Philipps Universität Marburg

Mechanisms of Fatigue in Everyday Life

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

(Dr. rer. nat.)

Dem Fachbereich Psychologie der Philipps-Universität Marburg vorgelegt von

Dipl.-Psych. Johanna Marie Dörr

aus Wallau an der Lahn

Marburg an der Lahn, Februar 2016

Vom Fachbereich Psychologie der Philipps-Universität Marburg (Hochschulkennziffer 1080)
als Dissertation angenommen am 03.05.2016
Erstgutachter: Prof. Dr. Urs M. Nater
Zweitgutachter: Prof. Dr. Winfried Rief
Tag der mündlichen Prüfung: 03.05.2016

Content

List of abbreviations

AAR = Alpha-Amylase Awakening Response

ACTH = Adrenocorticotropic Hormone

ANS = Autonomic Nervous System

CAR = Cortisol Awakening Response

CDC = Centers for Disease Control and Prevention

CFS = Chronic Fatigue Syndrome

CRH = Corticotropin Releasing Hormone

DSM = Diagnostic and Statistical Manual of Mental Disorders

FMS = Fibromyalgia Syndrome

HLM = Hierarchical linear modelling

HPA = Hypothalamic-Pituitary-Adrenal

IOM = Institute of Medicine

sAA = salivary Alpha-Amylase

List of Figures

Mechanisms of Fatigue in Everyday Life

1. Introduction

1.1 Defining Fatigue

Fatigue is a phenomenon we all experience every day. It presents as a sense of exhaustion, tiredness, weakness, or a subjective lack of energy (Riley et al., 2010; R. Schwarz, Krauss, & Hinz, 2003). Similar to pain, fatigue is a subjective phenomenon that can only be measured via self-report (Dittner, Wessely, & Brown, 2004). Further, it can be assessed unidimensionally (fatigue intensity) as well as multidimensionally. The underlying assumption of multidimensional measures is that fatigue has different qualities, of which mental (i.e. feeling of emptiness or boredom, difficulties concentrating) and physical (weakness, low energy) are the most prominent (Hardy & Studenski, 2010). Fatigue is distinct from sleepiness, although the concepts are related to each other. Whereas sleepiness describes a drive to fall asleep, fatigue comprises a state of subjective energy depletion (Akerstedt, Axelsson, Lekander, Orsini, & Kecklund, 2014). Fatigue can be seen as a normal response to mental or physical demands and serves the purpose of triggering resting behavior to achieve recovery and ultimately reinstate homeostasis (Chrousos, 2009; Dantzer, Heijnen, Kavelaars, Laye, & Capuron, 2014). As such, it serves allostasis − the ability of the organism to respond to demands or threats to safety or homeostasis (Sterling & Eyer, 1988). In line with this, fatigue typically increases throughout the day, with the highest levels in the evening, partly depending on how strenuous the day has been (Buysse et al., 2007; Dahlgren, Kecklund, & Akerstedt, 2005). The proper functioning of this cycle of demands, fatigue, and recovery (see Figure 1), which repeats itself every day and also within days (e.g. when executing physically or mentally demanding tasks), is very important for health, as will be explained in greater detail in the following sections. Although fatigue is generally perceived as a subjectively unpleasant state, an organism would most likely not survive without it.

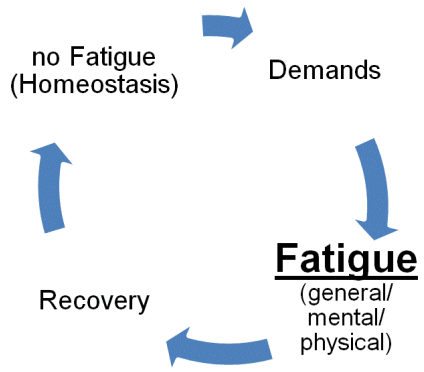


Figure 1 Functionality of fatigue illustrated using the allostasis model. Homeostasis is challenged by demands; responding to demands leads to fatigue (which can be measured on different dimensions of which mental physical are the most prominent ones), fatigue in turn triggers resting behavior and therefore recovery; recovery reduces fatigue (which could, again, be assessed on different dimensions, but has been omitted in this part of the figure for the sake of simplicity) and reinstates homeostasis

Clinically relevant fatigue

Understanding which mechanisms influence fatigue is of great importance, because there are cases in which the “allostatic cycle” of demands, fatigue, and recovery is disrupted or pathologically altered. Fatigue can reach clinical significance when it is not diminished by resting behavior (recovery) or when it presents with such intensity that it interferes with daily living and well-being (Riley, et al., 2010). In a sample of 2552 persons representative of the German population, Hiller, Rief, and Brähler (2006) found a point prevalence for fatigue (excessive tiredness) of 17.5% (2.1% with severe or very severe intensity) and a 2-year prevalence of 8% for fatigue on mild exertion. In another German survey of 20,000 people from the working population, as many as 45.8% reported having suffered from fatigue within the last 12 months, of whom 18.8% (8.6% of the whole sample) sought medical attention because of their fatigue (Wittig, Nöllenheidt, & Brenscheidt, 2012). In other surveys, prevalence rates of 11.3% for chronic fatigue (i.e. longer than six months) (Wessely, Chalder, Hirsch, Wallace, & Wright, 1997) were found in primary care. In a US population-based survey, the authors estimated the costs for society caused by fatigue to be about 136.4 billion US Dollars annually (Ricci, Chee, Lorandeau, & Berger, 2007). Besides personal

impairment and distress of the affected individual, fatigue is therefore a problem for society, with a high economic impact.

With regard to socioeconomic influencing factors, surveys show that women report higher fatigue levels than men and that fatigue levels increase with increasing age (Kroenke, Wood, Mangelsdorff, Meier, & Powell, 1988; Loge, Ekeberg, & Kaasa, 1998; R. Schwarz, et al., 2003; van't Leven, Zielhuis, van der Meer, Verbeek, & Bleijenberg, 2010; Vermeulen, 2006). Fatigue is also heightened as part of various diseases (e.g. severe or chronic medical conditions, anxiety and depressive disorders, and sleep disorders), and is a common side effect of medication intake (Chen, 1986; Pawlikowska et al., 1994). Chronic fatigue often occurs in diseases such as cancer (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010), HIV infection (Barroso, 1999), or multiple sclerosis (Bethoux, 2006). However, in some cases, no underlying somatic explanation can be found for fatigue based on present-day medical knowledge. In these cases, fatigue is referred to as “medically unexplained”. Medically unexplained fatigue often occurs in combination with other medically unexplained somatic symptoms. These symptom complexes can be referred to as “functional somatic syndromes” (for an overview see Fischer & Nater, 2012; Wessely, Nimnuan, & Sharpe, 1999). If medically unexplained chronic fatigue is the main complaint and is accompanied by cognitive problems, sore throat, tender lymph nodes, myalgia and joint pain, headaches, unrefreshing sleep, as well as post-exertional malaise, this condition is referred to as “Chronic Fatigue Syndrome” (CFS, Fukuda et al., 1994). Slightly differing symptom constellations might be classified differently. One example is fibromyalgia syndrome (FMS, Wolfe et al., 2010). In FMS, medically unexplained chronic widespread pain is the main symptom, accompanied by fatigue, waking unrefreshed, and cognitive symptoms. We and others have proposed that conditions presenting with clinically relevant, chronic medically unexplained fatigue can be seen as one end of a continuum, with mild, infrequent fatigue representing the other end (Dawson, Ian Noy, Harma, Akerstedt, & Belenky, 2011; Nater & Doerr, 2012).

Chronic medically unexplained fatigue is a phenomenon that is hard to grasp and poorly understood, although it has been a problem for society throughout history and has drawn the (documented) attention of researchers and practitioners for at least the last one and a half centuries (Johannisson, 2006). Besides the aforementioned definition of CFS, several other attempts have been made to define, classify (by means of diagnostic criteria), and label conditions that present with chronic medically unexplained fatigue as the main symptom, prominent examples of which include “Neurasthenia” (World Health Organization, 1992) and “Burnout” (Maslach & Jackson, 1981). Uncertainties about when and how to use which label, and an interchangeable use of the label “depression”, can be observed from media to health care professionals. In an attempt to reduce uncertainties and raise awareness of the problems inherent in the use of these labels, we recently addressed the problem of differentiation and overlap between these concepts (CFS, Neurasthenia, and Burnout), as well as the distinction between these concepts and depression (Doerr & Nater, 2013). Three important conclusions can be drawn from this narrative review, which guided the empirical studies summarized in the present thesis. First, it became clear that the existing definitions for fatigue syndromes overlap and (at least concerning Neurasthenia and Burnout) lack validity and reliability. In light of the heterogeneity of persons who are grouped together when using one of these diagnostic entities, it seems warranted to move away from the level of syndromes and look for mechanisms that influence fatigue on the symptom level. Second, definitions of conditions that present with fatigue are highly susceptible to the ideas that we (or our society) currently hold about fatigue and fatigue development. Gaps in the knowledge regarding fatigue development, and the necessary continuous change through research findings, lead to uncertainties and also to diverse revisions of (and conflicts about) classification criteria. More research on mechanisms influencing fatigue is therefore needed to fill the knowledge gaps and at some point reduce uncertainties. Third, we observed that another source of uncertainties and conflicts is the dualistic mind-body view, which still prevails in society but is not very helpful when dealing with fatigue. Therefore, research is

needed that takes an integrative approach, combining biological, psychological, and behavioral observations as well as their interplay.

1.2 Influences on fatigue

An overview of current research suggests that fatigue most likely develops and becomes chronic as a consequence of a complex interplay between psycho-social, cognitive-behavioral, and biological mechanisms. The key player in this interplay seems to be “stress” (e.g. Nater, Fischer, & Ehlert, 2011; Nijrolder, van der Horst, & van der Windt, 2008). In epidemiological studies, higher stress levels were found to predict higher fatigue levels cross-sectionally (Chen, 1986) as well as longitudinally (Pawlikowska, et al., 1994). Similar studies also show that chronically fatigued persons report more stressful life events than controls in the year before symptoms begin (Lutgendorf et al., 1995; Masuda, Munemoto, Yamanaka, Takei, & Tei, 2002; Reyes et al., 1996) and higher levels of chronic stress throughout the life span (Nater, Maloney, Heim, & Reeves, 2011).

1.2.1 Defining Stress

The concept of stress was originally based on the finding that exposing an organism to stimuli like heat, cold, or toxic agents, leads to a specific biological response that prepares the body for “fight or flight” (Cannon, 1914). Therefore, Hans Selye (who was the first to call this biological pattern “stress”) defined stress as the unspecific response of the body to any demand (Selye, 1956). Later, Lazarus and Folkman (1984) took an interest in the psychological side of stress and extended Selye’s stress definition. In their cognitive-transactional stress theory, they concluded that the sense of being stressed is triggered in situations in which demands subjectively exceed a person’s coping abilities and are, as such, interpreted as threatening. The same demand can therefore trigger a stress response in one person but not in another. If a demand triggers a stress response, it is also referred to as “stressor”. Research shows that the strength of the subjective sensation of being stressed, as well as the strength of the biological response, depends on the type, intensity, and novelty of the stressor to the individual person (Kemeny, 2003). Therefore, stress is not merely a

demand or a response, but can be defined as an interaction of demands and a person's coping abilities, which results in a specific psycho-biological response. It is conceivable that higher fatigue per se can reduce coping abilities and, in turn, might trigger stress - a thought that will be of greater importance later on.

The stress response is an allostatic mechanism − it enables the organism to dynamically cope with stressors to reinstate homeostasis. Coming back to the cycle of demands, fatigue, and recovery, it becomes clear that stress poses a greater threat to homeostasis than demands that do not trigger a stress response. Stress therefore leads to an enhanced need for recovery, and consequently enhanced fatigue levels. Stress is a common phenomenon and the organism is prepared to deal with it. However, if stress exceeds the range within which the organism's individual recovery potential is sufficient, stress might be the very process that disrupts or alters the "demands – fatigue – recovery" cycle.

Little is, however, known about *how* stress might translate into to clinically relevant fatigue. One theory that might be able to explain this process is the "allostatic load" theory: McEwen proposed that illness develops when the body is faced with repeated or prolonged stress which prevents the organism from recovering properly (1998). He suggested that through repeated or prolonged stress, stress-responsive biological systems "wear out" and ultimately fail to respond adequately to stressors, which leads to a number of adverse health outcomes, including chronic fatigue (McEwen, 2000). Hence, a shift towards the clinically relevant end of the fatigue continuum might be triggered by chronic stress, probably by "wearing out" the body's stress-responsive systems. The two most important stress-responsive biological systems are the Hypothalamic-Pituitary-Adrenal axis (HPA axis) and the Autonomic Nervous System (ANS, Kemeny, 2003).

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis' response to stress is triggered by the release of corticotropin-releasing hormone (CRH) by the hypothalamus, which in turn stimulates the pituitary to release

adrenocorticotropic hormone (ACTH), ultimately causing the release of the glucocorticoid cortisol by the adrenal glands. The release of cortisol, in turn, reduces hypothalamic CRH production as well as the release of ACTH by the pituitary as part of a negative feedback loop (Barrett, 2005). Whereas ANS activity increases immediately, the highest concentrations of cortisol can be found about 20-40 minutes after a stressful event (Dickerson & Kemeny, 2004). Cortisol is the gold standard marker of HPA axis activity. It can be measured in a variety of body fluids such as blood samples, 24hour accumulated urine samples, saliva samples. As almost every cell in the body has glucocorticoid receptors, the influence of cortisol on the body is manifold. For example, cortisol is able to suppress immune activity.

HPA axis activity shows a circadian pattern which is reflected by a typical nocturnal and diurnal secretion pattern of cortisol. During the day, cortisol increases in the morning (the cortisol awakening response, CAR) and decreases during the remainder of the day (Barrett, 2005). The CAR in particular has been found to be a reliable measure for the responsive capability of the HPA axis (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999) and has been associated with diverse health outcomes (Fries, Dettenborn, & Kirschbaum, 2009).

Autonomic Nervous System

The ANS adjusts the body's internal environment to external demands through efferent and afferent pathways. It has a sympathetic, parasympathetic, and enteric division (which controls bowel movements and will not be in the focus of this thesis). The sympathetic and parasympathetic divisions work antagonistically: Basically, sympathetic activity increases when the body is activated, whereas parasympathetic activity dominates in states of relaxation (Richerson, 2005). During the stress response, the sympathetic part of the ANS is thus activated and the parasympathetic part is inhibited. Activation of the sympathetic part leads to a release of norepinephrine through postganglionic fibers (sympathetic-neural system) and a release of primarily epinephrine (80%) and, in small parts, also norepinephrine (20%), by the adrenal medulla (sympatho-adrenomedullary system). Therefore, ANS activity

can be measured by determining epinephrine and norepinephrine levels in blood samples or accumulated 24hour urine samples. The ANS targets smooth muscles of the organs, cardiac muscles, and glands. Heightened ANS activity thus also leads to increases in heart rate and blood pressure. Cardiovascular measures (heart rate, heart rate variability, blood pressure) therefore serve as non-invasive measures of ANS activity (for an overview of ANS measures see Fischer & Nater, 2015). Further, binding norepinephrine to the adrenergic receptors on acinar cells of the salivary glands stimulates the production and release of salivary proteins into the oral cavity. As the most abundant protein in human saliva, salivary alpha-amylase (sAA) has gained much interest as a surrogate marker of ANS activity (Nater & Rohleder, 2009; Rohleder & Nater, 2009). Similar to cortisol, SAA activity also shows a diurnal pattern. However, the pattern itself is antagonistic to cortisol: It decreases in the first hour after awakening (also called the “alpha-amylase awakening response”, AAR), and then shows an increase until the evening, when it stagnates or slightly decreases until bedtime (Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007).

1.2.2 Taking an integrative view

In light of allostatic load theory, studies on the influence of stress on fatigue should include measures of stress-responsive biological mechanisms (HPA axis and ANS). Moreover, mechanisms on all levels of observation that have been found to increase or buffer psycho-biological effects of stress on health are likely highly relevant for fatigue. As mentioned above, it is of utmost importance to include these different levels of observation in studies in order to pursue an integrative view of what influences fatigue. Figure 2 depicts a model of influences on fatigue that extends Figure 1 by stress-relevant mechanisms (including social, behavioral, and biological mechanisms, as well as the mechanisms at the level of subjective experience). Another aspect of taking an integrative view is that fatigue can be seen as having different qualities and therefore can be assessed on different dimensions. With regard to the different levels of stress-relevant mechanisms, psychobiological stress measures were found to interact with (i.e. be influenced by as well as exert an influence on) recovery mechanisms like sleep (e.g. Akerstedt, Kecklund, &

Axelsson, 2007; Hall et al., 2004). Additionally, social influences have repeatedly been shown to impact psycho-biological stress and health measures (Ditzen & Heinrichs, 2014). Relevant mechanisms might be social support (buffering of stress), social conflicts (increasing stress), or co-regulation of mood and biological measures within cohabitating persons (e.g. within couples). Of course, how a person behaves also has a strong influence on psychobiological stress measures, and therefore most likely on fatigue. A behavioral mechanism that has been widely discussed to buffer effects of stress on health is physical activity (Gerber & Puhse, 2009).

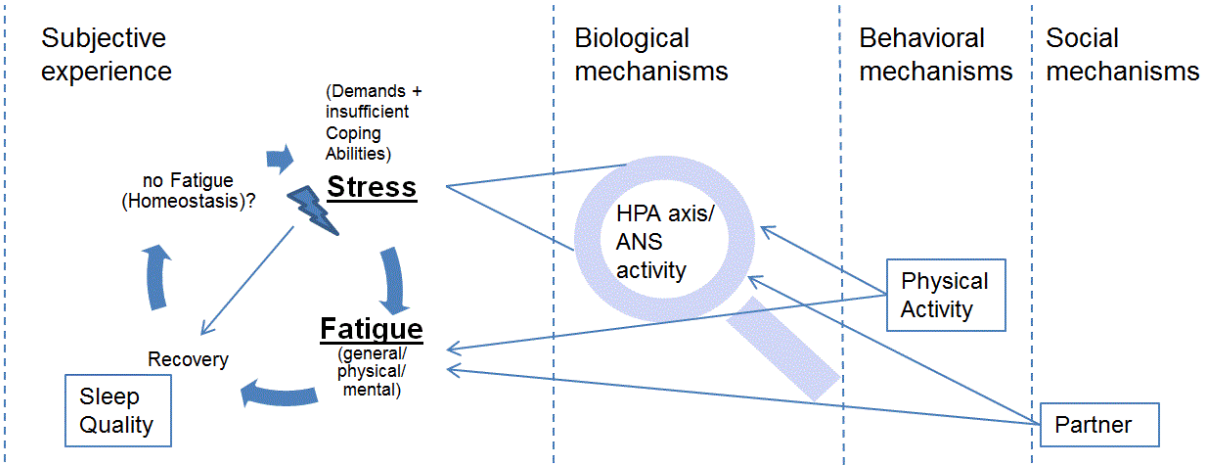


Figure 2. Model of stress as the disruptive element of the "allostatic cycle" (depicted on the left-hand side) and sleep quality as one indicator for recovery at the level of subjective experience, as well as important mechanisms on the social (partner) and behavioral (physical activity) level that likely influence fatigue (directly and/or through changes in stress-responsive biological mechanisms). HPA axis = Hypothalamic-Pituitary-Adrenal axis, ANS = Autonomic Nervous System

1.3 A methodological consideration: Thinking "everyday life"

We now know that when attempting to find out *how* stress leads to fatigue, we ultimately have to look at what happens within a person when he or she experiences stress, what mechanisms on different levels of observation exert their influence on this biological response − and how what happens relates to fatigue. Although surveys have the advantage of potentially comprising large sample sizes which can be assessed longitudinally, they rely on questionnaire data, which are prone to retrospective bias. Moreover, when using surveys, a real-time assessment of mechanisms is not possible and no biological markers can be

assessed. Laboratory studies, on the other hand, have the advantage of assessing mechanisms in a highly controlled setting, but they have little ecological validity and do not normally comprise a time span of more than one or two days. This means that findings from surveys as well as laboratory studies might not be applicable to everyday-life conditions and it is not possible to investigate changes that occur within and between several days. In the past two decades, a branch of research has been established which collects data in the everyday life of participants using so-called "ambulatory assessment" or "ecological momentary assessment" designs (Fahrenberg, Myrtek, Pawlik, & Perrez, 2007; Shiffman, Stone, & Hufford, 2008). Usually, this includes the use of self-report at different time points (e.g. by diary entries), which can be assessed in combination with biological (e.g. measurement of salivary cortisol) and/ or behavioral data (e.g. physical activity). This type of research has three important advantages: 1. It is highly ecologically valid (i.e. results can be applied to everyday life) because it directly assesses phenomena in the place where they usually occur (Reis, 2012), 2. It assesses phenomena not only *where*, but also *when* they occur, i.e. in real time. Therefore, retrospective biases are less likely (N. Schwarz, 2012), 3. Due to (micro-)longitudinal designs, changes from one time point to another can be observed within persons, which makes a stronger case for causal attributions than between-person designs (Hamaker, 2012). Thus, insights from ambulatory assessment studies have been found to be very helpful for research investigating the interplay between psychological and biological parameters (Smyth & Stone, 2003) and should also be applied in fatigue research.

1.4 Relationship between stress and fatigue in everyday life – state of research

Only two studies have explicitly assessed the relationship between stress and fatigue in everyday life using intra-individual designs (i.e. assessing how fatigue changes within a person in everyday life due to different levels of stress). One found fatigue levels to be significantly higher during academic stress as opposed to at the beginning of the academic year in a sample of students (Dittner, Rimes, & Thorpe, 2011). The other study found that mean daily stress levels prospectively predicted bedtime fatigue in a healthy sample (Akerstedt, et al., 2014). In concert with cross-sectional studies showing an association

between stress and fatigue, it might be assumed that stress predicts fatigue on a daily basis. However, a replication of Åkerstedt and colleagues' findings also including within-day changes is warranted. Additionally, as mentioned before, it is conceivable that in a state of higher fatigue, it is harder to cope with demands, which in turn leads to higher stress levels. However, no study so far has assessed the prospective influence of fatigue on stress.

Importantly, more research is needed that examines mechanisms which influence or mediate the stress-fatigue relationship as depicted in Figure 2. Therefore, the next part of this thesis provides an overview of the literature on mechanisms that are likely to influence fatigue in everyday life in the light of allostatic load theory (i.e. stress-responsive biological systems as well as important stress-associated factors on the social, psychological, and behavioral level).

As mentioned above, fatigue can be seen as a continuum ranging from mild, infrequent fatigue to chronic medically unexplained clinically relevant fatigue. Therefore, the literature review will include studies on fatigue in healthy populations (where fatigue is likely a transient, non-clinical phenomenon), populations with heightened or prolonged stress levels (which might suffer from heightened fatigue levels), as well as populations suffering from clinically relevant fatigue. As CFS criteria, as opposed to Burnout or Neurasthenia, require careful consideration and exclusion of medical conditions that might explain fatigue (Doerr & Nater, 2013), the focus of this review will be on CFS literature as defined by the Centers for Disease Control (Fukuda, et al., 1994; Holmes et al., 1988) when looking at mechanisms that are relevant for the clinically relevant end of the fatigue continuum. Furthermore, research on FMS will be included. As explained in section 1.1 ("clinically relevant fatigue"), CFS and FMS are overlapping syndromes. This has led researchers to discuss whether they are essentially the same condition (Wessely, et al., 1999). Fatigue is a predominant feature in FMS (Overman, Kool, Da Silva, & Geenen, 2015; Vincent et al., 2013), and CFS prevalence rates of up to 80% are found in FMS patients (Aaron & Buchwald, 2003). Therefore, studies on fatigued patient populations often include CFS as well as FMS, or mixed CFS/FMS samples, and find similar divergences from healthy subjects.

Research on the influence of HPA axis and ANS activity on fatigue (biological mechanisms) in everyday life is discussed in the first part of the review. Following this, research concerning the influence of sleep quality (recovery mechanism) on fatigue is presented. Additionally, data relevant for daily relationship-specific influences on fatigue (social mechanism) and the association between physical activity (behavioral mechanism) and fatigue in everyday life are outlined. Results from ambulatory assessment studies assessing intra-individual associations of the aforementioned parameters with fatigue levels in healthy as well as fatigued subjects are summarized if available. Moreover, changes in relation to heightened stress conditions (within as well as between persons) are described. In the final parts, differences between chronically fatigued patients (i.e. patients with CFS or FMS) and healthy controls are introduced. Where no ambulatory assessment studies are available, important findings from surveys or laboratory studies that might be applicable to everyday life are referred to.

4.1 Biological mechanisms

Hypothalamic-Pituitary-Adrenal axis

There are several studies investigating the influence of HPA axis activity on fatigue in healthy populations. Eek, Karlson, Garde, Hansen, and Orbaek (2012) found a positive correlation between the CAR and lack of energy, lack of motivation, and physical exertion (referring to a “typical workday”) in a population-based sample. Furthermore, Lindeberg and colleagues (2008) found a negative association between diurnal cortisol variability and fatigue levels (referring to the last four weeks), also in a population-based sample. Few studies have assessed prospective associations between daily cortisol output and fatigue in healthy samples: Adam, Hawkley, Kudielka, and Cacioppo (2006) found low morning cortisol levels to be associated with higher fatigue levels at the end of the day in a population of older adults. Kumari and colleagues (2009) found that low cortisol at awakening and a flat cortisol slope throughout the day were associated with fatigue levels 2.5 years later in a population-based sample. However, results of another study (Dahlgren, Kecklund, Theorell, & Akerstedt,

2009) did not indicate that cortisol levels predict subsequent fatigue in a healthy sample, but did find that fatigue (retrospective measurement at bedtime) was associated with high evening cortisol levels and predicted low cortisol at awakening the next day.

When we recall that HPA axis activity is heightened as part of an acute stress response, which we know from laboratory studies, it is likely that stress alters HPA axis activity in everyday life too. And indeed, Schulz, Kirschbaum, Pruessner, and Hellhammer (1998) found that participants with heightened chronic stress levels had a steeper increase in cortisol after awakening in comparison with participants with lower chronic stress. Steptoe, Cropley, Griffith, and Kirschbaum (2000) found higher morning cortisol levels in participants with higher job strain (assessed one year before cortisol measurement) compared to participants with lower job strain. Moreover, using an intra-individual design, Dahlgren and colleagues (2005) found a flattened diurnal cortisol pattern, which was based on a reduced decline from morning levels to 10am, during a stress as compared to a non-stress week. The same research group also found higher stress levels to be associated with higher cortisol levels at bedtime in another study (Dahlgren, et al., 2009). Additionally, Smyth and colleagues (1998) reported evidence that current problems as well as anticipated stress were associated with increased salivary cortisol levels 20 min after data entry in an ambulatory assessment design. These findings suggest an association of heightened stress levels with heightened daily cortisol levels.

Interestingly, in CFS as well as FMS samples, *reduced* daily cortisol levels compared to healthy controls have been found in blood samples (e.g. Demitrack et al., 1991; Gur, Cevik, Nas, Colpan, & Sarac, 2004), 24h urine samples (e.g. Crofford et al., 1994; Scott & Dinan, 1998), and saliva samples (e.g. Nater, Youngblood, et al., 2008; Riva, Mork, Westgaard, Ro, & Lundberg, 2010; Strickland, Morriss, Wearden, & Deakin, 1998). Furthermore, CFS as well as FMS patients were found to present with an attenuated CAR compared to healthy controls (Nater, Maloney, et al., 2008; Riva, Mork, Westgaard, & Lundberg, 2012). Accordingly, there is meta-analytical evidence of a basal hypocortisolism

(i.e. lower basal levels of cortisol) in CFS patients and (female) FMS patients when compared with healthy control subjects (Tak et al., 2011). Furthermore, another meta-analysis concluded that in particular, blunted diurnal variability of the HPA axis (i.e. CAR and slope of decrease throughout the day) is related to fatigue states (Powell, Liossi, Moss-Morris, & Schlotz, 2013). However, as most of these studies employed cross-sectional designs, it remains unclear whether this blunted or reduced HPA axis activity is a cause or a consequence of the fatigue syndrome. When interpreting these findings in light of allostatic load theory, blunted or reduced HPA axis activity might be a sign of "wearing out", where a state of heightened activity is followed by a state of blunted activity in the face of chronic stress conditions (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Studies on the prospective association between daily cortisol secretion and fatigue in CFS or FMS patients are lacking.

In sum, there is some indication that reduced cortisol levels predict fatigue longitudinally in healthy populations, although studies are sparse. Populations with heightened stress levels present with heightened cortisol levels (compared with non-stressed populations and when comparing high- and low-stress episodes intra-individually). Reduced levels and reduced variability of cortisol throughout the day have been found in chronically fatigued patients when compared with healthy samples. In healthy as well as chronically fatigued persons, it remains unclear whether stress exerts its influence on fatigue through HPA axis activity on a daily basis.

Autonomic Nervous System

To date, no study has investigated the prospective association between ANS measures and fatigue in everyday life. In laboratory studies of healthy samples, however, an increase in heart rate with increasing fatigue is reported over the course of fatigue-inducing tasks (e.g. Tran, Wijesuriya, Tarvainen, Karjalainen, & Craig, 2009). Studies on the effect of stress on ANS activity in daily life show increased activity of blood pressure and heart rate in relation to increased stress (e.g. Shapiro, Jamner, Goldstein, & Delfino, 2001; Steptoe,

2000). There is also one study that did not find ANS activity (measured by sAA) to be influenced by the participants' acute stress level (self-reported estimate referring to one hour before saliva sampling) in everyday life (Nater, et al., 2007). SAA levels were, however, positively associated with chronic stress and stress reactivity in this study.

There has been a great deal of laboratory research on differences in ANS activity between CFS or FMS patients and healthy controls. However, the results of these studies are more equivocal than those regarding HPA axis activity (for an overview see Nater, Fischer, et al., 2011; Tak & Rosmalen, 2010). While some studies found higher basal heart rate and lower heart rate variability (i.e. higher sympathetic and lower parasympathetic activity) in CFS patients compared to controls (e.g. Boneva et al., 2007; Duprez et al., 1998), two studies investigating baseline levels of epinephrine and norepinephrine in blood samples showed no differences between CFS patients and healthy controls (Boneva, et al., 2007; De Lorenzo, Hargreaves, & Kakkar, 1997). In FMS, results also point towards a basal hyperactivity of the sympathetic (reviewed in Martinez-Lavin, 2007) and a basal hypoactivity of the parasympathetic nervous system in this patient group (e.g. Cohen et al., 2000 measuring heart rate variability). Two studies in controlled hospital-hotel settings investigated the association between fatigue and ANS activity in patients with CFS or FMS: Boneva and colleagues (2007) reported a moderate positive correlation between heart rate over 2 days and fatigue scores (measured by questionnaires referring to "lately") in a sample of CFS patients. Riva, Mork, Westgaard, Okkenhaug Johansen, and Lundberg (2012) found a negative association between 24h urinary epinephrine and physical fatigue in FMS patients.

In sum, both stress and fatigue have been found to be associated with heightened ANS activity in healthy samples. In CFS and FMS, heightened basal sympathetic and lower basal parasympathetic activity compared to healthy controls were reported. It might be assumed that stress causes fatigue through heightened ANS activity. However, results are far from unequivocal, and due to the multitude of measures (see section 1.2.1 "Autonomic Nervous System") and laboratory settings, they are not easily comparable. Studies

investigating the relationship between stress, ANS activity, and fatigue in everyday life are lacking.

4.2 Recovery: Sleep Quality

Sleep is seen as the key recovery mechanism (Akerstedt & Nilsson, 2003) and can be roughly classified into two aspects: sleep quantity and sleep quality (Heitmann et al., 2011). Sleep *quantity* is measured using indices such as number of awakenings after sleep onset, sleep onset latency, as well as time points of falling asleep and awakening. Although some associations have been found between objective sleep measures and subjective sleep quality (e.g. Akerstedt, Hume, Minors, & Waterhouse, 1994), sleep *quality* remains, for the most part, a subjective evaluation (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). In large cross-sectional studies, sleep quality was found to be a better predictor of health outcomes and well-being than sleep quantity (Lavidor, Weller, & Babkoff, 2003; Pilcher, Ginter, & Sadowsky, 1997).

Low sleep quality was associated with heightened fatigue levels in population-based surveys cross-sectionally (Lavidor, et al., 2003) as well as in a study using an ambulatory assessment design (Akerstedt, et al., 2014). Furthermore, subjective sleep problems were related to heightened stress levels in large cross-sectional studies (e.g. Akerstedt et al., 2002; Knudsen, Ducharme, & Roman, 2007) and sleep quality was reduced during a period of heightened stress levels in ambulatory assessment studies (Dahlgren, et al., 2005; Petersen, Kecklund, D'Onofrio, Nilsson, & Akerstedt, 2012). In one cross-sectional study, sleep quality significantly mediated the relationship between stressful life events and fatigue (Thorsteinsson & Brown, 2009). Moreover, there is evidence suggesting a difference in sleep quality, but not sleep quantity, measures between CFS as well as FMS patients and healthy controls (Landis et al., 2003; Majer et al., 2007; Reeves et al., 2006).

In sum, sleep quality likely plays a very important role in fatigue development and can be reduced by stress. Therefore, it is likely that sleep quality mediates the day-to-day stress-fatigue relationship. However, this has not been investigated so far.

4.3 Social mechanisms: Relationship-specific influences

As one very important social mechanism, being in a close relationship has been found to have beneficial effects concerning diverse health outcomes (Holt-Lunstad, Smith, & Layton, 2010). From a large cross-sectional population-based survey, there is also evidence that cohabitation with a partner is associated with lower levels of fatigue (Watt et al., 2000). Throughout the literature, the partner is either seen as a source of social support that reduces stress, or as a source of stress when the relationship quality is bad (Robles & Kiecolt-Glaser, 2003).

Given that being in a close relationship might affect health via stress, a number of studies have found activation and buffering of ANS and HPA axis activity by positive or negative couple interaction (for an overview see Ditzen & Heinrichs, 2014). The effect of couple interaction on fatigue has, however, not been investigated so far. Furthermore, there is an accumulating body of research assessing co-regulation of mood (Anderson, Keltner, & John, 2003; Butner, Diamond, & Hicks, 2007; Schoebi, 2008) as well as biological parameters (Timmons, Margolin, & Saxbe, 2015) as important mechanisms underlying how partners influence each other. Co-regulation is defined as a reciprocal, momentary exchange of emotional and physiological arousal between partners and is assumed to serve purposes of attachment and within-couple homeostasis (Sbarra & Hazan, 2008). Two ambulatory assessment studies assessed co-regulation of HPA axis activity and found that co-regulation of cortisol occurs within the everyday life of partners, especially in couples with low relationship quality (Liu, Rovine, Klein, & Almeida, 2013; Saxbe & Repetti, 2010). To the best of our knowledge, co-regulation of the ANS has not been studied in an everyday-life setting so far. However, laboratory studies have suggested a co-regulation of ANS markers such as heart rate, blood pressure, and breathing rate within couples (e.g. Ferrer & Helm, 2013; Reed, Randall, Post, & Butler, 2013). To date, no study has investigated the influence of a partner on psycho-biological stress measures or fatigue in chronically fatigued populations.

In sum, partners can likely influence each other's fatigue levels by interacting with each other or by co-regulation of fatigue and psycho-biological stress measures within the couple. However, studies testing these assumptions in everyday-life conditions are lacking.

4.4 Behavioral mechanisms: Physical Activity

A widely discussed behavioral mechanism influencing the stress-health relationship is physical activity. Physical activity is defined as any body movement that causes energy expenditure (Caspersen, Powell, & Christenson, 1985). Therefore, exercise (which is defined as planned and structured movement to improve physical fitness) is a type of physical activity, but not every physical activity is exercise.

In an overview of epidemiological evidence in the general population, Puetz (2006) concluded that persons with higher physical activity levels report less fatigue than sedentary persons. This has also been shown using longitudinal survey designs (Bultmann et al., 2002). Given that fatigue is influenced by stress, this effect might be due to the buffering of the adverse effects of stress by physical activity, which has been shown in many studies (reviewed in Gerber & Puhse, 2009). This buffering effect might be mediated by HPA axis and ANS activity. For instance, an attenuated cortisol response (Klaperski, von Dawans, Heinrichs, & Fuchs, 2013) as well as better cardiovascular recovery after challenge (Jackson & Dishman, 2006; Traustadottir, Bosch, & Matt, 2005) was found in physically active samples.

On the other hand, heightened physical activity poses a demand on the body and might increase fatigue levels in the short term. This might lead patients suffering from chronic fatigue to reduce their activity levels because they expect symptom exacerbation. Indeed, in a number of studies, CFS patients were found to show reduced physical activity levels in comparison to healthy control subjects (for an overview see van Weering, Vollenbroek-Hutten, Kotte, & Hermens, 2007). One study using a mixed CFS/FMS sample found reduced levels of peak activity in daily activity levels in patients as compared to healthy controls (Kop et al., 2005). Likewise, there is evidence of reduced general physical activity levels in FMS

patients (McLoughlin, Colbert, Stegner, & Cook, 2011). Another study in patients with FMS found negative associations between objectively recorded physical activity and subjects' estimates of their general and physical fatigue levels during the last three months (Segura-Jimenez et al., 2015). One study by Kop and colleagues (2005), which employed several measurements per day, suggested that physical activity levels do not necessarily predict fatigue in chronically fatigued patients, but that higher fatigue levels predict subsequently reduced physical activity. It thus seems important to investigate both causal directions and different time frames. Most studies used only a couple of days of assessment, whereas a period of at least seven days, including evenings and weekends, is recommended to assess everyday-life physical activity in these patient populations (van Weering, et al., 2007). Therefore, a replication of these findings using longer periods of assessment is warranted.

In sum, there is evidence that adverse effects of stress can be buffered by physical activity. However, no study has assessed the direct interplay between physical activity, HPA axis or ANS activity, and fatigue, in an everyday-life setting.

2. Summary and aim of thesis

Fatigue is the subjective experience of energy depletion that triggers resting behavior and recovery. It can be assessed on different dimensions, of which mental and physical are the most prominent ones. Fatigue is a normal and important part of our daily lives, but can reach clinical relevance when fatigue is not diminished by resting behavior or exceeds normal intensities. If this clinically relevant fatigue is not explained by an underlying medical condition, it is referred to as medically unexplained fatigue. To get to the core of this symptom, more research is needed that investigates how fatigue develops, ideally using highly ecologically valid designs in order to ensure real-life applicability. Existing research suggests that stress plays a key role in fatigue development and perpetuation. Considering that stress is triggered when coping abilities are estimated to be insufficient to cope with a demand, fatigue might also increase stress. However, this direction of causality has not been investigated in everyday life so far. With regard to stress predicting fatigue, it remains unclear

how stress translates into fatigue. Therefore, studies are needed that look for mechanisms that happen within a person taking an integrative view – this means investigating biological changes as well as interacting mechanisms on other levels of observation (e.g. social and behavioral) in a micro-longitudinal manner. Concerning the most relevant stress-responsive biological systems, a blunted daily HPA axis activity and increased basal ANS activity have been found to be associated with changes in fatigue intra-individually. Moreover, enhanced daily HPA axis and ANS activity can be found due to increases in stress levels in everyday-life settings. A reduced daily HPA axis and enhanced daily ANS activity was, on the other hand, found in patients with CFS or FMS (i.e. patients suffering from chronic medically unexplained fatigue). Referring to allostatic load theory, stress responsive systems might be "worn out" by prolonged stress, and hypoactivity of the HPA axis and hyperactivity of the ANS might be signs of this. However, whether these changes in biological activation explain variability in fatigue, or act as mediators between stress and fatigue on a daily basis, remains unclear. With regard to mechanisms that interact with psychobiological stress measures, sleep quality (recovery mechanism at the subjective level), the influence of a partner (social level), and physical activity (behavioral level) seem of special importance. Sleep quality is the most important mechanism of recovery and has been found to be negatively associated with stress and with fatigue. However, no study so far investigated if sleep quality mediates the relationship of stress with next-day fatigue. Partners likely exert influence on each other's fatigue by interacting with each other (buffering or increasing stress) and co-regulation of fatigue, stress, or biological measures within couples. However, no study has investigated relationship-specific influences on fatigue in an everyday-life setting. On the behavioral level, increased physical activity may buffer the detrimental effects of stress on fatigue. Studies are lacking investigating the association of physical activity with psychobiological stress measures and fatigue in everyday life.

The aim of this thesis was thus to find out which factors predict and increase fatigue in everyday life with the aim of shedding light on mechanisms relevant for the chronification of fatigue. We expected stress to (prospectively) predict fatigue. Also, we expected fatigue to

(prospectively) predict stress because it diminishes subjective coping abilities. Further, we expected hypoactivity of the HPA axis and hyperactivity of the ANS to be associated with fatigue, and the relationship between stress and fatigue to be mediated by these biological mechanisms. Moreover, sleep quality was expected to mediate the stress-fatigue relationship from one day to the next. Being in a close relationship and physical activity are investigated as important factors directly influencing fatigue, or influencing fatigue mediated by HPA axis and ANS activity.

First, in light of the multitude of existing labels and definitions, we decided to review different attempts to define and classify chronic fatigue conditions and their differentiation from depression (Doerr & Nater, 2013). This review helps to grasp the concept of chronic medically unexplained fatigue and shed light on why difficulties with and conflicts regarding this symptom are present in society. In the first empirical study, we then investigated the influence of stress on fatigue and the mediating capability of HPA axis activity, ANS activity, as well as sleep quality in a student sample. As part of these analyses, we were also interested in whether the stress-fatigue relationship is reciprocal in nature (Doerr et al., 2015). In a second study, relationship-specific influences on fatigue were analyzed using a dyadic ambulatory assessment approach (Doerr, Nater, Spoerri, Ehlert, & Ditzen, ready to be submitted). In a third study, we investigated the association of HPA axis, ANS, and physical activity, with fatigue in a sample of female FMS patients (Doerr, Fischer, Nater, & Strahler, under review).

