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 Zieme a, Nadine Skoluda a, Christiane A. Hoppmann a, 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.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Stress is associated with numerous bodily complaints, such as fatigue—a very common symptom in the general population (Nijolde, 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, & Hinze, 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 & Thorsteinson, 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_ziemenk@web.de (J. Ziemenk), 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/© 2015 Elsevier B.V. All rights reserved.
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., Aksterstedt, 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 (Aksterstedt et al., 2012). Furthermore, subjective sleep quality has also been found to be a predictor of fatigue (Aksterstedt 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 Schlottz (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, 1998). In an intra-individual comparison, Dahlgren, Kecklund, and Akerstedt (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, Karlsson, 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 Cacippio (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, Ehler, & 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, C. 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.
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 SalıCap® (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 Korcharos & 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{ reference model}} - \sigma^2_{\text{ final model}})/\sigma^2_{\text{ reference model}}”, where the reference model is the final model excluding the predictor in question, based on suggestions by Singer & 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 Korcharos and Kenny (Kenny, Korcharos, & Bolger, 2003; Korcharos & Kenny, 2003).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive analyses of relevant parameters.</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>M (SD)</td>
</tr>
<tr>
<td>Control condition</td>
</tr>
<tr>
<td>Item “At the moment, I feel fatigued”</td>
</tr>
<tr>
<td>Item “At the moment, I feel stressed out”</td>
</tr>
<tr>
<td>Item “How well did you sleep last night?”</td>
</tr>
<tr>
<td>MFI general fatigue</td>
</tr>
<tr>
<td>MFI physical fatigue</td>
</tr>
<tr>
<td>MFI reduced motivation</td>
</tr>
<tr>
<td>MFI reduced activity</td>
</tr>
<tr>
<td>MFI mental fatigue</td>
</tr>
</tbody>
</table>

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.
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-$R^2 = 0.08$).

Table 2

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Model 1a</th>
<th>Model 1a.1</th>
<th>Model 1b</th>
<th>Model 1b.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>UC</td>
<td>SE</td>
<td>t-ratio</td>
<td>UC</td>
</tr>
<tr>
<td>Level 2</td>
<td>2.40</td>
<td>0.12</td>
<td>19.75***</td>
<td>2.29</td>
</tr>
<tr>
<td>Sex</td>
<td>0.29</td>
<td>0.15</td>
<td>1.92</td>
<td>0.29</td>
</tr>
<tr>
<td>Level 1</td>
<td>0.26</td>
<td>0.04</td>
<td>6.29***</td>
<td>0.22</td>
</tr>
<tr>
<td>Momentary stress</td>
<td>0.18</td>
<td>0.09</td>
<td>1.96</td>
<td>0.01</td>
</tr>
<tr>
<td>Cond. × momentary stress</td>
<td>0.01</td>
<td>0.05</td>
<td>0.26</td>
<td>0.15</td>
</tr>
<tr>
<td>Stress at previous t.p.</td>
<td>0.51</td>
<td>0.26</td>
<td>694.74***</td>
<td>0.55</td>
</tr>
<tr>
<td>Cond. × stress at previous t.p.</td>
<td>0.24</td>
<td>0.06</td>
<td>186.43***</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Random effects

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Model 1a</th>
<th>Model 1a.1</th>
<th>Model 1b</th>
<th>Model 1b.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.51</td>
<td>0.26</td>
<td>694.74***</td>
<td>0.55</td>
</tr>
<tr>
<td>Momentary stress</td>
<td>0.24</td>
<td>0.06</td>
<td>186.43***</td>
<td>0.23</td>
</tr>
<tr>
<td>Cond. × momentary stress</td>
<td>0.44</td>
<td>0.20</td>
<td>76.94</td>
<td>0.44</td>
</tr>
<tr>
<td>Stress at previous t.p.</td>
<td>0.10</td>
<td>0.01</td>
<td>42.46</td>
<td>0.15</td>
</tr>
<tr>
<td>Cond. × stress at previous t.p.</td>
<td>0.14</td>
<td>0.02</td>
<td>49.11</td>
<td>0.14</td>
</tr>
</tbody>
</table>

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).

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

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Model 2a</th>
<th>t-Ratio</th>
<th>Model 2a.1</th>
<th>t-Ratio</th>
<th>Model 2b</th>
<th>t-Ratio</th>
<th>Model 2b.1</th>
<th>t-Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>UC</td>
<td>SE</td>
<td>1.14</td>
<td>0.11</td>
<td>10.38***</td>
<td>0.93</td>
<td>0.11</td>
<td>8.37***</td>
</tr>
<tr>
<td>Level 2</td>
<td></td>
<td></td>
<td>0.16</td>
<td>0.14</td>
<td>1.20</td>
<td>0.12</td>
<td>0.13</td>
<td>0.94</td>
</tr>
<tr>
<td>Level 3</td>
<td></td>
<td></td>
<td>0.25</td>
<td>0.04</td>
<td>6.04***</td>
<td>0.16</td>
<td>0.04</td>
<td>3.90***</td>
</tr>
<tr>
<td>Momentary fatigue Condition</td>
<td></td>
<td></td>
<td>0.45</td>
<td>0.14</td>
<td>3.25**</td>
<td>0.23</td>
<td>0.04</td>
<td>5.73***</td>
</tr>
<tr>
<td>Con. x momentary fatigue</td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.05</td>
<td>0.36</td>
<td>0.46</td>
<td>0.16</td>
<td>2.89**</td>
</tr>
<tr>
<td>Fatigue at previous t.p.</td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.03</td>
<td>2.67*</td>
<td>0.09</td>
<td>0.04</td>
<td>2.33*</td>
</tr>
<tr>
<td>Con. x fatigue at previous t.p.</td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.05</td>
<td>0.23</td>
<td>0.13</td>
<td>0.02</td>
<td>0.58*</td>
</tr>
</tbody>
</table>

Random effects

<table>
<thead>
<tr>
<th>SD</th>
<th>VC</th>
<th>χ²</th>
<th>SD</th>
<th>VC</th>
<th>χ²</th>
<th>SD</th>
<th>VC</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.49</td>
<td>0.24</td>
<td>686.44***</td>
<td>0.50</td>
<td>0.25</td>
<td>400.72***</td>
<td>0.48</td>
<td>0.23</td>
<td>426.13***</td>
</tr>
<tr>
<td>0.26</td>
<td>0.07</td>
<td>220.90***</td>
<td>0.23</td>
<td>0.05</td>
<td>123.25***</td>
<td>0.19</td>
<td>0.04</td>
<td>91.45***</td>
</tr>
<tr>
<td>0.18</td>
<td>0.03</td>
<td>66.18</td>
<td>0.12</td>
<td>0.01</td>
<td>58.36</td>
<td>0.59</td>
<td>0.35</td>
<td>57.41</td>
</tr>
<tr>
<td>0.13</td>
<td>0.02</td>
<td>58.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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).

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-R² = 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-R² = 0.04; see Fig. 3C). This implies that the association between fatigue and morning cortisol levels 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-R² = 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-R² = 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...
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, Härnä, & 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.

![Fig. 3. Difference in (A) fatigue level, (B) stress level, (C) cortisol level, and (D) salivary alpha amylase level between control and exam condition.](image)
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, Ehler, & 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 (Elö, Leppänen, & Jähkola, 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 Philips-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


