Stress in Healthy Young Women: Psychophysiological Stress Response and Sleep in the Context of Adverse Childhood Experiences and Daily Stress

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Declaration of Independence

The submitted articles in partial fulfilment of the requirements for the degree of Doctor of Philosophy were written in collaboration with the mentioned co-authors. Three original articles were produced. Neither the author, co-authors nor any other persons published the articles elsewhere. All citations are indicated and only the tools cited were used.

For the purpose of the cumulative dissertation, the following papers have been submitted for publication in various journals. Copies of the articles are found in the appendix:

Article 1:

Winzeler, K., Voellmin, A., Schaefer, V., Meyer, A. H., Cajochen, C., Wilhelm, F. H., & Bader, K. (2014). Daily stress, presleep arousal, and sleep in healthy young women: a daily life computerized sleep diary and actigraphy study. *Sleep Medicine, 15(3)*, 359-366.

Article 2:

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Article 3:

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Abstract

The aim of the present dissertation is to contribute to the knowledge about different aspects of stress and their impact on healthy young women. The relationship between daily stress, presleep arousal, and sleep was investigated and additionally, the association between adverse childhood experiences (ACEs) and psychophysiological stress response was analysed.

Daily stress and prelseep arousal are well-known factors in the development of sleep disturbances and insomnia. The article *daily stress, presleep arousal, and sleep in healthy young women: a daily life computerized sleep diary and actigraphy study* aimed to further elucidate the mediating role of presleep arousal in the relationship between daily stress and sleep. Subjective sleep quality and actigraphic sleep efficiency were investigated both within- and between-participants. Multilevel modelling was applied on electronically assessed data comprising 14 consecutive nights in 145 healthy young women. The relationship between daily stress and worsened subjective sleep quality was mediated by somatic arousal on the between-participant level, and by cognitive arousal on the within-participants level. Unexpectedly, healthy young women showed higher actigraphic sleep efficiency following days with above average stress and somatic arousal. It was concluded, that healthy young women might even be able to compensate for days with above average levels of stress and arousal, which suggests further exploration of the mechanism causing this potentially adaptive regulation.

ACEs have been associated with alterations of psychobiological stress systems and various negative health outcomes. Studies on healthy participants are still scarce, however, attenuated endocrine and cardiovascular stress reactivity in relation to childhood adversity has been observed. Therefore, the article *blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity* aimed to replicate the attenuated endocrine and cardiovascular stress reactivity in association with ACEs in 104 healthy young women. Furthermore, the association between stress reactivity and duration, as well as age of occurrence of ACEs was investigated. Participants underwent psychosocial stress testing and free saliva cortisol and heart rate were assessed. Results confirmed that a higher number of ACEs was associated with a blunted endocrine and cardiovascular stress response to the psychosocial stress task, and that especially longer duration and occurrence before menarche of ACEs were significantly associated with attenuated cortisol response. It was concluded that ACEs, particularly if they occurred repeatedly or chronically, show an association with blunted stress reactivity in healthy young women.

The article *adverse childhood experiences are associated with blunted sympathetic stress responsivity in healthy young women* aimed at clarifying the role of the sympathetic and parasympathetic branches of the autonomic nervous system in the relationship between ACEs and blunted heart rate response. Systolic blood pressure (SBP) and respiratory sinus arrhythmia (RSA) were assessed during baseline and psychosocial stress testing in 129 healthy young women as measures of sympathetic and parasympathetic cardiovascular activity, respectively. Higher number of ACEs was correlated with blunted SBP stress reactivity but not with RSA reactivity after controlling for respiratory rate. Also, earlier age of occurrence of ACEs was associated with blunted SBP reactivity on a trend level. In conclusion, childhood adversity was associated with down-regulation of sympathetic stress responsivity but no alteration of parasympathetic functioning in adulthood. Future research will need to clarify whether this indicates a risk for negative health outcomes or might even be a sign of adaptive stress resistance.

1. Theoretical Background

The aim of the present dissertation is to contribute to the knowledge about different aspects of stress and their impact on healthy young women. First of all, an overview of stress as an important factor concerning health and general well-being is given and different kinds of stressors are shortly described. In a next step, the most important facts about sleep disturbances, including their development as well as means of measurements will be outlined and stress as an essential precipitating factor in insomnia and sleep disturbances will be discussed. Finally, an introduction in the human stress system will be given and the potential of stress in the form of adverse childhood experiences (ACEs) to alter human stress response, as well as subsequent health consequences, will be outlined.

1.1. Stress

The term stress is derived from the Latin words *stringere* (to draw tight) and *strictus* (compressed; Online Dictionary, 2014). After being formerly used in a physical context, it was introduced into medicine and was considered to be a factor of bad health. In 1936 Hans Seyle prominently used the term for a physical state, which he called General Adaptation Syndrome, and included diverse changes of physiological processes in reaction to any form of potentially threatening stimuli (Lazarus & Folkman, 1984). Today, an important and most influential concept is the concept of homeostasis, which assumes that organisms function owing to a complex and dynamic equilibrium (homeostasis), including the balanced cooperation and interactions of a wide range of physical, behavioural, and mental processes (Chrousos & Gold, 1992; McEwen, 1998). In this context, stress is defined as a state of coping with all kinds of internal or external stressors which threaten homeostasis (Chrousos, 2009; Ehlert, La Marca, Abbruzzese, & Kübler, 2013). Therefore, successful adaptive responses are necessary in order to counteract the effects of stressors, to maintain or re-establish homeostasis, and to assure survival of the individual and the species (Chrousos, 2009). This functional adaptation in response to stressors (including the ANS as well as the HPA axis) is often referred to as allostasis (or stability through change; Sterling & Eyer, 1988). It is thought to provide effective coping and re-establishment of homeostasis as long as the adaptive systems are turned on and off efficiently and appropriately in terms of both magnitude, and duration. Exceeding, prolonged or chronic activation of allostatic systems potentially leads to failure of their adaptive function because they may become over-reactive, fail to shut of, or because they may fail to respond (Chrousos, 2009; McEwen, 1998). These

physiological costs can lead to disease and negative health outcomes and were therefore referred to as allostatic load (or the price of adaptation; McEwen, 1998).

1.1.1. Different kinds of stress

The range of possible events, situations or conditions, which could constitute a potential stressor is vast and can include physical as well as emotional threats (Chrousos, 2009). Also, there are large individual differences concerning the perception and appraisal of potentially stressful events or situations, and how severe they are subjectively perceived, as well as concerning the selection of coping strategies (Ehlert et al., 2013; Lazarus & Folkman, 1984) Situations, which are perceived to be novel and significant, but unpredictable or uncontrollable for the individual do have the potential to constitute especially intensive stressors according to Mason (1968). Life events, such as severe illness or significant losses (e.g., death, divorce, work loss), are often described as major stressors, while minor stressors are usually thought to appear with higher frequency and more likely on a daily basis (e.g., arguments, time pressure, work demands; Brantley, Waggoner, Jones, & Rappaport, 1987). Further, a differentiation can be made in terms of duration between acute or time-limited, versus long-term or chronic stressors, which cause prolonged stimulation of the stress systems. Both acute, as well as chronic stressors can vary in their severity and intensity: Acute stressors could range from daily hassles (such as the above mentioned minor stressors), exams, and artificially induced laboratory stress to personally significant events, such as the birth of a child or work loss, to the point of severe and life-threatening events. Long-term or chronic stressors are usually associated with long-lasting high work demands or pressure, poverty, chronic illness, childhood neglect, but also with repeated adversity, such as physical or sexual abuse, or war captivity (Ehlert et al., 2013). The examples at the severe end of those spectrums represent a special case of stress, namely the incidence of trauma, which includes exposure to actual or threatened death, serious injury or sexual violation of one self or another person involved, and is associated with immense fear, horror, and helplessness as well as a risk for posttraumatic stress disorder (PTSD; DSM-IV; Sass, 2003).

1.1.2. The impact of stress

Despite the fact, that stressors can vary according to situational as well as individual factors, and therefore cannot be absolutely defined or operationalized, their impact seems to be almost inconceivable. Stress is one of the most omnipresent topics in western societies and one of the most frequently named reasons for impaired subjective wellbeing. As a well-known example, work stress and its consequences are associated with tremendous costs due to absenteeism,

turnover, diminished productivity as well as medical, legal, and insurance expenses (APA Practice Organization, 2010). In Switzerland, a national survey examining work-related stress in 2010 showed that 52.4% of working people reported having stress *sometimes*, while 34.4% reported suffering from stress at a *frequent or very frequent* basis, which constituted an increase by 22.7% compared to a survey conducted ten years earlier (Grebner, Berlowitz, Alvarado, & Cassina, 2011).

In addition to the subject of work stress and the frequent subjective association of stress with a vast array of issues in our population, stress officially constitutes a potential preceding or causing factor in the models of a variety of psychiatric disorders such as insomnia, PTSD or depression (Espie, 2002; Hautzinger, 1997; Sass, 2003). Also, research has confirmed stress to be associated not only with a variety of major negative health outcomes but also with potential causes of death, such as cardiovascular disease, depression, immune dysfunction or HIV progression (Cohen, Janicki-Deverts, & Miller, 2007; Glaser & Kiecolt-Glaser, 2005; Marin et al., 2011). Especially stress in childhood, often referred to as early adversity, childhood adversity, early live stress (ELS), or ACEs, has been shown to constitute an important risk factor for the development and persistence of mental and physical health problems often conceptualized as stress-related disorders, such as depression, anxiety disorders, substance abuse, cardiovascular disease, autoimmune disorders, as well as earlier mortality from a range of diseases (Felitti et al., 1998; Gilbert et al., 2009; Wegman & Stetler, 2009). Childhood adversity has been pronounced a major public health problem and according to the US Department of Health and Human services, approximately 3.8 million children were subject of at least one report of suspected maltreatment in 2012, and 678'810 victims of child abuse and neglect were confirmed. Most common forms of reported maltreatment included neglect, and sexual, as well as physical abuse (U. S. Department of Health and Human Services, 2013). One mechanism, which has been suggested as a cause for higher vulnerability to stress-related disorders, are changes in the functioning of stress response systems due to repeated or long-lasting ACEs or trauma (Chrousos, 2009; McEwen, 1998).

In summary, exceeding or prolonged exposure to stress, especially in early life, is known to be able to alter stress response systems in humans, which constitutes a risk for future negative health consequences. Additionally, stressful live-events or increased daily stress in adulthood do also have the potential to contribute to the development of impairment and health outcomes, such as, for example, sleep disorders or sleep disturbances.

1.2. Sleep

Sleep is considered to be an essential process concerning the physiological as well as psychological regeneration of our organism. It is nowadays agreed that sleep constitutes an active condition of recovery, and is associated with brain activity, which cannot be interpreted as a passive state of rest as earlier believed. This concept is supported by the fact that sleep is associated with specific changes in central and autonomic nervous systems, as well as various hormonal processes. One example for the beneficial effects of sleep is the stimulation of important cognitive functions, such as memory consolidation (Morin, 1993; Saletu, 2004; Tononi & Cirelli, 2006). One of the most well-known examples of changes in brain activity and other body functions during sleep is the alternation of slow-wave sleep phases and stages of rapid eye movement sleep (REM-sleep). While slow-wave sleep phases dominate during the beginning of the night, REM-sleep increases towards the end of the night. Slow-wave sleep is characterized by low tonicity and little eye movements, while REM-sleep evidently is associated with rapid eye movements, but also with increased body movement and vivid dreaming (Saletu, 2004).

It is difficult to define *good* or *normal* sleep. Although an average sleep time of approximately 7-8 hours, a sleep efficiency of 85% or above, and a sleep latency of up to 30 minutes are usually considered to indicate good sleep, there are large individual differences, which can vary with age, gender, environmental, and psychological factors. (Röschke & Mann, 1998; Saletu, 2004). Sleep loss or severe disruptions of sleep are associated with impaired homeostasis and can lead to significant impairment of psychological and cognitive functions, such as impaired concentration and performance, sleepiness and fatigue, as well as mood alterations (Bonnet & Arand, 2010; Horne, 1985). Sleep can be disturbed in a variety of ways. The current International Classification of Sleep Disorders (ICSD-3; American Academy of Sleep Medicine (AASM), 2014) includes seven categories of sleep disorders: insomnia, sleep related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep related movement disorders, and other sleep disorders. Even below the threshold of clinically relevant and officially diagnosed sleep disorders, there is a wide range of phenomena, which are commonly associated with terms such as *sleep disruptions, sleep disturbances,* or *impaired sleep*. The present dissertation aimed at contributing to the knowledge about the impact of stressful daily experiences on sleep in healthy young women. Therefore, the above mentioned sleep disturbances on a non-clinical level, such as impaired sleep efficiency or worse subjective sleep quality, played an important role in our sample. Because subclinical sleep disturbances or accompanying factors

(e.g. arousal) are often considered to be a preceding factor of sleep disorders, such as insomnia (Fernandez-Mendoza et al., 2010; Jansson & Linton, 2006; Morin, 1993), and since it contributes to the understanding of the development of sleep disturbances, a short introduction into insomnia and the knowledge about its cause and maintenance will be given in the next paragraph.

1.2.1. Insomnia

Insomnia is described as a disorder with a deprivation of sleep quantity or efficiency due to either difficulty of getting asleep, frequent awakening during the night, or awaking very early in the morning. Very often it is accompanied by the subjective feeling of impaired sleep quality (Morin, 1993). Daytime fatigue, exhaustion, impaired functioning, lack of concentration, and mood disturbances are also commonly reported (Bonnet & Arand, 2010; Morin, 1993). The deprivation of sleep has been verified by polysomnography (PSG), showing prolonged sleep latency, higher number of nocturnal awakenings, as well as reduced sleep efficiency in patients with insomnia (Perlis, Gehrman, Terzano, Cote, & Riemann, 2010). Still, it has to be mentioned, that patients suffering from insomnia do have the tendency to underestimate their sleep quantity (Means, Edinger, Glenn, & Fins, 2003; Perlis et al., 2010). Two common factors, which are usually associated with insomnia and sleep disturbances, are stress and arousal. Many conceptual or integrative models name both, the occurrence of stressful preceding events (e.g. daily hassles, life-events, or changes in sleep-wake balance), as well as the occurrence of so-called hyperarousal as core features of insomnia (Espie, 2002; Morin, 1993). Concerning the relationship between hyperarousal and sleep, theories postulate that physiological or cognitive arousal before bedtime is detrimental for sleep, and contributes to the worsening of sleep problems. Cognitive arousal consists of intrusive cognitions experienced as being uncontrollable, while physiological or somatic arousal is described as the perception of vegetative arousal (e.g., elevated heart rate, sweating; Nicassio, Mendlowitz, Fussell, & Petras, 1985). In his integrative model, Morin (1993) indicated that the balance between sleep and wakefulness is regulated by the amount of arousal, and only low levels of arousal are compatible with sleep. Espie (2002) further proposed that particularly the inhibition of de-arousal processes leads to the development of insomnia. Subsequently, dysfunctional cognitions about sleep, such as worrying about sleep loss, unhelpful believes, ensuing maladaptive coping strategies (e.g. prolonging bedtimes, daytime napping), and fear of sleeplessness every night, even enhance psychophysiological arousal and lead to the maintenance of the disorder (Harvey, 2002). Also, following the principles of conditioning, the sleep environment is believed to become a conditioned

stimulus, creating conditioned arousal and sleeplessness, which further contributes to the development and maintenance of insomnia (Bootzin, 1972).

The point prevalence of primary insomnia is estimated to lie between 2% and 6%, though self-reported sleep disturbances in healthy populations range up to more than 40% (Hajak, 2001; Ohayon, 2002), which makes sleep disturbances a widely prevalent and momentous health problem in the general population. The impact of insomnia and other sleep disturbances is known to be severe and includes reduced quality of life and well-being as well as impaired daytime-functioning and working ability, and thus is a potential risk factor for subsequent health problems (Hajak, 2001; Kyle, Morgan, & Espie, 2010). Accordingly, insomnia and sleep difficulties are associated with increased work absenteeism and healthcare costs (Ohayon, 2002; Stoller, 1994).

1.2.2. Measurement of sleep

Besides frequently used subjective measures of sleep, polysomnography (PSG) is the most objective method in sleep assessment. With the usually combined instruments of electroencephalography (EEG), electromyography (EMG), and electro-oculography (EOG), which are often complemented with additional measures such as respiration, electrocardiography (ECG), and oxygen saturation, it is possible to accurately identify sleep stages, as well as sleep duration, sleep efficiency, sleep latency, and different parameters of REM-periods (Rechtschaffen & Kales, 1968). Due to the necessity of being attached to electrodes and thereby to various equipment, PSG is usually conducted in sleep laboratories and is therefore accompanied by significant effort and financial costs. Another possibility to measure sleep is the use of actigraphy or actigraphic sleep measures, which is a non-invasive method for recording motor activity. An actigraph is a small device, usually looking similar to a wrist watch, which is carried on the non-dominant arm. It is capable of detecting arm movement through the use of an accelerometer and therefore represents a useful instrument for detecting rhythms of motor calm as well as activity during day and night (Ancoli-Israel et al., 2003). By the use of algorithms, it is possible to detect rates of movement, which are representative of sleep or wakefulness. Therefore, actigraphy is a useful instrument for detecting sleep-wake cycles under conditions of daily life and has been shown to provide accurate estimates of global sleep parameters (Ancoli-Israel et al., 2003; Sadeh, 2011). It represents an unobtrusive technique with relatively low effort and costs but compared to PSG bears the disadvantage of not being able to detect sleep stages as well as sleep depth.

1.3. Stress, arousal and sleep

Various psychological factors, such as stress, daily hassles, rumination, and hyperarousal have been found to play an essential role in the development of sleep disturbances (Guastella & Moulds, 2007; Morin, Rodrigue, & Ivers, 2003; Riemann et al., 2010), but the search for the specific roles and interplay among these factors is still ongoing. As mentioned above, stress is one of the most common and well-known antecedents of insomnia and has been associated with impaired sleep in a variety of ways. Major stressors (e.g. life events) repeatedly have been found to occur with greater incidence in the time preceding the onset of insomnia or to be associated with increased risk for the development of sleep problems (e.g. Bastien, Vallieres, & Morin, 2004; Vahtera et al., 2007). Especially traumatic events have repeatedly been linked to the development of sleep disorders, which even constitute a core symptom of PTSD (Harvey, Jones, & Schmidt, 2003; Spoormaker & Montgomery, 2008). But even minor stressors have been associated with more disturbed sleep (Jansson & Linton, 2006; Kashani, Eliasson, & Vernalis, 2012). Additionally, long-term stressors, such as childhood adversities, have been found to predict sleep problems several years later (e.g. Bader, Schafer, Schenkel, Nissen, & Schwander, 2007; Greenfield, Lee, Friedman, & Springer, 2011; Gregory, Caspi, Moffitt, & Poulton, 2006). On a more acute daily basis, the experience of acute stress during the day is associated with impaired sleep the following night (e.g. Bader, Bauer, Christen, & Schafer, 2011; Sadeh, Keinan, & Daon, 2004).

Based on the theoretical frameworks mentioned above, various studies tested the association between arousal and sleep and have confirmed that hyperarousal plays a major role in insomnia and sleep disturbances: high arousal is more prevalent in poor than in good sleepers and can be measured on various physiological levels, such as sympathetic nervous system activation, hormone secretion, and high-frequency EEG activation (Bonnet & Arand, 2010; Riemann et al., 2010). In addition to the higher prevalence of arousal in insomniacs, there is evidence that high physiological and cognitive arousal also are prevalent in healthy populations and might constitute a preceding factor in the development of sleep disorders (Fernandez-Mendoza et al., 2010; Jansson-Fröjmark & Linton, 2008). Even deliberately induced stress in the laboratory and the following increase in arousal at bedtime acutely worsen sleep in both poor and good sleepers (Hall et al., 2004; Wuyts et al., 2012).

Empirical studies in healthy young samples on the relationship between stress and sleep on a day-to-day basis using within-participant data measured over time are still scarce. Garde, Albertsen, Persson, Hansen, and Rugulies (2011) found evidence for a bidirectional association between stress and sleep, indicating a self-reinforcing vicious circle: in a

representative sample of the Danish population, higher ratings of stress at bedtime were associated with ratings of poor sleep the following night. In addition, higher ratings of poor sleep in the morning were associated with higher ratings of stress during the subsequent day. In a study by Hanson and Chen (2010), the daily number of stressors reported by healthy young adults was associated with decreased subsequent sleep time when moderated by family risk. Akerstedt et al. (2012) studied the relationship between stress and sleep over a period of 6 weeks in 50 healthy adults. They found bedtime stress and worries to be the two main predictors of subjective sleep quality. Still, the potentially mediating effect of arousal between stress and sleep was not tested in those studies.

Morin et al. (2003) tested the relationship between all three variables and found a significant relationship between daytime stress and night-time sleep, with presleep arousal playing a mediating role. The authors collected prospective daily paper and pencil measures for 21 consecutive days in men and women aged 19–60 years, and included both, persons suffering from insomnia as well as good sleepers. Data showed that subjective stress during the day was a significant predictor of self-reported subjective sleep quality the following night for both groups and higher levels of presleep arousal mediated this relationship. Objective sleep measures were not used in this study.

1.4. The human stress system

The endocrine system and the autonomic nervous system (ANS) with their central and peripheral components are key players in orchestrating bodily stress responses in cases where the functioning of our organism is threatened by internal or external stressors. Besides cognitive changes, such as enhanced attention, alertness, as well as focus on perceived threat, increased cardiovascular tone and respiration, increased catabolism, and therefore adaptive redirection of energy to brain, heart, and skeletal muscles are central to a functioning stress response (Charmandari, Tsigos, & Chrousos, 2005; Chrousos, 2009; Chrousos & Gold, 1992). At the same time, non-adaptive functions during acute stress, such as reproduction and growth, are temporary suppressed (Chrousos & Gold, 1992). Importantly, the orchestration of stress responses requires a highly-integrated and well-coordinated connection between all involved systems, including not only the endocrine system, the ANS, and the central nervous system (CNS), but also the immune system. Therefore, these systems have the potential to initiate, reinforce, or inhibit each other by mutual innervation, for example by central control systems in the paraventricular nucleus (PVN) and locus coeruleus (LC) (Tsigos & Chrousos, 2002; Ulrich-Lai & Herman, 2009).

The thalamus, the amygdala, and the sensory cortex all play an important role in the detection and evaluation of potential threats and stressors (Danese & McEwen, 2012). The amygdala is well known for its role in identifying environmental threats for survival and in linking external stimuli to defence reactions, which can lead to conditioned fear responses (LeDoux, 2003). It is under inhibitory control by the hippocampus (based on learning processes and memory of previous experiences) and by the prefrontal cortex (based on executive functions; Herman, Ostrander, Mueller, & Figueiredo, 2005; McEwen, 2007). If this combined network of brain areas detects a potential threat of homeostasis by an occurring stressor, the above mentioned multi-layered stress response is induced. This includes the neuroendocrine response of the HPA axis, as well as the sympathetic and parasympathetic branches of the ANS (Chrousos, 2009; Ulrich-Lai & Herman, 2009).

1.4.1. The hypothalamic-pituitary-adrenal (HPA) axis

Concerning the endocrine system, exposure to stress causes an increased activation of the HPA axis. It is initiated by firing in the paraventricular nucleus (PVN) in the hypothalamus, releasing corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which in turn synergistically stimulate the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. ACTH travels through the blood stream and stimulates the adrenal cortex to produce glucocorticoid hormones such as cortisol (e.g. Tsigos & Chrousos, 2002; Ulrich-Lai & Herman, 2009). Cortisol levels start to rise approximately 5-20 minutes after stressor onset and peak levels occur about 10-30 minutes after the stressor is finished (Kirschbaum & Hellhammer, 2000). Main functions of cortisol are the insurance of a steady supply of glucose by strong catabolic action under stressful conditions, but also the improvement of cardiovascular tone, the prevention of an overshooting immune response to the stressor, as well as the shaping of future stress response through actions in the CNS (Danese & McEwen, 2012; Hellhammer, 2008; McCormick & Mathews, 2007). Besides a wide range of stressors with the potential to activate the HPA axis, situations, which are perceived to be novel, unpredictable, uncontrollable, or to involve social-evaluative threat for the individual, have been shown to be especially effective in eliciting HPA responses (Dickerson & Kemeny, 2004; Mason, 1968).

Apart from its role in stress response, the HPA axis has a major function in regulating daily cortisol release according to a circadian rhythm. During non-stressful conditions CRH, AVP, and subsequently ACTH and cortisol are secreted in a pulsatile fashion and show peak levels in the early morning hours, approximately 30 minutes after awakening (Horrocks et al., 1990; Kirschbaum & Hellhammer, 2000). This response has been found to show high intra-

individual stability over weeks and months if not disturbed by changes in lightning, activity, diet, or stress (Kirschbaum & Hellhammer, 2000).

As the final effector of the HPA axis, cortisol has not only the function to regulate but also to terminate HPA stress response by an inhibitory feedback, which directly acts at all levels (hypothalamic centres, PVN and the pituitary gland) in order to prevent further CRH and AVP secretion. This negative feedback serves a protective mechanism by limiting the duration of total tissue exposure to glucocorticoids (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Tsigos & Chrousos, 2002).

1.4.2. The autonomic nervous system (ANS)

The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) of the ANS together regulate a wide range of functions, including cardiovascular, respiratory, gastrointestinal, renal, and endocrine systems (Gilbey & Spyer, 1993; McCorry, 2007). Within seconds after the occurrence of a stressor, the ANS generates a fight-or-flight response pattern with corresponding physiological changes. Importantly, a stress response in heart rate and other organismic functions is often comprised of both, sympathetic activation and parasympathetic withdrawal. Therefore, both branches of the ANS may play a role in regulating stress-induced arousal (Berntson, Cacioppo, & Quigley, 1991; Chrousos & Gold, 1992).