3. Summary of Articles

3.1 Summary of narrative review

Doerr, J. M., & Nater, U. M. (2013). Erschöpfungssyndrome – Eine Diskussion verschiedener Begriffe, Definitionsansätze und klassifikatorischer Konzepte. [Fatigue Syndromes – An Overview of Terminology, Definitions and Classificatory Concepts.] *Psychotherapie, Psychosomatik, Medizinische Psychologie, 63,* 69-76.

Fatigue is a subjective phenomenon that is hard to grasp as a pathological state. We observed that different terms related to medically unexplained fatigue were used inaccurately or interchangeably in the media and among health care professionals. Therefore, this narrative review discusses different definitions of chronic fatigue syndromes, differentiation among each other, and differentiation between these syndromes and depression. As the most prominent examples of defining and ultimately classifying conditions that present with medically unexplained fatigue, we chose Neurasthenia, Chronic Fatigue Syndrome (which is also referred to as “Myalgic Encephalomyelitis” by some researchers and patient advocacy groups) (CFS/ME), and Burnout. In the first part of the review, we define fatigue, and what constitutes “chronic” and “medically unexplained” fatigue. Subsequently, we outline a short history of attempts to classify fatigue syndromes. This is followed by a discussion of the respective criteria of each syndrome. In the final part of the narrative review, we reflect on overlapping and differentiating criteria of the syndromes. If available, studies that compare the constructs on an empirical basis are outlined. The same approach is taken in terms of the differentiation between Neurasthenia, CFS/ME, Burnout, and depression.

We conclude that fatigue has been a meaningful phenomenon throughout history. At this point in time, it is not possible to differentiate between the aforementioned syndromes in an unambiguous manner. The functionality of different labels that describe medically unexplained fatigue depends on the given zeitgeist and is highly susceptible to cultural influences. Reflecting on the functional meaning of the respective label before using it thus seems of utmost importance. One problem that leads to uncertainties seems to be the

dualistic mind-body view that still prevails in society. Clear-cut somatic diseases are generally perceived to be more legitimate than mental disorders. Ultimately, promoting a more integrative mind-body view in both research and clinical practice, but also in society in general, would be helpful for addressing at least some of the issues surrounding fatigue syndromes. We conclude that Neurasthenia should be seen in a historical and cultural context. It has lost meaning in Western cultures, but is still a common diagnosis in East Asian cultures. For CFS, the CDC criteria are currently the gold standard. Burnout can, in its current form, be defined as work-related fatigue and should not be used as a diagnosis, but can serve as a research construct. We also conclude that depression should not be used interchangeably with the aforementioned terms, because it comprises symptoms that differentiate it from fatigue syndromes and there is evidence associating it with different biological underpinnings than those of fatigue syndromes. With regard to diagnostics, we stress the importance of carefully assessing patient history and exclusionary criteria when diagnosing fatigue states.

3.2 Summary of empirical studies

Study 1: Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students.

Doerr, J.M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., Hoppmann, C.A., & Nater, U.M. (2015). *Biological Psychology, 110,* 42-49.

As outlined above, stress might translate into fatigue through changes in ANS and HPA axis functioning. A further important contributor to fatigue development might be a reduction in sleep quality which is triggered by stress. Besides assessing whether the stress-fatigue association is mediated by HPA axis and ANS activity as well as sleep quality, we were interested in the direction of causality between stress and fatigue (i.e. whether stress leads to fatigue or whether fatigue could also be a precursor of stress). To test these associations in an everyday-life environment, we conducted a study in a sample of university students. The design of the study also allowed for assessment of possible differences in the aforementioned associations between a condition with lower stress levels and a condition with higher stress levels.

Methods

Participants were recruited via university student mailing lists or notices on campus. Each participant completed an assessment period of five days at the beginning of the semester (control condition) and five days at the end of the semester during a period of exam preparation (exam condition). Participants indicated their stress (“At the moment, I feel stressed out”) and fatigue (“At the moment, I feel fatigued”) level on a scale from 1 to 5. These items were presented at five time points (at awakening, 10 am, 2 pm, 6 pm, and 9 pm) each day using a pre-programmed iPod touch®. Sleep quality was assessed at awakening on a visual analogue scale from 0 to 100. Additionally, half of the participants collected saliva samples at each of the time points on two consecutive days in each condition, with one additional sample 30min after awakening to calculate the biological awakening response. From the saliva samples, cortisol and sAA values were derived. Data analyses were

conducted using hierarchical linear models (Raudenbush, Bryk, Cheong, & Congdon, 2005) to account for the nested data structure (time points /days within persons).

Results

Fifty healthy participants (31 women, 24 ± 3 years) completed the assessments, and 25 of the participants additionally collected saliva samples. Stress was associated with simultaneously measured fatigue as well as with fatigue at the subsequent time point within days (i.e. higher stress levels at 10 am predicted higher fatigue levels at 2 pm). However, the same was true in terms of fatigue predicting stress levels. Results showed higher stress and fatigue levels during the exam condition. Moreover, cortisol levels at awakening were higher during the exam condition than during the control condition. SAA showed a steeper daily slope during the exam condition. A mediation of the association between previous-day mean stress level and mean daily fatigue level by subjectively reported sleep quality of the night in-between was confirmed. Morning cortisol value positively predicted mean daily fatigue; however, this effect disappeared when controlling for condition, suggesting that the association was based on an increase in both parameters during the exam condition. Cortisol and sAA measures (CAR, AAR, morning values, cortisol slope and sAA slope) were not associated with fatigue, and therefore had to be ruled out as mediators of the stress-fatigue relationship.

Discussion

Our findings indicate that stress and fatigue negatively influence each other in a bi-directional manner (a “vicious cycle”). This might be interpreted in light of an increased need for recovery when being stressed, and a decline in coping abilities when being fatigued. Further, stress likely decreases the restorative capacity of sleep, which leads to an increase in fatigue the next day. Future studies should aim at revealing the mechanisms that translate fatigue into stress (for instance by addressing cognition) and examine whether these findings can be replicated in clinical populations.

Study 2: Dyadic co-regulation of fatigue and psychobiological stress measures in everyday life.

Doerr, J.M., Nater, U.M., Spoerri, C., Ehlert, U., & Ditzen, B. (ready to be submitted)

On the level of the social environment, we were especially interested in dyadic effects (i.e. effects of being part of a couple) on fatigue. Interaction with a partner might buffer stress through social support, or increase stress in times of arguments. Therefore, being part of a couple might also have beneficial or detrimental effects on fatigue. However, most of the data concerning dyadic mechanisms are cross-sectional or based on laboratory studies, and the mechanisms by which these partner-to-partner effects are exerted remain unclear. One such mechanism might be co-regulation of fatigue levels within couples, which has been reported concerning mood and biological parameters. We expected that positive couple interaction is negatively associated with fatigue and that co-regulation of fatigue, stress, HPA axis activity and ANS activity occurs in the everyday life of couples.

Methods

Forty heterosexual couples (28 ± 5 years) reported subjective fatigue (on a scale from 1 “full of energy” to 5 “exhausted”) and stress (on a scale from 1 “stressed out” to 5 “relaxed”) levels 4 times a day for 5 consecutive days. They also indicated whether they interacted with their spouse (yes/no) and, if yes, rated the valence of this interaction from 1 (negative) to 10 (positive). Salivary cortisol and sAA were analyzed from samples obtained at the same time points. Data were analyzed using multilevel models of distinguishable dyads (Bolger & Laurenceau, 2013; Laurenceau & Bolger, 2005), with models including separate intercept and slope terms for women and men while adjusting for the nested design (time points within persons within couples) using two-level hierarchical linear models.

Results

Co-regulation within couples was found for fatigue and stress (partly dependent on whether the partners had interacted since the last measurement time point) as well as for cortisol

levels (independent of interaction). SAA values were only co-regulated with those of the partner in women. Stress and fatigue were not associated with each other on a momentary basis (neither an individual's own stress nor stress of the partner predicted an individual's own fatigue). Further, sAA levels were negatively associated with fatigue in women. The valence of interaction was negatively associated with fatigue levels in both genders (i.e. less fatigue was reported when the interaction was positive).

Conclusions

This study shows that fatigue is influenced by relationship-specific mechanisms. Partners influence each other's fatigue through the mechanism of co-regulation as well as through interaction with each other. One implication of this finding is that couple interventions should aim at enhancing a positive valence of couple interaction in everyday life in order to promote individual well-being. Research is needed that assesses these associations in a chronically fatigued population and their partners.

Study 3: Influence of stress systems and physical activity on different dimensions of fatigue in female patients with fibromyalgia.

Doerr, J. M., Fischer, S., Nater, U. M., & Strahler, J. (under review at Journal of Psychosomatic Research).

To assess associations of HPA axis and ANS activity with fatigue in a population suffering from clinically relevant fatigue, we conducted an ambulatory assessment study in a population of female patients with FMS. As mentioned in the introduction, reduced basal HPA axis activity and increased basal ANS activity have been found in patients with FMS compared to healthy controls. However, research is needed that assesses the association of HPA axis and ANS activity with fatigue in patients with FMS intra-individually. Further, we were interested in the effect of physical activity, because this is a behavioral mechanism which might influence fatigue as well as the association between HPA axis or ANS activity and fatigue. We further included the aspect of multidimensionality in this study, because there is evidence that different mechanisms might be relevant for mental as compared to physical fatigue in FMS. Therefore, in this study, we assessed differential influences of HPA axis and ANS activity as well as physical activity on general, mental, and physical fatigue.

Methods

The final sample consisted of 26 female patients with FMS (53 ± 7 years), who reported general (“At the moment, I feel fatigued”), mental (“At the moment, I can concentrate well”), and physical fatigue (“At the moment, I feel physically fit”) levels on a scale from 0 to 4 at six time points (at awakening, 30 min after awakening, at 11 am, 2 pm, 6 pm, and 9 pm) each day for 14 consecutive days. They also collected saliva samples at the same time points, from which cortisol and sAA were derived. Wrist actigraphy was used for assessment of physical activity. From the cortisol and sAA values of the first two daily saliva samples, the CAR and AAR were calculated. Due to lagged analyses of actigraphy data, only four of the six daily self-reports (excluding morning values) were included in data analyses. Data were analyzed on a within-day (or momentary) basis and with daily measures (e.g. mean levels of each fatigue dimension and CAR or AAR) using HLM.

Results

A lower CAR predicted higher mean daily levels of general as well as physical fatigue. Physical fatigue was also positively associated with cortisol values on a momentary basis. Physical activity, on the other hand, neither predicted any fatigue dimension, nor biological parameters on a within-day basis. Mean daily levels of physical activity positively predicted next-day mean levels of general fatigue. Furthermore, momentary physical fatigue negatively predicted subsequent physical activity within days. Heightened physical activity was associated with heightened stress levels within days. Pain and fatigue levels co-varied throughout the measurement period. SAA values were not predictive of any fatigue dimension (either on a momentary or a daily basis).

Conclusions

In this clinical sample, we found evidence for an important role of changes in HPA axis activity when explaining variance in daily general and physical fatigue. This is the first study to show these effects in a design with high ecological validity. This implies that interventions should ideally be interdisciplinary in nature, targeting psychological as well as biological aspects of this syndrome. Future studies should further compare work and leisure physical activity with respect to their predictive value for fatigue.

4. Discussion

4.1 Summary of results

The narrative review revealed that current definitions of syndromes that present with medically unexplained fatigue as the major symptom overlap and cannot be clearly differentiated. Nevertheless, each of their labels has a different underlying functionality, and one should be aware of this before applying them. As concluded in this review, research on the symptom of fatigue is warranted, and not necessarily comparisons between healthy subjects and persons suffering from fatigue syndromes (as they lack valid definitions). Our empirical studies therefore assessed the role of stress and stress-related changes in HPA axis and ANS activity, as well as related sleep quality and factors on the social (being part of a couple) and the behavioral (physical activity) level, in fatigue development using highly ecologically valid micro-longitudinal designs in a student sample, a sample of couples, and a sample of patients with FMS (FMS sample).

Stress and fatigue. Stress and fatigue co-varied within persons in the student sample and the FMS sample, but not in the sample of couples. Moreover, we found a prospective reciprocal association between stress and fatigue within days as well as between days in the student sample. Fatigue levels were also heightened in the student sample in the exam condition.

HPA axis activity. Neither in the student sample nor in the sample of couples was there a momentary association between cortisol and fatigue. The CAR emerged as a negative predictor of mean daily fatigue in the FMS sample, but was not associated with fatigue levels in the student sample. Furthermore, momentary cortisol levels were positively associated with physical fatigue in the FMS sample. In the student sample, morning cortisol levels were heightened in the exam condition.

ANS activity. ANS activity, as measured by sAA, only explained variance in momentary fatigue in the women of the couple sample (negative association). It was not associated with fatigue levels in any of the other studies. It was, however, altered (steeper slope) during exam preparation in the student sample.

Sleep quality. Sleep quality was found to be a mediator between mean daily stress levels and mean daily fatigue levels in the student sample.

Relationship-specific influences. Fatigue, stress, and HPA axis activity were co-regulated within couples. Furthermore, ANS activity co-varied with that of the partner in women. Positive interaction with the partner was associated with reduced fatigue levels.

Physical activity. Objectively measured mean daily physical activity was positively associated with mean same-day stress level and negatively associated with mean next-day fatigue in the FMS sample. However, it was not associated with HPA axis or ANS activity.

4.2 Integration into the literature

Concerning our narrative review, it is important to point out that the discussion about fatigue syndromes has been ongoing since the review was published. Two recent developments are particularly noteworthy: 1. The US-American Institute of Medicine (IOM) has proposed new criteria for CFS and suggested re-naming the syndrome “systemic intolerance disease” (Institute of Medicine, 2015). The biggest difference between these criteria and the CDC criteria or Canadian Consensus Criteria is the suggestion that it should no longer be a diagnosis of exclusion. This has led to a great deal of criticism due to the obvious risk of missing important information in the patient’s medical history as well as increases in prevalence (Jason, Sunnquist, Kot, & Brown, 2015; White, 2015). Whether the IOM report has a lasting impact and ultimately leads to changes in healthcare systems remains to be seen. It is expected that the use of the terms CFS/ME will continue in the medium term. 2. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association) was published at the beginning of 2013, with mentionable changes in the somatoform disorders section. Now, chronic fatigue might be classified as “somatic symptom disorder” (300.82) when presenting with excessive thoughts, feelings, or behaviors related to fatigue. These psychological criteria have been added to the previously existing criteria of somatoform disorders in the DSM IV. On the other hand, fatigue (or another respective symptom) no longer has to be “medically unexplained” in character to

qualify for this diagnosis, which is similar to the change in CFS/ME criteria proposed by the IOM.

In sum, the controversy surrounding the definition of fatigue syndromes seems to be ever ongoing, which is still due to the reasons addressed in our narrative review. Laying the groundwork for understanding fatigue on a symptom basis, we now take a closer look at how the results of the three ambulatory assessment studies that were presented can be interpreted in light of existing research:

Taken together, our empirical studies suggest that heightened stress levels predict fatigue in almost every time constellation (immediately, moment-to-moment within days, between days, and referring to prolonged stress). The finding that stress and fatigue are closely related to each other is in line with existing cross-sectional research (Brown & Thorsteinsson, 2009; Kalimo, Tenkanen, Härmä, & Poppius, 2000) as well as other ambulatory assessment studies (Akerstedt, et al., 2014; Dahlgren, et al., 2005; Dittner, et al., 2011; Kato, Sullivan, Evengard, & Pedersen, 2006). However, the results of the student sample in particular add valuable information as the prospective analyses generated evidence for causal interpretations (i.e. stress being a precursor of fatigue on a daily basis). Moreover, we showed that fatigue also predicted stress levels, which might be part of a "vicious cycle" and should be further explored in future studies. The lack of momentary co-variation of stress and fatigue in the sample of couples might be attributable to methodological differences (fewer measurement time points, verbal anchoring of the items). This led to a lower intraclass correlation, which suggested that there was less variance within persons, thus making it harder to detect within-person changes in the sample of couples.

We were unable to confirm our assumption that HPA axis activity mediates the stress-fatigue relationship on a daily basis. However, our results fit well with the existing data showing that (prolonged) stress is associated with heightened HPA axis activity (Dahlgren, et al., 2005; Dahlgren, et al., 2009; Steptoe, et al., 2000). Additionally, we were the first to show that the CAR is prospectively negatively associated with fatigue within persons on a daily

level, but exclusively in a clinical population (FMS sample). On the other hand, momentary fatigue was associated with higher momentary cortisol values within persons in this sample. In light of allostatic load theory (McEwen, 1998), it might be suspected that the negative association of the CAR with fatigue is a sign of a “worn out” HPA axis function, thus resulting in fatigue. The CAR can be interpreted as a sign of the responsive capability of the HPA axis (Fries, et al., 2009). Interestingly, we did not find the CAR to be associated with pain in the same sample of patients with FMS (Fischer et al., 2016). It is therefore conceivable that changes in the responsive capability of the HPA axis (as opposed to general activity) have a specific influence on fatigue. On the other hand, we found physical fatigue (Doerr et al., under review) and pain (Fischer et al., 2016) to be associated with heightened cortisol values on a momentary basis. Therefore, an involvement of HPA axis activity in the general fatigue/pain symptom complex in FMS seems likely. Although HPA axis activity seems to be a relevant predictor of fatigue, we did not find it to be a mediator between stress and fatigue in any of the studies. As we only looked for within- and between-day associations covering a period of two weeks at the most, this does not necessarily contradict allostatic load theory, which assumes longer-term changes. It is necessary to consider that, to this day, there is no evidence of a “wearing out” of the HPA axis activity. Longer-term longitudinal studies are needed to search for such an effect.

ANS activity (as measured with sAA) was not associated with fatigue in the student or the FMS sample. In women in the sample of couples, we found a negative association between momentary sAA levels and fatigue, suggesting that the women rated their fatigue levels as lower (and energy levels as higher, considering the verbal anchoring of the item) when ANS activity was higher, which is contrary to our assumptions about the relationship between ANS activity and fatigue. However, in view of the fact that higher ANS activity serves the activation of the body and should make energy accessible for a “fight-or-flight” response (Kemeny, 2003), this finding is not surprising in a healthy sample. Our finding of an enhanced ANS activity due to higher stress levels in the student sample is in line with other daily life studies (Nater, et al., 2007; Shapiro, et al., 2001; Steptoe, 2000). ANS activity, like

HPA axis activity, was not a mediator between daily stress and fatigue in any of our studies. Again, a longer-term relationship might be suspected, which should be explored in longitudinal designs covering a longer period of time than our studies (5 to 14 consecutive days). However, current evidence provides less support for the assumption that changes in ANS activity are a precursor of fatigue, and more support for the assumption that changes in HPA axis activity are a causal contributor to fatigue development. Therefore, another line of interpretation is that changes in ANS activity are an effect, and not a cause, of chronic fatigue conditions. Furthermore, it is important to distinguish between basal ANS activity and ANS re-activity. There is some evidence that the ANS shows an altered reactivity to stressors in patients with FMS and CFS when compared with healthy participants in laboratory studies (e.g. Cohen, et al., 2000). The question whether the ANS response to stress is associated with fatigue in everyday life can, for instance, be investigated using event-based ambulatory assessment designs (i.e. self-triggering of data entry and saliva sampling by the participants after a stressful event has occurred). Ideally, this should be combined with a time-based design in order to avoid overlooking changes in diurnal rhythmicity.

Sleep quality was a mediator between mean daily stress and mean daily fatigue. As several other studies also suggest a high impact of sleep quality on fatigue (Akerstedt, et al., 2014; Lavidor, et al., 2003), it is safe to conclude that impairments in sleep quality play a major part in day-to-day variations of fatigue. Furthermore, the mediation of sleep quality between stress and next-day mean fatigue in the student sample shows that this is one mechanism by which stress transfers into fatigue, which was already suggested on a cross-sectional basis (Thorsteinsson & Brown, 2009). The restorative capacity of sleep seems to be impaired by stress, resulting in non-achievement of homeostasis (compare Figure 2), which is associated with higher fatigue levels.

As one social mechanism, we were the first to show co-regulation of fatigue in couples. We also found co-regulation of stress, which is in line with other studies (Saxbe &

Repetti, 2010). Given this co-regulation of both stress and fatigue, partners of chronic fatigue patients might be at high risk of developing fatigue themselves. Therefore, the partner perspective should be implemented in future fatigue research. We also showed that partners' HPA axis activity is co-regulated, which is in accordance with two other ambulatory assessment studies (Liu, et al., 2013; Saxbe & Repetti, 2010). We found co-regulation with the partner's ANS activity exclusively in women, which is in line with the finding that women are generally more affected by relationship parameters than men (Kiecolt-Glaser & Newton, 2001). This might be of special importance as women are more strongly affected by chronic fatigue conditions and report higher fatigue levels than men (Loge, et al., 1998; van't Leven, et al., 2010). However, the fact that positive couple interaction was associated with reduced fatigue in both partners implies that couple interventions might generally be beneficial in fatigue treatment and prevention programs.

Concerning physical activity, our results suggest no immediate, but a (one-day) delayed positive association with general fatigue in patients with FMS. Further, an immediate reduction of physical activity by heightened physical fatigue levels was found in this sample (in line with Kop, et al., 2005). On the other hand, other studies have shown beneficial effects of exercise programs (Busch, Schachter, Overend, Peloso, & Barber, 2008 for an overview) and a negative association between physical activity and longer-term fatigue (Segura-Jimenez, et al., 2015) in this patient population. Moreover, studies in healthy participants suggest an immediate positive association between physical activity and feeling awake (Kanning, Ebner-Priemer, & Brand, 2012). One of our own analyses (using an actigraph-wearing sub-sample of the same sample of students as in Doerr et al., 2015) might bridge these findings: We found that only persons with low chronic stress levels reported reduced fatigue levels after heightened physical activity (Strahler et al., submitted). Integrating our findings with existing research, two important suggestions emerge: 1. On a short-term basis, patients with FMS report no effects or negative effects of enhanced physical activity, but seem to benefit from exercise programs in the longer term. 2. The ability to immediately benefit from heightened physical activity might be dependent on impairment status – the

higher the impairment (e.g. chronic stress), the lower the benefit (or fatigue might even worsen). Again, these suggestions should be investigated using longer-term designs and could also serve as a starting point for experimental studies (i.e. manipulation of activity level). They do, however, highlight the difficulties which patients with FMS (and likely other persons suffering from chronic fatigue) face when engaging in exercise programs, which will be discussed below (section 4.5).

4.3 Strengths and limitations

The most important advantage of our empirical studies is the ambulatory assessment design, which ensures high ecological validity, reduces retrospective bias, and gives room for the assessment of (within- and between-day) prospective associations. Furthermore, we assessed and related data on different levels of observation (person level, subjective daily experiences, objective behavioral and biological data, social influences), and therefore gained a more integrative view of everyday-life influences on fatigue than previous studies. We additionally employed relatively strict exclusion and inclusion criteria and controlled for a multitude of possible confounding variables, which increased internal validity as much as possible considering the ambulatory assessment design.

Although we took these measures, we cannot completely rule out the possibility that a third, non-assessed, variable influenced the outcomes, which is a weak spot in any ambulatory assessment study. Furthermore, our relatively strict exclusion criteria might have reduced the representativeness of the samples. For instance, we did not include obese persons or frequent smokers in any of the samples. Therefore, we cannot claim that our results are applicable to the general population. However, these measures were necessary to control for the effects of these person variables on biological parameters and fatigue. Another concern lies in the complexity of our study designs, which required a high level of compliance on the part of the participants. On the one hand, persons who did not have enough time or flexibility (and a presumably higher stress level) might not have taken part in the first place, which again reduces representativeness. On the other hand, noncompliance

of participants might have decreased the quality of the data. To ensure high compliance during the assessment periods, we put a great deal of effort into explaining the relevance and importance of the studies during the introductory session (including going over and handing out a manual which explained the study design and answered frequently asked questions in detail). Moreover, we implemented a study phone which could be called at all times during the assessment period if any problems or questions occurred. Additionally, we checked for possible compliance-reducing circumstances as part of a post-monitoring interview. In terms of analysis, HLM uses listwise deletion and only includes time points with complete data, resulting in rather conservative effect estimates. Further, we checked the effects of day of assessment on the variables, which did not turn out to be a predictor in any of the studies. Overall, we can be confident in the validity of the presented results.

4.4 Future research directions

Concerning research design, it becomes clear that studies are now needed which continue to employ ambulatory assessment techniques on different levels of observation (subjective, biological, social, behavioral) over longer periods of time (ideally follow-up across years). This is especially important considering support for allostatic load theory (i.e. showing a “wearing out” of biological systems by prolonged stress intra-individually). Ideally, event sampling should be added to time sampling methods. Moreover, additional laboratory studies can provide deeper insights into the association of HPA axis and ANS stress responses (as opposed to basal activity) with everyday-life fatigue.

One strength of the studies in this thesis is, as explained above, the integration of data from a biological, subjective and behavioral level up to the social level, with the aim of gaining an integrative view of fatigue. We defined stress as an interaction of demands and a person’s characteristics, and measured the subjective experience of being stressed. The subjective experience of being stressed is therefore, when referring to Lazarus and Folkman (1984), already a product of a specific demand and the subjectively estimated ability to cope with this demand. Two recent ambulatory assessment studies suggest that high personal

resources (Nagel & Sonnentag, 2013) as well as the use of coping strategies (Schmitt, Zacher, & Frese, 2012) can reduce stress and therefore buffer its effect on fatigue. Therefore, it seems promising to add the assessment of personal resources as well as cognitive mechanisms to future studies. As everyday-life fatigue has also been associated with suppression of anger (van Gelderen, Bakker, Konijn, & Demerouti, 2011), the assessment of emotional mechanisms is also conceivable. On the other hand, physical activity is, of course, not the only behavioral mechanism that might influence stress or fatigue; and nor is sleep the only recovery mechanism, the partner the only social influence, or HPA axis and ANS activity the only important biological mechanisms. Therefore, future research might benefit from assessing, for instance, the ability to relax during the day as another way to recover, or interaction with colleagues as another social mechanism. Moreover, assessing markers of immune activation seems warranted as a further biological mechanism. Thus, there are many options to continue the list of interesting mechanisms and levels of observation (and complement Figure 2) when considering the association between stress and fatigue in everyday life. Although the current studies add important and valuable information to existing research and take a more integrative perspective than most, they do not claim to paint an exhaustive picture and there is still a great deal of scope to pursue research questions.

Another open question is whether the same mechanisms we found in our samples exist in conditions which present with fatigue but which are not considered conditions of medically unexplained fatigue. One example is HPA axis activity in patients suffering from cancer, which shows similar differences concerning the daily cortisol profile to those in patients with CFS and FMS. For instance, a flattened HPA axis slope was found in fatigued patients with cancer compared to non-fatigued patients with cancer (Bower et al., 2005) as well as compared to healthy samples (Abercrombie et al., 2004). It is likely that changes in HPA axis functioning, or especially its hypoactivity, are associated with fatigue independently of whether or not fatigue is considered “medically unexplained”. Another important group is patients with depression, a condition which also presents with fatigue as one major symptom.

In this population, research indicates heightened, as opposed to reduced, HPA axis activity (for an overview see Rief, Hennings, Riemer, & Euteneuer, 2010; Stetler & Miller, 2011). One explanation for this might be that HPA axis hyperactivity is associated with negative emotions (or “emotional distress”), whereas HPA axis hypoactivity is associated with fatigue. However, more research is needed, comparing different clinical samples, with regard to the association between HPA axis activity as well as other stress-associated mechanisms and different symptoms in everyday life.

4.5 Conclusions for chronic fatigue treatment and prevention

The implication that emerges most clearly from our studies is that stress is a risk factor for fatigue. Therefore, stress management training can be seen as the most important approach for prevention and treatment of chronic fatigue. One part of stress management training should be an enhancement of sleep hygiene in order to increase sleep quality. Further, as mentioned above, research suggests that the implementation of programs to enhance physical activity is beneficial for patients suffering from chronic fatigue as well as for healthy persons. Our results add the insight that special care should be taken in explaining the difference between short- and long-term effects to patients with chronic fatigue and preparing them for short-term increases in fatigue. The most comprehensive treatment study for patients with CFS revealed that a combination of specialist medical care, cognitive behavioral therapy, and graded exercise therapy is likely to be the most helpful approach for reducing fatigue in this population (White et al., 2011). We showed that another crucial part of fatigue interventions might be the inclusion of the partner in the process. Furthermore, couple intervention techniques seem promising as a part of prevention programs. Concerning the association of HPA axis hypoactivity with fatigue, it might be assumed that chronically fatigued persons benefit from intake of hydrocortisone. However, results of treatment studies with low-dose hydrocortisone show inconsistent results and no long-term effects (Blockmans, Persoons, Van Houdenhove, Lejeune, & Bobbaers, 2003; Cleare et al., 1999; Cleare et al., 2001; McKenzie et al., 1998). On the other hand, one study suggests that dysfunction of HPA axis activity might be reversed by cognitive behavioral therapy (Roberts,

Papadopoulos, Wessely, Chalder, & Cleare, 2009). Implementation of HPA axis activity measures thus seems crucial for future treatment studies. Concerning ANS hyperactivity, relaxation techniques seem inductively helpful. However, there are no studies on the influence of relaxation on ANS activity (or HPA axis activity for that matter) in patient populations (i.e. CFS or FMS). There are, however, some studies suggesting short-term beneficial effects of relaxation for fatigue (for an overview see Meeus et al., 2015). On the other hand, relaxation as a stand-alone treatment for fatigue conditions was found to be inferior to cognitive behavioral therapy (Deale, Husain, Chalder, & Wessely, 2001). In light of the inter-individual differences in symptom exacerbation and variability, a tailored treatment using ambulatory assessment and ambulatory feedback techniques is a very promising approach for future treatment studies.

5. References

Aaron, L. A., & Buchwald, D. (2003). Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. *Best Practice and Research. Clinical Rheumatology, 17*(4), 563-574. doi: S1521694203000330 [pii]

Abercrombie, H. C., Giese-Davis, J., Sephton, S., Epel, E. S., Turner-Cobb, J. M., & Spiegel, D. (2004). Flattened cortisol rhythms in metastatic breast cancer patients. *Psychoneuroendocrinology, 29*(8), 1082-1092. doi: 10.1016/j.psyneuen.2003.11.003 S030645300300221X [pii]

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience--cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences of the United States of America, 103*(45), 17058-17063. doi: 10.1073/pnas.0605053103

Akerstedt, T., Axelsson, J., Lekander, M., Orsini, N., & Kecklund, G. (2014). Do sleep, stress, and illness explain daily variations in fatigue? A prospective study. *Journal of Psychosomatic Research, 76*(4), 280-285. doi: 10.1016/j.jpsychores.2014.01.005 S0022-3999(14)00022-1 [pii]

Akerstedt, T., Hume, K., Minors, D., & Waterhouse, J. (1994). The meaning of good sleep: a longitudinal study of polysomnography and subjective sleep quality. *Journal of Sleep Research, 3*(3), 152-158. doi: jsr003003152 [pii]

Akerstedt, T., Kecklund, G., & Axelsson, J. (2007). Impaired sleep after bedtime stress and worries. *Biological Psychology, 76*(3), 170-173. doi: S0301-0511(07)00120-2 [pii] 10.1016/j.biopsycho.2007.07.010

Akerstedt, T., Knutsson, A., Westerholm, P., Theorell, T., Alfredsson, L., & Kecklund, G. (2002). Sleep disturbances, work stress and work hours: a cross-sectional study. *Journal of Psychosomatic Research, 53*(3), 741-748. doi: S0022399902003331 [pii]

Akerstedt, T., & Nilsson, P. M. (2003). Sleep as restitution: an introduction. *Journal of Internal Medicine, 254*(1), 6-12. doi: 1195 [pii]

American Psychiatric Association. (2013). *DSM-5 Diagnostic and Statistical Manual of Mental Disorders - fifth Edition*. Arlington, VA: American Psychiatric Publishing.

Anderson, C., Keltner, D., & John, O. P. (2003). Emotional convergence between people over time. *J Pers Soc Psychol, 84*(5), 1054-1068.

Barrett, E. (2005). The Adrenal Gland. In W. F. Boron & E. L. Boulpaep (Eds.), *Medical Physiology - a cellular and molecular approach* (pp. 1049-1066). Philadelphia, Pennsylvania: Elsevier Saunders.

Barroso, J. (1999). A review of fatigue in people with HIV infection. *Journal of the Association of Nurses in AIDS Care, 10*(5), 42-49.

Barsevick, A., Frost, M., Zwinderman, A., Hall, P., & Halyard, M. (2010). I'm so tired: biological and genetic mechanisms of cancer-related fatigue. *Quality of Life Research, 19*(10), 1419-1427. doi: 10.1007/s11136-010-9757-7

Bethoux, F. (2006). Fatigue and multiple sclerosis. *Annales de Réadaptation et de Médecine Physique, 49*(6), 265-271, 355-360. doi: 10.1016/j.annrmp.2006.04.023

Blockmans, D., Persoons, P., Van Houdenhove, B., Lejeune, M., & Bobbaers, H. (2003). Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. *Am J Med, 114*(9), 736-741. doi: S0002934303001827 [pii]

Bolger, N., & Laurenceau, J. P. (2013). Design and Analysis of Intensive Longitudinal Studies of Distinguishable Dyads *Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research* (pp. 143-176). New York: Guilford.

Boneva, R. S., Decker, M. J., Maloney, E. M., Lin, J. M., Jones, J. F., Helgason, H. G., . . . Reeves, W. C. (2007). Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. *Autonomic Neuroscience, 137*(1-2), 94-101. doi: S1566-0702(07)00446-8 [pii] 10.1016/j.autneu.2007.08.002

Bower, J. E., Ganz, P. A., Dickerson, S. S., Petersen, L., Aziz, N., & Fahey, J. L. (2005). Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology, 30*(1), 92-100. doi: 10.1016/j.psyneuen.2004.06.003

Brown, R. F., & Thorsteinsson, E. B. (2009). Stressful life-events and fatigue in a nonclinical sample. *Journal of Nervous and Mental Disease, 197*(9), 707-710. doi: 10.1097/NMD.0b013e3181b3af36 00005053-200909000-00012 [pii]

Bultmann, U., Kant, I. J., Kasl, S. V., Schroer, K. A., Swaen, G. M., & van den Brandt, P. A. (2002). Lifestyle factors as risk factors for fatigue and psychological distress in the working population: prospective results from the Maastricht Cohort Study. *Journal of Occupational and Environmental Medicine, 44*(2), 116-124.

Busch, A. J., Schachter, C. L., Overend, T. J., Peloso, P. M., & Barber, K. A. (2008). Exercise for fibromyalgia: a systematic review. *Journal of Rheumatology, 35*(6), 1130-1144. doi: 08/13/0512 [pii]

Butner, J., Diamond, L. M., & Hicks, A. M. (2007). Attachment style and two forms of affect coregulation between romantic partners. *Personal Relationships, 14*, 431-455.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193-213.

Buysse, D. J., Thompson, W., Scott, J., Franzen, P. L., Germain, A., Hall, M., . . . Kupfer, D. J. (2007). Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep Med, 8*(3), 198-208. doi: S1389-9457(06)00629-0 [pii] 10.1016/j.sleep.2006.10.006

Cannon, W. B. (1914). The emergency function of the adrenal medulla in pain and the major emotions. *American Journal of Physiology, 33*, 356-372.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports, 100*(2), 126-131.

Chen, M. K. (1986). The epidemiology of self-perceived fatigue among adults. *Preventive Medicine, 15*(1), 74-81.

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

Cleare, A. J., Heap, E., Malhi, G. S., Wessely, S., O'Keane, V., & Miell, J. (1999). Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet, 353*(9151), 455-458. doi: S0140-6736(98)04074-4 [pii] 10.1016/S0140-6736(98)04074-4

Cleare, A. J., Miell, J., Heap, E., Sookdeo, S., Young, L., Malhi, G. S., & O'Keane, V. (2001). Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy. *J Clin Endocrinol Metab, 86*(8), 3545-3554. doi: 10.1210/jcem.86.8.7735

Coan, J. A., & Sbarra, D. A. (2015). Social Baseline Theory: The Social Regulation of Risk and Effort. *Curr Opin Psychol, 1*, 87-91. doi: 10.1016/j.copsyc.2014.12.021

Cohen, H., Neumann, L., Shore, M., Amir, M., Cassuto, Y., & Buskila, D. (2000). Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Seminars in Arthritis and Rheumatism, 29*(4), 217-227. doi: S0049-0172(00)80010-4 [pii]

Crofford, L. J., Pillemer, S. R., Kalogeras, K. T., Cash, J. M., Michelson, D., Kling, M. A., . . . Wilder, R. L. (1994). Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis and Rheumatism, 37*(11), 1583-1592.

Dahlgren, A., Kecklund, G., & Akerstedt, T. (2005). Different levels of work-related stress and the effects on sleep, fatigue and cortisol. *Scandinavian Journal of Work, Environment and Health, 31*(4), 277-285. doi: 883 [pii]

Dahlgren, A., Kecklund, G., Theorell, T., & Akerstedt, T. (2009). Day-to-day variation in saliva cortisol--relation with sleep, stress and self-rated health. *Biological Psychology, 82*(2), 149-155. doi: 10.1016/j.biopsycho.2009.07.001

Dantzer, R., Heijnen, C. J., Kavelaars, A., Laye, S., & Capuron, L. (2014). The neuroimmune basis of fatigue. [Review]. *Trends in Neurosciences*.

Dawson, D., Ian Noy, Y., Harma, M., Akerstedt, T., & Belenky, G. (2011). Modelling fatigue and the use of fatigue models in work settings. *Accident Analysis and Prevention, 43*(2), 549-564. doi: 10.1016/j.aap.2009.12.030 S0001-4575(10)00005-9 [pii]

De Lorenzo, F., Hargreaves, J., & Kakkar, V. V. (1997). Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome. *Clinical Autonomic Research, 7*(4), 185-190.

Deale, A., Husain, K., Chalder, T., & Wessely, S. (2001). Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry, 158*(12), 2038-2042. doi: 10.1176/appi.ajp.158.12.2038

Demitrack, M. A., Dale, J. K., Straus, S. E., Laue, L., Listwak, S. J., Kruesi, M. J., . . . Gold, P. W. (1991). Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *Journal of Clinical Endocrinology and Metabolism, 73*(6), 1224-1234.

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. doi: 10.1037/0033-2909.130.3.355 2004-13724-001 [pii]

Dittner, A. J., Rimes, K., & Thorpe, S. (2011). Negative perfectionism increases the risk of fatigue following a period of stress. *Psychology and Health, 26*(3), 253-268. doi: 10.1080/08870440903225892 919362411 [pii]

Dittner, A. J., Wessely, S. C., & Brown, R. G. (2004). The assessment of fatigue: a practical guide for clinicians and researchers. *Journal of Psychosomatic Research, 56*(2), 157-170. doi: 10.1016/s0022-3999(03)00371-4

Ditzen, B., & Heinrichs, M. (2014). Psychobiology of social support: the social dimension of stress buffering. *Restor Neurol Neurosci, 32*(1), 149-162. doi: 10.3233/RNN-139008 M0228K0TM4T20210 [pii]

Doerr, J. M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., . . . Nater, U. M. (2015). Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students. *Biological Psychology, 110*, 42-49. doi: S0301-0511(15)30014-4 [pii] 10.1016/j.biopsycho.2015.06.009

Doerr, J. M., Fischer, S., Nater, U. M., & Strahler, J. (under review). Influence of stress systems and physical activity on different dimensions of fatigue in fibromyalgia patients. *Journal of Psychosomatic Research*.

Doerr, J. M., & Nater, U. M. (2013). Erschöpfungssyndrome – Eine Diskussion verschiedener Begriffe, Definitionsansätze und klassifikatorischer Konzepte. *Psychotherapie, Psychosomatik, Medizinische Psychologie, 63*, 69-76.

Doerr, J. M., Nater, U. M., Spoerri, C., Ehlert, U., & Ditzen, B. (ready to be submitted). Dyadic coregulation of fatigue and psychobiological stress in everyday life.

Duprez, D. A., De Buyzere, M. L., Drieghe, B., Vanhaverbeke, F., Taes, Y., Michielsen, W., & Clement, D. L. (1998). Long- and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome. *Clinical Science, 94*(1), 57-63.

Eek, F., Karlson, B., Garde, A. H., Hansen, A. M., & Orbaek, P. (2012). Cortisol, sleep, and recovery - Some gender differences but no straight associations. *Psychoneuroendocrinology, 37*(1), 56-64. doi: 10.1016/j.psyneuen.2011.05.003 S0306-4530(11)00156-9 [pii]

Ekmann, A., Avlund, K., Osler, M., & Lund, R. (2012). Do negative aspects of social relations influence fatigue? A cross-sectional study on a non-clinical sample of middle-aged Danish men. *J Psychosom Res, 73*(4), 277-282. doi: 10.1016/j.jpsychores.2012.08.005 S0022-3999(12)00210-3 [pii]

Fahrenberg, J., Myrtek, M., Pawlik, K., & Perrez, M. (2007). Ambulatory Assessment – Monitoring Behavior in Daily Life Settings: A Behavioral-Scientific Challenge for Psychology. *European Journal of Psychological Assessment, 23*(4), 206-213. doi: 10.1027/1015-5759.23.4.206

Ferrer, E., & Helm, J. L. (2013). Dynamical systems modeling of physiological coregulation in dyadic interactions. *Int J Psychophysiol, 88*(3), 296-308. doi: 10.1016/j.ijpsycho.2012.10.013 S0167-8760(12)00629-0 [pii]

Fischer, S., Doerr, J. M., Strahler, J., Mewes, R., Thieme, K., & Nater, U. M. (2016). Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome-The role of cortisol and alpha-amylase. *Psychoneuroendocrinology, 63*, 68-77. doi: S0306-4530(15)00921-X [pii] 10.1016/j.psyneuen.2015.09.018

Fischer, S., & Nater, U. M. (2012). Funktionelle somatische Syndrome - Konzeptualisierung, Epidemiologie und Behandlung. *Zeitschrift für Medizinische Psychologie, 21*(4), 148-160.

