DISSERTATION

CARDIOVASCULAR REACTIVITY

–

VALIDATION OF A NEW PARADIGM AND ITS ASSOCIATION WITH PSYCHOSOCIAL FACTORS

---

submitted by

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STATUTORY DECLARATION

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been given in the text to all other material used. Throughout this thesis and in all related publications, I followed the "Standards of Good Scientific Practice" and Ombuds Committee at the Medical University of Graz.

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m.p. Kathrin Hilgarter

D I S C L O S U R E S

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All co-authors have explicitly agreed to the use of the published data in this thesis.

A C K N O W L E D G E M E N T S

'Life is a journey, with problems to solve, lessons to learn, but most of all, experiences to enjoy'
– Unknown

'A journey of a thousand miles begins with a single step'
– Lao Tzu

A PhD is a magnificent journey; you know the destination but not the exact way. And sometimes... yes sometimes, you just stop there to break, take a deep breath, and recharge your batteries. Or sometimes, you just take a rest to enjoy the wonderful view and reflect on the most important things of life. The path, which often seemed very rocky, always related to immense personal and professional growth for me. After many years of intense work, the journey is slowly coming to an end, and it is now in front of you: my thesis. So, it is time to thank those who have accompanied me on this journey and who have walked a part of the way with me. First and foremost, I would like to thank my supervisor ***Helmut Lackner*** and the dissertation committee ***Elisabeth Weiss*** and ***Andreas Rössler***. My thanks also go to ***Manfred Mörtl***, who gave me an interesting and unforgettable insight into everyday clinical practice and made resources available in his clinic department. I would also like to mention ***Anja Nischelwitzer*** with her open and friendly nature, who supported me in recruiting. I would also like to express my thanks to ***Karin Schmidt-Zalaudek***, who always had advice for me in questions about statistics. I gratefully thank all the ***participants*** who volunteered in this study. Further, I would like to thank all members of the ***Doctoral School Translational Molecular and Cellular Biosciences*** for the interesting lectures and discussions, and the ***Medical University of Graz*** for the doctoral program. I would particularly like to thank my colleague and friend ***Regina Csanady-Leitner*** who walked the often-arduous path with me side-by-side. We have always

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TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ANOVA	Analysis of variance
ANS	Autonomic nervous system
BMI	Body mass index
BP	Blood pressure
CES-D	Center for Epidemiological Studies-Depression
CHD	Coronary heart disease
CI	Cardiac index
CNS	Central nervous system
CO	Cardiac output
CPT	Cold Pressor Test
CVD	Cardiovascular diseases
CVR	Cardiovascular reactivity
CVLT-II	California Verbal Learning Test – second edition
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EI	Emotional intelligence
G-CEST	Grazer Cognitive and Emotional Stress Test
HF	High frequency
HPA	Hypothalamic-pituitary adrenal axis
HR	Heart rate
HRV	Heart rate variability
ICG	Impedance cardiography
LF	Low frequency
LDFR	Long delay free recall
ln	Logarithms
LVET	Left ventricular ejection time
MAP	Mean arterial pressure
MPT	Mittenecker Pointing Test
NA	Negative affect

PA	Positive affect
PANAS	Positive and Negative Affect Schedule
PEP	Pre-ejection period
PNS	Parasympathetic nervous system
PR	Peripheral resistance
PSQ-R	Perceived Stress Questionnaire – revised form
RF	Respiration frequency
RMSSD	Root mean square standard deviation of NN intervals
SBP	Systolic blood pressure
SDFR	Short delay free recall
SDNN	Standard deviation of NN intervals
SD1	Standard deviation of the Poincaré plot perpendicular to the line-of-identity
SD2	Standard deviation of the Poincaré plot along the line-of-identity
SEAS	Self-report Emotional Ability Scale
SI	Stroke index
SNS	Sympathetic nervous system
STAI-T	State-Trait Anxiety Inventory (trait fear)
SV	Stroke volume
SVF	Stressverarbeitungsfragebogen (stress coping questionnaire)
TFM®	Task Force® Monitor
TPR	Total peripheral resistance
TPRI	Total peripheral resistance index
TSST	Trier Social Stress Test
ULF	Ultra-low frequency
VLF	Very low frequency

LIST OF FIGURES

LIST OF TABLES

ABSTRACT (GERMAN)

Einleitung: Bei der Erfassung der kardiovaskulären Reaktivität ist ein effizientes Stressparadigma erforderlich, um gültige Schlussfolgerungen für psychophysiologische Prozesse ziehen zu können. Bisherige Paradigmen weisen jedoch einige Einschränkungen auf und führen tendenziell zu inkonsistenten Ergebnissen, da unterschiedliche Stressoren genutzt werden und diese vor ihrem Einsatz zumeist nicht bei gesunden Personen getestet werden. Der erste Forschungsschwerpunkt dieser Arbeit umfasst daher die Validierung eines neuen psychologischen Stressparadigmas namens Grazer Cognitive and Emotional Stress Test (G-CEST) bei gesunden Individuen, unabhängig von Alter und Geschlecht. Darüber hinaus kann ein inadäquater Umgang mit psychosozialen Prozessen das physiologische System langfristig schädigen und scheint ein Prognosefaktor für pathologische Veränderungen zu sein. Daher befasst sich der zweite Forschungsschwerpunkt dieser Arbeit mit der Untersuchung, wie die tonische und phasische Herzratenvariabilität (HRV) durch unterschiedliche Facetten psychosozialer Aspekte beeinflusst wird. ***Methode:*** Insgesamt nahmen 95 gesunde Teilnehmer*innen (34 Männer, 61 Frauen; alle kaukasischer Herkunft) im Alter zwischen 20 und 70 Jahren an dieser Studie teil. Die Validierung des G-CEST erfolgte durch verschiedene physiologische Parameter während der Phasen Ruhe, Antizipation, Stress und Erholung. In Bezug auf den zweiten Forschungsschwerpunkt wurde untersucht, wie die tonische und phasische HRV durch verschiedene Facetten psychosozialer Aspekte beeinflusst wird. ***Ergebnisse:*** Die Analyse ergab, dass die kardiovaskulären Parameter entlang der Phasen (Ruhe, Antizipation, Stress, Erholung) einen statistisch signifikanten Unterschied in der Herzfrequenz und in den Blutdruckvariablen zeigten. Variablen der Impedanzkardiographie wie etwa Schlagindex, Herzzeitvolumen, Präejektionsperiode und linksventrikuläre Auswurfzeit scheinen in dieser Studie weitgehend von den Ausgangswerten beeinflusst zu werden. Die Ergebnisse des zweiten Forschungsschwerpunkts zeigten, dass negative Bewältigungsstrategien (grübeln) und geringe emotionale Kompetenzen (Wahrnehmung der eigenen Emotionen) mit einer niedrigeren tonischen HRV verbunden sind, während Schwierigkeiten bei der Wahrnehmung von Emotionen bei anderen mit einer höheren HRV einhergehen. ***Schlussfolgerung:*** Insgesamt zeigen die Ergebnisse der vorliegenden Studie, dass der G-CEST bei gesunden Individuen geeignet ist, um moderaten Stress zu induzieren und kardiovaskuläre Veränderungen, unabhängig von Alter und Geschlecht, sichtbar zu machen.

Darüber hinaus trug diese Studie zu einer zunehmenden Anzahl psychophysiologischer Forschung bei und diente dazu, das Verständnis der HRV und ihre Assoziation mit psychosozialen Aspekten zu vertiefen, indem gezeigt wurde, dass Bewältigungsstrategie und emotionale Kompetenz die physiologischen Zustände bei gesunden Personen modulieren können.

***Schlüsselwörter**:* Kardiovaskuläre Reaktivität; Stressor; Laborstressparadigma; Grazer kognitiver und emotionaler Stresstest; G-CEST; Herzfrequenzvariabilität; psychosoziale Aspekte; emotionale Kompetenzen; Bewältigung; Psychophysiologie

ABSTRACT (ENGLISH)

Introduction: When measuring cardiovascular response to stress, an efficient stress paradigm is mandatory to draw valid conclusions for psychophysiological processes. However, psychological stress paradigm demonstrates some limitations and tends to produce inconsistent results through using different stressors which are non-validated prior to their application on healthy individuals. Therefore, the first research focus of this thesis includes the validation of a new psychological stress paradigm named the Grazer Cognitive and Emotional Stress Test (G-CEST) in healthy individuals, irrespective of their age and sex. Further, an inappropriate handling of psychosocial processes might cause long-term damage to the physiological system and seems to be predictable for physiological disorders. Therefore, the second research focus of this thesis aims to explore how tonic and phasic heart rate variability (HRV) is influenced by different facets of psychosocial factors. ***Method:*** In total, 95 healthy participants (34 males, 61 females; all Caucasian) aged between 20 and 70 years take part in this study. The validation of the G-CEST is through several physiological parameters during the main time points of rest, anticipation, stress and recovery. Regarding the second research focus, analyses were used to explore how tonic and phasic HRV were influenced by different facets of self-reported psychosocial factors. ***Results:*** The analysis determined that cardiovascular parameters showed a statistically significant difference along the main time points (rest, anticipation, stress, recovery) in heart rate and in blood pressure variables. However, impedance cardiography variables such as stroke index, cardiac index, pre-ejection period and left-ventricular ejection time seem to be largely influenced by baseline levels in this study. The findings of the second research focus showed that negative coping strategy (mental occupation) and low emotional competence (perception of one's own emotions), controlled for sociodemographic variables, were associated with lower tonic HRV, whereas difficulties in the perception of emotions in others were linked with higher HRV. ***Conclusion****:* Overall, the results of the present study indicate that in healthy individuals the G-CEST is successful in producing stress and enables making visible cardiovascular changes. Moreover, the new paradigm provides an easy and effective way to induce moderate stress, irrespective of age and sex. Further, this study adds to a growing body of psychophysiological research and serves to deepen the understanding of HRV and its association with psychosocial factors by showing that coping strategy and emotional competence might modulate physiological states in healthy individuals.

Key words: Cardiovascular reactivity; stressor; laboratory stress paradigm; Grazer Cognitive and Emotional Stress Test; G-CEST; heart rate variability; psychosocial aspects; emotional competence; coping; psychophysiology

1. INTRODUCTION

The human organism is based on homeostasis, a core concept which presents a dynamic balance in order to maintain physiological functions. When humans are exposed to internal or external disturbance, various reactions are activated to restore the homeostasis. This is an adaptive stress response of the organism which takes place continuously to deal with threats. [1,2] When homeostasis is disturbed by so called stressors, two essential stress systems seem to play an important role; the nervous system with the immediate activation of the sympatho-adrenal medullary system and the associated release of catecholamines, adrenaline and noradrenaline, which leads to increasing heart rate (HR) and arterial blood pressure (BP) during acute stress. Contrastingly, there is the endocrine system including the activation of the hypothalamic-pituitary adrenal axis (HPA) and the associated release of cortisol from the adrenal cortex. Both systems are key components in coping with threats by preparing the organism to handle the situation and to restore homeostasis. [2] Since this study focuses on rapid stress responses, which is often referred to as fight-or-flight reactions, the approach is restricted to physiological variables which influence the sympatho-adrenal medullary system. In the survival process, fight-or-flight represents the primary physiological responses to a stressor, followed by neutralization as the stressor wears off. A change in various physiological and psychological reactions occurs to restore and maintain stability. [3] Previous studies reported that cardiovascular adjustment during active performance situations was mainly characterized by changes in the HR, respiratory frequency (RF) and systolic blood pressure (SBP) [4–7]. The extent to which a human responds to an induced stressor and the followed recovery might be an important indicator of physiological and psychological health [8–10].

The concept of cardiovascular reactivity (CVR), understood as the physiological reflection of changes from one or more cardiovascular parameters between a rest and a stress condition[a] [11], has increasingly received attention in scientific interest since its first description [12]. There is a lot of controversy in science about which CVR is more adaptive in stressful situations. The reactivity hypothesis postulates that exaggerated CVR to mental stress may increase the risk of cardiovascular disease (CVD) [12]. Previous studies reported an association between exaggerate CVR and the development of hypertension [13,14], arteriosclerosis [15], increasing left ventricular mass or hypertrophy of the heart [8,16], poorer subsequent

[a] In a lesser extent, CVR has also been studied by measuring transient changes.

cardiovascular risk status [9] and increased mortality in CVD [13]. In contrast, other studies reported that a blunted CVR was associated with negative health outcomes [17] such as obesity [17,18], depressive symptomatic [19,20], poorer subjective health [21], eating disorders [22] and poorer cognitive function [23,24], and they could be observed in smokers [25] and in individuals with substance abuse [26]. Moreover, studies reported an association between blunted CVR and personality traits such as Type D individuals [27] or neuroticism [28]. However, both, exaggerated and blunted CVRs seem to be maladaptive and might be associated with prospective negative health outcomes as both tendencies imply a homeostatic dysregulation [29]. Additionally, it is well documented that a fast recovery when the stressor wears off is more adaptive in most settings [30,31]. Consequently, an insufficient stress response or recovery might lead to dysregulation of the stress system and seems to impair the organism, which can be accompanied by a physiological, behavioural or neuropsychiatric clinical manifestation [2].

Importantly, CVR seems to be used as an early predictor for preclinical states including adverse cardiovascular outcomes [30], or increased left ventricular mass and hypertension [8], which are often clinical manifest and causes a CVD in later life. Indeed, CVD is the most common cause of death with about 17.3 million people dying of it annually worldwide and more than 4 million deaths reported annually in Europe [32]. However, the most common death results from coronary heart diseases (CHD) [33] of which 90% might be prevented [34]. Accordingly, the CVR might represent an important predictor for the CVD risk in later life and might detect early dysfunction. Undoubtedly, these facts clearly show the importance of cardiovascular research.

Indeed, the cardiovascular response to stress is influenced by several factors. The most discussed factors include age [35–44] and sex [41,44–50]. Other factors affecting cardiovascular response to stress include weight [51–53] and physical activity level [54]. Human aging is associated with a decrease in resting cardiac index (CI) (↓ 25%), HR (↓ 25%), end diastolic volume (↓ 30%), left ventricular contractility (↓ 60%), ejection fraction (↓ 15%), as well as cardiac and vascular response to ß-adrenergic stimulation. Contrastingly, an age-related increase is seen in end systolic volume (↑ 275%), and systemic vascular resistance (↑ 30%). [37,40] These changes often manifest at the age of 65 but might already find their starting point at the age of 30 years [40]. However, several studies reported contradictory findings about age-related effects of CVR. Studies reported age-related blunted CVR [55,56] as well as

exaggerated CVR [57,58] to psychological challenges. In addition, sex-related differences in CVR are discussed in a wide range of studies [48,59,60]. In this context, previous research reported a predominance of parasympathetic nervous system (PNS) in females in contrast to a predominant sympathetic nervous system (SNS) in males [48]. In contrast, another study reported higher HR reactions in females than in males independent of task type [59]. However, females tend to react more to social threats such as rejection whereas males tend to react more to achievement threats [60] and the reaction from females seems to be affected by the menstrual cycle indexed by a greater activation of the PSN in the follicular phase and a higher activation of SNS in the luteal phase [48]. CVR might also be influenced by factors including socioeconomic status [61,62], lifestyle-related factors such as fitness [63], sleep behaviour [64], and psychosocial factors such as social support [65], loneliness [66], or emotional abilities [67,68]. Other factors such as genetic [69], or individual factors [28] are found to affect also the CVR patterns.

1.1. OVERVIEW OF THEORETICAL FRAMEWORKS FOR STRESS

To date, several theories and models have emerged to explain the physiological response to stress. Three main categories of theoretical frameworks can be distinguished. Approaches primary based on physiology [70–72], approaches mainly based on psychology [73] and approaches based on the complex interplay of psychophysiology indicated by sympathetic and vagal activation [74,75].

In the late 18th century, Claude Bernard's research formed the basis for the term '*internal milieu'*, which has proven to be fundamental for the understanding of the entire metabolic physiology. Internal milieu is '*the ability of an organism to maintain a constant fluid environment bathing cells of the body—the "milieu intérieur"—is essential for life independent of the external environment' [76, p. 109]*.

In the early 1900s, Walter Cannon was an early pioneer to describe the reactions of the physiological system in consequence of changes in the surroundings. The term, '*homeostasis'*, was used for the first time in this context. Homeostasis is a functional core concept of the body, which describes the pursuit of maintaining a balance, also called equilibrium, of several physiological variables. Changes in the surroundings, today known as stressors, disrupt the homeostasis of an organism, thereby triggering a physiological reaction to restore equilibrium. [71] Homeostasis was based on the basic assumption that for every physiological system (e.g.

BP, HR, hormone concentrations, activity of the immune system, etc.) there was exactly one optimal set point which should be maintained by internal regulatory processes [77]. Several acute changes (e.g. cold, pain, emotional distress, haemorrhage) might disturb homeostasis and form the basis of the concept of fight-or-flight responses, after Cannon observed that various stress elicited activation of the adrenal medulla and SNS, termed sympathoadrenal activation, indexed by an increase, for example, in BP and HR to restore homeostasis [76].

In the mid-19th century, Hans Selye was the initiator of stress research and coined the stress concept. The term, '*stress',* was defined as *'(...) the state manifested by a specific syndrome which consists of all the nonspecifically-induced changes within a biologic system. (...)'* [70, p. 64]. The conceptualized response pattern to stress*,* named '*general adaptation syndrome'*, include the stages: alarm, resistance, and exhaustion. The alarm stage starts with the initial shock phase which occurs immediately after the stress stimulus activates the SNS. If the stressor persists or the individual is not capable of overcoming it, a counter shock phase follows, namely fight-or-flight, as described by Cannon. [71] Within the stage of resistance, the organism endeavours to reduce the current stress caused by the stress-triggering stimuli and attempts to restore the original state. In an organism unable to restore the original state, a stage of exhaustion ensues. [70] Selye first proposes that prolonged stress can lead to physical disease and mental disorders [76]. Several studies have validated these results [30,31]. To date, there has been wide acceptance of an association between psychological stress and physiological diseases [78,79] or mental disorders [80].

From a critical point of view, the previous stress research up to this point was mainly based on animal experiments which only partially allowed explanations for the human organism. Moreover, it remained unclear why the same stressor could cause different stress responses. In this context, it became clear that both the individual perception and assessment of a situation must have an important meaning.

In the late 1900s, a psychological appraisal-based theory, namely the cognitive theory of stress and coping, was presented [73]. The stress theory has received several revisions since its first publication [81]. In the latest version, '*stress'* is understood as a rational concept of a relationship (*transaction*) between individuals and their environment. The theory is based on two crucial concepts, namely appraisal and coping. The former is characterized by the evaluation of a situation regarding the individual significance of subjective well-being after exposure to stress, and the latter refers to the individual efforts (cognitive and behavioural) to

handle the required demands. The concept of appraisal consists of two main component processes. Within the primary appraisal, individuals judge a situation regarding the significance of their well-being as irrelevant, benign-positive, or stressful. The latter appraisal determines the transaction as harm, threat, or a challenge. The challenge appraisal is accompanied by positive emotion of excitement, eagerness, and confidence. In contrast, both the harm and threat appraisals are associated with negative emotion of sadness or anger and anxiety or fear and require a further, that is, secondary appraisal which includes the evaluation of the available resources and options for coping with the transaction. If the judgement of resources and options is insufficient, a stress reaction occurs and coping strategies have to be used. Coping has the function of regulating distress emotions *(emotion-focused coping)* or changing the person–environment realities *(problem-focused coping)*. [73,82]

Based on previous theories, modern physiological concepts of stress emerged. A modern concept of allostasis, allostatic load and allostatic overload were proposed [72], which was originated from results of allostasis. This model postulates that a physiological and behavioural stress response is given when stress is classified as threatening. However, individual variations in stress response result from experience, genetics, and social status. Contrary to Cannon's understanding, homeostasis as stability of physiological systems does not refer to all physiological systems rather it points only to essential ones such as pH, body temperature, glucose levels, and oxygen tension. The framework assumes that allostasis, understood as a process, is achieving stability through changes, and will be supported by homeostasis. [72] In the context of allostasis, there is no fixed set point for a target variable, rather it is changeable and depends on the environment. If the body is overstressed by allostatic processes, the stress system can malfunction *(allostatic load).* This is the case if stressors occur at frequent intervals; the physiological stress response does not recover quickly after the stressor wears off, or the stress response is inadequate. [3] Two different forms of allostatic overload can be distinguished. Type 1 occurs when the energy demands exceed the income and Type 2 including the consequence, when energy consumption is sufficient or even exceeds, but is associated with types of social dysfunction. The latter type can only be neutralized through changes in the social structure or learning. [72] According to this concept, both types activate mediators of allostasis such as the secretion of glucocorticosteroids and autonomic nervous system, amongst others, and leads to decrease and increase with allostatic load. As a result, pathologies might develop

through a permanent high allostatic load and their associated chronically high concentrations of mediators. [72]

In recent years, several psychophysiological theories emerged. Two main frameworks, namely the polyvagal theory [74] and the neurovisceral integration model [75], explain the close relationship between cardiac vagal control and self-regulation. The polyvagal theory postulates the important role of vagus nerve and other cranial nerves in behavioural, physiological, and psychological processes from an evolutionary viewpoint [74,83]. The SNS triggers a reaction to external challenges and the PNS promotes homeostasis by modulating the recovery. Regarding the polyvagal theory, '*stress'* is defined as the '*autonomic state that reflects a disruption of homeostasis due to depressed parasympathetic tone'* [74, p. 227]. The cardiac vagal tone, the complex interplay of SNS and PNS, represents an indication of normal homeostatic function in non-challenging situations, whereas during challenges an index of adaptive function is provided. Commonly, high levels of vagal tone might be seen as more adaptive. [74] The neurovisceral integration model describes in detail the close interaction between cognitive, affective (emotional), behavioural, and physiological processes involved in self-regulation and adaptability by integrating these components into a functional and structural network. Thus, the central autonomic network acts as a neurophysiological headquarter and manages psychological and physiological processes through predominantly inhibitory processes indexed by heart rate variability (HRV). This inhibition, viewed as negative feedback circuits, takes place through synaptic relay within the brain and is mediated by the vagus in the periphery. [75,84] In this context, cardiac vagal tone indicated by HRV, which is defined as an *index of central–peripheral neural feedback* and central nervous system (CNS)–autonomic nervous system (ANS) integration [75], enables the central system to control emotional reactions. Indeed, higher levels of vagus-mediated HRV might be seen as more adaptive. Further, HRV is related to affective information processing, attentional regulation, cerebral blood flow, and physiological flexibility [75,84].

