive protein; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; HbA1c = glycosylated hemoglobin; TC/HDL = total cholesterol to high-density lipoprotein cholesterol ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist-hip ratio; DHEA-S = dehydroepiandrosterone-sulfate; HDL = high-density lipoprotein cholesterol.

Explanation Table 16: In order to rule out that the group difference in the AL-index is driven by one single AL-parameter, we exploratively calculated alternative AL-indices, omitting one parameter at any one time. Therefore, each alternative AL-index was calculated based on 13 parameters instead of 14 parameters (original AL-index).

Table 16

Results of unpaired t-tests contrasting the burnout and the healthy comparison group regarding alternative AL-indices with one AL-parameter being omitted at any time

	BO group	HC group
AL-index without hsCRP (*SD*)	3.96 (2.28)	2.85 (2.03)**
AL-index without TNF-α (*SD*)	3.84 (2.27)	2.85 (2.12)*
AL-index without IL-6 (*SD*)	3.96 (2.32)	2.91 (2.04)**
AL-index without fibrinogen (*SD*)	3.82 (2.19)	2.85 (2.02)*
AL-index without d-dimer (*SD*)	3.71 (2.25)	2.86 (2.08)*
AL-index without PAI-1 (*SD*)	3.71 (2.20)	2.91 (2.23)*
AL-index without HbA1c (*SD*)	3.82 (2.24)	2.85 (2.16)*
AL-index without HDL (*SD*)	3.79 (2.22)	2.85 (2.09)*
AL-index without TC/HDL (SD)	3.82 (2.22)	2.83 (2.00)*
AL-index without DHEA-S (SD)	3.88 (2.34)	2.86 (2.14)*
AL-index without SBP (SD)	3.71 (2.19)	2.85 (2.17)*
AL-index without DBP (SD)	3.84 (2.24)	2.85 (2.18)*
AL-index without WHR (SD)	3.75 (2.18)	2.85 (2.03)*
AL-index without Body fat percentage *(SD)*	3.78 (2.24)	2.86 (2.10)*

Note. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.; hsCRP = high-sensitivity c-reactive protein; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; HbA1c = glycosylated hemoglobin; TC/HDL = total cholesterol to high-density lipoprotein cholesterol ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist-hip ratio; DHEA-S = dehydroepiandrosterone-sulfate; HDL = high-density lipoprotein cholesterol.

Extended study sample description contrasting the burnout and the healthy control group regarding additional private stressors.

- Children living in the household (yes/no): 46.4% of the BO group members and 36.9% of the HC group members stated that children live in their household; $\chi 2(1, N = 121) = 1.12, p = .29$.
- Number of children living in the household: BO group $M = 1.54$ ($SD = 0.50$); HC group $M = 1.63$ ($SD = 0.49$); $t\ (119) = -1.06, p = .29$).
- Childcare: "Who takes care of children living in the household?" ($N = 50$):

	Me alone	Predominantly me	Me together with another person	Predominantly another person	Children no longer live at home
BO group % $n = 26$	3.8%	19.2%	73.2%	3.8%	0%
HC group % $n = 24$	20.8%	12.5%	54.2%	8.3%	4.2%

Note. ($\chi 2(4, N = 50) = 5.55, p = .24$).

- Any additional private stressors (e.g., care of family members): 23.2% of the BO group members and 10.8% of the HC group members stated that they have significant additional private stressors; $\chi 2(1, N = 121) = 3.38, p = .07$. Excluding the participants with any additional private stressors ($n = 20$) did not change our main finding (higher AL-index in the BO compared to the HC group); $t\ (99) = 2.00, p = .049$).

Table 17

Correlations between AL-index and single AL-parameters

	AL-index
hsCRP	.40***
TNF-α	.19*
IL-6	.21*
Fibrinogen	.45*
D-dimer	.27**
PAI-1	.36***
HbA1c	.45***
TC/HDL	.51***
SBP	.43***
DBP	.45***
WHR	.50***
Body fat percentage	.40***
DHEA-S	-.23*
HDL	-39***

Note. ***$p \leq .001$ **$p \leq .01$; *$p \leq .05$. AL-index = allostatic load-index; CRP = high-sensitivity c-reactive protein; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; HbA1c = glycosylated hemoglobin; TC/HDL = total cholesterol to high-density lipoprotein cholesterol ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist-hip ratio; DHEA-S = dehydroepiandrosterone-sulfate; HDL = high-density lipoprotein cholesterol.