Fischer, S., & Nater, U. M. (2015). Autonomes Nervensystem. In W. Rief & A. Henningsen (Eds.), *Psychosomatik und Verhaltensmedizin* (pp. 193-201). Stuttgart: Schattauer.

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology, 72*(1), 67-73. doi: 10.1016/j.ijpsycho.2008.03.014 S0167-8760(08)00794-0 [pii]

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*(10), 1010-1016. doi: S0306-4530(05)00089-2 [pii] 10.1016/j.psyneuen.2005.04.006

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of Internal Medicine, 121*(12), 953-959.

Gerber, M., & Puhse, U. (2009). Do exercise and fitness protect against stress-induced health complaints? A review of the literature. *Scandinavian Journal of Public Health, 37*(8), 801-819. doi: Doi 10.1177/1403494809350522

Gur, A., Cevik, R., Nas, K., Colpan, L., & Sarac, S. (2004). Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and

chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Research and Therapy, 6*(3), R232-238. doi: 10.1186/ar1163 ar1163 [pii]

Hahlweg, K. (1996). Partnerschaftsfragebogen (PFB) *Fragebogen zur Partnerschaftsdiagnostik (FPD)* (pp. 7-24). Göttingen: Hogrefe.

Hall, M., Vasko, R., Buysse, D., Ombao, H., Chen, Q., Cashmere, J. D., . . . Thayer, J. F. (2004). Acute stress affects heart rate variability during sleep. *Psychosomatic Medicine, 66*(1), 56-62.

Hamaker, E. L. (2012). Why Researchers Should Think "Within Person": A Paradigmatic Rationale. In M. R. Mehl & T. S. Conner (Eds.), *Handbook of Research Methods for Studying Daily Life* (pp. 43-61). New York, NY: Guilford Press.

Hardy, S. E., & Studenski, S. A. (2010). Qualities of fatigue and associated chronic conditions among older adults. *Journal of Pain and Symptom Management, 39*(6), 1033-1042. doi: 10.1016/j.jpainsymman.2009.09.026

Heitmann, J., Cassel, W., Ploch, T., Canisius, S., Kesper, K., & Apelt, S. (2011). Messung von Schlafdauer und Schlafqualität. *Bundesgesundheitsblatt, 54*, 1276-1283.

Hiller, W., Rief, W., & Brahler, E. (2006). Somatization in the population: from mild bodily misperceptions to disabling symptoms. *Social Psychiatry and Psychiatric Epidemiology, 41*(9), 704-712. doi: 10.1007/s00127-006-0082-y

Hinz, A., Ströbel-Richter, Y., & Brähler, E. (2001). Der Partnerschaftsfragebogen (PFB): Normierung und soziodemographische Einflussgrößen auf die Partnerschaftsqualität. *Diagnostica, 47*(3), 132-141.

Holmes, G. P., Kaplan, J. E., Gantz, N. M., Komaroff, A. L., Schonberger, L. B., Straus, S. E., . . . et al. (1988). Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine, 108*(3), 387-389.

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS Medicine, 7*(7), e1000316. doi: 10.1371/journal.pmed.1000316

Institute of Medicine, B. o. t. H. o. S. P. (2015). Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Redefining an Illness.

Jackson, E. M., & Dishman, R. K. (2006). Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. *Psychophysiology, 43*(1), 57-72. doi: PSYP373 [pii] 10.1111/j.1469-8986.2006.00373.x

Jason, L. A., Sunnquist, M., Kot, B., & Brown, A. (2015). Unintended Consequences of not Specifying Exclusionary Illnesses for Systemic Exertion Intolerance Disease. *diagnostics, 5*, 272-286.

Johannisson, K. (2006). Modern fatigue: A historical perspective *Stress in health and disease* (pp. 3-19). Weinheim, Germany: Wiley-VCH Veriag GmbH & Co KGaA; Germany.

Johansson, S., Ytterberg, C., Hillert, J., Widen Holmqvist, L., & von Koch, L. (2008). A longitudinal study of variations in and perceptions of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*, 454-457. doi: 10.1136/jnnp.2007.121129

Kalimo, R., Tenkanen, L., Härmä, M., & Poppius, E. (2000). Job stress and sleep disorders: findings from the Helsinki Heart Study. *Stress Medicine, 16*(2), 65-75.

Kanning, M., Ebner-Priemer, U., & Brand, R. (2012). Autonomous regulation mode moderates the effect of actual physical activity on affective states: an ambulant assessment approach to the role of self-determination. *J Sport Exerc Psychol, 34*(2), 260-269.

Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2006). Premorbid predictors of chronic fatigue. *Archives of General Psychiatry, 63*(11), 1267-1272. doi: 63/11/1267 [pii] 10.1001/archpsyc.63.11.1267

Kemeny, M. E. (2003). The psychobiology of stress. *Current Directions in Psychological Science, 12*(4), 124-129. doi: http://dx.doi.org/10.1111/1467-8721.01246

Kiecolt-Glaser, J. K., & Newton, T. L. (2001). Marriage and health: his and hers. *Psychol Bull, 127*(4), 472-503.

Kirby, J. S., & Baucom, D. H. (2007). Treating emotion dysregulation in a couples context: a pilot study of a couples skills group intervention. *Journal of Marital and Family Therapy, 33*(3), 375-391. doi: JMFT037 [pii] 10.1111/j.1752-0606.2007.00037.x

Klaperski, S., von Dawans, B., Heinrichs, M., & Fuchs, R. (2013). Does the level of physical exercise affect physiological and psychological responses to psychosocial stress in women? *Psychology of Sport and Exercise, 14*(2), 266-274. doi: DOI 10.1016/j.psychsport.2012.11.003

Knudsen, H. K., Ducharme, L. J., & Roman, P. M. (2007). Job stress and poor sleep quality: data from an American sample of full-time workers. *Social Science and Medicine, 64*(10), 1997-2007. doi: S0277-9536(07)00067-6 [pii] 10.1016/j.socscimed.2007.02.020

Kop, W. J., Lyden, A., Berlin, A. A., Ambrose, K., Olsen, C., Gracely, R. H., . . . Clauw, D. J. (2005). Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome. *Arthritis and Rheumatism, 52*(1), 296-303. doi: 10.1002/art.20779

Kroenke, K., Wood, D. R., Mangelsdorff, A. D., Meier, N. J., & Powell, J. B. (1988). Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. *JAMA, 260*(7), 929-934.

Kumari, M., Badrick, E., Chandola, T., Adam, E. K., Stafford, M., Marmot, M. G., . . . Kivimaki, M. (2009). Cortisol secretion and fatigue: associations in a community based cohort. *Psychoneuroendocrinology, 34*(10), 1476-1485. doi: 10.1016/j.psyneuen.2009.05.001

Landis, C. A., Frey, C. A., Lentz, M. J., Rothermel, J., Buchwald, D., & Shaver, J. L. (2003). Self-reported sleep quality and fatigue correlates with actigraphy in midlife women with fibromyalgia. *Nursing Research, 52*(3), 140-147.

Laurenceau, J. P., & Bolger, N. (2005). Using diary methods to study marital and family processes. *J Fam Psychol, 19*(1), 86-97. doi: 2005-02946-009 [pii] 10.1037/0893-3200.19.1.86

Laurent, H., & Powers, S. (2007). Emotion regulation in emerging adult couples: temperament, attachment, and HPA response to conflict. *Biol Psychol, 76*(1-2), 61-71. doi: S0301-0511(07)00107-X [pii] 10.1016/j.biopsycho.2007.06.002

Lavidor, M., Weller, A., & Babkoff, H. (2003). How sleep is related to fatigue. *Br J Health Psychol, 8*(Pt 1), 95-105. doi: 10.1348/135910703762879237

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

Lindeberg, S. I., Eek, F., Lindbladh, E., Ostergren, P. O., Hansen, A. M., & Karlson, B. (2008). Exhaustion measured by the SF-36 vitality scale is associated with a flattened diurnal cortisol profile. *Psychoneuroendocrinology, 33*(4), 471-477. doi: 10.1016/j.psyneuen.2008.01.005 S0306-4530(08)00024-3 [pii]

Liu, S., Rovine, M. J., Klein, L. C., & Almeida, D. M. (2013). Synchrony of diurnal cortisol pattern in couples. *J Fam Psychol, 27*(4), 579-588. doi: 10.1037/a0033735 2013-27136-001 [pii]

Loge, J. H., Ekeberg, O., & Kaasa, S. (1998). Fatigue in the general Norwegian population: normative data and associations. *Journal of Psychosomatic Research, 45*(1), 53-65. doi: S0022-3999(97)00291-2 [pii]

Lutgendorf, S. K., Antoni, M. H., Ironson, G., Fletcher, M. A., Penedo, F., Baum, A., . . . Klimas, N. (1995). Physical symptoms of chronic fatigue syndrome are exacerbated by the stress of Hurricane Andrew. *Psychosom Med, 57*(4), 310-323.

Majer, M., Jones, J. F., Unger, E. R., Youngblood, L. S., Decker, M. J., Gurbaxani, B., . . . Reeves, W. C. (2007). Perception versus polysomnographic assessment of sleep in CFS and non-fatigued control subjects: results from a population-based study. *BMC Neurology, 7*, 40. doi: 1471-2377-7-40 [pii] 10.1186/1471-2377-7-40

Martinez-Lavin, M. (2007). Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Research and Therapy, 9*(4), 216. doi: ar2146 [pii] 10.1186/ar2146

Maslach, C., & Jackson, S. E. (1981). The measurement of experienced burnout. *Journal of Occupational Behaviour, 2*, 99-113.

Masuda, A., Munemoto, T., Yamanaka, T., Takei, M., & Tei, C. (2002). Psychosocial characteristics and immunological functions in patients with postinfectious chronic fatigue syndrome and noninfectious chronic fatigue syndrome. *J Behav Med, 25*(5), 477-485.

McCall, C., & Singer, T. (2012). The animal and human neuroendocrinology of social cognition, motivation and behavior. *Nature Neuroscience, 15*(5), 681-688. doi: 10.1038/nn.3084 nn.3084 [pii]

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci, 840*, 33-44.

McEwen, B. S. (2000). The neurobiology of stress: from serendipity to clinical relevance. *Brain Res, 886*(1-2), 172-189. doi: S0006-8993(00)02950-4 [pii]

McKenzie, R., O'Fallon, A., Dale, J., Demitrack, M., Sharma, G., Deloria, M., . . . Straus, S. E. (1998). Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. *JAMA, 280*(12), 1061-1066. doi: joc80695 [pii]

McLoughlin, M. J., Colbert, L. H., Stegner, A. J., & Cook, D. B. (2011). Are women with fibromyalgia less physically active than healthy women? *Medicine and Science in Sports and Exercise, 43*(5), 905-912. doi: 10.1249/MSS.0b013e3181fca1ea

Meeus, M., Nijs, J., Vanderheiden, T., Baert, I., Descheemaeker, F., & Struyf, F. (2015). The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: a systematic review. *Clinical Rehabilitation, 29*(3), 221-233. doi: 10.1177/0269215514542635 0269215514542635 [pii]

Nagel, I. J., & Sonnentag, S. (2013). Exercise and sleep predict personal resources in employees' daily lives. *Appl Psychol Health Well Being, 5*(3), 348-368. doi: 10.1111/aphw.12014

Nater, U. M., & Doerr, J. M. (2012). Cortisol and fatigue. In A. Esposito & V. Bianchi (Eds.), *Cortisol: Physiology, Regulation and Health Implications* (pp. 107-118). Happauge, NY: Nova Science Publishers.

Nater, U. M., Fischer, S., & Ehlert, U. (2011). Stress as a Pathophysiological Factor in Functional Somatic Syndromes. *Current Psychiatry Reviews, 7*, 152-169.

Nater, U. M., Heim, C., & Raison, C. (2012). Chronic fatigue syndrome. In M. J. Aminoff, F. Boller & D. F. Swaab (Eds.), *Handbook of Clinical Neurology 3rd Series*.

Nater, U. M., Heim, C., & Reeves, W. C. (2010). The role of stress in chronic fatigue syndrome. *International Journal of Medical and Biological Frontiers, 16*(7/8), 869-884

Nater, U. M., Maloney, E., Boneva, R. S., Gurbaxani, B. M., Lin, J. M., Jones, J. F., . . . Heim, C. (2008). Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. *J Clin Endocrinol Metab, 93*(3), 703-709. doi: 10.1210/jc.2007-1747

Nater, U. M., Maloney, E., Heim, C., & Reeves, W. C. (2011). Cumulative life stress in chronic fatigue syndrome. *Psychiatry Research, 189*(2), 318-320. doi: 10.1016/j.psychres.2011.07.015

Nater, U. M., & Rohleder, N. (2009). Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. *Psychoneuroendocrinology, 34*(4), 486-496. doi: S0306-4530(09)00032-8 [pii] 10.1016/j.psyneuen.2009.01.014

Nater, U. M., Rohleder, N., Schlotz, W., Ehlert, U., & Kirschbaum, C. (2007). Determinants of the diurnal course of salivary alpha-amylase. *Psychoneuroendocrinology, 32*(4), 392-401. doi: S0306-4530(07)00039-X [pii] 10.1016/j.psyneuen.2007.02.007

Nater, U. M., Youngblood, L. S., Jones, J. F., Unger, E. R., Miller, A. H., Reeves, W. C., & Heim, C. (2008). Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. *Psychosom Med, 70*(3), 298-305. doi: 10.1097/PSY.0b013e3181651025

Nijrolder, I., van der Horst, H., & van der Windt, D. (2008). Prognosis of fatigue. A systematic review. *Journal of Psychosomatic Research, 64*(4), 335-349. doi: 10.1016/j.jpsychores.2007.11.001 S0022-3999(07)00437-0 [pii]

Overman, C. L., Kool, M. B., Da Silva, J. A., & Geenen, R. (2015). The prevalence of severe fatigue in rheumatic diseases: an international study. *Clinical Rheumatology*. doi: 10.1007/s10067-015-3035-6

Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. J., & Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *BMJ, 308*(6931), 763-766.

Petersen, H., Kecklund, G., D'Onofrio, P., Nilsson, J., & Akerstedt, T. (2012). Stress vulnerability and the effects of moderate daily stress on sleep polysomnography and subjective sleepiness. *Journal of Sleep Research, 22*(1), 50-57. doi: 10.1111/j.1365-2869.2012.01034.x

Pilcher, J. J., Ginter, D. R., & Sadowsky, B. (1997). Sleep quality versus sleep quantity: relationships between sleep and measures of health, well-being and sleepiness in college students. *Journal of Psychosomatic Research, 42*(6), 583-596. doi: S0022399997000044 [pii]

Powell, D. J., Liossi, C., Moss-Morris, R., & Schlotz, W. (2013). Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology, 38*(11), 2405-2422. doi: S0306-4530(13)00254-0 [pii] 10.1016/j.psyneuen.2013.07.004

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., . . . Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences, 61*(26), 2539-2549. doi: S0024320597010084 [pii]

Puetz, T. W. (2006). Physical activity and feelings of energy and fatigue: epidemiological evidence. *Sports Medicine, 36*(9), 767-780. doi: 3694 [pii]

Raudenbush, S. W., Bryk, A. S., Cheong, Y. F., & Congdon, R. (2005). *HLM 5. Hierarchal linear and nonlinear modeling*. Chicago, IL: Scientific Software International.

Reed, R. G., Randall, A. K., Post, J. H., & Butler, E. A. (2013). Partner influence and in-phase versus anti-phase physiological linkage in romantic couples. *Int J Psychophysiol, 88*(3), 309-316. doi: 10.1016/j.ijpsycho.2012.08.009 S0167-8760(12)00581-8 [pii]

Reeves, W. C., Heim, C., Maloney, E. M., Youngblood, L. S., Unger, E. R., Decker, M. J., . . . Rye, D. B. (2006). Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: results from a population-based study. *BMC Neurology, 6*, 41. doi: 1471-2377-6-41 [pii] 10.1186/1471-2377-6-41

Reis, H. T. (2012). Why Researchers Should Think "Real World": A conceptual Rationale. In M. R. Mehl & T. S. Conner (Eds.), *Handbook of Research Methods for Studying Daily Life* (pp. 3-21). New York, NY: Guilford Press.

Reyes, M., Dobbins, J. G., Mawle, A. C., Steele, L., Gary, H. E., Jr., Malani, H., . . . Reeves, W. C. (1996). Risk factors for CFS: a case control study. *Journal of Chronic Fatigue Syndrome, 2*, 17-33.

Ricci, J. A., Chee, E., Lorandeau, A. L., & Berger, J. (2007). Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. *J Occup Environ Med, 49*(1), 1-10. doi: 10.1097/01.jom.0000249782.60321.2a 00043764-200701000-00001 [pii]

Richerson, G. B. (2005). The Autonomic Nervous System. In W. F. Boron & E. L. Boulpaep (Eds.), *Medical Physiology - a cellular and molecular approach* (pp. 378-398). Philadelphia, Pennsylvania: Elsevier Saunders.

Rief, W., Hennings, A., Riemer, S., & Euteneuer, F. (2010). Psychobiological differences between depression and somatization. . [Journal Article; Literature (10; 99)]. *Journal of Psychosomatic Research, 68*(5), 495-502. doi: http://dx.doi.org/10.1016/j.jpsychores.2010.02.001

Riley, W. T., Rothrock, N., Bruce, B., Christodolou, C., Cook, K., Hahn, E. A., & Cella, D. (2010). Patient-reported outcomes measurement information system (PROMIS) domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. *Quality of Life Research, 19*(9), 1311-1321. doi: 10.1007/s11136-010-9694-5

Riva, R., Mork, P. J., Westgaard, R. H., & Lundberg, U. (2012). Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. *Psychoneuroendocrinology, 37*(2), 299-306. doi: S0306-4530(11)00183-1 [pii] 10.1016/j.psyneuen.2011.06.014

Riva, R., Mork, P. J., Westgaard, R. H., Okkenhaug Johansen, T., & Lundberg, U. (2012). Catecholamines and heart rate in female fibromyalgia patients. *Journal of Psychosomatic Research, 72*(1), 51-57. doi: S0022-3999(11)00249-2 [pii] 10.1016/j.jpsychores.2011.09.010

Riva, R., Mork, P. J., Westgaard, R. H., Ro, M., & Lundberg, U. (2010). Fibromyalgia syndrome is associated with hypocortisolism. *Int J Behav Med, 17*(3), 223-233. doi: 10.1007/s12529-010-9097-6

Roberts, A. D., Papadopoulos, A., Wessely, S., Chalder, T., & Cleare, A. J. (2009). Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. *J Affect Disord, 115*(1-2), 280-286. doi: 10.1016/j.jad.2008.09.013

Robles, T. F., & Kiecolt-Glaser, J. K. (2003). The physiology of marriage: pathways to health. *Physiol Behav, 79*(3), 409-416. doi: S0031938403001604 [pii]

Rohleder, N., & Nater, U. M. (2009). Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology, 34*(4), 469-485. doi: S0306-4530(08)00330-2 [pii] 10.1016/j.psyneuen.2008.12.004

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev, 21*(1), 55-89. doi: 10.1210/edrv.21.1.0389

Saxbe, D., & Repetti, R. L. (2010). For better or worse? Coregulation of couples' cortisol levels and mood states. *Journal of Personality and Social Psychology, 98*(1), 92-103. doi: 10.1037/a0016959 2009-24670-014 [pii]

Sbarra, D. A., & Hazan, C. (2008). Coregulation, dysregulation, self-regulation: an integrative analysis and empirical agenda for understanding adult attachment, separation, loss, and recovery. *Pers Soc Psychol Rev, 12*(2), 141-167. doi: 10.1177/1088868308315702 12/2/141 [pii]

Schmidt-Reinwald, A., Pruessner, J. C., Hellhammer, D. H., Federenko, I., Rohleder, N., Schurmeyer, T. H., & Kirschbaum, C. (1999). The cortisol response to awakening in relation to different challenge tests and a 12-hour cortisol rhythm. *Life Sciences, 64*(18), 1653-1660. doi: S0024320599001034 [pii]

Schmitt, A., Zacher, H., & Frese, M. (2012). The buffering effect of selection, optimization, and compensation strategy use on the relationship between problem solving demands and occupational well-being: a daily diary study. *Journal of Occupational Health Psychology, 17*(2), 139-149. doi: 10.1037/a0027054 2012-02809-001 [pii]

Schoebi, D. (2008). The coregulation of daily affect in marital relationships. *J Fam Psychol, 22*(4), 595-604. doi: 10.1037/0893-3200.22.3.595 2008-10898-011 [pii]

Schulz, P., Kirschbaum, C., Pruessner, J. C., & Hellhammer, D. (1998). Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. *Stress Medicine, 14*, 91-97.

Schwarz, N. (2012). Why Researchers Should Think "Real Time": A Cognitive Rationale. In M. R. Mehl & T. S. Conner (Eds.), *Handbook of Research Methods for Studying Daily Life* (pp. 22-42). New York, NY: Guilford Press.

Schwarz, R., Krauss, O., & Hinz, A. (2003). Fatigue in the general population. *Onkologie, 26*(2), 140-144. doi: 10.1159/000069834

Scott, L. V., & Dinan, T. G. (1998). Urinary free cortisol excretion in chronic fatigue syndrome, major depression and in healthy volunteers. *J Affect Disord, 47*(1-3), 49-54.

Segura-Jimenez, V., Borges-Cosic, M., Soriano-Maldonado, A., Estevez-Lopez, F., Alvarez-Gallardo, I. C., Herrador-Colmenero, M., . . . Ruiz, J. R. (2015). Association of sedentary time and physical activity with pain, fatigue, and impact of fibromyalgia: the al-Andalus study. *Scandinavian Journal of Medicine and Science in Sports*. doi: 10.1111/sms.12630

Selye, H. (1956). *The stress of life*. New York: McGraw-Hill Book Company, Inc.

Shapiro, D., Jamner, L. D., Goldstein, I. B., & Delfino, R. J. (2001). Striking a chord: moods, blood pressure, and heart rate in everyday life. *Psychophysiology, 38*(2), 197-204.

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol, 4*, 1-32.

Singer, J. D., & Willett, J. B. (2003). *Applied Longitudinal Data Analysis*. New York: Oxford University Press.

Smyth, J., Ockenfels, M. C., Porter, L., Kirschbaum, C., Hellhammer, D. H., & Stone, A. A. (1998). Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. *Psychoneuroendocrinology, 23*(4), 353-370. doi: S0306-4530(98)00008-0 [pii]

Smyth, J., & Stone, A. A. (2003). Ecological Momentary Assessment research in behavioral medicine. *Journal of Happiness Studies, 4*, 35-52.

Steptoe, A. (2000). Stress, social support and cardiovascular activity over the working day. *International Journal of Psychophysiology, 37*(3), 299-308. doi: S0167876000001094 [pii]

Steptoe, A., Cropley, M., Griffith, J., & Kirschbaum, C. (2000). Job strain and anger expression predict early morning elevations in salivary cortisol. *Psychosom Med, 62*(2), 286-292.

Sterling, P., & Eyer, J. (1988). Allostasis: A New Paradigm to Explain Arousal Pathology. In S. Fisher & J. Reason (Eds.), *Handbook of Life Stress, Cognition and Health* (pp. 629-649). New York: John Wiley & Sons.

Stetler, C., Dickerson, S. S., & Miller, G. E. (2004). Uncoupling of social zeitgebers and diurnal cortisol secretion in clinical depression. *Psychoneuroendocrinology, 29*(10), 1250-1259. doi: 10.1016/j.psyneuen.2004.03.003 S0306453004000332 [pii]

Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine, 73*(2), 114-126. doi: 10.1097/PSY.0b013e31820ad12b PSY.0b013e31820ad12b [pii]

Steyer, R., Schwenkmezger, P., Notz, P., & Eid, M. (1997). *Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF)*. Göttingen: Hogrefe.

Strahler, J., Doerr, J. M., Ditzen, B., Linnemann, A., Skoluda, N., & Nater, U. M. (submitted). Physical activity buffers fatigue only under low chronic stress. *Stress*.

Strickland, P., Morriss, R., Wearden, A., & Deakin, B. (1998). A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. *J Affect Disord, 47*(1-3), 191-194.

Tak, L. M., Cleare, A. J., Ormel, J., Manoharan, A., Kok, I. C., Wessely, S., & Rosmalen, J. G. (2011). Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biol Psychol*. doi: S0301-0511(11)00032-9 [pii] 10.1016/j.biopsycho.2011.02.002

Tak, L. M., & Rosmalen, J. G. (2010). Dysfunction of stress responsive systems as a risk factor for functional somatic syndromes. *Journal of Psychosomatic Research, 68*(5), 461-468. doi: 10.1016/j.jpsychores.2009.12.004 S0022-3999(09)00509-1 [pii]

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A., & Updegraff, J. A. (2000). Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychol Rev, 107*(3), 411-429.

Thorsteinsson, E. B., & Brown, R. F. (2009). Mediators and moderators of the stressor-fatigue relationship in nonclinical samples. *Journal of Psychosomatic Research, 66*(1), 21-29. doi: 10.1016/j.jpsychores.2008.06.010 S0022-3999(08)00352-8 [pii]

Timmons, A. C., Margolin, G., & Saxbe, D. E. (2015). Physiological linkage in couples and its implications for individual and interpersonal functioning: A literature review. *J Fam Psychol, 29*(5), 720-731. doi: 10.1037/fam0000115 2015-30049-001 [pii]

Tran, Y., Wijesuriya, N., Tarvainen, M., Karjalainen, P., & Craig, A. (2009). The Relationship Between Spectral Changes in Heart Rate Variability and Fatigue. *Journal of Psychophysiology, 23*(3), 143-151.

Traustadottir, T., Bosch, P. R., & Matt, K. S. (2005). The HPA axis response to stress in women: effects of aging and fitness. *Psychoneuroendocrinology, 30*(4), 392-402. doi: S0306-4530(04)00178-7 [pii] 10.1016/j.psyneuen.2004.11.002

van't Leven, M., Zielhuis, G. A., van der Meer, J. W., Verbeek, A. L., & Bleijenberg, G. (2010). Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health, 20*(3), 251-257. doi: 10.1093/eurpub/ckp113

van Gelderen, B. R., Bakker, A. B., Konijn, E. A., & Demerouti, E. (2011). Daily suppression of discrete emotions during the work of police service workers and criminal

investigation officers. *Anxiety Stress Coping, 24*(5), 515-537. doi: 10.1080/10615806.2011.560665 933384305 [pii]

van Weering, M., Vollenbroek-Hutten, M. M., Kotte, E. M., & Hermens, H. J. (2007). Daily physical activities of patients with chronic pain or fatigue versus asymptomatic controls. A systematic review. *Clinical Rehabilitation, 21*, 1007-1023.

Vermeulen, R. C. (2006). Translation and validation of the Dutch language version of the CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome (CFS). *Popul Health Metr, 4*, 12. doi: 1478-7954-4-12 [pii] 10.1186/1478-7954-4-12

Vincent, A., Benzo, R. P., Whipple, M. O., McAllister, S. J., Erwin, P. J., & Saligan, L. N. (2013). Beyond pain in fibromyalgia: insights into the symptom of fatigue. *Arthritis Research and Therapy, 15*(6), 221. doi: ar4395 [pii] 10.1186/ar4395

Watt, T., Groenvold, M., Bjorner, J. B., Noerholm, V., Rasmussen, N. A., & Bech, P. (2000). Fatigue in the Danish general population. Influence of sociodemographic factors and disease. *Journal of Epidemiology and Community Health, 54*(11), 827-833.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., & Wright, D. (1997). The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *American Journal of Public Health, 87*(9), 1449-1455.

Wessely, S., Nimnuan, C., & Sharpe, M. (1999). Functional somatic syndromes: one or many? *Lancet, 354*(9182), 936-939. doi: S0140-6736(98)08320-2 [pii] 10.1016/S0140-6736(98)08320-2

Whisman, M. A., & Beach, S. R. (2012). Couple therapy for depression. *Journal of Clinical Psychology, 68*(5), 526-535. doi: 10.1002/jclp.21857

White, P. D. (2015, March 12th, 2015). Chronic Fatigue Syndrome: Right Name, Real Treatments Retrieved August 24th, 2015, 2015, from http://www.medscape.com/viewarticle/841289

White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., . . . Sharpe, M. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet, 377*(9768), 823-836. doi: 10.1016/S0140-6736(11)60096-2 S140-6736(11)60096-2 [pii]

Wittig, P., Nöllenheidt, C., & Brenscheidt, S. (2012). Grundauswertung der BIBB/BAuAErwerbstätigenbefragung 2012 mit den Schwerpunkten Arbeitsbedingungen, Arbeitsbelastungen und gesundheitliche Beschwerden. Dortmund, Berlin, Dresden: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin.

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken), 62*(5), 600-610. doi: 10.1002/acr.20140

World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders - Clinical descriptions and diagnostic guidelines*.

6. Appendix

6.1 Narrative Review

Doerr, J.M., & Nater, U.M. (2013) Erschöpfungssyndrome – Eine Diskussion verschiedener Begriffe, Definitionsansätze und klassifikatorischer Konzepte. [Fatigue Syndromes – An Overview of Terminology, Definitions and Classificatory Concepts.] *Psychotherapie, Psychosomatik, Medizinische Psychologie, 63,* 69-76.

Erschöpfungssyndrome – Eine Diskussion verschiedener Begriffe, Definitionsansätze und klassifikatorischer Konzepte

Fatigue Syndromes – An Overview of Terminology, Definitions and Classificatory Concepts

Autoren Johanna Dörr, Urs Nater

Institut Psychologie, Universität Marburg

Schlüsselwörter
- Erschöpfung
- chronisches Erschöpfungssyndrom
- Burnout

Key words
- fatigue
- chronic fatigue syndrome
- burnout

Zusammenfassung

Der Artikel setzt sich zum Ziel, verschiedene in der Literatur beschriebene Syndrome, die Erschöpfung als ein Kernsymptom beinhalten, vorzustellen und die Abgrenzung der Begrifflichkeiten zu diskutieren. Zunächst wird ein kurzer geschichtlicher Abriss der Entwicklung verschiedener Begriffe für Erschöpfungsphänomene aufgezeigt. Anschließend werden die gängigsten Definitionen von Neurasthenie, dem chronischen Erschöpfungssyndrom/myalgischer Enzephalomyelitis (CFS/ME) sowie Burnout vorgestellt und die Syndrome klassifikatorisch eingeordnet. Es folgt eine Diskussion der Abgrenzung der Syndrome voneinander, sowie der Abgrenzung von chronischem Erschöpfungssyndrom und Burnout zu Depression. Unsere Schlussfolgerungen ergeben, dass aufgrund der bisherigen Datenlage auf Symptomebene schlecht zwischen den verschiedenen Syndromen differenziert werden kann und erheblicher Forschungsbedarf bezüglich der definitorischen Einordnung und Klassifikation klinisch bedeutsamer Erschöpfung besteht. Depression ist durch spezifische Symptome von den anderen Syndromen abgrenzbar.

Abstract

This article aims at giving a general view of fatigue syndromes, their description, and their differentiation. The syndromes neurasthenia, chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), and burnout are discussed. First, the historical background of fatigue classification is shortly reviewed. Each syndrome is introduced in terms of definition and classification as well as differentiation from each other. The article discusses the differentiation of the syndromes from each other as well as differentiation of CFS/ME and burnout from depression. We conclude that it is difficult to differentiate criteria due to insufficient empirical evidence. More research is needed concerning integration of the diagnoses in classification systems as well as differentiation between syndromes. High comorbidity of depression with CFS and Burnout can be shown, but diagnoses also comprise distinct symptoms.

eingereicht 04. Mai 2012
akzeptiert 12. September 2012

Bibliografie
DOI http://dx.doi.org/10.1055/s-0032-1327706
Psychother Psych Med 2013; 63: 69–76

ISSN 0937-2032

Korrespondenzadresse
Prof. Dr. Urs Nater
Psychologie
Universität Marburg
Gutenbergstraße 18
35032 Marburg
nater@uni-marburg.de

Einführung

In der jüngeren medialen Berichterstattung scheint der Begriff „Erschöpfung" omnipräsent zu sein, häufen sich doch die Fälle von Prominenten, die aufgrund einer Erschöpfungssymptomatik oder eines Burnout-Syndroms an die Öffentlichkeit gehen oder aus derselben verschwinden. Die häufigste Beobachtung aus wissenschaftlicher Perspektive ist aber dabei, dass die Verwendung des Begriffs einer Beliebigkeit unterliegt, die Ihresgleichen sucht. Einer besonderen Beliebtheit erfreut sich, weil gesellschaftlich anerkannt, der Begriff „Burnout", der oft synonym mit „Depression" oder „Nervenzusammenbruch" verwendet und mit Begriffen wie „vegetative Erschöpfung" vermischt wird. Zwar trifft es zu, dass Erschöpfung ein wesentliches Merkmal der genannten Syndrome darstellt, jedoch sollten die verschiedenen Begriffe keinesfalls synonym verwendet werden. Die Konsequenz einer solchen Begriffsverwirrung schlägt sich in einer generellen Unklarheit bezüglich der Begriffsverwendungen in der allgemeinen Bevölkerung nieder. Die schreibenden Kollegen der großen Tageszeitungen und Informationsmagazine zu beschuldigen, unsystematisch mit Begrifflichkeiten umzugehen, greift jedoch zu kurz: Bereits eine kursori-

sche Durchsicht von deutschsprachigen Artikeln zum Thema deutet auf eine Unsicherheit im Umgang mit der adäquaten Terminologie hin. Dieser Artikel soll dazu dienen, die Beschreibung von Erschöpfung im Rahmen verschiedener Syndrome und Krankheiten näher zu beleuchten und damit Gemeinsamkeiten sowie Unterschiede aufzuzeigen, die es erlauben, verschiedene Syndrome voneinander abzugrenzen.

Erschöpfung ist ein subjektiv empfundenes Phänomen, das allen Menschen bekannt sein dürfte. Sie umfasst verschiedene Ebenen des subjektiven Erlebens. So wird sie oft mehrdimensional (wie etwa auf mentaler und körperlicher Ebene) beschrieben [1, 2]. Laut dem deutschen Bedeutungswörterbuch Duden beschreibt der Begriff „Erschöpfung" einen „durch größere Anstrengung hervorgerufene[n] Zustand der Mattigkeit, Kraftlosigkeit". Mit dem im Alltag gebräuchlichen Begriff wird also zunächst eine normale Reaktion des Organismus auf körperliche oder mentale Belastung beschrieben. Typische Belastungen sind z. B. sportliche Aktivität oder konzentriertes Arbeiten. Nach einer gewissen Zeit der Belastung oder Anstrengung stellt sich das Erleben von Schwäche und starker Müdigkeit ein – das, was als „Erschöpfung" bezeichnet wird [1]. Das Wort „erschöpft" trägt zudem die Bedeutung „bis zum letzten aufgebraucht, am Ende" (ebenfalls dem Bedeutungswörterbuch Duden entnommen). Analog dazu kann die mentale oder körperliche Energie als die Ressource angesehen werden, die erschöpft wurde. Die durch Anstrengung entstandene Empfindung der Erschöpfung legt dem Menschen nahe, sich auszuruhen, um neue Energie zu „tanken" bzw. die Ressource wieder aufzufüllen. Erschöpfung kann also als ein Zustand gelten, der biologisch sinnvoll ist und für das Wohlergehen eine wichtige Funktion erfüllt.

Klinisch bedeutsam wird Erschöpfung, sobald sie nicht oder nur noch mangelhaft durch Ruhe abgebaut werden kann und dadurch subjektives Leid hervorruft bzw. das normale Aktivitäts- und Funktionsniveau einer Person signifikant einschränkt [3–5]. Von „chronischer" Erschöpfung wird im Allgemeinen dann gesprochen, wenn über einen Zeitraum von mehr als 6 Monaten trotz Entspannungs- und Ruhephasen kein Rückgang der Erschöpfung empfunden wird, bzw. die Erholungsphase um ein vielfaches im Gegensatz zum prämorbiden Zustand verlängert werden muss, um einen Erholungseffekt zu erhalten [4]. Chronische Erschöpfung kann im Rahmen von schweren Erkrankungen wie Krebs [6, 7], Multipler Sklerose [8], HIV-Infektion [9] und weiteren Krankheitsbildern auftreten. Eine Erschöpfung, die körperlich begründbar ist, gilt als medizinisch erklärtes Symptom. Die hier im Rahmen der vorgestellten Syndrome besprochene Erschöpfung meint jedoch die medizinisch unerklärte, also eine klinisch bedeutsame Erschöpfung, für die es keine organmedizinisch ausreichende Erklärung gibt.

Im Folgenden soll zunächst ein geschichtlicher Abriss des Umgangs mit medizinisch unerklärter Erschöpfung aufgezeigt werden. Anschließend werden verschiedene Syndrome vorgestellt, die durch Erschöpfung als Kernsymptom definiert sind. Der Artikel stellt die Frage, wie und ob diese voneinander abgegrenzt werden können. Hierbei gilt der Anspruch, die bestehenden Schwierigkeiten in der Abgrenzung deutlich zu machen und eine Diskussion der bestehenden Kriterien anzuregen. Im weiteren Verlauf soll auch die Differenzierung zweier Syndrome, bei denen Erschöpfung das Kernsymptom ist, zu Depression dargestellt werden. Abschließend werden Schlussfolgerungen für den Umgang mit den Begrifflichkeiten im Allgemeinen, für die Diagnostik und für die Forschung gezogen.

Geschichtlicher Abriss

Das derzeitig starke Interesse an Erschöpfung als pathologischem Zustand ist kein Novum (für einen umfangreicheren geschichtlichen Überblick siehe [10–14]). Der Versuch, Erschöpfung nosologisch einzuordnen und damit erste Klassifikationsanstrengungen wurden bereits in der zweiten Hälfte des 19. Jahrhunderts unternommen. Die vorwiegende Beobachtung jener Zeit war, dass insbesondere bei Frauen der Mittel- und Oberschicht Erschöpfung fast schon epidemieartig auftrat. Damals prägte der New Yorker Arzt George Beard den Begriff der „Neurasthenie" (d. h. Nervenschwäche) [15], in die zwar Erschöpfung als Kernsymptom einging, die aber auch Krankheitsbilder umfasste, die nach heutigen Begriffen eher mit einer leichten depressiven Episode oder psychotischen bzw. manischen Episoden vergleichbar wären. Diese inhaltliche Ungenauigkeit führte dazu, dass es sich um 1900 um die meistgestellte Diagnose im neuro- und psychopathologischen Bereich handelte, und sie nicht zu Unrecht als „Mülleimer" für anders nicht erklärbare Symptome bezeichnet wird [13]. Erst ab der Mitte des 20. Jahrhunderts lassen sich neuere Entwicklungen feststellen: Die Namensgebung für Erschöpfungssyndrome orientierte sich zunehmend an der vermuteten Ursache des Krankheitsbildes. So wurde nach Entdeckung des Epstein-Barr-Virus (EBV) als Ursache für Mononukleose (auch bekannt als Pfeiffersches Drüsenfieber) in den 1960ern vermutet, dass es sich bei der Kombination von chronischer Erschöpfung und Muskelschmerzen um eine „chronische Mononukleose" oder „chronische EBV-Infektion" handeln muss. Ein Zusammenhang zwischen EBV und chronischer Erschöpfung konnte jedoch empirisch nicht bestätigt werden [16]. Die Begriffe „benigne Enzephalomyelitis" („gutartige" Entzündung des zentralen Nervensystems) oder „myalgische Enzephalomyelitis" (Muskelschmerz mit Entzündung des zentralen Nervensystems) entwickelten sich, nachdem 1955 im Royal Free Hospital in London eine Erschöpfungswelle auftrat, für die keine Erklärung gefunden werden konnte. Der Zusammenhang mit dem zentralen Nervensystem wurde vor allem wegen sensorischer und motorischer Symptome hergestellt. Wegen Ähnlichkeiten mit einer muskulären Entzündung wurde der Begriff „myalgisch" verwendet [17]. Erst Ende der 1980er Jahre wurde der Versuch unternommen, eine allgemein akzeptierte Nomenklatur für chronische Erschöpfung zu finden, die nicht mit einer Ursachenzuschreibung einherging. So entschieden sich die US Centers for Disease Control and Prevention (CDC) für den Begriff „Chronic Fatigue Syndrome" (CFS), um medizinisch nicht erklärte chronische Erschöpfung zu beschreiben [18]. Auch im deutschen Sprachraum erscheinen Anfang der 1990er Jahre die ersten Übersichten zu CFS [19, 20] und es wird bereits zu diesem Zeitpunkt die Frage diskutiert, ob CFS als körperliche oder psychische Erkrankung anzusehen ist [21]. Im Gegensatz zur Annahme von körperlichen Ursachen wird chronische Erschöpfung auch als „somatische Verkleidung von Angst" diskutiert [22], da die Symptomatik große Ähnlichkeiten mit der von Freud beschriebenen Angstneurose aufzeigt, die dieser noch einmal von der Neurasthenie abtrennt [23].

