Effects of stress-related psychosocial factors on physiological outcomes

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KAROLINE PIERITZ

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Erstgutachter: Dr. Frank Euteneuer (Philipps-Universität Marburg)

Zweitgutachter: Prof. Dr. Winfried Rief (Philipps-Universität Marburg)

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1. Objectives

According to Lazarus' Theory of Cognitive Appraisal, an individual experiences stress when an imbalance between environmental demands and his or her adaptive capacity occurs [1]. The human body is adapted to cope with and recover from acute physical threats. In this day and age, however, we mostly have to deal with prolonged mental and psychosocial stressors [2]. Basically, there are three major categories of psychosocial stressors: Life events such as the death of a loved one, or experiencing sexual assault, chronic strains such as a demanding job or a troubled relationship, and daily hassles such as an argument with a friend or being stuck in a traffic jam [3]. Experiences of acute psychosocial stress are accompanied by various physiological changes. This seems to be adaptive for coping in the short term, a process also referred to as *allostasis*. The concept of allostasis claims, however, that repeated allostatic changes due to chronic psychosocial stress may result in a dysfunction of allostatic systems. This may cause wear and tear of the body, the so-called *allostatic load,* and eventually lead to disease [4,5].

Psychosocial stress has been related to various negative physical and mental health outcomes. There is evidence that stress plays a role in the onset and/or progression of clinical depression, chronic pain syndromes, autoimmune diseases, viral infections, cancer, and cardiovascular disease. Research suggests that prolonged psychosocial stress may affect health indirectly through health behaviors (e.g., smoking, exercising) or directly through alterations of interacting physiological systems such as endocrine, immune, and autonomic nervous systems (Figure 1) [2,6–9]. However, additional studies are necessary to further clarify the mechanisms by which psychosocial stressors affect health.

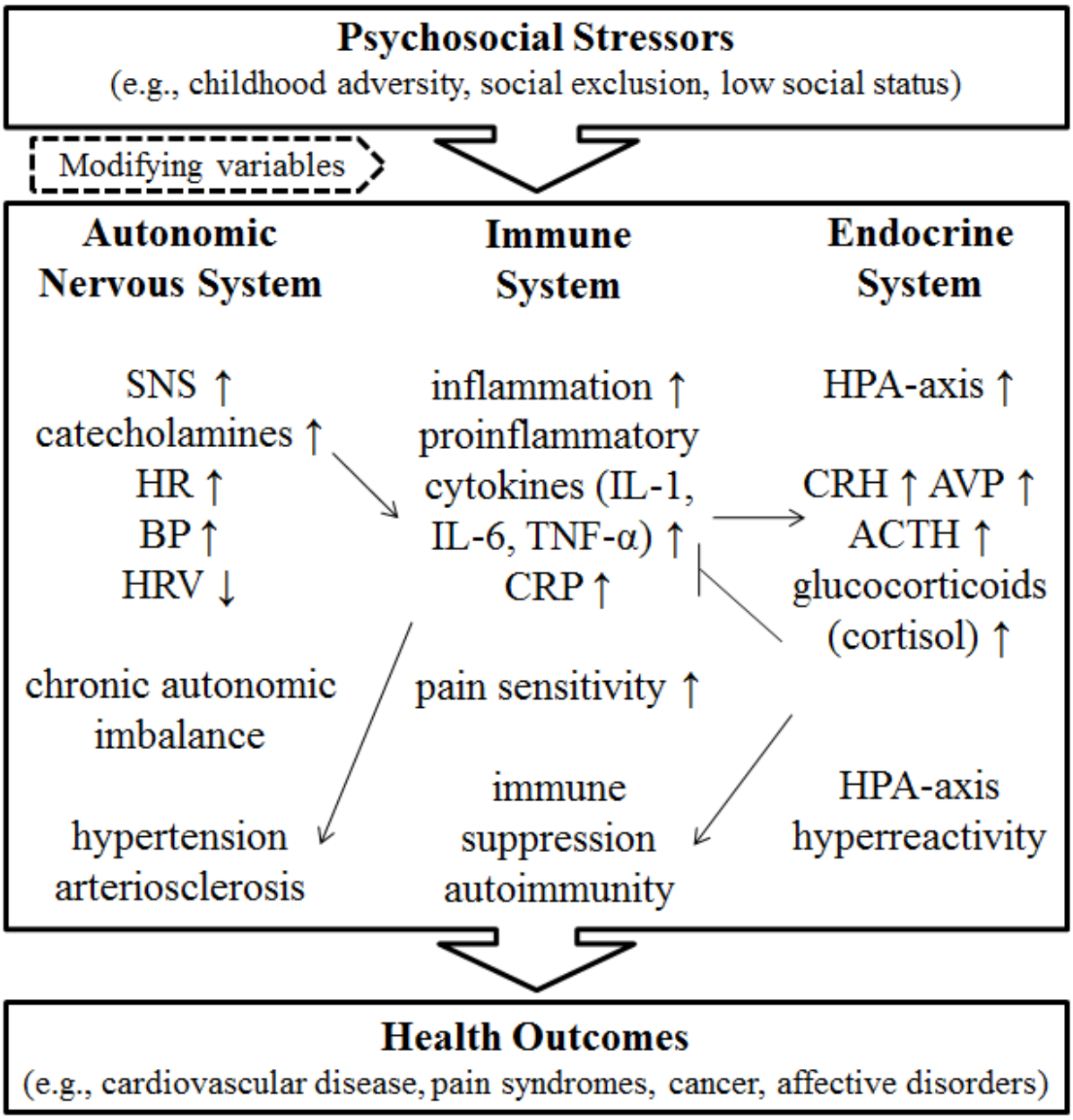

Figure 1. Mechanisms by which psychosocial stressors may affect health. Stress could influence health indirectly through changes in health behavior (e.g., smoking, exercising, alcohol consumption; not shown) and directly by affecting the autonomic nervous system, immune system and endocrine system. Effects might be modified by variables such as social support or chronic life stress. There is evidence that these systems interact with each other. After exposure to an acute stressor, the sympathetic branch of the autonomic nervous system becomes activated. Catecholamines are released into the blood stream, blood pressure and heart rate increase, HRV decreases. Sympathetic activity can also enhance immunity including increased secretion of proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α) and CRP which might be accompanied by an increased sensitivity to pain. Proinflammatory cytokines can also activate the HPA-axis. CRH is released from the hypothalamus, stimulating the anterior pituitary to release ACTH which then stimulates the adrenal cortex to secrete glucocorticoids, including cortisol. Prolonged cortisol secretion may have a suppressive effect on the immune system. Numerous repeated stressors, however, might induce hyperreactivity of the HPA-axis, resulting in an increased risk for autoimmunity. Persisting SNS over-activation and chronic inflammation might result in permanent physiological changes such as chronic autonomic imbalance, hypertension and arteriosclerosis. Consequences following the described pathophysiological alterations include cardiovascular and autoimmune diseases, cancer, viral infections, pain syndromes, affective disorders [2,7–11]. ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; BP = blood pressure; CRH = corticotropin-releasing hormone; CRP = C-reactive protein; HPA = hypothalamic-pituitary-adrenal; HR= heart rate, HRV = heart rate variability; IL-1 = interleukin-1; IL-6 = interleukin-6; SNS = sympathetic nervous system; TNF-α = tumor necrosis factor-α.

The present thesis on "Effects of stress-related psychosocial factors on physiological outcomes" aims to take a closer look at the causal influence of different psychosocial stressors (i.e., childhood adversity, social exclusion, low subjective social status) on physiological outcomes (i.e., pain sensitivity, cardiovascular processes) that might be involved in the pathogenesis of disease. It consists of three research articles reporting one cross-sectional and two experimental studies.

Adverse childhood experiences – some of the most severe early life stressors – have been linked to somatic and pain complaints, in later life. It has been suggested that early life stressors might alter biological pathways resulting in an amplified perception of bodily signals, including pain. Article I, therefore, focuses on the association of five different forms of childhood adversity and two components of laboratory pain: affective (i.e., heat pain tolerance) vs. sensory (i.e., heat pain intensity). Bivariate analyses indicated that emotional abuse but no other forms of childhood adversity were significantly related to decreased heat pain tolerance. Accordingly, multiple regression analyses revealed that only emotional abuse was a significant predictor of heat pain tolerance when entering all forms of childhood adversity simultaneously. This relationship was not mediated by self-reported somatic symptoms, depressive symptoms, or pain catastrophizing. These findings indicate that the severity of emotional childhood adversity is associated with decreased pain tolerance, an affective component of pain, but not with heat pain intensity, a sensory component of pain.

The results reported in article I are also in line with evidence suggesting partly overlapping systems processing physical pain and experiences of social pain (Figure 2) and that feelings of social pain may increase physical pain, especially its affective component. Social pain refers to the painful feelings following actual or anticipated psychological distance from others. This includes feeling rejected, being treated unfairly, or having a relationship that is threatened, damaged or lost. Article II aims to extend the existing findings by examining the impact of the social pain due to social exclusion on both an affective (i.e.,

heat pain tolerance) and a sensory component of pain of physical pain (i.e., heat pain intensity). Additionally, potential moderators on this effect – chronic life stress, social status and social support – were examined. Results indicated that chronic stress moderates the impact of social exclusion on pain tolerance. When chronic stress was high, socially excluded participants showed a lower heat pain tolerance than participants who were socially included. This finding suggests that higher levels of chronic stress may enhance the vulnerability of affective pain processing to acute social exclusion.

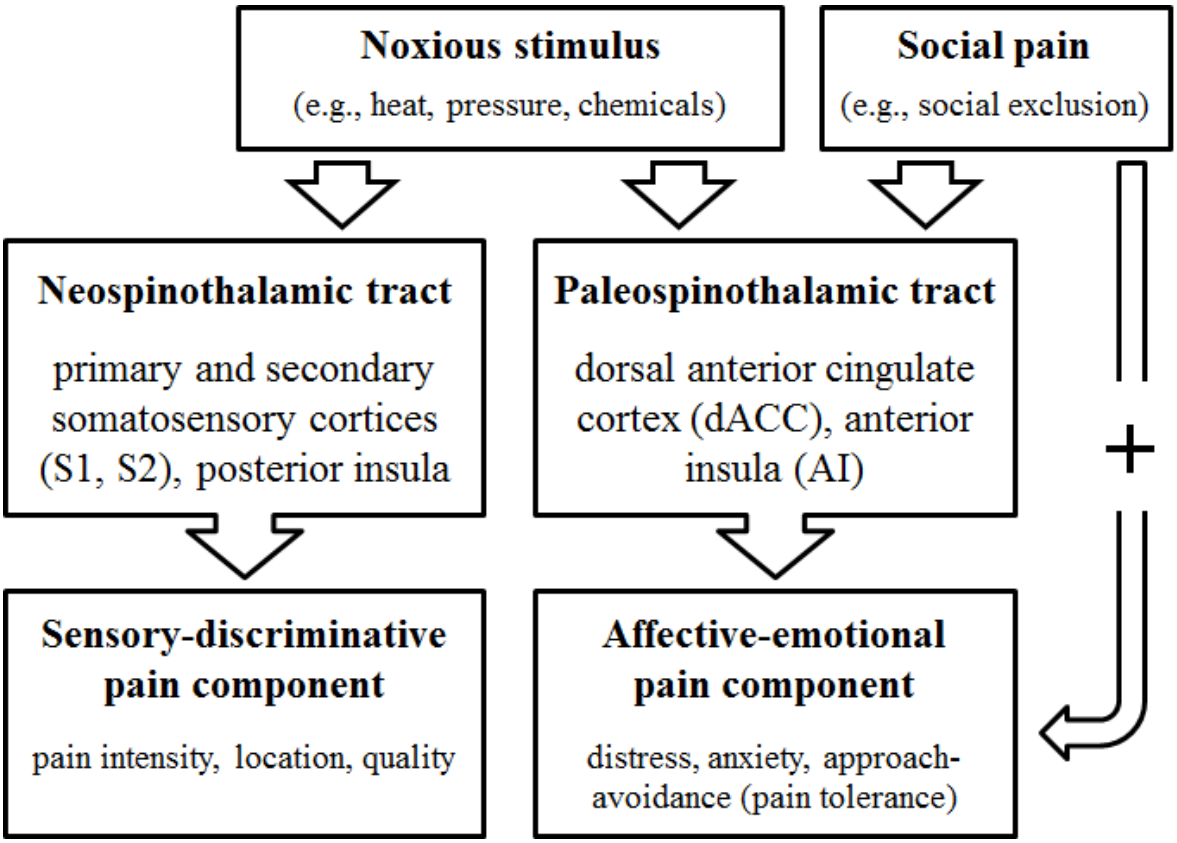

Figure 2. Simplified heuristic working model of systems processing experiences of physical and social pain. The neospinothalamic tract transmits sensory-discriminative information about location, quality and intensity of a noxious stimulus to the primary and secondary somatosensory cortices and the posterior insula. Affective-emotional information is transmitted via the paleospinothalamic tract to the dorsal anterior cingular cortex and the anterior insula. Experiences of social pain are processed in similar neurocognitive systems and, therefore, may increase the affective component of physical pain [12–16].