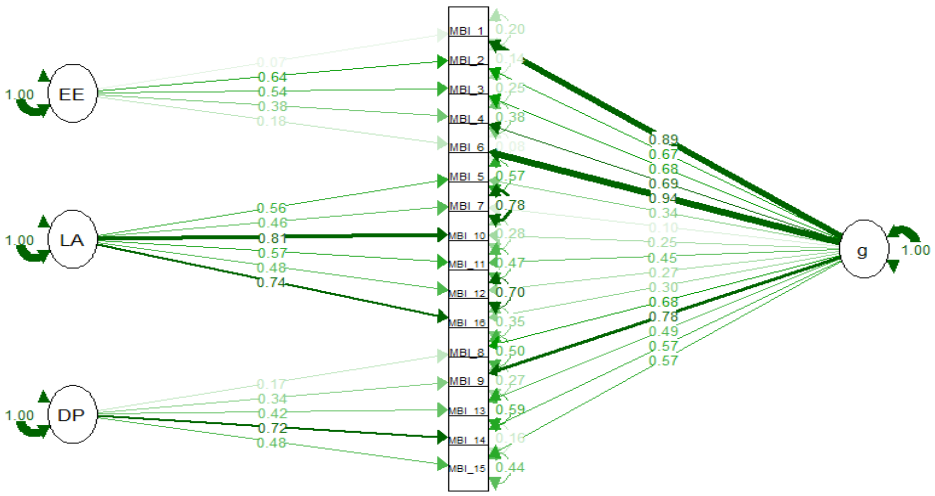
Bifactor analysis of the Maslach Burnout Inventory-General Survey

Due to the given relatively small sample size for a psychometric analysis, we analyzed the model fit of the MBI-GS with a bifactor model using the lavaan package (Rosseel, 2012) with the robust maximum likelihood estimator with mean and variance adjusted test statistic (estimator = "MLMVS"). We modeled one general factor and three special factors based on the theoretic model, all tau-congeneric and without additional intercorrelations. The fit parameters indicate a heterogeneous result with the adjusted $\chi 2$ (df = 25.58) = 40.03 being small but statistically significant (p = .034). While the CFI = .78 was rather small, the TLI = .93 was acceptably high. Although the model did not have to be rejected based on the RMSEA = .068 [.048;.087], this was not a strong argument for the model either. Especially the MBI-subscale lack of personal accomplishment (LA) seems to be less related to the general factor (see Figure 14).

To further estimate the reliability of the scales and the adequacy of the model, we used the "guide give" by Rodriguez et al. (2016) and used the "omegaFromSem function" from the psych package (Revelle, 2021). We found ω_{total} to be acceptably high for each scale ($\omega_{tot.g}$=.94, $\omega_{tot.EE}$=.94, $\omega_{tot.LA}$=.82, $\omega_{tot.DP}$=.88), but noticeable reduced when taken the bifactor structure into account (ω_h=.72, $\omega_{HS.EE}$=.78, $\omega_{HS.LA}$=.15, $\omega_{HS.DP}$=.60). The explained common variance (ECV) of the general factor was .57, which means that "only" a bit more than half of the common variance is explained by the general factor. The factor determinacy (.97, .85, .92, .88), which should be greater .90, showed, that the factor score of the general factor and the LA factor could be applied. The Construct Reliability H (.95, .57, .82, .64), which should be greater than .70, gives an argument for applying a weighted score for g and LA, too. Therefore, we estimated the factor scores (= composite scores) based on the bifactor model and compared them with the summed scores (see Figure 15). There are high correlations between the composite general factor scores and their summed or weighted-summed counterparts. This is also true for the LA factor. Finally, controlling for a general factor reduced the common variance between the summed and the composite scores of emotional exhaustion (EE) and depersonalization (DP), which means that these aspects would be represented by the general factor quite well.

