Chapter 7
Psychobiological Pathways from Work Stress to Reduced Health: Naturalistic and Experimental Studies on the ERI Model

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7.1 Introduction

Stress at work and its negative impact on the health status of employees are major problems for modern societies. According to statistics from the UK Health and Safety Executive from 2006 to 2007, mental health problems especially stress, depression and anxiety accounted for 46 % of days lost due to work-related illness, thereby constituting the main cause of absences due to work-related illness (Cooper 2008). A wide body of epidemiological and prospective evidence has been accumulated during the last decade, showing associations between psychosocial stress at work and disease endpoints such as cardiovascular disease, the metabolic syndrome, type 2 diabetes as well as psychiatric conditions (Kivimäki et al. 2006; Eller et al. 2009; Siegrist 2010, 2013; Angerer et al. 2014; Backe et al. 2012; Glozier et al. 2013; Li et al. 2013; Schmidt et al. 2015). The two organizational stress models that inspired most of the above cited research activities over the last decade are the job-demand-control model (Karasek and Theorell 1992) and the effort-reward-imbalance model (Siegrist 2002; Siegrist and Peter 1996), which is the focus of the present volume.

The model of effort-reward-imbalance, as already described in great detail in previous chapters, postulates that the experience of a failed reciprocity between high work-related costs and low occupational rewards leads to a state of emotional distress, which can result in sustained strain reactions and consequently leads to

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adverse health effects and reduced well-being over time. Over-commitment (OC), the intrinsic component of the ERI model (Siegrist 2002; Siegrist and Peter 1996), is conceptualized as a motivational pattern of excessive work-related commitment and a high need for approval, which is assumed to increase the risk of strain due to unreciprocated exchange. Evidence has shown that ERI and OC impact on self-rated health and well-being, health behaviors as well as physical diseases (Bosma et al. 1998; Kivimäki et al. 2002; Tsutsumi and Kawakami 2004; van Vegchel et al. 2005; Siegrist 2005; Rugulies et al. 2009; Siegrist and Rödel 2006). To gain a deeper understanding of the link between ERI/OC and health which is suggested by these findings and in order to develop effective interventions to prevent health impairments, a precise definition of the term stress as well as knowledge of potential underlying psychobiological pathways are essential. Previous work has implicated two main pathways through which stress can impact on physical health. On the one hand stress can influence people's health behavior, like smoking, choice of diet, exercise or adherence to medical treatment and on the other hand stress can directly initiate unfavorable alterations in different physiological systems, thereby increasing an individual's vulnerability to a range of physical diseases. A review by Siegrist and Rödel (2006), based on 46 studies measuring psychosocial work stress in terms of the job-demand-control-model and the ERI model however found only moderate support for the relationship between work stress and health behavior. Heavy alcohol consumption among men, overweight as well as multiple co-occurring risk factors showed the strongest associations with health behavior.

The present chapter will therefore review current results on the relationship between ERI/OC and alterations in the regulation of the physiological stress response, which has evolved as a highly adaptive reaction to ensure survival when an organism is confronted with a physical or psychological challenge. The present chapter is organized in three main sections. After a brief introduction on organizational stress models as well as general conceptualizations of stress, the second section serves to introduce McEwen's Allostatic Load Model and gives an overview over main components of the biological stress system, namely the sympatho-adrenal-medullary (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis. The third section summarizes empirical findings that relate the effects of psychosocial work stress in terms of effort-reward-imbalance and over-commitment to alterations in stress related physiological systems, which increase the risk for a plethora of adverse health outcomes. The chapter closes with an outlook emphasizing the potential of the theoretical framework of the effort-reward-imbalance model to shape stress prevention programs in order to minimize health risks associated with work stress.

7.1.1 Brief History of the Stress Concept

Hans Selye, the father of modern stress research, first conceptualized stress as a non-specific response of the body to non-specific biological, chemical, physical or social challenges that were assumed to elicit a 'general adaptation syndrome' via

the secretion of glucocorticoids (Selye 1950). Focusing primarily on the role of the sympathetic nervous system in the response to emergency situations, Walter Cannon in turn defined stress in terms of the stimulus required to elicit adrenomedullary responses (Cannon 1914). He coined the term fight-flight response, describing the responses to an acute threat. However, it soon became apparent that stress cannot be defined solely by an organism's physiological reaction. Mason (1975) was able to demonstrate that specific situational and personal characteristics, such as novelty, ambiguity or a person's sense of control over a threatening challenge are a crucial element in the stress process, triggering different autonomic and neuroendocrine responses. It then became evident that stress responses varied according to the quality of the challenge and the availability of the person's ability to cope with this challenge. In line with this notion, the transactional stress model of Lazarus and Folkman (1984) emphasized the role of subjective appraisal processes as determinants of emotional and physiological responses to the experience of a challenging situation. They defined stress as the experience of a mismatch between the demands put on an individual in a challenging situation and his or her abilities to cope. Finally, the cognitive activation theory of stress (CATS) by Ursin and Eriksen (2004) offers a comprehensive definition of stress, which distinguishes four aspects: input or stress stimuli, the individual processing or the stress experience, the non-specific, general stress response and finally the experience of the stress response. The stress response is believed to serve as a general alarm in a homeostatic system and is therefore described as an essential and necessary physiological response. The alarm elicits specific coping behaviours, which are dependent on acquired expectancies of the outcomes of stimuli and available responses.