Cross-sectional and longitudinal studies displayed a strong association between subjective social status (SSS) and cardiovascular health. Hence, article III focuses on the causal influence of SSS on variables relevant for cardiovascular disease (CVD) (i.e., blood

pressure, heart rate variability [HRV]). A temporary shift toward high or low SSS was experimentally induced while blood pressure and HRV were measured. Participants in the low SSS condition had a significantly lower HRV during experimental manipulation than at baseline and recovery. They also showed a stronger HRV reactivity from baseline to experimental manipulation than participants in the high SSS condition. Our results suggest that even temporary shifts of one's SSS may have measureable effects on cardiovascular variables. They support the notion that SSS plays a causal role in the development of CVD.

The following pages provide structured summaries of all articles.

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2. Summaries of peer-reviewed articles

2.1 Article I

Pieritz, K., Rief, W., & Euteneuer, F. (2015). Childhood adversities and laboratory pain perception. *Neuropsychiatric Disease and Treatment*, *11*, 1-8.

2.1.1 Background

Adverse childhood experiences are some of the most severe early life stressors. They have been linked to negative health outcomes, including somatic complaints and pain syndromes, in later life. A possible mechanism underlying this link might be an alteration of biological pathways resulting in an amplified perception of bodily signals. For example, adverse childhood experiences have been related to a dysregulation of the hypothalamic pituitary-adrenal (HPA) axis and inflammatory immune alterations, features which have also been associated with somatic complaints and increased pain perception. If adverse childhood experiences lead to an amplification of the perception of bodily signals, individuals with more adverse childhood experiences should be characterized by an increased sensitivity to laboratory induced pain.

2.1.2 Methods

To investigate whether individuals with more adverse childhood experiences have an increased pain sensitivity, an affective component of pain (i.e., heat pain tolerance) and a sensory component of pain (i.e., heat pain intensity) were measured in a community-based sample of 62 healthy women (mean age 34.4 ± 12.2 years). Thermal stimuli between 32°C and 52°C were delivered using a peltier-based thermode. For heat pain tolerance, individuals were asked to stop the heat stimulus by pressing a button when they could not stand it any longer. Heat pain intensity was assessed directly after the pain tolerance measurements using a visual analogue scale. Childhood adversity was assessed using the Childhood Trauma

Questionnaire (CTQ), which includes five forms of childhood adversity: physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. As potential mediators somatic symptoms (PHQ-15), depressive symptoms (PHQ-9) and pain catastrophizing (PCS) were assessed via questionnaire.

2.1.3 Results

Spearman's rank correlations indicated that emotional abuse but no other forms of childhood adversities were significantly related to decreased heat pain tolerance. Accordingly, multiple regression analyses revealed that only emotional abuse was a significant predictor of heat pain tolerance when entering all CTQ subscales simultaneously. Although emotional abuse was also related to somatic symptoms, depressive symptoms and pain catastrophizing, none of these variables mediated the relationship between childhood adversity and laboratory pain. No significant associations were found between any forms of childhood adversity and heat pain intensity.

2.1.4 Discussion

Our findings indicate that the severity of emotional childhood abuseis associated with decreased heat pain tolerance, an affective component of pain, but not with heat pain intensity, which has been described as a sensory component of pain.

2.2 Article II

Pieritz, K., Schäfer, S. J., Strahler, J., Rief, W., & Euteneuer, F. (in revision for PLOS ONE). Chronic stress moderates the impact of social exclusion on pain tolerance.

2.2.1 Background

There is evidence that experiences of social pain (i.e., painful feelings following social exclusion) and experiences of physical pain may be processed in similar neurocognitive systems. Experimental findings in humans suggest that social exclusion may relate to affective components of pain processing (i.e., dACC, AI) rather than to sensory components of pain processing (i.e., primary and secondary somatosensory cortices, posterior insula). The present study examines the impact of social exclusion on both an affective (heat pain tolerance) and a sensory component of experimental pain (heat pain intensity). Since chronic stress, low social status, and social support may enhance vulnerability to acute social exclusion and have been found to increase the impact of social threats and other stressors on psychobiological pathways for pain, these psychosocial risk factors were examined as potential moderators.

2.2.2 Methods

A community-based sample of 59 healthy women (mean age 35 ± 12 years) played a virtual ball-tossing game called Cyberball, a commonly used and valid instrument to manipulate social exclusion in laboratory settings. Participants were randomly assigned to either being excluded or included by two other virtual players. Heat pain tolerance and intensity were assessed before and after the game using thermal stimuli between 32°C and 52°C delivered by a peltier-based thermode. For heat pain tolerance, individuals were asked to stop the heat stimulus by pressing a button when they could not stand it any longer. Heat pain intensity was assessed using a visual analogue scale. Potential psychosocial moderators,

social support (F-SozU), subjective social status (MacArthur Scale), and chronic stress (TICS) were assessed via questionnaire.

2.2.3 Results

Although there was no general group difference in pain tolerance, moderation analyses indicated that chronic stress affects the impact of social exclusion on pain tolerance. Socially excluded participants with high chronic stress had a lower heat pain tolerance than those who were socially included in the Cyberball game. For pain intensity, analyses of covariance (adjusted for baseline values) indicated that participants who experienced social exclusion reported significantly lower pain intensity ratings than participants who were socially excluded. This effect was not moderated by chronic stress, social support or SSS.

2.2.4 Discussion

The results of the present study add to the growing evidence of partly overlapping systems for social pain and physical pain. They further suggest that different components of pain may be differently affected by social pain due to social exclusion and that chronic stress may enhance the vulnerability of affective pain processing to acute social exclusion.

2.3 Article III

Pieritz, K., Süssenbach, P., Rief, W., & Euteneuer, F. (submitted). Subjective social status and cardiovascular reactivity: An experimental examination.

2.3.1 Background

Lower social status has been longitudinally and cross-sectionally associated with a wide range of biological risk factors for cardiovascular disease. In addition to traditional measures of objective social status (OSS), such as education, income, and occupation the

MacArthur Scale of Subjective Social Status (SSS) has been established. This tool asks individuals to rate their relative social position on the rung of a visual ladder. Research suggests that SSS is a better predictor of health than OSS, but no study has examined the impact of a temporarily experimental manipulation of SSS on physiological parameters yet. The present study aimed to examine the causal influence of SSS on processes relevant for cardiovascular health (i.e., blood pressure, heart rate variability [HRV]).

2.3.2 Methods

Participants were randomly assigned to one of two conditions in which they were instructed to compare themselves with either someone who has a higher SSS (low SSS condition) or a lower SSS (high SSS condition). Blood pressure and HRV were continuously measured before (baseline), throughout and after the manipulation (recovery) using a Task Force Monitor® device.

2.3.3 Results

Repeated measures ANOVA revealed a significant time x group interaction for HRV. Pairwise comparisons revealed that in the low SSS group, HRV during experimental manipulation was significantly lower than at baseline and recovery. There were no significant HRV differences between time points for the high SSS group. In a further analysis, we observed whether HRV reactivity differed between the low and high SSS groups. For this purpose, changes in HRV (delta) were calculated subtracting pre from post values. Analyses of covariance indicated that participants in the lower SSS group showed a significantly higher HRV reactivity from baseline to experimental manipulation than participants in the higher SSS group. All analyses were adjusted for household net income, sex, age, body mass index (BMI), and smoking status.

2.3.4 Discussion

Our results suggest that already temporary shifts of one's SSS may have measureable effects on cardiovascular processes. They further support the causal role of low SSS in the development of cardiovascular disease.

3. Summary in German

Psychosoziale Stressoren scheinen eine wichtige Rolle in der Entstehung und dem Verlauf von Depressionen, psychosomatischen Beschwerden, Schmerzerkrankungen, Autoimmunerkrankungen, viralen Infektionen, Krebs und kardiovaskulären Erkrankungen zu spielen. Nach dem transaktionalen Modell von Lazarus entstehen Stressreaktionen beim Menschen, wenn ein Ungleichgewicht zwischen psychosozialen Anforderungen und der eigenen Bewältigungs- bzw. Anpassungsfähigkeit wahrgenommen wird. Dem Allostase-Konzept zufolge sind die darauf folgenden physiologischen Veränderungen (*Allostase*) zwar zunächst adaptiv, um sich an veränderte Umweltbedingungen anpassen zu können. Langfristig gehen diese jedoch mit einer erhöhten körperlichen „Abnutzung“ *(Allostatische Last)* und damit einem erhöhten Erkrankungsrisiko einher.

Es wird angenommen, dass psychosozialer Stress die Gesundheit indirekt über eine Steigerung gesundheitsschädlicher Verhaltensweisen (z.B. Rauchen, Alkoholkonsum, körperliche Inaktivität) beeinflusst. Andererseits scheint anhaltender psychosozialer Stress auch einen direkten Einfluss auf interagierende physiologische Prozesse und Systeme zu haben, wodurch es zu nachhaltigen Veränderungen kommt, die auch an der Entstehung von Krankheiten beteiligt sein können. Dazu zählen u.a. eine gestörte Immunfunktion, Entzündungsprozesse, erhöhter Blutdruck und autonome Imbalance sowie eine Beeinträchtigung der HPA-Achsen-Funktion, die mit gestörter Cortisolsekretion einhergehen kann. Aufgrund ethischer Einschränkungen stammt der Großteil dieser Befunde aus Tierstudien oder Quer- und Längsschnittstudien am Menschen. Experimentelle Studien zur Untersuchung kausaler Mechanismen gibt es bisher nur wenige.

Die vorliegende Dissertation besteht aus drei Originalarbeiten mit einem querschnittlichen und zwei experimentellen Studiendesigns. Sie beschäftigt sich inhaltlich mit den Auswirkungen psychosozialer Faktoren auf physiologische Prozesse, die auch an der

Entstehung stressassoziierter körperlicher Erkrankungen beteiligt sein können. Dabei liegt ein besonderer Fokus auf der Untersuchung kausaler Mechanismen. Es werden die Einflüsse negativer Kindheitserlebnisse (z.B. Missbrauch oder Misshandlung) und sozialer Ausgrenzung auf die Schmerzwahrnehmung untersucht. Dabei werden auch potentiell modifizierende Faktoren (z.B. soziale Unterstützung, chronischer Stress) betrachtet. Weiterhin soll der Einfluss des subjektiven sozialen Status auf kardiophysiologische Prozesse, die potentiell an der Entstehung kardiovaskulärer Erkrankungen beteiligt sind (Blutdruck, HRV), untersucht werden.

Traumatische Kindheitserlebnisse, als besonders frühe und intensive psychosoziale Stressoren, werden mit somatoformen und schmerzassoziierten Beschwerden im Erwachsenenalter in Verbindung gebracht. Studie I **„Childhood adversities and laboratory pain perception"** befasst sich daher mit dem Einfluss unterschiedlicher Dimensionen von negativen bzw. traumatischen Kindheitserlebnissen auf zwei Komponenten (affektiv und sensorisch) von laborinduziertem Schmerz. Thermische Stimuli zwischen 32 ° C und 52 ° C wurden mithilfe einer Peltier-basierten Thermode appliziert, um die Hitzeschmerztoleranz (affektive Schmerzkomponente) und -intensität (sensorische Schmerzkomponente) in einer Stichprobe von 62 gesunden Frauen zu bestimmen. Für die Hitzeschmerztoleranz wurden die Teilnehmerinnen gebeten, den Hitzereiz durch Tastendruck zu stoppen, wenn sie ihn nicht mehr aushalten konnten. Die Hitzeschmerzintensität wurde direkt nach der Schmerztoleranz Messung mithilfe einer10 cm langen visuellen Analogskala („kein Schmerz" bis „schlimmster vorstellbarer Schmerz") erfragt. Physischer, sexueller und emotionaler Missbrauch sowie emotionale und körperliche Vernachlässigung wurden retrospektiv mit der deutschen Version des Childhood Trauma Questionnaire (CTQ) erfasst. Zusätzlich wurden somatische Symptome (PHQ-15) und das Ausmaß der Schmerzkatastrophisierung (PCS) erfragt. Die Ergebnisse bivariater Analysen zeigen, dass die CTQ-Unterskala „emotionaler Missbrauch" am stärksten mit verringerter Hitzeschmerztoleranz und einem höheren Ausmaß depressiver

und somatischer Symptome und Schmerzkatastrophisierung zusammenhängt. Eine multiple Regressionsanalyse, bei der alle CTQ-Skalen gleichzeitig berücksichtigt wurden, ergab, dass emotionaler Missbrauch als einzig signifikanter Prädiktor eine verringerte Hitzeschmerztoleranz vorhersagt. Dieser Zusammenhang wurde weder über depressive oder somatische Symptome noch über Schmerzkatastrophisierung mediiert. Die Ergebnisse weisen darauf hin, dass emotional traumatische Kindheitserlebnisse mit einer Reduktion der Schmerztoleranz, einer eher affektiven Komponente des Schmerzes, zusammenhängen, nicht jedoch mit der Schmerzintensität, die in der Literatur eher als sensorische Komponenten von Schmerz beschrieben wird.