Figure 14

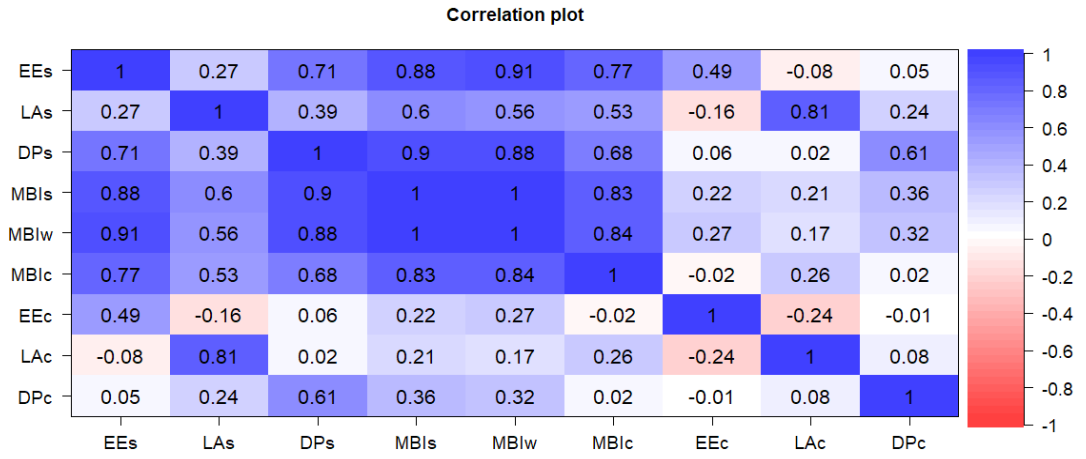
Bifactor analysis of the Maslach Burnout Inventory-General Survey



Note. EE = emotional exhaustion; LA = lack of personal accomplishment; DP = depersonalization; MBI = Maslach Burnout Inventory.

Figure 15

Correlation plot for sum and composite scores of the Maslach Burnout Inventory-General Survey



Note. EE_s = emotional exhaustion sum score; LA_s = lack of personal accomplishment sum score; DP_s = depersonalization sum score; MBI_s = Maslach Burnout Inventory sum score; MBI_w = weighted Maslach Burnout Inventory-score; MBI_c = Maslach Burnout Inventory composite score; EE_c = emotional exhaustion composite score; LA_c = lack of personal accomplishment composite score; DP_c = Depersonalization composite score.

Discriminant analysis

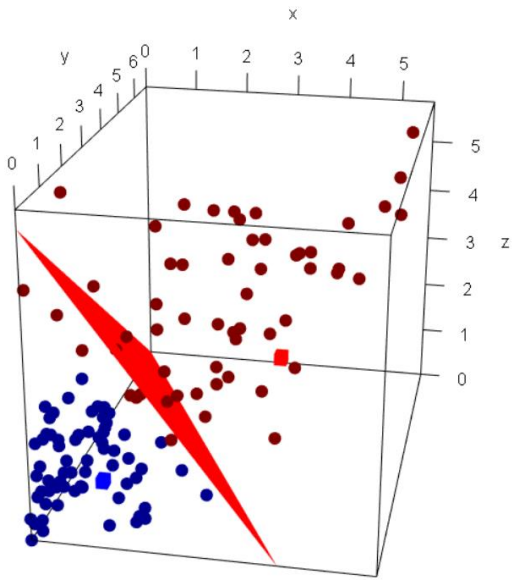
To check if the criterion of Kalimo et al. (2003) (burnout risk: weighted MBI-score ≥ 1.5; no burnout risk: weighted MBI-score < 1.5) can be applied as an unidimensional criterion, we first plotted the three subscale scores of each subject colored by the category (burnout risk/no burnout risk) with the plot3D package (Soetaert, 2021) (see Figure 14). Based on the three subscales, we aimed at replicating the classification (burnout risk/no burnout risk) by estimating a discriminant analysis using the lda function of the MASS package (Venables & Ripley, 2002). The discriminating function (b_{EE}=0.796, b_{LA}=0.174, b_{DP}=0.396) with the two group centroids no risk = (0.883,1.01,0.585) and risk = (3.714, 1.717, 2.789) resulted in an efficiency of 94%. We plotted the perpendicular discriminant plane between the two centroids to visualize the quite similar discriminant property (see Table 18 and Figure 16).

Table 18
Results of the discriminant analysis

	DA predict "no risk"	DA predict "risk"
No risk (weighted MBI-score < 1.5)	65	0
Risk (weighted MBI-score ≥ 1.5)	7	49

Note. DA = discriminant analysis; MBI = Maslach Burnout Inventory.