7.2 From Allostasis to Allostatic Load

McEwen's allostatic load model aims to outline a theoretical framework explaining how chronic stress can lead to health impairments. It postulates that an organism responds to challenge by initiating an allostatic response, a complex pathway for adaptation and coping, and shuts off this response when the challenge has passed. The term allostasis was originally introduced by Sterling and Eyer (1988) to describe how the cardiovascular system adjusts to resting and active states of the body. Allostasis depicts a fundamental physiological principle 'maintaining stability through change': In order to maintain stability, an organism must vary all the parameters of its internal milieu and match them appropriately to environmental demands. The effective coordination of allostatic responses depends on the brain's evaluation of threat (McEwen 2007; Herman et al. 2005) and subsequent physiological responses, which are predefined by inter-individual differences in various factors such as genetics, experiences (trauma, life events), coping styles or health behaviors (Juster et al. 2010).

7.2.1 Core Stress Systems Involved in Allostatic Responses

In case of challenge, the sympathetic–adrenal–medullary (SAM) axis initiates the release of catecholamines (adrenaline and noradrenaline) and the hypothalamic–pituitary–adrenal (HPA) axis secretes glucocorticoids that mobilize energy necessary for fight-or-flight responses (Sapolsky et al. 2000). The SAM axis functions as a global alarm system and is comprised of two pathways. The neural pathway of the SAM axis is characterized by the innervation of effector organs by noradrenergic synapses, whereas the endocrine pathway describes the release of catecholamines by the adrenal glands. Circulating catecholamines stimulate effector organs via adrenergic receptors. These receptors are exemplary transmembrane proteins that, through coupling with G-proteins, stimulate or inhibit intracellular signalling pathways. Catecholamine secretion leads to a rapid mobilisation of energy stores (through increased supply of free fatty acids and glucose by glycogenolysis and lipolysis) as well as a down-regulation of less important organ functions (e.g. gastrointestinal tract and reproductive systems). Furthermore, catecholamines have a substantial impact on cardiovascular functioning during stress, increasing heart rate, cardiac output, and blood pressure (Kudielka and Kirschbaum 2007). Noradrenaline also activates the amygdala, the principal brain locus for fear-related behaviours, and enhances the long-term storage of emotional memories in the hippocampus and striatum (Tsigos and Chrousos 2002).

The HPA axis serves as a central control system of an organism, connecting the central nervous system (CNS) with the endocrine system. The HPA axis is vital for the support of normal physiological functioning and enables the organism to maintain homeostasis under acute stress. In the face of challenge, neural stimulation of the hypothalamic paraventricular nucleus of the hypothalamus (PVN) leads to the release of corticotropin-releasing hormone (CRH). After its release into the hypophyseal portal system, CRH initiates the cleavage of pro-opiomelanocortin (POMC) into adrenocorticotropin (ACTH), beta-endorphin, and other peptides and their subsequent release from the anterior pituitary gland. The primary target of ACTH is the adrenal cortex, where it triggers the secretion of glucocorticoids (GCs) and adrenal androgens from the zonae fasciculata and reticularis (Chrousos and Gold 1992). GCs have a wide range of physiological effects. In order to adapt to the increased metabolic demands under acute stress, GCs enhance circulating levels of energy substrates like glucose, free amino acids and free fatty acids, thereby amplifying catabolic processes whilst simultaneously suppressing anabolic processes. This is achieved through their action on a number of enzyme systems in the liver, muscles and fat. In the liver for example GCs enhance gluconeogenesis. Additionally, GCs may increase circulating free fatty acids by inhibiting lipoprotein lipase, initiating lipolysis and mobilising free fatty acids from fat depots (Chrousos and Gold 1992; McEwen 2003). Finally, GCs temporarily dampen immune system activity and processes involved in reproduction and cellular growth, thereby ensuring access to resources essential for coping with challenge.

However, GCs also play a key role in the termination of the stress response, preventing it from being pathologically over-activated (Chrousos and Gold 1992; Herman et al. 2003). Additionally, GCs have important regulatory effects on the cardiovascular system, the regulation of fluid volume and response to haemorrhage as well as on behaviour, appetite control and affective and cognitive processes, like learning and memory (McEwen 2003). The HPA axis is regulated by the negative feedback action of cortisol on receptors in the hippocampus, hypothalamus and pituitary gland. This feedback loop suppresses the secretion of CRH, ACTH and cortisol itself. In humans, the typical cortisol secretion follows a distinct circadian rhythm, with a marked increase (about 50–100 %) during the first hour after morning awakening in the majority of people (Dockray et al. 2008; Wüst et al. 2000) and decreasing levels over the remaining day. Pruessner and colleagues (1997) first suggested that this rise in cortisol after awakening might represent a useful index of adrenocortical activity. In a highly controlled study under sleep laboratory conditions, Wilhelm and co-workers (2007) showed that this elevation in cortisol is a genuine response to awakening, as the transition from sleep to the waking state was found to be a prerequisite for the cortisol awakening rise (CAR) to occur. Very recently, expert consensus guidelines for the assessment of the cortisol awakening response have been established (Stalder et al. 2016).

7.2.2 Allostatic Overload

As long as these allostatic responses are limited to the period of challenge, adaptation and thus protection is ensured. However, the same processes that are adaptive under acute stress conditions, may ultimately promote disease development when occurring chronically (Tsigos and Chrousos 2002; McEwen 2007; Chrousos and Gold 1992). Thus, if allostatic responses are sustained over months and years, the individual reaches the state of allostatic load (AL). Chronic over-activity or inactivity of physiological systems that are involved in the adaptation to environmental challenge result in a wear-and-tear on the body and brain (McEwen 1998b). Four scenarios have been proposed, eventually leading to AL. The first is frequent stress. In especially susceptible individuals, for example, repeated blood pressure surges can trigger myocardial infarctions. Secondly, AL can be caused by a failure to habituate to repeated challenges, leading to the over-exposure to stress mediators. An example for this type of AL is the finding that a minority of subjects fail to habituate to repeated exposures to psychosocial laboratory stress and continue to show high cortisol responses (Wüst et al. 2005). The third origin of AL is the inability to shut off allostatic responses, which could be reflected in a lack of recovery of blood pressure after a mental stressor, leading to the development of atherosclerosis due to hypertension. The fourth scenario is conceptualized as an inadequate allostatic response in one allostatic system, that gives rise to compensatory increases in other allostatic systems. An inadequate hormonal stress response for example allows inflammatory cytokines to become overactive (McEwen 1998a).