Die Ergebnisse von Studie I, dass insbesondere emotional traumatische Kindheitserlebnisse mit der affektiven Schmerzkomponente zusammenhängen, stehen auch im Einklang mit Befunden, dass sozialer Schmerz auf ähnlichen neurobiologischen Mechanismen zu beruhen scheint wie physischer Schmerz. Unter sozialem Schmerz werden die unangenehmen Gefühle verstanden, die als Folge tatsächlicher oder antizipierter sozialer Distanz zu anderen entstehen. Dazu gehört beispielsweise Erfahrungen von Ablehnung oder Ungerechtigkeit oder eine zwischenmenschlichen Beziehung, die bedroht oder gar beendet ist. So gibt es gibt u.a. Hinweise aus bildgebenden Studien, dass sozialer Schmerz, verursacht durch soziale Ausgrenzung, in ähnlichen Arealen wie affektive Aspekte körperlicher Schmerzen verarbeitet wird (z.B. dorso-anteriorer cingulärer Kortex [dACC], anteriore Insula [AI]). Deshalb wird angenommen, dass sozialer Schmerz auch zu einer Verstärkung körperlicher Schmerzen führen kann. In Artikel II **„Chronic stress moderates the impact of social exclusion on pain tolerance”** wurden daher die Auswirkungen sozialer Ausgrenzung auf zwei Schmerzkomponenten, laborinduzierte Hitzeschmerztoleranz (affektive Komponente) und -intensität (sensorische Komponente), in einer Stichprobe von 59 gesunden Frauen experimentell untersucht. Soziale Ausgrenzung wurde mithilfe des bereits etablierten Cyberball Paradigmas manipuliert. Dabei handelt es sich um ein virtuelles Ballwurfspiel, das

dem Spieler suggeriert, er würde mit zwei anderen Personen zusammen spielen, die jedoch in Wirklichkeit computergeneriert sind. Während die Spieler in der Einschlussbedingung über die gesamte Spielzeit hinweg regelmäßige Ballkontakte haben, werden die Spieler der Ausgrenzungsbedingung nach den ersten Ballkontakten nicht mehr von ihren Mitspielern angespielt. Hitzeschmerztoleranz und -intensität der Teilnehmerinnen wurden jeweils vor und nach dem Cyberball Spiel bestimmt. Dazu wurden thermische Stimuli zwischen 32 °C und 52 °C mithilfe einer Peltier-basierten Thermode appliziert. Für die Bestimmung der Hitzeschmerztoleranz wurden die Teilnehmerinnen gebeten, den Hitzereiz durch Tastendruck zu stoppen, wenn sie ihn nicht mehr ertragen konnten. Die Hitzeschmerzintensität wurde direkt nach den Schmerztoleranz Messungen mithilfe einer 10 cm langen visuellen Analogskala („kein Schmerz“ bis „schlimmster vorstellbarer Schmerz“) erfragt. Kovarianzanalysen (ANCOVAs; adjustiert für Baselinewerte) wurden durchgeführt, um auf Gruppenunterschiede bezüglich Hitzeschmerztoleranz und -intensität zu testen. Unter Berücksichtigung der Befunde, dass chronischer Stress, ein niedriger sozialer Status und geringe soziale Unterstützung die Vulnerabilität gegenüber sozialer Ausgrenzung verstärken können, wurden diese Variablen mittels Fragebögen erfasst und mithilfe von PROCESS für SPSS als potentielle Moderatoren analysiert. Obwohl eine ANCOVA keinen allgemeinen Gruppenunterschied in der Schmerztoleranz (affektive Komponente) ergab, konnten die Ergebnisse der Moderationsanalysen zeigen, dass chronischer Stress den Effekt von virtueller sozialer Ausgrenzung auf die Schmerztoleranz moderiert. Bei hohem chronischen Stress (+ 1SD) hatten soziale ausgegrenzte Teilnehmerinnen eine niedrigere Schmerztoleranz als Teilnehmerinnen in der sozialen Einschlussbedingung. Bei durchschnittlichem und niedrigem chronischen Stress gab es keine signifikanten Gruppenunterschiede. Bezüglich der Schmerzintensität ergab die ANCOVA einen signifikanten Gruppenunterschied dahingehend, dass die Teilnehmerinnen der Ausgrenzungsbedingungen im Vergleich zur Einschlussbedingung niedrigere Schmerzintensitäten berichteten. Eine mögliche Erklärung

könnte sein, dass die Teilnehmerinnen der Einschlussbedingung diese als einen Indikator für eine sichere soziale Umgebung wahrnahmen und damit eher bereit waren, mehr Schmerzen zu äußern. Diese Interpretation steht im Einklang mit Befunden, dass Frauen in Gegenwart einer Freundin mehr Schmerzen äußern sowie mit Modellen sozialer Verstärkung chronischer Schmerzen.

In Studie III **„Subjective social status and cardiovascular reactivity: An experimental examination“** wurden erstmalig die Auswirkungen eines experimentell manipulierten subjektiven sozialen Status (SSS) auf kardiophysiologische Prozesse untersucht, die auch an der Entstehung kardiovaskulärer Erkrankungen beteiligt sein können. Der subjektive soziale Status eines Menschen ist seine wahrgenommene soziale Position *in Relation* zu anderen Menschen in seinem sozialen Umfeld bzw. seiner Nation und ein potentiell besserer Prädiktor für Gesundheit als traditionelle objektive Statusmaße, wie Bildung, Beruf oder Einkommen. Ein niedriger SSS konnte mit kardiovaskulären Risikofaktoren bzw. Erkrankungen, z.B. einer reduzierten Herzratenvariabilität (HRV), erhöhtem Blutdruck, gestörter Cortisolsekretion und verminderter Immunabwehr, in Verbindung gebracht werden. Der Großteil dieser Befunde stammt jedoch aus querschnittlichen und prospektiven Studien. Daher wurde in der vorliegenden Studie der kausalen Fragestellung nachgegangen, ob sich die Auswirkungen eines niedrigen subjektiven sozialen Status auf kardiovaskuläre Risikofaktoren auch kurzfristig experimentell zeigen lassen. Dazu wurde ein bereits etabliertes Paradigma von Kraus et al. (2012) angewendet, bei dem 64 gesunde Probanden randomisiert einer von zwei Bedingungen zugewiesen wurden, in der sie sich entweder mit einer statushöheren (Bedingungen niedriger SSS) oder einer statusniedrigeren Person (Bedingung hoher SSS) vergleichen sollten. Anschließend wurde mithilfe der MacArthur Skala der subjektive soziale Status der Teilnehmer erfragt. Als Manipulationscheck wurden die durchschnittlichen SSS Ratings der beiden Gruppen miteinander verglichen. Vor der Manipulation (Baseline), währenddessen sowie danach

(Recovery) wurden der kontinuierlichen Blutdruck und die HRV mittels eines elektronischen Diagnosesystems (Task Force Monitor®) aufgezeichnet. Die Ergebnisse messwiederholter Varianzanalysen (ANOVA) ergaben eine signifikante Interaktion von Messzeitpunkt x Statusbedingung für die HRV, wobei die HRV in der niedrigen SSS Bedingung während der Experimentalphase signifikant niedriger war als zur Baseline und Recovery. Zusätzliche Analysen zeigten, dass die HRV Reaktivität (Grad der Veränderung) von Baseline zur Experimentalphase in der niedrigen SSS Bedingung signifikant größer war als in der Gruppe mit hohem SSS. Es fanden sich keine Gruppenunterschiede bezüglich der Höhe des Blutdrucks. Die Ergebnisse des Experiments deuten darauf hin, dass bereits kurzfristige Statusveränderungen einen messbaren Einfluss auf kardiophysiologische Prozesse haben und unterstützen die kausale Rolle subjektiven sozialen Status für die kardiovaskuläre Gesundheit.

4. Appendix

Article I

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Childhood adversities and laboratory pain perception

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Karoline Pieritz
Winfried Rief
Frank Euteneuer

Division of Clinical Psychology and Psychotherapy, Philipps University Marburg, Marburg, Germany

Abstract: Childhood adversity has frequently been related to a wide range of psychosomatic complaints in adulthood. The present study examined the relationship between different forms of childhood adversity and laboratory measures of pain. Heat pain tolerance and perceived heat pain intensity were measured in a community-based sample of 62 women (aged 20–64 years). Participants completed the Childhood Trauma Questionnaire (CTQ), which assesses five forms of childhood adversity: physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. Somatic symptoms, depressive symptoms, and pain catastrophizing were assessed as potential mediators. Bivariate analyses indicated that emotional abuse but no other forms of childhood adversity were significantly related to decreased heat pain tolerance (r=–0.27; P<0.05). Accordingly, multiple regression analyses revealed that only emotional abuse was a significant predictor of heat pain tolerance (β=–0.62; P=0.034) when entering all CTQ subscales simultaneously. Although emotional abuse was also related to somatic symptoms, depressive symptoms, and pain catastrophizing, none of these variables mediated the relationship between childhood adversity and laboratory pain (P>0.1). No significant associations were found between any forms of childhood adversity and heat pain intensity. Our findings indicate that the severity of emotional childhood abuse is associated with decreased pain tolerance, an affective component of pain, but not with heat pain intensity, which has been described as a sensory component of pain.

Keywords: childhood adversity, emotional abuse, pain tolerance, pain intensity, somatic symptoms

Introduction

Adverse childhood experiences have been linked to the development of various physical and mental health problems in adulthood. Such negative health outcomes include conditions accompanied by distressing somatic symptoms such as somatization disorder, chronic pain, conversion disorder, functional somatic syndromes, and hypochondriasis.[1–6] One possible explanation for the association between adverse childhood experiences and somatic complaints might be that early life stressors affect biological pathways which amplify the perception of bodily signals.[3] For example, adverse childhood experiences have been related to a dysregulation of the hypothalamic–pituitary–adrenal axis[7,8] and inflammatory immune alterations,[9,10] features which have also been associated with somatic complaints and increased pain perception, respectively.[11]

If adverse childhood experiences lead to an amplification of the perception of bodily signals, subjects with more adverse childhood experiences should be characterized by an increased sensitivity to laboratory-induced pain. However, little research has been done on this issue, and findings have been mixed. One study examined pain perception

Correspondence: Karoline Pieritz
Division of Clinical Psychology and Psychotherapy, Philipps University Marburg, Gutenbergstrasse 18, D-35032 Marburg, Germany
Tel +49 6421 282 3754
Fax +49 6421 282 8904
Email karoline.pieritz@uni-marburg.de

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in female patients with painful gastrointestinal disorders with and without a history of sexual/physical abuse. Compared to non-abused patients, abused patients had significantly lower pressure pain thresholds and lower cognitive standards for judging stimuli as noxious.[12] In another study, including women with irritable bowel syndrome and healthy controls with and without a history of sexual abuse, no abuse-related differences emerged for the perception of pain induced by rectal distension.[13] Finally, a study examining healthy young women and men found no differences for thermal or ischemic pain tolerance between participants with and without a self-reported history of sexual or physical abuse. However, women with a positive history of abuse showed significantly decreased sensitivity to experimentally induced pain compared to women with no childhood abuse history. There were no abuse-related group differences for men.[14]

So far, the most commonly studied forms of childhood adversity have been sexual and physical abuse. However, assessing other types of adversity may be important to fully understand the relationship between adverse childhood experiences and pain perception in adulthood. The present study aims to extend the existing findings on childhood adversities and pain by examining the association between five different forms of childhood adversity and two components of pain: an affective component of pain (ie, heat pain tolerance) and a sensory component of pain (ie, heat pain intensity). Since childhood adversity has been linked with depressive mood, somatic symptoms, and pain catastrophizing,[1–5,15,16] and these variables in turn have been linked to altered pain perception,[17–20] we further examined whether they mediate the association between childhood adversity, pain tolerance and pain intensity. We firstly hypothesized that more exposure to childhood adversity would be associated with experiencing more pain (ie, decreased tolerance and increased sensitivity to laboratory heat pain). We further hypothesized that these associations would be mediated by the severity of depressive symptoms, somatic symptoms, and/or pain catastrophizing.