Figure 16
Visualization of the discriminant property of the weighted Maslach Burnout Inventory-score



Note. x = emotional exhaustion; y = lack of personal accomplishment; z = depersonalization; red dots = risk; blue dots = no risk.

Table 19

Assessment regarding health- and/or job-related changes between t1 and t2

Open response question
1) Have there been any relevant occupational changes since the first appointment? If yes, which ones?
2) Have there been any other private-related stressors (e.g., care of relatives) since the first appointment? If yes, which ones?
3) Have you suffered from any physical illnesses since the first appointment? If yes, which ones?
4) Have you suffered from any mental illnesses or have you received psychological treatment since the first appointment? If yes, which ones?
5) Have you used any medication since the first appointment? If yes, which ones?
6) Are you or have you been in a phase with extraordinary life events (e.g., death of a relative or a close friend)? If yes, which one?

Table 20

Dropout analysis contrasting the dropped-out participants and the final study sample (t2)

	Dropouts (n = 14)	Study sample t2 (n = 100)
Chi-squared tests		
Group (%)	4 BO group (29%)	51 BO group (51%)
Sex (%)	8 females (57%)	55 females (55%)
Unpaired *t*-tests		
Age (*SD*)	38.79 (9.41)	41.59 (10.69)
Working hours/week (*SD*)	41.48 (9.37)	42.59 (11.86)
Body-mass-index$_{t1}$ (*SD*)	30.90 (6.57)	25.83 (3.88)*
HCC$_{t1}$	0.74 (0.28)	0.67 (0.26)
MBI-weighted$_{t1}$ (*SD*)	1.58 (1.49)	1.82 (1.16)

Note. *$p \leq .05$. HCC = log-transformed hair cortisol concentrations (pg/mg); MBI-weighted = weighted Maslach Burnout Inventory-General Survey score.

Table 21

Results of the multiple regression analysis examining the cross-sectional association between MBI-weighted$_{t1}$ and HCC$_{t1}$

R^2 = .09; F (9, 113) = 1.192; p = .308	
	ß-values
MBI-weighted$_{t1}$	.07
Sex (female = 0; male = 1)	-.09
Age	.01
Hormonal contraception (no = 0; yes = 1)	-.08
Body-mass-index$_{t1}$	.23*
Number of hair washes/week$_{t1}$	-.10
Tint$_{t1}$ (no = 0; yes = 1)	.07
Coloration$_{t1}$ (no = 0; yes = 1)	-.11
Permanent wave$_{t1}$ (no = 0; yes = 1)	-.11

Note. * $p \leq .05$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 22

Results of the multiple regression analysis examining the cross-sectional association between MBI-weighted$_{t1}$ and HCC$_{t1}$ within the burnout group

R^2 = .20; F (9, 54) = 1.265; p = .282	
	ß-values
MBI-weighted$_{t1}$	.36*
Sex (female = 0; male = 1)	-.14
Age	.14
Hormonal contraception (no = 0; yes = 1)	-.06
Body-mass-index$_{t1}$	.16
Number of hair washes/week$_{t1}$	-.01
Tint$_{t1}$ (no = 0; yes = 1)	.04
Coloration$_{t1}$ (no = 0; yes = 1)	-.11
Permanent wave$_{t1}$ (no = 0; yes = 1)	-.26

Note. * $p \leq .05$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 23

Results of the multiple regression analysis examining the cross-sectional association between MBI-weighted$_{t2}$ and HCC$_{t2}$

R^2 = .10; F (9, 99) = 1.099; p = .37	
	ß-values
MBI-weighted$_{t2}$	-.05
Sex (female = 0; male = 1)	.01
Age	.04
Hormonal contraception (no = 0; yes = 1)	-.10
Body-mass-index$_{t2}$	.04
Number of hair washes/week$_{t2}$	-.28*
Tint$_{t2}$ (no = 0; yes = 1)	.07
Coloration$_{t2}$ (no = 0; yes = 1)	-.02
Permanent wave$_{t2}$ (no = 0; yes = 1)	-.19

Note. * $p \leq .05$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 24

Results of the multiple regression analysis examining the cross-sectional association between MBI-weighted$_{t2}$ and HCC$_{t2}$ within the burnout group