The sympathetic branch of the ANS is activated by a prolonged and powerful discharge from the locus coeruleus (LC) in the brain stem once a stimulus is perceived as a threat. The SNS response is characterized by the release of catecholamines, such as epinephrine (EPI), and norepinephrine (NE). In the CNS the LC releases NE (therefore referred to as the LC-NE system), which enables the brain to higher alertness, attention, and arousal. In the periphery, SNS activation enhances cardiovascular and pulmonary function, induces constriction of blood vessels, and provides energy to relevant organs, thereby enabling the fight-or-flight reactions. This involves postganglionic fibers releasing NE, as well as the stimulation of the adrenal medulla of the adrenal gland, releasing mainly EPI, and is therefore referred to as the sympathetic/adrenomedullary system (SAM; Hellhammer, 2008; Ulrich-Lai & Herman, 2009). Sympathetic discharges occur with a variety of physical as well as psychological stressors but are also observed independent of fight and flight conditions as, for example, mental and physical work, or exposure to novel stimuli (Hellhammer, 2008).

Sufficient blood supply to muscles and other organs during stress responding is assured by up-regulation of blood pressure. Particularly systolic blood pressure (SBP) is known to be regulated almost exclusively by the sympatho-adrenal axis via beta-adrenergic

receptors and thus constitutes a putative index of sympathetic cardiovascular activity (Obrist, 1981; Silvestrini & Gendolla, 2011).

The parasympathetic branch of the ANS serves an opposing set of functions, promoting growth and restoration. It inhibits sympathetic activation after stressful events and enables return to homeostasis but also facilitates initial sympathetic activation in threatening situations by withdrawing its inhibitory influence. Importantly, the SNS und PNS do not always operate in an antagonist fashion but may exhibit independent activation (Berntson et al., 1991; Porges, 2007). Concerning cardiovascular activity, the PNS exerts an inhibitory influence on heart rate via the vagus nerve, which originates in the brain stem and terminates at the sino-atrial node of the heart. This parasympathetic control over heart rate is often referred to as vagal tone, regulating autonomic arousal and promoting calm states (e.g. Porges, 2007). High cardiac vagal tone during states of calm has been associated with higher physiological and behavioural flexibility as well as with the ability of social engagement, while appropriate withdrawal (greater decrease) of vagal influence during threatening or demanding situations enables SNS mobilisation and corresponding reaction (Fabes & Eisenberg, 1997; Kok & Fredrickson, 2010; Porges, 2007).

Respiratory sinus arrhythmia (RSA) is often used as a non-invasive index of parasympathetic cardiovascular response. It refers to the rhythmic oscillation of heart rate linked to the phases of the respiratory cycle and indicates the efferent activity of the PNS innervating the heart, or cardiac vagal control. Specifically, heart rate accelerates during inspiration and decelerates during expiration and this systematic variability has been found to be influenced solely by vagal influence to the heart, which decreases its influence during inspiration and reinstates during expiration. The amplitude of RSA as an index of this variability therefore provides an estimate of general efficiency but also potential flexibility of cardiac vagal tone in regulating cardiovascular functioning (Berntson et al., 1997; Grossman, Stemmler, & Meinhardt, 1990). Spectral analysis of heart rate variability over several minutes within the frequency range of 0.15-0.50 Hz (the frequency band typically associated with respiration), has been established as the method of choice for quantifying RSA (Camm et al., 1996; Grossman et al., 1990).

1.5. Adverse childhood experiences and alterations in stress response

As mentioned above, ACEs have been shown to constitute an important risk factor for the development and persistence of mental and physical health problems often conceptualized as stress-related disorders (Felitti et al., 1998; Wegman & Stetler, 2009). These detrimental consequences of early adversity are supported by findings from animal models showing

higher risk for pathology in association with early-live stress (Sanchez, Ladd, & Plotsky, 2001). Changes in the functioning of stress response systems due to exceeding, repeated, or long-lasting stressors, such as ACEs or trauma, have been suggested to be the cause for higher vulnerability to stress-related disorders. Current models assume that these stressors have the potential to alter patterns of endocrine and autonomic discharge in the long-term by disturbing the complex and integrated system of positive and negative feedback-loops, thereby creating a state of allostatic load that potentially results in adverse health outcomes (see for review: Chrousos, 2009; Heim & Nemeroff, 2001; McEwen, 1998; Miller, Chen, & Parker, 2011). Importantly, previous evidence and theoretical considerations suggest that allostatic load can take either the direction of failure to shut off the stress response and a resulting chronic hyperactivity, but also the direction of failure to mobilize a full response and a resulting blunted pattern (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Lovallo, 2011; McEwen, 1998). At various levels of endocrine and autonomic response, these processes can be mediated or moderated by genetic predisposition and by epigenetic programming during early brain development. For example, genetic and epigenetic influences can lead to an alteration of relevant receptors in regulatory feedback loops (e.g. Pütz, 2008; Tyrka, Price, Marsit, Walters, & Carpenter, 2012; Weaver et al., 2004).

From a developmental perspective, age at stress exposure is believed to be an important factor since there is evidence for developmental periods with high sensitivity for the formation of enduring alterations in stress responsivity (Fumagalli, Molteni, Racagni, & Riva, 2007; Tarullo & Gunnar, 2006; Tottenham & Sheridan, 2010). During prenatal and early postnatal life the brain grows rapidly and therefore is characterized by high plasticity, which then slows down during childhood and adolescence (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). This implies, that events causing exceeding or prolonged stimulation of the stress system during these critical developmental periods could lead to lasting alterations in stress reactivity (Charmandari et al., 2003; Tottenham & Sheridan, 2010).

Inadequately increased stress system activity and responsiveness due to chronic and prolonged activation of the system, for example due to disturbed negative feedback, may impair growth, development, and metabolism (Chrousos, 2009). Hyper-secretion of CRH has been associated with depression, anxiety, substance abuse, as well as eating disorders. Furthermore, disruptions of the HPA axis and the functions of the SNS have been found in obesity, metabolic syndrome, type 2 diabetes mellitus, and hypertension (Chrousos, 2009; Klingmann & Hellhammer, 2008; Pütz, 2008). Sensitization to the stimulation of noradrenergic nerves, accompanied by higher heart rate reactions and increased levels of

catecholamines, have been associated with anxiety disorders (Bremner, Krystal, Southwick, & Charney, 1996; Klingmann & Hellhammer, 2008). Additionally, enhanced plasma NE levels have been found to constitute an important risk factor for later life mortality and also, the risk of increased blood pressure (which is strongly promoted by sympathetic outflow) for cardiovascular disease is well known (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Guyenet, 2006). Finally, some disorders with exceeding SNS activation were found to be associated with a parallel decrease in parasympathetic functioning or vagal tone (low tonic RSA or inadequate RSA withdrawal), leading to autonomic imbalance (Friedman & Thayer, 1998; Giese-Davis et al., 2006; Thayer & Lane, 2007).

On the other hand, decreased stress system activity and reactivity could compromise necessary psychobiological processes in response to stress. It is assumed that persistent hyper-activation or -reactivity of the stress system may ultimately lead to failure or down-regulation, for example due to a compensatory increase in negative feedback, and hence to a blunted response pattern, with the system not launching appropriate reactions anymore (Fries et al., 2005; Miller, Chen, & Zhou, 2007). While it may be adaptive that the stress system shuts down the stress response in order to minimize the potential dangers of chronic activation (Fries et al., 2005), chronically low stress system activity is nevertheless associated with negative health outcomes: Decreased activity and responsiveness of the HPA axis has been associated with conditions such as chronic pain, chronic fatigue, atypical depression, fibromyalgia, and rheumatoid arthritis (Chrousos, 2009; Fries et al., 2005; Heim, Ehlert, & Hellhammer, 2000). Additionally, depletion of NE storage vesicles as a consequence of chronic stress is characterized by symptoms of pronounced fatigue, cognitive impairment, such as lack of initiative and motivation, burnout, as well as symptoms promoted by low sympathetic but high parasympathetic activity (Gold & Chrousos, 2002; Klingmann & Hellhammer, 2008).

Importantly, on the CNS level, exceeding or chronic stress, including ACEs and associated alterations of stress response, have repeatedly been associated with structural and functional abnormalities in the prefrontal cortex, the amygdala, and the hippocampus, as well as with accompanying cognitive impairment in attention, memory function, and processes concerning fear conditioning (McEwen, 2007; McEwen & Gianaros, 2011).

In addition to the above mentioned health outcomes, both catecholamines as well as glucocorticoids can induce quantitative and qualitative changes in immune function. The immune system becomes activated in a wide range of stressful situation, resulting in a release of pro-inflammatory cytokines (Chrousos, 1995). Therefore, immunosuppressive and anti-

inflammatory effects of HPA and ANS activation (amongst others through a shift from cellular to humoral immunity) have the function to prevent an overshooting of immune response in order to restrain the inflammatory reaction and protect the body from tissue destruction (Elenkov, Webster, Torpy, & Chrousos, 1999; Hellhammer, 2008). Thus, excessive stress response due to chronic stress has been associated with increased susceptibility to infectious agents but enhanced resistance to autoimmune or inflammatory disease (Chrousos, 1995; Elenkov et al., 1999). Implications for health include infectious-disease risk, reactivation or progression of latent viruses, such as HIV or herpesviruses, or impaired wound healing (see for review: Glaser & Kiecolt-Glaser, 2005). On the other hand, a defective stress response can thus lead to a disinhibition of immune functions with prolonged inflammatory effects due to elevation of pro-inflammatory cytokines, such as tumor necrosis factor alpha or interleukin-6, causing resistance to infections but increased susceptibility to autoimmune or inflammatory disease, such as the above mentioned chronic pain or rheumatoid arthritis (Chrousos, 1995; Heim, Ehlert, et al., 2000). Still, those processes are complex and stress might result in a wide range of changes in acute and chronic immunocompetence rather than a specific pattern of suppression or enhancement (Elenkov et al., 1999).

As mentioned above, individual differences in functional as well as disrupted stress response depend on a multitude of factors, such as genetic disposition, as well as epigenetic programming in association with age at stress exposure (e.g. Del Giudice, Ellis, & Shirtcliff, 2011; Weaver et al., 2004). Also, stress response is influenced by gender, type of adversity, environmental, and protective factors, including sensitive parenting, coping, positive affect, or social support (Bostock, Hamer, Wawrzyniak, Mitchell, & Steptoe, 2011; Carpenter et al., 2007; McCormick & Mathews, 2007). Furthermore, stress response systems can be disturbed at different levels of their central and peripheral regulatory feedback loops (Hellhammer, 2008; Klingmann & Hellhammer, 2008), and finally, due to interconnection, integration, and mutual innervation, the different arms of the stress system have the potential to initiate, reinforce, or inhibit each other (Bauer, Quas, & Boyce, 2002; Ulrich-Lai & Herman, 2009).

Due to this amount of influencing factors, discrepant or seemingly opposite findings concerning activity and reactivity patterns of stress response have been observed (e.g. Kudielka, Hellhammer, & Wust, 2009; Miller et al., 2007). Further research is needed in order to integrate findings into a more consistent picture concerning the relationship between adversity, stress response alterations, and subsequent health outcomes. Therefore, the next section will concentrate on a brief introduction on the specific findings, which were relevant

for the conceptual design of the two articles on endocrine as well as sympathetic and parasympathetic stress response in healthy young women.

1.5.1. Findings regarding the HPA axis

While PTSD in adults has been associated with basal hypo-activity of the HPA axis (see for review: Yehuda, 1997), different reactivity phenotype patterns have emerged in the context of ACEs and psychopathology with a number of studies showing exaggerated HPA axis reactivity (Bremner et al., 2003; Heim & Nemeroff, 2001; Heim, Newport, et al., 2000; Rao, Hammen, Ortiz, Chen, & Poland, 2008). For example, in patients with PTSD related to childhood abuse, cortisol levels in anticipation and during a cognitive challenge were significantly higher than in controls (Bremner et al., 2003). Also, Heim, Newport, Mletzko, Miller, and Nemeroff (2008) showed that woman with a history of childhood adversity in combination with major depressive disorder exhibited increased cortisol responses to psychosocial stress compared to control groups, and furthermore, that a history of childhood abuse was the strongest predictor of ACTH responsiveness. Still, in clinical samples, effects may be confounded with current psychiatric symptoms.

In contrast to clinical samples, a growing number of studies on healthy participants reported blunted endocrine stress responses in association with ACEs (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; Elzinga et al., 2008; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012). For example, Carpenter et al. (2007) reported blunted plasma cortisol responses to a psychosocial stress test in a healthy sample with a history of ACEs compared to participants without a history of childhood maltreatment. Also, a recent study by Lovallo et al. (2012) showed diminished cortisol as well as heart rate responses in a large sample of healthy participants with an increasing number of adverse life events, indicating an inverse dose-response relationship of ACEs and reactivity to a mental stress test.

1.5.2. Findings regarding the ANS

Since heart rate is regulated by both, sympathetic and parasympathetic efferent activity of the ANS, it remains unclear whether attenuated heart rate reactivity, such as the above mentioned by Lovallo et al. (2012), is caused by sympathetic hyporeactivity or less parasympathetic withdrawal, or a combination of both (Berntson et al., 1991). It is therefore important to clarify the role of the sympathetic (indexed by SBP) and the parasympathetic (indexed by RSA) cardiovascular stress responsivity in association with ACEs.

Elevated tonic sympathetic activity has frequently been reported in samples with PTSD and persistent hyperarousal is considered to be a core symptom of the disorder

(Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007; Buckley & Kaloupek, 2001; Kirsch, Wilhelm, & Goldbeck, 2011). In non-clinical samples, similarly elevated tonic sympathetic activity has been found in association with adversity in some studies (Lee, Tsenkova, & Carr, 2014; Paulus, Argo, & Egge, 2013; Su et al., 2014), while others have found no baseline differences in heart rate or SBP (Leitzke, Hilt, & Pollak, 2013; Lovallo et al., 2012).

Concerning sympathetic stress reactivity, results are mixed in samples with PTSD with either heightened (Heim, Newport, et al., 2000) or blunted heart rate or electrodermal responses to acute stress (Blechert et al., 2007; Cohen et al., 2000). In non-clinical samples, some studies have produced evidence for heightened SNS reactivity in response to stressors (Oosterman, de Schipper, Fisher, Dozier, & Schuengel, 2010; Otte et al., 2005). On the other hand, the above mentioned study by Lovallo et al. (2012) showed diminished heart rate responses to a stress task with an increasing number of adverse life events in a large sample of healthy participants (N=354). Also, Leitzke et al. (2013) found blunted SBP response in maltreated compared to non-maltreated youth (N=111).

Concerning adversity and parasympathetic regulation, there is evidence for lower tonic RSA in association with both, non-clinical samples with the experience of ACEs (Dale et al., 2009; Miskovic, Schmidt, Georgiades, Boyle, & MacMillan, 2009), and clinical samples with PTSD (Blechert et al., 2007; Cohen et al., 1997). Concerning RSA withdrawal in response to stressors, Cohen et al., (1998) found that in participants with PTSD, RSA did not change from resting condition to trauma recall compared to a withdrawal of RSA in controls. In non-clinical samples, there is evidence for lower RSA stress reactivity or lower recovery in the context of adversity (Arditi-Babchuk, Feldman, & Gilboa-Schechtman, 2009; Dale et al., 2009). However, these patterns might be complicated by different factors, such as family environment, mediating or moderating the relationship between ACEs and RSA, especially in children and adolescents. Also, there is evidence that tonic RSA or RSA stress reactivity themselves constitute moderating factors between early adversity and adaptive or maladaptive outcomes (El-Sheikh & Whitson, 2006; Ellis, Essex, & Boyce, 2005; Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). For example, Obradovic et al. (2010) found high RSA withdrawal to be associated with more maladaptive outcomes in the context of high adversity but with more adaptive outcomes in the context of low adversity in children. Still, others found no differences in RSA baseline or reactivity in association with ACEs (Shenk, Putnam, Rausch, Peugh, & Noll, 2014; van Ockenburg et al., 2014).

1.5.3. Difficulties in examining alterations of stress response

Some of the divergent findings in the relationship between ACEs and endocrine as well as autonomic stress response may be due to the fact that studies differ regarding sample characteristics, age groups, type of adversity, and stressors assessed: many studies have used clinical samples with the problem of comorbid symptomatology (e.g. Blechert et al., 2007; Cohen et al., 2000; Heim, Newport, et al., 2000). Studies on RSA have often focused on children and adolescents and have examined RSA as a mediator between ACEs and other outcome variables (e.g. Ellis et al., 2005; Obradovic et al., 2010). Also, the simultaneous investigation of the different stress response systems, including endocrine, parasympathetic, and sympathetic indices is essential due to their close interaction and mutual innervation, but it is not always considered and previous results are mixed because of methodological differences (Andrews, D'Aguiar, & Pruessner, 2012; Bauer et al., 2002; Sapolsky, Romero, & Munck, 2000). Further, some of the inconsistencies in prior findings might be the result of inadequate adjustment for confounding factors such as hormonal contraceptives in HPA axis, respiratory rate in RSA, physical fitness, or depressive symptomatology (Grossman & Taylor, 2007; Heim et al., 2008; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Finally, since most studies used brief self-report questionnaires or life events checklists to assess ACEs (e.g. Carpenter et al., 2011; Lovallo et al., 2012), questions of their duration and the age of occurrence in association with stress response in adulthood often remain unanswered, especially in healthy samples.

2. Research Questions

The first objective of the present dissertation was to extend previous findings on the relationship between daily stress, presleep arousal, and sleep on a day-to-day basis. The second aim was to gain further knowledge regarding the understanding of the psychophysiological consequences of stress experiences during childhood and adolescence. Altogether, the main objective was to contribute to the knowledge about the impact of stress on a non-clinical sample of healthy young women.

2.1. Research Question Article 1

Various psychological factors, such as stress, daily hassles, and hyperarousal have been found to play an essential role in the development of sleep disturbances (e.g. Riemann et al., 2010), but the search for the specific roles and interplay among these factors is still ongoing. Morin et al. (2003) showed that in both, persons suffering from insomnia as well as good sleepers, subjective stress during the day was a significant predictor of worse subjective sleep quality the following night and that higher levels of presleep arousal mediated this relationship. However, objective sleep measures were not used in this study. Also, empirical studies in healthy young samples on the relationship between stress and sleep on a day-to-day basis using within-participant data measured over time are still scarce.

A daily life sleep-diary and actigraphy study was conducted in order to replicate the mediating role of presleep arousal between stress and sleep considering both, subjective and actigraphic sleep measures, as well as between- and within participant data. Multilevel modelling was used to evaluate the relationship across days. Furthermore, computerized diaries were used to enhance compliance and reliability compared to paper-and-pencil data.

2.2. Research Question Article 2

As stated in the theoretical part of this work, ACEs have been shown to constitute an important risk factor for the development and persistence of physical and mental disorders (Wegman & Stetler, 2009). Changes in the functioning of stress response systems due to repeated or long-lasting ACEs or trauma have been suggested to be the cause for higher vulnerability to stress-related disorders (e.g. Chrousos, 2009; Heim & Nemeroff, 2001). While many studies stated exaggerated HPA axis and SNS responses in the context of ACEs and psychopathology (e.g. Heim, Newport, et al., 2000; Rao et al., 2008), other studies observed blunted cortisol or heart rate responses in non-clinical samples after laboratory stress induction (Carpenter et al., 2011; Lovallo et al., 2012). Due to evidence that exceeding or

prolonged stimulation of the stress system during critical developmental periods could lead to lasting alterations in stress reactivity, it is important to examine the role of the age of occurrence of ACEs as well as the duration of ACEs in the relationship between early adversity and stress reactivity (Tottenham & Sheridan, 2010).

Therefore, the aim of the second article was to replicate the findings of attenuated endocrine and cardiovascular stress reactivity in association with ACEs in a young and healthy female sample. Additionally, the association between the age of occurrence as well as the duration of adverse events and cortisol as well as heart rate reactivity in adulthood was examined. The Early Trauma Inventory-Self Report (ETI-SR) served as a validated and detailed method in measuring ACEs (Bremner, Bolus, & Mayer, 2007), enabling the assessment of a wide range of stress and trauma exposure before the age of 18, as well as age of occurrence and duration of events.

2.3. Research Question Article 3

In accordance with the study by Lovallo et al. (2012), we found blunted cardiovascular stress response in association with higher number of ACEs in the second article. However, since heart rate is regulated by both, sympathetic and parasympathetic efferent activity of the ANS, it remains unclear whether attenuated heart rate reactivity is caused by blunted sympathetic response or less parasympathetic withdrawal, or a combination of both (Berntson et al., 1991).

Therefore, the third article aimed at clarifying the role of the sympathetic (indexed by SBP) and the parasympathetic (indexed by RSA) cardiovascular stress response in the observed blunted heart rate reactivity in association with ACEs as well as age of occurrence of ACEs. The objective was to extend previous findings by investigating the relationship between ACEs, SBP, and RSA during baseline and in reaction to a psychosocial stress task in healthy young women, including the consideration of potentially confounding variables. In exploratory analyses, the different ACE subscales and their association with SBP and RSA were analysed in order to be able to compare different types of adversity in the same sample.

3. Methods

Three original articles, all analysing different aspects of the interaction between ACEs, stress and sleep in young women, were conducted. In the following section the study designs and methods are briefly described.

All data were collected in the context of a large study investigating acute stress, emotion regulation, and sleep in healthy young women with a history of stress exposure. Therefore, the general procedure of the study is described first, followed by specific methodic details of the three original articles.

3.1. General study procedure

Participants were recruited using flyers posted at schools for healthcare professions and social work in Basel, Switzerland, or by e-mails sent by the schools. Potential study participants contacted the study office by e-mail or phone. They were sent a screening questionnaire assessing the following inclusion criteria: female sex, age range between 18 and 25 years, German speaking, and good health. All participants were screened on inclusion and exclusion criteria in a first office appointment, provided written informed consent, and filled in relevant questionnaires before they started a two-week ambulatory assessment of stress, presleep arousal, and sleep. Exclusion criteria for all participants included physical or psychiatric illness, pregnancy, regular heavy tobacco use (>5 cigarettes a day), use of illegal drugs, night shift work, and use of any medication, which interferes either with sleep or with the nervous or the adrenocorticoid system. The absence of psychiatric illness was assessed with the German version of the Structured Clinical Interview for DSM-IV (SKID I for DSM-IV; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). Further relevant data including age, physical health, and other exclusion criteria were assessed by interview.

After one week of assessment, participants reported to the laboratory for a stress examination, which took place between 3:30 pm and 6:00 pm to control for circadian variation and lasted for approximately 2.5 hours. Participants were told that the laboratory assessment would include a test on cognitive performance. After initial accommodation, a baseline period and a paced breathing task followed. Participants then engaged in the stress task, which was followed by a recovery period. At the end of the laboratory testing, participants were debriefed. After another week of ambulatory sleep assessment, participants returned their materials and received monetary compensation.

The Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) was used to induce a psychosocial stress response. The MIST is a standardized psychosocial stress test during

which participants have to solve arithmetic tasks under time pressure and social evaluation. Participants have to complete three experimental runs while their success rate is artificially restrained to a maximum 45-50% and at the same time social evaluative threat is enhanced by negative feedback by the investigator.

In contrast to other often used psychosocial stress tasks like the Trier Social Stress Test (TSST, Kirschbaum, Pirke, & Hellhammer, 1993), the MIST does not require speaking during stress assessment and also, participants remain in a quiet sitting position. This has the advantage that fewer artifacts due to movement or speaking are caused in psychobiological parameters like heart rate. It also ensures that respiratory pattern change (steep, short inspiration and long expiration, (Wilhelm, Handke, & Roth, 2003) due to speaking cannot interfere with RSA assessment.

3.2. Methods Article 1

3.2.1. Study Design and Procedure

A daily life computerized sleep diary and actigraphy study was conducted to investigate the mediating role of presleep arousal in the relationship between daily stress and sleep. After receiving instructions during the first office appointment, participants started the two-week ambulatory assessment. Sleep logs were completed every morning immediately after rising while daily stress and presleep arousal were measured every evening immediately before bedtime. This repeated-measures design enabled to investigate effects on both levels, between participants and within participants, with multilevel modelling.

3.2.2. Study Sample

The sample included 145 young and healthy women (mean age 21.7 ± 1.6 years). One participant had to be excluded because sleep parameters could not be calculated reliably due to incomplete information about sleep and wake times.

3.2.3. Data Assessment

Participants wore an ambulatory wrist actigraph (Micro Mini-Motionlogger, Ambulatory Monitoring Inc., Ardsley, NY) for 14 successive days and nights on the non-dominant arm. Additionally, daily sleep logs were completed by the participants to cross-validate sleep start and end times. The dependent variable sleep efficiency (SE) was calculated as the ratio of total time asleep to time in bed.

For the assessment of daily self-report measures, a menu-driven computerized questionnaire was developed to repeatedly measure subjective estimates of sleep quality, daily

stress, and presleep arousal. Concerning subjective sleep quality, participants were instructed to fill in a computerized Likert-type scale ranging from 1 (very good sleep quality) to 5 (very poor sleep quality). For statistical analyses, the scale was reversed to have higher values for higher sleep quality. Presleep arousal was assessed with the Presleep Arousal Scale (PSAS; Nicassio et al., 1985, German version; Gieselmann, de Jong-Meyer, & Pietrowsky, 2012), which contains 16 items with eight symptoms of cognitive and eight symptoms of somatic arousal experienced at bed-time. Ratings range from 1 (not at all) to 5 (extremely). A total score was computed for both subscales with higher scores indicating higher arousal. The occurrence of daily stressors was measured by the Daily Stress Inventory (DSI; Brantley et al., 1987, German version; Traue, Hrabal, & Kosarz, 2000), which is a 58-item self-report questionnaire assessing the occurrence and the impact of 58 possible daily stressors. Three scores can be derived: the actual number of events that occurred during the day (frequency); the sum of impact ratings (total impact of all events); and the average impact rating (sum of all ratings divided by the frequency).