Methods

Participants

Sample characteristics are shown in Table 1. Participants were a nonclinical sample of 62 women (aged 20–64 years) recruited from the general population via advertisements, leaflets, and press releases in local newspapers. There were no specific inclusion criteria except female sex and age between 18 and 65 years. We only included women since a number of recommendations suggest investigating female samples because of the greater prevalence of pain conditions in women and because of differences in pain processing between men and women. Furthermore, interaction effects of experimenter sex and participant sex should be avoided.[21–23] The study was conducted between April and June 2012. It was approved by the ethics committee of the Philipps University of Marburg (Marburg, Germany). Before participation and giving of informed consent, telephone screenings were conducted using a standardized checklist to control for the following exclusion criteria: neurological disease (eg, epilepsy, multiple sclerosis, dementia, neuropathy), metabolic disorders (eg, diabetes), any organic illnesses with a significant impact on pain perception (eg, Raynaud's phenomenon, irritable bowel syndrome, interstitial cystitis, fibromyalgia), cardiovascular disease, psychotic symptoms, and alcohol and/or drug abuse.

Table 1 Sample characteristics (N=62)

Variable	Mean (SD)
Age (years)	34.4 (12.2)
Body mass index (kg/m²)	23.2 (4.9)
Menstrual cycle phase, n (%)	
Menstruation phase	12 (19.4)
Follicular phase	1 (1.6)
Ovulation phase	10 (16.1)
Luteal phase	12 (19.4)
Premenstrual phase	12 (19.4)
Menopause	13 (21.0)
Depressive symptoms (PHQ-9, 0–27)	5.3 (4.0)
Somatic symptoms (PHQ-15, 0–30)	6.3 (4.0)
Pain catastrophizing (PCS, 0–52)	25.7 (9.3)
CTQ total score (25–125)	40.2 (16.4)
Emotional abuse (5–25)	9.7 (5.0)
Physical abuse (5–25)	6.4 (3.4)
Sexual abuse (5–25)	6.5 (4.2)
Emotional neglect (5–25)	11.0 (4.9)
Physical neglect (5–25)	6.7 (2.4)
Heat pain tolerance (°C)	46.4 (2.3)
Heat pain intensity (VAS)	6.2 (2.0)

Notes: All values are shown as mean (SD), except for menstrual cycle phase, which is n (%). Values in parentheses indicate the range of the total scores.
Abbreviations: CTQ, Childhood Trauma Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-9, nine-item depression subscale of the Patient Health Questionnaire; PHQ-15, 15-item somatic symptom subscale of the Patient Health Questionnaire; SD, standard deviation; VAS, visual analog scale.

Childhood adversity

Exposure to childhood adversity was assessed using the German version of the Childhood Trauma Questionnaire (CTQ)-Short Form.[24] This self-report questionnaire measures five forms of childhood adversity including emotional, physical, and sexual abuse as well as emotional and physical neglect. Each subscale consists of five items, rated on a five-point Likert scale from 1 (never true) to 5 (very often true). The CTQ subscale scores range from 5 to 25 and the total score ranges

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from 25 to 125. Similar to the American original,[25] the German CTQ version has been proved to be a reliable and valid tool for the retrospective assessment of child maltreatment.[26,27]

Depressive symptoms

Depressive symptoms were assessed using the German version of the nine-item depression subscale of the Patient Health Questionnaire (PHQ-9).[28] This self-administered depression module scores each of the nine *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria[29] of depression from 0 (not at all) to 3 (nearly every day). The total score for the nine items ranges from 0 to 27 (0–4= minimal; 5–14= mild; 15–19= moderate; 20–27= severe depression). The German version of the PHQ-9 is considered to be a reliable and valid measure of depressive symptom severity.[28]

Somatic symptoms

Participants completed the somatic symptom subscale of the Patient Health Questionnaire (PHQ-15), a 15-item self-report questionnaire covering the most prevalent symptoms of DSM-5 somatic symptom disorder. Subjects are asked to rate the severity of 13 different symptoms from 0 (not bothered at all) to 2 (bothered a lot). Two additional physical symptoms (feeling tired or having little energy, trouble sleeping) are contained in the PHQ-9. Thus, the total score ranges from 0 to 30 (0–4= minimal; 5–9= low; 10–14= medium; 15–30= high somatic symptom severity). The PHQ-15 is considered a reliable and valid instrument for measuring somatic symptom severity[30,31] and was strongly associated with functional impairment, disability, and health care use.[32]

Pain catastrophizing

Participants completed the German version of the Pain Catastrophizing Scale (PCS)[33] in order to assess the extent of catastrophizing thoughts, feelings, and behaviors when they are in pain. The PCS is a 13-item self-report questionnaire with a five-point Likert-style response scale ranging from 0 (strongly disagree) to 4 (strongly agree). Total scores range from 0 to 52 (30= 75th percentile, clinically relevant level of catastrophizing). The psychometric properties of the German version of the PCS were comparable to those reported in previous studies for the original English version.[34]

Laboratory pain measures

Individuals' heat pain tolerance was determined using thermal stimuli between 32°C and 52°C. Stimuli were delivered to the nondominant forearm via a 3×3 cm Peltier-based thermode (TSA II: Thermal Sensory Analyzer; Medoc Ltd, Israel). Heat stimulation started at 32°C and rose with a slope of 0.5°C per second. Individuals were asked to stop the heat stimulus by pressing a button when they could not stand it any longer. For further analyses, heat pain tolerance was determined by calculating the average of three measurements.

Heat pain intensity was assessed directly after each of the three pain tolerance measurements using a visual analog scale (VAS). The VAS consisted of a 100 mm-long horizontal line representing a continuum of pain intensity. The VAS ranged from "no pain" (0 mm) to "worst imaginable pain" (100 mm). Participants were asked to make a single mark on the line indicating their present pain intensity. The individual scores were determined by measuring the distance (mm) between the "no pain" anchor and the patient's mark. For further analyses, an overall intensity mean value was computed by averaging the three intensity ratings. The VAS is widely used by anesthesia providers when assessing the intensity of acute pain in clinical research. It provides sensitive measurements, since subjects may mark any point on the line between the two verbal anchors.[35]

Confounding variables

Since higher age[36] and a higher body mass index (BMI)[37] may decrease pain tolerance and increase pain sensitivity and because of contradictory findings concerning the influence of menstrual cycle phase on pain perception,[38,39] these variables were considered as potential confounders in the analyses.

Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics version 22.0 for Windows (IBM Corporation, Armonk, NY, USA). Since not all variables were normally distributed, Spearman's rank correlations were conducted to examine bivariate associations between study variables.

To examine the relative impact of different forms of childhood adversity on laboratory heat pain tolerance and heat pain intensity, we performed hierarchical regression analyses with potential confounders (age, BMI, phase in menstrual cycle) entered on step 1 and all five CTQ subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) simultaneously entered on step 2.

To test for potential mediation effects of depressive symptoms (PHQ-9), self-reported somatic symptoms (PHQ-15), and pain catastrophizing (PCS) in the relationship between CTQ subscales and laboratory heat pain perception, exploratory simple mediation analyses were run using PROCESS model 4 for SPSS.[40] Potential confounding variables such as age, BMI, and menstrual cycle phase were included as covariates.

Results

Childhood adversity and heat pain tolerance

Bivariate analyses revealed a significant association between emotional abuse and heat pain tolerance (r=–0.27, P<0.05) (Table 2). There were no significant associations between heat pain tolerance and any other CTQ subscale (P>0.1) (Table 2). Results indicate that more exposure to adverse emotional childhood experiences is associated with a decreased tolerance to heat pain. When entering all CTQ subscales simultaneously into a multiple regression model (adjusted for age, BMI, and menstrual cycle phase), emotional abuse significantly predicted heat pain tolerance (β=–0.62; P=0.034) (Table 3). Additionally, the emotional neglect subscale tended to predict heat pain tolerance (β=0.45; P=0.095) (Table 3). The relationship between emotional abuse and heat pain tolerance was not mediated by depressive symptoms, somatic symptoms, and pain catastrophizing (P>0.1) (results not shown).

Childhood adversity and heat pain intensity

Bivariate analyses revealed no significant associations between laboratory heat pain intensity and any of the CTQ subscale scores (P>0.1) (Table 2). When entering all CTQ subscales simultaneously into a multiple regression model (adjusted for age, BMI, and menstrual cycle phase), sexual abuse and emotional neglect tended to predict laboratory heat pain intensity (P<0.1) (Table 3). This trend indicates that the more exposure to these types of childhood adversity, the higher was the likelihood of rating a stimulus as painful. These relationships were not mediated by depressive symptoms, somatic symptoms, or pain catastrophizing (P>0.1) (results not shown).

Further results

Bivariate analyses revealed significant associations between depressive symptoms and all five CTQ subscales (Table 2). Self-reported somatic symptoms were significantly associated with adverse emotional childhood experiences (Table 2). Pain catastrophizing was significantly associated with all CTQ subscales except physical neglect (Table 2). In all cases, the strongest associations were found for the emotional abuse subscale. Results indicate that exposure to adverse childhood experiences, especially emotional abuse, leads to more self-reported depressive symptoms, more somatic symptoms, and higher pain catastrophizing in adulthood.

Discussion

The primary objective of this study was to examine the association of different forms of childhood adversity with pain tolerance and pain intensity. Our main finding is that

Table 2 Spearman correlations between study variables (N=62)

	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect	Heat pain tolerance	Heat pain intensity	PHQ-9	PHQ-15	PCS	Age	BMI
Emotional abuse	0.52**	0.44**	0.69**	0.48**	–0.27*	0.02	0.46**	0.35**	0.45**	0.26*	0.04
Physical abuse		0.36**	0.54**	0.57**	–0.25	0.00	0.30*	0.17	0.27*	0.10	0.24
Sexual abuse			0.20	0.13	–0.12	0.07	0.33*	0.23	0.35**	0.08	0.01
Emotional neglect				0.57**	–0.05	0.09	0.27*	0.24	0.32*	0.21	0.02
Physical neglect					–0.13	0.03	0.28*	0.24	0.25	0.15	0.08
Heat pain tolerance						0.09	–0.06	–0.17	–0.18	–0.10	–0.27*
Heat pain intensity							–0.11	0.04	0.08	–0.02	–0.10
PHQ-9								0.66**	0.42**	–0.16	–0.27*
PHQ-15									0.43**	–0.20	–0.03
PCS										–0.06	–0.02
Age											0.24
BMI											

Notes: *P<0.05; **P<0.01.

Abbreviations: BMI, body mass index; PCS, Pain Catastrophizing Scale; PHQ-9, nine-item depression subscale of the Patient Health Questionnaire; PHQ-15, 15-item somatic symptom subscale of the Patient Health Questionnaire.

Appendix

Table 3 Predicting laboratory heat pain tolerance and intensity by CTQ subscale scores using hierarchical regression analyses (N=62)

	Heat pain tolerance				Heat pain intensity			
	b	SE of *b*	*β*	*P*-value	*b*	SE of *b*	*β*	*P*-value
Step 1								
Age	−0.04	0.03	−0.22	*P*=0.197	−0.01	0.03	−0.07	*P*=0.688
Body mass index	−0.07	0.06	−0.15	*P*=0.262	−0.05	0.06	−0.11	*P*=0.418
Menstrual cycle phase	−0.11	0.22	−0.09	*P*=0.611	0.12	0.19	0.11	*P*=0.519
Step 2								
Age	−0.04	0.03	−0.22	*P*=0.197	−0.02	0.03	−0.12	*P*=0.503
Body mass index	−0.07	0.07	−0.15	*P*=0.279	−0.03	0.06	−0.07	*P*=0.648
Menstrual cycle phase	−0.23	0.22	−0.18	*P*=0.306	0.08	0.20	0.07	*P*=0.690
Emotional abuse	−0.28	0.13	−0.62	*P*=0.034	−0.14	0.11	−0.36	*P*=0.218
Physical abuse	−0.05	0.17	−0.08	*P*=0.753	−0.10	0.15	−0.16	*P*=0.535
Sexual abuse	0.11	0.09	0.21	*P*=0.203	0.14	0.08	0.30	*P*=0.075
Emotional neglect	0.21	0.12	0.45	*P*=0.095	0.19	0.11	0.47	*P*=0.093
Physical neglect	−0.04	0.25	−0.05	*P*=0.863	−0.04	0.218	−0.05	*P*=0.852
	R^2=0.06 for step 1; ΔR^2=0.10 for step 2, ns				R^2=0.05 for step 1; ΔR^2=0.08 for step 2, ns			

Notes: *b*= unstandardized regression coefficient; *β*= standardized regression coefficient; *P*= significance value; R^2= total variance explained by the model; ΔR^2= variance explained by CTQ subscales after adjusting for age, body mass index, and menstrual cycle phase.
Abbreviations: CTQ, Childhood Trauma Questionnaire; ns, not significant; SE, standard error.

women who experience more emotional abuse exhibited lower levels of pain tolerance, an affective component of pain. This result remained robust after adjusting for possible confounders such as age, BMI, and menstrual cycle phase in multiple regression analyses.