To sum up, AL captures the cumulative physiological burden exacted on the body through repeated attempts of adaptation, by postulating a sequential and reciprocal chain of dysregulation in multiple systemic mediators. Stress hormones (cortisol, dehydroepiandrosterone-sulfate (DHEA-S), adrenaline and noradrenaline) in combination with pro- and anti-inflammatory cytokines (such as interleukin-6 or tumor necrosis factor-α) are termed primary mediators (McEwen 2003), as the prolonged secretion of the stress hormones might damage the brain and body (McEwen 2006). Secondary outcomes are changes in metabolic (such as blood lipids (total cholesterol, high density lipoprotein cholesterol, triglycerides), visceral fat, insulin, glucose and glycosylated haemoglobin (HbA1c)), cardiovascular (systolic and diastolic blood pressure), immune (c-reactive protein (CRP)) and coagulation (fibrinogen, D-dimer) parameters on a sub-clinical level, as a result of the compensation for over and/or under production of primary mediators. Allostatic overload is finally reached when physiological dysregulation leads to manifested disease endpoints, referred to as tertiary outcomes.

7.3 The Relationship Between ERI and Health Mediators: Findings from Naturalistic and Experimental Studies

In the remaining part of this chapter, naturalistic studies on the relationship between ERI/OC and physiological stress markers will be reviewed according to the above described taxonomy proposed by McEwen.

7.3.1 Findings on Primary Mediators

7.3.1.1 Cortisol

To-date, at least a handful of studies have investigated associations between components of the ERI/OC model and HPA axis functioning. Most of these studies focused on basal cortisol regulation with only very few studies investigating HPA axis reactivity by the use of psychological stress tasks or pharmacological stimulation procedures (for review see Chandola et al. 2010). Results on basal cortisol measures in relation to ERI/OC are mixed. Several studies could not demonstrate significant associations between ERI/OC and the CAR or cortisol profiles across the day (Hanson et al. 2000; Harris et al. 2007; Bellingrath et al. 2008; Ota et al. 2014). However, other studies report on a higher CAR or higher cortisol day concentrations in relation to some ERI/OC components (Steptoe et al. 2004; Eller et al. 2006, 2011a, 2012; Almadi et al. 2013; Wright 2011; Maina et al. 2009; Marchand et al. 2015). In accordance with these latter studies, Qi et al. (2014) recently observed a significant positive association between the ERI-ratio and cortisol concentrations in hair, as a recently introduced measure of long-term accumulated cortisol

concentration. Though, most of the observed associations could only be found in men (Steptoe et al. 2004; Eller et al. 2006, 2011a, 2012), in respective subpopulations (Maina et al. 2009), for the ERI-ratio OR a subcomponent (like effort, reward or over-commitment) but not both (Steptoe et al. 2004; Wright 2011). Only one study reported on a lower CAR as well as lower diurnal secretory activity in individuals scoring higher on ERI (Maina et al. 2009) and in the SALVEO study OC was related to increased awakening cortisol levels and decreased afternoon and bedtime cortisol (Marchand et al. 2015).

Other studies further raise the idea that ERI/OC might not be associated with generally higher versus lower cortisol day activity but with flatter circadian profiles (Karlson et al. 2011; Liao et al. 2013). Typically, such studies are based on small- to medium-sized samples (N = ~50–200 subjects). Only Liao et al. (2013) could analyze a large occupational cohort of N = 2,126 study participants derived from the Whitehall II study. They observed that higher ERI (and lower reward) related to a flatter slope in cortisol across the day. Most importantly, they report that effect sizes for significant findings were relatively small. This could be one major reason why the results picture so far is relatively mixed. However, other reasons for the, in part, inconsistent results could be the heterogeneous occupational study cohorts hampering generalizability across study samples, differences in the saliva sampling protocols, as well as use of different versions of the ERI/OC measure.

In an own study, we aimed at additionally investigating HPA axis negative feedback sensitivity as part of basal HPA axis functioning (Bellingrath et al. 2008). Besides cortisol day profiles across work and leisure days (see above), saliva samples were collected after pre-medication with 0.25 mg of the synthetic glucocorticoid dexamethasone the night before sampling. After DEX administration (only) lower reward from work was significantly related to stronger cortisol suppression. This finding raises the idea of a subtle dysregulation of the HPA axis manifested as heightened negative feedback functioning, even though all subjects were working and in a good health condition. Finally, very few studies investigated HPA axis responsivity to stress. Three of these studies applied a psychological stress task to provoke HPA axis responses. All three studies point to a reduced HPA axis responsivity. While Siegrist et al. (1997) observed a dampened cortisol stress response applying the Stroop task in relation to high ERI, in two studies using the Trier Social Stress Test (TSST), Wirtz et al. (2008) observed reduced salivary cortisol responses in healthy men and, in an own study, we observed HPA axis hyporeactivity in overcommitted teachers (Bellingrath and Kudielka 2008). Finally, two studies applied the combined DEX-CRH-stimulation test. Wirtz et al. (2010) observed unaltered ACTH but enhanced cortisol responses in overcommitted healthy men and women. This pattern of results was interpreted as heightened reactivity of the adrenal cortex but normal reactivity of the anterior pituitary in overcommitted individuals. However, in an own study applying the DEX-CRH-test as well as the Synacthen-test ($ACTH_{1-24}$-test), we could not find any indication for increased adrenal cortex sensitivity in subjects with higher OC by stimulation of the cortex with synthetic ACTH (Wolfram et al. 2013). At the same time, we observed hyporeactive pituitary as well as adrenal cortex responses to the DEX-CRH-test as reflected in reduced

ACTH, total plasma, and free salivary cortisol concentrations in overcommitted teachers.