3.2.4. Statistical Analyses

Because of the hierarchical structure of the data (days and nights nested within participants) and with the aim to be able to predict fluctuations from night to night in the variables, a multilevel modelling approach was used. Multilevel models are an extension of the general linear model and do not require observations to be independent. Because of their autoregressive nature and hierarchical structure, multi-level models are especially useful to study time-dependent changes (Bauer, Preacher, & Gil, 2006; Preacher, Zyphur, & Zhang, 2010). By applying this approach, we were able to examine the relationship between daily stress, presleep arousal, and sleep within and between participants.

Analyses on the between-participants level addressed the question if participants who experienced higher levels of daily stress also reported higher levels of arousal and worse sleep compared to participants reporting lower levels of daily stress and arousal. Analyses on the within-participant level addressed the question if individuals reported higher arousal and worse sleep on days when they also reported above average stress levels compared to their individual average level.

3.3. Methods Article 2

3.3.1. Study Design and Procedure

A quasi-experimental approach was used to investigate the relationship between ACEs and endocrine as well as cardiovascular reactivity after psychosocial stress induction. Participants completed the Early Trauma Inventory self-report (ETI-SR; Bremner et al., 2007) and engaged in the MIST while salivary cortisol and heart rate responses were assessed. For women taking no oral contraceptives, the laboratory assessment was held in the luteal phase of the participant's menstrual cycle (Kirschbaum et al., 1999).

3.3.2. Study Sample

The sample included 104 young and healthy women (mean age 21.7 ± 1.5 years). Participants with acute illness during laboratory testing, failure in recording devices or unlikely high and fluctuating cortisol values had to be excluded.

3.3.3. Data Assessment

ACEs before the age of 18 were assessed using a German translation of The Early Trauma inventory self-report (ETI-SR; Bremner et al., 2007). The questionnaire includes general trauma (31 items), as well as physical (9 items), emotional (7 items), and sexual abuse (15 items). Participants were asked a series of yes or no questions regarding potential trauma and stress exposure. For positively answered items, age of occurrence, frequency/duration, and emotional impact were assessed, and different ACE scores were built: Events with an emotional impact of at least 1 ("slightly negative") were summed up to *ACE total sum score*. Furthermore, a sum score for ACEs lasting less than a year (*ACEs < one year*) and for ACEs lasting more than a year (*ACEs > one year*) was computed. Age of occurrence was assessed in two ways: In a first step, events which occurred before or after a participants' menarche were summed up to *ACEs before* and *after menarche,* respectively. Additionally, *age of first ACE occurrence* was determined for each subject by taking the earliest age of onset across all domains.

Free salivary cortisol was measured using salivettes at seven measurement points, twice before the stress task (-10 and -1 minutes) and five times after the stress task (+1, +10, +25, +40 and +55 minutes). Electrocardiogram (ECG) recordings were taken using electrode placement on the thorax, and heart rate was averaged for Baseline, Stress 1, Stress 2, Stress 3 and Recovery periods in reference to manually set time markers in accordance with the

various sections of the experiment. Subjective emotional response to the MIST was assessed using Visual Analogue Scales (VAS) for mood, tension, and stress.

3.3.4. Statistical Analyses

In a first step, repeated measures General linear model (GLM) was used to assess if the stress task led to a significant physiological and subjective emotional stress response. Further, GLMs for repeated measures served to determine the effects of ACEs on endocrine and cardiovascular responses. The different ACE scores were used as continuous variables to examine effects of time, ACE scores, and the interaction of time by ACE scores. Covariates included in all statistical models were BMI, the use of oral contraceptives, and, in post-hoc analyses, the emotional responses to the MIST (mood, tension, and stress).

3.4. Methods Article 3

3.4.1. Study Design and Procedure

A quasi-experimental approach was used to investigate the relationship between ACEs and sympathetic as well as parasympathetic cardiovascular stress reactivity after psychosocial stress induction. Participants completed the ETI-SR (Bremner et al., 2007), and engaged in the MIST while SBP and RSA were assessed. Respiratory rate was assessed in order to be able to include it as a covariate in statistical analyses to account for its potential confounding influence on RSA in within-subject change analyses (Grossman & Taylor, 2007). After baseline, a paced breathing task was conducted in order to standardize respiratory rate between individuals during assessment of individual differences in resting RSA (Wilhelm, Grossman, & Coyle, 2004).

3.4.2. Study Sample

The sample included 129 young and healthy women (mean age 21.7 ± 1.7 years). Participants with acute illness during the laboratory session or missing data due to technical failure of recording devices had to be excluded.

3.4.3. Data Assessment

ACEs before the age of 18 were assessed using a German translation of the ETI-SR (see article two; Bremner et al., 2007). Events were summed up to a total score of occurred events (*ACE total score*). For exploratory purposes, separate scores were computed for the four subscales (general trauma, physical, emotional, and sexual abuse). Additionally, the variable

age of first ACE occurrence was determined for each subject by taking the earliest age of onset across all domains.

SBP was assessed using an ambulatory blood pressure monitor (Aponorm® Basis Control, Germany) during the last minute of baseline and about 30 seconds after the start of each of the stress runs. A baseline-to-stress reactivity score was computed by subtracting SBP at baseline from SBP during the stress task (mean of all three stress runs). For the assessment of RSA, electrocardiogram (ECG) recordings were acquired using electrode placement on the thorax in a standard Lead II configuration with three disposable electrodes. Respiration pattern was recorded using an inductive plethysmograph (Respiband, Ambulatory Monitoring Inc., Ardsley, NY) applied around the upper rip cage. Both RSA and mean respiratory rate were determined for baseline, paced breathing, and the three experimental stress runs. These intervals were defined by markers, which were manually set and recorded in the course of the experiment. RSA withdrawal was computed by subtracting baseline RSA from RSA during the stress task (mean of all three stress runs). Therefore, higher values stand for less RSA withdrawal (less decrease of RSA).

3.4.4. Statistical Analyses

To examine whether the stress task induced significant increase in SBP and decrease in RSA, a paired samples *t*-test was conducted. Pearson correlations were used in order to examine the relationship between *ACE total score* as well as *age of first ACE occurrence* and indices of sympathetic and parasympathetic functioning (i.e., SBP at baseline, SBP reactivity, RSA at baseline, and RSA reactivity).

Partial correlations were performed for RSA reactivity controlling for the potentially confounding influence of changes in respiratory rate from baseline to stress condition (Grossman & Kollai, 1993). For assessment with standardized respiratory rate, a Pearson correlation between RSA during paced breathing and *ACE total score* was calculated.

Exploratory analyses were used to examine the association between the four ACE subscales and SBP as well as RSA using a more conservative $p < 0.01$ significance criterion to reduce type-I error. Since distributional assumptions were not met for all ACE subscales, non-parametric Spearman correlations were conducted.

4. Summary of Results

The following section gives a brief overview of the results of the three articles. For further descriptions and information, the articles are contained in the appendix.

4.1. Daily stress, presleep arousal, and sleep in healthy young women: a daily life computerized sleep diary and actigraphy study

The average subjective sleep quality of 3.81 ± 1.0 (*SD*) (range from 0 (lowest sleep quality) to 5 (highest sleep quality)) and a mean SE of 93.7% ± 5.1% (*SD*) indicated good sleep during the study period in our sample of healthy young women. Participants reported an average of 10.52 ± 6.68 (*SD*) (out of 50 possible) daily stress events per day. Mean cognitive presleep arousal was 11.61 ± 4.10 (*SD*) and mean somatic presleep arousal was 10.69 ± 3.07 (*SD*), which indicated overall levels at the lower end of the continuum (range 8-35 for both scales).

On the between-participant level a strong positive relationship was found between stress and arousal in general (i.e., significant associations ($p < .001$) for all three types of stress scores with somatic as well as cognitive arousal). A significant association between presleep arousal and sleep was only found for the relationship between somatic arousal and subjective sleep quality but not for any other mediator-outcome pair. As a consequence, there was only one significant mediating effect of somatic arousal for the relationship between stress (as expressed by all three types of measures) and subjective sleep quality ($p < .01$ for all three stress measures). Thus, participants who reported higher average stress compared to others also reported higher somatic arousal and worse subjective sleep quality. All other indirect effects tested did not yield significance: in contrast to subjective sleep quality, somatic arousal did not play a mediating role between stress and actigraphic SE, and cognitive arousal did not play a mediating role between stress and both SE and subjective sleep quality.

As seen for the between-participant level, there was a strong positive relationship between stress and arousal on the within-participant level ($p < .001$ for all associations). Thus, both cognitive, and somatic presleep arousal were increased on days with reported increased stress. There was a significant mediating effect of somatic arousal for the relationship between stress (sum and average impact of stress) and actigraphy-recorded SE (in the unexpected direction of higher SE, $p < .05$ for both stress measures). Thus, subsequent SE was increased on days with reported increased stress (compared to participant's own mean), which was significantly mediated by somatic arousal. Additionally, there was a significant mediating effect of cognitive arousal on the relationship between stress (as expressed by all three types of measures) and subjective sleep quality ($p < .05$ for all three stress measures).

Thus, on days with reported increased stress (compared to days with a lower level of stress), participant's subsequent subjective sleep quality was decreased, which was significantly mediated by cognitive arousal.

4.2. Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity

Results obtained by repeated GLM measure analyses indicated that the stress task induced a significant increase in cortisol levels [$F(1.87, 185.52) = 27.16$, $p < .001$; $\eta_p^2 = .22$] and heart rate [$F(1.85, 164.95) = 216.86$, $p < .001$; $\eta_p^2 = .71$]. Subjects experienced significant worsening of mood [$F(3.53, 360.36) = 31.72$, $p < .001$; $\eta_p^2 = .24$], as well as increases in tension [$F(3.78, 385.39) = 32.82$, $p < .001$; $\eta_p^2 = .24$], and emotional stress [$F(3.90, 389.15) = 28.45$, $p < .001$; $\eta_p^2 = .22$]. There was no significant association between the subjective emotional responses to the MIST and the total number of ACEs, or cortisol and heart rate responses (all $p > .1$).

Concerning cortisol responses to stress, repeated measures analysis showed a significant interaction of time x *ACE total sum score* [$F(2.33, 221.60) = 5.89$, $p < .001$; $\eta_p^2 = .06$] as well as a significant main effect of *ACE total sum score* [$F(1, 95) = 7.52$, $p < .01$; $\eta_p^2 = .07$], indicating that more ACEs were associated with attenuated cortisol responses. Further, results showed a significant main effect of duration of *ACEs > one year* [$F(1, 95) = 10.10$, $p < .01$; $\eta_p^2 = .10$] and a significant interaction of time and duration of *ACEs > one year* [$F(2.33, 221.16) = 5.36$, $p < .01$; $\eta_p^2 = .05$]. However, these effects were not observed for the association between ACEs that lasted shorter in duration (*ACEs < one year*) and cortisol responses to the stress task [main effect, $F(1, 95) = .64$, $p = .43$; interaction effect, $F(2.24, 213.21) = 1.05$, $p = .36$]. Concerning the age of occurrence, a significant interaction effect [$F(2.33, 220.99) = 6.48$, $p < .01$; $\eta_p^2 = .06$], and a significant main effect were observed for the sum of events which occurred *before menarche* [$F(1, 95) = 10.26$, $p < .01$; $\eta_p^2 = .09$]. For events which occurred *after menarche*, these effects were not observed [main effect, $F(1, 95) = .18$, $p = .67$; interaction effect, $F(2.24, 212.34) = .63$, $p = .55$]. For the specific *age of first ACE occurrence*, no significant associations were observed [main effect, $F(1, 78) = .71$, $p = .40$; interaction effect, $F(2.24, 174.75) = .56$, $p = .58$].

Concerning heart rate response to the stress task, repeated measure analysis showed a significant main effect of *ACE total sum score* [$F(1, 85) = 7.13$, $p < .01$; $\eta_p^2 = .08$] as well as a significant interaction effect of time x *ACE total sum score* [$F(1.98, 168.32) = 5.86$, $p < .01$; $\eta_p^2 = .07$], indicating that more ACEs were associated with attenuated heart rate responses. Further analyses with duration as well as age of occurrence of ACEs revealed no significant

association with heart rate responses to the stress task. All results remained significant when the emotional responses to the stress task were entered additionally as covariates.

4.3. Adverse childhood experiences are associated with blunted sympathetic stress responsivity in healthy young women

Results from paired samples *t*-tests indicated that the stress task had high potency and induced significant increase in SBP ($t(128) = -23.87$, $p = .000$, $d = 1.59$) as well as decrease in RSA ($t(128) = 9.63$, $p = .000$, $d = 0.82$).

A significant negative correlation was found for *ACE total score* and SBP reactivity ($r = -0.295$, $p = 0.001$). For *ACE total score* and SBP at baseline, there was an association being short of significance ($r = -0.159$, $p = 0.072$). Specifically, higher *ACE total score* was associated with lower SBP reactivity as well as a trend for lower SBP at baseline.

No significant correlation was found for *ACE total score* and RSA at baseline ($r = -0.036$, $p = 0.688$) or RSA during paced breathing condition ($r = 0.161$, $p = 0.102$). There was a significant association between *ACE total score* and RSA reactivity ($r = 0.188$, $p = 0.033$). Specifically, higher *ACE total score* was associated with lower RSA reactivity. However, when respiratory rate reactivity was controlled for, the association between *ACE total score* and RSA reactivity was no longer significant ($r = 0.123$, $p = 0.188$).

Concerning *age of first ACE occurrence*, Pearson correlations showed a significant association with SBP reactivity ($r = 0.241$, $p = 0.010$). Earlier ACE occurrence was associated with lower SBP reactivity. *Age of first ACE occurrence* correlated moderately with *ACE total score* ($r = -0.298$, $p = 0.001$). When total score was entered as a covariate, the association between *age of first ACE occurrence* and SBP reactivity was short of significance ($r = 0.183$, $p = 0.052$). Also, there was an association between earlier age of ACE occurrence and lower RSA reactivity being short of significance ($r = -0.161$, $p = 0.088$). Again, this association was no longer significant after controlling for respiratory rate ($r = -0.131$, $p = 0.190$). No significant associations were observed for the relationship between *age of first ACE occurrence* and SBP at baseline or RSA at baseline.

Spearman correlations showed a significant association between general trauma and SBP reactivity ($\rho = -0.282$, $p = 0.001$). A higher ACE score in general trauma was associated with lower SBP reactivity. Using the more conservative criterion of $p < 0.01$, no further significant associations between ACE subscales and SBP baseline, RSA baseline, and RSA reactivity were observed.

5. Discussion

The aim of the present dissertation was to contribute to the knowledge about different aspects of stress and their impact on healthy young women. The first objective was to extend previous findings on the relationship between daily stress, presleep arousal, and sleep since empirical studies on a day-to-day basis using between- and within-participant data are still scarce. Both subjective and actigraphic sleep measures were assessed in a daily life study in healthy young women. The second aim was to gain further knowledge regarding the understanding of the psychophysiological consequences of stress experiences during childhood and adolescence. Therefore, the association between ACEs and endocrine as well as cardiovascular stress reactivity in response to a psychosocial stress task was investigated with the subsequent third aim to clarify the role of the sympathetic and the parasympathetic branches of the ANS in cardiovascular stress responsivity.

5.1. Daily stress, presleep arousal, and sleep in healthy young women: a daily life computerized sleep diary and actigraphy study

The first article examined the relationship between daily stress, presleep arousal, and sleep in healthy young women using multilevel structural equation models. In summary, our results confirm that presleep arousal plays an important role in mediating the effects of daily stress on sleep quality and SE in healthy young women. On the between-participant level, our results showed a mediating role of somatic presleep arousal between higher daily stress and worse subjective sleep quality, while there was no mediating role of presleep arousal between daily stress and actigraphy-assessed SE. On the within-participant level, results showed a mediating role of cognitive presleep arousal between increased daily stress and worse subjective sleep quality. Further, results showed a mediating role of somatic presleep arousal between daily stress and actigraphic SE in an unexpected direction. On days with higher levels of daily stress relative to their own mean, participants experienced higher somatic presleep arousal and showed subsequent higher SE during the following night as indexed by reduced wake time during sleep.

The mediating role of cognitive arousal on the within-participant level as well as the mediating role of somatic arousal on the between-participant level are in accordance with our hypothesis. However, there is evidence for a more general influence of arousal, with somatic and cognitive arousal being relevant on both levels, between and within-participants (Fernandez-Mendoza et al., 2010; Morin et al., 2003; Wuyts et al., 2012), which we could not corroborate. A possible explanation for this discrepancy may be the fact that our study

volunteer sample differed from samples in other studies regarding age and gender distribution. Furthermore, it is important to bear in mind that our sample consisted of young and overall good sleepers with no clinical sleep impairment, as confirmed by the overall high SE and subjective sleep quality. In addition, the women of our sample showed generally low levels of stress and arousal, which might further explain why we did not find arousal to significantly influence sleep in several of our analyses. In accordance with our results, Morin et al. (2003) mentioned that associations between arousal and subjective sleep quality were low in their sample.

We consistently found higher levels of stress to be associated with higher levels of cognitive and somatic presleep arousal, which is in accordance with current models of insomnia, all including some sort of interplay between stress and arousal in the development of insomnia (Espie, 2002; Morin, 1993; Riemann et al., 2010). While the results on the level of subjective sleep quality did partially fit the assumption of higher stress and arousal being associated with worse subjective sleep quality, this relationship did not seem to apply for actigraphy-assessed sleep data, which does not fit into insomnia models at first sight. Still, this finding is not necessarily contradictory since it is well-known that the subjective perception of impaired sleep is not always objectively measurable in actigraphic or polysomnographic sleep data (Jackowska, Dockray, Hendrickx, & Steptoe, 2011; Means et al., 2003). Also, all models require some sort of dysregulation or malfunctioning of the homeostatic or regulatory processes in the development of insomnia (e.g., de-arousal processes, sleep habits, chronobiologic timing, attentional focus, coping strategies; Espie, 2002; Morin, 1993; Riemann et al., 2010). Therefore, it fits into the models that these homeostatic processes are still intact and sleep is not automatically impaired after experiencing higher levels of stress and arousal in a sample of healthy women without clinically significant sleep impairment. It might be possible that higher levels of stress and arousal might not yet influence actigraphic sleep measures in a young and healthy sample but could still constitute a factor preceding the development of subsequent sleep disturbances (e.g. Fernandez-Mendoza et al., 2010; Jansson-Fröjmark & Linton, 2008). Finally, subjective sleep quality and actigraphy-recorded SE measure different aspects of sleep, which are not exactly comparable. Actigraphy-assessed measures detect sleep–wake cycles by an accelerometer and objectively quantify sleep duration and number of awakenings in relation to the time spent in bed. Subjective sleep quality estimates include a variety of perceived sleep features, such as consciously perceived sleep disruptions, well-being, and sleep inertia on awakening, all entering the total, subjective perception of sleep quality. Interestingly,

participants even showed higher SE on days with above average levels of stress and somatic arousal, which may indicate an adaptive response to stress.

In conclusion, the first study provides important knowledge regarding the relationship between daily stress, presleep arousal, and sleep. It confirms that arousal plays a mediating role between stress and subjective sleep quality, even in a sample of healthy young women. This mediating role was restricted to somatic arousal being relevant on the interindividual level and cognitive arousal on the intraindividual level. To the best of our knowledge, our study is the first to investigate between- and within-participant levels, along with subjective and actigraphy-assessed sleep outcomes in young adults. Actigraphic SE was not impaired by stress and arousal in healthy young women, who might even be able to compensate for days with above average levels of stress and arousal during the subsequent night.

5.2. Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity

The results of the second article confirmed previous reports of attenuated endocrine (Carpenter et al., 2007; Carpenter et al., 2011; Elzinga et al., 2008; Lovallo et al., 2012) as well as cardiovascular (Lovallo et al., 2012) stress responses to a psychosocial stress test in healthy adults with a history of ACEs. To the best of our knowledge, it is the first study to demonstrate that in healthy female subjects, especially long enduring, chronic ACEs seem to be associated with blunted cortisol reactivity. While the sum of events which occurred before menarche was significantly associated with blunted cortisol reactivity, the sum of events after menarche was not. Also, in this sample, the specific age of occurrence did not contribute to a further understanding of the association between timing of ACEs and endocrine reactivity. Besides the finding of diminished heart rate responses in association with the total number of ACEs, duration as well as age of occurrence of ACEs were not associated with cardiovascular reactivity. Importantly, blunted cortisol and heart rate responses were independent of emotional responses, suggesting that the diminished endocrine and cardiovascular stress reactivity cannot be explained by a reduced emotional reaction to stress after a history of childhood adversity.

Our results in participants free of mental and physical illness show a deviation from heightened endocrine and cardiovascular stress response often reported in other samples in association with a history of ACEs (e.g. Heim, Newport, et al., 2000; Rao et al., 2008). However, according to recent findings on stress reactivity (Ellis et al., 2005; Obradovic, 2012) in the context of early adversity, and considering the diversity of mediating factors mentioned in the background, it is more accurate to state that exposure to early life stress may lead to

dysregulated physiological phenotypes rather than to a particular pattern of hyper- or hyposensitivity. Also, the recently proposed adaptive calibration model (Del Giudice et al., 2011) offers an evolutionary-developmental theory of individual differences in physiological reactivity processes. The authors hypothesize that, at a very general level, a nonlinear relation between adverse life event exposure and stress response exists. In the context of high adversity, the model predicts an either vigilant profile, characterized by high biological stress responsiveness, or an unemotional, under-responsive profile, characterized by generally low SNS and HPA axis activity. These different phenotypes might be mediated by the interaction of various factors such as the study sample, the type of maltreatment, complex environmental, and genetic factors.

In terms of environmental factors, studies have demonstrated that the HPA axis in early human development is under strong social regulation (Tarullo & Gunnar, 2006). Therefore, sensitive environments (such as sensitive parenting or caregiving) have been suggested to moderate HPA reactivity by buffering cortisol responses to stress (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Tarullo & Gunnar, 2006), whereas being deprived of an evolutionarily expectable level of care (e.g. institutional rearing) has been associated with dysregulated cortisol response (Carlson & Earls, 1997; Gunnar, Morison, Chisholm, & Schuder, 2001). However, studies with institutionalized children were also able to show that improved caregiving environments had an effect on normalizing diurnal rhythms of the HPA axis (see for review: Slopen, McLaughlin, & Shonkoff, 2014). The social buffering of the HPA axis is supported by findings in animal models. In their extensive summary of literature, Hostinar et al. (Hostinar, Sullivan, & Gunnar, 2014) report results from animal studies, which suggest that neural mechanisms are responsible for behavioural and neuroendocrine changes due to social buffering.

These findings in human and animal studies provide support for an adaptive response of the stress system to its environment, probably in order to enhance survival odds. This might support the hypothesis, that in a chronically stressful environment, after an initial hypersecretion of cortisol, the HPA axis could counter-regulate its response and cortisol output might rebound to below normal. A plausible biological explanation could be an increased glucocorticoid negative feedback with a down-regulation of CRF receptors, or a diminished release of cortisol by the adrenal glands (Fries et al., 2005; Heim, Ehlert, et al., 2000). The finding that especially chronic events were associated with a blunted cortisol response supports this view.

In terms of genetic and epigenetic factors, preliminary evidence links genetic and epigenetic alterations to stress reactivity in association with ACEs. For example, a history of ACEs has been linked to an epigenetic regulation of hippocampal glucocorticoid receptor expression (McGowan et al., 2009). Moreover, a recent study on healthy adults who experienced the loss of a parent during childhood, maltreatment, or low parental care showed epigenetic alterations (increased methylation) of a region of the human glucocorticoid receptor gene, which in turn was associated with blunted cortisol reactivity after a neuroendocrine challenge test in these participants (Tyrka et al., 2012). Another study linked prenatal maternal depression to increased methylation of the glucocorticoid receptor gene in newborns, and showed exaggerated salivary cortisol output to stress at three months of age (Oberlander et al., 2008).

In summary, our results raise the challenging question of whether the observed alterations in stress responsivity can be interpreted as a potential risk factor or as a sign of resilience to the development of later mental and physical disorders. Even if initially adaptive, blunted cortisol reactivity could compromise future and necessary psychobiological stress reactivity. As already mentioned, low cardiovascular and/or endocrine reactivity to acute psychological stress has been associated with fibromyalgia, adiposity, burn out, atypical depression, and chronic pain syndromes (e.g. Gold & Chrousos, 2002; Heim, Ehlert, et al., 2000; Jones et al., 2012; Phillips, Hunt, Der, & Carroll, 2011; Pruessner, Hellhammer, & Kirschbaum, 1999).

5.3. Adverse childhood experiences are associated with blunted sympathetic stress responsivity in healthy young women

The third article extends the previous finding of blunted heart rate reactivity in response to the stress task by clarifying the role of the sympathetic and parasympathetic branches of the ANS. Our results show blunted SBP reactivity in association with higher number of ACEs, indicating down-regulation of phasic sympathetic stress response. No significant association was found between ACEs and RSA reactivity after controlling for respiratory rate changes, which indicates that blunted heart rate response was not appreciably influenced by alterations in parasympathetic functioning. In addition to blunted SBP reactivity, participants with higher number of ACEs showed a trend for lower SBP at baseline.

Additionally, we found blunted SBP reactivity in association with earlier age of occurrence of ACEs. This implies that the finding of blunted SBP reactivity in the context of ACEs applies particularly to participants with early ACE occurrence, which is in accordance with the hypothesis that earlier developmental periods could be especially sensitive for lasting

alterations in stress response (Charmandari et al., 2003; Tottenham & Sheridan, 2010). Still, the association was only short of significance after controlling for ACE total score. The total number of ACEs and the age of first occurrence of ACEs are not independent from each other since it is known that early ACEs or traumatisation enhance the probability of future adversity (Desai, Arias, Thompson, & Basile, 2002).