R^2 = .16; F (8, 50) = 0.97; p = .47	
	ß-values
MBI-weighted$_{t2}$	.17
Sex (female = 0; male = 1)	-.11
Age	.16
Hormonal contraception (no = 0; yes = 1)	-.05
Body-mass-index$_{t2}$	.26
Number of hair washes/week$_{t2}$	-.20
Tint$_{t2}$ (no = 0; yes = 1)	-.10
Coloration$_{t2}$ (no = 0; yes = 1)	.05

Note. * $p \leq .05$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 25

Results of the multiple regression analysis examining the longitudinal association between MBI-weighted$_{t1}$ and HCC$_{t2}$

R^2 = .43; F (10, 99) = 6.694; $p \leq .001$	
	ß-values
MBI-weighted$_{t1}$	-.18*
HCC$_{t1}$	.59***
Sex (female = 0; male = 1)	.03
Age	.03
Hormonal contraception (no = 0; yes = 1)	-.05
Body-mass-index$_{t2}$	.02
Number of hair washes/week$_{t2}$	-.22*
Tint$_{t2}$ (no = 0; yes = 1)	.02
Coloration$_{t2}$ (no = 0; yes = 1)	-.03
Permanent wave$_{t2}$ (no = 0; yes = 1)	.02

Note. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 26

Results of the multiple regression analysis examining the longitudinal association between MBI-weighted$_{t1}$ and HCC$_{t2}$ within the burnout group

R^2 = .47; F (9, 50) = 4.002; $p \leq .001$	
	ß-values
MBI-weighted$_{t1}$	.05
HCC$_{t1}$	.59***
Sex (female = 0; male = 1)	-.03
Age	.05
Hormonal contraception (no = 0; yes = 1)	.02
Body-mass-index$_{t2}$	.17
Number of hair washes/week$_{t2}$	-.17
Tint$_{t2}$ (no = 0; yes = 1)	-.12
Coloration$_{t2}$ (no = 0; yes = 1)	.05

Note. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 27

Results of the multiple regression analysis examining the longitudinal association between HCC_{t1} and MBI-weighted$_{t2}$

$R^2 = .61$; $F\ (10, 99) = 13.97$; $p \leq .001$	
	ß-values
HCC_{t1}	.07
MBI-weighted$_{t1}$	.73***
Sex (female = 0; male = 1)	.09
Age	-.04
Hormonal contraception (no = 0; yes = 1)	.11
Body-mass-index$_{t1}$	.06
Number of hair washes/week$_{t1}$	-.03
Tint$_{t1}$ (no = 0; yes = 1)	-.06
Coloration$_{t1}$ (no = 0; yes = 1)	-.02
Permanent wave$_{t1}$ (no = 0; yes = 1)	-.01

Note. *** $p \leq .001$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Table 28

Results of the multiple regression analysis examining the longitudinal association between HCC_{t1} and MBI-$weighted_{t2}$ within the burnout group

$R^2 = .36$; $F\ (9, 50) = 2.504$; $p \leq .05$	
	ß-values
HCC_{t1}	-.01
MBI-$weighted_{t1}$	.57***
Sex (female = 0; male = 1)	-.02
Age	-.01
Hormonal contraception (no = 0; yes = 1)	.09
Body-mass-$index_{t1}$	.07
Number of hair washes/$week_{t1}$	.10
$Tint_{t1}$ (no = 0; yes = 1)	-.13
$Coloration_{t1}$ (no = 0; yes = 1)	-.16

Note. *** $p \leq .001$. MBI-weighted = weighted Maslach Burnout Inventory-General Survey score; HCC = log-transformed hair cortisol concentrations (pg/mg).

Figure 17
Scatterplot of the association between log-transformed duration of burnout symptoms (days) and log-transformed HCC_{t1} within the burnout group