We hypothesize that such an attenuated HPA axis response is not solely of pituitary and adrenal origin but also likely involves central mechanisms. This interpretation would also be in line with the above reported studies based on psychological stress provocation (Siegrist et al. 1997; Wirtz et al. 2008; Bellingrath and Kudielka 2008). In sum, while studies on basal HPA axis functioning are relatively mixed pointing to no or at least only modest alterations in circadian cortisol regulation, studies on HPA axis responsivity appear to be more consistent raising the idea of HPA axis hyporeactivity, especially related to the component over-commitment. Reasons for inconsistencies could be methodological differences between studies (see above) or some underpowered studies acknowledging the finding that underlying effect sizes might be relatively small. It is also possible that robust effects are only observable when the system is challenged (compare Seeman and Robbins 1994). Besides this, it is reasonable to assume that HPA axis regulation might change over time when human beings are exposed to chronic work stress. According to a time-course (Hellhammer and Wade 1993) or two-stage model (Siegrist et al. 1997), a state of chronic work stress like in the early stage of effort-reward-imbalance (characterized by hyperactivity of the HPA axis) could, in the long run, lead to a hypocortisolemic or hyporeactive state as result of a functional adaptation to excessive exposure to stress hormones. The development and progression of hypocortisolism may be due to reduced biosynthesis or depletion at several levels of HPA axis (CRH, ACTH, cortisol), CRH hypersecretion and adaptive down-regulation of pituitary CRH receptors or changes in receptor sensitivity, increased feedback sensitivity of the HPA axis, and morphological changes (Heim et al. 2000). Consequently, such changes over time could then blur results pattern and hyper- and hypocortisolemic effects in individuals could cancel each other out in group analysis.

7.3.1.2 Catecholamines

Although studies on psychosocial work place stressors and catecholamine excretion exist (for review see Chandola et al. 2010; Hansen et al. 2009), there is still a paucity of data reporting associations between components of the ERI/OC model and adrenaline/noradrenaline concentrations. In a study on various physiological parameters in the framework of allostatic load (see below), we could not find any relationship between ERI/OC and catecholamine levels as measured in overnight urine of schoolteachers. A subsample of these teachers was re-invited to the lab to perform a stress task. Here, we observed marginally higher noradrenaline concentrations ($p = 0.06$) across the session in subjects with higher versus lower over commitment scores (von Känel et al. 2009). However, in another study a somewhat contrasting result was reported. Wirtz et al. (2008) observed that higher OC was significantly associated with lower pre-stress baseline levels of noradrenaline. Two studies are available that report on catecholamine responses to acute psychological stress, both

pointing to reduced responsivity. Siegrist et al. (1997) observed reduced adrenaline responses to the Stroop task in relation to ERI and Wirtz et al. (2008) found suppressed noradrenaline responses in high versus low overcommitted subjects when exposed to the Trier Social Stress Test (TSST). Considering the scarce evidence so far, a final conclusion on catecholamine concentrations under basal conditions as well as in response to stress in respect to ERI/OC appears not advisable.

7.3.1.3 Inflammatory Cytokines

Although a number of studies have been published that aimed to investigate potential associations between the ERI/OC model and immune functions, studies that focus explicitly on inflammatory cytokines in terms of primary mediators are still rare. The term cytokine refers to a broad group of small proteins that play an important role in the communication and interaction between cells. They act in concert with specific cytokine receptors as well as cytokine inhibitors in order to regulate the human immune response, for example by modulating the balance between humoral and cellular immunity. Franke and colleagues (2010) compared job-related stress in terms of ERI and a set of pro- and anti-inflammatory mediators in a sample of law enforcement officers and a healthy control group. Law enforcement officers showed significantly elevated levels of ERI compared to the control group, mainly due to elevated effort. They also showed approximately two to three times higher levels of interleukin (IL)-1β, IL-6 and tumor-necrosis-factor (TNF)-α. No difference between the two groups was observed with respect to the anti-inflammatory cytokine IL-4, whereas IL-10 levels were significantly lower in the law enforcement officers. However, regression analyses revealed that less than 4 % of the variance in any of the inflammatory markers was explained by job-related stress, suggesting a different mechanism that explains the increased CVD risk in law enforcement officers, due to a pro-inflammatory state. Bellingrath et al. (2010) measured phytohemagglutinin (PHA)-stimulated lymphocyte production of TNF-α, interferon (IFN)-γ, IL-2, IL-4, IL-6 and IL-10, before and after an acute laboratory stressor in 55 healthy individuals. Subjects with higher levels of ERI showed an overall increase in pro-inflammatory activity, with higher TNF-a production at both time points and elevated pre-stress IL-6 production. Additionally, the production of IL-10 decreased after stress in subjects with higher levels of ERI, suggesting an impaired anti-inflammatory break, which could increase the risk of chronic low-grade inflammation.