Both frameworks, the polyvagal theory [74] and the neurovisceral integration model [75], have in common the crucial role of the PNS in emotional activities due to inhibitory processes which can regulate the autonomic level of arousal. Therefore, the HRV provides an adequate measure for processing the environmental requirements. In contrast to the polyvagal theory [74], the neurovisceral integration model [75] postulates an interaction between higher brain functions and the autonomic nervous system, which has primarily triggered research on

affective dysfunction, whereas the polyvagal theory has mainly triggered research based on social-related processes.

1.2. MEASURES OF THE CARDIOVASCULAR RESPONSES TO STRESS

In studies related to cardiovascular research, the effects of psychological stress are mostly triggered by so-called stressors. The term *'stressor'* indicates a situation which is judged as aversive and disturbs the homeostasis by touching physiological and psychological resources including evoking a physiological response [85]. In this context, electrocardiogram (ECG), impedance cardiography (ICG) and continuous BP measurement are suitable methods for monitoring cardiovascular response to stress because they enable a reproducible and sensitive measurement of haemodynamic changes [86], which can be monitored by the Task Force® Monitor (TFM®; CNSystems, Graz, Austria; Certification CE [TÜV-A-MT- 1/10/1Q034]). The TFM®, as a non-invasive measuring system, enables continuous signal monitoring of essential haemodynamic parameters by ECG, ICG and continuous BP measurement and provides a beat-to-beat analysis and visualization in real time [86,87].

ECG is the recording of the electrical potential alterations caused by the heart during a cardiac activity [88] and represents the electrical events of the heart [89]. Each heart function is preceded by an electrical excitation which, in normal cases, emanates from the sinus node and is passed on to the cardiac muscle cells via the excitatory conduction system. This is derived by means of electrodes attached to the body surface. ECG enables production of information about the characteristics and possible diseases of the heart. [88] Parameters that are meaningful for monitoring the cardiovascular response to stress using ECG includes HR [bpm] and different variables of the HRV [5,90–92].

HRV representing a physiological non-invasive measure reflects the fluctuations of the ANS indicated by time interval [ms] between two adjacent QRS complexes in the ECG (NN intervals[b]) [93,94]. It also indicates the sympathetic and vagal activation on the sinus node of the heart [95]. This is of particular interest given the close link of the PNS with several components of psychophysiology such as the close relation of self-regulation capacity with cognitive or affective functions and with several health aspects [83,96,97]. Nowadays, three main origins are used to analyse HRV [49,94,95,98]. First, the analysis by time domain includes

[b] NN intervals refer to the intervals between normal R peaks.

the fluctuation on time periods between adjacent heartbeats [49]. The standard deviations of all NN intervals (SDNN) and the square root of the mean of the sum of the squares of differences between adjacent NN interval (RMSSD) [94,95] are the most frequently investigated parameters across the scientific community. Evidence indicates that RMSSD is dominantly vagal-mediated, whereas SDNN is influenced by both branches of the PNS and SNS [49,95,98]. Second, the frequency domain determines the stored series of data by power spectral analysis to examine the amplitudes, frequencies, and other components that compose the HRV. This shows the magnitude of its relative intensity in the sinus rhythm of the heart. [95] Evidence suggests that the power spectrum can be divided into (a) ultra-low frequency (ULF), (b) very low frequency (VLF), (c) low frequency (LF) and (d) high frequency (HF) [93,94]. The ULF band (<0.003 Hz) reflects the circadian rhythm and metabolism, whereas the VLF band (<0.003–0.04 Hz) represents the mechanism of long-term regulation, thermoregulation, and hormonal mechanism. However, both, the ULF and the VLF are not considered in this study because the analysis requires longer recording periods (ULF: min. of 5 minutes, 24 hour preferred; VLF: 24 hour). [49] The more important HRV indices are the LF band (0.04–0.15 Hz) and the HF band (0.15–0.4 Hz). The former reflects both sympathetic and parasympathetic components and is thought to be an indicator of cardiac outflow [93,98]. Further, the LF band seems to be affected by baroreceptor sensitivity [98]. In contrast, the HF band reflects predominantly the vagal tone [93,98,99] and the oscillations in this frequency band particularly describe the respiratory sinus arrhythmia, and might be affected by the frequency of breathing [93–95]. Finally, the ratio between LF and HF reveals the activation of the sympathetic and parasympathetic branches [94,95,99]. Third, non-linear indices such as Poincarè plots involves a visual demonstration of time series signals. Evidence distinguishes between the (a) standard deviation of the Poincaré plot perpendicular to the line-of-identity (SD1) and the (b) standard deviation of the Poincaré plot along the line-of-identity (SD2). Regarding this differentiation, the SD1 reflects the short-term variability whereas the SD2 provides insight into the long-term variability. [100] However, it has to be considered that RMSSD and SD1 as well as SDNN and SD2 are identical metrics of HRV in statistical sense [101]. Regarding this redundant information, this study focuses on HRV in the time and in the frequency domain. Importantly, the HRV is affected by several factors which need to be considered. The most well-known influencing factors are sociodemographic variables including age [41,42,44] and sex [41,44,47–50]. Other important factors include weight [51], cardioactive or psychotropic medication and

physical or psychological health conditions [49,98,102]. Further, alcohol and nicotine intake prior to the experiment seems to affect also the HRV [102–105].

BP [mmHg] including SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) are also meaningful for monitoring cardiovascular response to stress [5,90–92]. The measurement of continuous BP uses the vascular unloading technique and is performed by the fingers. This is automatically corrected to oscillometric BP values and measured by the brachial artery because the small artery of the fingers is not representative of the systemic BP. The continuous BP provides an uninterrupted and continuous BP wave by temporary adjustment of the set point. [87] The left ventricle contracts and results in blood getting pumped into the aorta followed by a brief increase in the BP of the blood vessels. The maximum pressure of the BP wave when reached is defined as the SBP [mmHg]. After the left ventricle has contracted, the heart fills up again. For this phase, the chamber relaxes and, therefore, no further blood is pumped into the aorta. This leads to a slow decrease of the pressure in the blood vessels. The minimal pressure of the BP wave when reached is called the DBP [mmHg], whereas the average pressure in arteries during one cardiac cycle is named MAP [mmHg]. [106]

ICG is a method for monitoring haemodynamic changes. It utilizes the aspect that different tissues have different electrical resistance – also known as impedance. While bones, fat tissues, lungs and muscles have poor electrical conductivity, blood has good electrical conductivity. [107] ICG detects the change in transthoracic electrical resistance caused by cardiac activity. Since electrical current always seeks the path of least resistance, blood volume fluctuations during the cardiac cycle are responsible for different impedance levels [108]. ICG is based on the physical principles that can be derived from Ohm's Laws. Voltage variations are directly proportional to the changes in the measured impedance when a constant current is applied to the thorax. The baseline impedance (Z_0) is the sum of the impedances of overall thorax segments and includes fat, cardiac and skeletal muscles, lung and vascular tissues, and bone as well as air. The change in the volume of the lungs during breathing and the velocity of the blood during systole and diastole lead to changes (Z_0). Respiration variations can be filtered by ICG and, therefore, the rapidly changes might be attributed only to ventricular ejection. [109] Electrical resistance and changes in the thoracic impedance of blood and tissue caused by cardiac contractility are measured with three short-band electrodes placed at the thorax and neck [86]. Based on these impedance variations, haemodynamic parameters can be calculated [107]. The ICG waveform represents the mechanical events of the cardiac contraction [89]. The

TFM® offers a signal processing tool to eliminate the electrical influence of breathing and to detect maximal mechanical contraction (dZ/dt_{max}) and the opening and the closing of the aortic valve [87]. A variety of measured and calculated parameters can be observed by TFM®. Stroke volume (SV) is the amount of blood [ml] that the left ventricle pumps into the aorta during a heartbeat and can be detected by beat-to-beat ICG-signals $dZ/dt\,(t)$ and $Z_0(t)$ [106]. Left ventricular ejection time (LVET) [ms] reflects the time between the opening and the closing of the aortic valve [86]. The pre-ejection period (PEP) is defined as the time [ms] between electrical depolarization of the left ventricle (QRS) and the start of ventricular ejection. The cardiac output (CO) reflects the amount of blood [l/min] circulating in the entire cardiovascular system per minute and is formed by the product of SV and HR. [106] From this measure, parameters such as the total peripheral resistance (TPR) [dyne * s / cm^5] [106], which pumps the blood against the left ventricle into the small and large vessels, can be estimated [89]. The main associated problem is the difficulty in establishing the resistance of the blood and the assumption of the thorax as a cylinder. For underweight people, the model is more like a cylinder, whereas the thorax is shaped rather like a frustum in adipose people. [86] Therefore, the stroke index (SI) [ml/m^2], cardiac index (CI) [l/(min*m^2)], and total peripheral resistance index (TPRI) [dyne * s * m^2 / cm^5], all normalized on the body surface area [106], were used in this study. As shown in several studies, meaningful ICG parameters for monitoring cardiovascular response to stress are CI, SI, TPRI, LVET, and PEP [5,90–92]. In fact, ICG is non-invasive, easier and less expensive than comparable methods which result in patients not being at risk [107]. However, the ICG variables have faced increasing criticism because they are based on estimations of physiological variables and simplified physiological assumptions [110], which might limit their accuracy.

1.3. LABORATORY STRESS PARADIGM

When measuring cardiovascular responses to stress, an efficient stress paradigm is mandatory for drawing valid conclusions for psychophysiological processes. In this context, a considerable amount of literature has been published on distinct types of paradigm including different kinds of stressor causing physiological stress response. A differentiation occurs by the nature of the stressor. The physiological stress paradigm, which is not considered in this study, is often caused by uncomfortable sensory experience, for example pain, which is linked to potential damage of the human body. These paradigms often consist of head-up tilt test [90,92],

physiological exercises such as isometric hand grip test [111] or cold pressor test (CPT) [112]. The more relevant tasks in this context are psychological stress paradigms. These are induced by situations which are perceived as negative or threatening. As mentioned before, the psychological appraisal-based theory, namely the cognitive theory of stress and coping [73,81], postulates that stress is understood as a rational concept of a transaction between individuals and their environment. The response to stress is individual, whereas the concept of appraisal is necessary to understand these variations. From a physiological perspective, the concept of allostasis, allostatic load and allostatic overload [72] is proposed. This concept postulates that stress is an event which is considered threatening and which triggers a physiological and behavioural stress response. The framework assumes that allostasis, understood as process, achieves stability through changes and will be supported by homeostasis [72]. If the body is overstressed by the allostatic processes, the stress system can malfunction (*allostatic load*). This permanent activation of allostasis mediators is accompanied by the secretion of glucocorticosteroids and autonomic nervous system, amongst others. [3] As a result, pathologies might develop through a permanent high allostatic load and its associated chronically high concentrations of mediators [72]. Within the psychological stress paradigm, several studies reported the activation of SNS [4–7,113] during induced psychological stress. In contrast, another differentiation occurs through the active or passive contribution of participants [114]. The passive coping stress tasks include withstanding the procedure without influencing the task results [115] for instance, the paradigm based on psychological basis such as emotion-laden sound recordings [116,117], affective film clips [118–120], viewing affective pictures [121] or humorous material such as standardized cartoons [122]. The former includes active engagement of participants, requires performance and is often induced by situations in which goal-oriented performance is to be achieved such as in mental arithmetic tasks [4,91,123,124], speaking tasks such as giving a stressful presentation [125], and Stroop test [126]. Moreover, recent studies emerged from new technologies such as gaming, virtual reality and augmented reality [127].

A promising stressor including active engagement of participants is the commonly used California Verbal Learning Test – second edition (CVLT-II), which enables the evaluation of several aspects of episodic verbal learning and memory by presenting the stressor in an non-threatening manner, which can also arise in an everyday situation for example, reminding shopping list [128]. The psychometric properties of second edition of the CVLT show

respectable results for short-term test-retest reliability [129] and long-term test-retest reliability [130]. Further, the validity of the instrument is also supported by evidence [131]. The CVLT-II is considered as a reliable and valid neuropsychological assessment with a wide-ranging use in numerous scientific and clinical settings [129,132–134]. This broad use enables the availability of an extensive normative database. Moreover, the CVLT-II consists of an expanded age range from 16 to 89 years [128,135] and offers flexibility in test administration by using short, standard, and alternate forms [128]. CVLT-II seems to be less influenced by sociocultural factors compared to other instruments [132]. However, some of the CVLT-II scores decline with age [128,134–136] and females tend to perform better in verbal episodic memory tasks than males [128,134–136]. Therefore, age- and sex-related factors have to be considering when memory performance are analysed. Previous studies found negative associations between verbal memory measured by CVLT-II and brain volume [137] or left hippocampus volume [137]. The CVLT-II is also used in cardiovascular context to induce stress and acts as a moderate stressor [133,134]. Recent studies reported an association between CVLT scores and increased BP response to stress [138] and a reduced HRV regardless of age and sex [134].

There are also several mixed stress paradigms combining physiological (e.g. CPT) and psychological components (e.g. mental arithmetic tasks) such as the most commonly used and standardized stress test named Trier Social Stress Test (TSST) [139], the Socially Evaluated Cold Pressure Test [140] or the Maastricht Acute Stress Test [141]. However, active coping tasks induce greater effects on cardiac patterns whereas passive tasks tend to produce more vascular patterns [4–7,113,142]. In response to a stressor, a cardiac or vascular stress reaction might be distinguished depending on the increases in different cardiovascular parameters. Vascular reactions are mediated by alpha-adrenergic processes and increase the peripheral resistance, and decrease the HR and CO. [6,113,142] In contrast, cardiac reactions are mediated by beta-adrenergic processes and primarily increases the RF, HR, BP, and CO [4–7,113]. An increase in the CO is usually associated with an increase in the SBP and HR. In contrast, a decrease in the peripheral resistance is usually associated with a decrease in the DBP. A clearly higher increase in the systole as compared to the diastole with a simultaneous increase in the HR is indicative of a cardiac reaction. A single increase to approximately the same extent in systolic and diastolic BP without HR involvement is inductive for a vascular response. [6]

Therefore, the BP and the HR variables can be used as indicators of cardiac or vascular response to stress.

Nevertheless, there are several limitations to using some of the existing stress paradigms. In a passive emotional stress paradigm, often the long-term psychological effects of participants exposed to shock material are discussed [143]. One criticism of physiological or mixed stressors is that the true role of inducing mixed stress is not clear yet, thus making it difficult to interpret the results in an appropriate manner because it is unclear if the stress is a corresponding physiological aspect of pain or results from the psychological aspect of negative emotions such as anxiety or fear. The TSST, as a most common paradigm, requires numerous resources to carry out a study on the duration of the test which is about 131.2 min on average [144]. Further, most previous studies validate paradigms based on HR or BP [144–147]. However, a comprehensive validation by ICG variables enables a profound understanding of the underlying haemodynamic stress reactions. Finally, psychological stress paradigms tend to produce inconsistent results as different stressors are used. Therefore, validation of a standardized procedure in healthy individuals is obligatory before using a paradigm in clinical setting.

In order to overcome these limitations of existing paradigm, the Applied Interdisciplinary PsychoPhysiology (aiPP) team has developed a simple and easy psychological stress paradigm with moderate standardized stressors named the Grazer Cognitive and Emotional Stress Test (G-CEST). As described above, an efficient stress paradigm has to be validated within healthy individuals to use this standardized procedure further in clinical practice. Therefore, the aim of the present study is to validate the developed G-CEST by investigating cardiovascular changes indicated by HR, BP, SI, CI, TPRI, PEP, LVET, and RF during the main time points of rest, anticipation, stress and recovery; and to see whether it is appropriate for use on healthy individuals, irrespective of their age and sex. Thus, the application is further enabled in clinical research and practice. Importantly, a recently published study by the research group aiPP suggests that the G-CEST is appropriate to monitor HRV changes caused by psychological challenges [134]. Therefore, the validation of the paradigm concerning HRV indices was not reported again due to redundant information.

1.4. CARDIOVASCULAR HEALTH AND PSYCHOSOCIAL FACTORS

The second aim of the thesis is to focus on HRV and its association to psychosocial-related aspects. The adaptation of the physiological system to psychological stress represents a

complex reciprocal and dynamic network in which stress response takes place not only through a stimulus, but also through the appraisal of the situation [148]. An index of the autonomic regulation of cardiac functions, which provides information about how individuals manage the environmental demands [75,83], is given by HRV. The two most influential theories of HRV, the polyvagal theory [74] and the neurovisceral integration model [75], postulate the dispositional character of HRV, in which PNS plays an important role in inhibitory processes. Regarding this close link between the heart and the brain, HRV constitutes an important indicator of physiological adaptability [149,150] as well as self-regulatory capacity [97,151] and seems to be a crucial predictor for health [149]. Previous research reported that reduced variations in HRV might indicate age-related decline, chronic stress, pathological state, or inadequate function of self-regulatory control systems [93,96,150].

1.4.1. MENTAL HEALTH

A long line of research has focused on associations between cardiovascular health and psychosocial traits [27,152,153]. Importantly, previous studies report a close link between reduced HRV and the development of physiological pathologies, such as heightened risk of cardiovascular events [154], mortality [155] and other morbidities [156], or mental disorders such as anxiety [157,158], post-traumatic stress disorder, schizophrenia [159] and depression [159,160]. A longitudinal study reports that individuals with lower HRV are more likely to develop depressive symptoms over a 10-year period [161]. However, mental health seems to be also influenced by life-style related factors [162]. Further, a close link between positive affect (PA) and personality traits such as conscientiousness or extraversion, and negative affect (NA) with neuroticism or anxiety [163,164] has been reported. Several studies found associations between negative psychosocial traits, such as neuroticism, with higher risk of CVD [152,153], CHD [165] and higher risk of mortality [153]. In contrast, PA, seems to be protective and is linked with better cardiovascular recovery [166], lower mortality risk from CHD [9,165], decreasing risk of stroke [165], reducing incidence of CHD [167] and a lower risk of atherosclerosis [168]. Further, several studies report that PA and NA seem to be associated with HRV [169]. However, it depends on the activation level and seems to be influenced by demographic and behavioural confounders [169,170].

1.4.2. PERCEIVING STRESS AND COPING

A link between stress and cardiovascular health, in which perceptions of stress and coping play a key role, was presented in previous studies. It is assumed that psychological stressors trigger certain appraisal processes which will classify situations as irrelevant, benign-positive or stressful [73]. If a stressor is rated as threatening, certain areas of the brain are likely to be activated, which cause cardiovascular activity in order to provide metabolic resources for coping [171]. Frequent exposures to stress combined with missing adaptive coping resources might contribute to a dysregulation of the physiological system, which leads to an increasing risk of developing CVD [3,76,78,79].

In the context of stress-coping strategies, evidence differs between adaptive coping strategies, resulting in reducing stress and maladaptive strategies which are associated with behaviour that enhances stress [172]. Additionally, coping strategies can be distinguished in problem-focused and emotion-focused coping [173]. Previous studies indicate that less threatening appraisal and consequently lower psychological stress response are related to individuals focusing on adaptive and active coping strategies [174] and the lower the emotional-oriented coping strategy, the lower the risk of physiological pathologies [175]. Furthermore, a greater HRV is related to focusing on adaptive-coping strategies, whereas lower HRV indicates emotional dysregulation accompanied by emotions of anxiety, depressive symptomatic and non-flexible attentional processing of threat [176] which, in turn, is associated with lifestyle-related factors [177]. A maladaptive coping is seen in perseverative cognition and understood '*as the repeated or chronic activation of the cognitive representation of one or more psychological stressors'* [178, p. 114]. The perseverative cognition hypothesis postulates that chronic perseveration might prolong the stress response and it seems to be associated with negative physiological and psychological health [179–183]. In this context, the HRV, as an indicator of effective cognitive and emotional functioning, seems to be negatively associated with rumination and worry [181,184]. Considering the questionnaire used in this study, the term mental occupation, also known as rumination, which means the process of recurrent series of thoughts about feelings and problems [182], was used.

1.4.3. EMOTIONAL COMPETENCE

Noteworthy cardiovascular adjustment also occurs in the context of emotional processes [4,120,122,185]. Mainly, it is discussed that inappropriate handling of emotions can cause long-

term damage to the physiological system [186]. It is thought that emotional intelligence (EI), as a set of skills, contributes to the accurate appraisal and expression, effective regulation, and utilization of emotions, which is necessary for adequate social functioning and for attaining health [187–190]. EI is defined in a number of different contexts, but most definitions have in common that EI describes the ability to perceive, understand, regulate and manage emotional information of one's own emotions and of the emotions of others to facilitate goal-oriented behaviour [187,191,192]. The evidence differentiates between two constructs to operationalize EI. The ability to use objective maximum performance in like manner as tests for intelligence quotient to measure EI is conceptualized as cognitive ability [193]; and to assess trait EI by using self-report questionnaires referring to self-perceptions is conceptualized as personality trait [194]. However, trait EI is a better health predictor than ability EI [188] because it seemingly better modulates physiological response to stress [195]. This study, therefore, focuses on trait EI. Trait EI seems to be associated with academic success [196], job performance [197] and various health outcomes especially in psychosomatic health [188,190] because high EI can work as a buffer against psychopathology [198]. Moreover, EI seems to be linked with healthier lifestyle [199], and might have a vital role in the occurrence of CHD [200]. Previous studies show that HRV seems to be a transdiagnostic biomarker to demonstrating psychopathology [151]. Moreover, evidence suggests a positive association between emotional competence and HRV, as an objective index of emotional capacity [149,176]. In addition, HRV might affect self-regulation, social engagement, social approach behaviour, and psychological flexibility [158]. Previous studies also demonstrate that individuals with higher HRV show higher emotional well-being [151,158], higher recognition of emotions [201], and more adaptive emotion regulation strategies [176]. Conversely, lower HRV seems to be linked with greater difficulties in emotional regulation [202,203] and with higher levels of trait anxiety or rumination [184]. This in turn is predictable for psychological disorders [75,178]. Overall, HRV seems to be an indicator that can deepen the understanding of emotions in psychophysiological processes [176].