Parallel zu den Bemühungen, chronische Erschöpfung terminologisch festzumachen, etablierte sich in den 1970er Jahren ein Phänomen, das der Psychoanalytiker Freudenberger als Burnout bezeichnete. Er stellte bei sich selbst und einigen Mitarbeitern seiner Klinik eine übermäßig starke Erschöpfung fest, von der besonders die engagiertesten Mitarbeiter betroffen waren.

Aus der Beobachtung, dass Personen, die vorher sozusagen für ihren Beruf „brannten“ und nun völlig erschöpft sowie der Arbeit gegenüber negativ eingestellt („ausgebrannt“) waren, umschrieb er das Phänomen mit dem Begriff Burnout [24]. Damit war er jedoch nicht der Erste; es lassen sich angefangen beim Alten Testament bis hin zu den Buddenbrooks von Thomas Mann immer wieder Beschreibungen ausgebrannter Charaktere finden (für einen detaillierten geschichtlichen Überblick des Begriffs siehe [25–28]). Der 1974 veröffentlichte Artikel „Staff burn-out“ von Freudenberger wird jedoch als „Geburt“ von Burnout als wissenschaftlichem Begriff gesehen ([26], S.32). Da Burnout historisch bedingt zunächst in einem Arbeitskontext beschrieben wurde, wurde in den nachfolgenden Jahrzehnten dieser Begriff insbesondere im Bereich der Arbeitsmedizin und -psychologie weiter beforscht.

Es lässt sich zusammenfassend festhalten, dass Erschöpfung als klinisch relevantes, medizinisch unerklärtes Phänomen im Laufe der letzten 100 Jahre mit vielen verschiedenen Bezeichnungen assoziiert wurde. Im Folgenden sollen die Syndrome (sozusagen in „chronologischer“ Reihenfolge) Neurasthenie, CFS und Burnout getrennt voneinander etwas ausführlicher dargestellt werden. Der Fokus liegt dabei jeweils auf einer umfassenden Definition, klassifikatorischen Einordnung, sowie Abgrenzung bzw. Überschneidung zu anderen, ähnlichen, Begriffen.

Verschiedene Syndrome und ihre Abgrenzung voneinander

Neurasthenie

Die oben dargestellte Beschreibung der Neurasthenie als Sammelbegriff für eine Reihe von Beschwerdebildern im geschichtlichen Kontext spiegelt sich heutzutage noch in 2 Verwendungskontexten wider: als diagnostische Entität in der International Classification of Diseases (ICD)-10 und als Diagnose in nichtwestlichen Kulturen.

1. Die ICD-10 Kriterien (F48.0) [5] beschreiben ein Syndrom, das sich durch vermehrte geistige Ermüdbarkeit oder Gefühle körperlicher Schwäche auszeichnet. Als mögliche Begleitsymptome sind akute oder chronische Muskelschmerzen, Benommenheit, Spannungskopfschmerz, Schlafstörung, die Unfähigkeit, zu entspannen, sowie Reizbarkeit aufgelistet. Weiterhin werden als Kriterien eine überdurchschnittlich verlängerte Erholungsphase sowie eine Dauer der Symptome von mind. 3 Monaten angesetzt (vgl. **Tab. 1**). Zu den Ausschluss-Kriterien gehören verschiedene neurologische Erkrankungen sowie affektive (inkl. Depression) und Angststörungen. Die Ausschlusskriterien für Neurasthenie weisen bereits darauf hin, dass es sich um eine Art „Sekundärdiagnose“ handelt [29], die nur dann gestellt wird, wenn keine andere psychiatrische Diagnose erfüllt wird. Auch die weitgehend fehlenden empirischen Studien mit aktuellem Bezug auf die ICD-10 Kriterien deuten darauf hin, dass die Diagnose wissenschaftlich wenig populär ist. In einer Umfrage unter deutschsprachigen Psychiatern wurde diese Diagnose am häufigsten zur Streichung vorgeschlagen [30].
   Es ergibt sich der Eindruck, dass der Begriff der Neurasthenie eher in einem historischen Kontext zu verorten ist und aktuell vorwiegend im asiatischen Kulturbereich angewendet wird. Bei Durchsicht der vorhandenen Literatur lassen sich keine Hinweise darauf finden, dass die in der ICD-10 formulierten Diagnosekriterien wissenschaftlich untermauert sind oder in der klinischen Praxis noch eine entscheidende Rolle einnehmen (Ausnahme s. o.).
2. In asiatischen Ländern wie Japan und China entwickelte sich die Diagnose der Neurasthenie anders als in den westlichen Kulturen und ist heute gesellschaftlich anerkannter. Da Neurasthenie zunächst eine rein somatische Konnotation hatte, konnte man mithilfe dieser Diagnose dem Stigma, das psychischen Störungen anhaftete, elegant ausweichen. Weil bei Patienten wie Ärzten beliebt, weitete sich im Verlaufe der Zeit die Diagnose soweit aus, dass sie letztlich alle psychischen Störungen bis auf psychotische Störungen umfasste. So war Neurasthenie z. B. in China bis in die 1980er Jahre die mit Abstand am häufigsten gestellte psychiatrische Diagnose [31]. In den 1980ern wurde diese Diagnosebildung durch verstärkten internationalen Austausch, verstärkte Strukturierung der psychiatrischen Diagnostik und die Re-Evaluierung der Diagnose im Vergleich mit dem Diagnostic and Statistical Manual of Mental Disorders (DSM)-III [32] reformiert und den genannten westlichen Systemen angepasst. Im chinesischen Diagnosesystem CCMD (Chinese Classification of Mental Disorders) [33] beinhaltet Neurasthenie Symptome der Schwäche, emotionalen Instabilität, Aufregung, Nervenschmerzen und Schlafstörungen, wobei 3 der 5 Symptome vorhanden sein müssen. Es lässt sich erkennen, dass die Definition auch heute noch weiter gefasst ist als in der ICD-10. Besonders in ländlichen Gebieten Chinas wird die Diagnose nach wie vor häufig gestellt und ist speziell bei der älteren und weniger gebildeten Bevölkerung wesentlich weniger mit Stigmatisierung verbunden als etwa die Diagnose einer Depression (für eine Übersicht siehe [34]). In Japan scheint der Begriff, wenn auch einflussreicher als in westlichen Kulturen, weniger populär als in China zu sein, da er nach dem Zweiten Weltkrieg durch den amerikanischen Einfluss durch den Begriff der „Neurose“ abgelöst wurde [35]. Weiterhin unterlag der Begriff in Japan bereits in den 1920er Jahren einer Veränderung der Konnotation durch den Begründer der Morita-Therapie, der den Begriff „Neurasthenie“ als zu umfassend ablehnte und das Syndrom „Shinkeishitsu“ einführte, das sich am ehesten mit Angststörungen gleichsetzen lässt [36].
   Es kann festgehalten werden, dass der Begriff der Neurasthenie in asiatischen Kulturen besonders als „Camouflage“ für psychiatrische Erkrankungen eine höhere Bedeutung hat als in westlichen Kulturen [37]. Es lässt sich bei der Sichtung der Literatur jedoch auch erkennen, dass der internationale wissenschaftliche Austausch dazu beiträgt, dass (zumindest in der Forschung) auch in diesen Kulturen der Begriff der Neurasthenie mehr und mehr in den Hintergrund rückt.

Chronisches Erschöpfungssyndrom/myalgische Enzephalomyelitis

Das Chronische Erschöpfungssyndrom (engl. chronic fatigue syndrome, CFS[1]), das auch als chronisches Müdigkeitssyndrom bezeichnet wird, ist ein weiteres Syndrom, dessen Kernsymptomatik sich durch eine starke Erschöpfung auszeichnet. In der ICD-10 ist das Syndrom unter G93.3 („sonstige Krankheiten des Nervensystems“) kodierbar. Einschlägige Kriterien wurden 1988 von den US Centers for Disease Control and Prevention (CDC) vorgestellt [18]. Eine Revision fand 1994 Eingang in die For-

[1] Nachfolgend soll die Abkürzung CFS verwendet wenden, da der Hauptteil der entsprechenden Literatur im angelsächsischen Raum entstanden ist und sich entsprechend dieser Begriff auch hierzulande durchgesetzt hat.

Tab. 1 ICD-10 Kriterien (Hauptkriterien im Fettdruck).

Kriterien-Bereiche	Kriterien Neurasthenie [5]	CFS [4]	ME [39]	Burnout [49]	Depressive Episode [5]	Major Depression [71]
Erschöpfung	**schwere Erschöpfung nach geringer geistiger/körperlicher Anstrengung**	**schwere Erschöpfung**	**Neuroimmun-Erschöpfung nach Belastung**	**schwere (emotionale) Erschöpfung**	**verminderter Antrieb oder gesteigerte Ermüdbarkeit**	Müdigkeit und Energieverlust
Zeitkriterium	seit mind. 3 Monaten	seit mind. 6 Monaten			seit mind. 2 Wochen	seit mind. 2 Wochen
		akuter Beginn				
kognitive Symptome	Benommenheit	kognitive Probleme	neurokognitive Defizite	**verminderte subjektive Leistungsbewertung**	verminderte subjektive Leistungsfähigkeit	verminderte kognitive Funktionen
Schmerzen	akute oder chronische Muskelschmerzen	Halsschmerzen; Muskel-/Gelenkschmerzen	Arthralgien und/oder Myalgien			
	Spannungskopfschmerz	Kopfschmerzen	Kopfschmerzen			
Schlaf	Schlafstörung	unerholsamer Schlaf	Schlafstörungen (verändertes Schlafmuster oder unerholsamer Schlaf)		Schlafstörungen	Schlaflosigkeit oder vermehrter Schlaf
Reaktion auf Anstrengung	schwere Erschöpfung nach geringer geistiger/körperlicher Anstrengung	Unwohlsein nach Anstrengung	schnelle Erschöpfbarkeit nach Belastung; Symptom-Schub nach Belastung; verminderte Ausdauer; verlängerte Erholungsphase			
Motorik			neurosensorische, perzeptuelle und motorische Störungen		psychomotorische Agitiertheit oder Hemmung	psychomotorische Unruhe/Verlangsamung
sonstige körperliche Symptome		empfindliche Lymphknoten	Immun-, gastrointestinale und Harn- und Geschlechtsprobleme Energieproduktions- und Transportprobleme			
Stimmung	Reizbarkeit			**Depersonalisation/Zynismus**	**depressive Stimmung Interessen-/Freudeverlust** Verlust des Selbstvertrauens oder Selbstwertgefühls unbegründete Selbstvorwürfe oder unangemessene Schuldgefühle wiederkehrende Gedanken an Tod, Suizid oder suizidales Verhalten	**depressive Verstimmung Interessen-/Freudverlust** Gefühl von Minderwertigkeit oder übermäßige Schuldgefühle Gefühl von Minderwertigkeit oder übermäßige Schuldgefühle wiederkehrende Gedanken an den Tod
Appetit					Appetitverlust	Gewichtsverlust/-zunahme; Appetitverlust/-zunahme

schungsliteratur [4]. Bis heute ist diese revidierte Falldefinition im Bereich der CFS-Forschung die am häufigsten verwendete. Nach diesen Kriterien ist CFS vor allem durch eine starke, mindestens 6 Monate anhaltende, Erschöpfung gekennzeichnet. Die Erschöpfung sollte einen akuten Beginn aufweisen, unabhängig von Anstrengung auftreten sowie mit Einschränkungen in wichtigen Funktionsbereichen einhergehen. Weiterhin sollen mindestens 4 der folgenden Begleitsymptome auftreten: kognitive Probleme, Halsschmerzen, empfindliche Lymphknoten, Muskel- und Gelenkschmerzen, Kopfschmerzen, unerholsamer Schlaf sowie Unwohlsein nach Anstrengung (vgl. **Tab. 1**). Da es sich bei allen genannten Symptomen nicht um für CFS spezifische Symptome handelt, erlangt die Ausschlussdiagnostik eine besondere Bedeutung. Zur Diagnosestellung „CFS" dürfen keine aktuellen oder unklar remittierten körperlichen Krankheiten sowie keine schwerwiegenden psychiatrischen und neurologischen Störungen vorliegen, die eine Erklärung für die beobachtete Erschöpfung bieten könnten. Auch das Vorliegen von Substanzmissbrauch und Adipositas führen zum Ausschluss der Diagnose. Mit CFS überlappende, jedoch distinkte Erkrankungen wie etwa Depression (mit Ausnahme des melancholischen oder psychotischen Subtyps) oder das Schmerzsyndrom Fibromyalgie führen nicht zum Ausschluss von CFS [4]. Der Begriff „myalgische Enzephalomyelitis" (ME), der im geschichtlichen Abriss bereits Erwähnung gefunden hat, bezeichnet das gleiche Syndrom. Es gibt neuerdings vermehrt Bemühungen, den Begriff ME zu verwenden (oftmals in Kombination mit CFS, d.h. CFS/ME), da damit eine körperliche Ursache des Syndroms impliziert wird und die Patienten damit einer (vermeintlichen) Trivialisierung ihrer Erkrankung und einer Stigmatisierung als „psychisch krank" entgehen sollen [38, 39]. Neben den CDC-Kriterien für CFS [4] wurden 2003 kanadische klinische Kriterien für ME/CFS [3] und aufbauend darauf 2011 internationale Consensus-Kriterien für ME vorgeschlagen [39]. Die Kriterien von 2011 unterscheiden sich von den CDC-Kriterien vor allem darin, dass das 6-Monats-Kriterium fallen gelassen und Depression als Ausschluss-Diagnose hinzugenommen wurde. Außerdem liegt diesen Kriterien die klare Annahme zugrunde, dass CFS eine körperliche Ursache hat, während dieser Aspekt in den CDC-Kriterien offen gehalten wird. Die Annahme rein körperlicher Ursachen wird von den meisten Patientenverbänden begrüßt. Einen breiten wissenschaftlichen Konsens findet er jedoch nicht, da bisher keine klare körperliche Ursache für das Syndrom gefunden werden konnte und weil dieser Ansatz das komplexe Zusammenspiel von Körper und Psyche, welches bei jeder Erkrankung eine Rolle spielt, außer Acht lässt. Die Vielzahl der empirischen Studien, die die Rolle von psychologischen Faktoren bei der Genese und Aufrechterhaltung des Syndroms aufzeigen, zeichnen hier ein klares Bild (für die Rolle von Stress siehe dazu z.B. [40–42]).

Exkurs: Idiopathische chronische Erschöpfung

Beim Vorliegen einer medizinisch unerklärten chronischen Erschöpfung ohne Erfüllung aller der oben genannten Kriterien wird von „idiopathischer chronischer Erschöpfung" (idiopathic chronic fatigue, ICF) gesprochen [4]. Ob es sich bei ICF und CFS um das gleiche Phänomen, jedoch mit unterschiedlichen Schweregraden, oder um 2 voneinander unterscheidbare Syndrome handelt, ist noch nicht geklärt. Für die Annahme unterschiedlicher Schweregrade spricht, dass sich sowohl bei CFS als auch bei ICF ähnliche Veränderungen auf physiologischer Ebene, wie z.B. eine relative Hypoaktivität der endokrinen Stressachse, feststellen lassen [43, 44]. In einer Stichprobe von Personen, die wegen chronischer Erschöpfung in Behandlung waren, fanden Evengard et al. [45] vor allem bezüglich Begleitsymptomen und funktioneller Beschwerden Unterschiede zwischen ICF und CFS. So berichteten CFS-Patienten mehr körperliche Begleitsymptome und größere funktionelle Einschränkungen. Auch konnte bei den meisten CFS-Patienten ein akuter Beginn der Symptomatik beobachtet werden, während der Verlauf bei etwa der Hälfte der ICF-Patienten schleichend war. Wessely [46] hält es für am wahrscheinlichsten, dass es mehrere Subgruppen von CFS gibt, die sich durch ihren Beginn (schleichend vs. plötzlich), ihre Dauer, sowie die Zusammenstellung der gleichzeitig auftretenden Symptome voneinander unterscheiden lassen. Entsprechende Forschungsansätze sind jedoch erst im Entstehen begriffen.

Burnout

Der Begriff „Burnout" bezeichnet sowohl den Prozess („to Burnout") als auch den Zustand des „Ausbrennens" bzw. „Ausgebranntseins" im übertragenen Sinne. Das mit diesem Begriff beschriebene Syndrom wurde in verschiedenen Theorien (die Burnout teilweise als Prozess, teilweise als Zustand sehen) beschrieben und mit zahlreichen Symptomen in Verbindung gebracht (eine Übersicht findet sich in ([47, 48]). Im Kontext dieser Übersicht soll die Definition des Burnout-Syndroms herangezogen werden, die sich in der Literatur mit Abstand am häufigsten findet. Hierbei handelt es sich um die Definition von Maslach [27, 49]. Demnach ist Burnout durch folgende Symptome (auch „Burnout-Triade" genannt) definiert: 1. Emotionale Erschöpfung, 2. Depersonalisation/Zynismus (gegenüber der Arbeit und/oder gegenüber den Klienten) und 3. verminderte subjektive Leistungsbewertung. Diese Kriterien stehen unter starker Kritik, da die empirischen und klinischen Belege für deren Validität und Reliabilität fehlen [48]. Kristensen et al. [50] nehmen an, dass es sich bei den 3 beschriebenen Faktoren nicht um Symptome im eigentlichen Sinne handelt. Lediglich emotionale Erschöpfung sei als Symptom einzustufen, während die anderen Faktoren eher als Coping-Strategie (Zynismus/Depersonalisation) oder als Resultat (verringerte subjektive Leistung) in Reaktion auf länger währenden Stress zu bewerten seien. Weiterhin sei eine Attribuierung der Erschöpfung als von bestimmten Bereichen des Lebens (z.B. Arbeit) der betroffenen Person verursacht, ausschlaggebend.

Es wird also angenommen, dass Burnout vor allem dann entsteht, wenn sich Personen zu sehr in ihrer Arbeit engagieren und dadurch Energien verloren gehen [24]. Zunächst wurde Burnout vor allem in helfenden Berufen beobachtet und untersucht, inzwischen wird die Forschung auch auf andere Arbeitskontexte ausgedehnt (z.B. Bachelor-Studierende [51], IT-Fachleute [52] oder SportlerInnen [53]). Laut Schaufeli und Taris [54] muss Burnout immer in einem Arbeitskontext oder arbeitsähnlichen Kontext zu verorten sein. Den Begriff in anderen Kontexten zu verwenden, ist demnach nicht angebracht bzw. läuft der ursprünglichen Intention zuwider. Die „Diagnose" Burnout zu vergeben gestaltet sich sowohl in der Forschung als auch in der Praxis schwierig. In der Literatur finden sich kaum Angaben, wie die Kriterien erfasst werden. Schaufeli et al. beschrieben Schwellenwerte im Maslach Burnout Inventory – General Survey (MBI-GS) [55] für die klinische Relevanz von Burnout-Symptomen [56, 57]. Die Autoren betonen jedoch, dass diese Kriterien vermutlich nur auf niederländische Stichproben anwendbar sind, da kulturelle Unterschiede im Ausdruck der Symptome bestehen können. Interessant ist auch, dass die Autoren unter klinisch relevantem Burnout „arbeitsbezogene Neurasthenie" verstehen, als Validie-

rungskriterien also die ICD-10-Kriterien für Neurasthenie mit zusätzlichem (durch die Patienten berichteten) Arbeitsbezug der Symptome verwenden. In der „Maastricht Kohortenstudie" wurden Forschungskriterien für Burnout beschrieben [58]. Bisher gibt es jedoch keine ableitbaren Leitlinien für Forschung oder klinische Praxis, die als verbindlich anerkannt wären. In der ICD-10 wird das Syndrom unter „Probleme mit Bezug auf Schwierigkeiten bei der Lebensbewältigung" als mögliche klinische Zusatzdiagnose kodiert (Z73.0) und wird mit „Ausgebranntsein" oder „Zustand der totalen Erschöpfung" erläutert – eine diagnostische Einordnung, die dem klinisch Tätigen keine besondere Hilfe sein kann. Auch Korczak und Kollegen [48] halten in ihrem Health Technology Assessment (HTA) – Bericht für das Deutsche Institut für Medizinische Dokumentation und Information (DIMDI) fest, dass es bisher „kein standardisiertes, allgemeingültiges Vorgehen, um eine Burnout-Diagnose zu stellen" (S. 97) gibt. Sie weisen darauf hin, dass noch erheblicher Forschungsbedarf besteht (vor allem hinsichtlich längsschnittlichen, klinisch relevanten sowie bevölkerungsrepräsentativen Ansätzen) und daher auf dem heutigen Stand von einer Diagnosestellung „Burnout" in der klinischen Praxis abgesehen werden sollte [59].

Es sei darauf hingewiesen, dass das Konstrukt des Burnouts aus Patientenperspektive wegen der Implikation, über die individuellen Grenzen hinaus geleistet zu haben, als entlastend und entstigmatisierend empfunden wird. Aus diesem Grund erlangt es in der klinischen Praxis einen besonderen Stellenwert hinsichtlich seiner Funktion in der Kommunikation mit dem Patienten (z. B. bei der Vermittlung eines Störungsmodells), der nicht zu unterschätzen ist [60].

Differenzierung zwischen CFS und Neurasthenie

Bei bloßer Betrachtung der notwendigen Symptome lassen sich CFS und Neurasthenie (wie in der ICD-10 definiert) kaum voneinander abgrenzen. Der stärkste Unterschied scheint das unterschiedliche Zeitkriterium zu sein (vgl. **Tab. 1**). Weiterhin müssen für die ICD-10 Diagnose einer Neurasthenie u. a. affektive Störungen sowie Panikstörung, generalisierte Angststörung und auch CFS (G93.3) ausgeschlossen werden (F48.0, [5]). Gemäß den CDC-Kriterien für CFS führen eine depressive Episode (ohne melancholische oder psychotische Merkmale) sowie Angststörungen nicht zum Ausschluss der Diagnose, Neurasthenie wird nicht erwähnt [4]. Aus der Literatur lässt sich erkennen, dass die Begriffe entweder synonym verwendet werden [61], CFS als eine aktuellere Variante von Neurasthenie gesehen wird [12, 62, 63] oder dass die beiden Begriffe im Kontext verschiedener Kulturen diskutiert werden (Neurasthenie als asiatisch, CFS als westlich geprägt) [64, 65]. Mit der Frage, inwiefern sich das heutige, westliche, Symptombild der Neurasthenie (wie in der ICD-10 definiert) mit CFS überschneidet, haben sich nur wenige Forscher empirisch auseinandergesetzt [29]. Eine Studie von Farmer und Kollegen [66] fand bei 97% der untersuchten CFS-Patienten ebenfalls die ICD-10 Kriterien für Neurasthenie erfüllt, wenn die Ausschlusskriterien nicht beachtet wurden. Mit Berücksichtigung der Ausschlusskriterien betrug die Überschneidung noch 40%. Die Studie weist darauf hin, dass die Symptombilder der Neurasthenie nach ICD-10 und des CFS nach CDC-Kriterien sich prinzipiell nicht unterscheiden. Hier besteht weiterer Klärungsbedarf.

Differenzierung zwischen CFS und Burnout

Die Menge der empirischen Bemühungen, CFS und Burnout voneinander abzugrenzen, ist ebenfalls sehr gering. Dies lässt sich höchstwahrscheinlich durch unterschiedliche „Zuständigkeit" durch die verschiedenen Fachrichtungen erklären, d. h. Medizin für CFS und (Arbeits-)Psychologie für Burnout. Huibers et al. [67] untersuchten 151 Arbeiter, die wegen Erschöpfung krankgeschrieben waren und fanden, dass sich die Burnout- und CFS-Fälle vor allem in den kausalen Attributionen bezüglich der erlebten Symptome unterschieden: Die CFS-Fälle attribuierten ihre Erschöpfung somatisch und die Burnout-Fälle psychologisch. Die Autoren nehmen an, dass es sich bei CFS und Burnout um überlappende Syndrome handelt, bei denen die Erschöpfung unterschiedliche subjektive Qualitäten aufweist. Leone et al. [68] untersuchten den zeitlichen Zusammenhang von länger andauernder medizinisch unerklärter Erschöpfung und Burnout. Sie stellten fest, dass beide Konstrukte sich im 4-Jahres-Follow-Up gegenseitig vorhersagen. Weiterhin steigt mit dem Auftreten einer Symptomatik die Wahrscheinlichkeit dafür, dass bei Follow-up sowohl länger andauernde medizinisch unerklärte Erschöpfung als auch Burnout-Symptomatik vorliegen. Die Autoren schlussfolgern, dass die beiden Beschwerdebilder sich im Sinne einer „Abwärtsspirale" gegenseitig beeinflussen. Den Schluss zuzulassen, es handele sich um das gleiche Phänomen, stößt v. a. bei CFS-Betroffenen auf starken Widerstand, da eine „Psychologisierung" als einer Trivialisierung des Syndroms gleichkommend empfunden wird.

Differenzierung zwischen CFS und Depression

Die Rolle von Depression bei Erschöpfung ist oben bereits verschiedentlich angeklungen. Es lohnt sich deshalb, das chronische Erschöpfungssyndrom CFS und Depression einander gegenüberzustellen. Aus der Literatur geht hervor, dass bis zu 75% der CFS-Patienten über die Lebensspanne hinweg ebenfalls mindestens zu einem Zeitpunkt an einer depressiven Episode leiden [69]. Für erschöpfte Personen, die die Kriterien für CFS nicht erfüllen, wird die Lebenszeit-Prävalenz für mindestens eine Episode einer Major Depression auf etwa 45% geschätzt [70]. In derselben Studie wurde bei 22% der CFS-Patienten eine aktuelle komorbide Major Depression festgestellt. Die Hauptkriterien einer depressiven Episode umfassen in der ICD-10 neben depressiver Verstimmung und Interessen- oder Freudeverlust auch verminderten Antrieb oder gesteigerte Ermüdbarkeit [5], wobei bei Vorliegen der anderen beiden Symptome verminderter Antrieb und gesteigerte Ermüdbarkeit nicht vorliegen müssen (2 von 3). Das DSM-IV stellt den Erschöpfungs-Aspekt nicht in den Vordergrund der depressiven Symptomatik (er gehört also nicht zu den Hauptkriterien), er taucht jedoch innerhalb der Nebenkriterien (von denen mind. 5 erfüllt sein müssen) ebenfalls auf [71]. Die Haupt- und Nebenkriterien für beide Klassifikationssysteme sind in **Tab. 1** noch einmal dargestellt. Es lässt sich nachvollziehen, dass (unter dem Gesichtspunkt von Erschöpfung als Kriterium für Depression) Syndrome, bei denen eine Erschöpfungssymptomatik im Vordergrund steht, leicht als Depression fehldiagnostiziert werden können. Auch besteht die Gefahr, ein Erschöpfungssyndrom zu übersehen, wenn komorbid ebenfalls eine Depression vorhanden ist. Viele Personen, die die Kriterien für CFS oder Burnout erfüllen, erfüllen aufgrund der Überschneidungen der Definitionen auch mindestens ein Kriterium einer depressiven Episode. Es besteht weiterhin die Gefahr, dass in einigen Studien die Komorbiditätsrate durch besagte Symptomüberschneidungen überschätzt wird, da auch in den Depres-

sions-Instrumenten Erschöpfung und Müdigkeit als Depressions-Symptome mit erfasst werden (z.B. im BDI-II [72]: Energieverlust, Konzentrationsschwierigkeiten, Ermüdung oder Erschöpfung). Daher wird vorgeschlagen, bei einer Stichprobe aus CFS-Patienten verschiedene Dimensionen des BDI-II (somatisch-affektiv und kognitiv) separat zu betrachten [73].
Hinweise auf distinkte Krankheitsentitäten finden sich in Studien, die auf endokriner Ebene einen erhöhten Kortisolspiegel bei Personen mit einer derzeitigen depressiven Episode, jedoch erniedrigte Konzentrationen bei Personen mit CFS (jeweils im Vergleich zu gesunden Kontrollprobanden) berichten [74–77]. Griffith und Zarrouf [78] stellen in einer Zusammenschau der Unterschiede von Depression und CFS fest, dass vor allem die körperlichen Begleitsymptome (wie Halsschmerzen, empfindliche Lymphknoten usw.) eher spezifisch für CFS sind, jedoch bei Depression selten vorkommen. Weiterhin unterscheiden sich nach diesen Autoren die Patientengruppen vor allem in ihrer Reaktion auf Aktivität – während körperliche Betätigung bei CFS zu einer Verschlechterung der Symptomatik führt, profitieren depressive Patienten von (körperlichem) Aktivitätsaufbau.

Differenzierung zwischen Burnout und Depression

Auch zwischen Burnout und Depression gibt es starke Überschneidungen (für eine Übersicht siehe auch [79]). So wird das Risiko bei hohen Werten im MBI-GS [55] auf etwa 50% geschätzt, an einer Major Depression zu erkranken [80]. Firth und Kollegen [81, 82] konnten zeigen, dass der Zusammenhang von Depression und der „Emotionale Erschöpfung"-Skala des MBI [83] von r=0,50 auf r=0,59 steigt, wenn ein Arbeitsbezug der Depressions-Items im BDI [84] hergestellt wird. Glass und McKnight [85] halten dazu in ihrer systematischen Review fest, dass die Überlappung zwischen Depression und Burnout vor allem in dem Symptom der Erschöpfung zu finden ist. Auch hierbei sei angemerkt, dass sowohl Depressions- als auch Burnout-Inventare Erschöpfungs-Items enthalten. Eine Studie zur Konstruktvalidität von Burnout in Abgrenzung zur Depression von Reime und Steiner [86] zeigt eine moderate Korrelation von r=0,44 zwischen der allgemeinen Depressionsskala (ADS [87]) und der Subskala „emotionale Erschöpfung" aus dem MBI, jedoch lediglich eine geringe Korrelation (von r=0,22) mit der Skala „Depersonalisation/Zynismus" des MBI und eine nicht signifikante Korrelation mit abnehmender subjektiver Leistungsfähigkeit (r= −0,18). Die Studien weisen darauf hin, dass es sich bei Depression und Burnout um 2 unterscheidbare Konstrukte handelt, deren Überlappung insbesondere durch das Symptom „Erschöpfung" bedingt ist.
Es wird weiterhin darüber diskutiert, in welchem zeitlichen Zusammenhang die beiden Syndrome stehen. So wird Depression in einigen Theorien als logische Folge eines Burnout-Prozesses gesehen [88]. Toker und Biron [89] stellen in einer längsschnittlichen Untersuchung fest, dass sowohl Burnout (erhoben mit dem Shirom-Melamed-Burnout-Inventar [90, 91]) ein guter Prädiktor für die Entwicklung einer depressiven Symptomatik (erhoben mit dem PHQ-9 [92]) ist, als auch depressive Symptome für die Entwicklung von Burnout-Symptomen [93]. Mehr noch stellt sich in der Untersuchung von Toker und Biron Depressivität als ein stärkerer Prädiktor für Burnout heraus als umgekehrt. Die Autoren begründen dies damit, dass eine depressive Symptomatik mit der Zeit auf alle Lebensbereiche übergreift (und damit z.B. eine zynische Einstellung gegenüber der Arbeit bewirkt), während dies bei einer Burnout-Symptomatik nicht unbedingt der Fall sein muss, da Burnout-Betroffene losgelöst vom Arbeitskontext zu Hause eine Erleichterung der Symptomatik empfinden könnten.

Schlussfolgerungen

▼

Generelle Aspekte

Zusammenfassend kann festgehalten werden, dass es sich bei medizinisch unerklärter Erschöpfung um ein Phänomen handelt, das in unserer Gesellschaft eine große Bedeutung hat. Darauf weisen die verschiedenen Begrifflichkeiten hin. Aus dem historischen Einblick wird deutlich, dass die unterschiedlichen Begriffe in ihrer Funktionalität immer von dem jeweiligen Zeitgeist abhängig sind. Begriffe werden neben der historischen Einordnung auch stark von der Kultur geprägt, was sich insbesondere am Beispiel der Neurasthenie nachvollziehen lässt. Die verschiedenen Syndrome klar voneinander abzugrenzen scheint gemäß derzeitigem Wissensstand nicht möglich zu sein. Es ist (gerade im klinischen Kontext) jedoch wichtig, sich der (funktionellen) Bedeutung des jeweiligen Begriffs (hier sei z.B. auf die Debatte der Begrifflichkeiten CFS vs. ME hingewiesen [38] sowie auf die entstigmatisierende Wirkung des Begriff „Burnout" [60]) für betroffene Personen bewusst zu sein.
Es lässt sich weiterhin feststellen, dass ein schwerwiegendes Problem bei der Differenzierung der verschiedenen Erschöpfungssyndrome die sowohl bei Patienten als auch bei vielen Wissenschaftlern nach wie vor vorherrschende Dichotomisierung von psychischen und körperlichen Erkrankungen darstellt. Auf der einen Seite steht die Stigmatisierung von psychischen Erkrankungen, auf der anderen Seite die Hilflosigkeit der Patienten im Angesicht medizinisch nicht erklärbarer körperlicher Beschwerden. Sowohl Patienten als auch Behandler würden von einer integrativeren Sichtweise von Krankheit, die auf körperlicher wie psychischer Seite ansetzt (sowohl bei der Diagnostik als auch bei der Behandlung), profitieren. An dieser Stelle sei Donald Oken zitiert, der schrieb: „There are no „psychosomatic disorders", because there are no *non*-psychosomatic ones." ([94], S. 831).

Begriffsverwendung

Alle besprochenen Begriffe beschreiben Syndrome, bei denen Erschöpfung im Mittelpunkt steht. Für Neurasthenie bestehen ICD-10-Kriterien [5], für CFS gelten die Kriterien des CDC [4] als Goldstandard. Es handelt sich in beiden Fällen um ein Syndrom, das medizinisch unerklärte Erschöpfung beschreibt, wobei der Begriff „Neurasthenie" eher in einem historischen Kontext zu verorten ist und aktuell vorwiegend im asiatischen Kulturbereich angewendet wird. „Burnout" wiederum bezeichnet Erschöpfung im Arbeitskontext [54] und ist derzeit eher als wissenschaftliches Konstrukt denn als Diagnose zu begreifen. Depression ist eine psychische Erkrankung, bei der neben Erschöpfung weitere Symptome im Vordergrund stehen und die keinesfalls mit vorher genannten Syndromen gleichzusetzen ist. Solange keine klare (Ausschluss-) Diagnostik vorliegt, kann letztlich nur von „Erschöpfung" auf Symptomebene gesprochen werden.

Diagnostik

Es scheint, dass die Diagnose, die eine Person mit Erschöpfungserscheinungen erhält, stark von ihrer eigenen Attribution der Symptome sowie der Person des Behandlers abhängt [14]. Zudem überschneiden sich die Kriterien teilweise und schließen

sich nicht gegenseitig aus. Ein Patient, der die Kriterien für CFS erfüllt, könnte damit in einem psychiatrischen Kontext mit Neurasthenie diagnostiziert werden. Die Abgrenzung von Neurasthenie und CFS ist schwierig und es spricht einiges dafür, dass es sich phänomenologisch um 2 Begriffe für das gleiche Syndrom handelt (wobei für Neurasthenie zusätzlich affektive und diverse Angststörungen ausgeschlossen werden müssen). Es scheint, dass die Diagnosen auch von den meisten Klinikern als synonym angesehen werden [14], jedoch sind sie (mit G93.3 für CFS und F48.0 für Neurasthenie) in der ICD-10 unterschiedlich klassifiziert und sollen sich sogar gegenseitig ausschließen. Diese Annahme ist jedoch nicht empirisch begründet. Eine gewissenhafte Ausschlussdiagnostik sowie eine möglichst ausführliche Anamnese sollten am Anfang der Diagnostik stehen. Dieser Prozess findet idealerweise sowohl auf körperlicher als auch auf psychischer Ebene statt (für eine Übersicht siehe [95]). In einem psychiatrischen (oder klinisch-psychologischen) Kontext kann ein Patient mit medizinisch unerklärter Erschöpfung nach den DSM IV-Kriterien auch mit einer undifferenzierten somatoformen Störung diagnostiziert werden (300.82 [71]), laut ICD-10 müssen hierzu jedoch „multiple und wechselnde" medizinisch unerklärte Symptome vorliegen (F45.1 [5]). Erschöpfung steht nicht im Fokus dieser Diagnosekategorie, kann jedoch darunter fallen [96–98]. Es sei darauf hingewiesen, dass sich mit der Überarbeitung des Diagnosesystems DSM (DSM V) noch einmal entscheidende Veränderungen im Bereich dieser Diagnosekategorie ergeben, die sich auch auf die Diagnostik von Erschöpfung auswirken werden (zur aktuellen Diskussion siehe [99–101]). Im Hinblick auf die differenzialdiagnostische Abklärung von Erschöpfungssyndromen zur Depression gilt es vor allem, sich über die nicht-überschneidenden Symptome im Klaren zu sein (vgl. **Tab. 1** sowie [78]). Was den Begriff „Burnout" betrifft, kann er als Kommunikationsmittel mit Patienten sinnvoll sein. Die Diagnose „Burnout" ergibt nach den bisher bestehenden Kriterien in der klinischen Praxis jedoch wenig Sinn. Zu beachten ist hierbei auch, dass sie als reine Zusatzdiagnose keine Therapie rechtfertigt. Um einen Patienten behandeln zu können, müsste aufgrund der bisherigen Betrachtungen im psychiatrischen/psychotherapeutischen Kontext also entweder eine Depression im Vordergrund der Erschöpfung stehen oder auf die Diagnose „Neurasthenie" zurückgegriffen werden.

Forschung

Es besteht Bedarf an weiteren Studien, die die differenzierenden Symptome (falls diese denn tatsächlich bestehen) der genannten Syndrome herausarbeiten. Das Interesse an und die Verwendung der Diagnose „Neurasthenie" scheinen in unseren Breitengraden nachgelassen zu haben, während CFS und Burnout zunehmend an Bedeutung gewinnen. Hier zeigt sich eine dringende Notwendigkeit, die Kriterien und Terminologie in den relevanten Diagnosesystemen anzupassen. Die Frage, ob es sich nicht letztlich um ein übergeordnetes „Erschöpfungssyndrom" handelt, das unterschiedliche Auslöser haben kann und sich in Subgruppen unterteilen lässt, kann (noch) nicht beantwortet werden. Es erscheint von großer Wichtigkeit, eine klarere Operationalisierung der Kriterien zu erreichen. Eventuell ist eine Herangehensweise auf Symptomebene einer Herangehensweise auf Syndromebene vorzuziehen.

Fazit für die Praxis

Gewissenhafte Ausschlussdiagnostik ist Dreh- und Angelpunkt der Diagnostik von Erschöpfung. Diese sowie eine möglichst ausführliche Anamnese sollten am Anfang der Diagnostik stehen. Im Hinblick auf die differenzialdiagnostische Abklärung zur Depression gilt es vor allem, sich über die nicht-überschneidenden Symptome im Klaren zu sein (vgl. **Tab. 1**). Die Diagnose „Burn-out" sollte nach den bisher bestehenden Kriterien in der klinischen Praxis nicht gestellt werden, da diese noch zu wenig wissenschaftlich untermauert und operationalisiert ist.

Interessenkonflikt: Die Autoren geben an, dass kein Interessenkonflikt besteht.

Literatur

Die Literaur zu diesem Beitrag finden Sie unter http://dx.doi.org/10.1055/s-0032-1327706.