Furthermore, in a second study changes in lipopolysaccharide (LPS)-induced IL-6 production and inhibition of IL-6 production by dexamethasone in reaction acute psychosocial stress were assessed in 46 healthy schoolteachers (Bellingrath et al. 2013). Higher ERI was associated with an increase in pro-inflammatory potential, reflected in elevated IL-6 production before and after stress and with a lower capacity of dexamethasone to suppress IL-6 production in vitro over all measurement time points (GC sensitivity), suggesting a less effective anti-inflammatory regulation by glucocorticoids in relation to ERI. Already, earlier research has

demonstrated that clinical depression is associated with a diminished sensitivity to the anti-inflammatory properties of glucocorticoid hormones, possibly due to elevated resting levels of cortisol (Miller et al. 2005). As high levels of ERI have been established to be a risk factor for the development of depression it can be speculated, that reduced glucocorticoid sensitivity might help to explain how chronic work stress can lead to disease. To conclude, there appears to be preliminary evidence for an association between chronic work stress and a pro-inflammatory state. Due to the small number of studies however a final conclusion seems to be premature.

7.3.2 Findings on Secondary Outcomes

7.3.2.1 Body Weight (BMI) and Blood Lipids

It can be hypothesized that adverse body composition might be related to stressful working conditions. Indeed, epidemiological, longitudinal and cross-sectional studies revealed some evidence for positive, but weak, associations between components of the ERI/OC model and body mass index (BMI) (Kouvonen et al. 2005; Ostry et al. 2006; Berset et al. 2011). It is assumed that the underlying pathways behind a stress – weight gain – relationship are unhealthy eating habits and/or a sedentary behavioral life style. Interestingly, these relatively weak, or only marginally significant, associations might be explained by a bidirectional effect. Data from the Whitehall II prospective cohort study, for example, point to the idea that work strain might further increase body weight in obese men while body weight is decreased in thin men (Kivimäki et al. 2006). Indeed, in line with this reasoning, Takaki et al. (2010) found that ERI is more positively associated with over-eating in men with higher BMIs. There also exist, at least, a handful of studies that investigated blood lipids in order to measure established metabolic risk factors for CHD in relation to chronic work stress.

Thus, such studies capture relevant criteria for the so-called metabolic syndrome (MetS) which is defined by five CVD risk factors, namely obesity, elevated blood pressure (hypertension), high triglycerides, low high-density lipoprotein cholesterol (HDL), and impaired glucose tolerance (hyperglycemia). The MetS is considered a highly potential mechanism linking chronic job stress with incidence of CHD. The majority of the larger studies (for example from the WOLF or the SHISO study) report on unfavorable lipid profiles in relation to components of the ERI/OC model (Xu et al. 2011; Peter et al. 1998b; Irie et al. 2004; Siegrist et al. 1997), though contradictory findings are also available (Vrijkotte et al. 1999; Söderberg et al. 2012). Three further recent cross-sectional occupational studies on a sample of radiologists, in Korean blue-collar workers and in different occupational groups derived from the Mannheim Industrial Cohort Study (MICS) confirm that ERI is related to a significant higher risk of being affected by the metabolic syndrome (Schmidt et al. 2015; Magnavita and Fileni 2014; Hwang and Lee 2014). However, the referenced

studies also point to the fact that such associations might be more prevalent in men compared to women as, for example, observed in the Mannheim Industrial Cohort Study (MICS). In this respect, it should also be of note that most of the studied samples are predominantly (or even solely) male and in some studies results in women are actually in the opposing direction (Söderberg et al. 2012; Hwang and Lee 2014). In sum, there appears to be clear evidence for an association between chronic work stress and unfavorable metabolic factors in men, though, it remains somewhat unclear if these associations are comparably valid for women.

7.3.2.2 HbA1c

Since haemoglobin A1c (HbA1c) reflects serum-glucose concentrations retrospectively over the past 4–5 weeks, this parameter has been established as screening marker for diabetes mellitus. To date, available studies on the relationship between elevated HbA1c in serum (in percent of total haemoglobin) on the one hand and adverse psychosocial working environment on the other appears relatively consistent. Several cross-sectional as well as longitudinal studies, including one population-based study, reported increased HbA1c in relation to a negative psychosocial working environment (reviewed in Hansen et al. 2009). So far, studies focusing on ERI/OC and glycemic control are rare. However, we identified at least three studies. All three studies reported at minimum on partially significant associations between chronic work stress and glycosylated haemoglobin (HbA1c) or incidence of diabetes. In a prospective cohort study of 10.308 civil servants aged 35–55 years at baseline, Kumari et al. (2004) observed that in men ERI was related to incidence of diabetes across four follow-up phases (total time span >10 years). Accordingly, Li et al. (2013) observed that higher ERI is related to (pre)diabetes status (verified by HbA1c, fasting plasma glucose and supplementary self-reports) in men while associations in women were weaker and remained non-significant (total N = 2.674, 77 % male). In a Chinese population (N = 680 subjects) from the SHISO study (Stress and Health in Shenzhen Workers), ERI was positively related with HbA1c in women but not men. Finally, Virtanen et al. (2012) tested whether ERI in medical staff is associated with glycemic control among their diabetes patients, though, they could not confirm this transfer effect. However, perceptions of higher levels of procedural justice among medical staff were associated with better glycemic control in patients. In sum, there exists evidence linking chronic work stress in terms of ERI with HbA1c and incidence of diabetes mellitus.

7.3.2.3 Blood Pressure

A growing body of research has investigated associations between psychosocial work factors in terms of ERI/OC and elevated blood pressure as one of the most critical risk factors for the development of CVD. ERI as well as OC have both been related to BP levels and hypertension, however results for ERI seem to be more

consistent. In an early investigation by Peter et al. (1998b) only ERI but not OC was associated with hypertension in male but not female participants. Similarly, Vrijkotte and colleagues found (2000) ERI but not OC to be related to ambulatory systolic blood pressure over the workday in male white-collar workers. Steptoe et al. (2004), on the contrary reported higher ambulatory systolic BP levels among men in relation to OC. No significant effects were found for women.