Our finding is consistent with previous research by Scarinci et al reporting lower pressure pain thresholds in abused compared to non-abused women with gastrointestinal disorders. Using sensory decision theory methods, the authors found no group difference with respect to the discrimination ability of stimulus intensity. However, abused patients exhibited lower cognitive standards for judging stimuli as noxious. Scarinci et al therefore concluded that psychosocial factors rather than sensory factors underlie the difference in pain threshold levels.[12] Nevertheless, there are contradictory findings suggesting no tolerance differences for pain from rectal distension in abused women with irritable bowel syndrome[13] and no difference for thermal or ischemic pain tolerance in healthy participants with a history of abuse.[14] However, all studies conducted so far studied sexual or physical abuse only. All of them applied different pain stimuli and investigated different samples, so comparing results is difficult. Since previous studies addressing this issue primarily focused on patients derived from clinical settings, results may also be confounded by the severity of clinical pain. The present study examined a nonclinical community-based sample of women between 18 and 65 years to increase validity.

Research examining the relationship between different forms of childhood adversity and the severity of self-reported somatic/pain complaints in adulthood found the strongest associations for emotional abuse.[15,41,42] To our knowledge, the present study is the first to demonstrate a similar association for emotional childhood adversity and laboratory pain tolerance.

The connection of emotional childhood adversity and decreased pain tolerance might be explained by a common affective component in both of them. For instance, earlier findings have suggested a particular association between emotional childhood adversity and difficulties concerning the ability to regulate one's emotions, including the acceptance of negative emotions, controlling impulsive behaviors, and limited access to effective emotion-regulation strategies.[43–45] A further consequence may be an amplified response to stressful life events, including the affective response to pain and other somatic complaints. Potential underlying neurobiological changes such as a dysregulation of the hypothalamic–pituitary–adrenal axis, neuroendocrine changes,[3,46–48] and inflammatory immune alterations[9,10] have frequently been found in individuals with a history of childhood adversity. Brain imaging research also suggests structural changes (eg, corpus callosum, cerebellum, prefrontal cortex) as well as functional changes (eg, anterior cingulate cortex, amygdala) in brain regions that have been linked to both the processing of emotional pain as well as the affective component of physical pain.[47,48]

Self-reported depressive symptoms, somatic symptoms, and pain catastrophizing did not mediate the relationship between childhood adversity and laboratory heat pain tolerance and intensity. However, results for bivariate analyses of CTQ subscales and self-report measures showed a similar association pattern as for laboratory pain outcomes. This finding indicates that exposure to childhood adversity, especially adverse emotional experiences, is not only associated with decreased pain tolerance but with an increased impairment due to perceived somatic symptoms, higher pain catastrophizing, and depressive symptoms as well. Our findings are consistent with those of the previously mentioned studies reporting similar associations between emotional childhood adversity and somatic complaints in adulthood[15,41,42] and one study suggesting associations between all types of childhood adversity and pain catastrophizing scores, with the strongest associations for emotional abuse.[15] Clinical studies reporting higher trauma rates in patients with fibromyalgia and other chronic pain syndromes support this relationship.[5,49] The association between childhood maltreatment in general and depression in later life has been well established.[3,50] A particular association with emotional abuse has been proposed as well.[16,51,52]

Results of the present study add to the growing evidence supporting a relationship between exposure to childhood adversity and altered pain perception in adulthood. They extend previous research by demonstrating that especially a history of emotional childhood adversity is associated with decreased pain tolerance, an affective component of pain. This finding suggests that an affective component seems to play a major role in the association between childhood adversity and pain/somatic complaints in adulthood. It further emphasizes the importance of assessing multiple types of childhood adversity and their relative impact on different components of pain perception and somatic outcomes as well as examining potential mediating and confounding factors on this relationship. Our findings also may have important clinical implications for the treatment and prevention of pain and related disorders. Practitioners working in the field of pain should consider a patient's history of abuse and consider it in their treatment. Studies have shown that an additional treatment of psychological factors accompanying the experience of pain is superior to an exclusively physical treatment.[53–55]

This study has a number of limitations. First, the sample size was relatively small. Replication of our results in larger samples is necessary. Second, causality for these associations cannot be determined. Prospective studies which focus on the longitudinal relationship between different types of childhood adversity and pain perception and on other potential mediators or moderators may be promising. An additional limitation is that childhood adversity was assessed via questionnaire. Although the questionnaire used in this study has been shown to be reliable and valid,[25–27] inclusion of additional measures (eg, interview, peer evaluation) may be beneficial.

Conclusion

Our findings suggest that the severity of emotional childhood adversity is associated with decreased pain tolerance, an affective component of pain, but not with heat pain intensity, which has been described as a sensory component of pain.

Disclosure

The authors report no conflicts of interest in this work.

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Article II

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Chronic stress moderates the impact of social exclusion on pain tolerance

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Order of Authors:	Karoline Pieritz
	Sarina J Schäfer
	Jana Strahler
	Winfried Rief
	Frank Euteneuer
Opposed Reviewers:	
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Chronic stress moderates the impact of social exclusion on pain tolerance

Karoline Pieritz [1], Sarina J. Schäfer [2], Jana Strahler [3], Winfried Rief [1], and Frank Euteneuer [1*]

[1] Division of Clinical Psychology and Psychotherapy, Philipps University, Marburg, Germany

[2] Division of Methodology and Social Psychology, Philipps University, Marburg, Germany

[3] Division of Clinical Biopsychology, Philipps University, Marburg, Germany

[*]Corresponding author

frank.euteneuer@staff.uni-marburg.de

Abstract

Experiences of social pain due to social exclusion may be processed in similar neural systems as experiences of physical pain. The present study aimed to extend the findings on social exclusion and pain by examining the impact of social exclusion on an affective (i.e., heat pain tolerance) and a sensory component of pain (i.e., heat pain intensity). We further examined whether a potential effect may be moderated by chronic life stress, social status or social support. We studied a community-based sample of 59 women. Social exclusion and inclusion were experimentally manipulated using a virtual ball-tossing game called Cyberball in which participants were randomly assigned to either being excluded or included by two other virtual players. Heat pain tolerance and intensity were assessed before and after the game. Our main finding is that chronic stress moderates the impact of social exclusion on pain tolerance ($p < .05$). When chronic stress was high, socially excluded participants showed a lower heat pain tolerance than participants who were socially included. Contrary to our hypothesis pain sensitivity was increased in socially included compared with socially excluded participants after the game ($p < .05$). Higher levels of chronic stress may enhance the vulnerability of affective pain processing to acute social exclusion.

Keywords: social exclusion; chronic stress; pain tolerance; pain intensity; Cyberball

1. Introduction

Previous findings indicate that the experiences of social pain (i.e., the painful feelings following social exclusion) may rely on some of the same neurocognitive systems that process the experience of physical pain [1]. The most obvious connection between social and physical pain is the use of physical pain words to describe negative social experiences across different languages and countries [2]. From an evolutionary perspective, it has been suggested that both social exclusion and physical damage pose threats to individuals' survival. A system for processing physical pain is supposed to have developed early in the evolution. As human civilization advanced, this system provided the foundation for a system processing social pain which punishes individuals who do not avoid social exclusion [2]. Evidence for shared systems underlying social pain and physical pain comes from both animal and human research. For example, findings in non-human primates indicate that morphine, which is known for its analgesic effect, reduces separation-induced distress [3]. Lesion and stimulation studies in animals suggest that the anterior cingulate cortex (ACC), a region which has been linked to the affective component of pain, may also process distress associated with social separation and disconnection [4,5]. Studies among healthy and clinical human samples have demonstrated that experiences of social pain (e.g., poor social support, loneliness, low social status) relate to a number of pain indicators [6–10].

In the last decade, a growing number of studies in humans have examined the impact of social exclusion on psychological and physiological outcomes under laboratory conditions [11–14]. The most frequently used method has been the Cyberball paradigm, a virtual ball-tossing game which has been demonstrated a valid instrument to induce feelings of being socially included and excluded [15]. Neuroimaging studies have shown that social exclusion (versus inclusion) during Cyberball activates the dorsal ACC (dACC) and the anterior insula (AI) [16]. In line with animal studies [4,5], these findings suggest that social exclusion may

relate to affective components of pain processing (i.e., dACC, AI) rather than to sensory components of pain processing such as the primary and secondary somatosensory cortices, as well as the posterior insula [1,17,18].

Little research has been done on the impact of Cyberball social exclusion on experimental pain. Eisenberger et al. [19] demonstrated that in the social exclusion condition, baseline sensitivity to pain (i.e., lower heat pain unpleasantness threshold) was associated with greater self-reported social distress in female undergraduate students. Additionally, for socially excluded participants, greater reported levels of social distress were associated with greater reported levels of pain unpleasantness to the thermal stimuli delivered at the end of the Cyberball paradigm. There were no significant differences between excluded and included participants in thermal pain unpleasantness ratings after Cyberball [19]. A second study has shown that undergraduates who were socially excluded during the Cyberball task exhibit increased pain sensitivity (i.e., an overall measure based on pain tolerance and pain threshold measures) [20]. It is important to note that analgesic responses may also result from the experience of social threats if those threats are particularly severe (e.g., if participants are told that one will be alone in the future) [20,21]. However, these findings may be consistent with research showing that both hyperalgesia and analgesia can follow nociceptive stimulation [22].

The present study aims to extend the existing findings on social exclusion and pain by examining the impact of social exclusion on both an affective component of pain (i.e., heat pain tolerance) and a sensory component of pain (i.e., heat pain intensity). With respect to the inconsistent findings in existing studies we further examine whether a potential effect may be moderated by major psychosocial determinants of health such as chronic life stress, social status and social support [23–27]. High levels of chronic stress, as well as low social status and social support may enhance vulnerability to acute social exclusion and have been found to increase the impact of social threats and other stressors on psychobiological pathways which

may be of relevance for pain processing (e.g., ACC activation; autonomic imbalance, endocrine and inflammatory responses) [28–39]. While previous research has predominantly included female undergraduate students [19,20], the present study examined a community sample of women between 18 and 65 years to increase validity [40]. We hypothesized that i) socially excluded participants experience more pain compared to socially included participants, ii) social exclusion may predominantly affect the affective component of pain (i.e., pain tolerance) and iii) the effects of social exclusion on pain are stronger in participants who rank high levels on psychosocial risk factors compared with participants who rank low levels on psychosocial risk factors.

2. Methods

2.1. Participants

Participants were 59 healthy women (mean age 35 ± 12 years). Participants were recruited from the local community by advertisements, leaflets and press releases in local newspapers. Exclusion criteria were: chronic illness and health problems which may affect pain processing (e.g., cardiovascular disease, neuropathy, diabetes, Raynaud's phenomenon), as well as mental health conditions which may affect pain and attention respectively (e.g., psychotic symptoms, alcohol and/or drug abuse). The study was approved by the ethics committee of the Philipps University of Marburg. Informed consent was obtained from all participants.

2.2 The Cyberball paradigm

Participants played a virtual ball-tossing game called Cyberball, a commonly used and valid instrument to manipulate social exclusion in laboratory settings [15,41]. Participants were told that they were going to be playing the game with two other players in different rooms and they would be connected to these players via the Internet. In reality, there were no

other players. Participants played with a preset computer program that displayed cartoon images of the participant and the other players on a computer screen. The program was set for 30 throws per game and lasted between one and a half and two and a half minutes. Participants were randomly assigned to either i) a social inclusion condition or ii) a social exclusion condition. Individuals in the inclusion condition played the interactive ball-tossing game for the entire time. Individuals in the exclusion condition were included for the first three throws of the game and then excluded by the two virtual players who stopped throwing the ball to them.

2.3 Manipulation check

As a psychometric manipulation check, participants' current mood states were measured before and after the Cyberball game. For this purpose, six 10-point Likert scales ranging from "strongly disagree" to "strongly agree" were used to assess how a) embarrassed, b) anxious, c) angry, d) depressed, e) frustrated or f) happy participants felt.