Ergänzendes Material

Literatur

1 *Smets EM, Garssen B, Bonke B et al.* The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995; 39: 315–325
2 *Hardy SE, Studenski SA.* Qualities of fatigue and associated chronic conditions among older adults. J Pain Symptom Manage 2010; 39: 1033–1042
3 *Carruthers BM, Kumar Jain A, De Meirleir KL et al.* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. JCFS 2003; 11: 7–36
4 *Fukuda K, Straus SE, Hickie I et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953–959
5 *Weltgesundheitsorganisation.* Internationale Klassifikation psychischer Störungen – ICD-10 Kapitel V (F) – Klinisch-diagnostische Leitlinien. Bern: Verlag Hans Huber; 2005
6 *Kuhnt S, Brähler E.* Tumorassoziierte Fatigue. PPmP 2010; 60: 402–411
7 *Barsevick A, Frost M, Zwinderman A et al.* I'm so tired: biological and genetic mechanisms of cancer-related fatigue. Qual Life Res 2010; 19: 1419–1427
8 *Bethoux F.* Fatigue and multiple sclerosis. Ann Readapt Med Phys 2006; 49 265–271, 355–360
9 *Barroso J.* A review of fatigue in people with HIV infection. J Assoc Nurses AIDS Care 1999; 10: 42–49
10 *Gaab J.* Suche nach der Ursache des chronischen Erschöpfungssyndroms – eine Geschichte mit Fortsetzung. Psychotherapeut 2011; 56: 211–215
11 *Johannisson K.* Modern fatigue: A historical perspective. In: Stress in health and disease. Weinheim, Germany: Wiley-VCH Veriag GmbH & Co KGaA; Germany; 2006; 3–19
12 *Schafer ML.* [On the history of the concept neurasthenia and its modern variants chronic-fatigue-syndrome, fibromyalgia and multiple chemical sensitivities]. Fortschr Neurol Psychiatr 2002; 70: 570–582
13 *Shorter E.* Chronic fatigue in historical perspective. In: Bock GR, Whelan J, Hrsg. Chronic fatigue syndrome – Ciba Foundation Symposium 173. Chichester, England: John Wiley and Sons Ltd; 1993
14 *Leone SS, Wessely S, Huibers MJ et al.* Two sides of the same coin? On the history and phenomenology of chronic fatigue and burnout. Psychol Health 2011; 26: 449–464
15 *Beard G.* Neurasthenia, or Nervous Exhaustion. Boston Med Surg J 1869; 3: 217–221
16 *Soto NE, Straus SE.* Chronic Fatigue Syndrome and Herpesviruses: the Fading Evidence. Herpes 2000; 7: 46–50
17 *Compston ND.* An outbreak of encephalomyelitis in the Royal Free Hospital Group, London, in 1955. Postgrad Med J 1978; 54: 722–724
18 *Holmes GP, Kaplan JE, Gantz NM et al.* Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988; 108: 387–389
19 *Nix WA.* Das Chronic fatigue syndrome – Ein neues Krankheitsbild? Nervenarzt 1990; 61: 390–396
20 *Ewig S, Dengler HJ.* Chronic-fatigue-syndrom. Klin Wochenschr 1990; 68: 789–796
21 *Nix WA.* Das Chronic-fatigue-Syndrom: Erkrankung des Muskels oder der Seele? Aktuel Neurol 1991; 18: 185–187
22 *Kütemeyer M.* Das Chronic-fatigue-Syndrom: Eine Form der Angstneurose. Aktuel Neurol 1991; 18: 188–191
23 *Freud S.* Über die Berechtigung, von der Neurasthenie einen bestimmten Symptomkomplex als‚Angstneurose' abzutrennen. In: Freud A, Hrsg. Gesammelte Werke 8. Frankfurt a.M.: S. Fischer; 1913; 422–427
24 *Freudenberger HJ.* Staff Burn-Out. J Soc Issues 1974; 30: 159–165
25 *Burisch M.* Einführung. In: Burisch M, Hrsg. Das Burnout-Syndrom – Theorie der inneren Erschöpfung. Heidelberg: Springer; 2006; 1–12
26 *Rösing I.* Ist die Burnout-Forschung ausgebrannt? – Analyse und Kritik der internationalen Burnout-Forschung. Kröning: Asanger; 2003
27 *Maslach C, Schaufeli W, Leiter MP.* Job burnout. Annu Rev Psychol 2001; 52: 397–422
28 *Maslach C, Schaufeli W.* Historical and conceptual development of burnout. In: Schaufeli W, Maslach C, Marek T, Hrsg. Professional Burnout: Recent Developments in Theory and Research. Washington, DC: Taylor & Francis; 1993; 1–16
29 *Starcevic V.* Neurasthenia: cross-cultural and conceptual issues in relation to chronic fatigue syndrome. Gen Hosp Psychiatry 1999; 21: 249–255
30 *Zielasek J, Freyberger HJ, Janner M et al.* Assessing the opinions and experiences of German-speaking psychiatrists regarding necessary changes for the 11th revision of the mental disorders chapter of the International Classification of Disorders (ICD-11). Eur Psychiatry 2010; 25: 437–442
31 *Cheung P.* Adult psychiatric epidemiology in China in the 80s. Cult Med Psychiatry 1991; 15: 479–496
32 *Kleinman A.* Neurasthenia and depression: a study of somatization and culture in China. Cult Med Psychiatry 1982; 6: 117–190
33 *Chinese Medical Association.* Chinese Classification of Mental Disorders. Changsha, China: 1990
34 *Lee S, Kleinman A.* Are somatoform disorders changing with time? The case of neurasthenia in China. Psychosom Med 2007; 69: 846–849
35 *Suzuki T.* The concept of neurasthenia and its treatment in Japan. Cult Med Psychiatry 1989; 13: 187–202
36 *Kitanishi K, Nakamura K, Miyake Y et al.* Diagnostic consideration of Morita shinkeishitsu and DSM-III-R. Psychiatry Clin Neurosci 2002; 56: 603–608
37 *Schwartz PY.* Why is neurasthenia important in Asian cultures? West J Med 2002; 176: 257–258
38 *Hyde B.* A new and simple definition of Myalgic Encephalomyelitis and a new simple definition of Chronic Fatigue Syndrome and A Brief History of Myalgic Encephalomyelitis and an Irreverent History of Chronic Fatigue Syndrome. In: London Conference; London: 2006
39 *Carruthers BM, van de Sande MI, De Meirleir KL et al.* Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011; 270: 327–338
40 *Nater UM, Maloney E, Heim C et al.* Cumulative life stress in chronic fatigue syndrome. Psychiatry Res 2011; 189: 318–320
41 *Heim C, Nater UM, Maloney E et al.* Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. Arch Gen Psychiatry 2009; 66: 72–80
42 *Nater UM.* Bedeutung von Stress bei chronischer Erschöpfung. Psychotherapeut 2011; 56: 203–210
43 *Nater UM, Doerr JM.* Cortisol and fatigue. In: Esposito A, Bianchi V, Hrsg. Cortisol: Physiology, Regulation and Health Implications. Happauge, NY: Nova Science Publishers; 2012; 107–118
44 *Papadopoulos A, Cleare AJ.* Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. Nat Rev Endocrinol 2011
45 *Evengard B, Jonzon E, Sandberg A et al.* Differences between patients with chronic fatigue syndrome and with chronic fatigue at an infectious disease clinic in Stockholm, Sweden. Psychiatry Clin Neurosci 2003; 57: 361–368
46 *Wessely S.* Chronic fatigue: symptom and syndrome. Ann Intern Med 2001; 134: 838–843
47 *Burisch M.* Definitorische Eingrenzung. In: Burisch M, Hrsg. Das Burnout-Syndrom – Theorie der inneren Erschöpfung. Heidelberg: Springer; 2006; 13–78
48 *Korczak D, Kister C, Huber B.* Differentialdiagnostik des Burnout-Syndroms. Köln: DIMDI; 2010Available from: http://portal.dimdi.de/de/hta/hta_berichte/hta278_bericht_de.pdf
49 *Maslach C, Jackson SE.* The measurement of experienced burnout. J Occup Behav 1981; 2: 99–113
50 *Kristensen TS, Borritz M, Villadsen E et al.* The Copenhagen Burnout Inventory: A new tool for the assessment of burnout. Work and Stress 2005; 19: 192–207
51 *Gumz A, Brähler E, Erices R.* Burnout und Arbeitsstörungen bei Studenten. Psychother Psych Med 2012; 62: 33–39
52 *Gerlmeier A.* Stress und Burnout bei IT-Fachleuten – auf der Suche nach Ursachen. In: Gerlmaier, Anja, Latniak, Erich. Burnout in der IT-Branche Ursachen und betriebliche Praevention Kroening: Asanger 2011; 53–89
53 *Goodger K, Gorely T, Lavallee D et al.* Burnout in sport: A systematic review. The Sport Psychologist 2007; 21: 127–151
54 *Schaufeli W, Taris TW.* The conceptualization and measurement of burnout: Common ground and worlds apart. Work and Stress 2005; 19: 256–262
55 *Schaufeli W, Leiter MP, Maslach C.* The Maslach Burnout Inventory – General Survey. In: Maslach Burnout Inventory Manual. Paolo Alto, CA: Consulting Psychologists Press; 1996
56 *Schaufeli W, Van Dierendock D.* UBOS, Utrechtse Burnout Schaal, Handleiding [Utrecht Burnout Scale Manual]. Lisse, The Netherlands: Swets Test Publishers; 2000
57 *Schaufeli W, Bakker AB, Hoogduin K et al.* On the clinical validity of the maslach burnout inventory and the burnout measure. Psychol Health 2001; 16: 565–582

Übersicht

58 *Kant IJ, Bültmann U, Schröer KA et al.* An epidemiological approach to study fatigue in the working population: the Maastricht Cohort Study. Occup Environ Med 2003; 60 (Suppl 1): i32–i39
59 *Kaschka WP, Korczak D, Broich K.* Modediagnose Burnout. Deutsches Aerzteblatt 2011; 108: 781–787
60 *Hillert A, Marwitz M.* Burnout: eine kritische Analyse mit therapeutischen Implikationen. Ärztliche Psychotherapie 2008; 4: 235–241
61 *Sharpley A, Clements A, Hawton K et al.* Do patients with "pure" chronic fatigue syndrome (neurasthenia) have abnormal sleep? Psychosom Med 1997; 59: 592–596
62 *Greenberg DB.* Neurasthenia in the 1980s: chronic mononucleosis, chronic fatigue syndrome, and anxiety and depressive disorders. Psychosomatics 1990; 31: 129–137
63 *Arcari R, Crombie HD.* Mark Twain and his family's health: Livy Clemens' neurasthenia in the gilded age and chronic fatigue syndrome of today. Conn Med 2003; 67: 293–296
64 *Ware NC, Kleinman A.* Culture and somatic experience: the social course of illness in neurasthenia and chronic fatigue syndrome. Psychosom Med 1992; 54: 546–560
65 *Abbey SE, Garfinkel PE.* Neurasthenia and chronic fatigue syndrome: the role of culture in the making of a diagnosis. Am J Psychiatry 1991; 148: 1638–1646
66 *Farmer A, Jones I, Hillier J et al.* Neuraesthenia revisited: ICD-10 and DSM-III-R psychiatric syndromes in chronic fatigue patients and comparison subjects. Br J Psychiatry 1995; 167: 503–506
67 *Huibers MJ, Beurskens AJ, Prins JB et al.* Fatigue, burnout, and chronic fatigue syndrome among employees on sick leave: do attributions make the difference? Occup Environ Med 2003; 60 (Suppl 1): i26–i31
68 *Leone SS, Huibers MJ, Knottnerus JA et al.* The temporal relationship between burnout and prolonged fatigue: a 4-year prospective cohort study. Stress and Health 2009; 25: 365–374
69 *Afari N, Buchwald D.* Chronic fatigue syndrome: a review. Am J Psychiatry 2003; 160: 221–236
70 *Nater UM, Lin JM, Maloney EM et al.* Psychiatric comorbidity in persons with chronic fatigue syndrome identified from the Georgia population. Psychosom Med 2009; 71: 557–565
71 *Saß H, Wittchen HU, Zaudig M et al.* Diagnostische Kriterien DSM-IV-TR. Göttingen: Hogrefe; 2003
72 *Hautzinger M, Keller F, Kühner C.* BDI-II. Beck-Depressions-Inventar. Revision. Frankfurt: Pearson Assessment; 2009
73 *Brown M, Kaplan C, Jason L.* Factor Analysis of the Beck Depression Inventory-ii With Patients With Chronic Fatigue Syndrome. J Health Psychol 2011
74 *Cleare AJ, Bearn J, Allain T et al.* Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. J Affect Disord 1995; 34: 283–289
75 *Scott LV, Dinan TG.* Urinary free cortisol excretion in chronic fatigue syndrome, major depression and in healthy volunteers. J Affect Disord 1998; 47: 49–54
76 *Strickland P, Morriss R, Wearden A et al.* A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. J Affect Disord 1998; 47: 191–194
77 *Nater UM, Maloney E, Boneva RS et al.* Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. J Clin Endocrinol Metab 2008; 93: 703–709
78 *Griffith JP, Zarrouf FA.* A systematic review of chronic fatigue syndrome: don't assume it's depression. J Clin Psychiatry 2008; 10: 120–128
79 *Nil R, Jacobshagen N, Schächinger H et al.* Burnout – eine Standortbestimmung. Schweiz Arch Neurol Psychiatr 2010; 161: 72–77
80 *Ahola K, Honkonen T, Isometsa E et al.* The relationship between job-related burnout and depressive disorders – results from the Finnish Health 2000 Study. J Affect Disord 2005; 88: 55-62.
81 *Firth H, McIntee J, McKeown P et al.* Burnout and professional depression: related concepts? J Adv Nurs 1986; 11: 633–641
82 *Firth H, McKeown P, McIntee J et al.* Burn-out, personality and support in long-stay nursing. Nurs Times 1987; 83: 55–57
83 *Maslach C, Jackson SE.* Maslach Burnout Inventory. Research Edition. Palo Alto: Consulting Psychologists Press; 1986
84 *Beck AT, Beck RW.* Screening depressed patients in family practice. A rapid technic. Postgrad Med J 1972; 52: 81–85
85 *Glass DC, McKnight JD.* Perceived control, depressive symptomatology, and professional burnout: A review of the evidence. Psychol Health 1996; 11: 23–48
86 *Reime B, Steiner I.* Burned-out or depressive? An empirical study regarding the construct validity of burnout in contrast to depression. Psychother Psychosom Med Psychol 2001; 51: 304–307
87 *Hautzinger M, Bailer M.* Allgemeine Depressionsskala. Göttingen: Hogrefe; 1993
88 *Hallsten L.* Burning out: a framework. In: Schaufeli W, Maslach C, Marek T, Hrsg. Professional burnout: Recent developments in theory and research. Washington, D.C.: Taylor and Francis; 1993; 95–113
89 *Toker S, Biron M.* Job burnout and depression: Unraveling their temporal relationship and considering the role of physical activity. J Appl Psychol 2012
90 *Shirom A.* Burnout in work organizations. In: Cooper CL, Robertson I, Hrsg. International review of industrial and organizational psychology. New York: Wiley; 1989; 25–48
91 *Shirom A.* Job-related burnout. In: Quick JC, Tetrick LE, Hrsg. Handbook of occupational health psychology. Washington, DC: American Psychological Association; 2003; 245–265
92 *Kroenke K, Spitzer RL, Williams JB.* The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606–613
93 *Ahola K, Hakanen J.* Job strain, burnout, and depressive symptoms: a prospective study among dentists. J Affect Disord 2007; 104: 103–110
94 *Oken D.* Evolution of psychosomatic diagnosis in DSM. Psychosom Med 2007; 69: 830–831
95 *Donner-Banzhoff N, Maisel P, Dörr C et al.* DEGAM-Leitlinie Nr. 2: Müdigkeit. Düsseldorf: Verlag omikron publishing; 2011
96 *van Staden WC.* Conceptual issues in undifferentiated somatoform disorder and chronic fatigue syndrome. Curr Opin Psychiatry 2006; 19: 613–618
97 *Wessely S, Nimnuan C, Sharpe M.* Functional somatic syndromes: one or many? Lancet 1999; 354: 936–939
98 *Fischer S, Nater UM.* Funktionelle somatische Syndrome – Konzeptualisierung, Epidemiologie und Behandlung. Z Med Psychol im Druck
99 *Sykes R.* Somatoform disorder and the DSM-V Workgroup's interim proposals: two central issues. Psychosomatics 2012; 53: 334–338
100 *APA.* Somatic Symptom Disorder. Available from: http://www.dsm5.org/proposedrevision/Pages/SomaticSymptomDisorders.aspx
101 *Hausteiner-Wiehle C, Henningsen P.* Diskussion um Konzepte und Diagnostik somatoformer Störungen. Nervenarzt 2012; 83: 1097–1105

6.2 Study 1

Doerr, J.M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., Hoppmann, C., & Nater, U.M. (2015). Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students*. Biological Psychology, 110,* 42-49*.*

Biological Psychology 110 (2015) 42–49

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students

Johanna M. Doerr[a,*], Beate Ditzen[b], Jana Strahler[a], Alexandra Linnemann[a], Jannis Ziemek[a], Nadine Skoluda[a], Christiane A. Hoppmann[c], Urs M. Nater[a,*]

[a] Clinical Biopsychology, Department of Psychology, University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany
[b] Institute of Medical Psychology in the Center for Psychosocial Medicine, University Hospital Heidelberg, Bergheimer Str. 20, 69115 Heidelberg, Germany
[c] Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC V6T 1Z4, Canada

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 26 March 2015
Accepted 22 June 2015
Available online 2 July 2015

Keywords:
Autonomic nervous system
Cortisol
Fatigue
Sleep quality
Stress

ABSTRACT

We investigated whether stress may influence fatigue, or vice versa, as well as factors mediating this relationship. Fifty healthy participants (31 females, 23.6 ± 3.2 years) completed up to 5 momentary assessments of stress and fatigue during 5 days of preparation for their final examinations (exam condition) and 5 days of a regular semester week (control condition). Sleep quality was measured by self-report at awakening. A sub-group of participants ($n = 25$) also collected saliva samples. Fatigue was associated with concurrent stress, stress reported at the previous measurement point, and previous-day stress. However, momentary stress was also predicted by concurrent fatigue, fatigue at the previous time point, and previous-day fatigue. Sleep quality mediated the association between stress and next-day fatigue. Cortisol and alpha-amylase did not mediate the stress–fatigue relationship. In conclusion, there is a reciprocal stress–fatigue relationship. Both prevention and intervention programs should comprehensively cover how stress and fatigue might influence one another.

1. Introduction

Stress is associated with numerous bodily complaints, such as fatigue—a very common symptom in the general population (Nijrolder, van der Horst, & van der Windt, 2008; Pawlikowska et al., 1994) that can be defined as a subjective state of exhaustion, tiredness, weakness, and lack of energy that impairs daily activities (Riley et al., 2010; Schwarz, Krauss, & Hinz, 2003). Both clinical evidence and individual experiences indicate that it may be assumed that high stress puts people at risk of developing fatigue. Yet, most available data on the interaction between stress and fatigue come from cross-sectional studies with only one point of assessment (e.g., Brown & Thorsteinsson, 2009; Kocalevent, Hinz, Brahler, & Klapp, 2011). There are only very few longitudinal studies showing that stress may temporally precede fatigue (e.g., Kato, Sullivan, Evengard, & Pedersen, 2006). Nevertheless, the mechanisms of how stress may ultimately translate into fatigue are not well understood. While experimental studies have the advantage of being able to control for a variety of potentially confounding variables, they are also limited in terms of the generalization of the findings to real life, i.e., they result in reduced ecological validity. There is a relative scarcity of studies examining the relationship between stress and fatigue as individuals engage in their daily life routines in their own environments. One notable exception is a study by Dittner, Rimes, and Thorpe (2011), in which the authors showed that fatigue levels in first-year college students were significantly higher following a period of academic stress than at the beginning of the academic year. However, in this study, perceived stress was only measured at the second time point. In a recent study by Akerstedt, Axelsson, Lekander, Orsini, and Kecklund (2014), fatigue at bedtime was found to be associated with average stress during the day. The results do not take into account influences on short-term changes in fatigue within individual days.

Besides evidence that stress may precede fatigue, it might also be considered that fatigue precedes stress (e.g., because fatigue limits coping abilities which might help the individual not to feel stressed by challenging situations). To the best of the authors' knowledge, there has been no study investigating this direction of causality.

* Corresponding authors. Fax: +49 6421 28 24 094.
E-mail addresses: johanna.doerr@staff.uni-marburg.de (J.M. Doerr), Beate.Ditzen@med.uni-heidelberg.de (B. Ditzen), jana.strahler@staff.uni-marburg.de (J. Strahler), linnemann@staff.uni-marburg.de (A. Linnemann), jannis_ziemek@web.de (J. Ziemek), skoluda@staff.uni-marburg.de (N. Skoluda), choppmann@psych.ubc.ca (C.A. Hoppmann), urs.nater@staff.uni-marburg.de (U.M. Nater).

http://dx.doi.org/10.1016/j.biopsycho.2015.06.009
0301-0511/

Apart from choosing an appropriate design to tackle the question of directionality, it is also important to consider mediating factors that might explain the predicted association between stress and fatigue. One of these factors is subjective sleep quality: a negative relationship between stress and sleep quality was found in several cross-sectional studies (e.g., Akerstedt, Fredlund, Gillberg, & Jansson, 2002; Knudsen, Ducharme, & Roman, 2007). This effect was also shown in an everyday life study using an end-of-day measurement of stress (Akerstedt et al., 2012). Furthermore, subjective sleep quality has also been found to be a predictor of fatigue (Akerstedt et al., 2014; Lavidor, Weller, & Babkoff, 2003). Interestingly, one (cross-sectional) study indicated that sleep quality mediated the relationship between stress and fatigue (Thorsteinsson & Brown, 2009). It thus seems reasonable to predict that subjective sleep quality may be an important mediating factor that needs to be considered in studies examining the relationship between stress and fatigue.

The effects of stress on fatigue are also likely to be impacted by the body's stress systems, i.e., the hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system (ANS). Powell, Liossi, Moss-Morris, and Schlotz (2013) point out the relevance of measures of cortisol (the main effector of the HPA axis) variability, which indicate general "responsiveness" of the HPA axis, especially cortisol concentrations in the morning (e.g., morning values, cortisol awakening response, CAR), and measures assessing the decrease in cortisol throughout the day (slope). Previous studies have shown higher morning values in chronically stressed individuals compared to non-stressed controls (e.g., Schulz, Kirschbaum, Pruessner, & Hellhammer, 998). In an intra-individual comparison, Dahlgren, Kecklund, and Ackerstedt (2005) reported no abnormalities in the morning, but an overall flattened diurnal cortisol slope during a period of higher stress. Other studies indicate that fatigue is associated with a reduction of cortisol variability across the day (e.g., Dahlgren, Kecklund, Theorell, & Akerstedt, 2009). On the other hand, Eek, Karlson, Garde, Hansen, and Orbaek (2012) found positive associations between cortisol increases in the morning and several aspects of fatigue (lack of energy, lack of motivation, physical exertion). Furthermore, Adam, Hawkley, Kudielka, and Cacioppo (2006) found an association between low morning cortisol values and high fatigue levels throughout the day in a sample of older adults. Thus, research illustrates the importance of considering measures of cortisol variability when analyzing associations between stress and fatigue.

As fatigue is a prominent feature in autonomic dysregulation, it can be assumed that it is related not only to changes in HPA axis activity, but also to changes in ANS (Nater, Heim, & Raison, 2012). Some studies indeed point to ANS alterations in fatigued individuals: Boneva et al. (2007), for instance, report higher heart rates as well as lower heart rate variability in persons with chronic fatigue syndrome. De Vente, Olff, Van Amsterdam, Kamphuis, and Emmelkamp (2003) found higher resting heart rate in fatigued persons compared to healthy controls. In a recent study using a sample of persons with chronic fatigue syndrome, we found a lower response of epinephrine to a physical stress test compared to healthy controls, indicating altered ANS dynamics in the affected persons (Strahler, Fischer, Nater, Ehlert, & Gaab, 2013). Overall, previous findings point to signs of ANS dysregulation in fatigued persons, but the results are far from unequivocal. Furthermore, we are not aware of any studies examining associations between ANS activity and fatigue in everyday life.

In summary, research has established a positive relationship between stress and fatigue, but few studies have examined this relationship across multiple time points. The question of directionality, i.e., whether stress temporally precedes fatigue or vice versa, has, to our knowledge, never been addressed. To investigate this, temporal associations (carry-over effects within individual days from one time point to the next and/or between days) need to be considered. Furthermore, an analysis of possible mediators is crucial when examining the association between stress and fatigue. We expect sleep quality as well as changes in the biological stress systems, i.e., the HPA axis and the ANS, to be of particular importance in this regard. Concerning the question of how the organism changes and adapts to higher stress levels, a within-subjects design clearly allows for stronger conclusions than a between-subjects design. An adequate paradigm to test such associations is to examine students during a period of exam preparation and during a more relaxed phase of the term (for an overview see Biondi & Picardi, 1999).

In the current study, we, thus, examined whether and how stress translates into fatigue in everyday life. We also wanted to be open to the alternative hypothesis that fatigue may influence stress experiences. To maximize ecological validity, we used an ambulatory assessment design. Rather than exploring differences between groups, we assessed students in two different everyday life conditions: on five days during the beginning of the semester (control condition) and on five days during the preparation for final exams (exam condition).

2. Methods

2.1. Participants

Data collection took place during the summer term (May through August) of 2012 at the Philipps-Universität Marburg, Germany. Participants were recruited via university student mailing lists or notices on campus. Inclusion criteria were being a university student, speaking German fluently, age 18–35 years, no obesity (body mass index of 29 or less), no psychiatric or medical illness known to affect endocrine or autonomic functioning, smoking less than 5 cigarettes per week, no drug use, and for women not being pregnant, no breast feeding and having regular menstruation. The initial sample consisted of 55 participants (35 women, 23.3 ± 3.11 years), of whom three declined to participate further after completing the first assessment period. A fourth person had to be excluded due to device failures. After completion of data collection, a fifth person was removed from statistical analysis due to incomplete data (more than 50% missing data in exam condition). Thus, data from 50 participants were included in the final statistical analyses. Participants received 50 Euro (about 64 USD) or course credit. The study was approved by the local ethics committee of the Faculty of Psychology at the Philipps-Universität Marburg, Germany. All participants provided written informed consent.

2.2. Materials and procedure

We used an ambulatory assessment approach. Participants were assessed for 5 days during the first weeks of the semester (control condition) and for 5 days during the preparation for final examinations within the last weeks of the semester (exam condition). Following the initial contact, participants were invited to the laboratory of the department of Clinical Biopsychology, Philipps-Universität Marburg, Germany, for an assessment to rule out exclusion criteria. Furthermore, they were instructed in the use of a pre-programmed (iDialogPad, G. Mutz, Cologne, Germany) iPod touch® as well as, in a sub-sample, ambulatory saliva sampling with the SaliCap® system (IBL, Hamburg, Germany). Finally, participants were instructed to complete questionnaires online at home. During both assessment conditions, the iDialogPad program was activated by the participants every morning upon awakening. There was a pre-programmed alarm 30 min after initial activation (i.e., after awakening), at 10 am, 2 pm, 6 pm, and 9 pm.

Table 1
Descriptive analyses of relevant parameters.

	M (SD)			
	Control condition	Exam condition	*t*	*p*
Item "At the moment, I feel fatigued"	2.39 (1.07)	2.75 (1.09)	−8.63	<0.001
Item "At the moment, I feel stressed out"	2.11 (1.04)	2.65 (1.10)	−12.28	<0.001
Item "How well did you sleep last night?"	66.02 (23.38)	65.11 (20.43)	0.49	0.627
MFI general fatigue	9.29 (3.04)	10.74 (3.27)	−3.14	0.004
MFI physical fatigue	8.17 (3.24)	9.00 (3.51)	−2.07	0.005
MFI reduced motivation	7.58 (2.69)	7.94 (3.08)	−0.82	0.420
MFI reduced activity	9.89 (3.22)	10.08 (3.59)	−0.53	0.600
MFI mental fatigue	9.73 (3.36)	10.70 (3.94)	−2.65	0.012

Note: The items "At the moment, I feel fatigued" and "At the moment, I feel stressed out" were assessed on a scale from 1 to 5 (five times per day); the item "How well did you sleep last night?" was assessed on a scale from 0 to 100 (every morning directly after awakening). The MFI (Multidimensional Fatigue Inventory) was applied once per condition.

2.2.1. Measurement of fatigue

At the person level, self-reported fatigue levels were measured using the Multidimensional Fatigue Inventory (MFI; Smets, Garssen, Bonke, & De Haes, 1995), a questionnaire which was presented to the participants during the control condition as well as during the exam condition. The MFI comprises 5 subscales: general fatigue, reduced motivation, reduced activity, mental fatigue, and physical fatigue. To assess changes in fatigue in everyday life, participants additionally rated their fatigue level at 5 time points each day (at every time point except at the 30 min after awakening time point) by answering the item "At the moment, I feel fatigued" on a scale from 1 (not at all) to 5 (very) (Stone, Broderick, Porter, & Kaell, 1997). The scaling was based on the MFI. Similar items reflecting the other four MFI dimensions were also assessed, but were not included in the current analysis. Descriptive values are reported in Table 1.

2.2.2. Measurement of stress

During ambulatory assessment, momentary stress levels were assessed using the item "At the moment, I feel stressed out" on a scale from 1 (not at all) to 5 (very) (descriptive values in Table 1).

2.2.3. Measurement of sleep quality

Every morning directly after awakening, participants estimated how well they had slept on a visual analog scale ranging from 0 to 100. The item was based on the subjective sleep quality item of the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and adapted for use in ambulatory assessment. Using a single item to assess subjective sleep quality is a common approach (Hawkins & Shaw, 1992; Pilcher, Ginter, & Sadowsky, 1997). Descriptive values are shown in Table 1.

2.2.4. Biological parameters

In order to investigate associations between fluctuations in stress, fatigue, and biological parameters, a sub-group of participants ($n = 25$, 19 women) provided saliva samples after each iPod touch® entry on two consecutive days during both assessment conditions (procedure in accordance with recommendations by Hellhammer et al. (2007)). The SaliCap® (IBL, Hamburg, Germany) system allows for collection of saliva via passive drool. Participants were instructed to collect saliva for two minutes in their mouths (not swallowing) then fill the saliva collection vials using a straw or by salivating directly into the tube. Participants entered the number of the respective tube into their iPod touch® to ensure compliance. They were instructed to keep their samples as cool as possible (i.e., in their freezer or fridge) until they returned them to the study personnel. The samples were then frozen at −20 °C until analysis. Cortisol was analyzed using a commercially available enzyme-linked immunoassay (IBL, Hamburg, Germany). For the measurement of salivary alpha-amylase (sAA), a kinetic colorimetric test and reagents obtained from Roche quantitative enzyme were used. Inter- and intra-assay variation of both assays was below 10%.

2.3. Statistical analyses

Accounting for the nested structure of the data, and in order to include control variables at the person level, two-level hierarchical linear models (HLM; Raudenbush, Bryk, Cheong, & Congdon, 2005), with time points at level 1 nested within persons at level 2, were conducted for data analysis (see list of equations, Supplemental digital content 1). SAA and cortisol values were checked for outliers and normal distribution using the Kolmogorov–Smirnov (KS) test. As none of the tests reached statistical significance (all $p > 0.09$), the following analyses were conducted with absolute cortisol and sAA values. Morning cortisol value (level of cortisol directly after awakening), cortisol awakening response (CAR: delta of morning value and cortisol value 30 min after awakening) as well as cortisol slope throughout the day (time points taken into account: 10 am, 2 pm, 6 pm, 9 pm) were chosen for analysis. For sAA, the same parameters were analyzed (morning sAA value, sAA awakening response and sAA slope throughout the day). Analyses of the biological parameters controlled for the effects of sex and body mass index (BMI) on the outcome variable. Mean values of stress and fatigue for each day were calculated to assess between-day associations as well as associations with biological markers.

Based on the procedure described by Korchmaros and Kenny (2003), the first step of analysis was to determine whether random analyses show an advantage over fixed analyses for the respective model. No advantage of random analyses could be found for between-day analyses or for analyses including biological markers. This was probably attributable to the small number of measurements due to aggregated data. Subsequent analyses were treated accordingly (residuals were restricted for between-day analyses as well as analyses of associations with biological markers). "Condition" (control vs. exam) as well as the interaction term of condition × predictor was included in the models to test whether the associations differed between the two conditions. Pseudo-R^2 was determined using the following equation: "Pseudo-$R^2 = (\sigma^2_{\text{referencemodel}} - \sigma^2_{\text{finalmodel}})/\sigma^2_{\text{referencemodel}}$", where the reference model is the final model excluding the predictor in question, based on suggestions by Singer and Willett (2003). Analyses were controlled for the effect of sex on the outcome. If not indicated otherwise, all models explain significantly more variance in the respective outcome variable than the null model (model without predictors). Mediation analyses were based on the mediation steps suggested by Korchmaros and Kenny (Kenny, Korchmaros, & Bolger, 2003; Korchmaros & Kenny, 2003).

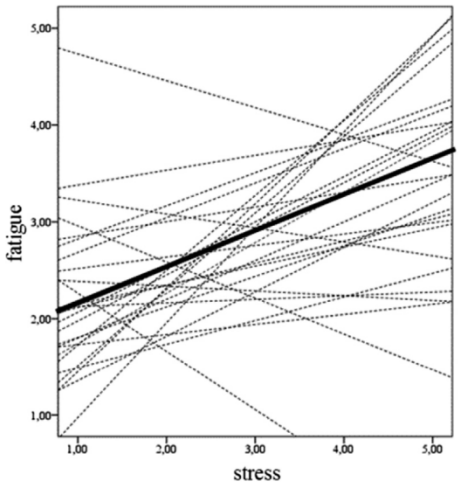


Fig. 1. Spaghetti plot of average (thick) and subject-specific (dotted) regression lines for momentary fatigue as a function of simultaneously measured stress.

3. Results

Thirty-two women and 19 men participated in the study (23.26 ± 3.19 years, BMI: 21.95 ± 2.50). Descriptive analyses of the fatigue, stress, and sleep item as well as the MFI questionnaire are shown in Table 1. Additionally, means and standard deviations for the fatigue- and stress-item for each time point in each condition can be found in the online Supplement (Table 1S).

There was a positive association between momentary stress and momentary fatigue (which were simultaneously measured, see Fig. 1 and Table 2, Model 1a, Pseudo-R^2 = 0.13). When "condition" was added as a predictor (see Table 2, Model 1a.1), the main effect for condition was only marginally significant, and the interaction term did not reach significance. This indicates that momentary stress predicted momentary fatigue (independent of control or exam condition). The association between stress reported at the previous measurement time point (i.e., the immediately preceding measurement time point) and momentary fatigue was positive and statistically significant (see Table 2, Model 1b, Pseudo-R^2 = 0.08). The effect of stress at the previous time point remained significant when condition was included in the model (see Table 2, Model 1b.1). The results again showed that fatigue levels were heightened during the exam condition, and no difference was found between conditions in terms of the effect of stress at the previous time point on fatigue.

The association between previous-day mean stress levels with mean fatigue levels the following day was positive, but only significant on a trend level (UC = 0.14; p = 0.072; Pseudo-R^2 = 0.01). Further, an effect of condition (UC = −1.05; p < 0.001; Pseudo-R^2 = 0.13) as well as a small positive interaction effect of "condition × previous-day mean stress level" (UC = 0.57; p < 0.001; Pseudo-R^2 < 0.01) were detected.

In a second set of analyses, momentary stress was treated as the outcome variable. The association between momentary fatigue and momentary stress was statistically significant (see Table 3, Model 2a, Pseudo-R^2 = 0.14). When "condition" was added as a predictor (see Table 3, Model 2a.1), it showed an additional effect on stress (Pseudo-R^2 = 0.16), but the interaction term did not reach significance. This indicates that higher stress was reported during the exam condition (see Fig. 3B) and that momentary fatigue predicted momentary stress independently of control or exam condition. The association between fatigue at the previous measurement point and momentary stress was positive and statistically significant (see Table 3, Model 2b, Pseudo-R^2 = 0.08). The effect of condition (see Table 3, Model 2b.1, Pseudo-R^2 = 0.01) showed that in the exam condition, participants reported higher stress levels. Further, fatigue from the previous measurement point predicted stress, independent of condition. The association between previous-day mean fatigue levels with mean stress levels during the following day was positive (UC = 0.25; p < 0.001; Pseudo-R^2 = 0.03). In addition, an effect of condition (UC = −2.05; p < 0.001; Pseudo-R^2 < 0.01) as well as a positive interaction effect of "condition × previous-day mean stress level" (UC = 0.73; p < 0.001; Pseudo-R^2 = 0.18) was detected.

3.1. Mediation analyses

3.1.1. Sleep quality

The mediation analysis testing the effect of sleep quality is illustrated in Fig. 2. Previous-day mean stress was a significant predictor of sleep quality the following night, and sleep quality was a significant predictor of mean fatigue level throughout the day (both

Table 2
Hierarchical linear models predicting momentary fatigue by momentary stress and stress at the previous time point (n = 50) using restricted maximum likelihood.

	Model 1a			Model 1a.1			Model 1b			Model 1b.1		
Fixed effects	UC	SE	t-ratio	UC	SE	t-ratio	UC	SE	t-ratio	UC	SE	t-ratio
Intercept	2.40	0.12	19.75***	2.29	0.13	18.31***	2.39	0.13	18.43***	2.23	0.13	16.64***
Level 2												
Sex	0.29	0.15	1.92	0.29	0.15	1.94	0.28	0.16	1.70	0.32	0.16	1.99
Level 1												
Momentary stress	0.26	0.04	6.29***	0.22	0.47	4.63***	0.20	0.04	5.62***			
Condition				0.18	0.09	1.96				0.22	0.12	1.87
Cond. × momentary stress				0.01	0.05	0.26						
Stress at previous t.p.							0.15	0.03	4.70***	0.17	0.04	3.99***
Cond. × stress at previous t.p.										0.02	0.06	0.36
Random effects	SD	VC	χ^2	SD	VC	χ^2	SD	VC	χ^2	SD	VC	χ^2
Intercept	0.51	0.26	694.74***	0.55	0.30	332.95***	0.54	0.29	567.86***	0.59	0.35	283.45***
Momentary stress	0.24	0.06	186.43***	0.23	0.05	102.61***	0.15	0.02	77.25***			
Condition				0.44	0.20	76.94**				0.57	0.33	78.54**
Cond. × momentary stress				0.10	0.01	42.46						
Stress at previous t.p.							0.15	0.01	57.62	0.12	0.01	57.13
Cond. × stress at previous t.p.										0.14	0.02	49.11

Note: UC: unstandardized coefficients, SE = standard error, d.f. = degrees of freedom, SD = standard deviation, VC = Variance Component, t.p. = time point, cond. = condition, ***p < 0.001, **p < 0.01, *p < 0.05, for all variables, higher values imply a higher level of the respective construct (a positive association implies an increase in fatigue with increasing stress); for analyses of associations across time, a time-lagged variable was created from momentary stress (one time point forward).

Table 3
Hierarchical linear models predicting momentary fatigue by momentary stress, stress at the previous time point and condition ($n = 50$) using restricted maximum likelihood.

	Model 2a			Model 2a.1			Model 2b			Model 2b.1		
Fixed effects	UC	SE	*t*-Ratio	UC	SE	*t*-Ratio	UC	SE	*t*-Ratio	UC	SE	*t*-Ratio
Intercept	1.14	0.11	10.38***	0.93	0.11	8.37***	1.12	0.11	9.79***	0.91	0.12	7.75***
Level 2												
Sex	0.16	0.14	1.20	0.12	0.13	0.94	0.27	0.14	1.91	0.23	0.14	1.68
Level 1												
Momentary fatigue	0.25	0.04	6.04***	0.16	0.04	3.90***	0.23	0.04	5.73***			
Condition				0.45	0.14	3.25**				0.46	0.16	2.89**
Cond. × momentary fatigue				0.02	0.05	0.36						
Fatigue at previous t.p.							0.09	0.03	2.67*	0.09	0.04	2.33*
Cond. × fatigue at previous t.p.										0.01	0.05	0.23
Random effects	SD	VC	χ^2	SD	VC	χ^2	SD	VC	χ^2	SD	VC	χ^2
Intercept	0.49	0.24	686.44***	0.50	0.25	400.72***	0.48	0.23	426.13***	0.52	0.27	275.46***
Momentary fatigue	0.26	0.07	220.90***	0.23	0.05	123.25***	0.19	0.04	91.45***			
Condition				0.65	0.42	81.78**				0.52	0.27	275.46
Cond. × momentary fatigue				0.18	0.03	66.18						
Fatigue at previous t.p.							0.12	0.01	58.36	0.59	0.35	57.41
Cond. × fatigue at previous t.p.										0.13	0.02	58.09

Note: UC: unstandardized coefficients, SE = standard error, d.f. = degrees of freedom, SD = standard deviation, VC = Variance Component, t.p. = time point, cond. = condition, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, for all variables, higher values imply a higher level of the respective construct (a positive association implies an increase in fatigue with increasing fatigue); for analyses of associations across time, a time-lagged variable was created from momentary fatigue (one time point forward).

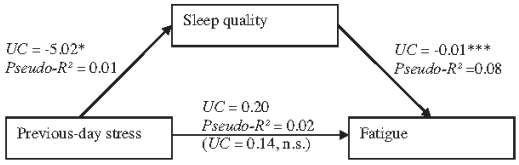


Fig. 2. Results of mediation analysis of subjective sleep quality between previous-day stress and fatigue controlled for the effect of condition. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; n.s. = not significant UC: unstandardized coefficients for the association between previous-day mean stress level and mean fatigue levels as mediated by sleep quality. The coefficient between previous-day stress and fatigue controlling for sleep quality is in parentheses (mediation).

associations negative). Previous-day stress directly predicted mean fatigue levels the following day. Thus, the first three criteria of mediation are met (Kenny et al., 2003). Fig. 2 also shows that the effect of previous-day stress on fatigue disappears when subjective sleep quality is controlled for. This suggests that subjective sleep quality is a mediator of the association between previous-day stress and general fatigue. A Sobel test (Preacher, 2010-2013; Sobel, 1982) shows that the indirect effect of previous-day stress on general fatigue via sleep quality is significantly different from zero ($z' = 2.12$ (SE = 0.03), $p = 0.034$).

3.1.2. Biological parameters

The sub-sample did not differ significantly from the overall sample in age, fatigue, or stress levels (data not shown). Neither cortisol slopes (UC = −5.16, $p = 0.662$) nor CAR (UC = −0.02, $p = 0.161$) predicted mean fatigue levels, but the morning cortisol value turned out to be a significant predictor of the mean fatigue level that same day (UC = 0.03, $p = 0.037$, Pseudo-$R^2 = 0.04$). However, when "condition" was included in this model, the effect of morning cortisol value on mean fatigue disappeared (condition: UC = 0.46, $p = 0.006$; morning cortisol value: UC = 0.02, $p = 0.196$). Condition turned out to be positively associated with morning cortisol values, indicating that morning cortisol values were heightened during the exam condition (UC = 2.99, $p = 0.038$, Pseudo-$R^2 = 0.04$; see Fig. 3C). This implies that the association between fatigue levels and morning cortisol values is completely based on changes in both parameters between conditions. Therefore, as none of the cortisol parameters show a clear association with mean fatigue levels, they do not meet the first criterion of mediation (Kenny et al., 2003) and therefore have to be ruled out as mediators. With regard to the relationship of the cortisol measures with stress level, the results are analogous to those concerning fatigue. No associations were found between CAR (UC = −0.01, $p = 0.635$), cortisol slopes (UC = −0.71, $p = 0.948$) or morning cortisol value (UC = 0.02, $p = 0.100$, Pseudo-$R^2 = 0.05$) with stress levels that same day.