Whether ERI prospectively predicts BP elevation was so far only investigated in one study using ambulatory BP measures (Gilbert-Ouimet et al. 2012). Significant effects of ERI on BP levels and hypertension were only observed in female participants over a follow-up of 3 years. Women younger than 45 years of age, which had high ERI levels at both measurement time points showed significantly higher BP means at follow-up. Women with high ERI levels at both measurement time points and older than 45 years of age on the other hand, showed an increased cumulative incidence of hypertension compared to those with low ERI scores. In a recent review, Gilbert-Ouimet and colleagues (2014) summarized the results of 74 studies that investigated adverse effects of work stress in terms of the demand-control-support (DCS) (64 studies) and the ERI- model (12 studies) on BP and hypertension. The majority of the studies reported significant deleterious effects of work stress on BP outcomes (Peter and Siegrist 1997; Gilbert-Ouimet et al. 2012; Yu et al. 2008; Maina et al. 2011; Peter et al. 1998a; Vrijkotte et al. 2000; Xu et al. 2004). Adverse effects on BP levels or hypertension risk were observed more consistently with respect to ERI compared to OC. It is furthermore noteworthy that overall the adverse effects of ERI/OC were shown to be less contradictory in men than in women (Gilbert-Ouimet et al. 2014). In sum, the evidence points to a link between psychosocial work stress in terms of ERI and BP elevations especially in men.

7.3.2.4 Heart Rate and Heart Rate Variability

Heart rate (HR), HR reactivity and HR variability (HRV) are established indicators of a stress-related activation of the autonomic nervous system (ANS) (Task Force 1996) and have been shown to be independent risk factors for the development of CVD. Under normal conditions, the two branches of the ANS – the sympathetic system, responsible for energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions, are in dynamic balance. However, the activity of the two branches can rapidly change in order to flexibly adapt to environmental demands (Thayer et al. 2010, 2012). Persisting autonomic imbalance, in terms of a hyperactive sympathetic system and a hypoactive parasympathetic system, has been linked to a lack of flexibility and to pathological conditions (Malliani et al. 1994). Low HRV is indicative of sympathetic predominance and a decreased vagal tone and has been repeatedly associated with stress vulnerability (Porges 1992), difficulties in emotion regulation (Souza et al. 2007), stress at work (Chandola et al. 2010) as well as adverse health outcomes such as CVD (Thayer et al. 2010). A recent review by Jarczok and colleagues (2013) including 19 studies summarized the accumulated findings on the relationship between psychosocial

workplace characteristics and HRV, showing that a decreased vagally-mediated HRV is indicative of adverse health profiles. Work stress was operationalized in terms of ERI in seven of the reviewed studies. ERI was significantly related to indicators of decreased vagal tone in four studies (Hanson et al. 2001; Hintsanen et al. 2007; Loerbroks et al. 2010; Uusitalo et al. 2011) and to decreased mixed sympathetic and parasympathetic indicators in three studies (Uusitalo et al. 2011; Eller et al. 2011a, b). Garza et al. (2014) recently assessed whether not only ERI but also OC are associated with greater decreases in HRV across a 2-h working period in 91 office workers. The results indicated that higher levels of ERI and OC are associated with a greater decrease in HRV throughout the measurement period.

Loerbroks and colleagues (2010) aimed to determine whether age might modify potential associations between work stress and HRV indicators. ERI was only related to HRV in employees aged 35–44. This finding was explained by age-dependent HRV declines on the one hand as well as a potentially increased susceptibility among those aged 35–44 due to stressors in the work life (i.e. advancing the career) in combination with stressors in private life (marriage, birth of children), which are characteristic for this age group.

Modifying effects of gender became apparent in a number of studies. Performing a gender stratified analysis, Eller et al. (2011a) found significant associations between high levels of ERI to be associated with low HRV only in women. Similarly, Hintsanen et al. (2007) reported an inverse association between ERI and HRV in women, but not in men. Furthermore, in a second study by Eller et al. (2011b) lower HRV in terms of total power was only found in men experiencing higher levels of ERI at work. Interestingly, a status by ERI interaction could be observed. Men with a higher social status and higher ERI levels had an increased HRV compared to men with a lower status and higher ERI. Vrijkotte et al. (2000) investigated vagal tone as well as HR reactivity in relation to ERI/OC in a sample of male white-collar workers on two workdays and one leisure-day. A trend was observed for the high ERI group to have lower vagal tone during all measurement periods. Additionally, a selective increase in HR during work and leisure time after work was observed in subjects with higher levels of ERI, whereas no alterations in HR were found during sleep and during the leisure-day. No significant effects of OC were found with respect to HR or vagal tone.

Finally, Falk et al. (2011) used an experimental design to analyze how perceptions of unreciprocated exchange in a work situation, which is the basic notion of the ERI model, relate to HRV. In a so-called principal agent experiment agents were asked to work on a tedious task, thereby producing revenue. Principals finally decided how to share this revenue between themselves and their agents. Falk and colleagues could show that if an agent received less reward than expected, thus considered the wage too low and thus unfair, a significantly impaired cardiac autonomic control was observed. These results suggest that the repeated perception of unfair exchange at work might affect health outcomes in the long run. To summarize, the available evidence suggests that work stress in particularly in terms of ERI is associated with a lower HRV and this relationship between ERI and HRV is modulated by age and gender.