Although a considerable amount of evidence presumes the link between HRV and mental health, the Positive and Negative Affect Schedule (PANAS) [204], the State-Trait Anxiety Inventory (trait fear) (STAI-T) [205], and the Centre for Epidemiologic Studies Depression (CES-D) Scale [206] are used in this study to measure affect, anxiety and depressive symptoms. Regarding the assumption that individual perception of stress and its underlying

coping strategies influence HRV, this study used the Perceived Stress Questionnaire revised form (PSQ-R) [207] to assess the subjectively experienced stress in the last few weeks. However, the PSQ-R limited the conclusion of the coping strategies that were in use, therefore the Stress Coping Scale (Stressverarbeitungsfragebogen – SVF-48) [208] was additionally used. Finally, due to a considerable amount of evidence reporting a link between HRV and emotional competence, the validated Self-report Emotional Ability Scale (SEAS) [209; see also 116,185,210] was used in this study to measure the trait of emotional competence.

Taken together, a substantial amount of evidence has reported a link between HRV and psychosocial factors. However, studies have not yet directly examined how mental health, varying facets of perceived stress and coping as well as specialized facets of emotional competence, controlled for sociodemographic factors, predict tonic and phasic HRV. Therefore, the second research focus of this thesis aims to explore how HRV is influenced by different facets of self-reported psychosocial factors such as mental health, stress perception as well as coping, and emotional competence. It is assumed that low mental health, high stress perception, negative coping strategy and specific aspects of low emotional competence predict lower HRV controlled for sociodemographic variables such as sex, age and body mass index (BMI). The overall assumed research model is illustrated in **Figure 1.1**.

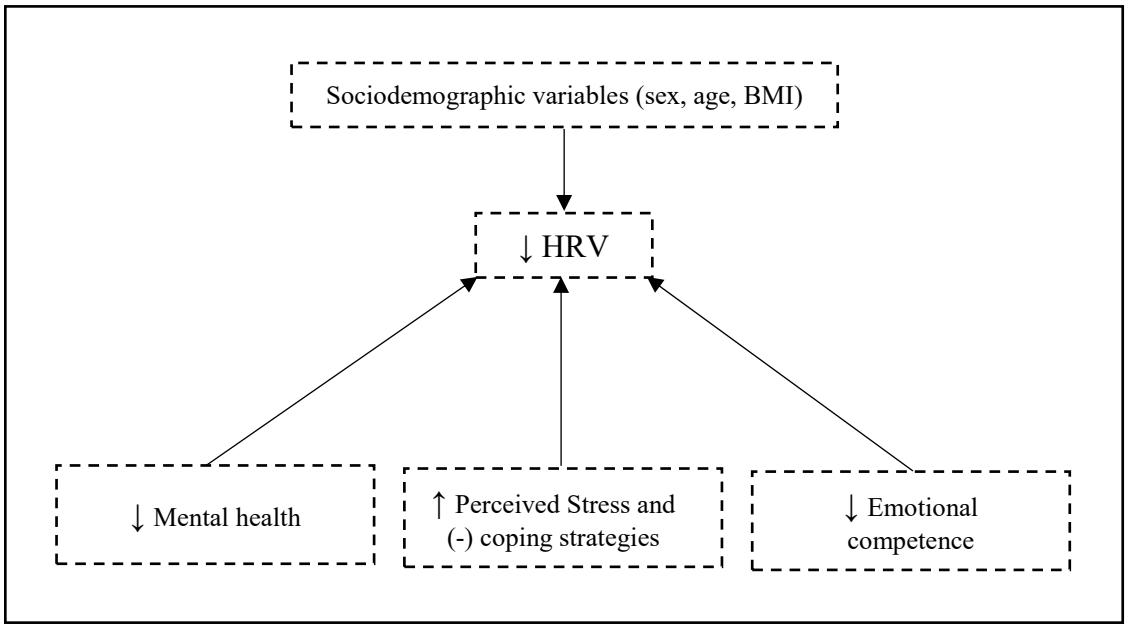

Figure 1.1: Research model of the HRV and psychosocial factors
↓ low, ↑ high, (-) negative

2. MATERIAL AND METHODS

A cross-sectional, multicentre (Graz and Klagenfurt) study with healthy individuals was performed in accordance with the 1964 Declaration of Helsinki and was approved by the authorized local ethics committee (EK-28-511 ex 15/16; EK-A23/16).

2.1. PARTICIPANTS AND SAMPLING

A random sample of participants was recruited by using brochures, information, and social media channels. As seen in **Table 2.1**, the criteria for selecting the participants were as followed: First, participants without existing and/or history of cardiovascular disorders (e.g. hypertension, chronic disease with cardiovascular component), psychological disorders (e.g. major depressive disorder, schizophrenia), medication intake or acute infection. Second, individuals without existing or history of addiction and BMI < 35 kg/m². Third, participants aged between 20 to 75 years. Regarding the focus of this thesis, a broad sample size, including males and females as well as a broad age range, was required to validate a new developed paradigm. However, to avoid biases which origin in age or sex, both variables were considered in the main statistical analysis. Fourth, participants should be able to speak, read and write German (language level at least B2). Fifth, there should be no existing pregnancy in females and no professional athletes were included. These inclusion criteria were examined according to self-report. Finally, a written informed consent was obligatory. As prior studies recommended [98,211], participants were asked not to consume alcohol 24 hours prior to the measurement and no intake of caffeine at least four hours before it.

Based on effect sizes found in previous studies that have analysed cardiovascular response to stress, effect size were expected for the present study based on a sample sizes calculation (a priori, F-test family, ANOVA repeated measures, within-between interaction). The effect size calculation suggests that to achieve a common significance level of $\alpha = .05$ and a common power of $1-\beta = .95$ using G*Power, a minimum sample of 72 participants is required for moderate effects.

Figure 2.1 illustrates the flowchart of the participants. In total, 168 participants were screened for eligibility, of which some were not recruited as they refused to participate (n = 21), did not reach in time (n = 7), or did not attend the appointment (n = 6). Therefore, 134 participants were registered for the study. Of them, one was ineligible due to BMI being ≥35

kg/m², one was excluded for being less than 20 years old, 14 were ineligible as they had an acute infection and/or were medicated at the measurement date, and three showed a pathological ECG, and hence rejected. In the final total, 115 participants fulfilled the inclusion criteria.

To ensure the quality of physiological data and to calculate the inter-beat intervals, the TFM was used, which allows the ECG signal to be sampled with millisecond accuracy. Further, a semi-automatic artefact handling was used, which was developed by our research group and was successfully used in a wide range of studies. At the beginning, there was a visual check of the data. Afterwards, single artefacts were replaced by interpolation and were recorded. The mean values were calculated over the 180 s time epochs. While analysing the time epochs, the periods were chosen in such a way that the first rapid change in physiological parameters was not included because the first section of changes would bias the analysis. The beat-to-beat values for HR and BP time series were resampled at 4 Hz using piece-wise cubic spline interpolation after artefact correction. Invalid data was marked for the determination of the proportion of valid data. The respiratory rate was derived from the raw data of the impedance cardiography. Owing to the strict artefact handling, during three-minute epochs, only data sets with at least 95% valid R-R intervals and 85% valid BP and ICG data sets were included in the analysis. Therefore, one data set was excluded due to quality restrictions on the ECG, four data sets were rejected following quality restrictions on the BP and 15 data sets were excluded from further analysis due to the presence of artefacts in ICG. Finally, the analysis included data sets of 95 healthy participants. **Table 2.2** provides an overview of the demographic characteristics of the final sample included in the further analysis. The sample should accurately reflect what exists in the population. Therefore, females with oral contraceptive pills and smoking participant were included in this study. However, participants were instructed not to consume nicotine at least four hours before the measurement, as recommended in previous studies [98,211].

Table 2.1: Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Health status	– General healthy individuals – No medication except oral contraception	– Existing and/or history of cardiovascular or psychological disorders – Medication – Acute infection
Lifestyle	– No existing or history of addiction – BMI < 35 kg/m²	– Frequent alcohol or recreation drug use – BMI ≥35 kg/m²
Age	– Age 20-75 inclusive	– 20 years< age > 75 years
Language	– Ability to speak, read and write German (language level at least B2)	– Missing language skills
Other	– No existing pregnancy in females – No professional athletes	– Pregnancy in females – Professional athletes
Informed consent	– Written informed consent	– Missing written informed consent

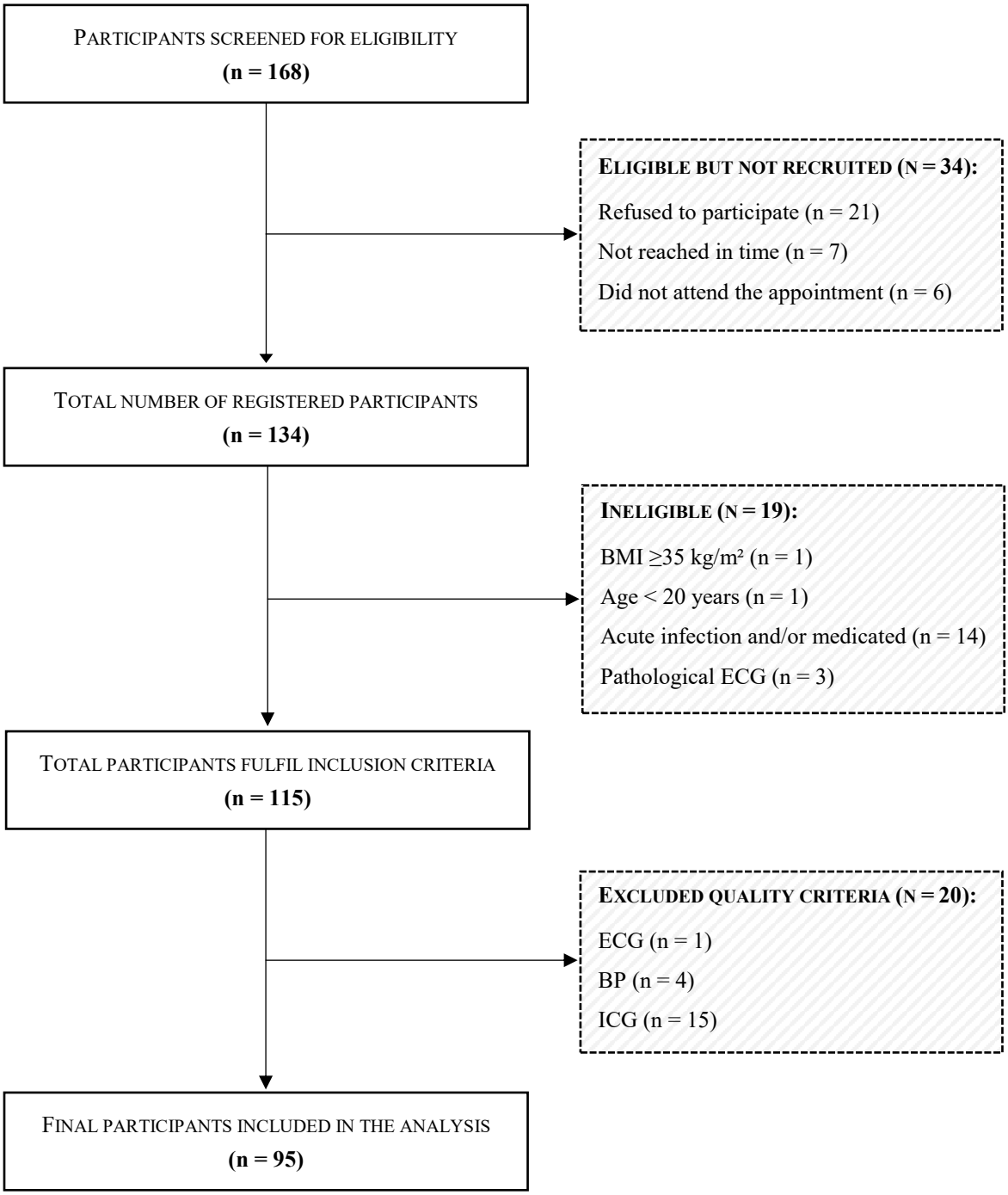

Figure 2.1: Flowchart of the participants

Table 2.2: Demographic characteristics of the final sample

Variables	male		female		total	
	n = 34		n = 61		n = 95	
Age years (Mean ± SD)	37.3±13.6		36.0±12.2		36.4±12.6	
Waist-to-hip-ratio (Mean ± SD)	.88±.06		.85±.06		.86±.06	
BMI (Mean ± SD)	24.74±3.20		22.94±2.97		23.58±3.16	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Cigarette smokers						
no	23	(24.21)	39	(41.05)	62	(65.26)
yes	8	(8.42)	16	(16.84)	24	(25.26)
n/a	3	(3.16)	6	(6.32)	9	(9.47)
Education						
Secondary education first stage	4	(4.21)	4	(4.21)	8	(8.42)
Secondary education second stage	12	(12.63)	37	(38.95)	49	(51.58)
Tertiary education	15	(15.79)	14	(14.74)	29	(30.53)
n/a	3	(3.16)	6	(6.32)	9	(9.47)
Family history of CVD						
no	10	(10.53)	31	(32.63)	41	(43.16)
yes	21	(22.11)	24	(25.26)	45	(47.37)
n/a	3	(3.16)	6	(6.32)	9	(9.47)
Allergy						
no	16	(16.84)	35	(36.84)	51	(53.68)
yes	15	(15.79)	19	(20.00)	34	(35.79)
n/a	3	(3.16)	7	(7.37)	10	(10.53)

n/a = not applicable

2.2. PROCEDURE

The procedure started with an introduction and a detailed explanation of the study. The participants were asked general questions to check the inclusion criteria and some questions on demographic data. Self-reported age, sex, the highest level of education, smoking status, last caffeine intake, allergy status, family history of diseases, and number of children of females were asked in the preliminary preparation of the measurement. The determination of the body weight, the height as well as the waist and hip circumference was followed. Thereafter, electrodes were attached and the electrophysiological signals were checked. All the measurements took place in a quiet room and before the measurement started, the participants were instructed to be seated comfortably and fill out several questions on the computer. This approximately 30-min period enables the participants to relax.

2.2.1. QUESTIONNAIRES

Since psychological factors play an important role in cardiovascular health, self-reported questions were used in this study to record psychosocial factors such as mental health including PA and NA [204], state-trait anxiety [205], symptoms of depression [206], perceived stress and coping [172,207], and emotional competence [209].

MENTAL HEALTH

The PANAS was developed to determine the emotional state based on two independent dimensions. A high positive affect is characterized by full concentration, high energy, and pleasurable engagement whereas low levels of positive affect are linked to sadness and lethargy. Conversely, high negative affect is more likely to be characterized by subjective distress and unpleasurable engagement expressed by moods of anger disgust, guilt, fear, and nervousness whereas a low negative affect is linked to calmness and serenity. [204] PANAS is a self-assessment tool expressed by 20-items of which half the items describe words associated with PA and the rest describe words linked to NA [204,212]. Each item is rated on a five-point Likert scale, ranging from 1 = ‘very slightly or not at all’ to 5 = ‘extremely’. The PANAS enables measuring the extent of individuals’ affect that has been experienced during the past year. Regarding the psychometric properties of the scale, the PANAS can be seen as a reliable (Cronbach’s alpha ranging from .84 to .90) and valid instrument to measure PA and NA.

Example items for PA are words such as ‘active’, ‘interested’, ‘strong’ and for NA words such as ‘nervous’, ‘distresst’ and ‘guilty’. [204,212]

The STAI [205] adapted German version [213] consists of two separate questionnaires, which can be specified separately or together and were used very often in stress and anxiety research. The questionnaires are based on the distinction between fear as a state (state fear) and fear as a trait (trait fear). In this study the latter questionnaire (STAI-T) including 20 items is used to measure self-assessed anxiety at the moment on a 4-point Likert scale, ranging from ‘never’ to ‘almost always’. Since fear, as a relatively persistent personality trait, relates to individual differences in the tendency to fear reactions, sample items include ‘I feel secure’, ‘I am happy’, and ‘I lack self-confidence’. The STAI-T shows satisfactory reliability and validity. [205]

The CES-D scale [206] in the German version [214] was used to measure symptoms of depression on a 4-point Likert scale, ranging from ‘rarely or non of the time’ to ‘most or all of the time’. The scale refers to the last few weeks, contains 20 items and is considered emotional, motivational, cognitive, and somatic as well as having motoric/interactional aspects. CES-D has shown satisfied reliabilities (Cronbach’s alpha ranging from .85 to .92) and validity. Example items include ‘I felt depressed’, ‘I felt sad’, and ‘I enjoyed life’. [206,214]

PERCEIVED STRESS AND COPING

The PSQ-R [207] was used to measure the current experienced stress from a subjective perspective. The original version contained 30 items on seven subscales named harassment, overload, irritability, joy, fatigue, worries, and tension. The German version used in this study was shortened to 20 items on four subscales (worries, tension, joy or reverse coded as lack of joy and demands) . [215] The answer is given on a four-point Likert scale ranging from ‘almost never’ to ‘usually’. Example items are: ‘You feel rested’, ‘You feel tired’, and ‘You feel tense’. Both, the English and the German version of the PSQ can be seen as reliable (Cronbach’s alpha ranging from .80 to .86) and valid instruments. [207,215]

The SVF [208] measures different coping strategies regarding time and situations. The SVF is currently available in several sub-forms, namely SVF-120, SVF-78, SVF-48 and SVF-KJ. The standard form, the SVF-120, contains 120 items in 20 subscales, the SVF-78 contained 13 subscales with 78 items and there is also a special SVF for children (SVF-KJ). The short version SVF-48, being use in this study, consists of 48 items in 8 subscales (deemphasizing, distraction,

control of situations, positive self-instructions, positive use of support, escape, mental occupation, and resignation). The Likert scale ranges from 0 ‘not at all’, to 4 ‘most likely’. Sample items are ‘When I am disturbed, excited or out of balance by anything or anyone’, ‘I tend to find everything senseless’, and ‘I'm trying to talk to someone about the problem’. The SVF can be seen as a reliable (Cronbach’s alpha ranging from .66 to .92.) and valid instrument for assess stress coping. [172,208]

EMOTIONAL COMPETENCE

The SEAS [209; see also 116,185,210] is used to measure self-assessed emotional abilities on a 6-point Likert scale ranging from ‘not true’ to ‘very true’. The scale consists of 49 items on six subscales which refer to the ‘perception of one’s own emotions’ (EE, e.g. ‘I often take a while to recognize my true feelings’), ‘the perception of the emotions of others’ (AE, e.g. ‘I can influence the feelings of others very well’), ‘control over the expression of emotions’ (EC, e.g. ‘In certain situations I cannot suppress my feelings even though I try to’), ‘the masking of emotions’ (M, e.g. ‘If I want I can simulate almost all kinds of feelings’), ‘regulation of one’s own emotions’ (ER, e.g. ‘It is easy for me to change my bad mood’), and ‘the regulation of the emotions of others’ (AR, e.g. ‘I can hardly change the feelings of others’). [209] Subscales of the SEAS show satisfactory internal reliabilities (Cronbach’s alpha ranged from .70 to .85) as well as convergent and discriminant validity [185,209,210].

ADDITIONAL QUESTIONNAIRE

Physical activity was determined by using a standardized German questionnaire, called the Freiburg questionnaire of physical activity—short form. This self-assessment tool enables the recording of activity behaviour and provides information about basic, leisure and training activity in relation to time and energy consumption. The instrument can be considered a reliable and valid tool. [216]

As seen in **Figure 2.2**, the questionnaire used in the first section of the measurement procedure included STAI-T, PANAS, PSQ-R, CES-D and SVF-48, whereas the questionnaire SEAS was queried in the last measurement section. The average duration of filling out several questions was 12.3 minutes for the first section and 8.2 minutes for the last section. Participants required 119.0±38.7 seconds for the STAI-T, 90.3±30.7 seconds for the PANAS, 99.3±30.1 seconds for

the PSQ-R, 134.4±55.0 seconds for the CES-D, 295.3±81.8 seconds for the svf-48, and 494.3±166.7 seconds for the SEAS.

2.2.2. STRESS INDUCED PARADIGM

The paradigm included a 5-min baseline period (rest) which was followed by a 3-min anticipation period (anticipation). Thereafter, a cognitive stressor period (stress) was initiated. After the induced stress, a 5-min recovery period (recovery) was performed, as seen in **Figure 2.2**. This study design consists of an emotion-related element (anticipation period) and a cognitive-related element (verbal learning task). A detailed description of the stress paradigm is also seen in recent research of the research group. [133,134]

EMOTIONAL STRESSOR

After the resting period, an emotional stressor was used to increase the stress level in the anticipatory period. The participants were told that memory function was a sensitive marker for identifying early age-related decline in the brain. Therefore, a memory performance test was presented after this instruction. The results of this test will be assessed by the psychiatric department in order to define if the memory performance matches participants' ages or not. [134]

COGNITIVE STRESSOR

The CVLT-II [128] German adaption [217] was used as moderate stressor and also to assess the cognitive episodic verbal learning performance of participants. The CVLT-II—a standardized verbal memory task—causes a cardiovascular reaction and enables a short assessment of verbal learning strategies and processes [218]. Participants were encouraged to memorize words that had been read out for 20-seconds and to verbally reproduce as many words as possible from a 16-word list. However, the verbal answering of participants started after a 30-second preparation count down. The same procedure was repeated five times and reflected the immediate recall (Trial 1–5; list A). Afterwards, the same process occurs once with an interference list (immediate free recall – list B). Subsequently, word list A is queried after a 30-second waiting period without being read out in advance; it is called short delay free recall (SDFR). Following a break of 20-minutes, during which no verbal test is carried out, the word list A is tested again without being read out in advance; it is called long delay free recall

(LDFR). [134] Regarding the psychometric properties of the CVLT II, previous research reported satisfactory reliability and validity [217]. After the SDFR and the LDFR, the participants were asked to retrospectively rate the subjectively perceived rating in terms of difficulty, effort and strain on a 17-point rating scale ranging from ‘not difficult at all’ to ‘extremely difficult’, from ‘not effort at all’ to ‘extreme effort’ and from ‘no strain at all’ to ‘extreme strain’ as presented in previous research [123,124,133].