The finding of blunted SBP at baseline as well as blunted SBP reactivity is contrary to several findings of heightened sympathetic activity and reactivity in clinical and non-clinical samples with adversity (Blechert et al., 2007; Heim, Newport, et al., 2000; Otte et al., 2005; Su et al., 2014). Still, the result of blunted reactivity is in accordance with the findings of Lovallo et al. (2012) and Leitzke et al. (2013), who reported blunted heart rate or SBP reactivity in their samples. Lovallo et al. (2012) explain their finding with altered functioning of stress systems towards a blunted response and argue that deviations from the norm in either direction (exaggerated or diminished stress reactivity) might signal a system's loss of efficient allostatic regulation. This is in accordance with theories of allostatic load (McEwen, 1998) as well as with evidence of adverse health outcomes in association with blunted stress response (see for review: Carroll, Lovallo, & C., 2009; Gold & Chrousos, 2002; Lovallo, 2011). Leitzke et al. (2013) consider the possibility of useful adaptation as an explanation for their finding of blunted SBP reactivity in youth. They argue that an attenuated stress response might be adaptive in the context of repeated significant but not overwhelming stress exposure because it reduces chronic activation, fearfulness, and psychophysiological activity to subsequent stressors (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009; Leitzke et al., 2013). One may add that brief intermittent stress exposure rather than zero-stress environments in early life induces subsequent stress resistance, which is referred to as stress inoculation (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). In our healthy sample, ACE scores were on the lower end of the continuum, which indicates that the dosage of stressful experiences in the high-ACE individuals was still low enough to promote the development of stress resistance. It is likely that much higher ACE scores would have the opposite effect. This is in accordance with the adaptive calibration model (Del Giudice et al., 2011), which predicts a nonlinear relation between exposure to adversity and stress response, with moderate stress environments leading to a buffered responsivity pattern while dangerous or unpredictable environments would lead to a vigilant responsivity pattern.

Although higher ACE scores significantly correlated with blunted RSA reactivity (i.e., vagal withdrawal), which is in accordance with impaired parasympathetic withdrawal or slower recovery in response to trauma recall in samples with adversity or PTSD (Arditi-

Babchuk et al., 2009; Cohen et al., 1998), the correlation was no longer significant after controlling changes in respiratory rate. This indicates that in our sample of healthy young women changes in parasympathetic functioning to stress did not depend on the number of ACEs, and that the blunted heart rate reactivity we found in the second article was primarily due to reduced sympathetic reactivity. Also, no significant association was found between ACEs and RSA at baseline (during spontaneous as well as paced breathing), indicating that the healthy young women did not differ in tonic vagal activity irrespective of the number of ACEs they have experienced. Although there is evidence showing lower baseline RSA in association with adversity (Blechert et al., 2007; Cohen et al., 1997; Dale et al., 2009), many of these studies involved clinical samples or were conducted with children or adolescents, while our finding is in accordance with results from a representative sample of the Dutch population showing no differences in RSA measures at rest in the context of ACEs (van Ockenburg et al., 2014).

In exploratory analyses we found evidence for an association between blunted SBP reactivity and more incidences of general trauma, such as natural disasters, death of a close person, or separation of parents. Findings regarding the association of different types of adversity and ANS functioning are still scarce but Lovallo et al. (2012) reported emotional adversity to be related to smaller heart rate responses. More studies have been conducted concerning endocrine stress response (Carpenter et al., 2011; Heim et al., 2008) but results are mixed with significant effects for different types of adversity in different samples. In conclusion, to our knowledge, there is not yet consistent evidence for a specific pattern of certain types of ACEs being associated with specific alterations of the stress response.

5.4. Strengths and Limitations

The present dissertation contains the first study to investigate the relationship between daily stress, presleep arousal, and sleep on both, between- and within-participant levels, along with subjective and actigraphy-assessed sleep outcomes in healthy young adults. It confirms that arousal plays a mediating role between stress and subjective sleep quality and contributes to the knowledge about the roles of somatic and cognitive arousal, as well as actigraphic SE.

The second article provides important knowledge about the psychobiological consequences of stress and specifically, the relationship between ACEs and endocrine as well as cardiovascular stress response. It strengthens the assumption that ACEs give rise to a blunted stress reactivity of the HPA axis and the ANS in healthy young adults. The finding that ACEs represent a risk factor in the development of alterations of the human stress system in the absence of current physical and mental illness contributes to a further understanding of

the consequences of stress experiences in childhood and adolescence. A further strength is the investigation of duration and age of occurrence of ACEs in the context of a laboratory stress task with the result that especially long enduring, chronic stress experiences, as well as experiences which occurred before menarche, were associated with blunted cortisol response.

The third article extends the finding of the second article by clarifying the role of the sympathetic and parasympathetic branches of the ANS in blunted heart rate reactivity in response to the MIST. To our knowledge, it is the first study so far that has examined the association between ACEs and both branches of the ANS at the same time in otherwise healthy young adults. It confirms blunted SBP reactivity but not blunted RSA reactivity in association with more ACEs in healthy young women, indicating down-regulation of phasic sympathetic stress response but no alteration of parasympathetic functioning with ACEs.

General strengths are the relatively large sample size and the control for potentially confounding variables in all three articles. Also, the confinement of the sample to physically and mentally healthy young women allowed to investigate the association between ACEs and stress response as well as daily stress and sleep in a homogenous non-clinical sample, free of psychiatric comorbidities and medications interfering with stress system assessment. Also, our sample represents an age group of healthy females, which has rarely been object to the investigation of ACEs and stress reactivity thus far.

Beside these strengths, the results of the studies have to be evaluated in the context of their limitations. The following limitations have to be considered for all three articles.

First, due to the characteristics of the study sample, the presented findings can only be generalized to young women free of mental and physical illness. To generalize these results to the whole population of healthy adults, it will be necessary to replicate the studies with participants of a broader age range and including both men and women. Also, the exclusion of participants with psychiatric diagnosis or physical pathology may have restricted the range of ACEs, stress reactivity, arousal, and sleep-related variables.

Secondly, our sample consisted of young women attending schools for healthcare professions and social work. It cannot be excluded that there is a sample bias in the direction that only individuals who are particularly stress-resilient and feeling capable of the demanding and straining work in healthcare chose this kind of occupational career. Compliance was extraordinarily high in our sample, which supports the assumption that the sample was resilient to additional stress and dedicated to social commitment.

Finally, the assessment of ACEs, daily stress, presleep arousal, and subjective sleep quality was based on subjective and self-report measures. Therefore, effects of memory as

well as selective recall due to retrospective bias cannot be excluded. Still, retrospective recall of sexual and physical abuse as well as physical and emotional neglect have been evaluated to be sufficiently valid (Hardt & Rutter, 2004). Also, participants assessed stress, arousal, and sleep quality on the same day to keep retrospective bias at a minimum. Compliance with adequate time of entry was improved by the use of computerized diaries because participants were aware that times of diary entries are recorded (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2003).

A specific limitation of the first article is the acquisition of sleep data being based on actigraphy and subjective sleep measures. Despite the value of those data, studies using PSG would be useful to confirm our findings due to the high validity of PSG and its ability to consider additional dimensions of sleep. For the second study on endocrine stress response, only peripheral readouts of stress hormone activation were measured, which implies that identifying the exact mechanisms or location of the observed dysregulation in the complex and multilayer system of the HPA axis was not possible. Also, for methodological reasons, the specification between ACEs shorter/longer than one year and pre-/post-menarche cannot be assumed to be completely independent from each other. Since some participants reported both, acute and chronic ACEs as well as pre- and post-menarche ACEs, it was not possible to have distinct orthogonal groups. In the third study, additional cardiovascular sympathetic indices, such as the pre-ejection period (PEP), would have been advantageous (Schachinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001). The assessment of data on pre- and postnatal stress exposure was beyond the scope of the present investigation, but would have been valuable, since both, prenatal maternal stress and postnatal adversity, have been associated with alterations in stress response (Bosch et al., 2012; Entringer, Kumsta, Hellhammer, Wadhwa, & Wust, 2009).

5.5. Clinical Implications and Future Research

As a main conclusion of the first article, daily stress is associated with higher somatic and cognitive presleep arousal and via this mediating path does influence subjective sleep quality in healthy young women. This implies that stress, even on a level of frequency and intensity which belongs to our daily life, does have an impact on subjective sleep and well-being and this seems to apply even for healthy samples of young female adults. As a consequence, besides of considering the potential impact of daily stressors in the treatment of sleep disorders, even young and healthy samples might profit from preventive actions concerning the regulation of stress and arousal. Especially, due to its mediating role, strategies targeting the reduction of arousal after stressful days, such as relaxations techniques or mindfulness, are

indicated. Future research should further examine the roles of somatic and cognitive arousal on the inter- and intra-individual levels since this might help to target more specific interventions.

Actigraphic SE was not impaired by stress and arousal in healthy young women, who might even be able to compensate for days with above average levels of stress and arousal during the subsequent night. This finding suggests that it might be useful to further explore the mechanisms causing this adaptive regulation in order to derive useful strategies for prevention. Still, it might also be possible that higher levels of stress and arousal might not yet influence actigraphic sleep measures in a young and healthy sample but could still constitute a factor preceding the development of subsequent sleep disturbances (Fernandez-Mendoza et al., 2010; Jansson-Fröjmark & Linton, 2008). Therefore, it would be interesting to compare our findings with a group of healthy sleepers with a broader age range to investigate if stress and arousal do influence sleep more strongly with higher age (i.e., if age moderates this relationship). Also, prospective research will have to show whether higher levels of stress and arousal constitute a risk for future sleep impairment. In order to gain additional knowledge, future studies on the above-mentioned topics should include measures of PSG and use samples with more occupational diversity. The inverse effect of sleep quality or quantity of the previous night on stress reports during the next day might be equally important to fully understand the relationship between stress, arousal, and sleep, and therefore could be a topic for further investigation (Garde et al., 2011).

The two articles on laboratory stress response showed blunted endocrine as well as blunted SNS reactivity in association with more ACEs in healthy young women. Furthermore, it identified longer duration of ACEs as well as age of occurrence before menarche to be associated with blunted cortisol response during the psychosocial stress task. Earlier age of first ACE occurrence was associated with blunted SBP reactivity on a trend level. In conclusion, these results confirm that ACEs are associated with alterations in human stress response systems, even in the absence of current physical or mental illness. Together with the evidence that blunted stress reactivity is associated with a variety of negative health outcomes (e.g. Chrousos, 2009; Lovallo, 2011) this would imply that blunted HPA and SNS reactivity serve as an important marker for future (psycho-) pathology and could indicate the need for appropriate preventive actions against those disorders in order to keep the potential consequences of ACEs associated with blunted stress response to a minimum. This is mentioned besides the ubiquitous agreement that the reduction of ACEs, traumas, and adverse

living conditions would be the most optimal preventive action, which constitutes one of the most difficult but fundamental challenges of our society.

On the other hand, in our healthy sample ACE scores were on the lower end of the continuum and, according to above-mentioned theories, could have been low enough to stand for the promotion of development of stress resistance: it is argued that repeated significant, but not overwhelming stress exposure in early life promotes an attenuated stress response (Gunnar et al., 2009; Leitzke et al., 2013; Parker et al., 2006). Also, low stress response might have beneficial effects since it guards the individual against health outcomes associated with exaggerated response. For example, blunted sympathetic stress response might from this point of view be protective regarding cardiovascular risk. In this case, it would be essential to further investigate the underlying factors, such as the intensity, frequency, and types of stressors promoting stress resistance and adaptive responses to stress, but also corresponding mediating and moderating factors, including genetics, epigenetic programming, as well as environmental factors. Knowing the underlying factors of adaptive responses might help to establish preventive actions and interventions regarding the pathway of non-adaptive outcomes. For example, protective effects due to maternal care have been reported in both HPA and LC-NE systems (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000) and knowledge about such mechanisms could help developing parenting programs. Since these considerations are speculative without longitudinal outcomes, only further research with prospective design can show whether blunted stress response represents a beneficial adaptation or is a predictor of long-term adverse health consequences.

According to the adaptive calibration model proposed by Del Giudice et al. (2011), different responsivity patterns or phenotypes evolve in adaptation to different stress environments in order to enhance survival and reproduction and are mediated by various factors, such as genetic and epigenetic alterations. This model may help to complete the picture and to integrate disparate findings in the literature. All proposed responsivity patterns represent the best possible adaptation in response to the environment but are nevertheless accompanied by costs of adaptation, such as negative health outcomes, which increase with more dangerous and unpredictable environments. Future research will have to further investigate those phenotypes and their potential consequences.

Additionally, it will be important to further investigate the important issue of the relevance of the age of occurrence of ACEs. Our results were mixed, with ACE occurrence before menarche but not specific age of occurrence being associated with blunted endocrine stress response. Also, age of ACE occurrence was associated with blunted SBP reactivity on a

trend level. Future studies might profit from further systematic differentiation concerning the age of occurrence, including the investigation of more specific age groups (Bosch et al., 2012). It will also be crucial to answer the question whether there is evidence for a specific pattern of certain types of ACEs being associated with specific alterations of the stress response. Methodologically, it might be interesting to combine timing of ACEs and type of trauma, investigating age of ACE occurrence in samples with a specific trauma or life-event. Additionally, further research is needed in order to extend the knowledge about the exact locations and mechanisms concerning the neural dysregulation, which is responsible for alterations in stress response, as well as the genetic and epigenetic factors, which potentially influence those processes on various levels.

While we assessed endocrine and autonomic function in the same sample and contribute to the knowledge about the specific nature of ANS alterations after ACEs in the third article, more empirical research is needed, not only concerning the simultaneous examination but also concerning the coordination and interactions between the endocrine, the immune and the two branches of the autonomic stress systems. Only a multisystem approach will help to understand the exact physiological correlates of different health outcomes and accordingly, help to target specific interventions (Bauer et al., 2002).

Importantly, due to evidence of ACEs being associated with exceeding stress response with corresponding vigilance and arousal in some samples (Chrousos, 2009; Heim et al., 2008), as well as hyperarousal playing a crucial role in the development of sleep disorders (Riemann et al., 2010), one could ask the question if ACEs, via the mediating path of altered stress response and hyperarousal, could also be associated with sleep impairment in our sample of healthy young women. This topic was beyond the scope of the present dissertation and should be further investigated. Still, in order to add to the picture, in our sample, we did not find an association between ACEs and sleep, which further underlines the health and potential resilience of the sample and is in accordance with our finding of not heightened but blunted stress response.

5.6. Conclusion

The results of the present dissertation confirm the potential danger of different kinds of stressors even in a healthy young sample. Enhanced stress and arousal significantly worsened subjective sleep quality and ACEs were associated with blunted endocrine and sympathetic stress response. On the other hand, as evidenced by higher actigraphic SE after above average stress, and the absence of negative health outcomes up to the present, stress did not impact our sample at all levels, which implies the presence of protective or adaptive mechanisms in healthy young women.

Understanding the underlying mechanisms in alterations and failure of stress response systems will aid in targeting interventions for persons at risk, and exposure to ACEs seems to be one important factor in determining this potential risk. In conclusion, future research should focus on a longitudinal, prospective investigation of endocrine as well as sympathetic and parasympathetic stress response in the context of ACEs. This will help to clarify whether blunted stress reactivity indicates a risk for negative health outcomes or might even be a sign of beneficial adaptation and as a consequence to either identify specific preventive actions or the potentially adaptive features that may promote beneficial outcomes. Similarly, longitudinal studies are needed in order to establish whether stress and arousal influence subjective and objective sleep quality in the long term in previously healthy samples.

Considering all this, discovering and establishing interventions with the aim to reduce the impact of chronic or exceeding stress on the stress system (by preventing it from overreacting in the first place as well as subsequent break-down), or even to improve dysfunctional stress regulation is a fundamental on-going challenge. Promising results show that family support, parenting programs, and improved caregiving environments for institutionalized children seem to have positive or normalizing effects on stress response systems (e.g. Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Furthermore, in healthy adult samples, cognitive-behavioural stress management proved effective in moderating neuroendocrine, and psychological stress reactivity (Gaab et al., 2003; Gaab, Sonderegger, Scherrer, & Ehlert, 2006), and stress management at the worksite has been successful in reversing ANS dysregulation with possible preventive effects regarding hypertension (Lucini, Riva, Pizzinelli, & Pagani, 2007).

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Appendix A

Winzeler, K., Voellmin, A., Schäfer, V., Meyer, A.H., Cajochen, C., Wilhelm, F.H., & Bader, K. (2014).

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Original Article

Daily stress, presleep arousal, and sleep in healthy young women: a daily life computerized sleep diary and actigraphy study

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ABSTRACT

Objective: Our study aimed to further elucidate the mediating role of presleep arousal in the relationship between daily stress and sleep by investigating subjective sleep quality and actigraphy-assessed sleep efficiency (SE) on both within- and between-participant levels in a sample of healthy young women.
Methods: Multilevel modeling was applied on electronically assessed data comprising 14 consecutive nights in 145 healthy young women to assess the relationship between daily stress, presleep (somatic and cognitive) arousal, and sleep on both levels between participants and within participants across days.
Results: Higher levels of daily stress were consistently and significantly associated with higher levels of somatic and cognitive arousal. Somatic arousal mediated the relationship between daily stress and worsened subjective sleep quality on the between-participant level, while cognitive arousal mediated the relationship between daily stress and worsened subjective sleep quality on the within-participants level. Unexpectedly, healthy young women showed higher SE following days with above-average stress with somatic arousal mediating this relationship.
Conclusions: Our data corroborate the role of presleep arousal mediating the relationship between daily stress and subjective sleep quality. Interestingly this effect was restricted to somatic arousal being relevant on interindividual levels and cognitive arousal on intraindividual levels. For young and healthy individuals who experience high stress and arousal, well-established cognitive–behavioral techniques could be useful to regulate arousal and prevent worse subjective sleep quality.

1. Introduction

Sleep disturbances are widely prevalent and represent a momentous health problem in the general population. The point prevalence of primary insomnia is estimated to lie between 2% and 6%, though self-reported sleep disturbances in healthy populations range up to more than 40% [1–5]. The impact of insomnia and other sleep disturbances is known to be severe and includes reduced quality of life and well-being as well as impaired daytime-functioning and working ability, and thus is a potential risk factor for subsequent health problems [1,2,6]. Accordingly, insomnia and sleep difficulties are associated with increased work absenteeism and healthcare costs [2–4,7].

Various psychological factors, such as stress, daily hassles, rumination, and hyperarousal have been found to play an essential role in the development of sleep disturbances [8–11], but the search for the specific roles and interplay among these factors is still ongoing. Our study aimed to further investigate the relationship between daily stress and hyperarousal and the influence of both factors on sleep and sleep disruptions.

Stress is one of the most common and well-known antecedents of insomnia and has been associated with impaired sleep in a variety of ways. Previous research shows that minor and major stressful events correlate with more sleep disturbances [12–15]. Major stressors usually are described as life events, such as severe illness or significant losses (e.g., death, divorce, work loss), and have been found to occur with greater incidence in the time preceding the onset of insomnia or to be associated with increased risk for the development of sleep problems [14–17]. Minor stressors usually appear with higher frequency and more likely on a daily basis (e.g., arguments, time pressure, work demands), and they have been associated with more disturbed sleep [12,13,18,19]. Additionally long-term stressors such as childhood adversities have been

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found to predict sleep problems several years later [20–24]. On a more acute daily basis, the experience of acute stress during the day was associated with impaired sleep the following night [25–30].

Well-established theories about hyperarousal and sleep postulate that physiological and cognitive arousal before bedtime is detrimental for sleep and contribute to the worsening of sleep problems [31,32]. Cognitive arousal consists of intrusive cognitions experienced as being uncontrollable, and physiological or somatic arousal is described as the perception of vegetative arousal (e.g., elevated heart rate, sweating [33]). In an integrative model, Morin [31] indicated that hyperarousal has a causal influence on sleep disturbances. In this model, the balance between sleep and wakefulness is regulated by the amount of arousal, and only low levels of arousal are compatible with sleep. Espie [32] further proposed that the inhibition of de-arousal processes in particular leads to the development of insomnia. Based on these theoretical frameworks, various studies tested the association between arousal and sleep and have confirmed that hyperarousal plays a major role in insomnia and sleep disturbances [10,11,34]. High arousal is more prevalent in poor than in good sleepers and can be measured on various physiological levels, such as sympathetic nervous system activation, hormone secretion, and high-frequency electroencephalogram activation [10,11,34]. In addition to the higher prevalence of arousal in insomniacs, there is evidence that high physiological and cognitive arousal also are prevalent in healthy populations and might constitute a preceding factor in the development of sleep disorders [35–37]. Even deliberately induced stress in the laboratory and the following increase in arousal at bedtime acutely worsen sleep in both poor and good sleepers [25,38,39].

Empirical studies on the relationship between stress and sleep on a day-to-day basis using within-participant data measured over time are still scarce. Garde et al. [40] found evidence for a bidirectional association between stress and sleep, indicating a self-reinforcing vicious circle. In a representative sample of the Danish population, higher ratings of stress at bedtime were associated with ratings of poor sleep the following night. In addition, higher ratings of poor sleep in the morning were associated with higher ratings of stress during the subsequent day [40]. In a study by Hanson and Chen [41], the daily number of stressors reported by healthy young adults was associated with subsequent sleep time when moderated by family risk. On days with elevated levels of stress, sleep time was significantly reduced the following night. Akerstedt et al. [30] studied the relationship between stress and sleep over a period of 6 weeks in 50 healthy adults. They found bedtime stress and worries to be the two main predictors of subjective sleep quality. Still the potentially mediating effect of arousal between stress and sleep was not tested in those studies.

Morin et al. [8] tested the relationship between all three variables and found a significant relationship between daytime stress and nighttime sleep, with presleep arousal playing a mediating role. The authors collected prospective daily paper and pencil measures for 21 consecutive days in men and women aged 19–60 years with insomnia in addition to good sleepers. Data showed that subjective stress during the day was a significant predictor of self-reported subjective sleep quality the following night for both groups and higher levels of presleep arousal mediated this relationship. Objective sleep measures were not used in this study [8].

Our study aimed to extend these findings on the relationship between stress, presleep arousal, and sleep considering various important aspects at the same time in a large healthy sample. Therefore, both subjective and actigraphic sleep measures were assessed and computerized diaries were used to enhance compliance and reliability compared to paper and pencil data [42]. Furthermore, multilevel modeling was used to evaluate the relationship on both levels (between participants and within participants across days). More specifically, it was hypothesized that participants reporting a higher level of stress compared to others also would experience a higher level of presleep arousal and comparably worse sleep (between-participant level). On the within-participant level, we expected that participants reporting a higher level of stress on a specific day compared to their own mean would experience higher presleep arousal and worse sleep the following night compared to days with a lower level of stress. It was further expected that presleep arousal would mediate the relationship between daily stress and sleep.

2. Methods

2.1. Participants

Data were collected in the context of a larger ongoing study about acute stress, emotion regulation, and sleep in young adults. Data for our analysis included a 2-week ambulatory assessment of sleep with actigraphic sleep measures and sleep diaries. The sample included young and healthy women (mean age, 21.7 ± 1.6 [standard deviation {SD} years]) who were recruited using flyers posted at two schools for healthcare professionals in Basel, Switzerland, or by e-mails within the schools. Potential study participants contacted the study office by e-mail or phone. They were first sent a screening questionnaire with the following inclusion criteria: female sex, age range between 18 and 25 years, German speaking, and good health.

Exclusion criteria for all participants included physical or psychiatric illness, pregnancy, regular and heavy tobacco use (>5 cigarettes a day), use of illegal drugs, use of any medication interfering with sleep, and night shift work. In a first office appointment, participants were further screened on inclusion and exclusion criteria and provided written informed consent. All remaining study participants were of either Swiss or German (86.9%) or other European nationality (13.1%), who received monetary compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Out of 246 individuals who responded to the advertisements, 38 (15.4%) were excluded because they did not meet the inclusion requirements (men [$n = 5$]; not meeting age criterion [$n = 4$]; physical illness [$n = 6$]; psychiatric illness [$n = 3$]; medication [$n = 7$]; no regular sleep–wake cycle [$n = 7$]; heavy tobacco use [$n = 5$]; and not German speaking [$n = 1$]). Further 24 (9.8%) did not return the screening questionnaire. Of the 184 participants who were invited for the first appointment, 23 (12.5%) dropped out due to time restrictions or personal reasons and 12 (6.5%) did not respond to repeated invitations. Out of the 149 individuals who came to the first appointment, another three had to be excluded due to physical illness ($n = 1$), psychiatric illness ($n = 1$), and dropout ($n = 1$). The remaining 146 participants were finally eligible for the study and started the 2 weeks of assessment.

All of the 146 participants completed the study and returned their material after 2 weeks, which corresponds to a total of 2044 actigraphy-recorded nights. The data set of one individual could not be used due to incomplete information about sleep and wake times (sleep parameters could not be reliably calculated). Three participants had two nights each for which sleep parameters could not be reliably calculated, in which case the data of those two nights were excluded. Nine participants reported illness during the 2-week assessment. Therefore, all nights affected by illness including one night of convalescence were excluded from analysis (a total of 49 nights). This response left data of 145 participants with 1976 nights (96.7%).

2.2. Procedure

All appointments took place in the laboratory of the CBT outpatient clinic of the Psychiatric Hospital of the University of Basel, Switzerland. Study volunteers were asked to wear the actigraphy device on their nondominant wrist and to complete their sleep logs every morning immediately after rising. Additionally daily stress and presleep arousal were measured every evening immediately before bedtime. After completion of the 2 weeks of ambulatory assessment, participants returned all material and were given their monetary compensation.