As a physiological manipulation check, heart rate variability (HRV) and heart rate (HR) were obtained from cardiovascular measurements using a Polar RS800 cardiac monitor (Polar Electro Ltd., Kempele, Finland). For analyses, a two min resting interval before the beginning of the experiment and another one and a half min interval during the Cyberball game (the last one and a half min before the game ends) were chosen. For quantification of HR and HRV, the most widely used time domain indices average HR (bpm), root mean square differences of successive heartbeat intervals (RMSSD) and additionally the percentage of successive intervals that differ by more than 50 ms (pNN50) were obtained [42]. Time domain variables were calculated because these are equivalent to frequency-domain variables as well as easier to perform [43]. Both RMSSD and pNN50 reflect short-term alterations of HRV and are considered to be predominantly a response to changes in parasympathetic tone and mainly the respiratory component of HRV. Despite being highly correlated to power

spectral measures of respiratory sinus arrhythmia (RSA), it has been suggested that RMSSD and pNN50 are not significantly affected by changes in breathing rate [44]. All analyses were performed with Polar ProTrainer 5 (Polar Electro Ltd., Kempele, Finland) and Kubios HRV 2.0 software (Biomedical Signal Analysis Group, University of Kuopio, Kuopio, Finland).

In the case of successful experimental manipulation, one would expect that participants who experience social exclusion exhibit higher intensities of negative mood states, lower intensities of positive mood states and lower HRV, compared with participants who experience social inclusion [45,46].

2.4 Pain tolerance and intensity

Thermal stimuli between from 32°C up to 52°C were employed to induce pain. Stimuli were delivered to the non-dominant forearm via a 3 x 3 cm peltier-based thermode (TSA II: Thermal Sensory Analyzer, Medoc Ltd, Israel). Heat stimulation started at 32°C and rose with a slope of 0.5°C per second. Individuals were asked to stop the heat stimulus by pressing a button when they could no longer stand it. For further analyses heat pain tolerance was determined by calculating the average of three measurements.

Heat pain intensity was assessed directly after each tolerance measurement using a 10 cm long visual analog scale (VAS). The minimum was anchored with 'no pain' and the maximum was anchored with 'worst imaginable pain'. For further analyses an overall intensity mean value was computed by averaging the three intensity ratings.

2.5 Psychosocial moderators

2.5.1 Social support

Social support was assessed using the short version of the Social Support Questionnaire (F-SOZU) [47]. This 14-item self-report questionnaire combines several aspects of social support (i.e., emotional support, practical support, social integration) to a

global social support score. Higher scores indicate a higher level of social support. This scale shows good psychometric-item properties and very acceptable reliability [47].

2.5.2 Subjective social status

Subjective social status (SSS, i.e., perceived social standing) was assessed with the German version [48] of the MacArthur Scale of Subjective Social Status [49]. Subjective social status, as assessed by this scale, refers to the individual's sense of their place on the social ladder. As in the English version, participants were asked to rate their place on two visual 10-rung social ladders i) in relation to those who are the best and worst off with respect to money, education, and respected jobs in Germany (SSS-G) and ii) in relation to those who have the highest and lowest standing in their social environment (SSS-SE). Lower scores indicate lower SSS. Of note, the English version of the second scale (SSS-SE) asks people about their standing in relation to people in their community. Because the word 'community' has no semantic equivalent in German, it was replaced by the term 'social environment'.

2.5.3 Chronic stress

The short version of the Trier Inventory for the Assessment of Chronic Stress (TICS) was used to measure chronic stress [50]. The TICS consists of 12 items which capture the intensity of self-perceived stress during the last three months in five life domains: chronic worrying, work-related and social overload, excessive demands, and lack of social recognition. The TICS provides an overall score for chronic stress. Higher scores indicate a higher level of chronic stress. The assessment achieves good profile reliability [51].

2.6 Procedure

All participants were tested individually. The examinations were conducted by a female student assistant. After giving written informed consent, participants completed

sociodemographic and psychological questionnaires followed by baseline assessment of mood states, physiological measures, heat pain tolerance and heat pain intensity. Subsequently, participants started playing the Cyberball game while physiological reactivity was recorded. When the game was finished participants were asked to rate their mood states again followed by a second assessment of heat pain tolerance and heat pain intensity. Before completing the study with a thorough debriefing, individuals were asked whether they had already known about the Cyberball paradigm which none of the participants had.

2.7 Data analysis

Statistical analyses were carried out with IBM SPSS Statistics version 21.0 for Windows (Chicago, SPSS, Inc.). Independent sample t-Tests and chi-square tests were used to control for baseline differences between experimental groups. Analyses of covariance were used to examine differences between participants in the exclusion condition and participants in the inclusion condition in heat pain tolerance and heat pain intensity, as well as in mood states, and physiological measures. Corresponding baseline values were included as covariates. PROCESS for SPSS [52] was used to examine whether psychosocial factors moderate a potential impact of experimentally induced social exclusion on pain tolerance and pain intensity. Analyses for pain tolerance and pain intensity were adjusted for theoretical confounders such as age and oral contraceptives [53–55]. All tests were two tailed.

3. Results

3.1 Baseline measures and manipulation check

Baseline sample characteristics are shown in Table 1. There were no significant differences between participants in the social exclusion group and in the social inclusion group ($p > 0.1$) indicating successful randomization.

Table 1. Baseline sample characteristics.

	Inclusion (N = 30)	Exclusion (N = 29)
Age, years	34.8 (12.6)	34.2 (12.2)
Winkler social class index, OSS		
Educational level	5.4 (2.1)	5.3 (1.7)
Profession	3.7 (1.6)	3.6 (1.4)
Household net income	1.9 (1.4)	1.6 (1.1)
Chronic Stress	1.6 (0.7)	1.6 (0.6)
Social Support	4.2 (0.5)	4.1 (0.8)
Subjective social status, MacArthur Scale		
National	6.2 (1.7)	5.5 (1.7)
Social environment	7.0 (1.5)	6.1 (1.8)
Mood states		
Embarrassed	0.3 (0.8)	0.03 (0.2)
Anxious	0.4 (0.6)	0.5 (1.5)
Angry	0.2 (0.5)	0.3 (0.8)
Depressed	0.7 (1.4)	1.0 (1.9)
Frustrated	0.5 (1.3)	0.5 (0.7)
Happy	4.6 (2.8)	4.2 (2.7)
Heart rate, bpm	75.0 (7.9)	77.3 (11.6)
Heart rate variability, HRV		
RMSSD	37.6 (14.7)	39.8 (22.5)
pNN50, %	16.3 (13.8)	14.5 (11.9)
Pain tolerance, °C	46.3 (2.3)	46.1 (2.2)
Pain intensity, VAS	6.3 (1.7)	5.9 (2.3)

Values shown as mean (SD) unless otherwise noted. bpm = beats per minute; HRV = heart rate variability; OSS = objective social status (mean scores equal: educational level = apprenticeship/vocational school; profession = middle grade of the civil service/qualified employee; household net income = 1000 < 1500 €), PCS = Pain Catastrophizing Scale; pNN50 = percentage of successive R-R (heartbeat) intervals that differ by more than 50 ms; RMSSD = root mean square differences of successive R-R intervals; VAS = visual analog scale.

Table 2 shows data after experimental manipulation. Compared to participants in the inclusion condition, participants in the social exclusion group were more angry [$F(1, 56) = 10.318$, $p = .002$], more frustrated [$F(1, 56) = 5.756$, $p = .020$] and less happy [$F(1, 56) = 7.972$, $p = .007$]. Moreover, pNN50 values were significantly lower in the social exclusion group compared with the social inclusion group [$F(1, 47) = 4.298$, $p = .044$].

Table 2. Measures after experimental manipulation.

	Inclusion (N = 30)	Exclusion (N = 29)
Mood states		
Embarrassed	0.3 (0.8)	0.5 (1.4)
Anxious	0.3 (0.9)	0.4 (1.2)
Angry **	0.1 (0.5)	1.5 (2.2)
Depressed	0.6 (1.3)	1.2 (2.3)
Frustrated *	0.7 (1.8)	1.9 (2.2)
Happy **	4.9 (2.9)	3.7 (2.6)
Heart rate, bpm	77.2 (9.6)	81.5 (10.9)
Heart rate variability, HRV		
RMSSD	42.6 (21.6)	34.2 (16.8)
pNN50, % *	20.6 (14.7)	12.3 (10.1)
Pain tolerance, °C	46.9 (2.0)	46.6 (1.8)
Pain intensity, VAS *	6.9 (1.8)	6.1 (2.3)

Note. Values shown as mean (SD); bpm = beats per minute; HRV = heart rate variability; pNN50 = percentage of successive R-R intervals that differ by more than 50 ms; RMSSD = root mean square differences of successive R-R intervals; VAS = visual analog scale. Differences between experimental conditions were analyzed using analyses of covariance (adjusted for baseline values): *p < 0.05; **p < 0.01.

3.2 The effect of social exclusion on heat pain tolerance and intensity

Although there was no general group difference in pain tolerance [$F(1, 54) = 0.17$, $p = .68$], moderation analyses indicated that chronic stress affects the impact of social exclusion on pain tolerance, $b = -1.10$, 95% CI [-2.01, -0.19], $t = -2.43$, $p < .05$. When chronic stress was high, socially excluded participants showed a lower heat pain tolerance than participants who were socially included ($b = -0.86$, 95% CI [-1.70, -0.02], $t = -2.04$, $p < .05$). Fig 1 illustrates this moderation. At the mean value of chronic stress ($b = -0.11$, 95% CI [-0.70, 0.49], $t = -0.36$) and when chronic stress was low ($b = 0.65$, 95% CI [-.23, -1.53], $t = 1.48$), there were non-significant effects ($p > .1$). The relationship between social exclusion and pain tolerance was not moderated by social support or SSS ($p > .1$). Results for pain intensity indicated that participants who experienced social exclusion reported significantly lower pain intensity ratings compared with the social inclusion group [$F(1, 54) = 4.46$, $p < .05$]. There were no significant moderator effects for chronic stress, social support or SSS ($p > .1$).

Fig 1. Chronic stress moderates the impact of social exclusion (vs. inclusion) on heat pain tolerance. When chronic stress is high (+ 1SD), socially excluded participants show a lower heat pain tolerance than participants who are socially included. At the mean value of chronic stress and when chronic stress is low (-1 SD), there are no significant conditional effects ($p > .1$). * $p > .05$.

4. Discussion

The present study aimed to extend previous research on social exclusion and pain by examining the particular effect of social exclusion on both an affective component of pain (i.e., heat pain tolerance) and a sensory component of pain (i.e., heat pain intensity). We further examined whether a potential effect may be moderated by major psychosocial determinants of health such as chronic life stress, social status and social support. Our main

finding is that chronic stress moderates the impact of social exclusion on pain tolerance. Consistent with our hypotheses, socially excluded participants with high chronic stress had a lower heat pain tolerance than those who were socially included in the Cyberball game. Thus, it appears that higher levels of chronic stress may enhance the vulnerability of affective pain processing to acute social exclusion. This finding is consistent with a study reporting increased psychological and physiological reactivity for individuals with chronic life stress after being challenged with an acute psychological stressor [56]. It is also in line with previous research demonstrating that chronic life stress and other social stressors (e.g. social exclusion) may cause hyperalgesia and increase physical pain distress [19,20,57–61]. The underlying mechanisms of this finding are not clear. With respect to the growing evidence of overlapping neural systems for social stressors and physical pain, chronic stress may lead to alterations within the body's pain pathways [61]. For example, chronic stress has been suggested to cause increased activation in brain regions relevant for pain processing, such as the ACC, insula and amygdala [61]. Stress-induced changes in neurotransmission and neuroendocrine systems relevant for pain processing have also been found [61]. Changes may include a desensitization of the endogenous opioid system, increased glutamate and decreased gamma-aminobutyric acid (GABA) expression in the dorsal horn of the spinal cord or dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis. Such alterations may impair the body's ability to suppress pain, resulting in lower pain tolerance [16,18,22,61–63].

Contrary to our hypotheses we found an increase in the sensory pain component as defined by higher pain sensitivity ratings in socially included compared to socially excluded participants after the Cyberball game. This finding contrasts with a recent study by Canaipa et al. [57] who reported lower pain intensity ratings for socially included participants. Unlike us, however they applied noxious electrical stimuli instead of thermal stimuli which might account for the different results. A possible explanation for our finding might be that participants perceived social inclusion as an indicator for a secure social environment. This

may have increased their willingness to show vulnerability by stating higher pain intensity ratings after the game. This interpretation is supported by findings of higher pain reports of women in the presence of a same-sex friends [64] and also by models of social reinforcement in chronic pain syndromes [65].