As seen in **Figure 2.2**, the paradigm (G-CEST) includes four periods with different lengths of time (rest = t0, anticipation = t1, stress = t2, recovery = t3). To enable at the comparison between the periods, three minutes were used for further analysis in each period. These periods were highlighted in green. The periods of the analysis were chosen in such a way that the first rapid change in physiological parameters in periods t2, and t3 was not included because the transient process of the autonomous control was often dominant in the first section of changes and would bias the analysis. The overall duration of the paradigm excluding questionnaires was approximately 51 minutes, of which the processing time of the CVLT-II was 30.9±3.9 minutes.

2.2.3. RANDOM SEQUENCE GENERATION TEST

During the prescribed time of minimum 20 minutes between SDFR and LDFR of the CVLT-II, the Mittenecker Pointing Test (MPT) [219] was performed to assess cognitive functioning of the participants. The MPT is used to assess the perseverative tendencies with a random sequence generation test. Based on this consideration, the MPT was further developed to a digital program in order to measure random motor generation behaviour automatically and objectively. [220] The participants were invited to type the available keys (prepared keyboard – covering all keys except nine irregular keys) as randomly as possible after an acoustic signal. Two main measures emerged from this computer-based random generation behaviour test. First, the symbol redundancy which *‘refers to the inequality of the relative frequencies of chosen keys’* [220, p. 335] and second, the context redundancy which *‘reflects the extent to which responses are continuously influenced by previously chosen alternatives’* [220, p. 336]. Afterwards, the participants were finally asked to retrospectively rate the individually perceived difficulty in terms of difficulty, effort and strain on a 17-point rating scale [123,124,133] as described above.

2.3. RECORDING OF CARDIOVASCULAR VARIABLES

Continuous haemodynamic monitoring of HR (3-lead electrocardiography, sampling rate = 1kHz), oscillometric and continuous BP (sampling rate = 100 Hz), and thoracic impedance (sampling rate = 100 Hz) was performed with the TFM®; CNSystems, Graz, Austria; Certification CE [TÜV-A-MT- 1/10/1Q034]) [106,221]. The TFM® enables the beat-to-beat signal monitoring of essential haemodynamic parameters and the calculation of essential parameters such as the SI, CI and TPRI. Data processing was fully automated by Matlab (MathWorks Natick, Massachusetts, MA, United States) as seen in previous studies [118,122]. In this study, cardiovascular variables such as BP (SBP, DBP, MAP), SI, CI, TPRI, PEP, LVET, RF and HR were used for further analysis. Finally, HRV variables were used by the origins of the time domain with SDNN [ms], RMSSD [ms] and by using the frequency domain with LF [ms^2], HF [ms^2], and LF/HF ratio [-].

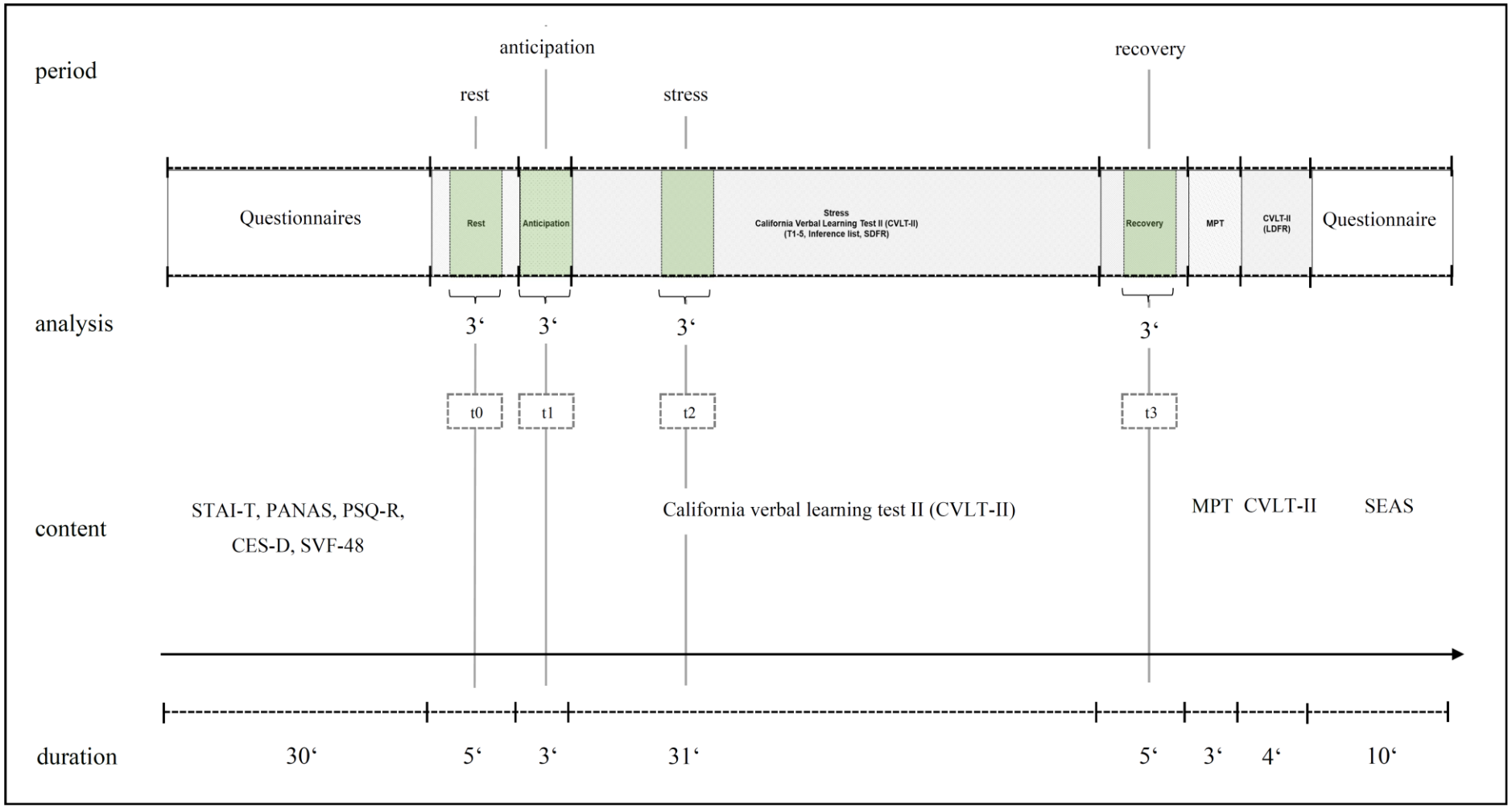

Figure 2.2: Experimental procedure (G-CEST)

2.4. STATISTICAL ANALYSIS

Overall, descriptive statistics are presented as mean ± standard deviation. General results of the sample were analysed by using one-way analysis of variance (ANOVA) for physiological and psychological variables. Differences in cardiovascular condition at baseline and psychosocial factors were compared between groups (sex, age, weight, self-reported physical activity, smoking). Age-related differences at baseline were analysed by three approximately same size age groups using visual binning with 33.33% cut points of the cases. The youngest age group included individuals ≤28 years, the middle age group comprised participants between 29 and 40 years and the oldest age group in this study consisted of individuals ≥41 years. Weight-related differences were defined by BMI into groups of healthy weight with BMI <25.0 kg/m² and overweight with BMI ≥25.0 kg/m². Differences in self-reported physical activity were defined through visual binning with 33.33% cut points of the cases in individuals with low physical activity (≤1.05 hours per week), medium physical activity (1.06-4.00 hours per week) and high physical activity (>4.01 hours per week). All variables except LF and HF were within the range of a normal distribution. Therefore, the parameters were log transformed for further analysis.

Regarding the first research focus including the validation of the G-CEST (paradigm), separate repeated-measures analyses of variance (ANCOVAs) were performed on all cardiovascular outcomes of interest (HR, SBP, DBP, MAP, SI, CI, TPRI, PEP, LVET, RF) using main time points (rest, anticipation, stress, recovery) as the within-subject variable, sex as the between-subject factor and age as a covariate. Additionally, significant results were considered covariation for baseline and testing of the baseline-by-treatment interaction. The Greenhouse–Geisser adjustment was used to correct violations of sphericity. Bonferroni correction for pairwise comparisons was used when probing significant effects. All significant effects were evaluated with (partial) eta squared (η^2) as an indicator of effect size.

Regarding the second research focus of this thesis, multiple hierarchical regression analyses were performed to explore how tonic and phasic HRV (dependent variable) indexed by SDNN, RMSSD, *ln*(LF), *ln*(HF) and LF/HF were influenced by different facets of self-reported psychosocial factors (independent variables) such as mental health, stress perception as well as coping, and emotional competence indicated by different questionnaires used in this study. The tonic HRV refers to the rest condition in baseline. In addition, change scores (Δ) are calculated to quantify reaction and recovery in phasic HRV. Reaction indicates the magnitude

of change between stress (CVLT-II) and baseline (rest). Recovery indicates the magnitude of change between post-stress phase (recovery) and baseline (rest). Thus, the mean values of baseline were subtracted from the mean values during stress task (Δreaction) or from the post-stress period (Δrecovery). The resulting variables were ΔSDNN reaction, ΔRMSSD reaction, Δ*ln*(LF) reaction, Δ*ln*(HF) reaction, ΔLF/HF reaction, ΔSDNN recovery, ΔRMSSD recovery, Δ*ln*(LF) recovery, Δ*ln*(HF) recovery, and ΔLF/HF recovery. All regression analyses contained additional covariates including age (years), BMI (kg/m²) and sex, which were coded in 1 = males and 2 = females. The first step of the respective hierarchical regression consisted of the integration of sociodemographic variables (age, sex, BMI). A facet of mental health was added as the second step. The third step consisted of important subscale of perceived stress and coping. Finally, relevant subscales of emotional competence were added in the last step.

Supplemental analysis including Cronbach's alpha (α) was performed for the reliability of the used questionnaires before integrating them into the hierarchical regression model. A common rule to draw reliable conclusions including reliability of $\alpha \geq .70$ [222]. Further, the Pearson correlation coefficient was used to determine correlations between the different questionnaires used in this study before integrating them into the hierarchical regression model.

All assumptions of the statistical analysis were met or otherwise stated. A two-tailed significance level of $\alpha = .05$ was used for all analyses that were conducted by the IBM SPSS Statistics for Windows (Version 26, Armonk, NY: IBM Corp.).

3. RESULTS

3.1. GENERAL RESULTS OF THE SAMPLE

Resting cardiovascular conditions revealed several differences at baseline. An overview of all cardiovascular differences at baseline was shown in **Table 3.1** and detailed descriptive statistics were demonstrated in **Table 3.2.** Additionally, the cardiovascular differences in baseline were illustrated in **Appendix C, Figure A.1.**

Females showed significantly higher values in SI [$F_{(1,93)} = 14.40$, $p < .001$], CI [$F_{(1,93)} = 16.27$, $p < .001$], RF [$F_{(1,93)} = 5.17$, $p < .05$], RMSSD [$F_{(1,93)} = 4.25$, $p < .05$] and *ln*(HF) [$F_{(1,93)} = 5.61$, $p < .05$], than males did at baseline, whereas TPRI [$F_{(1,93)} = 11.47$, $p < .001$] and LF/HF [$F_{(1,93)} = 17.23$, $p < .001$] were significantly higher in males than in females.

Significant age-related decline were observed in SI [$F_{(2,92)} = 7.63$, $p \leq .001$], CI [$F_{(2,92)} = 14.86$, $p < .001$], SDNN [$F_{(2,92)} = 18.45$, $p < .001$], RMSSD [$F_{(2,92)} = 14.72$, $p < .001$], *ln*(LF) [$F_{(2,92)} = 13.23$, $p < .001$], and in *ln*(HF) [$F_{(2,92)} = 23.26$, $p < .001$], whereas TPRI [$F_{(2,92)} = 8.86$, $p < .001$], LVET [$F_{(2,92)} = 3.94$, $p < .05$], and LF/HF [$F_{(2,92)} = 3.71$, $p < .05$] increased with age. Post hoc test revealed that the youngest age group differed significantly from the oldest age group in SI ($p < .001$), CI ($p < .001$), TPRI ($p < .001$), LVET ($p < .05$), SDNN ($p < .001$), RMSSD ($p < .001$), *ln*(LF) ($p < .001$), *ln*(HF) ($p < .001$), and LF/HF ($p < .001$). Further, the youngest age group and the middle age group differed significantly in CI ($p < .01$). Also, the middle age group differed significantly from the oldest age group in SDNN ($p < .001$), RMSSD ($p < .01$), *ln*(LF) ($p < .001$), and *ln*(HF) ($p < .001$).

Overweight individuals differed statistically significantly at higher levels of SBP [$F_{(1,93)} = 11.80$, $p < .001$], MAP [$F_{(1,93)} = 9.42$, $p < .01$], DBP [$F_{(1,93)} = 7.49$, $p < .01$], TPRI [$F_{(1,93)} = 29.86$, $< .001$], and in LF/HF [$F_{(1,93)} = 6.81$, $p \leq .01$]; and at significantly lower levels in SI [$F_{(1,93)} = 21.98$, $< .001$] and CI [$F_{(1,93)} = 26.27$, $< .001$].

Moreover, several significant differences in self-reported physical activity were observed in baseline. The analysis showed HR [$F_{(2,89)} = 6.12$, $p < .01$], SBP [$F_{(2,89)} = 6.44$, $p < .01$], MAP [$F_{(2,89)} = 5.05$, $p < .01$], and DBP [$F_{(2,89)} = 4.08$, $p < 0.05$] with lowest values in individuals with medium physical activity. Post hoc test revealed that HR at baseline was the highest in the low physical activity group and differed significantly from the medium physical activity group ($p < .001$) and from the low-to-high physical activity group ($p < .05$) with higher values in higher physical active individuals. SBP differs significantly between low physical activity and medium

physical activity individuals ($p < .05$) with higher values in low physical activity individuals and from medium physical activity to high physical activity group ($p < .001$) with higher values in the higher physical activity group. Post hoc test in MAP revealed that the low physical activity group differed significantly from the medium physical activity group ($p < .05$) with higher values in the low physical activity group and from medium physical activity to high physical activity individuals ($p < .001$) with higher values in the high physical activity group. Further, DBP differed significantly from medium physical activity to high physical activity group ($p < .05$) with higher values in the high physical activity group.

The level of resting HR [$F_{(1,84)} = 6.76$, $p \leq .01$] and RF [$F_{(1,84)} = 11.28$, $p \leq .001$] was significantly higher in smoking participants than in non-smoking individuals at baseline, whereas PEP [$F_{(1,84)} = 4.61$, $p < .05$] was lower in smoking individuals than in non-smoking individuals.

Table 3.1: Cardiovascular differences at baseline

Physiological variables	Total
ECG	
HR [bpm]	71.36±10.31[d,e]
SDNN [ms]	44.52±21.32[b]
RMSSD [ms]	34.70±21.05[a,b]
ln(LF) [ms²]	6.23±1.08[b]
ln(HF) [ms²]	5.74±1.31[a,b]
LF/HF ratio [-]	0.48±1.01[a,b,c]
Continuous BP	
SBP [mmHg]	110.36±11.73[c,d]
MAP [mmHg]	87.95±10.22[c,d]
DBP [mmHg]	72.31±9.38[c,d]
ICG	
SI [ml/m^2]	39.69±8.03[a,b,c]
CI [l/(min/m^2)]	2.80±0.57[a,b,c]
TPRI [dyne*s*m^2/cm^5]	2555.96±746.53[a,b,c]
PEP [ms]	123.62±8.29[e]
LVET [ms]	296.61±22.49[b]
RF [breath per minute]	14.79±3.14[a,e]

Absolute values are mean ± standard deviation, n = 95, $p < .05$. [a] Main effect of sex, [b] Main effect of age groups, [c] Main effect of weight, [d] Main effect of physical activity levels, [e] Main effect of smoking.

Table 3.2: Descriptive cardiovascular values at baseline

Physiological variables	Sex		Age group			Weight	
	males	females	youngest	middle	oldest	healthy weight	overweight
	n = 34	n = 61	n = 35	n = 29	n = 31	n = 66	n = 29
ECG							
HR [bpm]	70.46±8.68	71.86±11.16	73.51±11.02	70.63±10.37	69.62±9.29	71.73±11.07	70.53±8.45
SDNN [ms]	43.22±21.57	45.25±21.33	56.45±23.95	46.38±17.73	29.33±8.56	45.17±21.40	43.06±21.46
RMSSD [ms]	28.84±15.61	37.97±23.02	45.84±24.38	35.78±17.36	21.11±9.85	35.53±18.97	32.81±25.44
ln(LF) [ms²]	6.34±1.27	6.16±.97	6.65±1.05	6.49±1.07	5.50±.73	6.21±1.10	6.27±1.07
ln(HF) [ms²]	5.33±1.18	5.98±1.33	6.51±1.13	5.92±1.05	4.72±1.05	5.90±1.20	5.39±1.50
LF/HF ration [-]	1.02±1.00	.19±.90	.14±1.07	.57±.95	.79±.91	.31±.96	.88±1.03
Continuous BP							
SBP [mmHg]	111.85±13.35	109.53±10.74	109.75±9.34	110.62±14.87	110.81±11.18	107.77±10.44	116.26±12.51
MAP [mmHg]	88.40±12.37	87.71±8.90	86.28±8.85	88.03±11.45	89.78±10.45	85.91±9.27	92.60±10.89
DBP [mmHg]	73.15±11.17	71.84±8.29	70.08±8.51	72.40±9.91	74.75±9.50	70.62±8.72	76.16±9.85
ICG							
SI [ml/m^2]	35.77±6.43	41.88±8.05	43.27±7.89	39.27±7.22	36.05±7.37	42.01±7.45	34.42±6.81
CI [l/(min/m$^{2)}$]	2.51±.49	2.97±.54	3.14±.52	2.76±.54	2.47±.42	2.98±.52	2.41±.46
TPRI [dyne*s* m^2/cm^5]	2885.50±955.96	2372.27±524.06	2205.02±542.58	2590.15±758.82	2920.18±770.22	2313.29±580.02	3108.23±797.02
PEP [ms]	123.05±7.50	123.94±8.74	123.21±7.21	124.13±8.38	123.60±9.51	123.69±7.99	123.46±9.09
LVET [ms]	294.13±20.09	297.99±23.77	290.18±21.75	295.26±22.93	305.12±20.79	294.87±23.02	300.55±21.07
RF [breath per minute]	13.83±2.83	15.33±3.20	14.41±3.27	14.16±3.17	15.81±2.79	14.68±3.03	15.05±3.42

Table 3.2: Descriptive cardiovascular values at baseline (continued)

Physiological variables	Self-reported physical activity			Smoking status	
	low n = 31	medium n = 33	high n = 28	smoker n =24	non-smoker n = 62
ECG					
HR [bpm]	76.26±11.66	67.94±8.89	69.81±8.79	75.84±11.88	69.70±8.93
SDNN [ms]	41.78±20.74	47.52±21.72	43.34±21.18	37.22±17.82	46.83±22.53
RMSSD [ms]	34.16±24.96	37.04±20.22	32.73±18.09	27.71±17.12	35.98±21.43
ln(LF) [ms²]	6.05±.95	6.33±1.11	6.26±1.15	5.94±.92	6.35±1.17
ln(HF) [ms²]	5.75±1.45	5.88±1.31	5.57±1.22	5.29±1.32	5.81±1.30
LF/HF ration [-]	.30±.93	.45±1.10	.68±1.03	.65±.86	.54±1.06
Continuous BP					
SBP [mmHg]	111.84±10.95	105.04±11.03	114.83±11.02	110.29±12.06	110.44±11.80
MAP [mmHg]	89.71±9.06	83.73±10.18	91.06±9.88	87.76±10.25	88.26±10.27
DBP [mmHg]	74.10±8.47	68.75±9.54	74.62±9.04	72.24±9.16	72.87±9.40
ICG					
SI [ml/m^2]	38.50±8.22	42.46±7.65	38.47±7.59	37.60±6.82	40.27±8.44
CI [l/(min/$m^{2)}$]	2.90±.61	2.86±.53	2.67±.52	2.82±.52	2.78±.56
TPRI [dyne*s* m^2/cm^5]	2512.88±611.86	2367.76±697.80	2778.94±849.84	2495.51±585.89	2595.08±797.07
PEP [ms]	121.98±9.74	125.84±5.83	122.60±9.08	120.58±9.86	124.89±7.71
LVET [ms]	292.05±25.11	300.82±19.12	297.17±22.95	292.59±25.55	298.04±21.38
RF [breath per minute]	15.33±3.04	14.30±2.64	14.97±3.71	16.52±2.93	14.06±3.10

GENERAL PSYCHOSOCIAL RESULTS

Females reported significant lower scores in psqr worries [$F_{(1,93)} = 4.27$, $p < .05$] compared to males. However, no age-related differences in psychological aspects were found.

The analysis showed significant weight-related differences whereas overweight individuals showed lower levels of svf mental occupation [$F_{(1,93)} = 5.05$, $p < .05$].

The analysis differed between physical activity levels in PA [$F_{(2,89)} = 4.27$, $p < .05$], psqr joy [$F_{(2,89)} = 5.79$, $p < .001$], and svf deemphasizing [$F_{(2,89)} = 5.39$, $p < .001$]. Post hoc test revealed significant differences in PA among individuals with low levels to high levels of self-reported physical activity ($p < .001$) with higher values in higher physical activity individuals. In the subscale joy, the groups showed significant differentiations between groups of low levels to high levels of self-reported physical activity ($p < .001$) with higher values in the high physical activity group, and from medium self-reported physical activity to high levels of self-reported physical activity ($p < .001$) with higher values in high physical activity individuals. Additionally, in the subscale of svf deemphasizing, post hoc test showed that individuals with medium levels of self-reported physical activity differ from those with high physical activity levels ($p < .001$), with higher values in the high physical activity group.

Smoking individuals showed significant lower scores in PA [$F_{(1,84)} = 9.38$, $p < .001$] and psqr joy [$F_{(1,84)} = 5.64$, $p < .05$], but significantly higher scores in psqr tension [$F_{(1,84)} = 3.97$, $p < .05$].

Detailed information about psychosocial values is presented in **Tables 3.3** and **3.5**. All significant effects of the sociodemographic differences in general and of psychosocial factors were shown in **Appendix C, Figure A.2**.