2.3. Measures

2.3.1. Clinical interview

A structured clinical interview for psychiatric disorders (SKID I for DSM-IV; Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, [43]) was used to assess the absence of psychiatric illness.

2.3.2. Actigraphy

Participants wore an ambulatory wrist actigraph (Micro Mini-Motionlogger, Ambulatory Monitoring Inc., Ardsley, NY) for 14 successive days and nights on the nondominant arm. The Micro Mini-Motionlogger is capable of detecting arm movement through the use of an accelerometer and represents a useful instrument for detecting sleep–wake cycles [44]. Data were analyzed using the Software Package Action4 (Version 1.05) and the ACT Millennium (Version 3.47.0.3) software (Ambulatory Monitoring Inc., Ardsley, NY). For the calculation of sleep parameters, the Action4 scoring algorithm provided by the producers (Ambulatory Monitoring, Inc. Ardsley, NY) was used. Sleep efficiency (SE) was derived from this analysis and was calculated as the ratio of total time asleep to time in bed. Additionally daily sleep logs were completed by the participants to cross-validate sleep start and end times. Outcomes from wrist actigraphy have been repeatedly compared to polysomnography (PSG) measures and represent a validated and unobtrusive technique which provides accurate estimates of global sleep parameters and sleep–wake identification [44–46].

2.4. Daily self-report measures

A menu-driven computerized questionnaire was developed to repeatedly assess subjective estimates of sleep quality, daily stress, and presleep arousal. Palm Tungsten E handheld computers were used as recording devices. Questionnaires were programmed and displayed using Pendragon Forms 5.0 software (Pendragon Software Corporation, Buffalo Grove, IL).

2.4.1. Subjective sleep quality

To assess subjective estimates of sleep quality, participants were instructed to fill in a computerized Likert-type scale ranging from 1 (very good sleep quality) to 5 (very poor sleep quality). For statistical analyses, the scale was reversed to have higher values for higher sleep quality. Participants completed this question in their handheld computers every morning after rising. Such Likert-type scales are widely used to assess subjective sleep quality and have been shown to be highly correlated with multi-item measures [47].

2.4.2. Presleep arousal

The Pre-Sleep Arousal Scale (PSAS) [33] contains 16 items with eight symptoms of cognitive (e.g., intrusive thoughts) and eight symptoms of somatic (e.g., sweating) arousal experienced at bedtime. Ratings range from 1 (not at all) to 5 (extremely). A total score from 8 to 40 is computed for both subscales with higher scores indicating higher arousal. We used a German translation similar to that used by Gieselmann et al. [48]. The PSAS has been broadly used and has shown satisfactory internal consistency and test–retest reliability [33]. Study volunteers completed the PSAS on their handheld computers every evening before bedtime.

2.4.3. Daily stress

The Daily Stress Inventory (DSI) [49] (German version [50]) is a 58-item self-report questionnaire assessing the occurrence and the impact of 58 possible daily stressors. Participants specify which events occurred and, in case of occurrence, the impact of every event is rated on a Likert scale (1 = occurred, but was not stressful; 7 = caused me to panic). Three scores can be derived: the actual number of events that occurred during the day (frequency), the sum of impact ratings (total impact of all events), and the average impact rating (sum of all ratings divided by the frequency). Considering that daily stress levels fluctuate, internal consistency and test–retest reliability are adequate [49,50]. The participants completed this questionnaire on their handheld computers every evening before bedtime.

2.4.4. The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) [51] (German version [52]) was used to descriptively assess subjective sleep quality and potential sleep problems. Global scores of >5 distinguish poor sleepers from good sleepers [51,52]. The PSQI was administered twice: once at the beginning of the study period, examining the weeks prior to the study participation; and once at the end of the study period, examining the weeks of the study duration. This 2-fold application was used to investigate if sleep was significantly influenced by the study participation (i.e., if sleep changed during the study period).

2.5. Data analysis

Our study used daily data from 14 consecutive days. Because of the hierarchical structure of the data (days nested within participants) and with the aim to be able to predict fluctuations from night to night in the variables, a multilevel modeling approach was used. Multilevel models are an extension of the general linear model and do not require observations to be independent. Because of their autoregressive nature and hierarchical structure, multilevel models are especially useful to study time-dependent changes [53–56]. By applying this approach, we were able to examine the relationship between daily stress, presleep arousal, and sleep within and between participants. Analyses on the between-participants level addressed the question if participants who experienced higher levels of daily stress also reported higher levels of arousal and worse sleep compared to participants reporting lower levels of daily stress and arousal.

Analyses on the within-participant level addressed the question if individuals reported higher arousal and worse sleep on days when they also reported above average stress levels compared to their individual average level. Here we used a multilevel structural equation model (MSEM), which represents an extension of the multilevel model (for details see [54]). MSEMs have been shown to lead to nonconflated estimates of between- and within-level components of indirect effects, thereby avoiding biased estimates which can occur when using more traditional multilevel models [54]. Note that in MSEM model based participant mean centering is used by default, i.e., the involved variables on the within-participants level denote deviations from each individual's mean. Our MSEM confers to a fixed slopes model, i.e., only intercepts were allowed to vary between participants but not slope parameters. Allowing random slopes would have led to a more complex model, typically requiring more time points per participant. Note that we

included time as additional predictor variable in all analyses to account for temporal trends in the mediator and outcome variables during the 14-day period (Fig. 1).

The following steps were required to establish mediation in our study: (1) the predictor (stress) positively affected the mediator (arousal), i.e., *a* was significantly higher than zero; (2) the mediator (arousal) negatively affected the outcomes SE and subjective sleep quality after controlling for the predictor (stress), i.e., *b* was significantly lower than zero; and (3) the indirect effect *ab* was significantly lower than zero. In contrast to the common and well-known approach by Baron and Kenny [57] in 1986, this method of establishing mediation does not require the total effect of the predictor on the outcome variable to be significant, i.e., *c* need not be significantly different from zero. This method enabled other mediating factors to influence the outcome in an opposite direction, which then could result in the total effect *c* to be equal zero, thereby obscuring the assumed mediating effect [58–61].

Preliminary analyses were performed using SPSS (version 19.0; SPSS, Chicago, IL) and R (version 2.15.2; R Foundation for Statistical Computing, Vienna) software packages. The MSEM was performed with Mplus (version 6.12; Mplus, Los Angeles, CA), which allowed assessment of the total, direct, and indirect effects on both hierarchical levels. Prior to analysis, data were checked for multiple outliers and were transformed to meet distributional assumptions. To identify highly influential data within our hierarchical dataset we used the R package Influence.ME [62]. For each analysis outliers defined by the Cook distance criterion were separately assessed and excluded. The number of outliers varied between 2 and 7. Subjective sleep quality and the stress variables number of events and sum of impact ratings were square root transformed, SE was log transformed, and cognitive and somatic arousal were reciprocally transformed.

There were missing data for 70 nights (12 participants) due to technical failure of actigraphs and for 27 nights (13 participants), as participants either forgot to wear the actigraph or to report their bedtimes and wake times. In addition, there were missing data for 39 nights regarding subjective sleep parameters, for 32 nights regarding arousal measures, and for 30 nights regarding stress measures, as participants forgot to fill in the questionnaires on their electronic diaries. This response left 1855 nights (90.8%) with complete data for all analyses with actigraphy-assessed sleep measures and 1916 nights (93.7%) with complete data for all analyses with subjective sleep measures.

3. Results

3.1. Stress, arousal, and sleep characteristics

Table 1 shows the means and standard deviations for age, daily stress, and presleep arousal, as well as the subjective and actigraphic sleep variables. The average PSQI score of 4.10 ± 1.8 (SD) and a mean SE of 93.7% ± 5.1% (SD) both indicate good sleep during the study period in our sample of healthy young women [51,52]. PSQI scores before the study period and at the end of the study did not significantly differ from one another ($P > .5$), indicating that sleep was not influenced on average by the study participation.

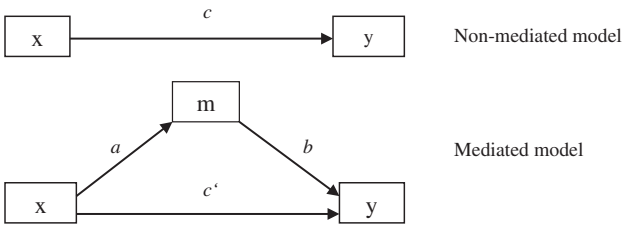

Fig. 1. Path diagram of the nonmediated (top) and mediated (bottom) effect of the predictor (stress) on the outcome (sleep). *c* denotes the effect of x on y in the absence of m; *c′* denotes the effect of x on y, corrected for m; *a* denotes the effect of x on m; and *b* denotes the effect of m on y, corrected for x.

3.2. Between-participant effects

Table 2 shows the results of the multilevel mediator model for subjective sleep quality and actigraphy-quantified SE on the between-participant level. A strong positive relationship was found between stress and arousal in general (i.e., significant results for parameter *a* in all 12 analyses performed; *P* value of at least <.001). A significant association between presleep arousal and sleep (parameter *b*) was only found for the relationship between somatic arousal and subjective sleep quality but not for any other mediator-outcome pair. As a consequence, there was only a significant mediating effect (*ab* significantly higher than 0) of somatic arousal for the relationship between stress (as expressed by all three types of measures) and subjective sleep quality. Thus participants who reported higher average stress compared to others also reported higher somatic arousal and worse subjective sleep quality.

All other indirect effects tested did not yield significance. In contrast to subjective sleep quality, somatic arousal did not appear to play a mediating role between stress and actigraphic SE, and cognitive arousal also did not appear to play a mediating role between stress and both SE and subjective sleep quality. Note that the total effect of stress on sleep (parameter *c*) was negative and significant in all 12 analyses performed, but the direct effect (parameter *c′*) was not significant in 11 of 12 analyses. This finding suggests that, although most mediating effects tested were nonsignificant, they still had an impact in that their inclusion in the model considerably reduced the total effect (compare *c* with *c′* in Table 2).

3.3. Within-participant effects

Table 3 shows the results of the multilevel mediator model for subjective sleep quality and actigraphy-quantified SE on the within-participant level. As seen for the between-participant level, there was a strong positive relationship between stress and arousal on the within-participant level (see significant results for parameter *a* in all 12 analyses performed; *P* value of at least <.001). Thus both cognitive and somatic presleep arousal also were increased on days with reported increased stress.

Significant associations between presleep arousal and sleep were found for the relationship between somatic arousal and actigraphy-assessed SE, though in the unexpected direction of higher SE, as well as for the relationship between cognitive arousal and subjective sleep quality with increased cognitive arousal leading to decreased subjective sleep quality (see parameter *b*). As a consequence, there was a significant mediating effect (*ab* significantly higher than 0) of somatic arousal for the relationship between stress as expressed by the sum of impact ratings, average impact rating, and (on a trend level, short of being significant) by the number of events and actigraphy-recorded SE. Additionally there was a significant mediating effect of cognitive arousal on the relationship between stress as expressed by all three types of measures and subjective sleep quality. Thus subsequent SE also was increased on days with reported increased stress. This effect was significantly mediated by somatic arousal. On days with reported increased stress, subsequent subjective sleep quality was decreased, which was significantly mediated by cognitive arousal.

Additional analyses revealed that the observed positive relationship between stress and SE could be explained by the fact that

Table 1
Sample characteristics, including age, daily stress, presleep arousal, subjective sleep estimates, and actigraphic sleep efficiency.

N = 145	Mean	SD	Range
Age (y)	21.74	1.64	18–25
Daily stress inventory[a]			
Number of events	10.52	6.68	0–50
Sum of impact ratings	24.41	18.84	0–134
Average impact rating[b]	2.19	0.85	0–5
Pre-sleep arousal scale[a]			
Cognitive arousal	11.61	4.10	8–35
Somatic arousal	10.69	3.07	8–35
Subjective sleep estimates			
Sleep quality[a]	3.81	1.03	1–5
PSQI-Score prior to study	3.99	2.26	0–15
PSQI-Score at study end	4.10	1.86	0–11
Actigraphic sleep measure[a]			
Sleep efficiency (%)	93.66	5.11	54.7–100.0

Abbreviations: SD, standard deviation; y, years; PSQI, Pittsburgh Sleep Quality Index.
[a] Mean values over all nights.
[b] Sum of ratings divided by the number of events.

Table 2
Direct, total, and mediated effects of stress on subjective sleep quality and actigraphic sleep efficiency with mediators of cognitive and somatic arousal (between-individual level).

Sleep	Arousal	Stress	*c* (SE)	*c′* (SE)	*a* (SE)	*b* (SE)	*ab* (SE)
Actigraphic sleep efficiency	Cognitive	Number of events	−0.680 (.324)*	−0.402 (.393)	1.194 (.131)***	−0.233 (.230)	−0.278 (.279)
		Sum of impact ratings	−0.517 (.183)**	−0.429 (.267)	0.753 (.067)***	−0.117 (.264)	−0.088 (.199)
		Average impact rating	−1.133 (.497)*	−0.876 (.602)	1.462 (.253)***	−0.175 (.221)	−0.256 (.326)
	Somatic	Number of events	−0.685 (.323)*	−0.469 (.383)	0.848 (.125)***	−0.255 (.267)	−0.216 (.232)
		Sum of impact ratings	−0.526 (.181)**	−0.373 (.275)	0.557 (.063)***	−0.274 (.321)	−0.153 (.179)
		Average impact rating	−1.321 (.486)**	−1.107 (.622)	1.246 (.219)***	−0.172 (.266)	−0.214 (.336)
Subjective sleep quality	Cognitive	Number of events	−0.397 (.162)*	−0.199 (.204)	1.265 (.115)***	−0.156 (.109)	−0.198 (.137)
		Sum of impact ratings	−0.271 (.091)**	−0.193 (.133)	0.760 (.064)***	−0.103 (.125)	−0.078 (.095)
		Average impact rating	−0.818 (.258)**	−0.673 (.307)*	1.430 (.254)***	−0.102 (.101)	−0.145 (.148)
	Somatic	Number of events	−0.440 (.154)**	−0.040 (.210)	0.951 (.117)***	−0.421 (.142)**	−0.400 (.142)**
		Sum of impact ratings	−0.250 (.087)**	0.045 (.126)	0.602 (.061)***	−0.491 (.149)**	−0.295 (.094)**
		Average impact rating	−0.653 (.255)**	−0.234 (.278)	1.090 (.212)***	−0.385 (.110)***	−0.419 (.142)**

Abbreviation: SE, standard error.
Estimated values and standard errors for direct, total, and mediated effects.
c: total effect of stress and arousal on sleep; *c′:* direct effect of stress on sleep, corrected for arousal; *a:* direct effect of stress on arousal; *b:* direct effect of arousal on sleep, corrected for stress; and *ab:* mediated effect of stress via arousal on sleep.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Table 3
Direct, total, and mediated effects of stress on subjective sleep quality and actigraphic sleep efficiency with mediators of cognitive and somatic arousal (within-individual level).

Sleep	Arousal	Stress	*c* (SE)	*c′* (SE)	*a* (SE)	*b* (SE)	*ab* (SE)
Actigraphic sleep efficiency	Cognitive	Number of events	0.813 (.197)***	0.815 (.198)***	0.489 (.056)***	−0.003 (.083)	−0.002 (.041)
		Sum of impact ratings	0.311 (.103)**	0.312 (.108)**	0.410 (.033)***	−0.003 (.088)	−0.001 (.036)
		Average impact rating	0.328 (.178)	0.273 (.192)	0.719 (.072)***	0.076 (.095)	0.055 (.069)
	Somatic	Number of events	0.815 (.197)***	0.735 (.203)***	0.494 (.054)***	0.160 (.097)	0.079 (.048)
		Sum of impact ratings	0.309 (.104)**	0.251 (.108)*	0.307 (.033)***	0.189 (.096)*	0.058 (.029)*
		Average impact rating	0.333 (.180)	0.249 (.184)	0.359 (.066)***	0.235 (.097)*	0.084 (.037)*
Subjective sleep quality	Cognitive	Number of events	−0.190 (.117)	−0.131 (.119)	0.488 (.054)***	−0.119 (.057)*	−0.058 (.029)*
		Sum of impact ratings	−0.097 (.060)	−0.047 (.062)	0.418 (.034)***	−0.121 (.056)*	−0.050 (.024)*
		Average impact rating	−0.033 (.111)	0.064 (.111)	0.715 (.076)***	−0.136 (.056)*	−0.097 (.042)*
	Somatic	Number of events	−0.178 (.118)	−0.147 (.121)	0.494 (.055)***	−0.062 (.060)	−0.030 (.030)
		Sum of impact ratings	−0.098 (.061)	−0.080 (.065)	0.319 (.032)***	−0.059 (.062)	−0.019 (.020)
		Average impact rating	−0.042 (.109)	−0.011 (.114)	0.404 (.065)***	−0.077 (.060)	−0.031 (.025)

Abbreviation: SE, standard error.
Estimated values and standard errors for direct, total, and mediated effects.
c: total effect of stress and arousal on sleep; *c′:* direct effect of stress on sleep, corrected for arousal; *a:* direct effect of stress on arousal; *b:* direct effect of arousal on sleep, corrected for stress; and *ab:* mediated effect of stress via arousal on sleep.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

increased stress was negatively related to wake time i.e., on days with elevated stress, as expressed by higher sum of impact ratings and number of events, participants exhibited significantly shorter wake time the following night ($P < .001$ for both stress measures) compared to days with lower stress. At the same time, increased stress compared to other days was not associated with total sleep time or time in bed the following night. Note that the total effects (parameter c) for the predictors number of events and sum of impact ratings were only slightly reduced, as shown by the corresponding significant direct effects (parameter c'). Therefore, additional mediators are likely to account for the relationship between stress and SE.

A significant positive temporal trend across the 14-day period was found for subjective sleep quality ($P < .001$), whereas no such amelioration in the course of the study was detected for SE and for somatic and cognitive arousal, the two mediator variables ($P > .05$ for all three variables).

4. Discussion

In our study, we examined the relationship between daily stress, presleep arousal, and sleep in a cohort of 145 healthy young women using multilevel structural equation models. Our results indicate and further extend previous findings that presleep arousal plays an important role in mediating the effects of daily stress on sleep quality and SE in healthy young women. On the between-participant level, our results confirmed a mediating role of somatic arousal but not cognitive presleep arousal between daily stress and subjective sleep quality. Healthy young female participants who experienced higher levels of daily stress compared to other young female participants also experienced higher somatic presleep arousal and reported worse subjective sleep quality. However, there was no mediating role of presleep arousal between daily stress and actigraphy-assessed SE.

On the within-participant level, results showed a mediating role of cognitive but not somatic presleep arousal between daily stress and subjective sleep quality. Participants reported worse subjective sleep quality after days with above-average stress and cognitive arousal relative to their own mean. Further, results showed a mediating role of somatic but not cognitive presleep arousal between daily stress and actigraphic SE in an unexpected direction. On days with higher levels of daily stress relative to their own mean, participants experienced higher somatic presleep arousal and showed subsequent higher SE during the following night as indexed by reduced wake time during sleep.

The mediating role of cognitive arousal between daily stress and subjective sleep quality on the within-participant level, as well as the mediating role of somatic arousal between daily stress and subjective sleep quality on the between-participant level, are in accordance with our hypothesis. However, Morin et al. [8] also found a mediating role of somatic arousal on the within-participant level, which we could not corroborate. On the between-participant level, previous findings showed that not only somatic but also cognitive arousal was associated with sleep disturbance [20,35,39]. Possible explanations for this discrepancy may be due to the fact that our study volunteer sample of healthy women differed from the sample of good sleepers of Morin et al. [8] regarding age and gender distribution.

The sample of good sleepers of Morin et al. [8] consisted of 27 men and women of all ages (mean age, 33.7 years [range, 19–60 years]), while our cohort consisted of 145 young women (mean age, 21.7 years [range, 18–25 years]). Additionally in accordance with our results, the authors mentioned that associations between arousal and subjective sleep quality were low [8]. Furthermore, it is important to bear in mind that our sample consisted of young and overall good sleepers with no clinical sleep impairment, as confirmed by the low PSQI scores. In addition, our women showed generally low levels of stress and arousal, which might further explain why we did not find arousal to significantly influence sleep in several of our analyses. The use of computerized diaries in comparison to paper and pencil format also constitutes a significant methodic difference. Stone et al. [42] found that computerized diaries enhance compliance compared to paper and pencil format, as participants are aware that times of diary entries are recorded.

Based on the results of our study it seems that it is not higher somatic arousal on a daily individual level that influenced subjective sleep quality, but rather higher somatic arousal on the interindividual level. On the other hand, it is not higher cognitive arousal on the interindividual level that influenced subjective sleep quality, but rather higher cognitive arousal on a daily individual level. This result is plausible considering the role of de-arousal processes introduced by Espie [32], assuming that good sleepers do not have the same kind of negative sleep-related cognitive intrusions compared to individuals with sleep disturbances or insomnia; in addition, they might be able to de-arouse more sufficiently than others with the result that presleep cognitive activity does not influence subjective sleep quality enough to be noticed on the between-participant level.

Although participants reported worse subjective sleep quality in association with higher stress and somatic arousal on the interindividual level and with higher stress and cognitive arousal on the intraindividual level, this relationship does not seem to apply for actigraphy-assessed sleep data. Still this finding is not necessarily contradictory, as it is well-known that the subjective perception of impaired sleep is not always objectively measurable in actigraphic or PSG sleep data [63–66]. Further, it might be possible that higher levels of stress and arousal might not yet influence actigraphic sleep measures in a young and healthy sample, but it could still constitute a factor preceding the development of subsequent sleep disturbances [35–37]. Therefore, it would be interesting to compare our findings with a group of healthy sleepers with a broader age range to investigate if stress and arousal do influence sleep more strongly with higher age (i.e., if age moderates this relationship). Finally subjective sleep quality and actigraphy-recorded SE measure different aspects of sleep, which are not exactly comparable. Actigraphy-assessed measures detect sleep–wake cycles by an accelerometer and objectively quantify sleep duration and number of awakenings, among others, in relation to the time spent in bed. Subjective sleep quality estimates include a variety of perceived sleep features, such as consciously perceived sleep disruptions, well-being, and sleep inertia on awakening, all entering the total perception of sleep resulting in a subjective rating. Interestingly participants even showed higher SE on days with above average levels of stress and somatic arousal, which may indicate an adaptive response to stress.

We consistently found higher levels of stress to be associated with higher levels of cognitive and somatic presleep arousal, which is in accordance with current models of insomnia, all including some sort of interplay between stress and arousal in the development of insomnia [10,31,32,67]. However, higher stress and arousal were not associated with lower actigraphic SE, which does not fit into insomnia models on the first sight. Still all models require some sort of dysregulation or malfunctioning of the homeostatic or regulatory processes in the development of insomnia (e.g., de-arousal processes, sleep habits, chronobiologic timing, attentional focus, coping strategies) [10,31,32,67]. Therefore, it fits into the models that these homeostatic processes are still intact and sleep is not automatically impaired after experiencing higher levels of stress and arousal in a sample of healthy women without clinically significant sleep impairment. The results on the level of subjective sleep quality did partially fit the assumption of higher stress

and arousal being associated with worse subjective sleep quality. Still it was only somatic arousal being relevant on the interindividual level and only cognitive arousal being relevant on the intraindividual level. This finding remains difficult to explain and could be a topic for further research.

It is important to note that there is evidence suggesting that the relationship between daily stress, presleep arousal, and sleep is bidirectional. Garde et al. [40] examined the relationship between psychological arousal and sleep and found a self-reinforcing vicious circle, with sleep and arousal as a bidirectional association. For our analysis, we decided to focus on the effect of stress and arousal on following sleep, and thus concentrated on the direction that Morin et al. [8] examined in their analysis. Still the inverse effect of sleep quality or quantity of the previous night on stress during the next day reports might be equally important to fully understand the relationship between stress, arousal, and sleep, and therefore could be a topic of further investigation. The positive temporal trend of subjective sleep quality over the 2 weeks of assessment could imply an initial reactivity bias to the start of the study habituating with time. Still time trends were included into the model and therefore did not significantly influence our results of mediation analysis.

Our study bears some limitations: the acquisition of sleep data was based on actigraphy and subjective sleep measures. Despite the value of those data, studies using PSG would be useful to confirm our findings due to the high validity of PSG and its ability to consider additional dimensions of sleep. We deliberately examined a sample of healthy young women in the context of our larger ongoing study about acute stress, emotion regulation, and sleep in young adults. To generalize these results to the whole population of healthy adults, it will be necessary to replicate the study with good sleepers and a broader age range. The assessment of daily stress and presleep arousal was based on subjective and self-report measures. Therefore, effects of memory and selective recall due to retrospective bias cannot be excluded in our study. Still participants assessed their stress and arousal levels on the same day to keep retrospective bias at a minimum and compliance with adequate time of entry was improved by the computerized diaries. Our sample consisted of young women attending schools for healthcare professions. It cannot be excluded that there is a sample bias in the direction that only individuals who are particularly resilient and capable of the demanding work in healthcare chose this kind of occupational career.

Compliance was extraordinarily high in our sample, which supports the assumption that the sample was resilient to additional stress and dedicated to social commitment. In addition, participants with any psychiatric diagnosis or psychopathology were excluded. This exclusion might further explain the low levels of presleep arousal and high SE in our sample. Finally it should be noted that five (within-participants) and three (between-participants) of the 12 statistical tests performed for indirect effects on each level yielded significance, which was 8.3 and 5 times higher, respectively, than the value 0.6 (=12∗.05) to be expected by chance based on an α of .05 and independent tests.