The results of the present study add to the growing evidence of overlapping neural systems for social stressors and affective pain processing. A strength of our study is that we measured two different dimensions of pain (i.e., pain tolerance as an affective component of pain, pain intensity as a sensory component of pain). Hence, it was possible to examine the specific impact of social exclusion vs. social inclusion on both components of pain processing. Our findings therefore extend previous research by suggesting that different components of pain may be differently affected by social exclusion. Another advantage of the current study is that pain stimuli were not delivered while participants were playing the Cyberball game, but right before and after the game. This procedure may avoid potentially distracting effects on pain perception [66–68]. Since chronic stress is known to exacerbate existing pain [58,61], our findings are also in accordance with recent recommendations for the clinical treatment of postoperative as well as chronic pain. Applying complementary methods to reduce social stressors and improve patients' mental well-being has been shown to be superior to an exclusively physical pain treatment [69–71].

This study has some limitations. The sample size is relatively small. Furthermore, because we only included participants from the area of Marburg, Hesse (Germany), the generalizability of our results may be limited. Future studies should replicate our findings and also extend knowledge of underlying mechanisms, for example by using neuroimaging techniques to examine the impact of social exclusion on both an affective and a sensory component of pain processing.

In conclusion, our findings extend previous research on social exclusion and pain by suggesting that different components of pain may be differently affected by social exclusion.

Our main result is that socially excluded participants with high chronic stress had a lower pain tolerance than those who were socially included in the Cyberball game. Higher levels of chronic stress may enhance the vulnerability of affective pain processing to acute social exclusion.

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Conflict of interest statement

The authors declare no conflict of interest.

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Figure

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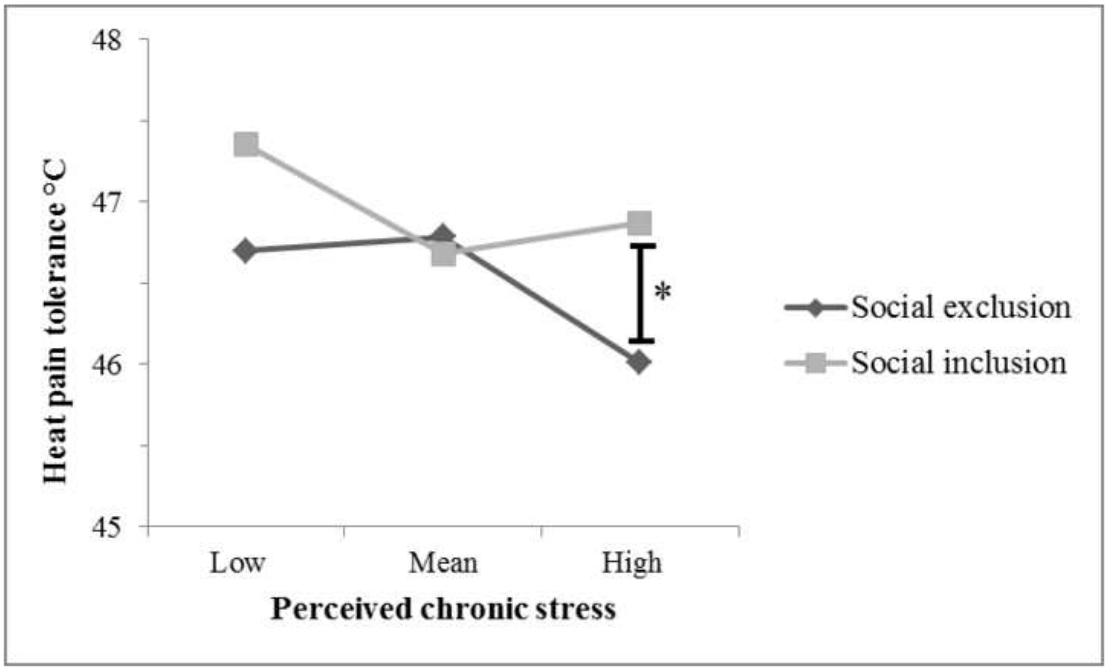

Article III

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RUNNING HEAD: STATUS AND CARDIOVASCULAR REACTIVITY

Subjective social status and cardiovascular reactivity:

An experimental examination

Karoline Pieritz [a], Philipp Süssenbach [b], Winfried Rief [a], and Frank Euteneuer [a*]

[a] Division of Clinical Psychology and Psychotherapy, Philipps University, Marburg, Germany

[b] Division of Psychological Methods, Philipps University, Marburg, Germany

[*] Corresponding author: Frank Euteneuer, PhD

Division of Clinical Psychology and Psychotherapy,

Philipps University of Marburg, Gutenbergstrasse 18,

D-35032 Marburg, Germany,

Phone: +49 6421 28 23350

Fax: +49 6421 28 28904

E-mail address: frank.euteneuer@staff.uni-marburg.de

Abstract

The present experiment examined the causal influence of subjective social status (SSS) on variables related to cardiovascular health (i.e., blood pressure, heart rate variability [HRV]). Participants were randomly assigned to one of two conditions involving a social comparison that either induced a temporary shift toward high SSS or toward low SSS. Cardiovascular variables were measured before (baseline), throughout, and after the manipulation (recovery). Participants in the low SSS condition had a significantly lower HRV during experimental manipulation than at baseline. They also showed a significantly stronger HRV reactivity compared to participants in the high SSS condition. Our results suggest that already temporary shifts of one's SSS have measureable effects on cardiovascular variables. They support the notion that social status plays a causal role in the development of cardiovascular disease.

Keywords: subjective social status, cardiovascular reactivity, blood pressure, heart rate variability

Introduction

Lower social status has been associated with a wide range of negative health outcomes including an increased risk for cardiovascular diseases (CVD) (Adler & Ostrove, 1999; Clark, DesMeules, Luo, Duncan, & Wielgosz, 2009; Euteneuer, 2014), the most common causes of death globally (World Health Organisation, 2014). In addition to traditional measures of objective social status (OSS) such as education, income, and occupation, research has increasingly focused on the link between subjective social status (SSS) and health. SSS refers to an individual's perceived social position relative to other members in her or his social environment.

Research suggests that the relationship between health and SSS is stronger than the relationship between health and OSS (Euteneuer, 2014). One explanation for the tighter relationship between SSS and health is that SSS provides a more comprehensive measure of one's social position – possibly by enabling a cognitive averaging of a broader range of status-related information, taking into account the social position *relative* to other members in one's social environment (Singh-Manoux, Marmot, & Adler, 2005). Cross-sectional and longitudinal studies found associations between lower SSS and poorer cardiovascular health, lower self-rated health, mental disorders including depression, higher substance use, diabetes and higher mortality (Euteneuer, 2014). Moreover, SSS is related to various stress-related biological risk factors for disease as well as alterations in the endocrine, immune, cardiovascular, and autonomic nervous systems such as sympathetic overactivation, increased resting heart rate and blood pressure, higher BMI, altered cortisol responses, and decreased immune functioning which might be relevant for the pathophysiology of CVD (see Euteneuer, 2014 for a review).

Importantly, the concept of SSS involves a situational component as it reflects a person's perception of his or her status *relative* to others. Thus, while SSS is predicted by

indicators of OSS that are relatively stable, it is also based on a social comparison with others. This comparison process provides an opportunity to experimentally manipulate an individual's SSS. On the basis of paradigms for cultural identity (Oyserman & Lee, 2008) and the MacArthur Scales (Adler, Epel, Castellazzo, & Ickovics, 2000; Cohen, 1999), Kraus et al. (2010) developed a paradigm for a temporal manipulation of SSS in which participants are instructed to compare themselves with people at the very top or at the very bottom of society. This comparison results in a contrast effect leading to temporarily reduced SSS versus elevated SSS, respectively. Studies applying this paradigm yielded promising results. They found that temporary changes in SSS affect social behavior such as empathic accuracy (Kraus, Côté, & Keltner, 2010), unethical behavior (Piff, Stancato, Côté, Mendoza-Denton, & Keltner, 2012), or charitable donations (Piff, Kraus, Côté, Cheng, & Keltner, 2010).

To our knowledge, no study has yet examined the impact of a temporary shift in SSS on physiological processes. With respect to the strong associations of SSS and cardiovascular health factors in cross-sectional and longitudinal studies, the present study aims to extend the existing findings on SSS and cardiovascular processes by examining whether an experimental manipulation of SSS affects physiological processes relevant for the pathophysiology of CVD such as blood pressure regulation and heart rate variability. We hypothesize that a social comparison with high-status individuals (low SSS condition) elicits stronger cardiovascular reactivity than a social comparison with low-status individuals (high SSS condition).

Methods

Participants

Participants were 64 healthy university students (mean age 24.3 ± 3.9 years). They were recruited via email announcements and university bulletin boards. Exclusion criteria were chronic illness, health problems and medication intake as well as mental health

conditions which may affect attention and/or cardiovascular processes. The study was approved by a local ethics committee. Written informed consent was obtained from all participants.

Experimental Manipulation of Subjective Social Status (SSS)

The experimental manipulation of SSS was adapted from a paradigm developed by Kraus et al. (2010) and the German version of the MacArthur Scales (Euteneuer, Süssenbach, Schäfer, & Rief, 2014). Participants were presented with an image of a ladder with 10 rungs. They were instructed to think of the ladder "as representing where people stand in Germany." They were then randomly assigned to one of two conditions in which they were instructed to compare themselves with someone who has a higher SSS (low SSS condition) or a lower SSS (high SSS condition):

„On the very bottom [top] of the ladder are people who are the worst [best] off—those who have the least [most] money, least [most] education, and the least [most] respected jobs. Now, please compare yourself to the people on the very bottom [top] of the ladder. We'd like you to think about how you are different from these people in terms of your own income, educational history, and job status and how you feel disadvantaged [advantaged] compared to them. Where would you place yourself on this ladder relative to these people at the very bottom [top]?"

To strengthen the manipulation, we instructed participants to talk loudly about these differences. Participants then indicated their own standing on the ladder; the bottom rung was coded as "1", and the top rung was coded as "10."

In the case of a successful experimental manipulation, one would expect that participants in the low SSS condition would place themselves significantly lower on the ladder than participants with a high SSS condition.

Cardiovascular Measures

Blood pressure (BP), heart rate (HR) and heart rate variability (HRV) were obtained using a Task Force Monitor® 3040i device (TFM, CNSystems, Graz, Austria). The TFM application allows an automated and computed beat-to-beat analysis of HR (electrocardiogram (ECG)) using oscillometric and noninvasive continuous blood pressure measurements. Haemodynamic and autonomic parameters are calculated on the basis of these signals. The TFM offers valid and reliable measurements of all parameters and has been used successfully in recent clinical studies (Fortin et al., 2006; Parati et al., 2003). Mean, median, minimum, maximum and standard deviation (SD) of all parameters were calculated automatically for three predefined 5 min intervals: resting interval before the beginning of the experiment (baseline), the experimental manipulation (experiment) and another resting interval after the experimental manipulation (recovery).

Systolic and diastolic BP were analyzed separately. For further analyses of HRV, two of the most widely used time domain indices, the standard deviation of normal-to-normal intervals (SDNN), and the square root of the mean squared differences of successive normal-to-normal intervals (RMSSD) were chosen (Rajendra Acharya, Paul Joseph, Kannathal, Lim, & Suri, 2006). We chose time domain variables because these are equivalent to frequency-domain variables and are easier to perform (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). SDNN is a good predictor of overall variability present at the time of recording. It reflects long-term variability of cardiac activity and is influenced by both sympathetic and parasympathetic activity (von Borell et al., 2007). RMSSD reflects short-term alterations of HRV and is considered to be predominantly a response to changes in parasympathetic tone. Despite being highly correlated to power spectral measures of respiratory sinus arrhythmia, it has been

suggested that RMSSD is not significantly affected by changes in breathing rate (Penttilä et al., 2001).

Objective social status

Since income is an important objective social determinant of health (Sapolsky, 2004), participants' average monthly household-income was assessed according to Winkler (Winkler & Stolzenberg, 2009). Scores range from 1 to 7. Lower scores indicate lower household net income.

Procedure

All participants were tested individually. The examinations were conducted by a male experimenter. After signing an informed consent, participants completed sociodemographic and psychological questionnaires which was followed by a baseline assessment of physiological measures. Subsequently, SSS was experimentally manipulated. Physiological parameters were measured throughout the manipulation. Participants' verbal responses were digitally recorded in order to check for accuracy of their responses at a later time. Experimental manipulation of SSS was followed by a third assessment of physiological measures (recovery). The study was completed with a thorough debriefing.