PSYCHOLOGICAL PARAMETERS

Regarding scale reliability, all scales and subscales of mental health indicated by PANAS, STAI-T and CES-D fulfilled the reliability criterion of being greater than .70. Reliability analysis of the perception of stress indexed by subscales of PSQ-R, and of coping strategies indicated by subscales of SVF-48 showed that all subscales except one, named ‘control of situations’ ($\alpha = .67$), met the reliability criterion. The reliability of emotional competence indicated by subscales of SEAS was limited and only half of the subscales (EC, ER, and AR) exceeded the required criterion for internal consistency. However, the subscales EE, AE, and M fulfilled the reliability criterion of ≥ .70. Overall, the reliability for all scales and subscales

are seen in **Table 3.3**. All subscales with reliability lower than .70 were excluded for further analysis. Detailed information about all items of the subscales is given in **Appendix C, Table A.1**. Finally, a correlation analysis showed high correlations among CES-D, PA, NA, psqr tension, psqr worries, svf escape, and svf resignation with STAI-T, which is demonstrated in **Table 3.4**. All subscales with correlations >.40 were excluded from further analysis to avoid multicollinearity. Further, since the research focused on negative coping strategies, the subscales svf joy, svf deemphasizing, svf distraction, svf positive self-instructions and svf positive use of support were excluded from further analysis.

Table 3.3: Characteristics of the questionnaires

Psychological parameters	Total	Cronbach alpha
STAI-T	32.43±6.74	.86
PA	36.96±5.12[d,e]	.81
NA	15.55±4.82	.84
CES-D	8.07±6.32	.83
psqr worries	0.18±0.16[a]	.77
psqr tension	0.26±0.17[e]	.71
psqr joy	0.76±0.18[d,e]	.76
psqr demands	0.30±0.19	.74
svf deemphasizing	12.37±4.61[d]	.86
svf distraction	13.07±4.26	.80
svf control of situations	18.03±3.06	.67[†]
svf positive self-instructions	19.30±3.60	.84
svf positive use of support	15.76±4.52	.87
svf escape	6.41±4.71	.89
svf mental occupation	13.15±6.00[c]	.93
svf resignation	5.20±3.63	.81
seas EE	40.56±5.59	.73
seas AE	48.15±6.45	.83
seas EC	25.88±4.82	.53[†]
seas M	27.46±6.37	.77
seas ER	24.43±4.32	.67[†]
seas AR	33.83±4.46	.60[†]

Absolute values are mean ± standard deviation, n = 95, p< .05. [a] Main effect of sex. [b] Main effect of age groups. [c] Main effect of weight. [d] Main effect of self-reported physical activity, [e] Main effect of smoking; [†] $\alpha \leq .70$ and were excluded from further analysis.

Table 3.4: Correlation of the questionnaires

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
(1) STAI-T	1	-.43**	.61**	.65**	.68**	-.63**	.29**	.64**	-.20	-.06	-.36**	-.07	.48**	.35**	.59**	-.32**	.11	.17
(2) PA		1	-.04	-.27**	-.30**	.59**	-.03	-.26**	.09	.07	.46**	.22*	-.28**	-.17	-.41**	.24*	.23*	-.09
(3) NA			1	.43**	.46**	-.25*	.22*	.53**	-.12	-.05	-.17	.06	.46**	.43**	.44**	-.33**	.14	.12
(4) psqr worries				1	.66**	-.56**	.50**	.64**	-.12	-.15	-.30**	-.09	.44**	.35**	.49**	-.19	.04	.17
(5) psqr tension					1	-.66**	.54**	.66**	-.12	-.18	-.22*	-.03	.28**	.35**	.37**	-.09	.14	.08
(6) psqr joy						1	-.28**	-.50**	.22*	.22*	.31**	.21*	-.23*	-.26*	-.32**	.18	.14	-.06
(7) psqr demands							1	.34**	-.01	-.08	-.10	.14	.15	.08	.12	-.05	.07	-.14
(8) CES-D								1	-.19	-.13	-.33**	.08	.44**	.42**	.53**	-.23*	.16	.06
(9) svf deemphasizing									1	.02	.23*	-.17	-.04	-.28**	-.16	-.03	.08	.14
(10) svf distraction										1	.17	.20	.20	.16	.08	-.16	.03	.03
(11) svf positive self-instructions											1	.13	-.30**	-.04	-.43**	.26*	.17	-.00
(12) svf positive use of support												1	.08	.17	.12	.09	.17	-.10
(13) svf escape													1	.46**	.73**	-.38**	-.06	.17
(14) svf mental occupation														1	.66**	-.23*	.11	.17
(15) svf resignation															1	-.42**	-.02	.08
(16) seas EE																1	.28**	.05
(17) seas AE																	1	.21*
(18) seas M																		1

The correlation is significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

☐ Small effect (≤ .3) ▒ Medium effect (.5 ≤ *r* > .3) ■ Large effect (> .5)

Table 3.5: Descriptive psychosocial values

Scales/Subscales	Sex		Age group			Weight	
	males	**females**	**youngest**	**middle**	**oldest**	**healthy weight**	**overweight**
	n = 34	n = 61	n = 35	n = 29	n = 31	n = 66	n = 29
STAI-T	32.24±7.25	32.54±6.49	32.66±6.49	32.45±6.20	32.16±7.65	33.30±6.94	30.45±5.88
PA	37.41±4.25	36.70±5.56	38.26±3.83	37.00±5.99	35.45±5.26	36.74±5.53	37.45±4.09
NA	15.79±4.36	15.41±5.08	15.69±5.28	15.52±3.48	15.42±5.45	15.89±5.40	14.76±3.04
CES-D	8.44±6.65	7.87±6.18	8.23±5.39	8.28±6.69	7.71±7.10	8.42±6.40	7.28±6.18
psqr worries	.23±.20	.15±.14	.16±.14	.20±.19	.18±.16	.17±.15	.19±.19
psqr tension	.27±.19	.25±.16	.24±.15	.30±.19	.24±.18	.25±.17	.28±.18
psqr joy	.74±.18	.77±.18	.78±.14	.71±.20	.77±.19	.75±.18	.78±.17
psqr demands	.33±.21	.29±.17	.26±.13	.36±.20	.30±.22	.29±.19	.32±.19
svf deemphasizing	13.47±4.31	11.75±4.69	11.66±5.11	13.21±4.79	12.39±3.78	11.92±4.70	13.38±4.32
svf distraction	12.21±3.25	13.56±4.68	12.43±4.95	12.59±4.20	14.26±3.21	12.70±4.56	13.93±3.39
svf positive self-instructions	18.61±3.21	19.67±3.77	19.21±3.70	18.83±4.16	19.84±2.91	19.22±3.92	19.48±2.81
svf positive use of support	14.79±3.90	16.30±4.78	16.03±4.35	14.76±5.72	16.39±3.27	16.33±4.03	14.45±5.34
svf escape	6.88±5.34	6.15±4.34	6.09±4.73	6.24±4.44	6.94±5.02	6.68±4.88	5.79±4.30
svf mental occupation	12.24±5.85	13.66±6.07	13.51±6.83	13.17±5.59	12.71±5.52	14.05±6.36	11.10±4.56
svf resignation	5.56±3.49	5.00±3.72	4.97±3.50	5.10±3.62	5.55±3.87	5.58±3.80	4.34±3.10
seas EE	40.18±6.27	40.77±5.23	41.29±6.09	41.07±4.43	39.29±5.94	40.26±5.68	41.24±5.43
seas AE	47.52±7.04	48.49±6.13	49.18±6.35	47.79±6.32	47.35±6.73	48.12±5.78	48.21±7.85
seas M	27.88±6.40	27.23±6.40	28.15±6.99	27.00±5.64	27.13±6.46	27.37±5.99	27.68±7.30

Table 3.5: Descriptive psychosocial values (continued)

Scales/Subscales	Self-reported physical activity			Smoking status	
	low	medium	high	smoker	non-smoker
	n = 31	n = 33	n = 28	n =24	n = 62
STAI-T	33.19±6.68	33.82±6.67	30.11±6.51	33.42±7.23	31.69±6.78
PA	35.10±6.00	37.12±4.51	38.89±4.25	34.21±5.00	37.94±5.09
NA	15.68±4.36	16.42±5.79	14.54±4.12	15.42±4.85	15.63±5.00
CES-D	8.61±5.24	9.27±8.28	6.36±4.48	8.96±6.45	7.73±6.35
psqr worries	.18±.16	.21±.19	.14±.14	.21±.17	.16±.16
psqr tension	.28±.15	.28±.21	.21±.15	.31±.16	.23±.17
psqr joy	.72±.17	.72±.20	.86±.11	.70±.20	.79±.17
psqr demands	.31±.21	.32±.19	.28±.16	.34±.20	.29±.19
svf deemphasizing	12.13±4.46	10.73±3.88	14.46±5.03	11.79±4.05	12.69±4.42
svf distraction	12.71±4.82	12.58±3.55	13.86±4.54	13.25±4.08	13.18±4.23
svf positive self-instructions	19.26±4.49	19.00±3.13	19.93±3.13	18.26±3.51	19.66±3.57
svf positive use of support	16.06±5.13	16.55±3.38	14.71±4.93	15.25±3.84	16.32±4.71
svf escape	6.29±3.87	7.24±4.82	5.54±5.55	6.38±5.44	6.27±4.45
svf mental occupation	13.13±6.46	14.12±5.47	12.11±6.06	13.33±6.90	12.84±5.64
svf resignation	5.55±3.70	5.52±3.55	4.36±3.81	5.33±4.09	5.11±3.70
seas EE	40.23±6.16	40.45±5.35	41.11±5.64	40.61±5.80	40.29±5.42
seas AE	47.45±7.26	47.58±6.55	49.89±5.36	47.52±6.13	48.31±6.47
seas M	27.71±6.67	27.84±5.66	26.61±7.20	28.58±6.45	26.35±6.18

3.2. VALIDATION OF THE NEW PARADIGM (G-CEST)

The repeated measures ANCOVA's determined that cardiovascular parameters showed a statistically significant difference along the periods (rest, anticipation, stress, recovery) in HR [$F_{(1.53,140.74)} = 23.85$, $p < .001$, $\eta^2 = .21$], SBP [$F_{(2.29,210.59)} = 13.58$, $p < .001$, $\eta^2 = .13$], MAP [$F_{(2.35,216.26)} = 12.11$, $p < .001$, $\eta^2 = .12$], DBP [$F_{(2.53,232.97)} = 9.13$, $p < .001$, $\eta^2 = .09$], SI [$F_{(2.49,228.99)} = 4.94$, $p < .001$, $\eta^2 = .05$]; in addition an age-related interaction were observed in SI [$F_{(2.49,228.99)} = 4.04$, $p < .001$, $\eta^2 = .04$]. Further, main effects among the periods were found in CI [$F_{(1.62,149.36)} = 10.89$, $p < .001$, $\eta^2 = .11$], PEP [$F_{(1.48,136.48)} = 7.55$, $p < .01$, $\eta^2 = .08$], LVET [$F_{(2.26,207.57)} = 4.96$, $p < .01$, $\eta^2 = .05$], RF [$F_{(2.08,191.05)} = 15.07$, $p < .001$, $\eta^2 = .14$] and also in addition an age-related interaction [$F_{(2.08,191.05)} = 4.83$, $p < .01$, $\eta^2 = .05$] and a sex-related interaction [$F_{(2.08,191.05)} = 5.69$, $p < .01$, $\eta^2 = .06$] were observed in RF. No significant difference between the main time points were found in TPRI [$F_{(2.43,223.30)} = 1.50$, $p = .22$]. An overview of all the data of the paradigm is seen in **Table 3.6.**

Bonferroni-corrected pairwise comparisons revealed that HR, SBP, MAP, DBP and CI increased from rest to anticipatory phase ($p < .05$), continued to increase from anticipatory phase to stress task ($p < .001$) and decreased from stress reaction to recovery ($p < .001$). No difference between rest and recovery period was observed in HR ($p = .34$) and CI ($p > .99$), whereas significant differences ($p < .001$) between baseline and recovery were seen in SBP, MAP, and DBP. Further, PEP and LVET decreased significantly from anticipation to stress ($p < .001$) and increased from stress response to recovery ($p < .001$). However, no significant effects were observed from rest to anticipation or between rest and recovery. RF increased significantly ($p < .001$) from anticipation to stress followed by a significant decrease ($p < .001$) from stress to recovery. No other significant pairwise comparisons were observed in RF. Finally, no significant Bonferroni-corrected pairwise comparisons were observed in SI.

The different significant cardiovascular reactivity pattern observed along the G-CEST is seen in **Figure 3.1**.

Table 3.6: Validation of the paradigm - overview of all effects

Origin	Variable	Rest	Anticipation	Stress	Recovery		F statistics
ECG	**HR**	71.36±10.31	73.12±10.65	79.57±11.99	71.92±10.12	**period**	$\mathbf{F_{(1.53,140.74)} = 23.85, p < .001, \eta^2 = .21}$
						period x age	$F_{(1.53,140.74)} = 3.13, p = .06$
						period x sex	$F_{(1.53,140.74)} = 2.48, p = .10$
Continuous BP	**SBP**	110.36±11.73	113.71±12.22	121.57±12.91	115.05±11.46	**period**	$\mathbf{F_{(2.29,210.59)} = 13.58, p < .001, \eta^2 = .13}$
						period x age	$F_{(2.29,210.59)} = .77, p = .51$
						period x sex	$F_{(2.29,210.59)} = .66, p = .54$
Continuous BP	**MAP**	87.95±10.22	90.20±10.46	96.65±10.81	91.69±9.85	**period**	$\mathbf{F_{(2.35,216.26)} = 12.11, p < .001, \eta^2 = .12}$
						period x age	$F_{(2.35,216.26)} = .61, p = .57$
						period x sex	$F_{(2.35,216.26)} = 1.71, p = .18$
Continuous BP	**DBP**	72.31±9.38	74.09±9.55	79.35±9.72	75.51±9.20	**period**	$\mathbf{F_{(2.53,232.97)} = 9.13, p < .001, \eta^2 = .09}$
						period x age	$F_{(2.53,232.97)} = .71, p = .52$
						period x sex	$F_{(2.53,232.97)} = 2.72, p = .06$

Table 3.6: Validation of the paradigm - overview of all effects (continued)

Origin	Variable	Rest	Anticipation	Stress	Recovery		F statistics
ICG	**SI**	39.69±8.03	39.30±7.92	39.02±7.57	39.34±8.12	**period**	**$F_{(2.49,228.99)} = 4.94, p < .01, \eta^2 = .05$**
						period x age	**$F_{(2.49,228.99)} = 4.04, p < .001, \eta^2 = .04$**
						period x sex	$F_{(2.49,228.99)} = 1.99, p = .13$
ICG	**CI**	2.80±0.57	2.84±0.57	3.07±.64	2.79±.54	**period**	**$F_{(1.62,149.36)} = 10.89, p < .001, \eta^2 = .11$**
						period x age	$F_{(1.62,149.36)} = .97, p = .41$
						period x sex	$F_{(1.62,149.36)} = .96, p = .37$
ICG	**TPRI**	2555.96±746.53	2584.80±735.98	2568.12±689.16	2670.87±750.11	period	$F_{(2.43,223.30)} = 1.50, p = .22$
						period x age	$F_{(2.43,223.30)} = 1.55, p = .21$
						period x sex	$F_{(2.43,223.30)} = 2.50, p = .07$
ICG	**PEP**	123.62±8.29	122.95±8.07	117.97±11.02	123.79±7.52	**period**	**$F_{(1.48,136.48)} = 7.55, p < .01, \eta^2 = .08$**
						period x age	$F_{(1.48,136.48)} = .60, p = .50$
						period x sex	$F_{(1.48,136.48)} = .41, p = .60$
ICG	**LVET**	296.61±22.49	294.88±22.09	290.54±22.79	298.07±23.07	**period**	**$F_{(2.26,207.57)} = 4.96, p < .01, \eta^2 = .05$**
						period x age	$F_{(2.26,207.57)} = 1.12, p = .33$
						period x sex	$F_{(2.26,207.57)} = 1.66, p = .19$
ICG	**RF**	14.79±3.14	15.01±2.96	16.55±2.90	15.04±2.95	**period**	**$F_{(2.08,191.05)} = 15.07, p < .001, \eta^2 = .14$**
						period x age	**$F_{(2.08,191.05)} = 4.83, p < .01, \eta^2 = .05$**
						period x sex	**$F_{(2.08,191.05)} = 5.69, p < .01, \eta^2 = .06$**

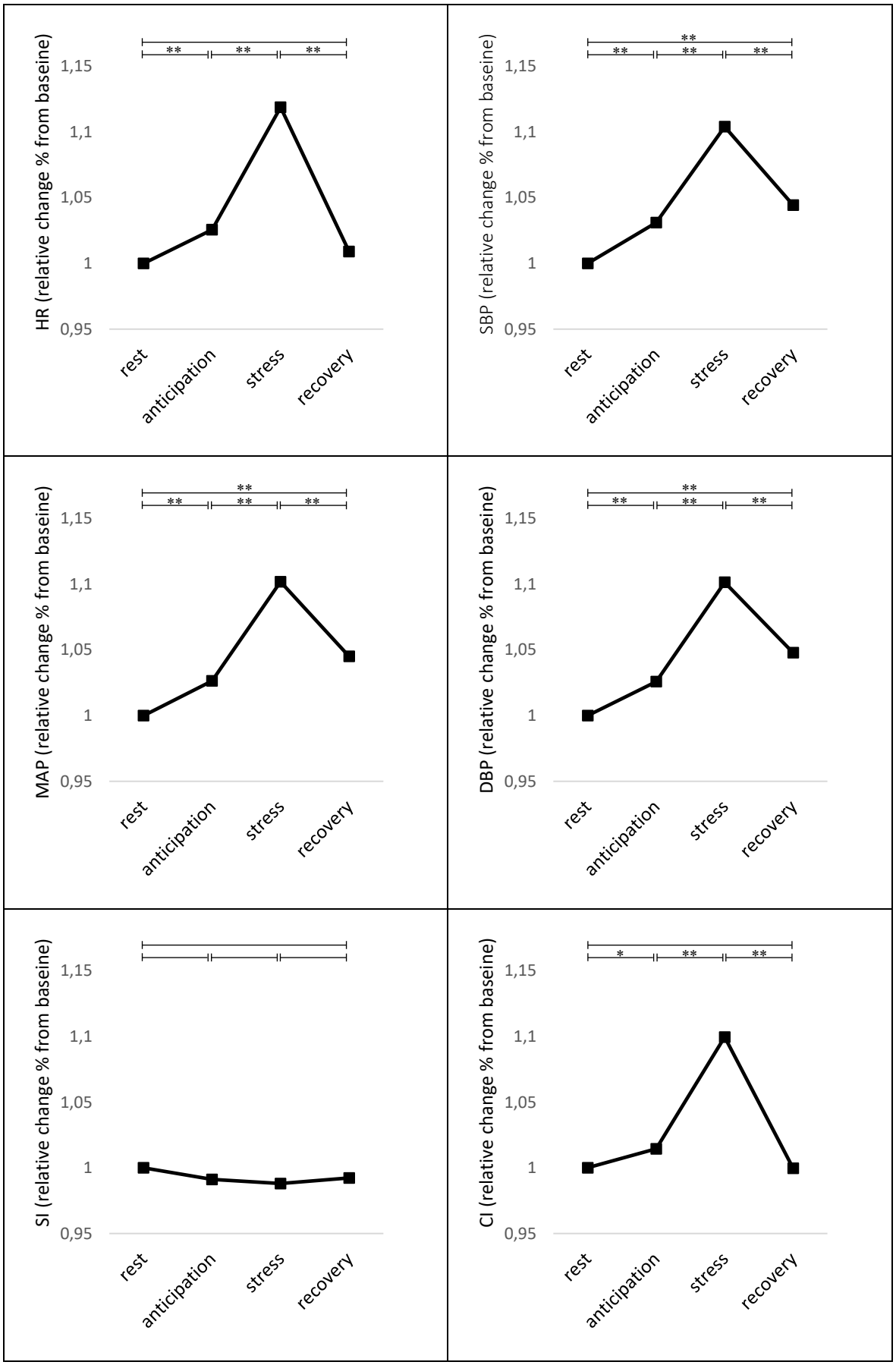

Figure 3.1: Cardiovascular parameter along the paradigm

Significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

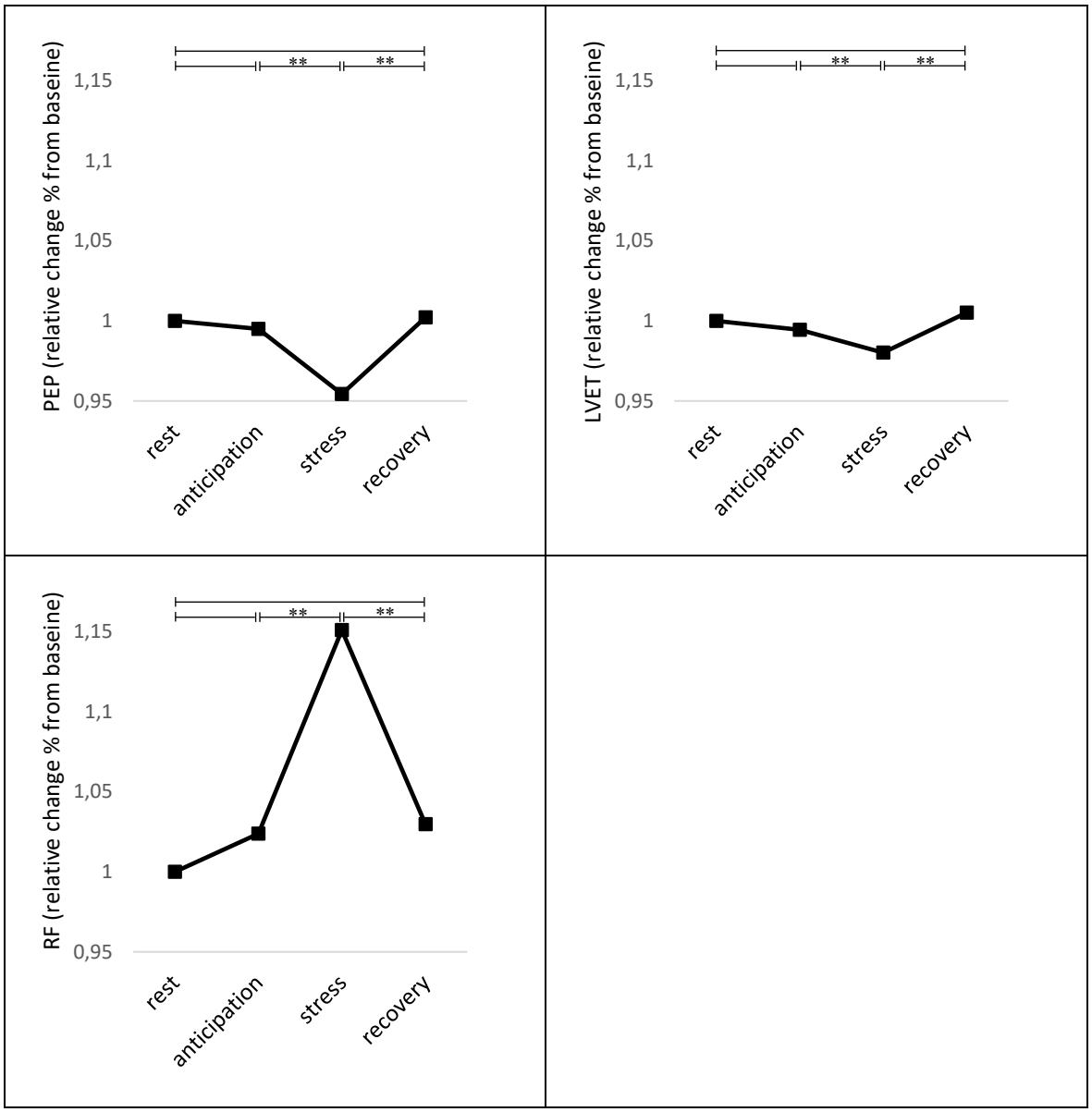

Figure 3.1: Cardiovascular parameter along the paradigm (continued)

Significant at the level of * p <.05 (2-sided) and ** p <.01 (2-sided).