Despite these limitations, our study provides important knowledge regarding the relationship between daily stress, presleep arousal, and sleep. It confirms that arousal plays a mediating role between stress and subjective sleep quality, even in a healthy sample of young women. This mediating role was restricted to somatic arousal being relevant on the interindividual level and cognitive arousal on the intraindividual level. To the best of our knowledge, our study is the first to investigate between- and within-participant levels, along with subjective and actigraphy-assessed sleep outcomes in young adults. Actigraphic SE was not impaired by stress and arousal in healthy young women, who might even be able to compensate for days with above average levels of stress and arousal during the subsequent night. This finding suggests that it might be useful to further explore the mechanisms causing this adaptive regulation to derive useful strategies for prevention.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.09.027.

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Appendix B

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Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity

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Trauma

Summary
Background: Chronic or prolonged stress exposure in childhood can alter structural and functional brain development, leading to mental and physical illness and alterations of psychobiological stress systems in adulthood. Recently, attenuation in stress reactivity of the hypothalamic—pituitary—adrenal (HPA) axis and cardiovascular system have been related to the number of adverse childhood experiences (ACEs). We set out to investigate the association of ACE duration and age of ACE occurrence on stress reactivity.
Methods: 104 women in the age range 18—25 years (mean = 21.7) free of mental and physical illness underwent psychosocial stress testing with the Montreal Imaging Stress Task (MIST). Free saliva cortisol and heart rate were assessed repeatedly before and after the MIST.
Results: Number of ACEs was associated with attenuated cortisol and heart rate responses to stress in a dose-response relationship. Whereas overall duration of ACEs was significantly associated with an attenuated cortisol response, the specific age of first ACE occurrence did not contribute further to the dampened stress response.

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Conclusions: ACEs are associated with blunted endocrine and cardiovascular stress reactivity in young and healthy women. Adverse life events in childhood, particularly if they occur repeatedly and chronically, show a strong association with alterations in stress reactivity in adulthood, potentially predisposing for later mental or physical disorders.

1. Introduction

Adverse childhood experiences (ACEs), including physical, emotional and sexual abuse, affect a significant portion of the population and have been shown to be risk factors for the development and persistence of mental disorders such as depression, anxiety disorders, substance use disorders, or attention-deficit/hyperactivity disorder. Changes in stress sensitivity and functioning of the hypothalamic–pituitary–adrenal (HPA) axis have been suggested as causal factors (De Bellis, 2002; Tarullo and Gunnar, 2006; Heim et al., 2008). The HPA axis, together with the sympathetic nervous system (SNS), are key players in the formation of the stress response (Chrousos, 2009). Models of stress reactivity and health outcomes have therefore been a main focus in research towards understanding adversity and resilience processes. Different reactivity phenotype patterns have emerged in different studies, with a number of studies showing exaggerated HPA axis and SNS responses in the context of ACEs and psychopathology (Heim et al., 2000b; Heim and Nemeroff, 2001; Bremner et al., 2003; Rao et al., 2008).

In contrast to findings in clinical samples, a growing number of studies on healthy participants reported blunted endocrine (Carpenter et al., 2007, 2011; Elzinga et al., 2008; Lovallo et al., 2012) and cardiovascular (Lovallo et al., 2012) responses in association with ACEs. For example, Carpenter et al. (2007) reported blunted plasma cortisol responses to a psychosocial stress test in a healthy sample with a history of ACEs compared to participants without a history of childhood maltreatment. Also, a recent study by Lovallo et al. (2012) showed in a large sample of healthy participants diminished cortisol as well as heart rate responses with an increasing number of adverse life events, indicating an inverse dose-response relationship of ACEs and reactivity to a mental stress test.

To the best of our knowledge, the association of age of occurrence and duration of ACEs has not been investigated in healthy samples so far. There is evidence that these factors could have a differential impact on stress reactivity in adulthood (Tarullo and Gunnar, 2006; Schoedl et al., 2010; Tottenham and Sheridan, 2010). Since most studies used brief self-report questionnaires or life events checklists to assess ACEs (e.g. Carpenter et al., 2011; Lovallo et al., 2012), questions of duration of the events or the respective age when they happened widely remain unanswered. From a developmental perspective, age at traumatization is believed to be an important factor (Bosch et al., 2012). Brain components involved in stress response show large plasticity during pre- and postnatal periods and during early childhood, and some plasticity during later childhood and adolescence (Fumagalli et al., 2007; Andersen et al., 2008). Also, the duration of adverse experiences could be associated with psychobiological constructs. Particularly those environmental events that cause exceeding or prolonged stimulation of the stress system during these critical developmental periods could be linked to abnormal neurodevelopment and therefore be risk factors for lasting alterations in stress reactivity of the HPA axis and the SNS (Schoedl et al., 2010).

Therefore, the aim of the present study was to replicate the findings of attenuated endocrine and cardiovascular stress reactivity in association with a history of ACEs in a young, healthy, female adult sample. Furthermore, we aimed to investigate the association of duration as well as age of occurrence of adverse life events in childhood and adolescence with the stress reactivity in adulthood. To elucidate the association of age of occurrence and duration, in this study, the Early Trauma Inventory-Self Report (ETI-SR) served as a more detailed method in measuring ACEs (Bremner et al., 2007). The questionnaire retrospectively assesses a wide range of stress and trauma exposure before the age of 18 and considers age of occurrence as well as duration of the events.

In contrast to Lovallo et al. (2012) who employed standard public speaking and mental arithmetic stressors, and in contrast to the standardly used Trier social stress test (TSST, (Kirschbaum et al., 1993), we used the Montreal imaging stress task (MIST), that has been developed to be compatible with functional magnetic resonance brain imaging (Dedovic et al., 2005), but can be used in laboratory stress studies as well (La Marca et al., 2011). The MIST offers a promising alternative to conventional psychosocial stress tests. Advantages of the MIST are that participants sit still during the stress protocol and do not speak, therefore causing fewer artifacts measuring psychobiological parameters like heart rate or electrodermal activity. Furthermore, since the MIST is considered to evoke a moderate endocrine stress response, the observed findings represent HPA activity close to naturalistic settings (Smyth et al., 1998).

2. Methods and materials

2.1. Participants

The sample included 104 young and healthy females in the age of 18 to 25 years ($M = 21.7$; $SD = 1.5$), recruited at three schools for health care professions and social work in Basel, Switzerland. The sample was part of an ongoing project, which included only female participants. The recruitment material referred to a 14-day sleep assessment describing the nature and prevalence of sleep and sleeping disorder and did not include explicit statements about childhood trauma or adverse childhood experiences.

Exclusion criteria were current physical or psychiatric illness, pregnancy, regular and heavy tobacco use (>5

cigarettes a day), the consumption of illegal drugs, and the use of medication that interferes with the central nervous or the adrenocorticoid system.

Furthermore, participants were requested to minimize physical exercise during the hour preceding the laboratory examination and not to take large meals, coffee, or cigarettes. For participants taking no oral contraceptives, the laboratory assessment was held in the luteal phase of the participant's menstrual cycle (Kirschbaum et al., 1999).

Participants received monetary compensation for their participation and provided written informed consent prior to participation. The ethical principles of the Declaration of Helsinki were followed and the study was accepted by the local Ethics Committee. All appointments took place in a laboratory of the Psychiatric Clinics of the University of Basel, Switzerland.

2.2. Procedure

After a preliminary screening assessment, participants reported to the laboratory for the stress examination, which took place between 3:30 pm and 6:00 pm to control for circadian variation and lasted for approximately 2.5 h. Participants were told that the laboratory assessment would include a test on cognitive performance.

Upon arrival, participants were seated in a comfortable chair in front of a table with a computer screen and several magazines. After the heart rate sensors were attached, a ten minute resting period followed to customize participants with the laboratory. Then, a baseline measurement was conducted for five minutes. Immediately before the baseline measurement, participants provided the first saliva sample. Another saliva sample was collected immediately before participants engaged in the MIST. Following the stress exposure, a recovery period was conducted during which five additional salivary cortisol samples were collected together with self-report measures of the participants' emotional response to the stress task. At the end of the laboratory testing, participants were debriefed and signed a second written informed consent to approve the further use of their data.

2.3. Stress induction

The MIST (La Marca et al., 2011) was used to induce a psychosocial stress response. The MIST (Dedovic et al., 2005) is a standardized psychosocial stress test during which participants have to solve arithmetic tasks displayed on a computer screen under time pressure and social evaluation. The software adapts the difficulty of the tasks to the individual performance level of each participant, so that it is not possible to correctly answer more than 45—50% of the arithmetic tasks in the experimental condition. Participants had to complete three experimental runs, each lasting four minutes.

To induce a social evaluative threat, participants are told that their performance has to be close or equal to the average performance of a normative sample that is shown on the top of the computer screen, and that otherwise, their data cannot be used for the research purposes. Also, participants are informed that the study leader is watching their performance next door. Furthermore, after each of the first two runs, to further enhance social evaluative threat, the study leader informs participants that their performance is poor. In concrete terms, after the first experimental run, the experimenter calls the study leader to ask what to do in such an unusual situation. The participant then is told to repeat the task and to do better. Then, after the second unsuccessful performance, the slightly annoyed and demanding study leader enters the laboratory and interrogates the participant about her individual reasons for her poor performance. The study leader explains the high costs of the experiment in case of a possible exclusion if the participant does not achieve a better performance. Then, the last run of the MIST starts while the study leader stays in the room and watches the subject's performance standing right behind her.

These behaviors were standardized and practiced before study onset.

2.4. Measures

2.4.1. Biological measures

Saliva was collected at seven measurement points, whereof two took place before the stress test (−10 and−1 min) and five after the stress test (+1, +10, +25, +40 and +55 min) using salivettes (Sarstedt, Sevelen, Switzerland). All saliva samples were first stored at −22 °C, then thawed and centrifuged at 3000 rpm, before cortisol concentration in saliva was determined by enzyme immunoassay (ALPCO Diagnostics, Salem, USA). Because of unexpected high values, cortisol concentration was reanalyzed with a more established commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 8%.

Heart rate was recorded using Vitaport 3 data acquisition system (TEMEC Instruments B.V., Netherlands). Electrocardiogram (ECG) recordings were taken using Lead-II electrode placement (RedDot™, 2248-50, 3F Health Care, Germany) on the thorax with three disposable electrodes. A sampling rate of 1024 Hz was used for ECG recordings with a low pass filter of 512 Hz and a high pass filter of 0.5 Hz. Anslab, a software for scientific analysis of physiological data, was used to analyze detected consecutive R-waves and calculate R—R intervals, which were transformed to heart rate (Autonomic nervous system laboratory, Wilhelm & Peyk, 2005). Heart rate was averaged for *Baseline*, *Stress 1, Stress 2*, *Stress 3*, and *Recovery* periods in reference to time markers manually set in accordance with the various sections of the experiment.

2.4.2. Psychological measures

A diagnostic screening including the German version of the ''Structured Clinical Interview for DSM-IV/Axis I Disorders'' (SCID-I) was conducted in order to detect and exclude participants suffering from a mental disorder (Wittchen et al., 1997). Lifetime history of mental disorders ($n = 9$) was assessed. Participants reported to have suffered from depression ($n = 7$), panic disorder ($n = 1$), and posttraumatic stress disorder comorbid with depression ($n = 1$) and were fully remitted at the time of the study. Relevant data including age, medication, drug consumption, age of menarche,

Table 1 Participant characteristics and ACE scores of the study sample ($N = 104$).

Variable	M	SD	Range/%
Age [yr]	21.66	1.54	18–25
Age of onset menarche[a] [yr]	12.95	1.28	10–16
Oral contraceptive use, *n* (%)			59 (56.7)
Body Mass Index [kg/m^2]	21.81	2.53	18.37–31.14
Depressive symptoms (ADS-K)	7.08	4.93	0–24
ACE total sum score	2.76	3.17	0–15
General trauma	1.43	1.63	0–7
Physical abuse	.53	.99	0–5
Emotional abuse	.54	1.25	0–6
Sexual abuse	.26	.57	0–3
ACEs $\geq$ 1 year	1.27	2.40	0–12
ACEs < 1 year	1.44	1.55	0–6
ACEs before menarche	1.96	2.99	0–15
ACEs after menarche	.76	1.05	0–6
Age of first ACE occurrence[b]	7.54	4.83	0–16

[a] $n = 103$.
[b] $n = 80$ (no experienced ACE, $n = 23$; no reported age of occurrence, $n = 1$).

BMI, date of last menstruation, and intake of hormonal contraceptives were also assessed during the interview.

ACEs before the age of 18 years were assessed retrospectively using a German translation of the ''Early Trauma Inventory-Self Report'' (ETI-SR) (Bremner et al., 2007), which includes general trauma (31 items), physical (9 items), emotional (7 items), and sexual abuse (15 items). The ETI-SR has been demonstrated to be a valid measure of early trauma, and has shown high internal consistency in all trauma domains (Cronbach $\alpha > 0.7$) (Bremner et al., 2007).

Participants were asked a series of questions concerning potential trauma and stress exposure, which they answered with yes or no. Next, on positively answered items, age of occurrence, frequency of trauma or abuse, and emotional impact (0 = no negative impact, 1 = slightly negative, 2 = moderately negative, 3 = strongly negative) were assessed. In total, five different ACE scores were built. First, a sum score was computed from all events rated with an emotional impact of at least 1 (*ACE total sum score*). Furthermore, a sum score for ACEs lasting less than a year (*ACEs < one year*) and for ACEs lasting more than a year (*ACEs > one year*) was computed. Age of occurrence was assessed in two ways. In a first step, events which occurred before or after a participants' menarche were summed up to *ACEs before* and *after menarche*, respectively. Next, age of first ACE occurrence was abstracted for each subject, while the emotional impact of at least ''slightly negative'' was considered. ACE mean scores of the study sample are depicted in Table 1.

Because the ETI-SR does not provide cut-off scores for grouping, for illustration purposes, evenly distributed quartile groups (*ACE total groups*) were built via rank function of SPSS for the *ACE total sum score*. The grouping via rank function resulted in the following group distributions: group 1 = 0 ACE, group 2 = 1 ACE, group 3 = 2–3 ACEs, and group 4 = 4 or more ACEs. Groups with regard to duration were then built according to the same group distribution as for the *ACE total groups*.

Depressive symptomatology was assessed via the German version of the Center for Epidemiological Studies Depression Scale (CES-D; German version: ADS-K; (Hautzinger and Bailer, 1993).

Visual analog scales (VAS) for mood, tension, and stress served as measures of subjective emotional response of participants during the psychosocial stress test. The scales ranged from ''not stressed'' (0) to ''very stressed'' (100), experiencing ''no tension'' (0) to ''extreme tension'' (100), and ''having a good mood'' (0) to ''having a bad mood'' (100), respectively.

2.5. Data analysis

Statistical analyses were performed using IBM SPSS Statistics, version 20 (SPSS Inc., Chicago, IL). Descriptive statistics were conducted for all variables. Skewed data were logarithmically transformed where appropriate.

First, repeated measures general linear model (GLM) was used to assess if the stress task led to a significant stress response for the dependent variables salivary cortisol, heart rate, as well as for the subjective emotional responses to the MIST. Next, GLMs for repeated measures served to determine the effects of ACEs on endocrine and cardiovascular responses. In these models, the *ACE total sum score* as well as the different scores for duration and age of occurrence were used as continuous variables to examine effects of time, ACE scores, and the interaction of time by ACE scores. In a second step, in order to visualize the results, the different ACE groups were then used as fixed factors for the GLMs, respectively.

To protect against violation of sphericity, Greenhouse–Geisser corrections were applied where appropriate. Effect sizes were determined by partial eta-square, reflecting small (.01), medium (.06), or large (.14) effect sizes (Green et al., 2000).

To account for their potential confounding influence on cortisol concentration (Kirschbaum et al., 1999), BMI and

use of oral contraceptives were included as covariates in all statistical models. In this sample, depressive symptoms were overall low and were neither related to cortisol, heart rate nor ACEs and therefore not controlled for in the analyses. Also, lifetime history of mental disorders ($n = 9$) was not related to the outcome measures and therefore not controlled for in the analyses. Emotional responses to the MIST (mood, tension, stress) were entered as covariates in post-hoc analyses, using the trapezoid formula for calculation (area under the curve with respect to ground, AUCg; Pruessner et al., 2003).

Technical difficulties with Vitaport 3 data acquisition system led to data loss in heart rate measurements (missing completely at random). Eventually, heart rate measures of 88 participants were available and went into the analyses. Cortisol data of four subjects had to be excluded because of unlikely high and fluctuating values, or because of acute illness, and therefore, cortisol measures of 100 participants went into the analyses.

3. Results

Demographic and trauma characteristics of the sample are displayed in Table 1. According to univariate analyses of variance, the ACE groups did not differ significantly in terms of demographic characteristics (e.g. age, age of onset of menarche, oral contraceptive use, and depressive symptoms). However, for the *ACE total groups*, BMI was significantly higher [$p = .02$] in women reporting 4 or more ACEs ($M = 23.38$, SD = 3.55) compared to women reporting no ACEs ($M = 21.16$, SD = 2.07).

Results obtained by GLM repeated measure analyses indicated that the stress task induced a robust and significant increase in cortisol levels [$F(1.87, 185.52) = 27.16$, $p < .001$; $\eta_p^2 = .22$] and heart rate [$F(1.85, 164.95) = 216.86$, $p < .001$; $\eta_p^2 = .71$]. Subjects experienced significant worsening of mood [$F(3.53, 360.36) = 31.72$, $p < .001$; $\eta_p^2 = .24$], as well as increases in tension [$F(3.78, 385.39) = 32.82$, $p < .001$; $\eta_p^2 = .24$], and stress [$F(3.90, 398.15) = 28.45$, $p < .001$; $\eta_p^2 = .22$] (Fig. 1). Regarding their emotional reaction to the MIST, participants did not show differences in their baseline and peak levels in relation to the total number of ACEs, as indicated by univariate analyses of variances (data not shown).

Furthermore, the associations of the subjective emotional responses to the MIST with cortisol and heart rate responses were tested. Results revealed no significant correlations (all $p > 1$). Depression symptom scores and ACE total sum score were uncorrelated ($r = .11$, $p = .27$).

3.1. Association of ACE and cortisol responses to stress

Repeated measures analysis of cortisol responses to stress showed a significant interaction of time × *ACE total sum score* [$F(2.33, 221.60) = 5.89$, $p < .001$; $\eta_p^2 = .06$] as well as a significant main effect of *ACE total sum score* [$F(1, 95) = 7.52$, $p < .01$; $\eta_p^2 = .07$]. Results remained significant when the emotional responses to the stress task were entered additionally as covariates. Results are depicted in Fig. 2.

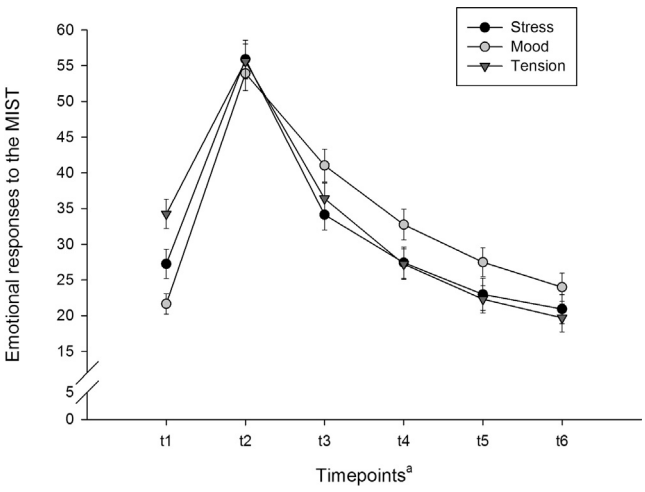

Fig. 1 Subjective emotional responses to the MIST. ([a]Timepoints relative to the MIST: $t1 = -1$ min, $t2 = +1$ min, $t3 = +10$ min, $t4 = +25$ min, $t5 = +40$ min, $t6 = +55$ min.).

Next, it was tested whether the duration of ACEs was associated with the cortisol responses to the stress task. Repeated measures analysis of cortisol response to the stress task resulted in a significant main effect of duration of *ACEs > one year* [$F(1, 95) = 10.10$, $p < .01$; $\eta_p^2 = .10$] and a significant interaction of time and duration of *ACEs > one year* [$F(2.33, 221.16) = 5.36$, $p < .01$; $\eta_p^2 = .05$] (Fig. 3). Results remained significant when the emotional responses to the stress task were entered additionally as covariates. However, these effects were not observed for the association between ACEs that lasted shorter in duration (*ACEs < one year*) and cortisol responses to the stress task [main

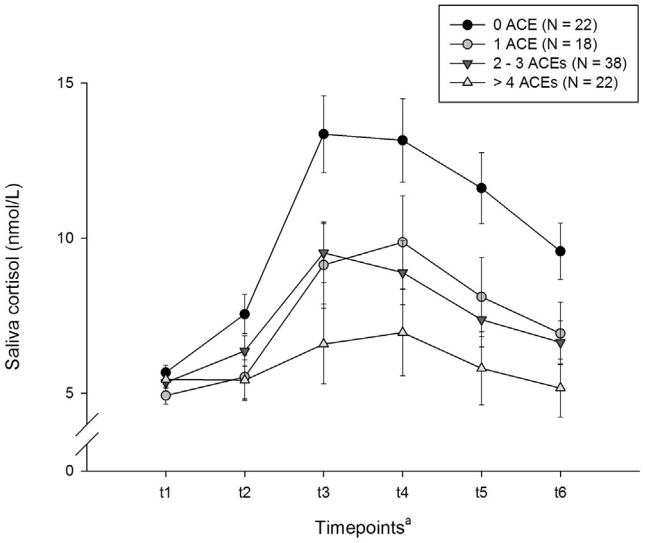

Fig. 2 Cortisol responses to the MIST are depicted for women who experienced 0, 1, 2–3 or 4 or more ACEs. Values represent average cortisol ± standard error of the mean for the *ACE total groups* controlled for oral contraceptive use and BMI. Higher ACE sum scores are associated with blunted cortisol responses. ([a] Timepoints relative to the MIST: $t1 = -1$ min, $t2 = +1$ min, $t3 = +10$ min, $t4 = +25$ min, $t5 = +40$ min, $t6 = +55$ min.).

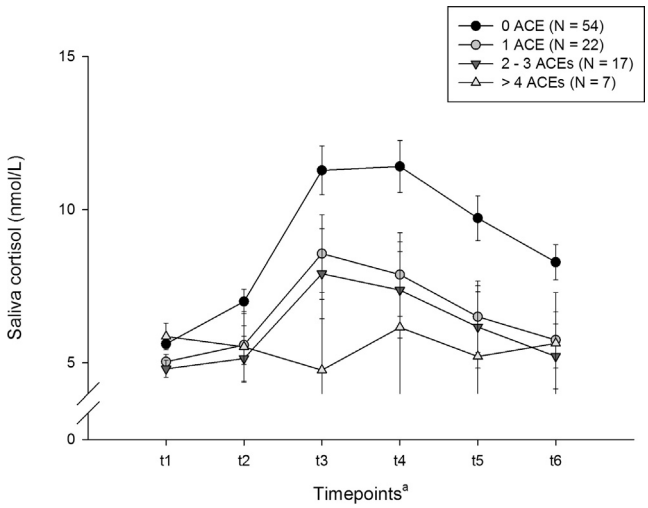

Fig. 3 Cortisol responses to the MIST are depicted for women who experienced 0, 1, 2—3 or up to 4 or more ACEs that lasted more than a year. Values represent cortisol ± standard error of the mean for the *ACEs > one year group* controlled for oral contraceptive use and BMI. Higher ACE sum scores are associated with blunted cortisol responses. ([a] Timepoints relative to the MIST: $t1 = -1$ min, $t2 = +1$ min, $t3 = +10$ min, $t4 = +25$ min, $t5 = +40$ min, $t6 = +55$ min.).

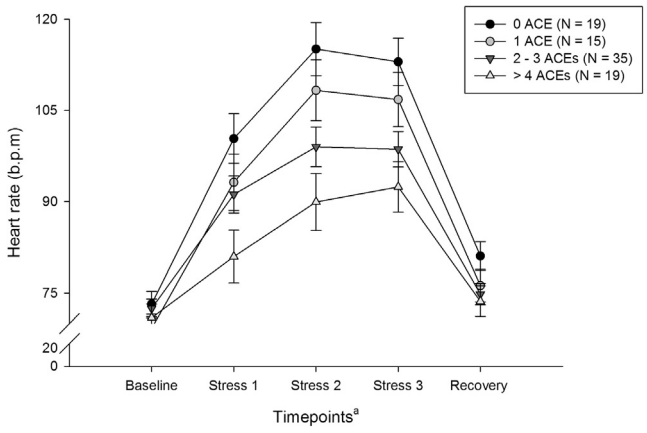

Fig. 4 Heart rate responses to the MIST are depicted for women who experienced 0, 1, 2—3, or 4 or more ACEs. Values represent average heart rate (beats per minute) ± standard error of the mean for the *ACE total groups* controlled for oral contraceptive use and BMI. Higher ACE sum scores are associated with attenuated heart rate reactivity. ([a] Timepoints relative to the MIST: Heart rate averaged for Baseline (—5 min), Stress 1 (first run), Stress 2 (second run), Stress 3 (third run), and Recovery period (first 5 min after last run).).

effect, $F(1, 95) = .64$, $p = .43$; interaction effect, $F(2.24, 213.21) = 1.05$, $p = .36$].

For age of occurrence, a significant interaction effect [$F(2.33, 220.99) = 6.48$, $p < .01$; $\eta_p^2 = .06$], and a significant main effect were observed for the sum of events which occurred before menarche [$F(1, 95) = 10.26$, $p < .01$; $\eta_p^2 = .09$]. For events which occurred after menarche, these effects were not observed [main effect, $F(1, 95) = .18$, $p = .67$; interaction effect, $F(2.24, 212.34) = .63$, $p = .55$]. For the specific age of first ACE occurrence, no significant associations were observed [main effect, $F(1, 78) = 71$, $p = .40$; interaction effect, $F(2.24, 174.75) = .56$, $p = .58$].