Morning sAA value did not predict mean fatigue level (UC = 0.00, $p = 0.339$), and nor did sAA slopes (UC = 0.04, $p = 0.567$) or morning sAA responses (UC = 0.00, $p = 0.848$). Again, these parameters have to be ruled out as mediators of the relationship between stress and fatigue because they are not associated with the outcome. Beyond this, sAA parameters were not associated with mean stress levels (morning sAA value: UC = 0.00, $p = 0.586$; sAA slope: UC = 0.00, $p = 0.930$; morning sAA response: UC = 0.00, $p = 0.088$). On the other hand, condition was positively associated with sAA slope (UC = 0.59, $p = 0.044$; Pseudo-$R^2 = 0.03$, see Fig. 3D), but there were no associations between condition and the other sAA parameters (UC = 13.60, $p = 0.388$ for morning sAA value; UC = 5.18, $p = 0.772$ for morning sAA response).

4. Discussion

The main impetus of this study was to test whether stress predicted fatigue in everyday life or whether this relationship was the other way around. We further tested the role of potential mediators (sleep quality, HPA axis and ANS markers) on these associations. In summary, we found that momentary fatigue was statistically predicted by momentary stress, stress experienced at the previous measurement point, and previous-day stress. However, the same also holds true for stress being predicted by fatigue. During exam preparation, stress, fatigue, and morning cortisol were higher and the sAA slope was steeper, suggesting that the participants were indeed more stressed during this period. However, momentary associations as well as associations from one time point to the next were independent of condition, meaning that the stress–fatigue relationship did not differ between a normal semester period and a period of heightened stress. Concerning previous-day carry-over effects, our results suggest a slightly stronger prediction of momentary fatigue by previous-day stress during a normal semester week than during an exam preparation period. Sleep quality was shown to be a mediator of the association between mean stress level and

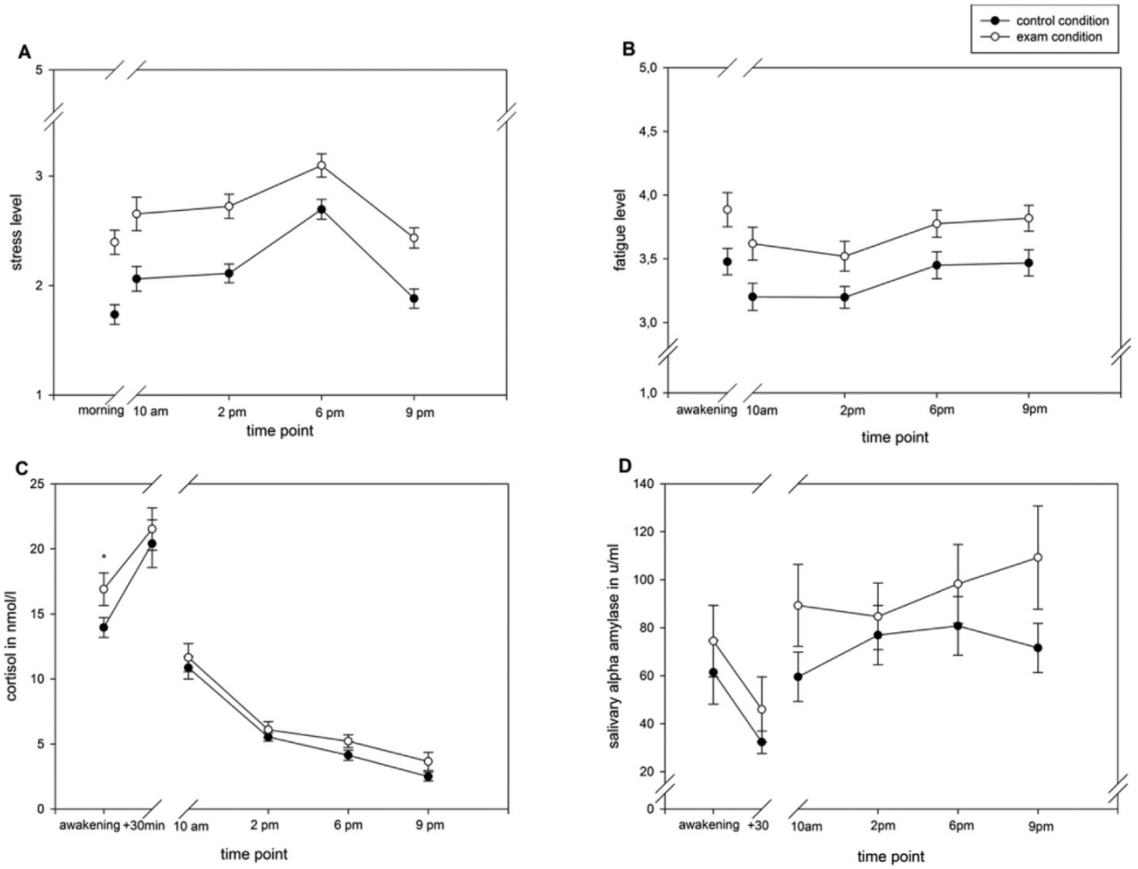


Fig. 3. Difference in (A) fatigue level, (B) stress level, (C) cortisol level, and (D) salivary alpha amylase level between control and exam condition.

next-day mean fatigue level. Biological parameters (cortisol and sAA) did not mediate the stress–fatigue association in this study.

Our finding of a strong association between momentary stress and fatigue is in line with results of existing cross-sectional studies (Brown & Thorsteinsson, 2009; Kalimo, Tenkanen, Härmä, & Poppius, 2000). We found that fatigue and stress are strongly associated when measured at the same time point. This indicates that the subjective experience of being stressed and being fatigued might be two symptoms of a general stress response. However, our lagged analyses showed that stress and fatigue also predicted each other across time independent of momentary associations. So far, only a small number of longitudinal studies have tested the stress–fatigue relationship, generally showing that stress predicted fatigue (Akerstedt et al., 2014; Dahlgren et al., 2005; Dittner et al., 2011; Kato et al., 2006). Our results are in line with these earlier studies and extend the existing data by suggesting that fatigue predicted stress both on a momentary basis as well as prospectively within days. Thus, there appears to be a reciprocal stress–fatigue relationship, which presents itself as a kind of "vicious cycle" (both experiences negatively influence each other in a bi-directional manner). Stress is commonly assumed to predict fatigue through exhaustion of the organism's resources. For example, participants might have reduced their resting behavior when feeling stressed, which increases fatigue levels. Also, stress is related to a decline in cognitive functioning (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). As fatigue also comprises a cognitive, or mental, dimension (e.g., difficulty to concentrate (Smets et al., 1995)) cognitive difficulties might present as fatigue. An explanation for fatigue influencing stress, on the other hand, might be that it reduces an individual's coping abilities (e.g., less ability to concentrate, feeling of weakness). In this respect, the threshold to exceed one's resources is decreased, which activates the process of being stressed (Cohen, Kessler, & Gordon, 1997).

Beyond this, our study suggests that the influence of stress on fatigue the next day is explained via impaired sleep quality. Thus, the present study may link existing findings of a negative association between stress and sleep quality (Akerstedt et al., 2012; Petersen, Kecklund, D'Onofrio, Nilsson, & Akerstedt, 2012), as well as between sleep quality and fatigue (Lavidor et al., 2003). The mediating role of sleep quality in the relationship between stress and fatigue was previously explored in a cross-sectional design (Thorsteinsson & Brown, 2009). We were able to confirm this finding using a design with high ecological validity. Previous research indicates that stress likely impairs sleep through bedtime worrying, which in turn results in more awakening events after sleep onset and a longer latency of slow wave sleep (Akerstedt, Kecklund, & Axelsson, 2007). Thus, the restorative capacity of sleep is diminished, and it becomes more important for the organism to rest and not deplete more energy. The feeling of being fatigued might be one possible way of signaling the body to get rest (Dantzer, Heijnen, Kavelaars, Laye, & Capuron, 2014). Clearly, more research is needed, ideally using ambulatory polysomnography and including variables assessing cognitive mechanisms.

In our study, we did not find altered cortisol profiles to be directly associated with fatigue, which have been linked in other studies (Dahlgren et al., 2005; Kumari et al., 2009; Nater et al., 2008). Furthermore, we did not find a mediating effect of morning cortisol value, CAR, or cortisol slope on stress–fatigue associations. These findings do not necessarily contradict previous results, as we did not investigate chronically fatigued participants, but rather healthy university students. It will be important to replicate our study in a clinical sample using more days of saliva assessments. Moreover, the stress experienced by our participants in the exam condition was not chronic. Chronic stress likely has a stronger impact on the adaptability of the HPA axis, and although HPA axis variability measures did not predict fatigue in this study, it might still play an important role in persons with chronic fatigue.

Because changes in ANS activity are part of the stress response and were found to be associated with fatigue (Boneva et al., 2007; De Vente et al., 2003), we expected ANS markers to be mediators of the relationship between stress and fatigue. However, the results did not show associations between mean stress or fatigue levels with any of the sAA parameters. This result is in accordance with one of our previous studies (Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007), in which we found that the diurnal course of sAA is independent of momentary stress in healthy participants. Again, the potentially mediating effect of ANS alterations needs to be tested in individuals with chronic fatigue (Nater et al., 2012).

A limiting factor in this study was that the sample consisted of university students, who differ from the general population concerning demographic and socioeconomic factors. The results are thus not necessarily generalizable to the population as a whole. Furthermore, students who anticipated being highly stressed by exam preparation might not have considered taking part in this study in the first place. This could have led to a conservative estimation of the effects in our results. Another limiting factor is that both stress and fatigue was assessed with one item each instead of using a more complex stress or fatigue measure. However, keeping each time point of measurement as short as possible was necessary to increase compliance. Also, one-item measures of stress and fatigue could be shown to have satisfactory validity (Elo, Leppänen, & Jahkola, 2003; Temel, Pirl, Recklitis, Cashavelly, & Lynch, 2006).

5. Conclusion

Our study suggests that the relationship between stress and fatigue is reciprocal in nature. From a clinical perspective, this finding may highlight the importance of addressing fatigue in order to decrease stress. So far, research has focused on the role of stress reduction in ameliorating fatigue. We believe, however, that the next step should be a detailed assessment of the mechanisms of how fatigue translates into stress, with a specific focus on cognitive, emotional, social, or biological mechanisms.

Acknowledgements

The authors acknowledge funding by the Volkswagen Foundation. We thank the Philipps-Universität Marburg for partial funding of participant reimbursements. Christiane Hoppmann gratefully acknowledges the support of the Michael Smith Foundation for Health Research and the Canada Research Chairs program. The authors thank Luisa Donath for her help with data collection.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2015.06.009

References

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(45), 17058–17063.

Akerstedt, T., Axelsson, J., Lekander, M., Orsini, N., & Kecklund, G. (2014). Do sleep, stress, and illness explain daily variations in fatigue? A prospective study. *Journal of Psychosomatic Research*, *76*(4), 280–285.

Akerstedt, T., Fredlund, P., Gillberg, M., & Jansson, B. (2002). Work load and work hours in relation to disturbed sleep and fatigue in a large representative sample. *Journal of Psychosomatic Research*, *53*(1), 585–588.

Akerstedt, T., Kecklund, G., & Axelsson, J. (2007). Impaired sleep after bedtime stress and worries. *Biological Psychology*, *76*(3), 170–173.

Akerstedt, T., Orsini, N., Petersen, H., Axelsson, J., Lekander, M., & Kecklund, G. (2012). Predicting sleep quality from stress and prior sleep—A study of day-to-day covariation across six weeks. *SleepMed*, *13*(6), 674–679.

Biondi, M., & Picardi, A. (1999). Psychological stress and neuroendocrine function in humans: The last two decades of research. *Psychotherapy and Psychosomatics*, *68*(3), 114–150.

Boneva, R. S., Decker, M. J., Maloney, E. M., Lin, J. M., Jones, J. F., Helgason, H. G., et al. (2007). Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: A population-based study. *Autonomic Neuroscience*, *137*(1–2), 94–101.

Brown, R. F., & Thorsteinsson, E. B. (2009). Stressful life-events and fatigue in a nonclinical sample. *Journal of Nervous and Mental Disease*, *197*(9), 707–710.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213.

Cohen, S., Kessler, R. C., & Gordon, L. U. (1997). Strategies for measuring stress in studies of psychiatric and physical disorders. In S. Cohen, R. C. Kessler, & L. U. Gordon (Eds.), *Measuring stress: A guide for health and social scientists* (pp. 3–26). New York: Oxford University Press.

Dahlgren, A., Kecklund, G., & Akerstedt, T. (2005). Different levels of work-related stress and the effects on sleep, fatigue and cortisol. *Scandinavian Journal of Work, Environment and Health*, *31*(4), 277–285.

Dahlgren, A., Kecklund, G., Theorell, T., & Akerstedt, T. (2009). Day-to-day variation in saliva cortisol-relation with sleep, stress and self-rated health. *Biological Psychology*, *82*(2), 149–155.

Dantzer, R., Heijnen, C. J., Kavelaars, A., Laye, S., & Capuron, L. (2014). The neuroimmune basis of fatigue. *Trends in Neurosciences*, *37*(1), 39–46.

De Vente, W., Olff, M., Van Amsterdam, J. G., Kamphuis, J. H., & Emmelkamp, P. M. (2003). Physiological differences between burnout patients and healthy controls: Blood pressure, heart rate, and cortisol responses. *Occupational and Environmental Medicine*, *60*(Suppl. 1), i54–i61.

Dittner, A. J., Rimes, K., & Thorpe, S. (2011). Negative perfectionism increases the risk of fatigue following a period of stress. *Psychology and Health*, *26*(3), 253–268.

Eek, F., Karlson, B., Garde, A. H., Hansen, A. M., & Orbaek, P. (2012). Cortisol, sleep, and recovery—Some gender differences but no straight associations. *Psychoneuroendocrinology*, *37*(1), 56–64.

Elo, A. L., Leppänen, A., & Jahkola, A. (2003). Validity of a single-item measure of stress symptoms. *Scandinavian Journal of Work, Environment and Health*, *29*(6), 444–451.

Hawkins, J., & Shaw, P. (1992). Self-reported sleep quality in college students: A repeated measures approach. *Sleep*, *15*(6), 545–549.

Hellhammer, J., Fries, E., Schweisthal, O. W., Schlotz, W., Stone, A. A., & Hagemann, D. (2007). Several daily measurements are necessary to reliably assess the cortisol rise after awakening: State- and trait-components. *Psychoneuroendocrinology*, *32*(1), 80–86.

Kalimo, R., Tenkanen, L., Härmä, M., & Poppius, E. (2000). Job stress and sleep disorders: Findings from the Helsinki Heart Study. *Stress Medicine*, *16*(2), 65–75.

Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2006). Premorbid predictors of chronic fatigue. *Archives of General Psychiatry*, *63*(11), 1267–1272.

Kenny, D. A., Korchmaros, J. D., & Bolger, N. (2003). Lower level mediation in multilevel models. *Psychological Methods*, *8*(2), 115–128.

Knudsen, H. K., Ducharme, L. J., & Roman, P. M. (2007). Job stress and poor sleep quality: Data from an American sample of full-time workers. *Social Science and Medicine*, *64*(10), 1997–2007.

Kocalevent, R. D., Hinz, A., Brahler, E., & Klapp, B. F. (2011). Determinants of fatigue and stress. *BMC Research Notes*, *4*, 238.

Korchmaros, J. D., & Kenny, D. A. (2003). *Step by step procedure for estimating lower-level mediation in random-effects multilevel models using HLM5*. University of Connecticut (manuscript) Retrieved from: <http://davidakenny.net/doc/mlm-med-hlm5.pdf/>

Kumari, M., Badrick, E., Chandola, T., Adam, E. K., Stafford, M., Marmot, M. G., et al. (2009). Cortisol secretion and fatigue: Associations in a community based cohort. *Psychoneuroendocrinology*, *34*(10), 1476–1485.

Lavidor, M., Weller, A., & Babkoff, H. (2003). How sleep is related to fatigue. *British Journal Health Psychology*, *8*(Pt 1), 95–105.

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. http://dx.doi.org/10.1016/j.bandc.2007.02.007

Nater, U. M., Heim, C., & Raison, C. (2012). Chronic fatigue syndrome. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.). *Handbook of clinical neurology 3rd series.*

Nater, U. M., Maloney, E., Boneva, R. S., Gurbaxani, B. M., Lin, J. M., Jones, J. F., et al. (2008). Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. *Journal of Clinical Endocrinology and Metabolism*, *93*(3), 703–709.

Nater, U. M., Rohleder, N., Schlotz, W., Ehlert, U., & Kirschbaum, C. (2007). Determinants of the diurnal course of salivary alpha-amylase. *Psychoneuroendocrinology*, *32*(4), 392–401.

Nijrolder, I., van der Horst, H., & van der Windt, D. (2008). Prognosis of fatigue. A systematic review. *Journal of Psychosomatic Research*, *64*(4), 335–349.

Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. J., & Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *BMJ (Clinical Research Ed.)*, *308*(6931), 763–766.

Petersen, H., Kecklund, G., D'Onofrio, P., Nilsson, J., & Akerstedt, T. (2012). Stress vulnerability and the effects of moderate daily stress on sleep polysomnography and subjective sleepiness. *Journal of Sleep Research*, *22*(1), 50–57.

Pilcher, J. J., Ginter, D. R., & Sadowsky, B. (1997). Sleep quality versus sleep quantity: Relationships between sleep and measures of health, well-being and sleepiness in college students. *Journal of Psychosomatic Research*, *42*(6), 583–596.

Powell, D. J., Liossi, C., Moss-Morris, R., & Schlotz, W. (2013). Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology*, *38*(11), 2405–2422.

Preacher, K. J. (2010–2013). Calculation of the Sobel Test - an interactive calculation tool for mediation tests. <http://quantpsy.org/sobel/sobel.htm/> Retrived 21.10.13.

Raudenbush, S. W., Bryk, A. S., Cheong, Y. F., & Congdon, R. (2005). *HLM5. Hierarchal linear and nonlinear modeling.* Chicago, IL: Scientific Software International.

Riley, W. T., Rothrock, N., Bruce, B., Christodolou, C., Cook, K., Hahn, E. A., et al. (2010). Patient-reported outcomes measurement information system (PROMIS) domain names and definitions revisions: Further evaluation of content validity in IRT-derived item banks. *Quality of Life Research*, *19*(9), 1311–1321.

Schulz, P., Kirschbaum, C., Pruessner, J. C., & Hellhammer, D. (1998). Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. *Stress Medicine*, *14*, 91–97.

Schwarz, R., Krauss, O., & Hinz, A. (2003). Fatigue in the general population. *Onkologie*, *26*(2), 140–144.

Singer, J. D., & Willett, J. B. (2003). *Applied Longitudinal Data Analysis.* New York: Oxford University Press.

Smets, E. M., Garssen, B., Bonke, B., & De Haes, J. C. (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*, *39*(3), 315–325.

Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological Methodology 1982* (pp. 290–312). Washington, DC: American Sociological Association.

Stone, A. A., Broderick, J. E., Porter, L. S., & Kaell, A. T. (1997). The experience of rheumatoid arthritis pain and fatigue: Examining momentary reports and correlates over one week. *Arthritis Care and Research*, *10*(3), 185–193.

Strahler, J., Fischer, S., Nater, U. M., Ehlert, U., & Gaab, J. (2013). Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biological Psychology*, *94*(1), 160–166.

Temel, J. S., Pirl, W. F., Recklitis, C. J., Cashavelly, B., & Lynch, T. J. (2006). Feasibility and validity of a one-item fatigue screen in a thoracic oncology clinic. *Journal of Thoracic Oncology*, *1*(5), 454–459.

Thorsteinsson, E. B., & Brown, R. F. (2009). Mediators and moderators of the stressor–fatigue relationship in nonclinical samples. *Journal of Psychosomatic Research*, *66*(1), 21–29.

6.3 Study 2

Doerr, J.M., Nater, U.M., Spoerri, C., Ehlert, U., & Ditzen, B. (ready to be submitted). Dyadic co-regulation of fatigue and psychobiological stress in everyday life.

Dyadic Co-Regulation of Fatigue and Psychobiological Stress in Everyday Life

Johanna M. Doerr[1], Urs M. Nater[1], Corinne Spoerri[2], Ulrike Ehlert[2], Beate Ditzen[2,3]

[1]Clinical Biopsychology, Department of Psychology, University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany

[2]Clinical Psychology and Psychotherapie, Department of Psychology, University of Zurich, Binzmuhlestr. 14, 8050 Zurich, Switzerland

[3]Institute of Medical Psychology, Center for Psychosocial Medicine, University of Heidelberg, Bergheimer Str. 20, 69115 Heidelberg, Germany

3608 words (excl. abstract, references, and tables)

1 Table

1 Figure

1 Online Supplement

Abstract

Background: There is limited knowledge about how fatigue develops and worsens and what influences fluctuations in daily fatigue. Stress was found to influence fatigue, and being in a relationship was found to either increase or decrease stress depending on the couple interaction. We investigated co-regulation of fatigue, stress, and biological markers in couples' everyday lives. Specifically, we focused on whether momentary interaction moderated this co-regulation and on the influence of stress and relationship measures on individual momentary fatigue.

Methods: Forty heterosexual couples (age: 28±5 years) reported subjective fatigue and stress levels 4 times a day for 5 consecutive days (1600 measures). Furthermore, participants reported if they had interacted with their partners since the last data entry and, if so, they rated the valence of this interaction. Salivary cortisol (as a measure of HPA axis activity) and alpha-amylase (as a measure of ANS activity) were analyzed from samples obtained at the same time points. Data were analyzed using multilevel models of distinguishable dyads to account for the nested design.

Results: Stress (women and men: $p<0.001$) and fatigue (women: $p=.003$, men: $p=.020$) were co-regulated within couples, especially if partners had interacted with each other since the previous data entry. Cortisol was also found to be co-regulated in both men and women (women: $UC=0.12$, $p<0.001$, men: $UC=0.18$, $p<0.001$), whereas the regulation of alpha-amylase levels depending on the partner's levels was only present in women ($UC=0.11$, $p=0.002$). Valence of interaction was negatively associated with fatigue (women: $UC=-0.13$, $p<0.001$, men: $UC=-0.06$, $p=0.011$). There was no momentary association of fatigue with an individual's own or the partner's subjective or biological stress markers.

Conclusions: Fatigue and stress levels during the day seem to be co-regulated within couples. These associations were particularly strong if the partners indicated that they interacted with each other since the last measurement time point. These data suggest that in

interventions to address stress and fatigue with clinical groups, a dyadic perspective might be implemented in order to improve individual well-being.

Dyadic Co-Regulation of Fatigue and Psychobiological Stress Measures in Everyday Life

Fatigue is a subjective phenomenon that can be defined as a state of exhaustion, tiredness, weakness, and lack of energy (R. Schwarz, et al., 2003). It is part of a wide array of normal experiences in everyday life and has the purpose of triggering resting behavior in order to achieve recovery. Thus, fatigue levels tend to be higher in the morning (directly after awakening) and evening, depending on how restful the night's sleep and how strenuous the day has been (Buysse, et al., 2007; Dahlgren, Kecklund, & Akerstedt, 2005). As fatigue during the day may interfere with productivity and well-being (Riley, et al., 2010), it is important to uncover the underlying psychological and biological mechanisms that can explain changes in fatigue. Although fatigue is an almost ubiquitous phenomenon, these mechanisms are not well understood and might help to develop targeted interventions to improve chronically fatigued individuals' lives.

We and others have postulated that stress may be a critical factor precipitating and/or facilitating fatigue. Previous studies have found that stress has the potential to influence fatigue levels in clinical samples (Kato, et al., 2006) as well as in the everyday life of non-clinical samples (Akerstedt, et al., 2014). In a recent study, we were able to show that not only does stress positively predict fatigue, but that increases in fatigue also predict increases in stress experienced by young healthy adults (Doerr et al., 2015). However, most research on stress and fatigue has been conducted with only one time point of measurement (e.g. Brown & Thorsteinsson, 2009), with the consistent finding of more stress being associated with increased fatigue levels. Thus, although the question of causality remains not fully answered, stress was found an important risk factor for increases in fatigue.

Given the close association between stress and fatigue, it can be assumed that the biological stress responses of the hypothalamic pituitary adrenal (HPA) axis and the autonomous nervous system (ANS) play an important role in the biological foundation of changes in fatigue severity (Nater, Heim, & Reeves, 2010). However, results regarding the

influence of the activity of the HPA axis and the ANS on fatigue are inconsistent. Some studies indicate that fatigue is associated with a reduction of cortisol variability across the day (e.g. Dahlgren, et al., 2009). Furthermore, Adam, Hawkley, Kudielka, and Cacioppo (2006) found an association between low morning cortisol values and high fatigue levels throughout the day in a sample of older adults whereas Eek, Karlson, Garde, Hansen, and Orbaek (2012) found positive associations between cortisol increases in the morning and several aspects of fatigue (lack of energy, lack of motivation, physical exertion). There are several additional studies suggesting changes in the HPA axis and ANS functioning in persons suffering from chronic fatigue syndrome, hinting toward a decreased responsiveness of the HPA axis (for an overview see Powell, Liossi, Moss-Morris, & Schlotz, 2013) and enhanced ANS activity (although some studies found no differences, for an overview see Nater, Heim, & Raison, 2012) in this group. In sum, activation of the ANS and HPA axis are part of the biological stress response (Sapolsky, Romero, & Munck, 2000), and stress is most likely an important risk factor for increased fatigue. However, the assumed association of the activities of the HPA axis and ANS with changes in everyday life fatigue was not conclusively shown so far.

More recently, health research has become increasingly aware of social influences on individual psychobiological functions, namely central nervous system mechanisms, hormones, and stress-sensitive autonomic markers (for an overview see McCall & Singer, 2012). The social perspective has strong implications for diverse health outcomes and treatment programs (Kirby & Baucom, 2007; Whisman & Beach, 2012). Most explanatory models on the effects of social relationships on health focus on couple relationships, with the partner as a source of social support to buffer stress, but also as a potential stressor (Ekmann, Avlund, Osler, & Lund, 2012; Robles & Kiecolt-Glaser, 2003). As a consequence, being in a close relationship can lead to both activation or buffering of the body's stress systems (Ditzen & Heinrichs, 2014). Indeed, co-regulation of mood as well as activity of the body's stress systems have been found in couples. This co-regulation within attachment bonds is thought to maintain psychobiological homeostasis (Coan & Sbarra, 2015; Sbarra &

Hazan, 2008) where the partners serve as “social zeitgebers” (Stetler, Dickerson, & Miller, 2004). In line with this concept, emotional similarity and convergence were found in adults who are close to each other (Anderson, et al., 2003; Butner, et al., 2007; Schoebi, 2008). Furthermore, cortisol levels have been found to be co-regulated in spouses, particularly when the partner was present (Saxbe & Repetti, 2010). Co-regulation of cortisol has also been found in other ambulatory as well as laboratory studies (Laurent & Powers, 2007; Liu, et al., 2013). Concerning the co-regulation of autonomic outcomes, experimental laboratory studies suggest equivocal results (Ferrer & Helm, 2013; Reed, et al., 2013). To our knowledge, no data on co-regulation of ANS outcomes between partners in everyday life are available yet.

Based on these findings, we aimed at extending the current data and focus on co-regulation of fatigue within couples, including HPA axis and ANS indicators as possible mediators of this relationship. We expected that fatigue levels would be co-regulated within couples. We also expected to find co-regulation of stress and HPA axis, as reported from previous studies, and in parallel to these data ANS co-regulation in couples’ everyday lives. We examined whether these relationships would be stronger when partners actually interacted (i.e. were in touch with each other in any way) during the course of one week. Of course, variance in fatigue levels might not only be influenced by interaction with the partner but also by shared lifestyle (sleeping patterns, sports, eating habits, etc.). These behaviors were, thus, included as control variables into the data analyses.

Methods

Participants

Couples were recruited via flyers, information brochures, internet ads, mailing lists of the University of Zurich, and social media. Inclusion criteria comprised being between 21 and 45 years old, exclusive dating and relationship length between one and 15 years, and cohabitation. Participants were excluded if they had children, had a current or chronic physical or psychiatric illness, or currently used medication (except for hormonal

contraceptives) or drugs (no alcohol intake on a daily basis, or smoking more than five cigarettes a day). Women not using hormonal contraception were studied during the early follicular phase of the menstrual cycle. All participants gave written informed consent. The study protocol was approved by the ethics committee of the Canton of Zurich and the study was monitored from the Clinical Trials Center Zurich.

Current analyses are based on a sub-sample (placebo group) that took part in the "Oxytocin, Couple Interaction, and Wound Healing" study (more information at clinicaltrials.gov, identifier NCT01594775). The sample consists of forty couples which all provided complete data sets. Of the forty women, twenty used hormonal contraception. Couples were randomized into two groups, one of which was instructed in a short verbal positive interaction intervention they should implement in their everyday lives during the assessment period. This randomization has been controlled for, but did not have an influence on a moment-to-moment level (data not shown).

Materials and Procedure

After inclusion and exclusion criteria had been checked during an initial phone contact, couples were invited to an instruction session at the laboratory. They provided information on their general awakening times (for the five days of ambulatory assessment). During the first laboratory appointment, participants provided urine samples to rule out drug consumption and pregnancy and completed electronic questionnaires to assess baseline relationship criteria. After that, participants were instructed in the use of a pre-programmed (iDialogPad, G. Mutz, Cologne, Germany) iPod touch® as well as ambulatory saliva sampling using the SaliCap® system (IBL, Hamburg, Germany).

An ecological momentary assessment (EMA) design was used with five consecutive days of data collection. Measurement time points were prompted by the iPod-Program directly after awakening, +30 minutes, + 2.5 hours, +8 hours, +16 hours, and at bedtime. At each time point, participants also provided saliva samples. Stress and fatigue levels were reported at four of the six time points (excluding awakening and +30min measurements).

The SaliCap® (IBL, Hamburg, Germany) system allows for the collection of saliva via passive drool. This means that participants collected their saliva for one minute in their mouths and then filled the saliva collection vials using a straw or by salivating directly into the tube. Participants were instructed to keep their samples in their refrigerators at home until they returned them to study personnel. Samples were frozen at -20°C until analysis. Cortisol was analyzed using a commercially available competitive luminescence immunoassay (IBL, Hamburg, Germany). For the measurement of salivary alpha-amylase (sAA), a kinetic colorimetric test and reagents from Roche (Roche Diagnostics, Mannheim, Germany) were used. Inter- and intra-assay variation of both assays was below 10%.

Participants rated their momentary stress and fatigue levels on a scale from 1 (stressed out/ full of energy) to 5 (relaxed/ exhausted) at each data entry using the multidimensional mood questionnaire (Steyer, Schwenkmezger, Notz, & Eid, 1997). Furthermore, participants indicated if they had interacted with their partners since the last data entry (“Since the last beep, did you interact with your partner?” yes/no) and, if so, they rated the valence of this interaction on a scale from 1 (negative) to 10 (positive).

As a measure of relationship satisfaction, the relationship questionnaire by Hahlweg (1996) was used. This questionnaire comprises three scales with 10 items each, which are measured on a scale from 0 (never) to 3 (very often). The scales are: 1. Quarreling (aggressive behavior of the partner during argument), 2. Tenderness (physical contact, and verbal as well physical intimacy), and 3. Togetherness (shared activities, communication, and feelings of belonging together). Furthermore, a general score can be calculated as a sum of the tenderness and togetherness-scales and the inverted quarreling-scale. Good validity and reliability of the measure have been shown in previous studies (e.g. Hinz, Ströbel-Richter, & Brähler, 2001).

Statistical Analyses

Data were analyzed using multilevel models of distinguishable dyads as described by Bolger and Laurenceau (Bolger & Laurenceau, 2013; Laurenceau & Bolger, 2005). All χ^2-tests for the specific outcomes were statistically significant ($p < .001$) indicating that there is

variance in the outcomes by person, which justifies the use of hierarchical linear modeling. Models included separate intercept and slope-terms for women and men while adjusting for the nested design (time points within persons within couples) using two-level hierarchical linear models (HLM, Raudenbush, et al., 2005). As a measure of effect size (level 1-variance of the outcome explained by the specific predictor), *Pseudo-R^2* was determined as described by Singer and Willet (Singer & Willett, 2003) where *Pseudo-R^2*=($\sigma^2_{referencemodel}$ - $\sigma^2_{finalmodel}$)/ $\sigma^2_{referencemodel}$. SAA and cortisol values were checked for outliers and tested for normal distribution using the Kolmogorov-Smirnov (KS) test. These parameters were not normally distributed and analyses were conducted using logarithmic values with an added constant ($ln_{(x)}$+10). All models explained significantly more variance in the outcome than the null model (model without predictors). Before finalizing the models, the influence of relevant confounders (see below) at level 1 was checked and these variables were included as control variables in the final model, if they had a significant effect on the respective outcome. At level 1, controlled confounders were: use of medication, food consumption, beverage consumption, caffeine intake, smoking, self-reported physical activity (since the last data entry), and time since awakening. At level 2 the influence of BMI, age, sleep quality. The effects reported refer to same time-point associations (i.e., the association between an individual's own momentary fatigue and the fatigue of the partner measured at the same time point). Exceptions are *interaction with the partner* which refers to the time span since the last data entry and *relationship satisfaction*, which was measured once in the beginning of the study and entered at the person level (level 2).

Results

The sample consists of 40 opposite-gender couples (age: 28 ± 5) with a relationship length of 3.72 ± 2.52 years and cohabitating for 1.98 ± 1.65 years. Participants reported light to moderate mean levels of fatigue (2.94 ± 1.10) and stress (2.23 ± 0.98) throughout the five days of measurement. Relationship satisfaction was high in this sample with a mean relationship questionnaire sum score of 73.75 ± 8.09 in women and 70.32 ± 8.71 in men

(total sample: 72.80 ± 7.42) which matches stanine values between 5 and 7 (average to high).

Co-Variation of momentary Fatigue and Stress Measures

Fatigue co-varied within couples (i.e. one partner's fatigue level at a given time point predicted the other partner's fatigue level, see table 1). When including "interaction with partner since the last data entry" (yes/no) as well as a product term "interaction with partner × partner's fatigue" into the model, it can be seen that this momentary co-variation depended on whether the participants had interacted with their partners since the last data entry (see Table 1 and Figure 1A, *Pseudo-R²* = 0.06).

Stress co-varied in both genders (see Figure 1B, women: *UC* = 0.26, *t*(39) = 6.16, *p* < .001, men: *UC* = 0.21, *t*(39) = 5.45, *p* < .001, *Pseudo-R²* = 0.11). An interaction effect of interacting with the partner since the last entry (yes/no) x the partner's momentary stress was also apparent (women: *UC* = 0.17, *t*(39) = 2.18, *p* = 0.035, men: *UC* = 0.09, *t*(39) = 2.14, *p*= .038, see Figure 1B). When including the product term "interaction with partner x partner's momentary stress" in the model, the effect of the partner's stress on an individual's own stress disappeared in women (*UC* = 0.15, *t*(39) = 2.00, *p* = .052), but not in men (*UC* = 0.14, *t*(39) = 2.99, *p* = .005). This result suggests that in women, stress co-variation was dependent on interaction (analogous to the effects concerning fatigue, see below). In men, stress co-varied more strongly with that of the partner when having interacted since the last data entry, but the effect was independent of interaction.

Cortisol levels also co-varied within couples (women: *UC* = 0.12, *t*(39) = 4.32, *p* < .001, men: *UC* = 0.18, *t*(39) = 5.18, *p* < .001; *Pseudo-R²* = 0.07) with this effect being unaffected by the interaction effect of interaction since the last entry (yes/no) x partner's momentary cortisol level. SAA levels only varied in association with those of the partner in women (women: *UC* = 0.11, *t*(39) = 3.24, *p* = .002, men: *UC* = 0.07, *t*(39) = 1.69, *p* = .098; *Pseudo-R²* = 0.07) independently of interaction since the last data entry (effect of product term:

women: *UC* = 0.01, *t*(39) = -0.32, *p*=.748, men: *UC*=0.08, *t*(39)=1.70, *p*=.097). An overview of the full models of these variables (including stress) is provided in the online supplement.

- Insert table 1 about here -
- Insert figure 1 about here -

Momentary Associations of Stress Measures and Relationship Variables with Fatigue

There was no association of an individual's own stress (women: *UC* = 0.08, *t*(39) = 1.67, *p* = .103, men: *UC* = 0.08, *t*(39) = 1.69, *p* = .099) or the partner's stress (women: *UC* = 0.05, *t*(39) = 1.01, *p* = .317, men: *UC* = 0.05, *t*(39) = 1.13, *p* = .264) with fatigue. Nor was an individual's own cortisol (women: *UC* = 0.04, *t*(39) = 0.77, *p* = .447, men: *UC* = 0.02, *t*(39) = 0.41, *p* = .686) or partner's cortisol levels related to momentary fatigue (women: *UC* = -0.02, *t*(39) = -0.61, *p* = .544, men: *UC* = 0.07, *t*(39) = 1.39, *p* = .172). SAA levels were negatively associated with an individual's own fatigue in women (women: *UC* = -0.11, *t*(39) = -2.57, *p* = .014, men: *UC* = -0.11, *t*(39) = -1.97, *p* = .056; *Pseudo-R²*=0.03), whereas men's fatigue was negatively associated with their partner's sAA levels (women: *UC* = -0.07, *t*(39) = -1.35, *p* = .184, men: *UC* = -0.08, *t*(39) = -2.07, *p* = .045; *Pseudo-R²* = 0.03).

Notably, fatigue was negatively associated with interaction (see Table 1) as well as with valence of interaction since the last data entry in both, women and men (women: *UC* = -0.13, *t*(39) = -4.34, *p* < .001, men: *UC* = -0.06, *t*(39) = -2.66, *p* = .011; *Pseudo-R²*=0.05), suggesting less fatigue after or during times of positive interaction with the partner. Relationship satisfaction neither had a direct effect on momentary fatigue (women: *UC* = 0.01, *t*(37) = 0.91, *p* = .369, men: *UC* = -0.02, *t*(37) = -1.98, *p* = .055) nor was there a cross-level interaction effect with co-regulation of fatigue (women: *UC* = -0.00, *t*(38) = -0.24, *p* = .810, men: *UC* = 0.00, *t*(38) = 0.76, *p* = .453).

Discussion

Fatigue, stress, and cortisol levels co-varied within couples during the five days of the assessment, in part depending on whether they had interacted with the partner since the

last data entry. In women, sAA levels varied dependent on their partner's levels, but not vice versa. Momentary fatigue was independent of an individual's own or the partners' stress and cortisol levels (measured at the same time point) in this sample. An individual's own momentary sAA levels were negatively related to same time-point fatigue in women, but not in men. Beyond this, momentary fatigue levels were associated with interaction, as well as with the valence of interaction with the partner since the last data entry (the more negative the interaction, the higher the reported fatigue).

Overall, our findings suggest that if and how one interacts with a partner can influence fatigue experience in everyday life. Given that partners can "pass on" their fatigue levels to each other when interacting, but are also able to reduce or worsen fatigue depending on the valence of the interaction, it seems important to include the dyadic perspective into studies and intervention or prevention programs addressing chronic fatigue.

This is, to our knowledge, the first study showing these effects in relation to fatigue in everyday life. Co-regulation of fatigue within couples has not been reported in this manner so far, but extends the finding that mood co-varies within couples (Saxbe & Repetti, 2010; Schoebi, 2008). One implication of the co-regulation of fatigue is that partners of patients suffering from high fatigue levels are at risk of developing fatigue symptoms themselves. Being in a relationship has been proposed as a protective factor for fatigue worsening in fatigued patients (e.g. Johansson, Ytterberg, Hillert, Widen Holmqvist, & von Koch, 2008), but symptoms of the partner are rarely assessed. This assessment should be implemented more strongly in future research. Furthermore, to involve the partner in the prevention and/ or treatment of fatigue might increase the success of such interventions (Kirby & Baucom, 2007; Whisman & Beach, 2012), either through changes in the shared lifestyle of these couples, but also on a more direct level through their co-regulated physiology.

The findings that own sAA levels were associated with the partner's sAA levels in women but not in men is in line with theories (Taylor et al., 2000) suggesting that women's physiology and health are generally more affected by the partner than the other way around

(Kiecolt-Glaser & Newton, 2001). To date, studies on co-regulation of ANS measures have used laboratory designs. In a study by Ferrer and Helm (2013), co-regulation of heart rate (another ANS measure) was achieved by gazing into the partner's eyes and try to "synchronize." Interestingly, the authors found that men increased the level of co-regulation when "trying to synchronize" as opposed to a control task where the partners relaxed in the same room (without interacting). Women, on the other hand, showed co-regulation independently of explicitly trying to synchronize. Relating those findings to ours, it might be assumed that women more easily synchronize their ANS activity to those of men than the other way around. However, in the present study the men's fatigue seems to be affected by the women's autonomic arousal and not vice versa. This is probably due to the fact that women's sAA levels predicted their own fatigue levels, and fatigue levels were co-regulated with the partners'.

This study has important strengths: One is the high ecological validity due to the assessment of couples in their everyday life. The dyadic approach further allowed us to assess processes as they happen within couples, which is an advantage towards studies that assess relationship parameters in persons in relationships without including the partner as a source of measurement. Furthermore, we included biological as well as subjective measurements while rigidly controlling for confounding variables, such as sleep, food and caffeine intake, hormonal contraceptives, menstrual cycle phase, etc. One limitation of our study is the selective sample. As our sample consisted of pre-menopausal adults in a stable relationship with relatively high relationship satisfaction but no children, results might not necessarily be applicable to all individuals living in a relationship. Furthermore, as is always the case in studies in an everyday life setting, we cannot rule out the possibility that third variables, which we did not assess (such as temperature, lighting, seasonal changes, or weather), might have influenced fatigue.