As seen in **Table 3.7**, when controlling for baseline, the repeated measures ANCOVAs determined that cardiovascular parameters showed a statistically significant difference along the periods (anticipation, stress, recovery) in HR [$F_{(1.29,117.02)} = 7.21$, $p < .001$, $\eta^2 = .07$], SBP [$F_{(1.81,165.04)} = 3.48$, $p < .05$, $\eta^2 = .04$], MAP [$F_{(1.87,169.98)} = 4.50$, $p < .001$, $\eta^2 = .05$], DBP [$F_{(2,182)} = 4.63$, $p < .001$, $\eta^2 = .05$], TPRI [$F_{(1.84,167.25)} = 5.06$, $p < .01$, $\eta^2 = .05$], and RF [$F_{(1.63,148.05)} = 23.26$, $p < .001$, $\eta^2 = .20$]. Moreover, interaction effects of period with baseline were seen in TPRI [$F_{(1.84,167.25)} = 5.61$, $p < .001$, $\eta^2 = .05$], LVET [$F_{(1.74,157.88)} = 3.76$, $p < .05$, $\eta^2 = .04$], and RF [$F_{(1.63,148.05)} = 9.65$, $p < .001$, $\eta^2 = .10$].

Table 3.7: Validation of the paradigm - overview of all effects (adjusted for baseline)

Origin	Variable	Anticipation	Stress	Recovery		F statistics
ECG	**HR**	73.12±10.65	79.57±11.99	71.92±10.12	**period**	$\mathbf{F_{(1.29,117.02)} = 7.21, p < .001, \eta^2 = .07}$
					period x age	$F_{(1.29,117.02)} = 3.23, p = .06$
					period x sex	$F_{(1.29,117.02)} = 3.10, p = .07$
					period x HRR	$F_{(1.29,117.02)} = 1.02, p = .33$
Continuous BP	**SBP**	113.71±12.22	121.57±12.91	115.05±11.46	**period**	$\mathbf{F_{(1.81,165.04)} = 3.48, p < .05, \eta^2 = .04}$
					period x age	$F_{(1.81,165.04)} = .48, p = .60$
					period x sex	$F_{(1.81,165.04)} = .79, p = .44$
					period x SBPR	$F_{(1.81,165.04)} = 1.71, p = .19$
Continuous BP	**MAP**	90.20±10.46	96.65±10.81	91.69±9.85	**period**	$\mathbf{F_{(1.87,169.98)} = 4.50, p < .001, \eta^2 = .05}$
					period x age	$F_{(1.87,169.98)} = 13.21, p = .46$
					period x sex	$F_{(1.87,169.98)} = 1.88, p = .17$
					period x MAPR	$F_{(1.87,169.98)} = 2.42, p = .10$
Continuous BP	**DBP**	74.09±9.55	79.35±9.72	75.51±9.20	**period**	$\mathbf{F_{(2,182)} = 4.63, p < .001, \eta^2 = .05}$
					period x age	$F_{(2,182)} = 1.20, p = .30$
					period x sex	$F_{(2,182)} = 3.00, p = .06$
					period x DBPR	$F_{(2,182)} = 3.01, p = .06$
ICG	**SI**	39.30±7.92	39.02±7.57	39.34±8.12	period	$F_{(2,182}= .88, p = .92$
					period x age	$F_{(2,182)} = 2.51, p = .08$
					period x sex	$F_{(2,182)} = 1.81, p = .17$
					period x SIR	$F_{(2,182)} = 1.86, p = .16$

Table 3.7: Validation of the paradigm - overview of all effects (adjusted for baseline) (continued)

Origin	Variable	Anticipation	Stress	Recovery		F statistics
ICG	**CI**	2.84±.57	3.07±.64	2.79±.54	period	$F_{(1.37,124.31)} = .23$, $p = .80$
					period x age	$F_{(1.37,124.31)} = .29$, $p = .66$
					period x sex	$F_{(1.37,124.31)} = .41$, $p = .59$
					period x CIR	$F_{(1.37,124.31)} = 1:24$, $p = .28$
ICG	**TPRI**	2584.80±735.98	2568.12±689.16	2670.87±750.11	**period**	$\mathbf{F_{(1.84,167.25)} = 5.06, p < .01, \eta^2 = .05}$
					period x age	$F_{(1.84,167.25)} = .37$, $p = .67$
					period x sex	$F_{(1.84,167.25)} = 1.90$, $p = .16$
					period x TPRIR	$\mathbf{F_{(1.84,167.25)} = 5.61, p < .001, \eta^2 = .05}$
ICG	**PEP**	122.95±8.07	117.97±11.02	123.79±7.52	period	$F_{(1.37,124.74)} = 2.94$, $p = .08$
					period x age	$F_{(1.37,124.74)} = .38$, $p = .60$
					period x sex	$F_{(1.37,124.74)} = .28$, $p = .67$
					period x PEPR	$F_{(1.37,124.74)} = .38$, $p = .60$
ICG	**LVET**	294.88±22.09	290.54±22.79	298.07±23.07	period	$F_{(1.74,157.88)} = 1.81$, $p = .17$
					period x age	$F_{(1.74,157.88)} = 2.40$, $p = .10$
					period x sex	$F_{(1.74,157.88)} = 1.67$, $p = .20$
					period x LVET	$\mathbf{F_{(1.74,157.88)} = 3.76, p < .05, \eta^2 = .04}$
ICG	**RF**	15.01±2.96	16.55±2.90	15.04±2.95	**period**	$\mathbf{F_{(1.63,148.05)} = 23.26, p < .001, \eta^2 = .20}$
					period x age	$F_{(2.08,191.05)} = 2.05$, $p = .14$
					period x sex	$F_{(2.08,191.05)} = 1.95$, $p = .15$
					period x RFR	$\mathbf{F_{(1.63,148.05)} = 9.65, p < .001, \eta^2 = .10}$

3.3. CARDIOVASCULAR CONDITION AND PSYCHOSOCIAL FACTORS

Based on preliminary considerations including the integration of questionnaires with reliability ≥ .70 (exclusion of seas ER, seas EC, seas AR, svf control of situations), low correlations of independent variables (exclusion of CES-D, PA, NA, psqr tension, psqr worries, svf escape, svf resignation because of their high correlations with STAI-T) and the focus on the research hypothesis (exclusion of subscales psqr joy, svf deemphasizing, svf distraction, svf positive self-instructions, and svf positive use of support) the following model was tested.

The first step of the hierarchical regression analysis consisted of the integration of sociodemographic variables (age, sex, BMI). Mental health with STAI-T was added as the second step. The third step consisted of the integration of the subscale of perceived stress (demands) and coping (mental occupation). Finally, subscales of emotional competence (seas EE, seas AE, seas M) were added in the last step.

The overall regression model predicted approximately 35% of the variance in *SDNN* at baseline [$F_{(9,82)} = 4.88$, $p < .001$, $R^2 = .35$, adjusted $R^2 = .28$]. Individuals predicted tonic SDNN was equal to 79.08 - .88 (age) and - .73 (mental occupation), where age was measured in years and mental occupation in scale scores in one subscale of the svf-48. Sociodemographic variables predicted approximately 27% ($R^2 = .27$, $p < .05$) of variance in SDNN at baseline although only age was a significant predictor with lower values with increasing number of years, as seen in **Figure 3.2**. After controlling for sociodemographic variables step two, mental health predicted <1% ($\Delta R^2 = .01$, $p = .32$). However, mental health was no predictor in this setting. Perceived stress and coping predicted approximately 6% ($\Delta R^2 = .06$, $p < .05$) of variance although mental occupation was a significant predictor in SDNN at baseline. The SDNN decreased with higher scores of mental occupation, as illustrated in **Figure 3.3**. Finally, emotional competence predicted approximately 2% ($R^2 = .02$, $p = .55$) of variance in SDNN at baseline although no predictor in emotional competencies was found, as seen in **Table 3.8.**

Table 3.8: Hierarchical linear regression model of SDNN

Model		B	SE B	β	p	r	sr
Step 1	(Constant)	74.05	18.11		.00		
	age	-.87	.16	-.51	.00	-.52	-.51
	sex	.92	4.14	.02	.83	.07	.02
	BMI	.04	.63	.01	.96	-.11	.01
Step 2	(Constant)	87.31	22.48		.00		
	age	-.87	.16	-.51	.00	-.52	-.51
	sex	.79	4.14	.02	.85	.07	.02
	BMI	-.12	.65	-.02	.86	-.11	-.02
	Mental health (STAI-T)	-.30	.30	-.09	.32	-.08	-.11
Step 3	(Constant)	88.75	21.84		.00		
	age	-.90	.15	-.53	.00	-.52	-.53
	sex	2.22	4.06	.05	.59	.07	.06
	BMI	-.22	.64	-.03	.73	-.11	-.04
	Mental health (STAI-T)	-.12	.35	-.04	.74	-.08	-.04
	Perceived stress (psqr demands)	4.83	3.55	.13	.18	.06	.15
	Coping (svf mental occupation)	-.82	.36	-.23	.03	-.18	-.24
Step 4	(Constant)	79.08	29.38		.01		
	age	-.88	.16	-.52	.00	-.52	-.53
	sex	1.99	4.11	.05	.63	.07	.05
	BMI	-.14	.64	-.02	.83	-.11	-.02
	Mental health (STAI-T)	.05	.37	.02	.89	-.08	.02
	Perceived stress (psqr demands)	4.11	3.64	.11	.26	.06	.12
	Coping (svf mental occupation)	-.73	.37	-.21	.05	-.18	-.22
	Emotional competence (seas EE)	.46	.38	.12	.23	.20	.13
	Emotional competence (seas AE)	-.24	.36	-.07	.46	-.05	-.08
	Emotional competence (seas M)	-.22	.32	-.06	.49	-.11	-.08

Note $R^2 = .27$ for Step 1 ($p < .001$), $\Delta R^2 = .01$ for Step 2 ($p = .32$), $\Delta R^2 = .06$ for Step 3 ($p < .05$), $\Delta R^2 = .02$ for Step 4 ($p = .55$). B = Regression coefficient, SE B = standard error of B, β = Beta, r = zero-order correlations, sr = semipartial correlations.

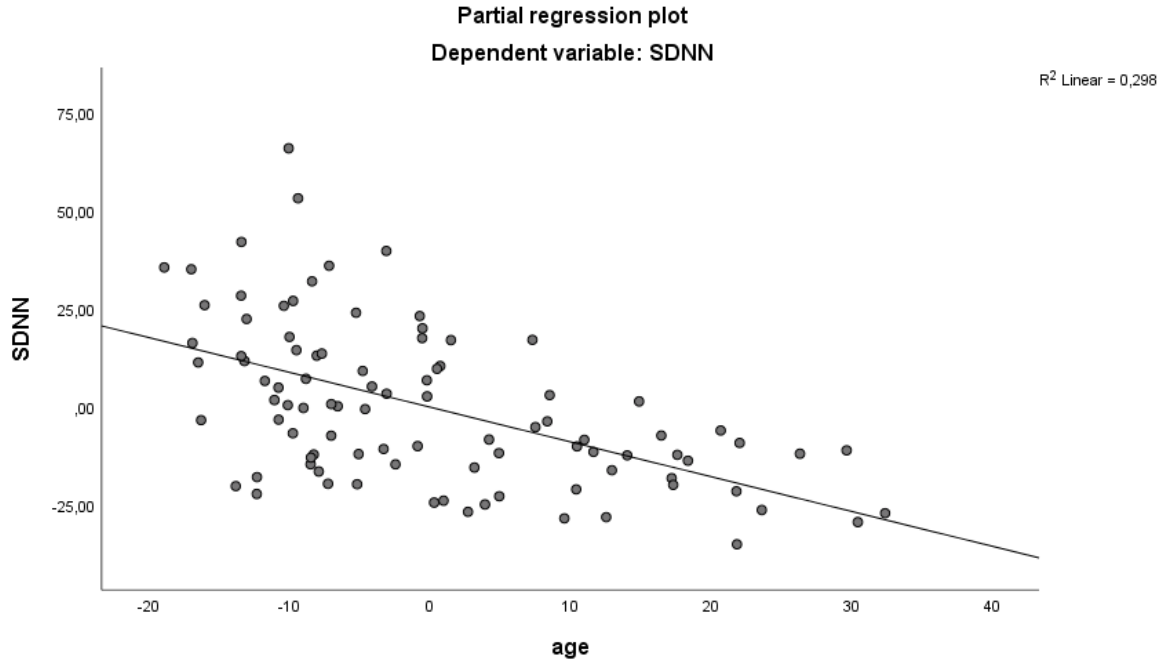

Figure 3.2: Age-related decline in SDNN

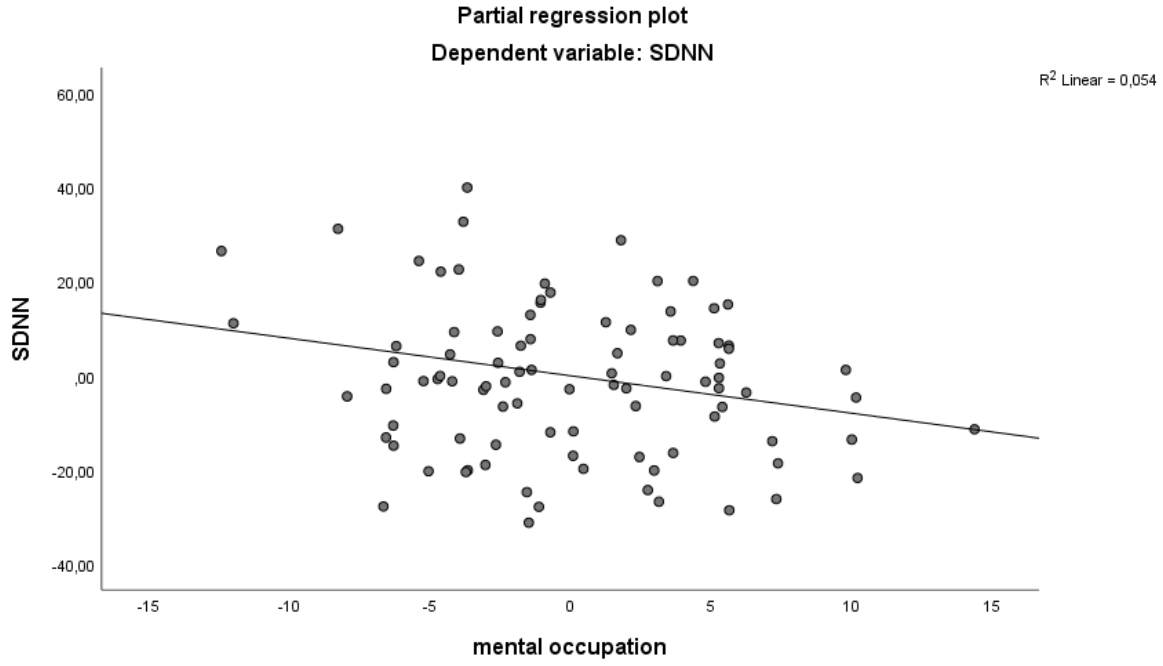

Figure 3.3: Mental occupation increasing with decreasing SDNN

The overall regression model predicted approximately 39% of the variance in *RMSSD* at baseline [$F_{(9,82)} = 5.78$, $p < .001$, $R^2 = .39$, adjusted $R^2 = .32$]. However, the constant in step 4 (including emotional competence) was close to but not quite statistically significant (p = .07). Therefore, results were reported based on step 3 (including sociodemographic variables, mental health, perceived stress and coping), as seen in **Table 3.9**. The overall regression model predicted approximately 36% of the variance in HRV *RMSSD* at baseline without emotional competence [$F_{(9,82)} = 5.78$, $p < .001$, $R^2 = .39$, adjusted $R^2 = .32$]. Individuals' predicted tonic RMSSD was equal to 50.62 - .89 (age) + 9.48 (sex) and - .87 (mental occupation), where age was measured in years, mental occupation in scale values and sex was coded as 1 = males and 2 = females. Sociodemographic variables predicted approximately 29% ($R^2 = .29$, $p < .05$) of variance in RMSSD at baseline where age and sex were significant predictors with lower values with increasing age, as illustrated in **Figure 3.4**, and higher values in females. After controlling for sociodemographic variables step two, mental health predicted <1% ($\Delta R^2 = .00$, $p = .65$). However, mental health was no predictor in this setting. Perceived stress and coping predicted approximately 7% ($\Delta R^2 = .07$, $p < .05$) of variance although mental occupation was a significant predictor in RMSSD at baseline. The RMSSD decreased with higher scores of mental occupation, as illustrated in **Figure 3.5**.

Table 3.9: Hierarchical linear regression model of RMSSD

Model		B	SE B	β	p	r	sr
Step 1	(Constant)	43.02	17.89		.02		
	age	-.86	.16	-.50	.00	-.51	-.50
	sex	8.00	4.09	.18	.05	.22	.20
	BMI	.43	.63	.06	.50	-.09	.07
Step 2	(Constant)	49.06	22.31		.03		
	age	-.85	.16	-.50	.00	-.51	-.50
	sex	7.95	4.11	.18	.06	.22	.20
	BMI	.36	.65	.05	.58	-.09	.06
	Mental health (STAI-T)	-.14	.30	-.04	.65	-.04	-.05
Step 3	(Constant)	50.62	21.53		.02		
	age	-.89	.15	-.52	.00	-.51	-.53
	sex	9.48	4.00	.22	.02	.22	.25
	BMI	.25	.63	.04	.70	-.09	.04
	Mental health (STAI-T)	.05	.34	.02	.88	-.04	.02
	Perceived stress (psqr demands)	5.25	3.50	.14	.14	.07	.16
	Coping (svf mental occupation)	-.87	.35	-.24	.02	-.16	-.26
Step 4	(Constant)	52.19	28.59		.07		
	age	-.87	.15	-.51	.00	-.51	-.53
	sex	9.69	4.00	.22	.02	.22	.26
	BMI	.33	.62	.05	.60	-.09	.06
	Mental health (STAI-T)	.23	.36	.07	.53	-.04	.07
	Perceived stress (psqr demands)	4.98	3.54	.13	.16	.07	.15
	Coping (svf mental occupation)	-.76	.36	-.21	.04	-.16	-.23
	Emotional competence (seas EE)	.46	.37	.12	.22	.17	.14
	Emotional competence (seas AE)	-.59	.31	-.18	.06	-.13	-.21
	Emotional competence (seas M)	-.06	.31	-.02	.86	-.08	-.02

Note $R^2 = .29$ for Step 1 ($p < .001$), $\Delta R^2 = <.01$ for Step 2 ($p = .65$), $\Delta R^2 = .07$ for Step 3 ($p < .05$). B = Regression coefficient, SE B = standard error of B, β = Beta, r = zero-order correlations, sr = semipartial correlations.