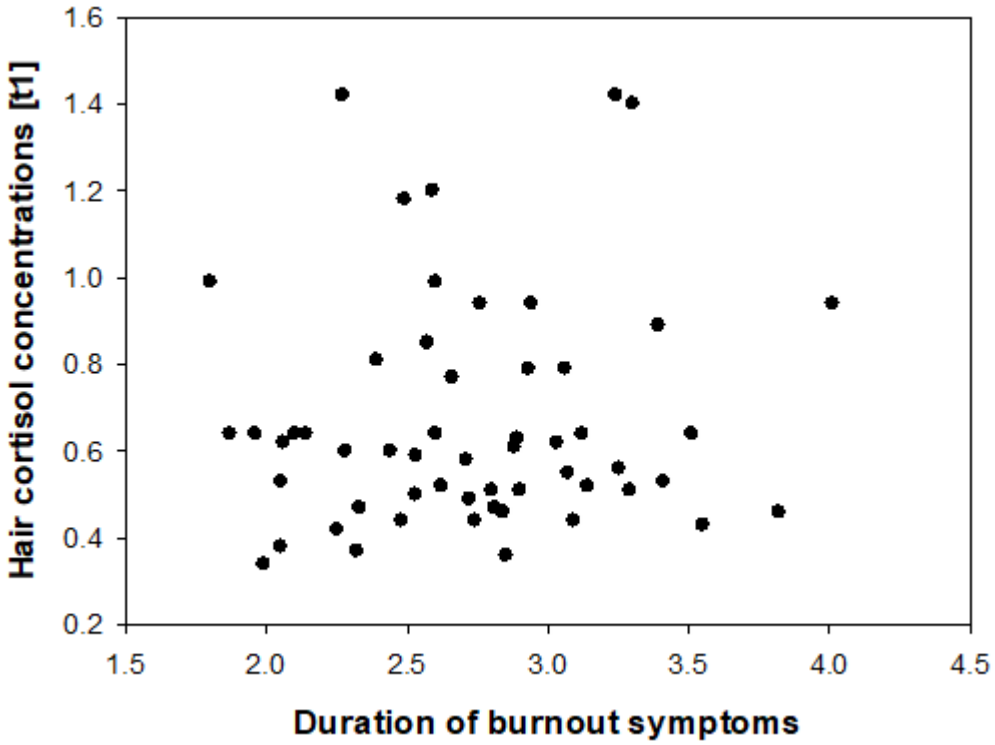


Figure 18
Scatterplot of the association between log-transformed duration of burnout symptoms (days) and log-transformed HCC_{t2} within the burnout group

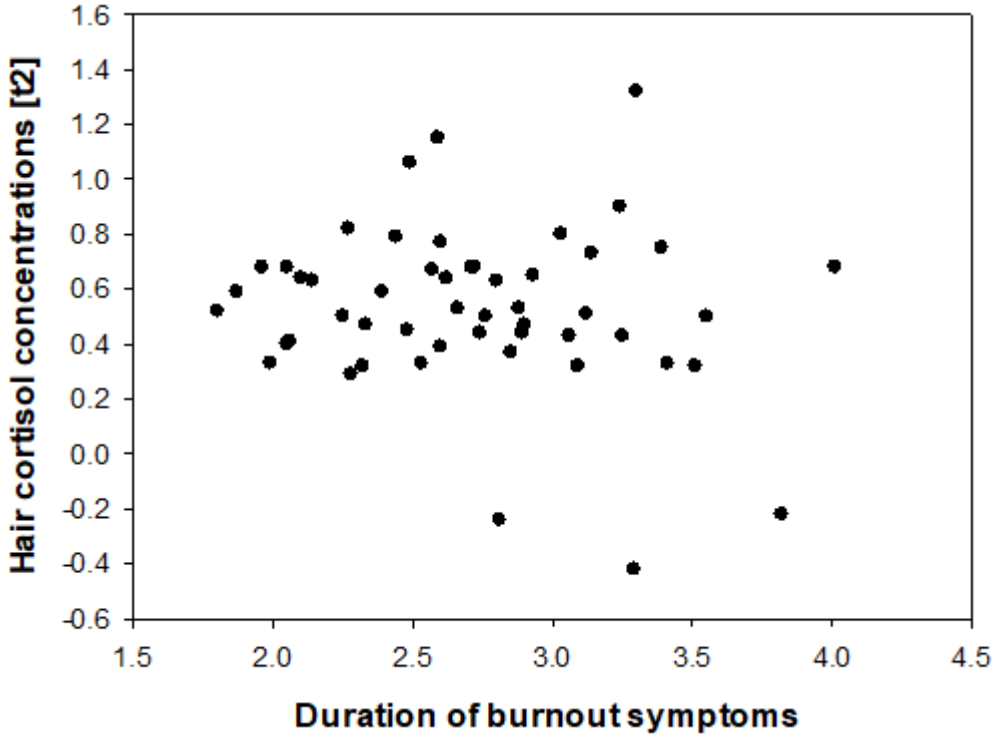


Table 29
fMRI acquisition parameters of blood oxygenation level-dependent gradient echo-planar imaging images

Repetition time	2000 ms
Echo time	30 ms
Flip angle	90°
Matrix	64 x 64
Field of view	192 mm
Slices	37 x 3 mm axial slices with 1 mm gap
Voxel size	3 x 3 x 3 mm

Note. The first five echo-planar imaging volumes were discarded to allow for T1 equilibration.