7.3.2.5 Blood Coagulation Markers

There is relatively clear evidence from population-based studies that an adverse psychosocial working environment is related to unfavorable coagulation markers like fibrinogen (for review see Hansen et al. 2009). Findings on the association between ERI/OC and parameters of the fibrinolytic and coagulation system are yet relatively scarce. However, although the available studies differ markedly in study samples, sample sizes, analyzed hemostatic markers and result patterns, the majority of studies, at least in parts, supports the assumption that chronic stress at work in terms of ERI/OC is associated with unfavorable changes in the blood coagulation system. For example, elevated fibrinogen levels have been related to ERI/OC in different samples (Siegrist et al. 1997; Xu et al. 2012). Though, other studies from different European countries could not confirm this relationship in medium-sized samples (Vrijkotte et al. 1999; Bellingrath et al. 2009) or even in a large cross-sectional sample of the WOLF (work, lipids, fibrinogen) study comprised of 3,427 men and women (Peter et al. 1998a). Beside fibrinogen, Vrijkotte and coworkers (1999) measured tissue-type plasminogen activator activity, tissue-type plasminogen activator tPA antigen, and type 1 plasminogen activator inhibitor antigen PAI-1 and found evidence for an impaired fibrinolytic system associated with overcommitment on their three measurement occasions. In a study by Irie et al. (2004), it was reported that ERI/OC is positively related to hematological values (e.g. red blood cells, hemoglobin, hematocrit). Beside these studies on basal measures, in an own study we investigated if chronic work stress might be reflected in an exaggerated pro-coagulant stress response (von Känel et al. 2009). We measured ERI/OC in schoolteachers at study entry and, after a mean follow-up of 21 ± 4 months when subjects returned to the lab for the stress testing. During recovery from acute stress, OC correlated with D-dimer increase and smaller fibrinogen decease. In sum, we found evidence that OC, but not ERI, is associated with a hypercoagulable state in response to acute psychosocial stress, particularly during the recovery period.

7.3.2.6 Immune System Mediators

Only a few studies so far assessed potential associations between ERI/OC and different immune cell populations. Bosch et al. (2009) were the first to examine the potential influence of ERI/OC on immunosenescence. To assess two components of an aging immune risk phenotype, the number and proportion of late-differentiated (CD27-CD28-) CD8 T cells (CTLs) as well as the CD4:CD8 ratio were measured in 537 factory workers. Lower reward and higher ERI were associated with a significantly lower CD4:CD8 ratio. Furthermore, higher overall levels of psychosocial work stress were associated with increased numbers in CD27-CD28-CTLs. These results suggest that psychosocial work stress may contribute to immunological aging. In an own study we investigated lymphocyte subset counts before and after acute stress in 55 healthy schoolteachers. High levels of ERI and OC were associated with lower numbers of natural killer (NK) cells (CD16+/56+) whereas only

high levels of OC were related to a lower increase in T-helper cells (CD4+) after stress, suggesting a dampened innate immune defense in relation to ERI/OC (Bellingrath et al. 2010). In line with this, Nakata and colleagues (2011) found NK cells to be significantly associated with ERI but only in male participants. Also, effort and reward but not OC were related to NK cells numbers. Finally, higher levels of reward were positively associated with NK cell cytotoxicity and inversely associated with B cells.

Secretory immunoglobulin A (sIgA), which can be found abundantly in saliva, is considered to be the best marker for mucosal immunity. SIgA acts as the first line of innate immune defense by preventing viral pathogens, which are mainly responsible for upper respiratory tract infections, entering the body via mucosal tissue. The relationship of mucosal immunity with the general immune defense, however, is not entirely clear and overall findings on the effects of stress on the sIgA response are contradictory so far. Bathman et al. (2013) observed significant associations between ERI and OC and sIgA in a sample of male dairy farmers (N = 66). In simple regressions where efforts, rewards and OC were entered as singular predictors of sIgA concentration, all components of the ERI model were significantly related to sIgA. Furthermore, Wright (2011) found effort and reward, entered together in linear regression analysis, to predict sIgA levels in a medium-sized sample of disability workers.

The association between pro-inflammatory biomarkers and CVD as well as metabolic syndrome has been shown in numerous studies during the past decade. Especially (high sensitivity) C-reactive protein (CRP), indicating not only acute inflammatory processes but also chronic low grade-inflammation, has been established to be an independent predictor for coronary artery disease (Danesh et al. 2004). In two studies, Almadi and colleagues (2012, 2013) investigated associations between ERI and CRP in male Jordanian employees. In the first study, ERI was shown to account for 5 % of the variability in CRP levels, when only the centrally obese subjects were considered and secondly, the odds of suffering from metabolic syndrome were observed to be significantly higher in centrally obese men with both higher ERI scores and higher CRP levels. Similarly, Xu et al. (2015) reported ERI to be positively related to hsCRP and reward to be inversely related to hsCRP in a sample of Chinese workers. Bellingrath et al. (2009) however did not observe a relationship between ERI and CRP levels in a solely female sample of German schoolteachers (N = 104). In line with this, Hamer and colleagues (2006) found no relationship between ERI and circulating levels of hsCRP in a sample of middle-aged healthy men. Subjects with higher levels of ERI however exhibited a significantly stronger increase in hsCRP in response to acute laboratory stress (speech task and mirror tracing) after adjustment for age, BMI, and baseline CRP levels. To sum up, ERI has repeatedly been associated with alterations in immune system functioning, ranging from a dampened innate immune defense, increased risk for immunosenescence as well as chronic low-grade inflammation. However, due to the variety of immunological biomarkers that have been implicated in the studies so far, general conclusions seem to be premature.

7.3.2.7 Oxidative Stress

Recently, researchers raised the idea that oxidative stress might be one possible pathway linking job stress with coronary heart disease since a critical amount of reactive oxygen species (ROS) can lead to oxidative DNA damage. Research on this topic is still extremely scarce. However, one study by Takaki (2013) points to a significant positive relationship between ERI-ratio in men (but not women) and urinary H_2O_2 (hydrogen peroxide), though, other studies did not observe significant associations between the ERI-model and other biomarkers of oxidative DNA damage, like 8-hydroxy-2′-deoxyguanosine (8-OHdG) or oxidative metabolites (Inoue et al. 2009; Irie et al. 2004). Further research is necessary to elucidate the potential role of oxidative biomarkers in chronic work stress.