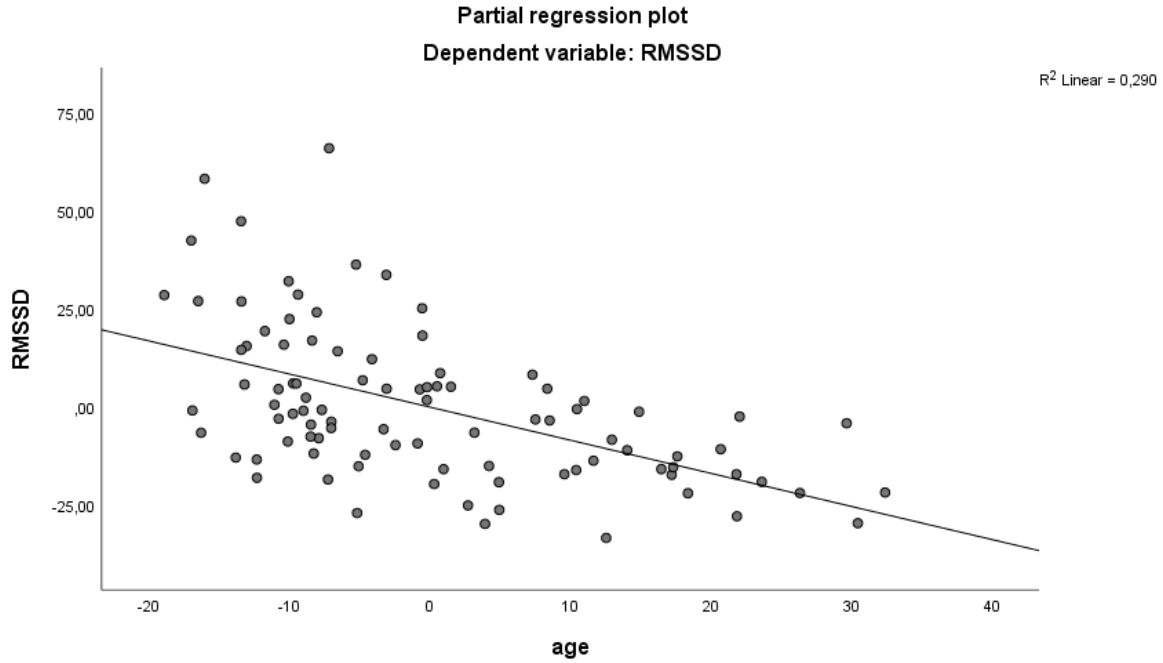

Figure 3.4: Age-related increasing with decreasing RMSSD

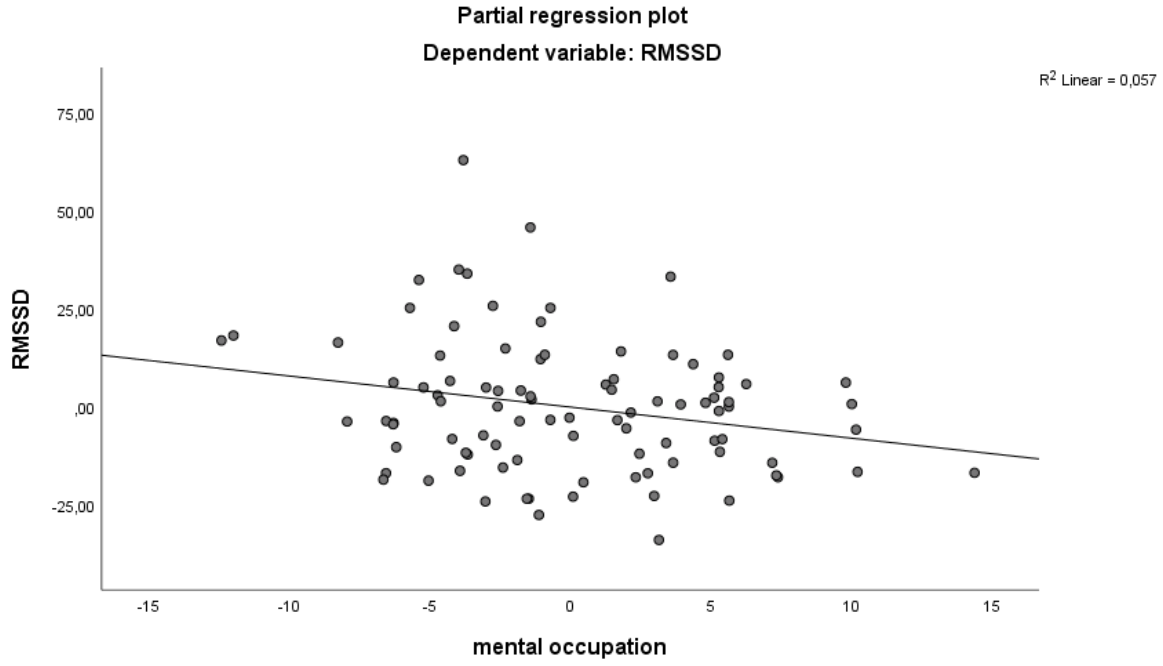

Figure 3.5: Mental occupation increasing with decreasing RMSSD

The overall regression model predicted approximately 53% of the variance in *ln*(*HF)* at baseline [$F_{(9,82)}$ = 10.27, $p < .001$, $R^2 = .53$, adjusted $R^2 = .48$]. Individuals predicted tonic *ln*(HF) was equal to 7.06 - .06 (age) + .56 (sex) - .04 (mental occupation) + .04 (EE) and - .04 (AE), where age was measured in years, mental occupation, seas EE as well as seas AE in scale scores and sex was coded as 1 = males and 2 = females, as seen in **Table 3.10**. Sociodemographic variables predicted approximately 45% ($R^2 = .45$, $p < .05$) of variance in *ln*(HF) at baseline where age, as illustrated in **Figure 3.6**, and sex were significant predictors with lower values with increasing age and higher values in females. After controlling for sociodemographic variables step two, mental health predicted <1% ($\Delta R^2 = .00$, $p = .89$). However, mental health was no predictor in this setting. Perceived stress and coping predicted approximately 4% ($\Delta R^2 = .04$, $p < .05$) of variance although mental occupation was a significant predictor in *ln*(HF) at baseline. The *ln*(HF) decreased with higher scores of mental occupation, as illustrated in **Figure 3.7**. Finally, emotional competence predicted approximately 4% ($R^2 = .04$, $p = .06$) of variance in *ln*(HF) at baseline. Seas EE and seas AE were found as predictors for *ln*(HF), whereas values of *ln*(HF) increased with higher emotional competence in seas EE and in turn, values of *ln*(HF) decreased with higher seas AE, as seen in **Figures 3.8 and 3.9**.

Table 3.10: Hierarchical linear regression model of *ln*(HF)

Model		B	SE B	β	p	r	sr
Step 1	(Constant)	7.40	.96		.00		
	age	-.06	.01	-.62	.00	-.64	-.63
	sex	.49	.22	.18	.03	.25	.23
	BMI	-.00	.03	-.01	.92	-.18	-.01
Step 2	(Constant)	7.50	1.20		.00		
	age	-.06	.01	-.62	.00	-.64	-.63
	sex	.49	.22	.18	.03	.25	.23
	BMI	-.01	.04	-.01	.90	-.18	-.01
	Mental health (STAI-T)	-.00	.02	-.01	.89	.01	-.01
Step 3	(Constant)	7.55	1.17		.00		
	age	-.07	.01	-.64	.00	-.64	-.65
	sex	.56	.22	.21	.01	.25	.27
	BMI	-.01	.03	-.02	.79	-.18	-.03
	Mental health (STAI-T)	.01	.02	.06	.54	.01	.07
	Perceived stress (psqr demands)	.16	.19	.07	.41	.01	.09
	Coping (svf mental occupation)	-.05	.02	-.21	.02	-.10	-.25
Step 4	(Constant)	7.06	1.52		.00		
	age	-.06	.01	-.62	.00	-.64	-.66
	sex	.56	.21	.21	.01	.25	.28
	BMI	-.00	.03	-.01	.91	-.18	-.01
	Mental health (STAI-T)	.03	.02	.13	.19	.01	.14
	Perceived stress (psqr demands)	.14	.19	.06	.46	.01	.08
	Coping (svf mental occupation)	-.04	.02	-.18	.05	-.10	-.22
	Emotional competence (seas EE)	.04	.02	.18	.04	.21	.22
	Emotional competence (seas AE)	-.04	.02	-.20	.02	-.11	-.26
	Emotional competence (seas M)	.00	.02	.01	.95	-.04	.01

Note $R^2 = .45$ for Step 1 ($p < .001$), $\Delta R^2 = <.01$ for Step 2 ($p = .89$), $\Delta R^2 = .04$ for Step 3 ($p < .05$), $\Delta R^2 = .04$ for Step 4 ($p = .06$). B = Regression coefficient, SE B = standard error of B, β = Beta, r = zero-order correlations, sr = semipartial correlations.

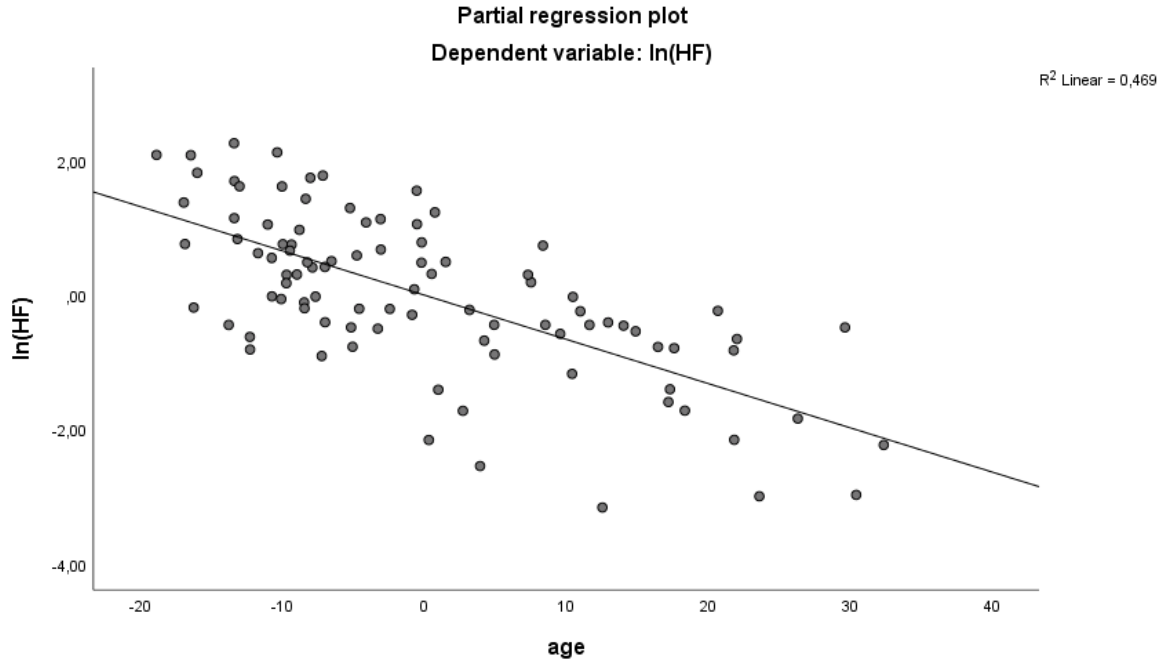

Figure 3.6: Age-related decline in *ln*(HF)

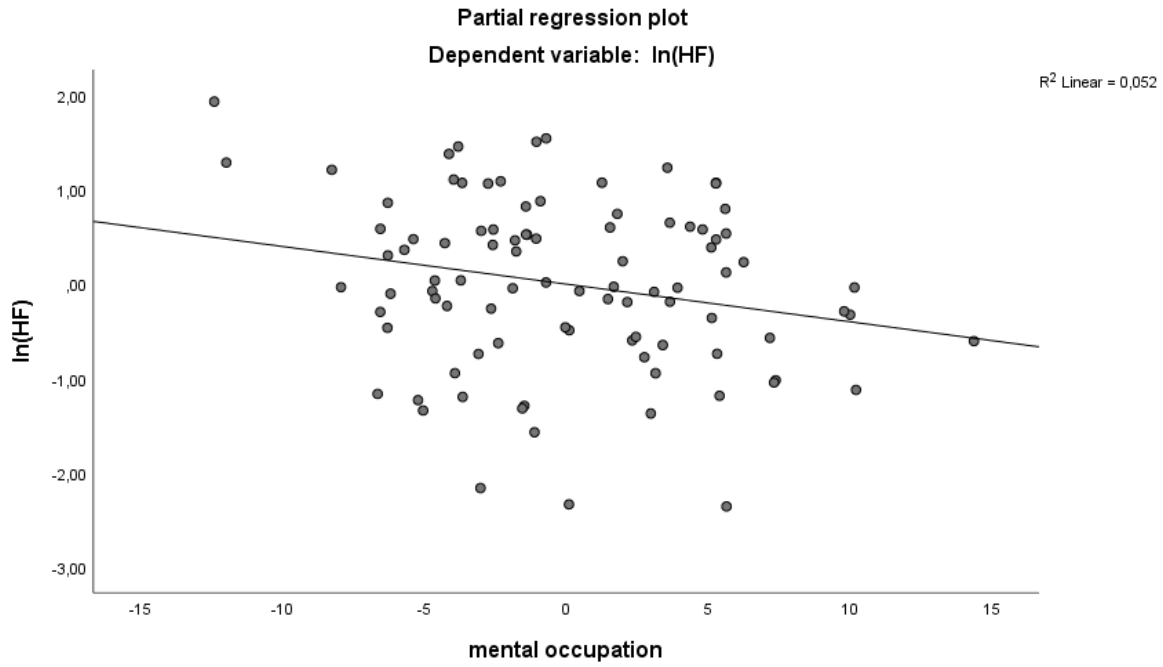

Figure 3.7: Mental occupation increasing with decreasing *ln*(HF)

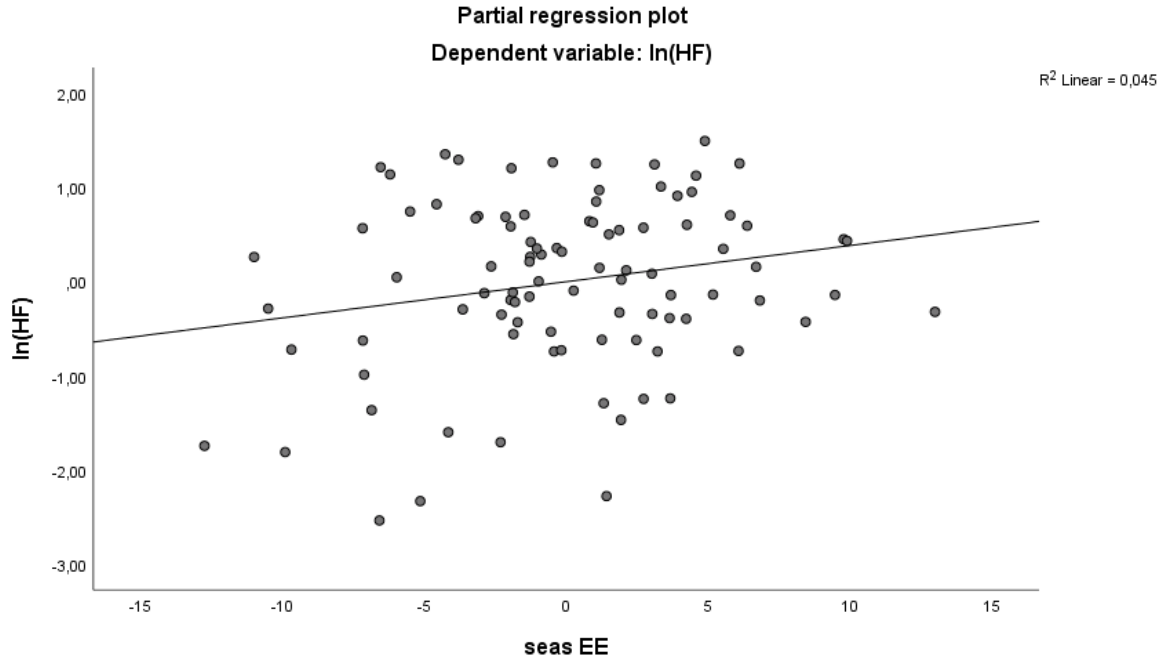

Figure 3.8: Emotional competence (perception of one's own emotions) increase with increasing *ln*(HF)

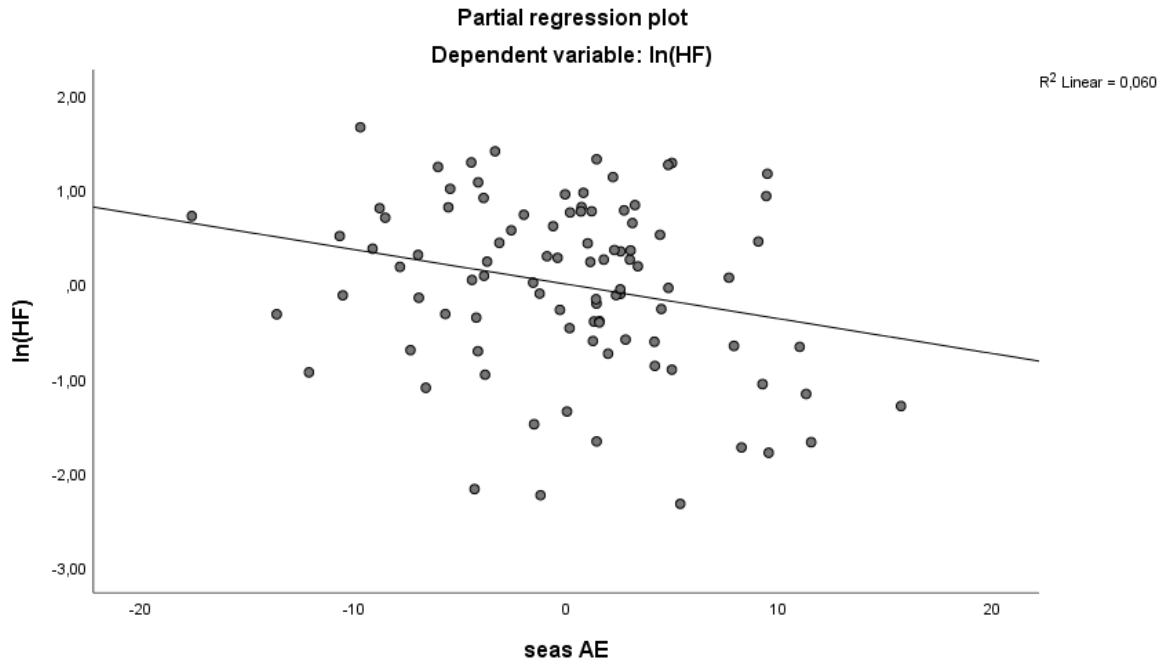

Figure 3.9: Emotional competence (perception of emotions in others) increase with decreasing *ln*(HF)

However, no effects were found in tonic HR, LF/HF as well as phasic heart rate variability [ΔHR reaction, ΔSDNN reaction, ΔRMSSD reaction, Δ*ln*(LF) reaction, Δ*ln*(HF) reaction, ΔLF/HF reaction, ΔHR recovery, ΔSDNN recovery, ΔRMSSD recovery, Δ*ln*(LF) recovery, Δ*ln*(HF) recovery, ΔLF/HF recovery].

4. DISCUSSION

A strong relationship and complex interplay between physiological system and psychological processes has been reported in numerous studies. When measuring cardiovascular responses to stress, an efficient stress paradigm is obligatory for drawing valid conclusions for psychophysiological processes. Therefore, this study validates the developed G-CEST by cardiovascular changes on healthy individuals during the main time points of rest, anticipation, stress, and recovery irrespective of their age and sex. Regarding the close interaction between physiological and psychological processes, this study further analyses the effects of mental health, perceived stress and coping as well as emotional competencies on tonic and phasic HRV controlled for sociodemographic variables.

Regarding general results, this study indicates both, age- and sex-related differences in resting cardiovascular conditions. However, the age-related effect in this study is visible in more variables than the sex-related effect. The finding of this study suggests a significant higher RF at rest in females compared to males. This is in accordance with previous research and might be explained by a smaller vital capacity which implies a lower maximal tidal volume and will be compensated by a higher respiration rate [45]. Contrary to evidence [39,46], females show higher CI and SI as well as lower TPRI compared to males. These results might suggest that males in this study demonstrate reduced SI and subsequently CI possibly due to an elevated afterload as indicated by higher TPRI. However, these sex-related results of ICG variables must be applied with caution due to the relatively small sample size of males included in this study. Regarding tonic HRV, the results show higher values in *ln*(HF) and RMSSD in females, whereas the values of the LF/HF are lower in females than in males. This results indicate the dominance of higher parasympathetic activity and, consequently, higher vagus-mediated HRV in females relative to males and is in accordance with previous research [41,44,47–49]. Potential mechanism for a greater parasympathetic cardiac control in females includes two possible explanations: the effect of hormones such as estrogen [223] or the influence of genetic factors such as brain structures [224]. However, the hormone explanation more closely explains the mechanism of sex-related difference in HRV relative to others because recent studies demonstrate that parasympathetic modulation decreases more in postmenopausal females than in younger females [225,226]. As expected, several age-related changes in cardiovascular conditions at baseline are reported in this study. Overall, the CI and SI decrease whereas TPRI and LVET increase with age under resting conditions. This is in accordance with previous

evidence which suggests an age-related decline in cardiac function at resting condition indicated by SV [35,39] and CO [35–37]. Further, this study supports evidence which suggests that TPRI [35,38] and LVET [227] increase with age. These resting changes might result from functional and structural age-related cardiovascular changes [37,38,40] and may partially explain the risk aspect of aging [36]. Previous studies indicate that structural age-related changes in the heart and vessels (increase and hypertrophy in myocyte cells, reduction of pacemaker cells) accompanied by increased vascular thickness (intimal thickness, left ventricular wall thickness), vascular stiffness and left atrial size seem to explain cardiovascular changes with age [36,37,40]. Contrary to the reported findings in this study, age is often accompanied by dysfunctions in the SBP and DBP. Moreover, delayed arterial baroreceptor reflex response, a decreased cardiopulmonary reflex, a decreased maximal HR, maximal CO, maximal oxygen uptake, a reduced threshold for cell Ca^{2+} overload seem to be also accompanied by age [37,38,40]. These aspects seem to reduce the ability of the heart to respond accordingly to increased workload [37,40]. In addition, evidence suggest that aging also plays an important role in autonomic alterations [41,50]. As reported in this study, all HRV variables are associated with age at rest. The dominance of parasympathetic cardiac control in typical HRV parameter such as *ln*(HF), RMSSD and LF/HF decreases with a continuous age-related decline in baseline. Moreover, an age-related decline in SDNN and *ln*(LF) are found at rest. These results are in accordance with existing literature, which has found significant differences in younger and older adults among linear and nonlinear HRV indices irrespective of sex, with a drastic decline between the age groups 45–54, 55–64 and 65–74 years with higher differences in females relative to males [41]. Furthermore, another study discovered a linear decline in SDNN with age and an parasympathetic outflow with U-shaped pattern in RMSSD [42]. The age-related diminished HRV indices might be caused by age-related changes to the cardiovascular system [43]. The diminished HRV might also be caused by structural (loss of sinoatrial pacemaker cells) or arterial (loss of distensibility) cardiovascular modifications [41]. As reported in this study, BP (SBP, DBP, MAP) differs with weight at baseline. This study indicates that overweight individuals tend to have higher BP compared to their healthy weight counterparts. This supports the evidence that shows a close association between DBP with BMI in both sexes and SBP with BMI specifically in females [52]. Contrary to existing evidence [53], SI and CI show reducing values and TPRI is increased in overweight individuals in this study. Previous research reported that obesity led to higher CO as well as blood volume and to lower SVR [53]

to meet the metabolic demand of the adipose tissue [228], which was seen as a predisposition for hypertension [53]. These divergent results must be interpreted with cautions and might be explained keeping in view that no participants were adipose because of inclusion criteria. However, only one-third of the participants were less overweight. Another explanation includes the limited accuracy of ICG which needs to be considered. ICG is based on estimations of physiological variables and simplified physiological assumptions [110] which might limit its transferability to all settings. A previous study reported that for pregnant females, the interpretation of the ICG variables was not recommended due to changes to the intrathoracic geometry [229]. Thus, it can also be predominant in obese individuals, which limit the estimation of ICG variables. As reported in this study, the LF/HF is higher in overweight individuals compared to their normal weight counterparts. This indicate that higher weight is associated with higher LF/HF, which is supported by a recent meta-analysis showing that individuals with weight gain tend to increase LF/HF [51]. Interestingly, the results of this study suggest that BP (SBP, MAP, DBP) is lowest in individuals with moderate self-reported physical activity. This is in accordance with previous evidence showing a trend of higher BP in individuals who train more than 10 h/week [54]. This indicates that excessive physical activity seems to be maladaptive for the physiological system. The findings of this study indicate that smoking participants show significant higher values in HR and RF at baseline compared to non-smokers. This is in accordance with previous research [103–105]. However, the underlying mechanism is not clear yet. A possible explanation might be that smoking individuals show frequent sympathetic activation and decreased baroreceptor sensitivity [230] which cause an increase in HR. An increasing RF in smokers might be caused by smoking-related inflammation of the airways [231] to compensate the lack of oxygen.