In sum, our results show that fatigue is influenced by relationship-specific variables (co-regulation, as well as interaction with the partner) in the everyday life of couples.

Furthermore, next to fatigue, we showed that stress, HPA axis activity, and ANS activity are co-regulated in couples – parameters that most likely influence fatigue in longer terms than we were able to assess in the current study. Future studies on fatigue should therefore implement the assessment of dyadic data and relationship interactions. Moreover, fatigue interventions should involve the partner in the treatment process.

References

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience--cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences of the United States of America, 103*(45), 17058-17063. doi: 10.1073/pnas.0605053103

Akerstedt, T., Axelsson, J., Lekander, M., Orsini, N., & Kecklund, G. (2014). Do sleep, stress, and illness explain daily variations in fatigue? A prospective study. *Journal of Psychosomatic Research, 76*(4), 280-285. doi: 10.1016/j.jpsychores.2014.01.005 S0022-3999(14)00022-1 [pii]

Anderson, C., Keltner, D., & John, O. P. (2003). Emotional convergence between people over time. *J Pers Soc Psychol, 84*(5), 1054-1068.

Bolger, N., & Laurenceau, J. P. (2013). Design and Analysis of Intensive Longitudinal Studies of Distinguishable Dyads *Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research* (pp. 143-176). New York: Guilford.

Brown, R. F., & Thorsteinsson, E. B. (2009). Stressful life-events and fatigue in a nonclinical sample. *Journal of Nervous and Mental Disease, 197*(9), 707-710. doi: 10.1097/NMD.0b013e3181b3af36 00005053-200909000-00012 [pii]

Butner, J., Diamond, L. M., & Hicks, A. M. (2007). Attachment style and two forms of affect coregulation between romantic partners. *Personal Relationships, 14*, 431-455.

Buysse, D. J., Thompson, W., Scott, J., Franzen, P. L., Germain, A., Hall, M., . . . Kupfer, D. J. (2007). Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep Med, 8*(3), 198-208. doi: S1389-9457(06)00629-0 [pii] 10.1016/j.sleep.2006.10.006

Coan, J. A., & Sbarra, D. A. (2015). Social Baseline Theory: The Social Regulation of Risk and Effort. *Curr Opin Psychol, 1*, 87-91. doi: 10.1016/j.copsyc.2014.12.021

Dahlgren, A., Kecklund, G., & Akerstedt, T. (2005). Different levels of work-related stress and the effects on sleep, fatigue and cortisol. *Scand J Work Environ Health, 31*(4), 277-285. doi: 883 [pii]

Dahlgren, A., Kecklund, G., Theorell, T., & Akerstedt, T. (2009). Day-to-day variation in saliva cortisol--relation with sleep, stress and self-rated health. *Biological Psychology, 82*(2), 149-155. doi: 10.1016/j.biopsycho.2009.07.001

Ditzen, B., & Heinrichs, M. (2014). Psychobiology of social support: the social dimension of stress buffering. *Restor Neurol Neurosci, 32*(1), 149-162. doi: 10.3233/RNN-139008 M0228K0TM4T20210 [pii]

Doerr, J. M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., . . . Nater, U. M. (2015). Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students. *Biol Psychol, 110*, 42-49. doi: 10.1016/j.biopsycho.2015.06.009 S0301-0511(15)30014-4 [pii]

Eek, F., Karlson, B., Garde, A. H., Hansen, A. M., & Orbaek, P. (2012). Cortisol, sleep, and recovery - Some gender differences but no straight associations. *Psychoneuroendocrinology, 37*(1), 56-64. doi: 10.1016/j.psyneuen.2011.05.003 S0306-4530(11)00156-9 [pii]

Ekmann, A., Avlund, K., Osler, M., & Lund, R. (2012). Do negative aspects of social relations influence fatigue? A cross-sectional study on a non-clinical sample of middle-aged Danish men. *J Psychosom Res, 73*(4), 277-282. doi: 10.1016/j.jpsychores.2012.08.005 S0022-3999(12)00210-3 [pii]

Ferrer, E., & Helm, J. L. (2013). Dynamical systems modeling of physiological coregulation in dyadic interactions. *Int J Psychophysiol, 88*(3), 296-308. doi: 10.1016/j.ijpsycho.2012.10.013 S0167-8760(12)00629-0 [pii]

Hahlweg, K. (1996). Partnerschaftsfragebogen (PFB) *Fragebogen zur Partnerschaftsdiagnostik (FPD)* (pp. 7-24). Göttingen: Hogrefe.

Hinz, A., Ströbel-Richter, Y., & Brähler, E. (2001). Der Partnerschaftsfragebogen (PFB): Normierung und soziodemographische Einflussgrößen auf die Partnerschaftsqualität. *Diagnostica, 47*(3), 132-141.

Johansson, S., Ytterberg, C., Hillert, J., Widen Holmqvist, L., & von Koch, L. (2008). A longitudinal study of variations in and perceptions of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*, 454-457. doi: 10.1136/jnnp.2007.121129

Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2006). Premorbid predictors of chronic fatigue. *Archives of General Psychiatry, 63*(11), 1267-1272. doi: 63/11/1267 [pii] 10.1001/archpsyc.63.11.1267

Kiecolt-Glaser, J. K., & Newton, T. L. (2001). Marriage and health: his and hers. *Psychol Bull, 127*(4), 472-503.

Kirby, J. S., & Baucom, D. H. (2007). Treating emotion dysregulation in a couples context: a pilot study of a couples skills group intervention. *Journal of Marital and Family Therapy, 33*(3), 375-391. doi: JMFT037 [pii] 10.1111/j.1752-0606.2007.00037.x

Laurenceau, J. P., & Bolger, N. (2005). Using diary methods to study marital and family processes. *J Fam Psychol, 19*(1), 86-97. doi: 2005-02946-009 [pii] 10.1037/0893-3200.19.1.86

Laurent, H., & Powers, S. (2007). Emotion regulation in emerging adult couples: temperament, attachment, and HPA response to conflict. *Biol Psychol, 76*(1-2), 61-71. doi: S0301-0511(07)00107-X [pii] 10.1016/j.biopsycho.2007.06.002

Liu, S., Rovine, M. J., Klein, L. C., & Almeida, D. M. (2013). Synchrony of diurnal cortisol pattern in couples. *J Fam Psychol, 27*(4), 579-588. doi: 10.1037/a0033735 2013-27136-001 [pii]

McCall, C., & Singer, T. (2012). The animal and human neuroendocrinology of social cognition, motivation and behavior. *Nature Neuroscience, 15*(5), 681-688. doi: 10.1038/nn.3084 nn.3084 [pii]

Nater, U. M., Heim, C., & Raison, C. (2012). Chronic fatigue syndrome. In M. J. Aminoff, F. Boller & D. F. Swaab (Eds.), *Handbook of Clinical Neurology 3rd Series*.

Nater, U. M., Heim, C., & Reeves, W. C. (2010). The role of stress in chronic fatigue syndrome. *International Journal of Medical and Biological Frontiers, 16*(7/8), 869-884

Powell, D. J., Liossi, C., Moss-Morris, R., & Schlotz, W. (2013). Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology*. doi: S0306-4530(13)00254-0 [pii] 10.1016/j.psyneuen.2013.07.004

Raudenbush, S. W., Bryk, A. S., Cheong, Y. F., & Congdon, R. (2005). *HLM 5. Hierarchal linear and nonlinear modeling*. Chicago, IL: Scientific Software International.

Reed, R. G., Randall, A. K., Post, J. H., & Butler, E. A. (2013). Partner influence and in-phase versus anti-phase physiological linkage in romantic couples. *Int J Psychophysiol, 88*(3), 309-316. doi: 10.1016/j.ijpsycho.2012.08.009 S0167-8760(12)00581-8 [pii]

Riley, W. T., Rothrock, N., Bruce, B., Christodolou, C., Cook, K., Hahn, E. A., & Cella, D. (2010). Patient-reported outcomes measurement information system (PROMIS)

domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. *Quality of Life Research, 19*(9), 1311-1321. doi: 10.1007/s11136-010-9694-5

Robles, T. F., & Kiecolt-Glaser, J. K. (2003). The physiology of marriage: pathways to health. *Physiol Behav, 79*(3), 409-416. doi: S0031938403001604 [pii]

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev, 21*(1), 55-89. doi: 10.1210/edrv.21.1.0389

Saxbe, D., & Repetti, R. L. (2010). For better or worse? Coregulation of couples' cortisol levels and mood states. *Journal of Personality and Social Psychology, 98*(1), 92-103. doi: 10.1037/a0016959 2009-24670-014 [pii]

Sbarra, D. A., & Hazan, C. (2008). Coregulation, dysregulation, self-regulation: an integrative analysis and empirical agenda for understanding adult attachment, separation, loss, and recovery. *Pers Soc Psychol Rev, 12*(2), 141-167. doi: 10.1177/1088868308315702 12/2/141 [pii]

Schoebi, D. (2008). The coregulation of daily affect in marital relationships. *J Fam Psychol, 22*(4), 595-604. doi: 10.1037/0893-3200.22.3.595 2008-10898-011 [pii]

Schwarz, R., Krauss, O., & Hinz, A. (2003). Fatigue in the general population. *Onkologie, 26*(2), 140-144. doi: 10.1159/000069834

Singer, J. D., & Willett, J. B. (2003). *Applied Longitudinal Data Analysis*. New York: Oxford University Press.

Stetler, C., Dickerson, S. S., & Miller, G. E. (2004). Uncoupling of social zeitgebers and diurnal cortisol secretion in clinical depression. *Psychoneuroendocrinology, 29*(10), 1250-1259. doi: 10.1016/j.psyneuen.2004.03.003 S0306453004000332 [pii]

Steyer, R., Schwenkmezger, P., Notz, P., & Eid, M. (1997). *Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF)*. Göttingen: Hogrefe.

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A., & Updegraff, J. A. (2000). Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychol Rev, 107*(3), 411-429.

Whisman, M. A., & Beach, S. R. (2012). Couple therapy for depression. *Journal of Clinical Psychology, 68*(5), 526-535. doi: 10.1002/jclp.21857

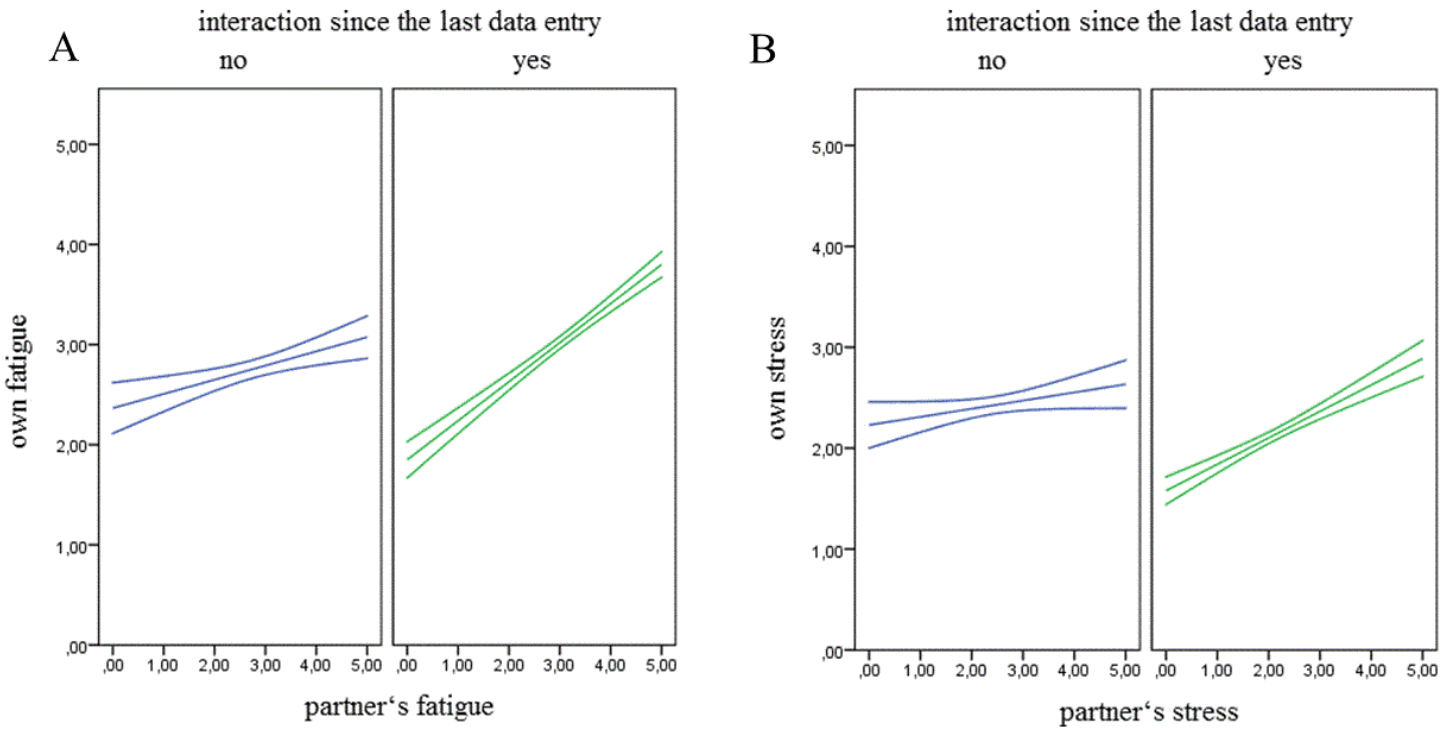


Figure 1. Average momentary fatigue (A), and stress (B) levels as a function of the partner's average momentary fatigue and stress levels by interaction since the last data entry: average regression lines (across all participants) with 95% confidence intervals.

Table 1.
Hierarchical linear models predicting momentary fatigue by partner's momentary fatigue and interaction (N=40 couples) using restricted maximum likelihood

	Model 1a						**Model 1b**					
	Women			**Men**			**Women**			**Men**		
Fixed Effects	*UC*	*SE*	*t-ratio*	*UC*	*SE*	*t-ratio*	*UC*	*SE*	*t-ratio*	*UC*	*SE*	*t-ratio*
Intercept	1.83	0.16	11.66***	1.73	0.16	10.99***	1.79	0.15	11.94***	1.76	0.16	11.15***
Momentary Level												
Partner's momentary fatigue	0.13	0.04	3.23**	0.08	0.03	2.43*	0.02	0.05	0.41	-0.00	0.04	-0.04
Interaction y/n							-0.44	0.15	-2.91**	-0.43	0.16	-2.63*
Interaction y/n × partner's momentary fatigue							0.18	0.06	3.12**	0.13	0.05	2.58*
Person Level												
Partner's general fatigue	0.82	0.04	19.69***	0.96	0.07	14.32***	0.76	0.07	11.73***	0.87	0.08	10.98***
Random Effects	*SD*	*VC*	χ^2	*SD*	*VC*	χ^2	*SD*	*VC*	χ^2	*SD*	*VC*	χ^2
female/male	0.65	0.42	63.17***	0.73	0.54	61.40***	0.60	0.36	37.58†	0.77	0.60	41.64*

Partner's momentary fatigue	0.17	0.03	64.87**	0.12	0.01	41.46	0.11	0.01	26.31	0.14	0.02	20.66
Interaction y/n							0.41	0.16	64.74	0.31	0.09	21.07
Interaction y/n × partner's momentary fatigue							0.14	0.02	31.67	0.05	0.00	15.95

Note. Models have been controlled for time since awakening, self-reported physical activity and caffeine intake at level 1, between-person centered self-reported physical activity and sleep quality were also included in the models at level 2, randomization into intervention groups did not have an effect on momentary fatigue; ****p*<0.001, ***p*<.01, **p*<.05

6.4 Study 3

Doerr, J. M., Fischer, S., Nater, U. M., & Strahler, J. (under review). Influence of stress systems and physical activity on different dimensions of fatigue in female patients with fibromyalgia. *Journal of Psychosomatic Research.*

Influence of stress systems and physical activity on different dimensions of fatigue in fibromyalgia patients

Johanna M. Doerr, MSc Susanne Fischer, PhD, Urs M. Nater, PhD, & Jana Strahler, PhD

Clinical Biopsychology, Department of Psychology, University of Marburg, Gutenbergstr. 18, 35037 Marburg, Germany

E-mail addresses: JMD: johannamdoerr@gmail.com, SF: susanne.fischer@kcl.ac.uk, UMN: nater@staff.uni-marburg.de, JS: strahler@staff.uni-marburg.de

Short running head: Stress systems, physical activity, and fatigue in FMS

Disclosures: None of the authors states any potential or actual conflict of interest.

Correspondence should be addressed to Jana Strahler (strahler@staff.uni-marburg.de), Clinical Biopsychology, Department of Psychology, University of Marburg, Gutenbergstr. 18, 35037 Marburg, Germany

Word count (abstract): 4002 (221)

Number of table(s): 2

Number of figure(s): 1

Number of supplementary material: 1

Abstract

Objective: Fatigue is a defining characteristic and one of the most debilitating features of fibromyalgia syndrome (FMS). The mechanisms underlying different dimensions of fatigue in FMS remain unclear. The aim of the current study was to test whether stress-related biological processes and physical activity modulate fatigue experience.

Methods: Using an ambulatory assessment design, 26 female FMS patients reported general, mental, and physical fatigue levels at six time points per day for 14 consecutive days. Salivary cortisol and alpha-amylase were analyzed as markers of neuroendocrine functioning. Participants wore wrist actigraphs for the assessment of physical activity.

Results: Lower increases in cortisol after awakening predicted higher mean daily general and physical fatigue levels. Additionally, mean daily physical activity positively predicted next-day mean general fatigue. Levels of physical fatigue at a specific time point were positively associated with momentary cortisol levels. The increase in cortisol after awakening did not mediate the physical activity – fatigue relationship. There were no associations between alpha-amylase and fatigue.

Conclusion: Our findings imply that both changes in hypothalamic-pituitary-adrenal axis activity and physical activity contribute to variance in fatigue in the daily lives of patients with FMS. This study helps to paint a clearer picture of the biological and behavioral underpinnings of fatigue in FMS and highlight the necessity of interdisciplinary treatment approaches targeting biological, behavioral and psychological aspects of FMS.

Key words: ambulatory assessment; fatigue; fibromyalgia; HPA axis; physical activity; autonomic nervous system

Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition with unknown etiology, which is accompanied by fatigue, sleep disturbances, and other somatic complaints (Wolfe, et al., 2010). Although fatigue is a major and very debilitating complaint in this population, most research focuses on pain (Vincent, et al., 2013). We therefore set out to assess biological and behavioral factors that might explain fluctuation of fatigue in FMS, focusing on endocrine and autonomic activity on the one hand and objectively recorded physical activity on the other.

High levels of chronic stress and related changes in the hypothalamic-pituitary-adrenal (HPA) axis as well as the autonomic nervous system (ANS) (the main regulatory biological stress systems) activity have been discussed as mechanisms of FMS symptom development and exacerbation (Nater, Fischer, et al., 2011). There is evidence of a diurnal HPA axis hypoactivity (reduced daily cortisol output (Crofford, et al., 1994; Gur, et al., 2004) and a reduced increase in cortisol after awakening (Riva, Mork, Westgaard, & Lundberg, 2012)) in patients with FMS. Concerning ANS activity, most studies in patients with FMS indicate a basal hyperactivity (Martinez-Lavin, 2007). It might therefore be suspected that reduced HPA axis and increased ANS activity contribute to fatigue manifestation in FMS. However, there are only two studies assessing intra-individual associations between HPA axis or ANS activity and fatigue in patients with FMS. McLean and colleagues (2005) found no association between cortisol (the most important peripheral marker of the HPA axis) and fatigue in patients with FMS. Riva and colleagues (2012), assessing the ANS, found a negative association between physical (but not mental) fatigue and 24h epinephrine, as well as heart rate during stress provocation. The inconsistent findings might be due to insufficiently long periods of investigation (one and two days, respectively). Further, Riva and colleagues did not account for within-day fluctuations of fatigue and used a controlled hospital-hotel setting, which might not be applicable to everyday life. In accordance with the findings of Riva and colleagues, there is research suggesting that measuring fatigue on

multiple dimensions is warranted in patients with FMS (Ericsson, Bremell, & Mannerkorpi, 2013). However, most studies on FMS did not account for the multidimensional nature of fatigue.

Everyday life physical activity is an important behavioral mechanism that might influence fatigue directly or indirectly, via alterations in HPA axis or ANS activity. Of the two studies using everyday life settings, one did not find objectively recorded physical activity levels to be predictive of subsequent momentary fatigue (Kop, et al., 2005), and the other found negative associations of objectively recorded physical activity with subjects' estimates of their general and physical fatigue levels during the last three months (Segura-Jimenez, et al., 2015). These findings seem to contradict laboratory findings and patient reports of symptom exacerbation due to enhanced physical activity (Lambin, Thibault, Simmonds, Lariviere, & Sullivan, 2011). To our knowledge, no study so far has assessed the direct interplay between objectively measured daily physical activity, neuroendocrine activity, and fatigue in patients with FMS in an everyday life setting.

In sum, studies are needed that assess associations between HPA axis as well as ANS activity with fatigue a) in the everyday life of patients with FMS to ensure high ecological validity, b) over a sufficiently long period of time, c) using a design that is suitable for detecting within-individual as well as within-day and between-day changes, and d) measuring fatigue on different dimensions. In a sample of patients with FMS, we expect fatigue levels to be negatively predicted by HPA axis and physical activity but positively predicted by ANS activity. We also expect the physical activity – fatigue association to be mediated by HPA axis and ANS activity.

Method

Participants

The current analyses are based on a data from a sub-sample of a larger study on psychobiological mechanisms in FMS. Previous findings in the whole sample have been

reported in Fischer et al. (2016) and Linnemann et al. (2015). Data collection took place between March 2013 and August 2014. Participants were recruited via advertisement in local newspapers, information leaflets placed in practices of local general practitioners, rheumatologists, and in rheumatology clinics, and via self-help groups. Inclusion criteria comprised female sex, speaking German fluently, being between 18 and 65 years of age, and fulfilling the Fibromyalgia Research Criteria (Wolfe et al., 2011). Exclusion criteria were a BMI above 30kg/m², current pregnancy or breast-feeding, irregular menstrual cycle, current major depressive disorder, substance abuse within the last two years, eating disorder within the last five years, lifetime psychotic or bipolar disorder, and any unmedicated medical condition that affects endocrine or autonomic functioning. Participants received 80 EUR for taking part in the study. The study protocol was approved by the institutional review board of the Department of Psychology, University of Marburg, and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Study protocol

Eligible participants were invited to the laboratory for an introductory session. During this session, baseline questionnaires were completed and participants were instructed in the use of a pre-programmed iPod touch®, in saliva sampling, and in how to wear the actigraph. Data collection took place over an assessment period of 14 days, with six time points of data entry each day (at awakening, 30 minutes later, at 11am, 2pm, 6pm, and 9pm) starting on the day after the introductory session. At each of these time points, participants answered several questions on the pre-programmed (iDialogPad App, momentary self-report data, G. Mutz, Cologne) iPod touch®, followed by a saliva sample. The saliva samples at awakening and 30 min after awakening were used to calculate the cortisol awakening response (CAR) and the alpha-amylase awakening response (AAR, see “biological measures”). After the 14-day ambulatory assessment period, participants returned the iPods, actigraphs, and saliva samples to the study personnel in a final laboratory session. In this session, they also

answered some follow-up questions concerning compliance with and reactivity to the testing procedures.

Questionnaires

Participants completed detailed medical histories[1] ,gynecological histories, and a list of current medication, which had been mailed to them after initial screening via telephone. These documents were brought to the introductory session and checked for compatibility with eligibility criteria.

In accordance with the Fibromyalgia Research Criteria (Wolfe, et al., 2011), the self-report measures *Widespread Pain Index* (WPI) as well as *Symptom Severity Score* (SSS) were used. The WPI measures in how many of 19 body areas participants experienced pain during the last three months. The SSS measures severity of fatigue, waking unrefreshed, and subjective cognitive impairment on a scale from 0 (“no problems”) to 3 (“severe problems”). Criteria were satisfied if the WPI was higher or equal to 7 pain sites and the SSS score was higher or equal to 5, or, alternatively, if the WPI was 3-6/19 and the SSS ≥ 9/12.

The *Patient Health Questionnaire 9* (PHQ-9, Löwe, L., Zipfel, & Herzog, 2002) was used to exclude patients with a current depressive episode, (i.e. who had experienced depressed mood or anhedonia on several days during the past two weeks).

Measures of fatigue and pain

To assess changes in fatigue in everyday life, participants rated their general, mental, and physical fatigue levels at 6 time points on each day. Phrasing and scaling were based on those items of the Multidimensional Fatigue Inventory (Smets, Garssen, Bonke, & De Haes, 1995) that had the highest loadings on the respective subscales general fatigue, mental fatigue, and physical fatigue (R. Schwarz, et al., 2003) and re-phrased so as to refer to the present moment. The item “At the moment… I feel fatigued” was used to measure general fatigue. “At the moment…I can concentrate well” was measured as a sign of mental fatigue.

[1] Of all the physical conditions assessed, thyroid dysfunction and high blood pressure emerged as significant predictors of general fatigue and were therefore included in the following statistical procedures.

"…I feel physically fit" was assessed to measure physical fatigue on a momentary basis. Each item was scaled from 0 (not at all) to 4 (very much) (Stone, Broderick, Porter, & Kaell, 1997). Pain was assessed on a visual analog scale "At the moment, I am in this much pain:" from 0 (no pain) to 100 (worst imaginable pain).

Measures of stress

Chronic stress was assessed using the screening scale (SSCS) of the Trier Inventory for the Assessment of Chronic Stress (Schulz, Schlotz, & Becker, 2004). This scale consists of 12 items that measure the occurrence of various stress experiences within the last three months on a scale from 0 ("never") to 4 ("very often"). Momentary stress levels were measured using the item "At the moment, I feel stressed out" from 0 (not at all) to 4 (very).

Control variables

Sleep quality had predictive value for general fatigue levels in one of our previous studies (Doerr, et al., 2015). Therefore, participants rated their sleep quality every morning at the first measurement time point using the item "How well did you sleep last night?" (on a visual analog scale from 0 to 100). The item was based on the sleep quality item of the Pittsburgh Sleep Quality Index (PSQI; Buysse, et al., 1989). Further control questions concerned eating, drinking, and smoking behavior, as well as the intake of medication since the last data entry, which were all measured dichotomously (0 "no", 1"yes").

Biological measures

Saliva samples were collected using the SaliCap® system (IBL, Hamburg, Germany). Participants accumulated saliva in their mouths for two minutes and subsequently salivated into a pre-labeled polypropylene tube via a straw. They were instructed to store saliva samples in their freezers or refrigerators and return them to the laboratory at the follow-up appointment, which was scheduled right after the collection period.

Biochemical analyses were conducted at the Biochemical Laboratory of the Department of Clinical Biopsychology, University of Marburg. Samples were kept frozen at -20°C, and on the day of analysis, thawed and centrifuged at 1620 × g for 11 min. Salivary cortisol (sCort, Kirschbaum & Hellhammer, 1994) levels were measured using a commercially available enzyme-linked immunoassay (IBL, Hamburg, Germany). As a measure of ANS activity, salivary alpha-amylase (sAA, Nater & Rohleder, 2009) was extracted from saliva samples using a kinetic colorimetric test and reagents from Roche (Roche Diagnostics, Mannheim, Germany). Inter- and intra-assay variance for both assays was below 10%. Awakening responses were calculated by subtracting the first from the "+30 min" - measurement time point. The CAR refers to a rise in cortisol within 30 to 45 minutes after awakening, while the AAR represents a decline within the same time frame (Nater & Rohleder, 2009; Pruessner, et al., 1997).

For objective measurement of physical activity, participants wore a triaxial wrist actigraph (Somnowatch, Randersacker, Germany) on their non-dominant wrist recording movement counts for every 1-second interval continuously during the 14 days of data collection. Recordings started at 6am on the morning of the first day of measurement and the signal was sampled at 32 Hz with 12 Bit ADC. Participants were instructed to take off the actigraph when bathing, swimming, or taking a shower. As we were interested in everyday-life physical activity in these analyses, night recordings were excluded. The excluded time span was based on the awakening and sleeping times participants reported on their iPods at awakening. Movement counts were aggregated per minute (sum score). Time spans during which the actigraph had obviously not been worn (mean activity count <10/minute) were excluded from analyses. Finally, mean values of the movement sum scores between two measurement time points (awakening until 11am, 11am until 2pm, 2pm until 6pm, 6pm until 9pm, 9pm until sleeping time – considering the actual time participants completed their iPod reports) as well as daily mean scores (awakening until sleeping time) were calculated.

Statistical procedure

As time points were nested within persons, we used hierarchical linear models for statistical analyses, using the HLM program (Raudenbush, et al., 2005). All χ^2 tests for the fatigue outcomes were statistically significant (p<.001); this indicates that there is variance in the outcomes by person, which justifies the use of hierarchical linear modeling. General fatigue, mental fatigue, physical fatigue, movement scores, sCort and sAA values, pain, and stress were considered as level-1 variables. At the person level (level 2), the intercept (β_0) was modeled as a function of BMI, thyroid dysfunction (yes/no), high blood pressure (yes/no), WPI score, and SSCS score. Age did not turn out to be a relevant predictor of any fatigue dimension in our analyses and was thus not included in the analyses. As we collected data at the level of time points within days as well as at a daily level, separate respective analyses were conducted. In these analyses, mean daily values of the different fatigue dimensions were used. As subjective sleep quality was measured once daily, it was included in the analyses at level 1 concerning daily measures and as person mean at level 2 for within-day analyses only. Further, time since awakening was included in within-day analyses at level 1 to account for diurnal patterns of biological parameters, fatigue, and physical activity. As a measure of effect size, we calculated "*Pseudo-R^2 = (σ^2reference model – σ^2final model)/ σ^2reference model*", where the reference model is the final model excluding the predictor in question (Singer & Willett, 2003). Missing data were automatically listwise excluded per measurement time point per person by the HLM program.

Results

Thirty-two women completed the 14 days of assessment, of whom three did not wear actigraphs due to incompatibility with their jobs. Two further data sets had to be excluded because of technical difficulties with the App that was used to collect momentary self-report data, and one data set was excluded because of technical difficulties with the actigraph. Thus, the final sample for the current analyses comprised 26 FMS patients with a mean age of 53 (±7) years. On average, 11 (±4) pain sites, a symptom severity of 8 (±2), and an illness

duration of 10 (±7) years were reported. Table 1 depicts momentary fatigue, pain, and stress mean values across the 14 days of assessment. The compliance rate was 96% (i.e. on average, participants responded to the iPod on 54 out of 56 occasions relevant for the analyses). The intraclass correlation (*ICC)* of general fatigue was 0.39 (mental fatigue: *ICC*=0.29, physical fatigue: *ICC*=0.15), indicating that 61% of the variance in general fatigue (71% in mental fatigue, 85% in physical fatigue) was explained at the level of time points. The course of fatigue dimensions and physical activity throughout the day (mean across 14 days of assessment) can be seen in Figure 1. As mental fatigue and physical fatigue were assessed in an inverted way (as subjective ability to concentrate and subjective physical fitness), positive unstandardized coefficients (UCs) indicate a negative association with the respective construct.

Pain and fatigue levels co-varied within participants, which was true for every fatigue dimension (general fatigue: *Pseudo-R^2*=0.11; mental fatigue: *Pseudo-R^2*=0.09, physical fatigue: *Pseudo-R^2*=0.13, see Table 2). No association was found between momentary sCort value and levels of general fatigue or mental fatigue, but a positive association was found with physical fatigue (see Table 2*, Pseudo-R^2* for physical fatigue: 0.02). This indicates that cortisol levels were higher when patients felt more physically fatigued. On a daily basis, CAR negatively predicted mean daily general fatigue (*UC*=-0.01, *t-ratio*=-2.18, *p*=.039, *Pseudo-R^2*=0.05) as well as mean daily physical fatigue (*UC*=0.00, *t-ratio*=2.08, *p*=.048, *Pseudo-R^2*=0.05), but was not associated with mean daily mental fatigue (*UC*=-0.00, *t-ratio*=-0.10, *p*=.921). SAA activity was neither associated with any fatigue dimension on a momentary basis (general fatigue: *UC*=-0.00, *t-ratio*=-0.98, *p*=.338, mental fatigue: *UC*=0.00, *t-ratio*=0.43, *p*=.671, physical fatigue: *UC*=0.00, *t-ratio*=0.65, *p*=.522), nor was there any association between AAR and any fatigue dimension on a daily basis (general fatigue: *UC*=0.00, *t-ratio*=1.91, *p*=.067; mental fatigue: *UC*=-0.00, *t-ratio*=-0.51, *p*=.618, physical fatigue: *UC*=-0.00, *t-ratio*=-0.06, *p*=.952).

There was no immediate effect of physical activity on any fatigue dimension (see Table 2) or on pain (*UC*=0.01, *t-ratio*=0.617, *p*=.543). However, physical fatigue negatively predicted subsequent physical activity (*UC*=6.67, *t-ratio*=5.49, *p*<.001, *Pseudo-R²*=0.04). Neither general fatigue (*UC*=-0.95, *t-ratio*=-1.28, *p*=.466), nor mental fatigue (*UC*=1.83, *t-ratio*=1.38, *p*=.179), nor pain (*UC*=0.06, *t-ratio*=0.99, *p*=.331) was associated with subsequent physical activity. Results from analyses considering daily measures show that mean daily physical activity levels were associated with higher mean daily general fatigue levels the next day (*UC*=0.00, *t-ratio*=2.35, *p*=.027, *Pseudo-R²*=0.05), and higher physical activity levels were associated with same-day higher stress levels (*UC*=5.38, *t-ratio*=4.62, *p*<.001, *Pseudo-R²*=0.05). However, the interaction effect of mean daily stress x mean daily physical activity on next-day mean daily fatigue was not significant (*UC*=0.00, *t-ratio*=1.29, *p*=.199). Furthermore, neither momentary sCort (*UC*=0.00, *t-ratio*=0.31, *p*=.759) nor momentary sAA values (*UC*=-0.04, *t-ratio*=-0.52, *p*=.611) were associated with physical activity since the last measurement time point. Additionally to table 2, which depicts complete models of momentary fatigue levels, complete models predicting same-day mean associations (including the daily effects of sleep quality) can be accessed in the online supplement.

As an association was found between mean daily physical activity and mean next-day general fatigue as well as between CAR and mean daily general fatigue, it seemed reasonable to expect a mediation of the physical activity – fatigue association by the CAR. However, physical activity did not turn not out to be a predictor of next-day CAR (*UC*=-0.00, *t-ratio*=-0.98, *p*=.339), which is a violation of the 2nd requirement for mediation (Korchmaros & Kenny, 2003). Therefore, the CAR had to be ruled out as mediator between physical activity and fatigue. The predictive effect of mean physical activity on next-day mean general fatigue and the predictive effect of the CAR on mean general fatigue therefore seem to be independent of each other.

Discussion

We found that higher momentary cortisol values were associated with higher immediate physical fatigue in patients with FMS. Additionally, we found evidence that the CAR is a negative predictor of general and physical fatigue. There was no immediate association between physical activity and any of the fatigue dimensions or pain measured on a momentary basis (within days). Mean physical activity level throughout the day, however, positively predicted mean daily general fatigue levels the next day. Neither the CAR nor momentary cortisol values were associated with physical activity. Moreover, there was no association between sAA (either momentary values or AAR) and any fatigue dimension or preceding physical activity.

The finding that a reduced CAR was intra-individually associated with higher fatigue symptoms during the remainder of the day complements research showing a reduced CAR in FMS (Riva, Mork, Westgaard, & Lundberg, 2012) or in other chronically fatigued populations (Powell, et al., 2013). In concert with the association of immediate cortisol values with physical fatigue, this implies that changes in daily HPA axis activity do indeed play an important role in symptom exacerbation in FMS. In contrast, we did not find an association between CAR and pain levels in a recent analysis in the same sample of patients with FMS (Fischer, et al., 2016), indicating a specific effect of changes in CAR on fatigue.

To our knowledge, this is the first investigation of associations between sAA, a rather new marker of autonomic activity, and fatigue symptomatology in patients with FMS. However, our analyses did not show sAA to be a significant predictor of fatigue. Thus, our results imply that diurnal autonomic activation is not associated with increases or decreases in daily fatigue in FMS, which constitutes a valuable addition to current research on the role of ANS activity in FMS symptomatology. Due to the multitude of possible settings, stress measures, and ANS markers, more research is needed to paint a clearer picture of ANS functioning in association with symptom exacerbation in FMS. Future studies will thus have

to include markers of different aspects of the autonomic nervous system to achieve a more comprehensive view.

The null results of HPA or ANS activity being a mediator between physical activity and fatigue levels speak for an independence of the influence of HPA axis activity and physical activity on fatigue on a daily basis. However, this does not automatically imply that there are no long-term effects of physical activity on fatigue that are mediated or moderated by HPA axis or ANS activity. Long-term prospective studies which address these assumptions, combining everyday with laboratory assessments, are lacking.

Our results further suggest that everyday physical activity is not responsible for immediate symptom exacerbation in patients with FMS. On the other hand, our participants seemed to reduce their physical activity when feeling physically fatigued. This finding is in accordance with other studies in chronic pain patients, which showed a decrease in physical activity when higher fatigue was reported (Kop, et al., 2005; Murphy, Alexander, Levoska, & Smith, 2013). Additionally to these studies, our results suggest that the physical fatigue dimension is responsible for the effect on subsequent physical activity, which again underlines the importance of measuring fatigue multidimensionally. The null finding of an association between physical activity and mental fatigue is in line with another recent study (Segura-Jimenez, et al., 2015). The fatigue-enhancing effect of previous-day physical activity must be interpreted in light of the fact that participants reported higher levels of stress on days with increased physical activity. It is therefore conceivable that increased physical activity reflected having a “busy day” as opposed to being physically active as part of leisure activities or exercise. However, as feeling stressed is not a direct measure of “busyness”, this interpretation remains speculative. Nevertheless, from this perspective, our results do not contradict studies showing that patients with FMS benefit from exercise programs (for an overview see Busch, et al., 2008) or that physical activity is negatively associated with longer-term fatigue levels (Segura-Jimenez, et al., 2015). Rather, our findings underline the fact that patients with FMS might find it hard to begin and adhere to exercise programs (e.g.

Schachter, Busch, Peloso, & Sheppard, 2003) in view of physical fatigue experience. Future studies should compare leisure physical activity (or exercise) with everyday life physical activity in the context of work or other obligatory activities in terms of their influence on fatigue in FMS and follow up on the recovery.

Our findings show that different dimensions of fatigue are influenced by different biological and behavioral factors. Specifically, the physical dimension of fatigue was more strongly related to markers of the HPA axis, whereas mental fatigue was associated neither with CAR nor with momentary cortisol. Despite not being a perfect match with our design, Riva and colleagues (2012) also found physical, but not mental, fatigue to be associated with urinary epinephrine levels. It thus seems that experiencing physical fatigue is more strongly related to biological processes than mental fatigue. This implies that patients probably benefit most from interdisciplinary treatment approaches targeting biological and psychological aspects of fatigue. Clearly, more research is needed on this matter.

One major strength of our study is the high ecological validity due to its ambulatory assessment approach. The assessment period of 14 days with five measurements each day produced a sufficiently high number of observations, and enhances statistical power and reliability. Due to these multiple observations, we were able to detect within-individual as well as within-day and between-day associations. Another strength is the objective and continuous assessment of physical activity. Furthermore, analyses were controlled for various potential confounders such as sleep quality or time since awakening. On the other hand, internal validity is always a critical issue in studies using ambulatory assessment designs, because it cannot be completely ruled out that measures are influenced by unassessed variables. Additionally, our sample size of 26 might have led to an underestimation of random effects (Maas & Hox, 2005). A sample size of about 20-30 is, however, well within the range of other studies on patients with FMS using similar designs, whereas a study period of 14 days (resulting in a large sample size at level 1) exceeds those of most comparable studies (e.g. Bellamy, Sothern, & Campbell, 2004; Kop, et al., 2005;

Korszun et al., 2002). Given that we additionally exclusively interpret fixed effects referring to level-1 variables, we are confident about the validity of our findings. Excluding male patients with FMS as well as FMS patients with a comorbid depressive episode reduced the representativeness of our sample. However, these measures were necessary to control for effects of those variables on biological markers.

In sum, we showed that HPA axis activity plays a critical role in fatigue experienced by patients with FMS during their normal daily living. ANS activity did not turn out to be a predictor of any fatigue dimension on a momentary or a daily basis. Furthermore, everyday life physical activity had no immediate effect on fatigue or pain exacerbation. The effects of HPA axis functioning and physical activity were independent of each other (concerning their influence on each other as well as on fatigue). Moreover, the physical fatigue dimension appeared to be more strongly associated with HPA axis functioning, whereas mental fatigue was not. Thus, our recommendation is to include different dimensions of fatigue in future studies, which ideally combine different levels of observation (subjective, behavioral, biological) in a long-term longitudinal design using both ambulatory and laboratory assessment strategies. Health care professionals should now consider the role of physical fatigue when trying to enhance physical activity in patients with FMS.

Acknowledgements

The authors acknowledge funding by the Volkswagen Foundation (AZ.:II/84905). SF and UMN additionally acknowledge funding by the Swiss National Science Foundation (105314 129764/1). We thank the Philipps-Universität Marburg for partial funding of participant reimbursements and biochemical assays (VB1.2-5.45.26.04).