Table 30
T1-weighted image acquisition parameters

Repetition time	2400 ms
Echo time	2.18 ms
Flip angle	8°
Distance factor	50%
Field of view	256 mm
Voxel size	0.8 x 0.8 x 0.8 mm

Table 31

Activated (stress > control) and deactivated (control > stress) structures during ScanSTRESS (z > 3.1, two-tailed combined test, FWE p < .05) including z- and p-values as well as the localization of peak voxels

Structure		**Statistics**			**MNI coordinates**		
		K	***p***	***z***	**X**	**Y**	**Z**
Insular cortex	**left**	**140804**	**< .001**	**12.4**	**-28**	**20**	**-4**
	right			12.3	34	20	-6
				12.2	28	20	-4
Subcallosal cortex	**right**	**9314**	**< .001**	**-10.4**	**6**	**22**	**-10**
				-10.2	8	30	-14
	left			-10.3	-8	22	-14
				-10.1	-8	30	-16
Frontal orbital cortex	right			-9.96	12	28	-22
				-9.92	2	34	-20
Postcentral gyrus	**left**	**1544**	**< .001**	**-7.23**	**-46**	**-26**	**60**
				-7.12	-52	-32	56
				-6.23	-30	-38	74
				-6.22	-56	-20	46
				-6.09	-32	-32	72
				-5.8	-22	-44	78
Postcentral gyrus	**right**	**1414**	**< .001**	**-6.62**	**50**	**-20**	**58**
				-6.55	44	-30	64
				-6.18	20	-34	78
				-6.14	38	-20	68
				-6.11	64	-8	36
				-6.10	24	-24	78
Central opercular cortex	**left**	**992**	**< .001**	**-5.66**	**-48**	**-6**	**4**

				-5.40	-52	-14	8
				-4.4	-54	-22	14
Insular cortex				-5.4	-38	-18	12
Central opercular cortex	**right**	**874**	**< .001**	**-5.56**	**44**	**-14**	**12**
				-4.59	50	-6	2
				-4.28	64	-6	10
				-4.18	54	-14	10
Planum polare				-4.36	60	-2	2
				-4.24	42	-16	-2
Precuneus cortex	**left**	**347**	**< .005**	**-4.98**	**-6**	**-56**	**24**
	right			-3.85	8	-54	22
Lateral occipital cortex, superior division	**left**	**318**	**< .005**	**-5.92**	**-52**	**-74**	**32**
				-4.96	-42	-76	44

Note. Global cluster maxima are in boldface.

Table 32

Activated structures during ScanSTRESS with run as regressor (FWE-corrected p < .05) including z- and p-values as well as the localization of peak voxels

Structure		**Statistics**			**MNI coordinates**		
		K	***p***	***z***	**X**	**Y**	**Z**
Occipital pole	**left**	**111134**	**< .001**	**9.32**	**-20**	**-98**	**8**
				9.11	-22	-94	16
				8.74	-30	-92	12
	right			8.82	12	-98	10
Lateral occipital cortex, superior division	right			9.08	30	-86	18
Lateral occipital cortex, inferior division				8.61	48	-68	-14

Note. Global cluster maxima are in boldface.

Table 33

Activated structures during ScanSTRESS with run as regressor showing a group specific effect (BO vs. HC group; FWE-corrected p < .05) including z- and p-values as well as the localization of peak voxels

Structure		**Statistics**			**MNI coordinates**		
		K	***p***	***z***	**X**	**Y**	**Z**
Precentral gyrus	**left**	**796**	**< .005**	**3.50**	**-34**	**-2**	**40**
Middle frontal gyrus				3.46	-28	0	46
Cingulate gyrus, anterior division				3.26	-12	-4	42
	right			3.20	6	24	38
Paracingulate gyrus	left			3.11	-8	22	44
				3.09	-10	12	46

Note. Global cluster maxima are in boldface.