3.2. Association of ACE and heart rate reactivity to stress

Repeated measures analysis of heart rate response to the stress task showed a significant main effect of *ACE total sum score* [$F(1, 85) = 7.13$, $p < .01$; $\eta_p^2 = .08$] as well as a significant interaction effect of time × *ACE total sum score* [$F(1.98, 168.32) = 5.86$, $p < .01$; $\eta_p^2 = .07$]. Results remained significant, when the emotional responses to the stress task were entered as covariates (Fig. 4).

However, the further analyses with duration as well as age of occurrence of ACEs revealed no significant relationships with heart rate responses to the stress task (data not shown).

4. Discussion

We set out to assess the association of ACEs and psychobiological stress reactivity and its modulation by the number, duration and age of occurrence of ACEs in healthy young women. Our results are in line with previous reports of attenuated endocrine (Carpenter et al., 2007, 2011; Elzinga et al., 2008; Lovallo et al., 2012) as well as cardiovascular (Lovallo et al., 2012) stress responses to a psychosocial stress test in healthy adults with a history of adverse childhood experiences. Furthermore, our results substantiate the importance of the mean number of ACEs on endocrine and cardiovascular response to psychosocial stress. Importantly, blunted cortisol and heart rate responses were independent of emotional responses, suggesting that the diminished endocrine and cardiovascular stress reactivity cannot be explained by a reduced emotional reaction to stress (which may be interpreted as flattened affect) after a history of childhood adversity.

To the best of our knowledge, the present study is the first to demonstrate that in healthy young women, especially long enduring, chronic ACEs show the strongest association with a blunted cortisol reactivity, adding valuable knowledge to the link between chronic childhood adversity and alterations of the HPA axis. Even though the sum of events which occurred before menarche showed an association with a blunted cortisol reactivity, whereas events after menarche did not, in this sample, the specific age of occurrence did not contribute to a further understanding of the association between timing of ACEs and endocrine and cardiovascular reactivity.

Per se, our results show a deviation from an expected endocrine and cardiovascular stress response in participants free of mental and physical illness in association with a history of ACEs. According to Obradovic (2012), taking together recent findings on stress reactivity in the context of early adversity, it is more accurate to state that exposure to early life stress may lead to dysregulated physiological phenotypes rather than to a particular pattern of hyper- or hyporesponsivity (Obradovic, 2012). The recently proposed adaptive calibration model (Del Giudice et al., 2011) offers an evolutionary-developmental theory of

individual differences in physiological reactivity processes. The authors hypothesize that, at a very general level, a nonlinear relation between adverse life event exposure and stress response exists. However, in the context of high adversity, the model predicts an either vigilant profile, characterized by high biological stress responsiveness, or an unemotional, underresponsive profile, characterized by generally low HPA axis and SNS activity. Thus, these opposite phenotypes might be mediated by other factors and their interactions, e.g. the study sample, the type of maltreatment or the interaction of various environmental and genetic factors.

In terms of environmental factors, studies have demonstrated that the HPA axis in early human development is under strong social regulation (Tarullo and Gunnar, 2006). Therefore, several studies suggested parental caregiving as a moderator of the HPA reactivity (Gunnar et al., 1992; Nachmias et al., 1996; Tarullo and Gunnar, 2006). Thus, sensitive parenting appears to buffer cortisol responses in fearful situations, whereas being deprived of an evolutionarily expectable level of care (e.g. institutional rearing) has been associated with blunted cortisol production (Carlson and Earls, 1997; Gunnar et al., 2001). However, studies with institutionalized children were also able to show that improved caregiving environments had an effect on normalizing dampened HPA axis diurnal rhythms (Dozier et al., 2008; Cicchetti et al., 2011; Fisher et al., 2011).

The social buffering of the HPA axis is supported by findings in animal models. In their extensive summary of literature, Hostinar et al. (2014) report findings from animal studies, which suggest that neural mechanisms are responsible for behavioral and neuroendocrine changes due to social buffering (Hostinar et al., 2014). Findings from animal studies report changes in the development of the HPA axis and its function in social buffering. In early development, a stress hyporesponsive period (e.g. Witek-Janusek, 1988) during which the mother strongly controls the infants corticosterone levels has been reported, which can be disrupted by maternal deprivation and result in a hyperresponsive HPA pattern. In later stages of development, peers can also become a source of social buffering (Hennessy et al., 2009). For example, social input has been shown to dampen HPA axis reactivity in rat pups if the mother was present (e.g. Stanton and Levine, 1990; Shionoya et al., 2007), in maturing rodents when cohabitating companions are present (Terranova et al., 1999), or in squirrel monkeys in the presence of familiar and unfamiliar conspecifics (Vogt et al., 1981; Hennessy, 1984).

The findings in human and animal studies provide support for an adaptive response of the stress system to its environment, probably in order to enhance survival odds. It could be speculated that after an initial hypersecretion of cortisol due to chronic stressful environments, the HPA axis could counter-regulate its response and cortisol output might rebound to below normal. A plausible biological explanation could be an increased glucocorticoid negative feedback with a downregulation of CRF receptors, or a diminished release of cortisol by the adrenal glands (Heim et al., 2000a; Fries et al., 2005). This view is supported by our finding that only chronic events, not acute events, were associated with a blunted cortisol response.

Recent studies link genetic and epigenetic alterations to stress reactivity in association with ACEs as well. A history of ACEs has been associated with an epigenetic regulation of the glucocorticoid receptor in the hippocampus (McGowan et al., 2009). Moreover, a recent study on healthy adults who experienced the loss of a parent during childhood, maltreatment, or low parental care showed epigenetic alterations of a region of the human glucocorticoid receptor gene, which in turn was associated with a blunted cortisol reactivity after a neuroendocrine challenge test in these participants (Tyrka et al., 2012). Another study linked prenatal maternal depression to increased methylation of the glucocorticoid receptor gene, and showed exaggerated salivary cortisol output to stress at 3 months of age (Oberlander et al., 2008). Further studies are needed to investigate these changes in central regulation of the glucocorticoid receptor in brain regions involved in stress responses in association to ACEs.

Our results raise the challenging question of whether the observed alterations in stress responsivity can be interpreted as a potential risk factor for or as a sign of resilience to the development of later mental and physical disorders. Even if initially adaptive, blunted cortisol reactivity could compromise future and necessary psychobiological stress reactivity. For example, low cardiovascular and/or endocrine reactivity to acute psychological stress has been associated with depression, fibromyalgia, obesity, burn out, substance use disorders, and chronic pain syndromes (Griep et al., 1998; Heim et al., 1998; Pruessner et al., 1999; Lovallo et al., 2000; Gold and Chrousos, 2002; Gur et al., 2004; Phillips et al., 2011; Jones et al., 2012).

Considering that participants in the present study were recruited from a school of higher education and were free of psychopathology in adulthood, they may have been selected in a way that the blunted stress reactivity pattern may stand for resilience to the development of mental illness in the aftermath of childhood adverse experiences. Longitudinal, population-based research is needed to investigate if participants without present psychopathology, who had shown blunted stress responses after stress induction, are at higher risk to develop psychiatric disorders later in life or remain healthy.

The present study revealed diminished heart rate responses in association with the total number of ACEs, but not with the subgroups regarding duration and age of occurrence. Recently, Bauer & Boyce have suggested the examination of the HPA axis and the SNS simultaneously for a better understanding of their coordination (additive or interactive; or opposing or complementary) (Bauer et al., 2002). Only few studies have examined the exact nature of their coordination in adult samples so far (Ali and Pruessner, 2012; Lovallo et al., 2012; Andrews and Pruessner, 2013), and results are mixed. Methodological differences between the reported studies could account for the different findings. More empirical research is needed to investigate the exact nature of SNS alterations after ACEs, as well as the coordination and interactions between the two stress systems.

Our results revealed no associations of the specific age of occurrence, which contrasts to findings of other studies. Bosch et al. (2012) reported that especially ACEs in pre- and postnatal developmental stages were associated with heightened cortisol reactivity (Bosch et al., 2012). However, their sample included 16-year old adolescents, and also

included concurrent psychopathology. In contrast to the present study, which used age of first ACE occurrence, and the distinction pre- and postmenarche, the authors used more distinct age groups to examine the association of age and cortisol reactivity. A limitation of our approach, by using the specific age of occurrence, is that type of trauma is neglected. Type of trauma is an important factor, which could also explain different HPA axis phenotypes. Future studies are needed to further analyze timing of ACEs, and methodologically, this might be assessed best in a sample of participants with one specific severe trauma/life event. Furthermore, a limitation of the present study is that no data on pre- and postnatal stress exposure was included. Prenatal maternal stress (Entringer et al., 2009) and postnatal adversity (Bosch et al., 2012) have been associated with increased HPA responses to stress, which could result in a sensitization to stressors in long-term.

Another limitation of the present study is that only peripheral readouts of stress hormone activation were measured. The HPA axis and the cardiovascular system are complex and multilayer systems and therefore we are not able to identify the exact mechanisms or location of the observed dysregulations. Furthermore, that only women were recruited and tested has to be mentioned as another potentially limitating factor. Especially as some of the recent models on stress reactivity changes after chronic or traumatic stress make mention of sex differences, it would have been informative to assess the stress response in men as well (Bangasser, 2013). Thus, due to the characteristics of the study sample, the presented findings can only be generalized to young women free of mental and physical illness. Also, participants were attendees of schools for health care professions and social work, which could have led to a selection bias as outlined above. Also, even though Hardt and Rutter (2004) concluded in their review of studies from 1980 to 2001 that the validity of retrospective recall of sexual/physical abuse, physical/emotional neglect or family discord is sufficiently valid (Hardt and Rutter, 2004). Still, the retrospectively assessed adversities could have been underestimated and/or biased, especially reported events in toddler and pre-verbal ages.

Because of methodological reasons, the specification between ACEs shorter/longer than one year cannot be assumed to be completely independent from each other. Since some participants reported both, acute and chronic ACEs, with our sample size, it was not possible to have fully distinct and statistically orthogonal groups.

Despite these limitations, the present study strengthens the assumption that adverse childhood experiences give rise to a blunted stress reactivity of the HPA axis and the SNS in young healthy women. In this study population, number and duration of adverse events in childhood showed the strongest association with an attenuated stress response in adulthood. These findings suggest that the reactivity of the human stress system is indeed shaped by the experience of extrinsic chronic stressors in childhood and adolescence.

Contributors

Klaus Bader (PI) and **Frank H. Wilhelm** designed the study and wrote the protocol.

Jens C. Pruessner developed the Montreal Imaging Stress Task and together with **Roberto La Marca** trained us in how to use it and supervised us in administrating the stress protocol outside the MRT.

Evelin Hug wrote the first draft of the paper, **Annette Voellmin** wrote the final draft of the manuscript and undertook the statistical analysis. **Annette Voellmin** managed the recruitment of the participants, together with **Katja Winzeler**, who was involved in the literature research and the proof reading of the manuscript.

Valérie Schaefer helped in the recruitment of the participants and was also part of the study design team.

Jens Gaab assisted Annette Voellmin in the manuscript preparation and in the statistical analyses.

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Conflict of interest statement

The authors have no biomedical financial interests or potential conflicts of interest to report.

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Appendix C

Winzeler, K., Voellmin, A., Hug, E., Kirmse, U., Helmig, S., Princip, M., Cajochen, C., Bader, K., & Wilhelm, F. H. (under review).

Adverse childhood experiences are associated with blunted sympathetic stress responsivity in healthy young women.

Adverse childhood experiences are associated with blunted sympathetic stress responsivity in healthy young women

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Abstract

Objective: Early adversity has been associated with alterations of psychobiological stress systems and negative health outcomes. While a previous report demonstrated blunted cortisol and heart rate stress reactivity in association with adverse childhood experiences (ACEs) in healthy young women (Voellmin et al., 2015), the present secondary analysis aimed at clarifying the role of the sympathetic and parasympathetic branches of the autonomic nervous system in this relationship. **Methods:** 129 healthy young women provided retrospective data on the occurrence of ACEs and underwent psychosocial stress testing. Systolic blood pressure (SBP) and respiratory sinus arrhythmia (RSA) were assessed during baseline and stress tasks as measures of sympathetic and parasympathetic cardiovascular activity, respectively. **Results:** Higher number of ACEs was correlated with blunted SBP stress reactivity ($r= -0.295$, $p=0.001$) and a trend for lower baseline SBP ($r= -0.159$, $p=0.072$). No significant association was found between ACEs and RSA baseline or reactivity after controlling for respiratory rate. **Conclusions:** Childhood adversity was associated with down-regulation of sympathetic but not parasympathetic cardiovascular stress responsivity in adulthood. Future research will need to clarify whether this indicates a risk for negative health outcomes or, quite on the contrary, is a sign of stress resistance developed during childhood and adolescence.

Keywords: systolic blood pressure, sympathetic nervous system, vagus nerve, childhood adversity, trauma.

Introduction

Early adversity has been associated with alterations of psychobiological stress systems and various adverse health outcomes (e.g., Gilbert et al., 2009; Miller, Chen, & Parker, 2011). In a recent study we found blunted endocrine and heart rate reactivity to a stress task in association with adverse childhood experiences (ACEs) in healthy young women (Voellmin et al., 2015). Since heart rate is regulated by both sympathetic (increase) and parasympathetic (decrease) efferent activity of the autonomic nervous system, it remains unclear whether this blunted heart rate reactivity is caused by sympathetic hyporeactivity or less parasympathetic withdrawal, or a combination of both (Berntson, Cacioppo, & Quigley, 1991). The present secondary analysis of data from this study aimed at clarifying the role of the sympathetic (indexed by systolic blood pressure, SBP) and the parasympathetic (indexed by respiratory sinus arrhythmia, RSA) cardiovascular stress responsivity in association with adverse childhood experiences in healthy, young women.

ACEs have been shown to constitute an important risk factor for the development and persistence of mental and physical health problems often conceptualized as stress-related disorders (e.g. Felitti et al., 1998; Wegman & Stetler, 2009). These detrimental consequences of early adversity are supported by findings from animal models showing higher risk for pathology in association with early-live stress (Sanchez, Ladd, & Plotsky, 2001).

Changes in the functioning of stress response systems due to repeated or long-lasting ACEs or trauma have been suggested to be the cause for higher vulnerability to stress-related disorders. Current models assume that ACEs have the potential to alter patterns of endocrine and autonomic discharge in the long-term by disturbing the complex and integrated system of positive and negative feedback-loops, thereby creating a state of allostatic load that potentially results in adverse health outcomes (see for review: Chrousos & Gold, 1992;

Lovallo, 2011; McEwen, 1998). Importantly, initial evidence and theoretical considerations suggest that allostatic load can take either the direction of failure to shut off the stress response and a resulting chronic hyperactivity but also the direction of failure to mobilize a full response and a resulting blunted pattern (Lovallo, 2011; McEwen, 1998).

From a developmental perspective, age at stress exposure is believed to be an important factor, since there is evidence for developmental periods with high sensitivity for the formation of enduring alterations in stress responsivity (Tottenham & Sheridan, 2010). During prenatal and early postnatal life the brain grows rapidly and therefore is characterized by high plasticity, which then slows down during childhood and adolescence (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003).

Since a stress response in heart rate and other organismic functions is often comprised of both, sympathetic activation and parasympathetic withdrawal, both branches of the ANS may play a role in regulating stress-induced arousal (Berntson et al., 1991). Sufficient blood supply to muscles and other organs during stress responding is assured by up-regulation of blood pressure. Particularly systolic blood pressure (SBP) is known to be regulated almost exclusively by the sympatho-adrenal axis via beta-adrenergic receptors and thus constitutes a putative index of sympathetic cardiovascular activity (Obrist, 1981; Silvestrini & Gendolla, 2011). On the other hand, respiratory sinus arrhythmia (RSA), referring to the rhythmic oscillation of heart rate linked to the phases of the respiratory cycle, indicates the efferent activity of the parasympathetic nervous system innervating the heart, or cardiac vagal control (Berntson et al., 1997; Grossman, Stemmler, & Meinhardt, 1990). Spectral analysis of heart rate variability over several minutes within the frequency range of 0.15-0.50 Hz, the frequency band typically associated with respiration (also termed high frequency heart rate variability), has been established as the method of choice for quantifying RSA (Camm et al., 1996; Grossman et al., 1990).

Elevated tonic sympathetic activity has frequently been reported in samples with posttraumatic stress disorder (PTSD) and persistent autonomic hyperarousal is considered to be a core symptom of the disorder (e.g., Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007; Buckley & Kaloupek, 2001; Kirsch, Wilhelm, & Goldbeck, 2011). In non-clinical samples, similarly elevated tonic sympathetic activity has been found in association with adversity in some studies (Lee, Tsenkova, & Carr, 2014; Paulus, Argo, & Egge, 2013; Su et al., 2014) while others have found no baseline differences in heart rate or systolic blood pressure (Leitzke, Hilt, & Pollak, 2013; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012).

Concerning sympathetic stress reactivity, results are mixed in samples with PTSD with either heightened (Heim et al., 2000) or blunted heart rate or electrodermal responses to acute stress (Blechert et al., 2007; Cohen et al., 2000). In non-clinical samples, some studies have produced evidence for heightened SNS reactivity in response to stressors (Oosterman, de Schipper, Fisher, Dozier, & Schuengel, 2010; Otte et al., 2005). On the other hand, two studies reported blunted cardiovascular responses to a social stress task in association with ACEs: Lovallo et al. (2012) showed diminished heart rate responses with an increasing number of adverse life events in a large sample of healthy participants (N=354) while Leitzke et al. (2013) found blunted systolic blood pressure response in maltreated compared to non-maltreated youth (total N=111).

Concerning adversity and parasympathetic regulation there is evidence for lower tonic RSA in association with both, non-clinical samples with the experience of ACEs (Dale et al., 2009; Miskovic, Schmidt, Georgiades, Boyle, & MacMillan, 2009) and clinical samples with PTSD (Blechert et al., 2007; Cohen et al., 1997). Concerning RSA withdrawal in response to stressors, Cohen et al. (1998) found that in participants with PTSD, RSA did not change from rest to trauma recall compared to a withdrawal of RSA in controls. In non-clinical samples, there is evidence for lower RSA stress reactivity or lower recovery in the context of adversity

(Arditi-Babchuk, Feldman, & Gilboa-Schechtman, 2009; Dale et al., 2009). However, these patterns might be complicated by different factors, such as family environment, mediating or moderating the relationship between ACEs and RSA, especially in children and adolescents. Also, there is evidence that tonic RSA or RSA stress reactivity themselves constitute moderating factors between early adversity and adaptive or maladaptive outcomes (El-Sheikh & Whitson, 2006; Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Still, others found no differences in RSA baseline or reactivity in association with ACEs (Shenk, Putnam, Rausch, Peugh, & Noll, 2014; van Ockenburg et al., 2014).

Some of the divergent findings may be due to the fact that studies differ regarding sample characteristics, age groups, type of adversity, and stressors assessed. Many studies on RSA have focused on children and adolescents and have examined RSA as a mediator between ACEs and other outcome variables. Other studies have used clinical samples with the problem of comorbid symptomatology or have not examined parasympathetic in addition to sympathetic indices of stress response. Further, some of the inconsistencies in prior findings might be the result of inadequate adjustment for confounding factors such as respiratory rate, physical fitness, or depressive symptomatology (Grossman & Taylor, 2007). To our knowledge, there is no study so far that has examined the association between sympathetic and parasympathetic cardiovascular stress response and ACEs in otherwise healthy young adults.

In accordance with the study by Lovallo et al. (2012), a recent study from our research group also found blunted cardiovascular stress response in association with ACEs in healthy young women (Voellmin et al., 2015). However, this does not allow drawing conclusions about the relative contributions of the sympathetic and parasympathetic nervous systems in blunting the heart rate response during stress. Therefore, the present study had two major objectives: First, it aimed at clarifying the role of the sympathetic and parasympathetic

cardiovascular stress response in the observed blunted heart rate reactivity in association with ACEs. Second, it aimed at extending previous findings on sympathetic and parasympathetic influences by investigating the relationship between ACEs, SBP, and RSA both during a resting baseline (being considered a snapshot of tonic, trait-like activity) and in reaction to a psychosocial stress task in healthy young women and by ensuring consideration of potentially confounding variables. The Early Trauma Inventory-Self Report (ETI-SR; (Bremner, Bolus, & Mayer, 2007) served as a validated and detailed method for measuring ACEs. We expected that participants with higher number of ACEs would show either blunted sympathetic (in terms of SBP) response or less parasympathetic (in terms of RSA) withdrawal, or both, in response to a psychosocial stress task. Any of these autonomic response patterns would explain the blunted HR reactivity in association with ACEs we recently observed in the current sample. Based on the relatively inconclusive picture from previous studies regarding baseline differences, we did not have a strong expectation that baseline SBP and RSA would show a relationship with ACEs in the present analysis. However, because several studies point at increased sympathetic activity and decreased parasympathetic activity, if anything, baseline SBP may be expected to be higher and baseline RSA to be lower in women reporting more ACEs. We additionally analysed the association between the age of first ACE occurrence and measures of SBP and RSA and expected earlier age of ACE occurrence to accentuate alterations in stress reactivity. Also, different ACE subscales (general trauma, physical, emotional, as well as sexual abuse) and their association with SBP and RSA were explored in order to be able to compare the effects of different types of adversity within the same sample.

Method

Participants

Data for the present analysis were collected in the context of a larger study investigating acute stress, emotion regulation, and sleep. The sample included 146 young and physically as well as mentally healthy women (mean age 21.7 ± 1.7 years) who were recruited at three schools for health care professions and social work in Basel, Switzerland. Potential study participants contacted the study office by email or phone and had to be female, aged between 18 and 25 years, German speaking, and in good health. Exclusion criteria for all participants included current physical or psychiatric illness, pregnancy, regular heavy tobacco use (> 5 cigarettes a day), consumption of illegal drugs, and the use of any medication interfering with the autonomic nervous or the adrenocorticoid system. A structured clinical interview for psychiatric disorders (SCID I for DSM-IV; Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorder*, fourth edition, Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) was used to assess the absence of psychiatric illness, followed by a structured interview about physical illness and the other exclusion criteria. Participants received monetary compensation of 150 CHF for their participation and provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethics committee.

Procedure

All appointments took place in the laboratory of the cognitive-behavioral treatment outpatient clinic of the Psychiatric Hospital of the University of Basel, Switzerland. At a first office appointment participants were screened for inclusion and exclusion criteria, and provided information on ACEs. On the second appointment, participants reported to the laboratory for the stress examination. They were told that the laboratory assessment would include a test on

cognitive performance and were requested to minimize physical exercise during the hour preceding the laboratory examination and to avoid large meals, coffee, or cigarettes. In order to control for circadian variations, the laboratory examination started in the afternoon between 3:30 pm and 6:00 pm (Stone et al., 2001) and lasted for approximately 2.5 hours.

Upon arrival, participants were seated in a comfortable chair, approximately 30 inches in front of a computer screen (21 inch diameter). After all sensors for psychophysiological measures were attached, a ten minute resting accommodation period followed. Then, a resting baseline measurement was conducted for five minutes. After baseline, a paced breathing task was conducted. The participants were instructed to breathe in and out in 5 second intervals according to audiotaped instructions. The tonal pattern was designed to induce a respiratory frequency of 12 cycles per minute and was presented for 1 minute. This procedure has been recommended to standardize respiration rate between individuals during assessment of individual differences in resting RSA (Grossman et al., 1990; Wilhelm, Grossman, & Coyle, 2004). Participants then engaged in the stress task, which was followed by a recovery period. At the end of the laboratory testing, participants were debriefed and the nature and goals of the preceding stress induction task were fully disclosed. Participants provided a second written informed consent approving the further use of their data.

Stress induction

The Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) is a standardized computer-supported psychosocial stress task and consists of a series of arithmetic challenges that need to be solved by entering the correct numbers on the keyboard, combined with social-evaluative threat. The software manipulates the difficulty of the arithmetic questions and the time limit, ensuring that no more than 45-50 % of the questions are answered correctly. Participants are further pressured by the constant display of their current individual

performance in contrast to the (fictitious) expected performance of their age group. Also, they are informed that the investigator is watching their performance online next door. There are three experimental runs, each lasting for four minutes with feedback of 2-3 minutes in between the three runs. After each of the first two runs, to further enhance social evaluative threat, the participants are reminded first by the investigator and then by the principal investigator that their performance was poor and are asked to do better. In contrast to other often used psychosocial stress tasks like the Trier Social Stress Test (TSST, Kirschbaum, Pirke, & Hellhammer, 1993), the MIST does not require speaking during stress assessment. This ensures that respiratory pattern change (steep, short inspiration and long expiration, Wilhelm, Handke, & Roth, 2003) due to speaking cannot interfere with RSA assessment.

Physiological Measures

Systolic blood pressure was assessed using an ambulatory blood pressure monitor (Aponorm® Basis Control, Germany) during the last minute of baseline and about 30 seconds after the start of each of the stress runs. A baseline-to-stress reactivity score was computed by subtracting systolic blood pressure at baseline from systolic blood pressure during the stress task (mean of all three stress runs).

Cardiovascular and respiratory data were collected using the Vitaport 3 data acquisition system (TEMEC Instruments B.V., Netherlands). Data reduction and editing of artifacts were performed using ANSLAB, a software for scientific analysis of physiological data (Autonomic Nervous System Laboratory, Wilhelm & Peyk, 2005, Wilhelm, Grossman, & Roth, 1999). Both RSA and mean respiratory rate were determined for baseline, paced breathing, and the three experimental stress runs. These intervals were defined by markers manually set and recorded in the course of the experiment. RSA withdrawal was computed

by subtracting baseline RSA from RSA during the stress task (mean of all three stress runs). Therefore, higher values stand for less RSA withdrawal (less decrease of RSA).

ECG data acquisition: Electrocardiogram (ECG) recordings were acquired using electrode placement on the thorax in a standard Lead II configuration with three disposable electrodes. The raw ECG signal was recorded with a sampling rate of 1024 Hz and a high pass filter of 0.5 Hz.