All authors have completed the Unified Competing Interest form and declare that they have no competing interests to report.

References

Bellamy, N., Sothern, R. B., & Campbell, J. (2004). Aspects of diurnal rhythmicity in pain, stiffness, and fatigue in patients with fibromyalgia. *Journal of Rheumatology, 31*(2), 379-389. doi: 0315162X-31-379 [pii]

Busch, A. J., Schachter, C. L., Overend, T. J., Peloso, P. M., & Barber, K. A. (2008). Exercise for fibromyalgia: a systematic review. *Journal of Rheumatology, 35*(6), 1130-1144. doi: 08/13/0512 [pii]

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193-213.

Crofford, L. J., Pillemer, S. R., Kalogeras, K. T., Cash, J. M., Michelson, D., Kling, M. A., . . . Wilder, R. L. (1994). Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis and Rheumatism, 37*(11), 1583-1592.

Doerr, J. M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., . . . Nater, U. M. (2015). Reciprocal relationship between acute stress and acute fatigue in everyday life in a sample of university students. *Biological Psychology, 110*, 42-49. doi: S0301-0511(15)30014-4 [pii] 10.1016/j.biopsycho.2015.06.009

Ericsson, A., Bremell, T., & Mannerkorpi, K. (2013). Usefulness of multiple dimensions of fatigue in fibromyalgia. *Journal of Rehabilitation Medicine, 45*(7), 685-693. doi: 10.2340/16501977-1161

Fischer, S., Doerr, J. M., Strahler, J., Mewes, R., Thieme, K., & Nater, U. M. (2015). Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome-The role of cortisol and alpha-amylase. *Psychoneuroendocrinology, 63*, 68-77. doi: S0306-4530(15)00921-X [pii] 10.1016/j.psyneuen.2015.09.018

Gur, A., Cevik, R., Nas, K., Colpan, L., & Sarac, S. (2004). Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Research and Therapy, 6*(3), R232-238. doi: 10.1186/ar1163 ar1163 [pii]

Kirschbaum, C., & Hellhammer, D. H. (1994). Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology, 19*(4), 313-333. doi: 0306-4530(94)90013-2 [pii]

Kop, W. J., Lyden, A., Berlin, A. A., Ambrose, K., Olsen, C., Gracely, R. H., . . . Clauw, D. J. (2005). Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome. *Arthritis and Rheumatism, 52*(1), 296-303. doi: 10.1002/art.20779

Korchmaros, J. D., & Kenny, D. A. (2003). *Step by step procedure for estimating lower-level mediation in random-effects multilevel models using HLM5*. manuscript. University of Connecticut. Retrieved from http://davidakenny.net/doc/mlm-med-hlm5.pdf

Korszun, A., Young, E. A., Engleberg, N. C., Brucksch, C. B., Greden, J. F., & Crofford, L. A. (2002). Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. *Journal of Psychosomatic Research, 52*(6), 439-443. doi: S0022399901002379 [pii]

Lambin, D. I., Thibault, P., Simmonds, M., Lariviere, C., & Sullivan, M. J. (2011). Repetition-induced activity-related summation of pain in patients with fibromyalgia. *Pain, 152*(6), 1424-1430. doi: 10.1016/j.pain.2011.02.030

S0304-3959(11)00139-4 [pii]

Linnemann, A., Kappert, M. B., Fischer, S., Doerr, J. M., Strahler, J., & Nater, U. M. (2015). The effects of music listening on pain and stress in the daily life of patients with fibromyalgia syndrome. *Front Hum Neurosci, 9*, 434. doi: 10.3389/fnhum.2015.00434

Löwe, B., L., S. R., Zipfel, S., & Herzog, W. (2002). *PHQ-D. Gesundheitsfragebogen für Patienten. Manual Komplettversion und Kurzform* (2nd ed.). Karlsruhe: Pfizer.

Maas, C. J., & Hox, J. J. (2005). Sufficient sample sizes for multilevel modeling. *Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, 1*(3), 86.

Martinez-Lavin, M. (2007). Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Research and Therapy, 9*(4), 216. doi: ar2146 [pii] 10.1186/ar2146

McLean, S. A., Williams, D. A., Harris, R. E., Kop, W. J., Groner, K. H., Ambrose, K., . . . Clauw, D. J. (2005). Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. *Arthritis and Rheumatism, 52*(11), 3660-3669. doi: 10.1002/art.21372

Murphy, S. L., Alexander, N. B., Levoska, M., & Smith, D. M. (2013). Relationship Between Fatigue and Subsequent Physical Activity Among Older Adults With Symptomatic Osteoarthritis. *Arthritis Care & Research, 65*(10), 1617-1624. doi: 10.1002/acr.22030

Nater, U. M., Fischer, S., & Ehlert, U. (2011). Stress as a Pathophysiological Factor in Functional Somatic Syndromes. *Current Psychiatry Reviews, 7*, 152-169.

Nater, U. M., & Rohleder, N. (2009). Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. *Psychoneuroendocrinology, 34*(4), 486-496. doi: S0306-4530(09)00032-8 [pii] 10.1016/j.psyneuen.2009.01.014

Powell, D. J., Liossi, C., Moss-Morris, R., & Schlotz, W. (2013). Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology, 38*(11), 2405-2422. doi: S0306-4530(13)00254-0 [pii] 10.1016/j.psyneuen.2013.07.004

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., . . . Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences, 61*(26), 2539-2549. doi: S0024320597010084 [pii]

Raudenbush, S. W., Bryk, A. S., Cheong, Y. F., & Congdon, R. (2005). *HLM 5. Hierarchal linear and nonlinear modeling*. Chicago, IL: Scientific Software International.

Riva, R., Mork, P. J., Westgaard, R. H., & Lundberg, U. (2012). Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. *Psychoneuroendocrinology, 37*(2), 299-306. doi: S0306-4530(11)00183-1 [pii] 10.1016/j.psyneuen.2011.06.014

Riva, R., Mork, P. J., Westgaard, R. H., Okkenhaug Johansen, T., & Lundberg, U. (2012). Catecholamines and heart rate in female fibromyalgia patients. *Journal of Psychosomatic Research, 72*(1), 51-57. doi: S0022-3999(11)00249-2 [pii] 10.1016/j.jpsychores.2011.09.010

Schachter, C. L., Busch, A. J., Peloso, P. M., & Sheppard, M. S. (2003). Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. *Physical Therapy, 83*(4), 340-358.

Schulz, P., Schlotz, W., & Becker, P. (2004). *TICS Trierer Inventar zum chronischen Stress*. Göttingen: Hogrefe.

Schwarz, R., Krauss, O., & Hinz, A. (2003). Fatigue in the general population. *Onkologie, 26*(2), 140-144. doi: 10.1159/000069834

Segura-Jimenez, V., Borges-Cosic, M., Soriano-Maldonado, A., Estevez-Lopez, F., Alvarez-Gallardo, I. C., Herrador-Colmenero, M., . . . Ruiz, J. R. (2015). Association of sedentary time and physical activity with pain, fatigue, and impact of fibromyalgia: the al-Andalus study. *Scandinavian Journal of Medicine and Science in Sports*. doi: 10.1111/sms.12630

Singer, J. D., & Willett, J. B. (2003). *Applied Longitudinal Data Analysis*. New York: Oxford University Press.

Smets, E. M., Garssen, B., Bonke, B., & De Haes, J. C. (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research, 39*(3), 315-325. doi: 002239999400125O [pii]

Stone, A. A., Broderick, J. E., Porter, L. S., & Kaell, A. T. (1997). The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis Care Res, 10*(3), 185-193.

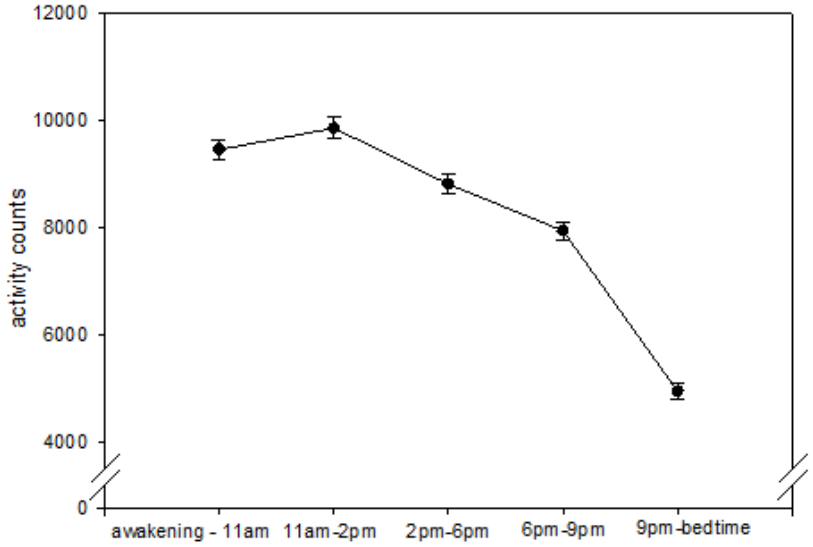
Vincent, A., Benzo, R. P., Whipple, M. O., McAllister, S. J., Erwin, P. J., & Saligan, L. N. (2013). Beyond pain in fibromyalgia: insights into the symptom of fatigue. *Arthritis Research and Therapy, 15*(6), 221. doi: ar4395 [pii] 10.1186/ar4395

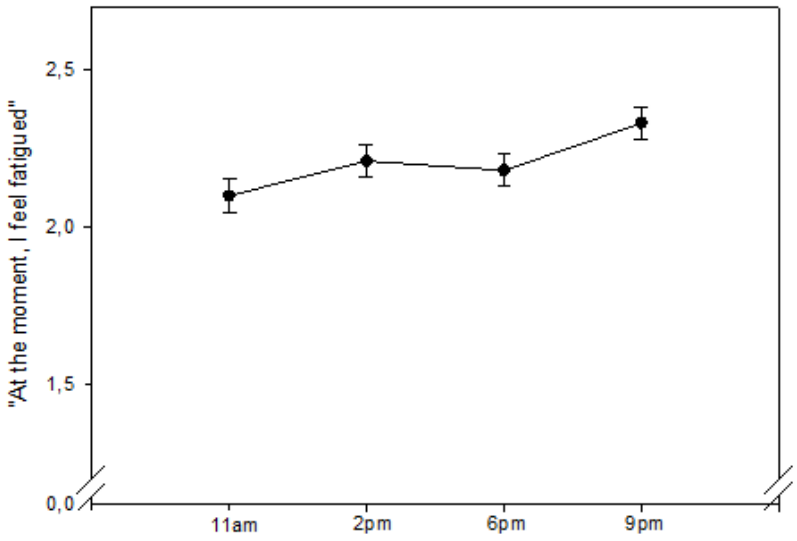
Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Hauser, W., Katz, R. S., . . . Winfield, J. B. (2011). Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol, 38*(6), 1113-1122. doi: 10.3899/jrheum.100594

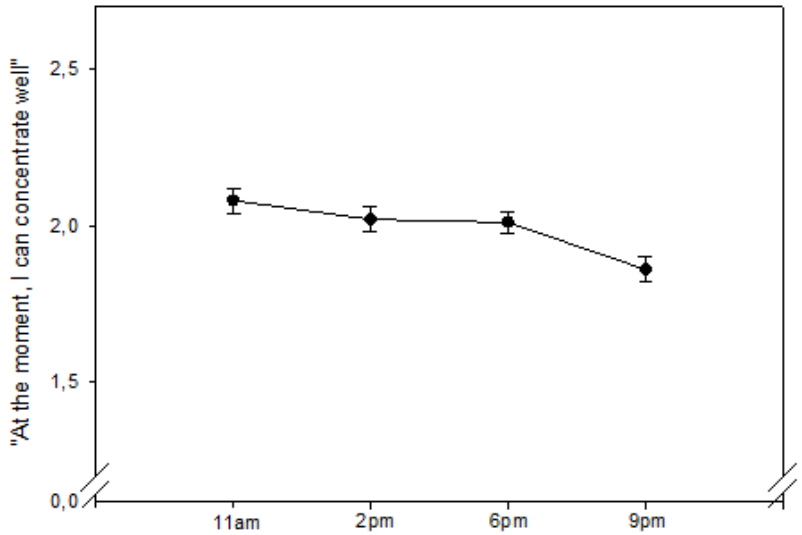
Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken), 62*(5), 600-610. doi: 10.1002/acr.20140

Figure legend

Fig. 1 Daily profiles of physical activity (upper left), general fatigue (upper right), mental fatigue (lower left), and physical fatigue (lower right) averaged across 14 days of measurement (mean ± standard error of mean), N = 26, general, mental, and physical fatigue were assessed on a scale from 0 (not at all) to 4 (very much).


12000
10000
8000
6000
4000
0
activity counts
awakening - 11am
11am-2pm
2pm-6pm
6pm-9pm
9pm-bedtime


2,5
2,0
1,5
0,0
"At the moment, I feel fatigued"
11am
2pm
6pm
9pm


2,5
2,0
1,5
0,0
"At the moment, I can concentrate well"
11am
2pm
6pm
9pm

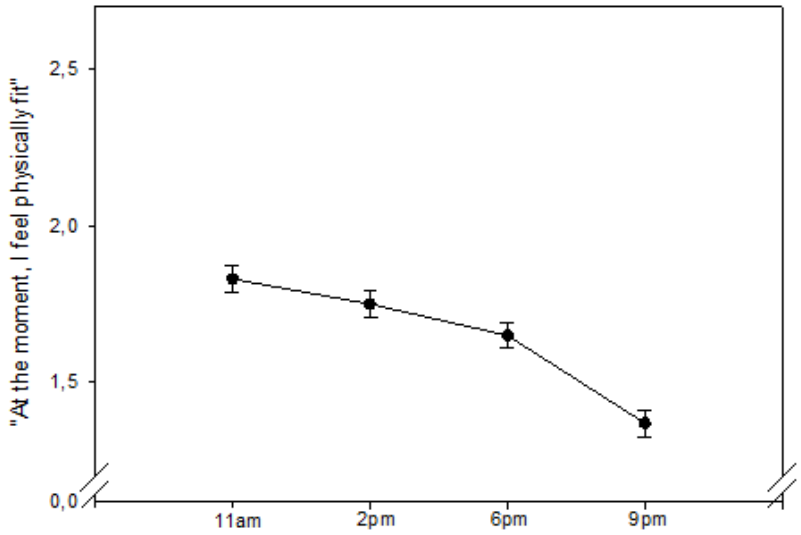

2,5
2,0
1,5
0,0
"At the moment, I feel physically fit"
11am
2pm
6pm
9pm

Table 1

Descriptive analyses of relevant parameters

	M (±SD)
At the moment…	
… I am in this much pain (0-100)	49.59 (±24.79)
… I feel fatigued (0-4)	2.21 (0.98)
… I can concentrate well (0-4)	1.99 (0.74)
… I feel physically fit (0-4)	1.64 (0.80)
… I feel stressed out (0-4)	1.48 (1.04)
"How well did you sleep last night?"	66.02 (23.38)

Note. Mean and standard errors of the items at four measurement time points per day (11am, 2pm, 6pm, 9pm) over 14 days, sleep quality was reported at awakening once daily

Table 2

Hierarchical linear models predicting momentary general, mental, and physical fatigue (N=26) using restricted maximum likelihood.

Outcome	**General fatigue**			**Mental fatigue**			**Physical fatigue**		
fixed effects	*UC*	*SE*	*t-ratio*	*UC*	*SE*	*t-ratio*	*UC*	*SE*	*t-ratio*
intercept	1.98	0.12	16.36***	2.24	0.13	17.43***	2.05	0.13	15.21***
level 2									
• Sleep quality (person mean)	0.00	0.01	0.14	0.01	0.01	1.69	0.00	0.00	0.25
• BMI	0.07	0.02	3.27**	0.03	0.02	1.63	-0.03	0.02	-1.71
• SSCS	0.03	0.01	2.65*	0.01	0.01	0.99	-0.00	0.01	-0.05
• WPI	0.05	0.02	2.59*	-0.02	0.03	-0.64	0.00	0.01	0.26
• Thyroid dysfunction	-0.43	0.13	-3.32**	-0.08	0.15	-0.44	0.03	0.11	0.30
• High blood pressure	0.86	0.12	6.97***	-0.08	0.12	-0.67	0.05	0.25	0.21
level 1									
• time since awakening	0.00	0.00	3.33***	-0.00	0.00	-3.61***	-0.00	0.00	-5.23***
• momentary pain	0.01	0.00	5.65***	-0.01	0.00	-6.86***	-0.02	0.00	-7.78***
• momentary stress	0.26	0.05	5.30***	-0.12	0.02	-4.70***	-0.01	0.03	-0.29
• momentary cortisol	-0.00	0.00	-0.03	-0.01	0.00	-1.89	-0.01	0.01	-2.73*

value									
• physical activity 2-3 hours before measurement	0.00	0.00	0.22	-0.00	0.00	-1.39	-0.00	0.00	-0.88
random effects	*SD*	*VC*	χ^2	*SD*	*VC*	χ^2	*SD*	*VC*	χ^2
Intercept	0.39	0.15	423.97***	0.45	0.20	664.42***	0.37	0.14	391.45***
momentary pain	0.01	0.00	75.29***	0.01	0.00	45.91**	0.01	0.00	50.49**
momentary stress	0.22	0.05	130.49***	0.09	0.01	48.46**	0.11	0.01	47.71**
momentary cortisol level	0.02	0.00	45.59**	0.01	0.00	41.94*	0.02	0.00	48.07**
physical activity	0.00	0.00	26.31	0.00	0.00	29.59	0.00	0.00	21.55

Note. UC: unstandardized coefficients, *SE*= standard error, *SD* = standard deviation, VC = Variance Component, SSCS = Screening Scale for Chronic Stress – Subscale of the Trier Inventory for Chronic Stress, WPI = Widespread Pain Index, CAR = cortisol awakening response; ****p*<.001, ***p*<.01, **p*<.05, for general fatigue, higher values imply a higher level of the construct (a positive association implies an increase in general fatigue with an increase in the respective predictor); for mental and physical fatigue, higher values imply a lower level of the construct (a positive association implies an increase in mental or physical fatigue with a decrease in the respective predictor)

6.5 Zusammenfassung (German summary)

Erschöpfung ist eine alltägliche subjektive Erfahrung, die als Reaktion auf eine mentale oder körperliche Belastung sowie im Laufe eines Tages gegen Abend vermehrt auftritt. Erschöpfung kann als eindimensional oder mehrdimensional (z.B. eine körperliche und eine mentale Qualität umfassend) begriffen werden. Sie deutet dem Organismus, sich zu erholen und erfüllt somit eine wichtige psychobiologische Funktion. Von klinisch bedeutsamer Erschöpfung wird dann gesprochen, wenn die Erschöpfung nur unzureichend durch Erholungsverhalten abgebaut werden kann. Als medizinisch unerklärt gilt sie, wenn kein bekannter somatischer Grund für die Erschöpfung gefunden werden kann. Klinisch bedeutsame, medizinisch nicht erklärte, Erschöpfung bedingt starke funktionale wie emotionale Beeinträchtigungen für die betroffene Person. Weiterhin werden immense Kosten im Gesundheitssystem auf Erschöpfungszustände zurückgeführt. Es liegen verschiedene Definitionen, Klassifikations-Richtlinien, und Bezeichnungen für Syndrome vor, deren Hauptsymptom medizinisch unerklärte Erschöpfung ist.

In Form eines Übersichtsartikels wurde daher zunächst ein Überblick über die prominentesten Beispiele von Definitionen von Erschöpfungssyndromen (Neurasthenie, das chronische Erschöpfungssyndrom und Burnout) erstellt (Doerr & Nater, 2013). Außerdem wurde in diesem Artikel die Abgrenzung der Syndrome zu Depression diskutiert. Der Übersichtsartikel schlussfolgert, dass die Syndrome in der Tat in ihren Kriterien stark überlappend und daher nicht sinnvoll voneinander abzugrenzen sind. Im Hinblick auf Depression liegen allerdings nicht-überschneidende Symptome vor, die eine Abgrenzung ermöglichen. Vor allem sollte Wert auf eine gründliche Ausschluss-Diagnostik gelegt und die Funktionalität der Begriffe reflektiert werden, bevor sie Verwendung finden.

Es scheint von besonderer Bedeutung, herauszufinden, wie das Symptom Erschöpfung entsteht und welche Mechanismen zu klinisch bedeutsamer, medizinisch unerklärter Erschöpfung führen. Ein solcher Mechanismus könnte „Stress“ sein, der als eine psycho- (sich „gestresst“ fühlen) biologische (Aktivierung des Körpers) Reaktion auf eine

Anforderung, die von der individuellen Person als bedrohlich erlebt wird, definiert ist. Als wichtigste Stress-responsive biologische Systeme gelten die Hypothalamus-Hypophysen-Nebennierenrinden-Achse (HHNA) sowie das Autonome Nervensystem (ANS).

Ziel der empirischen Untersuchungen, die in dieser Dissertation zusammengefasst sind, war es, den Zusammenhang zwischen Stress und Erschöpfung sowie interagierenden Faktoren auf biologischer Ebene (Aktivität der HHNA und des ANS), subjektiver Erlebens-Ebene (Schlafqualität als Zeichen für Erholung), sozialer Ebene (Partner), sowie behavioraler Ebene (körperliche Aktivität) im Alltag zu untersuchen. Hierfür wurden Studien in Ambulanten Assessment-Designs (Erhebungen von Daten im Alltag von Personen) durchgeführt, um eine direkte Überführbarkeit der Ergebnisse auf Alltags-Situationen zu gewährleisten. In allen Studien wurden die subjektiven Angaben der Probanden zu mehreren Messzeitpunkten täglich über mehrere Tage hinweg jeweils mit Hilfe von Eingaben in iPod touchs® erfasst. Biologische Parameter wurden mit Hilfe von Speichelproben ermittelt, die zu den gleichen Messzeitpunkten gesammelt wurden, und aus denen Cortisol als Marker der HHNA-Aktivität und Alpha-Amylase als Marker der ANS-Aktivität extrahiert wurden.

Die erste Studie überprüfte die mögliche Reziprozität von Stress und Erschöpfung sowie die Mediation des Zusammenhangs von Stress und Erschöpfung durch Schlafqualität oder HHNA- und ANS-Aktivität. Die Erhebung fand in einer Studierenden-Stichprobe in zwei unterschiedlichen Phasen (zu Beginn des Semesters sowie in der Prüfungsvorbereitung) statt. Die Reziprozität von Stress und Erschöpfung sowie die Mediation des Zusammenhangs von Stress am Vortag und Erschöpfung am nächsten Tag über Einschränkungen in der Schlafqualität bestätigten sich. Es fanden sich keine Hinweise auf eine Mediation des Zusammenhangs von Stress und Erschöpfung über die Aktivität der HHNA oder des ANS.

In der zweiten Studie wurde in einer Stichprobe aus Paaren (Doerr, Nater, Spoerri, Ehlert, & Ditzen, ready to be submitted) die Annahme überprüft, dass sich die alltägliche Erschöpfung abhängig von Einflüssen des Partners zeigt. So wurde von den Paaren eine

geringere Erschöpfung angegeben, je positiver die Interaktion mit dem Partner eingeschätzt wurde. Weiterhin konnte die Annahme, dass Erschöpfung, Stress, und der Ausstoß von Cortisol bei Paaren co-reguliert sind (also in positiver Abhängigkeit von den jeweiligen momentanen Werten des Partners stehen), bestätigt werden. Eine Co-Regulation der Alpha-Amylase-Werte mit denen des Partners zeigte sich nur bei Frauen.

Die dritte Studie (Doerr, Fischer, Nater, & Strahler, under review) umfasste eine Stichprobe aus Fibromyalgie-Patientinnen (die neben chronischen Schmerzen auch von klinisch bedeutsamer Erschöpfung betroffen sind). Neben den subjektiven Angaben und den biologischen Werten wurde hier zusätzlich die Bewegungsmessung mit Hilfe von Aktigraphie in die Analysen einbezogen. Es zeigte sich eine Vorhersage täglicher (genereller und körperlicher) Erschöpfung durch die Cortisol-Aufwachreaktion am morgen. Weiterhin hing momentane körperliche Erschöpfung mit erhöhten Cortisol-Werten zusammen. Körperliche Aktivität des Vortags zeigte einen Zusammenhang mit Erschöpfung am Folgetag, der jedoch nicht über Cortisol oder Alpha-Amylase-Werte mediiert wurde. Weiterhin zeigte sich momentane Erschöpfung unabhängig von vorausgehender körperlicher Aktivität. Körperliche Erschöpfung sagte jedoch anschließende körperliche Aktivität negativ vorher.

Als Schlussfolgerung lässt sich festhalten, dass Stress alltägliche Erschöpfung vorhersagt (was vor allem in der ersten Studie deutlich wird). Die Reziprozität dieser Beziehung sollte in zukünftigen Studien näher untersucht werden. Als wichtiger vermittelnder Mechanismus zwischen Stress und Erschöpfung von einem Tag auf den anderen stellte sich Schlaqualität heraus. In keiner Studie fanden sich Hinweise auf eine Mediation des Zusammenhangs von Stress und Erschöpfung über Veränderungen in der Aktivität der HHNA oder des ANS auf momentaner oder täglicher Ebene. Dies schließt jedoch nicht aus, dass sich, durch Stress verursachte, langfristigere Veränderungen in der Aktivität dieser Systeme auf Erschöpfung auswirken. Hinweise auf diese Annahme finden sich (bzgl. der HHNA) in der dritten Studie. Es sollten sich Studien anschließen, die einen längeren Zeitraum (Monate bis Jahre) umfassen. Bezüglich möglicher Interventions- und

Präventionsansätze scheint der Einsatz von Stress-Management-Techniken, inklusive einer Erhöhung der Schlafhygiene, sowie der Einbezug des Partners/ der Partnerin (sofern vorhanden) von herausragender Bedeutung. Weiterhin sollten Interventionen, die auf die Erhöhung von körperlicher Aktivität bei chronisch erschöpften Personen abzielen, diese auf einen möglichen kurzfristigen Anstieg von Erschöpfung psychoedukativ vorbereiten.

6.6 Content of supplementary CD

A:	online supplement of study 1: list of equations
B:	online supplement of study 2 (tables): overview of the full models of co-regulation of stress, cortisol, and salivary alpha-amylase
C:	online supplement of study 3 (table): overview of full models of same-day mean associations (including the daily effects of sleep quality)

6.7 Curriculum Vitae

6.8 Publication List

First author

Doerr, J.M., Nater, U.M., & Ditzen, B. (to be submitted). Co-Regulation of Fatigue and Biopsychological Stress in Couples.

Doerr, J.M., Fischer, S., Nater, U.M., & Strahler, J. (under review). Influence of stress systems and physical activity on different dimensions of fatigue in a sample of fibromyalgia patients. *Journal of Psychosomatic Research*.

Doerr, J.M., Ditzen, B., Strahler, J., Linnemann, A., Ziemek, J., Skoluda, N., Hoppmann, C.A., & Nater, U.M. (2015). Reciprocal relationship between acute stress and acute fatigue in everyday life of university students. *Biological Psychology,* 110, 42-90.

Doerr, J.M. & Nater, U.M. (2013). Erschöpfungssyndrome – Eine Diskussion verschiedener Begriffe, Definitionsansätze und klassifikatorischer Konzepte. [Fatigue syndromes – a discussion of terms, definitions and classifications]. *Psychotherapie, Psychosomatik, Medizinische Psychologie,* 63, 69-76.

Co-author

Jopp, D.S., **Doerr, J.M.**, Chajewski, M., Lin., J.-M.S., Reeves, W.C., & Nater, U.M. (in revision). Patterns of Control Beliefs in Chronic Fatigue Syndrome: results of a population-based survey. *BMC psychology*.

Strahler, J., **Doerr, J.M.**, Ditzen, B., Linnemann, A., Skoluda, N, & Nater, U.M. (submitted). Physical activity buffers fatigue only under low-stress conditions. *Stress*.

Klaus, K., Fischer, S., **Doerr, J.M.**, Nater, U.M., & Mewes, R. (submitted). Classifying Fibromyalgia as a Mental Disorder? – An Ambulatory Assessment Study. *European Journal of Pain*.

Fischer, S., **Doerr, J.M.**, Strahler, J., Mewes, R., Thieme, K., & Nater, U.M. (2016). Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome – The role of cortisol and alpha-amylase. *Psychoneuroendocrinology*, 63, 68-77.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.**, & Nater, U.M. (2015). Music listening as a means of stress reduction in daily life. *Psychoneuroendocrinology*, 60(0), 82-90.

Linnemann, A., Kappert, M.B., Fischer, S., **Doerr, J.M.**, Strahler, J., & Nater, U.M. (2015). The effects of music listening on pain and stress in the daily life of patients with fibromyalgia syndrome. *Frontiers in Human Neuroscience*, 9, 434.

Nater, U.M. & **Doerr, J.M.** (2012). Cortisol and fatigue. In A. Esposito & V. Bianchi (Eds.), *Cortisol: Physiology, Regulation, and Health Implications* (pp.107-118). Happauge, NY: Nova Science Publishers.

Bodden, M. & **Doerr, J.M.** (2010). Sozial-kognitive Leistungen bei Patienten mit REM-Schlaf-Verhaltensstörung. [Social-cognitive performance of REM sleep behavior disorder patients] *MedReview,* 13, 8-9.

Published abstracts – first author

Doerr, J.M., Fischer, S., Strahler, J., & Nater, U.M. (2015). Everyday life influences of neuroendocrine and physical activity on fatigue in fibromyalgia patients. *Psychosomatic Medicine,77*(3), A47-48.

Doerr, J.M., Nater, U.M., & Ditzen, B. (2015). Positive couple interaction reduces stress and fatigue. *Psychosomatic Medicine,77*(3), A104.

Doerr, J.M., Strahler, J., Fischer, S., & Nater, U.M. (2014). Acute stress influences momentary pain in women suffering from fibromyalgia. *International Journal of Behavioral Medicine, 21 (Suppl. 1),* S134.

Doerr, J.M., Ditzen, B., Strahler, J., & Nater, U.M. (2013). Effect of previous-day stress levels on cognitive dimensions of fatigue. *Psychosomatic Medicine*, *75(3)*, A20-21.

Published abstracts – co-author

Fischer, S., **Doerr, J.M.**, Strahler, J., & Nater, U.M. (2015). Stress exacerbates pain in the everyday lives of women with fibromyalgia – the role of cortisol and alpha-amylase. *Psychosomatic Medicine,77*(3), A81-82.

Strahler, J., Fischer, S., **Doerr, J.M.,** & Nater, U.M. (2014). Relationships between momentary stress, neuroendocrine stress markers, and symptoms in patients with fibromyalgia. *Psychosomatic Medicine,76*(3), A-121.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.,** & Nater, U.M. (2014) Music Listening Reduces Stress in Daily Life - A Psychobiological Perspective. *Psychosomatic Medicine, 76,* A82.

Linnemann, A., Ditzen, B., Strahler,J., **Doerr, J.M.**, & Nater, U. M. (2014). Listening to Music is Good for your Health - Findings from two Momentary Assessment Studies. *International Journal of Behavioral Medicine*, 21(Suppl. 1), S210-211.

Strahler, J., Linnemann, A., Ditzen, B., **Doerr, J.M.**, Skoluda, N., & Nater, U.M. (2014). Effekte von physischer Aktivität und Musikhören auf das subjektive Befinden: Neuroendokrine Mechanismen. [Effects of physical activity and music listening on subjective well-being.] in Frank, R., Nixdorf, I., Ehrlenspiel, F., Geipel, A., Mornell, A., & Beckmann, J. *Performing Under Pressure. Schriften der Deutschen Vereinigung für Sportwissenschaft*. *Band 234*. Deutsche Vereinigung für Sportwissenschaft (Ed.). Hamburg: Feldhaus Verlag.

Strahler, J., Ditzen, B., **Doerr, J.M.,** & Nater, U.M. (2013). Stress-induced elevations of fatigue are associated with physical activity: physical activity as a buffer of stress. *Psychosomatic Medicine*, 75(3), A33.

Markert, C., **Doerr, J.M.**, Fischer, S., Tepe, A., Sanchez, L., & Nater, U.M. (2013). Beeinflusst Stress das alltägliche Schmerzerleben von Frauen mit Fibromyalgie? [Does stress exert its influence on daily pain experiences in women with fibromyalgia?]. *Verhaltenstherapie und Verhaltensmedizin*, 34(Suppl. 1), 19.

Strahler, J., Ditzen, B., **Doerr, J.M.**, Skoluda, N., & Nater, U.M. (2013). Der stresspuffernde Effekt physischer Aktivität auf das subjektive Befinden: Neuroendokrine Mechanismen. [The stress buffering effect of physical activity: neuroendocrine mechanisms].*Verhaltenstherapie und Verhaltensmedizin*, 34(Suppl. 1), 55-56.

Conference presentations

First author

Doerr, J.M., Strahler, J., Fischer, S., Skoluda, N., Linnemann, A., & Nater, U.M. (2015). Der Einfluss von Stress auf Erschöpfung im Alltag [The influence of stress on fatigue in everyday life]. Talk given at the 12th conference of the German Society for Health Psychology (DGPs), Graz, Austria.

Doerr, J.M., Fischer, S., Strahler, J., & Nater, U.M. (2015). Everyday life influences of neuroendocrine and physical activity on fatigue in fibromyalgia patients. Poster presented at the 73rd annual scientific meeting of the American Psychosomatic Society (APS), Savannah, USA.

Doerr, J.M., Nater, U.M., & Ditzen, B. (2015). Positive couple interaction reduces stress and fatigue. Poster presented at the 73rd annual scientific meeting of the American Psychosomatic Society (APS), Savannah, USA.

Doerr, J.M., Strahler, J., Fischer, S., & Nater, U.M. (2014). Acute stress influences momentary pain in women suffering from fibromyalgia. Talk given at the 13th International Congress of Behavioral Medicine (ICBM), Groningen, Netherlands.

Doerr, J.M., Strahler, J., Fischer, S., & Nater, U.M. (2014). Der Effekt von akutem Stress im Alltag auf das Schmerzerleben bei Patientinnen mit Fibromyalgie [The effect of acute stress on pain experience in the everyday life of female fibromyalgia patients]. Poster presented at the 32nd symposium of the German Society for Clinical Psychology and Psychotherapy (DGPs), Braunschweig, Germany.

Doerr, J.M., Ditzen, B., Strahler, J., & Nater, U.M. (2013). Effect of previous-day stress levels on mental fatigue and reduced motivation. Talk given at the 3rd conference of the Society for Ambulatory Assessment (SAA), Amsterdam, Netherlands.

Doerr, J.M., Ditzen, B., Strahler, J., & Nater, U.M. (2013). Effect of previous-day stress levels on cognitive dimensions of fatigue. Talk given at the 71st annual scientific meeting of the American Psychosomatic Society (APS), Miami, USA.

Doerr, J.M.*, Fischer, S.*, Strahler, J., & Nater, U.M. (2013). Stress und Schmerz: Eine psychobiologische Untersuchung im Alltag von Patientinnen mit Fibromyalgie. [Stress and pain: a psychobiological assessment during everyday lives of fibromyalgia patients]. Poster presented at the 15th yearly conference of the German society for psychological pain therapy and research (DGPSF), Marburg, Germany. *shared first authorship

Doerr, J.M., Thoma, M.V., Ehlert, U., & Nater, U.M (2012). Psychological stress levels and autonomic activity in everyday life predict stress responses in the cold pressor test. Poster presented at the 70th annual scientific meeting of the American Psychosomatic Society (APS), Athens, Greece.

Doerr, J.M., Thoma, M.V., Ehlert, U. & Nater, U.M. (2012). Psychologisches Stressniveau und autonome Aktivität im Alltag sagen Reaktivität auf den “Cold Pressor Test” vorher [Stress reactivity in the “cold pressor test” is predicted by psychological stress level and autonomic activity in everyday life]. Poster presented at the 38th Annual Meeting „Psychologie und Gehirn“ of the DGPA and DGPs, June 19.-21, Jena, Germany.

Doerr, J.M., Bodden, M., Unger, M., Möller, C., Mayer, G., Stiasny-Kolster, K., Kalbe, E., Dodel, R., & Oertel, W.H. “Theory of Mind – Leistungen bei Patienten mit REM-Schlaf-Verhaltensstörung [Theory of Mind abilities in patients with REM sleep behavior disorder]” (2010). Poster presented at the yearly conference of the German neurological society (DGN), Mannheim, Germany.

Co-author

Linnemann, A., Kappert, M.B., Fischer, S., **Doerr, J.M.**, Strahler, J., & Nater, U.M. (2015). Can Music Ease the Pain? – Eine Untersuchung der schmerzreduzierenden Wirkung von Musikhören im Alltag bei Patientinnen mit Fibromyalgie [Can Music Ease the Pain? A study on the pain reducing effects of listening to music in the daily life of patients with fibromyalgia syndrome]. Talk given at the yearly conference of the German society for music psychology (DGM) in Oldenburg, Germany.

Fischer, S., **Doerr, J.M.**, Strahler, J., & Nater, U.M. (2015). Stress exacerbates pain in the everyday lives of women with fibromyalgia – the role of cortisol and alpha-amylase. Talk given at the 73rd annual scientific meeting of the American Psychosomatic Society (APS), Savannah, USA.

Linnemann, A., Ditzen, B., Strahler,J., **Doerr, J.M.**, & Nater, U.M. (2014). Listening to Music is Good for your Health - Findings from two Momentary Assessment Studies. Talk given at the 13th International Congress of Behavioral Medicine, Groningen, The Netherlands.

Klaus, K., **Doerr, J. M.**, Fischer, S., Nater, U. M., & Mewes, R. (2014). Psychologische Somatisierungssymptome bei Patientinnen mit Fibromyalgie: Eine ambulante Assessement-Studie [Psychological symptoms of somatization in fibromyalgia patientes: an ambulatory assessment study]. Poster presented at the 32nd symposium of the German Society for Clinical Psychology and Psychotherapy (DGPs), Braunschweig, Germany.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.**, & Nater, U.M. (2014). Musikhören reduziert Stress im Alltag - Befunde von zwei ambulanten Assessment-Studien [Music Listening Reduces Stress in Daily Life - Findings from Two Ambulatory Assessment Studies]. Poster presented at the 32nd symposium of the German Society for Clinical Psychology and Psychotherapy (DGPs), Braunschweig, Germany.

Strahler, J., Fischer, S., **Doerr, J.M.,** & Nater, U.M. (2014). Relationships between momentary stress, neuroendocrine stress markers, and symptoms in patients with fibromyalgia. Poster presented at the 72nd Annual Meeting of the American Psychosomatic Society, San Francisco, CA, USA.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.**, & Nater, U.M. (2014). Music Listening Reduces Stress in Daily Life - A Psychobiological Perspective. Poster presented at the 72nd Annual Meeting of the American Psychosomatic Society, San Francisco, CA, USA**.**

Strahler, J., Linnemann, A., Ditzen, B., **Doerr, J.M.**, Skoluda, N., & Nater, U.M. (2014). Stressreduzierende Effekte von Musikhören im Alltag: Neuroendokrine Mechanismen [Stress buffering effect of music listening in daily life: neuroendocrine mechanisms]. Poster presented at the 40. Annual Meeting „Psychologie und Gehirn“ of the DGPA and DGPs, June 19.-21, Luebeck, Germany.

Markert, C., **Doerr, J.M.**, Fischer, S., Tepe, A., Sanchez, L., & Nater, U.M. (2013). Beeinflusst Stress das alltägliche Schmerzerleben von Frauen mit Fibromyalgie [Does stress have an impact on daily pain experiences in women with fibromyalgia]? Talk given at the 14th Annual Meeting of the German Society for Behavioral Medicine and Behavior Modification (DGVM), Prien am Chiemsee, Germany.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.,** & Nater, U.M. (2013). Music as a Means of Stress Reduction in Daily Life – An Ambulatory Assessment Study among Students. Poster presented at the 3. International Conference on Music and Emotion in Jyväskylä, Finland.

Linnemann, A., Ditzen, B., Strahler, J., **Doerr, J.M.,** & Nater, U.M. (2013). Musik und Stress im Alltag – Wie kann Musik effektiv zur Stressbewältigung eingesetzt werden? [Music and Stress in Daily Life - How music can be effectively employed for stress reduction purposes] Talk given at the yearly conference of German society for music psychology (DGM) in Frankfurt a.M., Germany.

Skoluda, N**.**, **Doerr, J.M.**, Thoma, M. V., Ehlert, U. & Nater, U. M. (2012). Psychological stress levels and autonomic activity in everyday life are related to stress responses in the laboratory. Poster presented at the 42nd International Society of Psychoneuroendocrinology, New York, USA.

Skoluda, N**.**, **Doerr, J.M.**, Thoma, M. V., Ehlert, U. & Nater, U. M. (2012). Positive associations between stress experienced in everyday life and in the laboratory. Poster presented at the 12th International Congress of Behavioral Medicine, Budapest, Hungary.

Strahler, J., Skoluda, N., **Doerr, J.M.**, & Nater, U.M. (2012). How Stress gets in the Body - A Psychobiological Approach to the Pathophysiology of Chronic Fatigue. Poster presented at the "Tag der Wissenschaft" of the Graduate Center for Life- and Natural Sciences at the University of Marburg, February 17, Marburg, Germany.

6.9 Eidesstattliche Erklärung (Declaration of Academic Honesty)

Ich versichere, dass ich meine Dissertation

„Mechanisms of Fatigue in Everyday Life“

selbständig, ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderer als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg, 26. Februar 2016

_____

Johanna M. Dörr