Data analysis

Statistical analyses were carried out with IBM SPSS Statistics version 22.0 for Windows (Chicago, SPSS, Inc.). Pairwise comparisons were calculated with T-tests, Mann-Whitney U-tests or chi-square tests as appropriate. To test for differences in blood pressure and HRV, analysis of variance (ANOVA) for repeated measures using time (baseline, experiment, and recovery) as the repeated factor and group (high SSS or low SSS) as the

between-group factor were calculated. Significant time x group interactions were followed with pairwise comparisons. Since household net income, sex, age, body mass index (BMI), and smoking status have been shown to be associated with cardiovascular processes (Fagard, 2001; Faheem et al., 2010; Franklin, 1999; Franklin et al., 1997; Kuo et al., 1999; Omvik, 1996; Sapolsky, 2004; Thayer, Yamamoto, & Brosschot, 2010), analyses were adjusted for these variables.

Results

Baseline measures

Baseline sample characteristics are shown in Table 1. Although global OSS scores did not differ between groups, participants in the low SSS group reported a significantly higher household net income than participants in the high SSS condition (p = .046). This difference was no significant restriction since it was in the opposite direction of our hypotheses. There were no other significant baseline differences between participants in the low SSS and high SSS group (p > .1) indicating successful randomization.

Manipulation check

As a manipulation check, ratings of SSS between the two experimental conditions were compared. Since the Kolmogorov-Smirnov test indicated non-normality, non-parametric Mann-Whitney U-Test was used. As expected, participants in the high SSS condition (Median = 7) placed themselves significantly higher on the ladder than participants in the low SSS condition (Median = 5), U = 310, p = 0.034. Thus, the manipulation successfully shifted participants' social status perception in the expected direction.

The effect of SSS on cardiovascular processes

Table 2 shows cardiovascular measures before (baseline), during and after experimental manipulation (recovery). With respect to HRV, repeated measures ANOVA

revealed a significant time x group interaction for RMSSD, $F(2,98) = 3.27$, $p = .042$. This effect indicates that RMSSD at different time points differed between experimental conditions. Pairwise comparisons revealed that in the low SSS group, RMSSD during experimental manipulation was significantly lower than at baseline, $t(27) = 3.89$, $p = .001$, and significantly lower than at recovery, $t(27) = -3.39$, $p = .002$. There were no significant RMSSD differences between time points for the high SSS group ($p > .1$).

In a further analysis, we observed whether RMSSD reactivity differed between the low and high SSS groups. For this purpose, changes in RMSSD (delta) were calculated subtracting pre from post values (Table 2). Differences between the two experimental groups were examined using analyses of covariance (ANCOVA). Results indicated that participants in the low SSS condition showed a significantly higher RMSSD reactivity (as reflected by a significantly higher RMSSD decrease), $F(1,49) = 5.19$, $p = .027$, from baseline to experimental manipulation than participants in the higher SSS group. Figure 1 illustrates this effect. There were neither significant group differences in reactivity from experimental manipulation to recovery, nor from baseline to recovery ($p > .1$). So, as hypothesized, a social comparison with high-status individuals (low SSS condition) elicits stronger cardiovascular reactivity than a social comparison with low-status individuals (high SSS condition).

The experimental manipulation did not influence blood pressure ($p > .1$).

Discussion

The present study aimed to extend the existing findings on associations between SSS and cardiovascular health by examining whether a short-term experimental manipulation of SSS affects cardiovascular processes. Our main finding is that a temporarily lowered SSS leads to higher HRV (RMSSD) decreases.

This study is the first to show that an experimental manipulation of SSS effectively influences cardiovascular processes. HRV is an indicator of autonomic balance (i.e. dynamic balance of sympathetic and parasympathetic systems). Change in HRV reflects the ability of the autonomic nervous system to adapt to various bodily and environmental demands including respiration, hemodynamic and metabolic processes, sleep and posture changes, physical exercise and mental stressors (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). RMSSD, in particular, reflects short-term alterations of HRV. Decreased RMSSD indicates reduced parasympathetic activity, which has been considered a risk factor for cardiovascular disease (Thayer et al., 2012, 2010; Thayer & Sternberg, 2006). Thus, our findings are in line with previous cross-sectional and longitudinal research suggesting that lower SSS may cause autonomic imbalance, a potential risk factor for cardiovascular disease (Euteneuer, 2014; Hegar & Mielck, 2010).

Although the specific mechanisms by which SSS may lead to autonomic imbalance are in dire need of further research, one pathway might involve hyperactivity of the hypothalamic-pituitary-adrenal axis causing increased catecholamine release (Euteneuer, 2014). Catecholamines activate the sympathetic nervous system by binding to adrenergic and dopaminergic receptors. Chronically increased catecholamine levels would therefore result in chronic overactivation of the sympathetic nervous system, causing autonomic imbalance. This interpretation is also consistent with findings from a study among healthy adults, indicating that lower SSS predicts reduced in-vivo responsiveness of the β-adrenergic receptor, a marker for chronically increased catecholamine levels (Euteneuer, Mills, Rief, & Ziegler, 2012).

We did not find significant effects of SSS on blood pressure in this study. Although there are some studies suggesting associations between lower SSS and increased blood pressure or even hypertension, there are also some that did not (Hegar & Mielck, 2010). Short-term blood pressure depends on interactions between heart rate, cardiac output,

baroreflex, afterload, and arterial compliance. In the long term, blood pressure depends on salt and water balance which are hormonally controlled by the renin-angiotensin-aldosterone system and vasopressin (Chopra, Baby, & Jacob, 2011). The single short-term manipulation of SSS in our study may not have been sufficient to affect these complex regulatory systems; at least not during the time of measurement. Possibly, more intense or long-term experiences of lower SSS would affect blood pressure. There is evidence from both cross-sectional and prospective studies that chronic autonomic imbalance, as represented by a chronically decreased HRV, may at least partly account for the link between SSS and blood pressure (Thayer et al., 2010). This would support the assumption that increased blood pressure rather reflects long-term effects of SSS which might explain why no differences in blood pressure were obtained in this study.

It is important to recognize that our sample characteristics limit the generalizability of the present findings. Future studies should investigate community based samples to increase validity. Future studies could also try to use other manipulations, for example involving direct experiences of high versus low social status.

In conclusion, our results suggest that already temporary shifts of one's SSS have measureable effects on cardiovascular processes. They further support the causal role of SSS in the development of cardiovascular disease. A possible mechanism linking low SSS to poor cardiovascular health might be chronic autonomic imbalance as represented by decreased HRV.

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Author Notes

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Table 1

Baseline sample characteristics.

	High SSS (n = 33)	Low SSS (n = 31)
Age, years	23.9 (4.1)	24.8 (3.6)
Females, n (%)	19 (57.6)	19 (61.3)
Current smoker, n (%)	6 (18.2)	4 (12.9)
Body mass index, kg/m²	21.6 (2.2)	21.6 (2.2)
Household net income*	1.0 (0.0)	1.7 (1.8)
Blood pressure, mmHg		
Systolic	110.5 (8.8)	109.3 (8.1)
Diastolic	69.0 (7.2)	70.7 (8.9)
Heart rate, bpm	75.0 (11.5)	75.1 (11.2)
Heart rate variability		
RMSSD	62.5 (24.0)	69.1 (26.1)
SDNN	53.9 (23.9)	64.2 (25.7)

Note. Values shown as mean (SD). bpm = beats per minute; mmHg = millimeters of mercury; OSS = objective social status (mean scores equal: educational level = general qualification for university entrance; profession = student/trainee; household net income: higher SSS = ≤ 1250 €; lower SSS = 1250-1750 €), RMSSD = square root of the mean squared differences of successive normal-to-normal intervals; SDNN = standard deviation of normal-to-normal intervals; SSS = subjective social status; *p < .05.

Table 2

Cardiovascular measures at baseline, experimental manipulation, recovery, and change scores (delta).

	High SSS (n = 33)	Low SSS (n = 31)
Baseline		
Systolic blood pressure, mmHg	110.5 (8.8)	109.2 (8.1)
Diastolic blood pressure, mmHg	69.0 (7.2)	70.7 (8.9)
HRV, RMSSD	62.5 (24.0)	69.1 (26.1)
HRV, SDNN	53.9 (23.9)	64.2 (25.7)
Experiment		
Systolic blood pressure, mmHg	124.6 (10.4)	119.1 (14.2)
Diastolic blood pressure, mmHg	79.5 (6.6)	76.7 (10.8)
HRV, RMSSD	56.2 (24.0)	54.0 (15.9)
HRV, SDNN	76.0 (19.8)	82.0 (26.5)
Recovery		
Systolic blood pressure, mmHg	114.5 (10.6)	109.5 (12.7)
Diastolic blood pressure, mmHg	70.4 (6.2)	68.1 (12.0)
HRV, RMSSD	60.1 (18.8)	64.2 (23.1)
HRV, SDNN	54.2 (18.7)	58.4 (21.7)
Δ Baseline - Experiment		
Systolic blood pressure, mmHg	13.7 (7.6)	9.8 (11.2)
Diastolic blood pressure, mmHg	9.9 (5.3)	6.1 (7.4)
HRV, RMSSD*	-4.9 (16.0)	-15.1 (20.6)
HRV, SDNN	24.3 (22.1)	17.9 (26.9)
Δ Experiment - Recovery		
Systolic blood pressure, mmHg	-10.1 (6.9)	-9.6 (13.2)
Diastolic blood pressure, mmHg	-9.1 (5.3)	-8.7 (6.6)
HRV, RMSSD	4.0 (15.8)	10.2 (15.9)
HRV, SDNN	-23.5 (16.4)	-23.7 (17.5)
Δ Baseline - Recovery		
Systolic blood pressure, mmHg	3.6 (7.0)	0.2 (11.5)
Diastolic blood pressure, mmHg	0.9 (5.0)	-2.6 (7.7)

HRV, RMSSD	-1.0 (10.0)	-4.9 (18.3)
HRV, SDNN	0.8 (12.9)	-5.7 (20.6)

Note. Values shown as mean (SD). Note that due to missing data on some measurement occasion, deltas are not identical to time point differences. Δ = delta; HRV = heart rate variability; mmHg = millimeters of mercury; RMSSD = square root of the mean squared differences of successive normal-to-normal intervals; SDNN = standard deviation of normal-to-normal intervals; *p < .05.

Figure Captions

Figure 1. Differences in HRV (RMSSD) reactivity between groups. Participants in the low SSS group showed a significantly higher RMSSD decrease (± SE) from baseline to experimental manipulation compared to participants in the high SSS group. There were no significant group differences in change from experimental manipulation to recovery or from baseline to recovery ($p > .1$). *$p = .027$

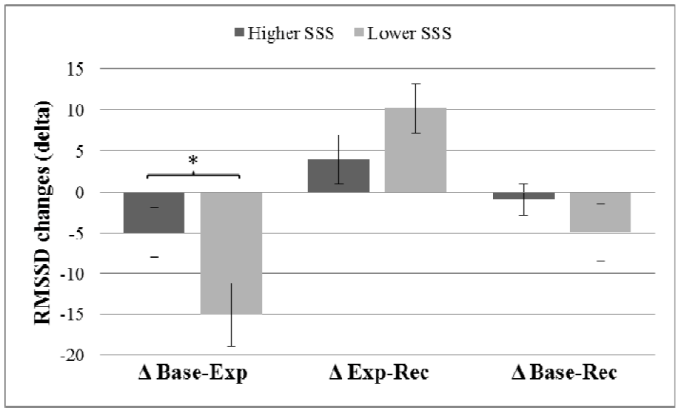
Higher SSS
Lower SSS
RMSSD changes (delta)
15
10
5
0
-5
-10
-15
-20
*
Δ Base-Exp
Δ Exp-Rec
Δ Base-Rec

Figure 1

Curriculum Vitae

[Der Lebenslauf ist nicht Teil der Veröffentlichung]

Publications and Scientific Presentations

[Der Lebenslauf ist nicht Teil der Veröffentlichung]

Declaration of academic honesty

Ich versichere, dass ich meine Dissertation „Effects of psychosocial stressors on physiological processes" selbständig, ohne unerlaubte Hilfe angefertigt habe. Ich habe dabei keine anderen als die angegebenen Quellen und Hilfsmittel genutzt und alle vollständig oder sinngemäß übernommenen Zitate als solche gekennzeichnet. Die Dissertation wurde weder in der vorliegenden noch in einer ähnlichen Form bei einer anderen in- oder ausländischen Hochschule anlässlich eines Promotionsgesuchs oder zu anderen Prüfungszwecken eingereicht.

Marburg/Lahn, März 2016 Karoline Pieritz