ECG data reduction: ECG data were filtered offline with a low pass filter of 40 Hz and R-waves were identified in the continuous ECG signal using an automated software algorithm. This algorithm estimated the time point of the R-wave using a threshold technique applied to the filtered and detrended ECG signal. Correction of missed or misidentified R-waves or ectopic extrasystoles was afterwards manually performed in ANSLAB and R-wave times were then converted to inter-beat intervals (IBIs). Successive IBIs defined the heart period series, which was resampled into continuous equal time intervals of 250 ms using cubic-spline interpolation and saved to disc for the subsequent analyses of heart period variability due to RSA.

RSA analysis: To compute RSA, edited IBI time series were linearly detrended and power-spectral densities for each experimental period were computed in the 0.15 to 0.5 Hz frequency band using the Welch algorithm (Welch, 1967), which creates ensemble averages of successive periodograms. Averages from spectra estimated for 60-s segments, overlapping by half, were derived. For each 60-s segment, 256 points, which includes 240 sampled points with zero padding, were included. The segments were Hanning-windowed and subjected to fast Fourier transform. Estimates of power were adjusted to account for attenuation produced by the Hanning window and distributions were normalized by natural-logarithm transformation.

Respiratory rate was assessed in order to be able to include it as covariate in statistical analyses to account for its potential confounding influence on RSA in within-subject change analyses (Grossman & Taylor, 2007). Respiration pattern was recorded with a 128 Hz sample rate using an inductive plethysmograph (Respiband, Ambulatory Monitoring Inc., Ardsley, NY) applied around the upper rip cage. Onsets of respiratory cycles were identified automatically in ANSLAB using an automated algorithm. Instantaneous respiratory rate (in cycles per minute, cpm) was then calculated as 60 divided by the time difference between successive respiration cycles and averaged for each experimental phase.

Psychological Measures

Adverse childhood experiences (ACEs) before the age of 18 years were assessed with a German translation of the Early Trauma Inventory Self-Report questionnaire (ETI-SR, Bremner et al., 2007), which includes 31 items on general trauma exposure (e.g., natural disasters, death of close person, separation of parents), 9 items on physical abuse, 7 items on emotional abuse, and 15 items on sexual abuse. Events were summed up to a total score of occurred events (ACE total score), which could range between 0 and 62. For exploratory purposes, separate scores were computed for the four subscales. Additionally, age of first occurrence was assessed for each reported event and the variable *age of first ACE occurrence* was determined for each subject by taking the earliest age of onset across all items and domains. The ETI-SR has shown high internal consistency (Cronbach $\alpha = 0.78$-0.90) as well as good validity in all trauma domains (Bremner et al., 2007).

Symptoms of depression were assessed with the German version of the Center for Epidemiological Studies Depression Scale (CES-D; German version: ADS-K, Hautzinger & Bailer, 1993). In order to obtain an approximate index of physical fitness (which may influence autonomic parameters) participants were asked to rate their degree of physical

activity during a typical week. Scores ranged from 1 (inactive), 2 (active daily routine), 3 (light sports activity), 4 (moderate sports activity), 5 (intensive sports activity), to 6 (competitive sports activity).

Data Analysis

Analyses were performed using SPSS (version 20.0; SPSS, Chicago, IL). Descriptive statistics were conducted for all variables. Prior to analysis, data were checked for outliers and were transformed logarithmically or by square root function where appropriate in order to meet distributional assumptions. The α-level was set at 0.05 for significant findings in all primary analyses.

To examine whether the stress task induced significant increase in SBP and decrease in RSA, a paired samples *t*-test was conducted. Cohen's *d* is reported as a measure of effect size. Pearson correlations were used in order to examine the relationship between ACE total score as well as age of first ACE occurrence and indices of sympathetic and parasympathetic functioning (i.e., SBP at baseline, SBP reactivity, RSA at baseline, and RSA reactivity). Analyses of respiratory rate showed that some participants were breathing at a rate slower than 0.15 Hz, but that all participants' breathing rates were within the frequency band between 0.12 to 0.5 Hz throughout the different experimental phases. Thus, following recommendations of Grossman and Taylor (2007), we adjusted the lower boundary of the frequency range used for assessment of RSA to 0.12 Hz. This assures that spectral HRV measures within this band capture RSA activity adequately.

Partial correlations were performed for RSA reactivity controlling for the potentially confounding influence of changes in respiratory rate from baseline to stress condition (Grossman & Kollai, 1993). We did not adjust for respiration for baseline RSA, as such respiratory adjustment is less useful for individual difference analyses where people differ in

basal respiratory function due to factors unrelated to vagal activity, such as basal metabolic rate and respiratory pacemaker function (Grossman & Kollai, 1993; Grossman & Taylor, 2007). However, we included a 12-cpm paced breathing task that standardizes respiratory rate during baseline assessment and calculated the Pearson correlation for the relationship between paced breathing RSA and ACE total score. In this sample, there was no significant association between either SBP, RSA or ACEs and the two potentially confounding variables, current depressive symptomatology and physical fitness, and therefore they were not controlled for in the analyses.

Exploratory analyses were used to examine the association between the four ACE subscales and SBP as well as RSA using a more conservative $p<0.01$ significance criterion to reduce type-I error. Since distributional assumptions were not met for all ACE subscales, non-parametric Spearman correlations were conducted.

While all of the 146 participants completed the study, two participants had to be excluded due to acute illness during the laboratory session and one participant because she had not eaten for several days before the stress task due to religious reasons, which left data of 143 participants. Technical difficulties with the data acquisition system led to data loss in RSA measurements of 14 participants (missing completely at random). Thus, for 129 participants all relevant data were available and went into analyses. Respiratory measures were missing for 11 participants due to technical failure of the respiration sensors (missing completely at random). These were excluded in analyses using respiratory rate as a covariate (remaining n=118). Since not all participants were able to adhere to the specified paced breathing rhythm the sample was further reduced for the analysis concerning paced breathing (remaining n=104). Note that the sample size was also reduced for physical fitness since data were only available for part of the sample (remaining n=118), and also for analyses

concerning age of first ACE occurrence since a score on this measure could not be obtained for participants not reporting any ACEs (remaining n=114).

Results

Sample characteristics for age, years of education, ACEs, systolic blood pressure, RSA, respiratory rate, ADS-K, and physical fitness are displayed in Table 1. Results from paired samples *t*-tests indicated that the stress task had high potency and induced significant increase in SBP (t (128) = -23.87, p = .000, d = 1.59) as well as decrease in RSA (t (128) = 9.63, p = .000, d = 0.82).

****Insert Table 1 about here ****

Relationship between ACEs and SBP

A significant negative correlation was found for ACE total score and SBP reactivity. For ACE total score and SBP at baseline, there was an association being short of significance (see Table 2). Specifically, higher ACE total score was associated with lower SBP reactivity as well as a trend for lower SBP at baseline (see Figure 1).

****Insert Table 2 about here ****

****Insert Figure 1 about here ****

Relationship between ACEs and RSA

No significant correlation was observed for ACE total score and RSA at baseline (see Table 2). Also, ACE total score was not associated with RSA during paced breathing condition (r = 0.161, p = 0.102).

There was a significant association between ACE total score and RSA reactivity (see Table 2). Specifically, higher ACE total score was associated with lower RSA reactivity. However, when respiratory rate reactivity was controlled for, the association between ACE total score and RSA reactivity was no longer significant (r = 0.123, p = 0.188).

Age of first ACE occurrence

Pearson correlations showed a significant association between age of first ACE occurrence and SBP reactivity (see Table 2). Specifically, earlier ACE occurrence was associated with lower SBP reactivity (see Figure 2). Age of first ACE occurrence correlated moderately with ACE total score (r = -0.298, p = 0.001). When total score was entered as a covariate, the association between age of first ACE occurrence and SBP reactivity was short of significance (r = 0.183, p = 0.052). Also, there was an association being short of significance with earlier ACE occurrence being associated with lower RSA reactivity (see Table 2). Again, this association was no longer significant after controlling for respiratory rate (r = -0.131, p = 0.190). No significant associations were observed for the relationship between age of first ACE occurrence and SBP at baseline or RSA at baseline.

****Insert Figure 2 about here ****

Exploratory analysis of ACE subscales

Spearman correlations showed a significant association between general trauma and SBP reactivity (see Table 3). Specifically, higher ACE score in general trauma was associated with lower SBP reactivity (ρ = -0.282, p = 0.001). Using the more conservative criterion of $p < 0.01$, no further significant associations between ACE subscales and SBP baseline, RSA baseline and RSA reactivity were observed.

****Insert Table 3 about here ****

Discussion

In this study, we examined the relationship between ACEs and SBP and RSA at baseline as well as in response to a psychosocial stress task in a sample of healthy, young women. The current results extend our previous finding of blunted heart rate reactivity in response to the stress task by clarifying the role of the sympathetic and parasympathetic branches of the

ANS. Our results show blunted SBP reactivity in association with higher numbers of ACEs, indicating down-regulation of phasic sympathetic stress response. No significant association was found between ACEs and RSA reactivity after controlling for respiratory rate changes, which indicates that blunted heart rate response was not appreciably influenced by alterations in parasympathetic functioning. In addition to blunted SBP reactivity, participants with higher number of ACEs showed a trend for lower SBP at baseline.

Additionally, we found blunted SBP reactivity in association with earlier age of occurrence. This implies that the finding of blunted SBP reactivity in the context of ACEs applies particularly to participants with early ACE occurrence, which is in accordance with the hypothesis that earlier developmental periods could be especially sensitive for lasting alterations in stress response (Charmandari et al., 2003; Tottenham & Sheridan, 2010). Yet, the association was only short of significance after controlling for ACE total score. The total number of ACEs and the age of first occurrence of ACEs are not independent from each other since it is known that early ACEs/ traumatisation enhances the probability of future adversity (Desai, Arias, Thompson, & Basile, 2002).

The finding of blunted SBP at baseline as well as blunted SBP reactivity is contrary to several findings of heightened sympathetic baseline activity and reactivity in clinical and non-clinical samples with adversity (Blechert et al., 2007; Heim et al., 2000; Otte et al., 2005; Su et al., 2014). Still, the result of blunted reactivity is in accordance with the findings of Lovallo et al. (2012) and Leitzke et al. (2013), who reported blunted heart rate or SBP reactivity in their samples. Lovallo et al. (2012) explain their finding with altered functioning of stress systems towards a blunted response, and argue that deviations from the norm in either direction (exaggerated or diminished stress reactivity) might signal a system's loss of efficient allostatic regulation. This is in accordance with theories of allostatic load (McEwen, 1998) as well as with evidence of adverse health outcomes in association with blunted stress

response (see for review: Carroll, Lovallo, & C., 2009; Gold & Chrousos, 2002; Lovallo, 2011). Leitzke et al. (2013) consider the possibility of useful adaptation as an explanation for their finding of blunted systolic blood pressure reactivity in youth. They argue that an attenuated stress response might be adaptive in the context of repeated significant, but not overwhelming stress exposure because it reduces chronic activation, fearfulness and psychophysiological activity to subsequent stressors (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009; Leitzke et al., 2013). One may add that brief intermittent stress exposure rather than zero-stress environments in early life induces subsequent stress resistance, which is referred to as stress inoculation (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). In our healthy sample, ACE scores were on the lower end of the continuum, which indicates that the dosage of stressful experiences in the high-ACE individuals was still low enough to promote development of stress resistance. It is likely that much higher ACE scores would have the opposite effect. This is in accordance with the recently proposed adaptive calibration model (Del Giudice, Ellis, & Shirtcliff, 2011), which predicts a nonlinear relation between exposure to adversity and stress response, with moderate stress environments leading to a buffered responsivity pattern while dangerous or unpredictable environments would lead to a vigilant responsivity profile. Since our considerations are speculative without long-term health outcomes, only further research with prospective design can show whether blunted SNS stress response represents a beneficial adaptation or is a predictor of altered stress responsivity with long-term adverse health consequences.

High cardiac vagal activity during states of calm has been associated with higher physiological and behavioural flexibility as well as with high ability of social engagement, while appropriate withdrawal (greater decrease) of vagal influence during demanding situations enables cardiovascular mobilisation and corresponding reaction (Kok & Fredrickson, 2010; Porges, 2007). We found a significant association between ACEs and

RSA reactivity, whereby higher ACE scores correlated with blunted RSA reactivity (i.e., vagal withdrawal). This is in accordance with studies indicating impaired parasympathetic withdrawal or slower recovery in response to demanding situations in samples with adversity or PTSD (Arditi-Babchuk et al., 2009; Cohen et al., 1998). However, after controlling for the severely confounding influence of within-subject changes in respiratory rate (Grossman & Taylor, 2007), the correlation was no longer significant. This indicates that in our sample of healthy young women, change in parasympathetic functioning to stress did not depend on the number of ACEs and that the blunted heart rate reactivity previously found (Voellmin et al., 2015) was primarily due to reduced sympathetic reactivity. Also, no significant association was found between ACEs and RSA at baseline (during spontaneous as well as paced breathing), indicating that healthy young woman did not differ in tonic vagal activity irrespective of the number of ACEs they had experienced. Although there is evidence showing lower baseline RSA in association with adversity (Blechert et al., 2007; Cohen et al., 1997; Dale et al., 2009), many of these studies involved clinical samples or were conducted with children or adolescents, while our finding is in accordance with results from a representative sample of the Dutch population showing no differences in RSA measures at rest in the context of ACEs (van Ockenburg et al., 2014).

In exploratory analyses we found evidence for an association between blunted SBP reactivity and more incidences of general trauma, such as natural disasters, death of a close person, or separation of parents. Findings regarding the association of different types of adversity and ANS functioning are still scarce, but Lovallo et al. (2012) reported emotional adversity to be related to smaller heart rate responses. More studies have been conducted concerning endocrine stress response (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; Heim, Newport, Mletzko, Miller, & Hemeroff, 2008) but results are mixed with significant effects for different types of adversity in different samples. In conclusion, to our knowledge,

there is not yet consistent evidence for a specific pattern of certain types of ACEs being associated with specific alterations of the stress response.

The present study bears some limitations: We deliberately examined a homogenous sample of healthy young women in the context of our larger ongoing study about acute stress, emotion regulation, and sleep in young adults. Nevertheless, our results are in accordance with findings of blunted blood pressure in samples with younger age, mixed gender and ethnicity (Leitzke et al., 2013; Lovallo et al., 2012). Our sample consisted of young women attending schools for health care professions, which could imply that there is a sample bias in the direction that only individuals who are particularly stress-resilient and feeling capable of coping with the demanding and straining work in health care chose this kind of occupational career. Compliance was very high in our sample, which supports the assumption that the sample was resilient to additional stress and dedicated to social commitment. Also, participants with psychiatric diagnosis or physical pathology had been excluded and this may have restricted the range of ACEs and stress reactivity. Further, the assessment of ACEs was based on subjective and retrospective self-report measures. Therefore, effects of memory as well as selective recall due to retrospective bias cannot be excluded. Still, retrospective recalls of sexual and physical abuse, as well as physical and emotional neglect, have been evaluated to be sufficiently valid (Hardt & Rutter, 2004).

Despite these limitations, the present study provides important knowledge regarding the relationship between ACEs and sympathetic as well as parasympathetic cardiovascular stress response. Strengths of the study are its relatively large sample size and control for potentially confounding variables. Also, the confinement of the sample to physically and mentally healthy young women allowed to investigate the association between ACEs and stress response in a homogenous non-clinical sample, free of psychiatric comorbidities and medications interfering with stress system assessment. The study extends our finding of

blunted heart rate reactivity in response to a stress task previously reported (Voellmin et al., 2015) by showing blunted SBP reactivity but not blunted RSA reactivity in association with more ACEs in healthy young women, indicating down-regulation of phasic sympathetic stress response but no alteration of parasympathetic functioning with ACE. Understanding the underlying mechanisms in alterations and partial failure of stress response systems will aid in targeting interventions for persons at risk, and exposure to ACEs seems to be one important factor in determining this potential risk. Future research may focus on prospective investigation of the relative contribution of sympathetic and parasympathetic regulation in the context of ACEs, which would help clarify whether blunted stress reactivity indicates a risk for negative health outcomes or might even be a sign of beneficial adaptation, and as a consequence to either identify specific preventive actions or the potentially adaptive features that may promote resilience.

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Table 1

Means (SD) of sample characteristics, ACE scores, and physiological measures during baseline and in response to stress (stress minus baseline difference scores) (N =129)

	Mean	Median	SD	Range
Age (years)	21.75	21.00	1.66	18-25
Education (years) [a]	12.52	12.00	1.42	9-17
ACE				
Total score (0-62)	4.09	3.00	3.58	0-18
Age of fist occurrence (0-18) [b]	6.09	6.00	4.27	0-16.5
General trauma (0-31)	2.17	2.00	2.07	0-10
Physical abuse (0-9)	0.91	1.00	1.08	0-5
Emotional abuse (0-7)	0.60	0.00	1.24	0-6
Sexual abuse (0-15)	0.40	0.00	0.74	0-4
SBP (mm Hg):				
Baseline	111.63	111.00	8.81	93.00-136.00
Reactivity	17.55	17.33	8.35	-7.67-35.00
RSA (ln ms^2)				
Baseline	7.74	7.75	1.02	4.64-10.23
Reactivity	-1.10	-0.80	1.30	-5.31-0.91
Paced Breathing [d]	8.81	8.99	1.05	6.28-11.00
Respiratory rate (cpm): [c]				
Baseline	19.44	19.05	3.21	8.72-28.27
Reactivity	0.89	0.40	3.35	-6.94-9.78
Paced Breathing [d]	12.69	12.46	0.91	11.53-15.83
ADS-K-Score	6.40	5.00	4.85	0-21
Physical fitness [c]	3.73	4.00	1.03	2-6

Note: ACE = adverse childhood experience from Early Trauma Inventory Self-Report (ETI-SR); SBP=systolic blood pressure; RSA=respiratory sinus arrhythmia; ADS-K = German version of the Center for Epidemiological Studies Depression Scale; CES-D.
[a] n=119, [b] n=114, [c] n=118, [d] n=104.

Table 2

Pearson correlations of ACE total score with SBP and RSA during baseline and in response to a psychosocial stress task (N=129 for ACE total score, N=114 for Age of first ACE occurrence)

	ACE total score		Age of first ACE occurrence	
	r	p	r	p
SBP baseline	-0.159	0.072	0.026	0.781
SBP reactivity	-0.295	0.001	0.241	0.010
RSA baseline	-0.036	0.688	0.057	0.550
RSA reactivity	0.188	0.033[a]	-0.161	0.088[a]

Note: For abbreviations, see Figure 1.

[a] Not significant after controlling for respiratory rate

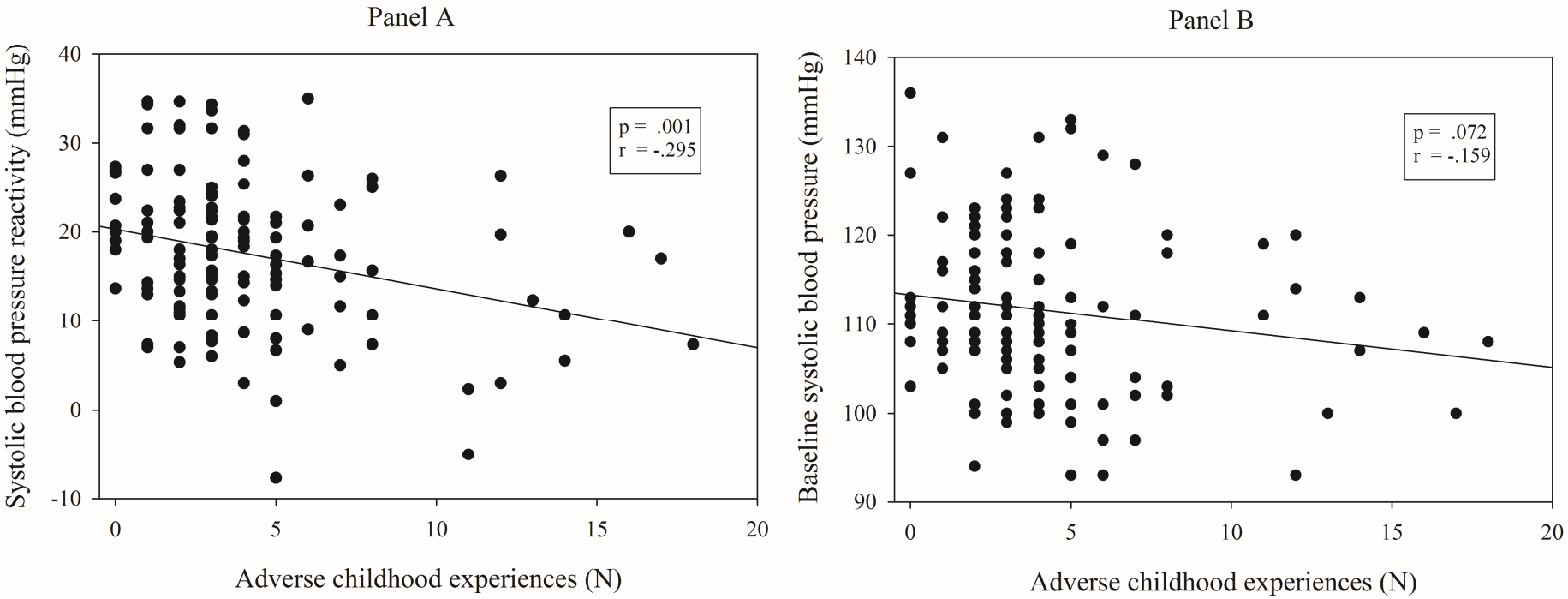

Figure 1. Scatterplots of the relationships between ACEs and SBP reactivity (Panel A) and ACEs and SBP baseline (Panel B). (SBP = systolic blood pressure) Note: For purposes of better illustration non-transformed variables with original scaling are depicted here. For inferential statistics variables were transformed if necessary; N = 129.

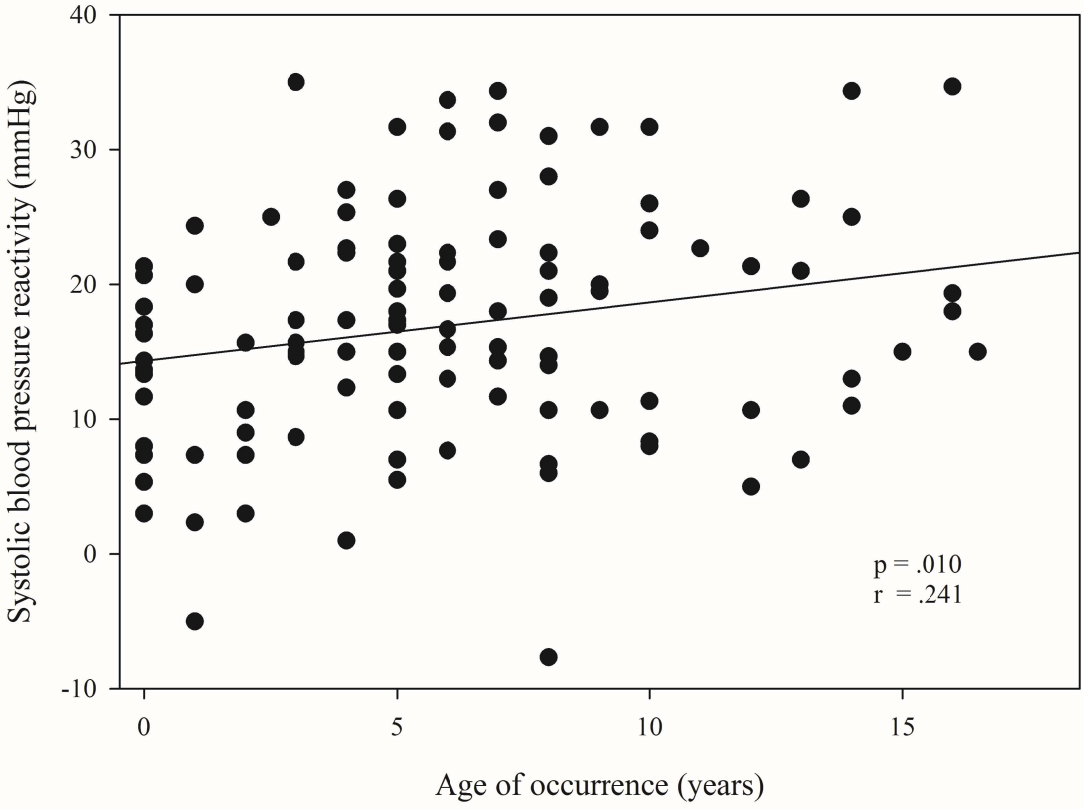

Figure 2. Scatterplot of the relationship between age of first occurrence of ACEs and SBP reactivity. (SBP = systolic blood pressure) Note: For purposes of better illustration non-transformed variables with original scaling are depicted here. For inferential statistics variables were transformed if necessary; N = 114 because only participants reporting any ACE could be included.

Table 3

Spearman correlations of ACE subscales with SBP and RSA during baseline and in response to a psychosocial stress task

	ACE general trauma		ACE physical abuse		ACE emotional abuse		ACE sexual abuse	
	ρ	p	ρ	p	ρ	p	ρ	p
SBP baseline	-0.151	0.088	-0.038	0.669	0.016	0.861	-0.098	0.271
SBP reactivity	-0.282	0.001	-0.091	0.304	-0.146	0.099	-0.114	0.200
RSA baseline	-0.017	0.849	-0.038	0.666	-0.044	0.620	-0.083	0.349
RSA reactivity	0.033	0.707	0.220	0.012	0.108	0.221	0.075	0.398

Note: N =129. SBP = systolic blood pressure, RSA = respiratory sinus arrhythmia, ACE = adverse childhood experiences.