7.3.2.8 Intima Media Thickness and Vascular Health

The vessel's intima media thickness (IMT) as well as the progression of the IMT are established indicators for cardiovascular health. There is few but reasonably consistent evidence pointing to an association between chronic work stress in terms of ERI on the one hand and IMT on the other. For example, in a large cross-sectional study, Xu et al. (2010) performed high-resolution carotic ultrasonography in 734 Chinese workers without coronary heart disease (508 men and 226 women). In women, effort, ERI-ratio, and OC were positively and reward negatively related to IMT (controlling for relevant covariates). In men, however, such associations rendered non-significant if controlling for covariates. In a longitudinal study across 4 years, Eller and Netterstrom (2007) assessed the relationship between psychosocial factors and the progression of intima media thickness (IMT) in 95 healthy volunteers. In the same vein, they found that different ERI-model components serve as significant independent predictors of IMT progression in men as well as women. In line with this, Fischer et al. (2009) set out to investigate whether ERI/OC is associated with numbers in circulating progenitor cells assessed by flow-cytometry in industrial employees. Progenitor cells are involved in the maintenance of vascular integrity and were found to be decreased in subjects with high cardiovascular risk. ERI was independently associated with lower progenitor cell counts, furthermore a significant interaction effect between smoking and ERI was observed. Such results strengthen the view that chronic work stress in terms of ERI/OC might promote atherosclerotic processes.

7.3.3 Findings on an Allostatic Load Summary Index

The allostatic load summary index has been used to establish relationships between work stress and health-related outcomes. Although there exist several studies on allostatic load in different occupational settings, almost no studies investigated the

association between adverse psychosocial working environment in terms of ERI/OC and a cumulative measure of physiological wear-and-tear. In almost all available studies, single parameters were analyzed although multiple parameters were collected (for reviews see Mauss et al. 2015; Hansen et al. 2009). A least in an own study, Bellingrath et al. (2009) assessed the relationship between indicators of work-related chronic stress in school teachers and disease risk not only with respect to single mediators but with a cumulative measure of physiological wear-and-tear prior to the onset of a manifest clinical disease, as suggested by McEwen and Seeman (1999). In this study, ERI/OC and a summary allostatic load index were assessed in 104 female teachers. Allostatic load was first analyzed according to McEwen's classical model comprised of ten parameters including cortisol, adrenaline and noradrenaline, dehydroepiandrosterone-sulfate (DHEA-S), waist/hip-ratio (WHR), HbA1c, high density lipoprotein (HDL), total cholesterol/HDL-ratio as well as systolic and diastolic blood pressure. To additionally account for immunological, blood coagulation, and metabolic processes, it was furthermore extended by TNF-α, CRP, fibrinogen, D-dimer, percent-body-fat, triglycerides, and glucose. Both composite AL-indices were significantly higher in women with higher ERI levels, reflecting subtle dysregulation across multiple stress-sensitive systems. Despite the limitations of a cross-sectional analysis in a relatively small, solely female study sample, these findings potentially underline an advantage of a composite AL score in quantifying future disease risk in apparently healthy and working cohorts, compared to a confined investigation of single biological risk factors.

7.4 Outlook

Taken together, the existing studies investigating the mechanisms which underlie the associations between job-related stress and negative health outcomes suggest that already healthy subjects with elevated ERI/OC show subtle changes in multiple psychobiological stress markers before a potential disease manifestation.

Advancing our knowledge about psychobiological mechanisms could help to develop prevention programs, based on the theoretical framework of the ERI-model, that complement the well-evaluated techniques of relaxation, meditation or stress inoculation, by focusing on the modification of dysfunctional work-related attitudes regarding achievement and commitment and the ability to gain mental distance from work-related obligations (Aust et al. 1997). Stress management interventions based on the ERI model could help to improve individual coping skills, such as declining inappropriate demands, developing a realistic appraisal of personal resources and to establish multiple sources of self-esteem, not only with regard to work-related achievement. An intervention study explicitly based on the ERI model by Limm and colleagues (2011) is especially encouraging as it could show that perceived stress reactivity after 1 year was significantly reduced in the intervention group. In recent years there has been growing research activity that aims to investigate the effects of stress management interventions not only on behavioral outcome

measures and subjective stress ratings but also on physiological stress markers, especially cortisol (Gaab et al. 2003; Storch et al. 2007; Flook et al. 2013; Hammerfald et al. 2006). In the above mentioned intervention study by Limm et al. (2011) however no effect on cortisol levels was found, whereas with respect to salivary α-amylase, an index for sympathetic activity and dysregulation of the autonomic nervous system, a trend could be observed for a stronger decrease in the intervention group (area under the daytime curve and daytime slope) compared to the control group.

Furthermore, a precise knowledge about psychobiological pathways from ERI/OC to health impairments is not only relevant for person-oriented interventions, it should also encourage the implementation of structural and organizational changes that target the communication and reward culture at the work place as well as organizational climate and organizational justice in order to improve psychosocial workplace characteristics. Finally, alternative methods of measuring stress in daily life, such as ambulatory assessment, that allow the investigation of subjective experiences linked to a particular time and context, could help to advance knowledge on psychobiological pathways to stress-related disease vulnerability due to job-related stress (Conner and Barrett 2012; Kudielka et al. 2012).

With this, the usefulness of the ERI/OC model in the area of psychobiological stress research is at least twofold. First, this work stress model helps us to gain a better understanding of the concrete mechanistic pathways leading from work stress to adverse health effects. Furthermore, the model helps us to identify person- as well as organizational-oriented targets for prevention– and with this, helps us to implement a salutogenic approach to face (chronic) stress at work.

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