Regarding the differences of psychosocial factors and sociodemographic factors, the results of this study reveal higher worries in males compared to females. This is in contradiction with existing evidence which suggests that females tend to report more worries than males and it might be caused by a more negative problem orientation [232]. However, in gender stereotypical issues, males have been attributed more worries about achievement and finances compared to females, whereas females have been attributed more worries about relationships [233]. Nevertheless, the sex-related differences should be interpreted with caution because the limited sample size of males in this study. Further, the results indicate that emotions of joy and PA are higher in individuals with high physical activity and non-smokers, whereas the

perceived tension is higher in smoking individuals. Moreover, this study indicates that positive coping strategies, such as deemphasizing are highest in individuals with high self-reported physical activity. This is in accordance with previous research reporting that non-smokers, leisure time, physical activity and higher educational level predict adaptive coping strategies and in contrast, maladaptive coping strategies are predicted by smoking, high perceived stress and lower education levels [177]. In sum, this study supports the evidence which suggests that lifestyle-related factors have been associated with better mental health [162], and adaptive coping strategies [177].

4.1. VALIDATION OF THE NEW PARADIGM (G-CEST)

Overall, the results of the present study indicate that, in healthy individuals the G-CEST is successful in producing moderate stress and that it enables visible cardiovascular changes. Almost all parameters changed significantly during the main time points of rest, anticipation, stress, and recovery caused by short-term psychological stress. This suggests that ECG-, BP- and ICG-based variables seem to be sensitive markers for psychological changes in different periods of stress and it is supported by previous research [90,91,124].

An increase in HR accompanied by rising BP, RF, CI and decreasing SI, LVET and PEP characterizes the cardiovascular response to psychological stress in this study. The mean values of both stressors, with higher activation in emotional rather than cognitive stressor, may be partially attributed to the mental challenge. Accordingly, several studies report heterogenic results. This variability in data across recent studies may be due to the nature of stressor to which an individual is exposed. Physiological or psychological stressor leads to different cardiovascular response patterns [145,146]. However, the highest physiological effects are observed during psychological stress tests [145,146]. Another explanation for data variability might be the origin of a stressor. Active stressors, as used as cognitive part in this study, are characterized by a higher beta-adrenergic activation indicated by increased HR, BP, RF, and CO [4–7,142], whereas passive tasks such as viewing emotional film clips or CPT without active engagement of participants are characterized by greater alpha-adrenergic activation which leads to higher vascular tonus indexed by lower CO and an increase in TPR [6,234]. The differences in TPRI are not significant between the main time points of rest, anticipation, stress, and recovery in this study. These results combined with significant increase in CI, which is associated with an increased SBP and HR, seem to emerge from beta-adrenergic activation

during mental tasks and is indicative of a reaction pattern which is more cardiac than vascular in nature. This is in accordance with existing research which reports minimal TPR changes during active stressor tasks [28,92,124]. However, the response to stress in TPR might also be associated with other factors such as time. A previous study reported that more cardiac reaction to mental stress was observed early in stress response, whereas more vascular reaction pattern was located late in stress response [235].

The G-CEST provided an effective way to induce moderate stress, irrespective of age and sex, in the same order as those elicited by other paradigms viewed over longer periods for example, in TSST [144]. As reported in this study, several cardiovascular variables changed during psychological stress. Nevertheless, ICG variables such as SI, CI, PEP and LVET seemed to be largely influenced by different baseline levels than by the induced stress in this study.

In contrast to other measured variables in this study, the RF is strongly influenced by age, and sex. The results of increasing RF during psychological stress, and decreasing during recovery, are in accordance with previous studies. Research examines that tachypnoea or hyperventilation is often used to handle psychological stress in healthy individuals [236]. However, respiration reactivity seems to be influenced by external effects such as temperature, equipment as well as the duration and intensity of the stressor [237]. Therefore, only focusing on RF is insufficient to describe respiration reactivity regarding to psychological stress [236]. However, the interaction effect of RF with age and sex disappears when controlling for baseline in this study. This suggests that RF during stress is strongly influenced by different baseline levels. As reported in this study, age-related interaction effects in SI also disappear when controlling for baseline. This might suggest that SI during stress is also more influenced by different baseline levels rather than by psychological stress. While other studies found age- or sex-related differences in BP [57,58], no differences were observed in this study. This might be caused by the small sample size of older adults and males which limited sex- or age-related effects.

The reaction patterns of the emotional stressor indicate that there is an anticipatory effect of the G-CEST. The instruction to do a memory performance task was strongly associated with increasing HR, BP (SBP, DBP, MAP), and RF. These results support previous evidence suggesting that anticipating a challenging situation itself seems to be stressful [238]. These cardiovascular responses to anticipation involve similar patterns to experiencing a stressor. This is in accordance with previous research suggesting an increase in BP during the anticipatory

period independent of a following active or passive stress task [239]. Moreover, individuals tend to prefer obtaining information prior to the stressor [240], and expected stressors where they are rated less threatening vis-à-vis unexpected stressors [241]. Thus, anticipation during the G-CEST might influence the subjective rating and the individual appraisal that a stressor is much more a challenge than a threat and might help to mobilize required resources for the following cognitive stressor task. This finding elucidates the results of studies showing that cardiac response patterns reflect energy mobilization or effort to the required demands to handle challenging situations [12]. Therefore, a less threatening appraisal of an expected stressor might be accompanied by a limited sudden shift of physiological reaction patterns in cognitive task. This indicates that anticipation might be adaptive in certain situations because individuals can prepare prior to the occurrence of the stressors and cope with them as postulated by the cognitive theory of stress and coping [82]. Nevertheless, anticipation is often associated with perseverative cognition and causing prolonged stress-related physiological activation [178]. This, in turn, might play a crucial role in negative health outcomes [178]. Moreover, there is evidence that perseverative cognition is associated with the activation of cardiovascular, autonomic, and endocrine nervous system indicated by higher BP (SBP, DBP) and HR [181]. As proposed by the allostatic overload concept [72], prolonged or repeated stress-related physiological activation of mediators leads to a permanent high allostatic load and can trigger negative health outcomes as reported in previous studies [9,12–14,29]. Nevertheless, the cardiovascular patterns in anticipation are mediated by a greater increase in cardiac, rather than vascular patterns, which is consistent with an active coping response [242].

The results of the G-CEST show that cardiovascular response to stress is induced by situations which can be interpreted as achievement claiming goal-directed performance as required in the cognitive stressor task (CVLT-II). Various stress protocols induce acute stress and evoke different physiological response patterns. As assumed, the G-CEST activates the SNS by increasing HR, BP (SBP, DBP, MAP) and RF. This is in line with other paradigms which report the activation of SNS during active psychological stress and show similar response pattern to the G-CEST. The TSST, Montreal Imaging Stress Task, Mannheim Multicomponent Stress Test and Stroop test activate the SNS in a similar way by increasing HR [139,145,243,244], and BP (SBP/DBP) [126,243]. Note that, from a neurobiological point of view, the effects of cognitive and emotional stress reaction, reported in this study, seem to result in as part of a fast stress response from the release of catecholamines, adrenaline and

noradrenaline. This helps to restore homeostasis and mobilize resources for a fight-or-flight response by inhibiting several other processes such as blood flow for muscles or gastro-intestinal tract [2,245].

After the stressor wears off, almost all physiological parameters come back to the baseline level in recovery. These results of recovery are predestined for healthy individuals investigated in this study. This is supported by recent studies which show the important role of recovery in CVD [9,30,31]. Within the cardiovascular recovery, the PNS through postganglionic nuclei and the vagus nerve play a key role in re-establishing homeostasis as part of a fast stress response [245]. However, a passive recovery including a quiet sitting period results in a faster decline compared to active recovery where individuals are exposed with lower intensity demands. With respect to physiological or psychological stressor tasks, in both types a prolonged stressor recovery has been predicted to show negative cardiovascular outcomes [9,30]. However, this is stronger for recovery from physiological rather than psychological stressors [30]. In psychological stress tests, there are several unpredictable individual factors such as perseverative cognition [178], anger [246], worry [178], and others compared to physiological stress tests. Previous research suggests that a prolonged HR recovery after a performance situation is linked to the tendency to ruminate [123]. Several causes such as cognitive demanding tasks seem to trigger rumination or a prolonged emotional processing of the stressor and they might result in prolonging psychophysiological activation [123]. However, the physiological recovery process seems to be disturbed by cognitive processes such as appraisal, rumination, and anticipation [31]. As reported in this study, the BP showed no recovery after the stressor wore off. This might support the previous theory of prolonged activation due to rumination in performance tasks. This indicates that psychological stressors might activate preservative cognition which, as a consequence, seems to trigger a maladaptive cardiovascular recovery pattern. Nevertheless, a methodological limitation may explain the apparently prolonged BP activation. BP per se reacts less rapidly than HR does and needs about 5.6 minutes to recover from a mild stressor [247] and recovery in this study was limited to 5 minutes (3 minutes analysis).

Finally, several important limitations need to be considered, which are related to the small sample size of males and older ages might limit the transferability. Thus, all age- and sex-related effects must be interpreted with caution. Also, caution must be applied as findings may not be transferable to all settings. Further work with greater sample sizes is needed to further validate

the G-CEST specialized for males and older ages. Although the G-CEST seems to evoke cardiovascular responses in healthy individuals, there is a need for further investigations in clinical setting. Furthermore, it cannot be certain that the involved participants are free of any underlying diseases due to self-reported information to screen for healthy individuals. Nevertheless, the cardiovascular reactivity and the activation of the SNS have been validated in this study. However, the question remains unclear as to what extent the paradigm activates the HPA axis by cortisol release. Thus, further studies should include cortisol measures to get a better insight into the G-CEST. Moreover, laboratory conditions are never completely uncontrollable as participants can withdraw from the test at any time. Thus, it remains unclear how the induced stress in this study reflects the daily stress exposure. Further, the ICG variable PEP seems to be overestimated by the TFM® and indicates imprecise values. Nevertheless, the total duration of LVET and PEP is accurate, but the classification of both variables seems to be inadequate. Finally, studies on G-CEST are required to establish the results of this study, especially in clinical context and with respect to habituation. Until that happens, it is more than justified to highlight several strengths of G-CEST compared to existing ones. The new paradigm provides an easy and effective way to induce moderate stress, irrespective of age and sex, in the same order as elicited by other paradigms viewed over longer periods or which require more resources. All included components such as cognitive stressor task (CVLT-II) or questionnaires are validated by previous studies. In addition, the cognitive stressor task is multifunctional. It can be used to induce moderate stress and it also gives insights into cognitive learning processes and strategies. Multiple trials of cognitive stressor task (CVLT-II) enable a detailed reflection of the underlying reaction patterns including their psychophysiological components. Long-lasting emotional consequences of the participants are excluded as affective pictures or videos are unavailable. The G-CEST combines cognitive and emotional stressors which enable differentiation between anticipation and stressor task. The same posture throughout the entire measurement helps to minimize changes due to physiology stressors so that the changes can only be attributed to psychological aspects. Initial results in the clinical setting show respectable results [133,248] and suggest that the G-CEST is also appropriate in clinical context. The G-CEST is a standardized paradigm, but it is still flexible and adaptable in its application, which enables its use in a variety of research hypothesis. The high level of standardization also enables a comparison between different studies.

4.2. CARDIOVASCULAR CONDITION AND PSYCHOSOCIAL FACTORS

The second focus of the thesis served to deepen the understanding of tonic and phasic HRV and its association with different aspects of self-reported mental health, perceived stress and coping as well as emotional competence, controlled for sociodemographic variables. In sum, the hypotheses that lower HRV reflected lower self-reported coping and lower emotional competence in the perception of one's own emotions, was supported in resting laboratory setting when controlling for sociodemographic variables in healthy individuals.

The results of this study revealed that higher self-reported scores in mental occupation were negatively associated with tonic HRV [SDNN, RMSSD, *ln*(HF)], when controlling for sociodemographic variables of age, sex and BMI. These results indicate that self-reported maladaptive coping strategy (mental occupation) can be displayed by tonic HRV. The association between individuals with lower resting physiological state (tonic HRV) and higher maladaptive psychological trait (mental occupation) is supported by the perseveration cognition hypotheses, which refer to the permanent activation of the cardiovascular stress system due to rumination [178]. Several studies found that rumination could prolong the negative effects of mental stress [179] which, in turn, seemed to have a negative impact on health [178] and might be linked to adverse physiological states [72]. The negative affect-laden thoughts of rumination seem to result in various psychopathologies and somatic disorders [181,249]. However, perseverative cognition is not limited to a clinical population, rather it occurs also in healthy individuals [250]. Thus, the result of this study suggests that decreased HRV, specifically vagus-mediated HRV [RMSSD, *ln*(HF)], is associated with higher trait rumination in healthy individuals. These results confirm previous findings [183,202,203] by reporting an association between HRV and rumination. Contrariwise, a study found only an association between state rather than trait perseverative cognition and reduced HRV [251]. These divergent results might occur due to a language bias in the reported study because the instrument, which was used to assess trait perseverative cognition, did not adapt to the language of the country, whereas in this study a validated questionnaire in the national language (German) was used. This ensured that all participants understood the questions in an adequate manner. Further, the results indicated that the vagus-mediated HRV served as indicator of adaptability in the context of coping strategies and emotional competence which were supported by previous findings. The result of this study seemed to be also supported by neurophysiological studies, showing a positive association between HRV and executive brain functions as indicated by cerebral blood flow in

prefrontal cortex and amygdala [149]. This was expanded by behavioural studies showing that tonic HRV predicted several self-regulatory processes such as emotional regulation [202] and seemed to lead to more adaptive coping strategies [176]. In contrast, lower tonic HRV is involved in more maladaptive emotion strategies (perseverative cognitions) [179,184].

As shown in this study, mental occupation as part of perseverative cognition is associated with lower vagus-mediated HRV. A recent study reported that individuals with lower resting HRV reported higher maladaptive perseverative cognition, specifically being depressive and brooding as two types of maladaptive rumination, whereas it was not found to be linked with adaptive (reflective rumination) forms of perseveration [184].

From a theoretical point of view, it can be presumed that the concentration on negative coping strategies results in a more threatening physiological pattern through a permanent activation of the physiological stress system. However, studies assume hyperactivity of the amygdala during stress, which is indicative of perseverative cognition, appears to reduce executive brain inhibition [149,180,250] and affects activation of the cardiovascular, autonomic, and endocrine nervous systems [181]. A diminished prefrontal inhibitory regulation might prolong the stress response [149,180,181,250] and lead to a chronic activation of the sympathetic branch which can disturb the allostasis and can be manifest as pathological states [72]. Interestingly, with reduced prefrontal inhibition, the organism is no longer capable of handling the emotional and behavioural responses in an adaptive way [180]. This in turn is associated with lower tonic HRV [149,252], suggesting that ruminative thinking is indicated by reduced tonic HRV.

The findings of this study are different in terms of mental health and the absence of its association with HRV. Several studies found a close link between reduced HRV and psychological disorders such as anxiety [157,158], depression [159,160], post-traumatic stress disorder and schizophrenia [159]. These divergent results might be explained by the aspect that within the sample of this study all individuals were healthy and there was apparently no large variation in anxiety scores.

When exploring self-reported difficulties in competence in the perception of one's own emotions, an association with lower tonic HRV [*ln*(HF)] was reported. In contrast, difficulties in the perception of others' emotions were associated with higher *ln*(HF). However, perception of one's own emotions had a stronger association with tonic HRV [*ln*(HF)]. These results indicate that self-reported emotional competence can be displayed by measured vagal nerve-

mediated HRV. This is in accordance with the neurovisceral integration model [96] that postulates a close interaction between higher brain functions and the autonomic nervous system and shows that emotion regulation is associated with HRV. Further, the results lend support to the polyvagal theory [74,83] which postulates a close link between vagal brake and behavioural, physiological, and psychological processes. Moreover, the findings support the idea that adjustment of physiological processes is linked with emotional capabilities, and also support the hypothesis that emotional competence has been linked with autonomic regulation, as reported by previous research [202]. These findings further provide evidence that autonomic regulation and emotional competence share neural networks, suggesting that high levels of HRV are linked to affective information processing, attentional regulation, cerebral blood flow, and physiological flexibility [75,84]. Moreover, previous research suggests that higher HRV is accompanied by stronger functional connectivity in the amygdala and the prefrontal cortex [252], which is also predominant in emotional processes [253].

The association between higher self-rated perception of one's own emotions with higher tonic HRV [*ln*(HF)] is congruent with previous research which suggests that higher emotional competence is associated with better psychological and physiological health [158]. A previous study reported that improved emotional perception was linked with higher levels of tonic HRV [201]. In contrast, lower HRV is linked with emotional dysregulation [176].

As reported in this study, higher scores of self-rated perception of the emotions of others are associated with lower tonic HRV [*ln*(HF)]. At first glance, this contradicts the assumption of the positive effect of high emotional competence on the physiological system, as reported in several studies [186,188–190]. However, the high competence in the perception of emotions in others, as reported in this study, seems to have a downside for the physiological system. A closer view reveals that emotional competence, such as the perception of emotion in others, is closely linked to empathy, which plays a crucial role in interpersonal and societal processes to connect individuals and strengthen relationships. Empathy enables one to perceive the emotions of others, interact on a cognitive and emotional level, and recognize, understand and empathize with other individuals [254]. This study suggests that high sensitivity in the perception of emotion in others seems to have a physiological cost. This seems to be in accordance with a recent study which reports the effect of parental empathy and also its close relationship with greater self-reported psychological well-being, self-esteem, and a deeper purpose in life. Nevertheless, the more empathic the parents, the more chronic low-grade inflammations [255]

were observed. In this context, the strands of empathy (cognitive, affective, and compassionate) seem to be crucial. However, individuals who imagine self-perspective taking seem to produce greater personal distress [256]. Moreover, a previous study demonstrated a close association between intensified emotion perception and increased physiological arousal [257]. Individuals with higher self-reported perception of others' emotions show a more pronounced cardiac pattern while viewing horrified film clips [120]. Previous studies indicate that in emotional situations, the SNS of individuals with difficulties in emotion regulation produces higher HR and the PNS is unable to decrease this high activation of the SNS. Thus, high activation of the SNS might result in lower HRV [176]. The close association between vagus-mediated tonic HRV and lower self-reported competence in the perception of emotions in others is also supported by neurological studies; and they reveal that particularly empathic individuals show neuroscience patterns that are similar to those of individuals who are in pain [258]. This chronic activation of the physiological stress system may disturb the allostasis and result in pathologies [72], which may be indicated by tonic HRV. This might explain the association between higher scores of the perception of emotion in others and lower tonic HRV. Thus, high perception of emotion in others seems to come with a physiological cost. Further studies should investigate this assumption, specifically the different strands of empathy and their association with long-term physiological changes.

Nevertheless, the results must be interpreted with caution because irrespective of the accurate measurement done in this study, and considering influencing factors such as age, sex and BMI, the tonic HRV might be affected by numerous elusive factors such as genetics [259], temperature (heat or cold) [211,259] or exposure to pollutants [211]. Previous studies show that other factors such as the daily constitution of the participants including sleeping routine or nutrition intake [98], work-related factors such as night shift work [259,260] or other aspects such as circadian rhythm [259], exposure to noise [259], posture [260], and meditation [260] may also influence the tonic HRV.

This study was unable to detect a significant link between phasic HRV and mental health, perceived stress and coping, or emotional competence and phasic HRV (reaction or recovery). This suggests that individuals do not seem to react strongly or weakly during cognitive stress or during recovery but perhaps the stress system is activated more often, which might cause changes in the tonic HRV. Another explanation might be that it was caused by the stressor (cognitive performance task) used in this study. A more emotional-laden stressor might trigger

other HRV reactions and recovery patterns, which were supported by a previous study, showing that HRV changes differed in various methods [44]. The vagal withdrawal and associated sympathetic activation during a stressor seem to be linked to cognitive load [261] and the reaction and recovery seem to depend on the task characteristics and situation [262]. This suggests that to show more clearly the association of phasic HRV with mental health, perceived stress and coping, and with emotional competence, it may be necessary to use an emotional stressor. This further supports the idea that rumination is triggered by emotional situations whereas performance task shows no possibility of rumination. Thus, further studies should examine phasic HRV and its association with mental health, perceived stress and coping, and with emotional competence under different stressors such as emotional versus cognitive reaction patterns and in the light of its relation to psychosocial factors.

Although the findings of the present study support the evidence that low emotional competence and negative coping strategies, controlled for sociodemographic variables, are associated with lower tonic HRV, several limitations need to be considered. First, the sample consists of fewer older individuals with a majority of females, which may limit the validity of age- and sex-related effects. Consequently, future research should use a broader sample across age groups and sexes to further expand the understanding between tonic and phasic HRV with coping strategies and emotional competence. Second, the use of limited number subscales to assess coping and emotional competence may limit the results, although both the svf-48 and the SEAS are commonly reliable and valid tools for assessing coping strategies and emotional competence. However, the limited selection of subscales may not capture the whole complexity of this concept. Further research is required to fully understand the possible psychophysiological mechanisms underpinning coping strategies and emotional competence. Third, the HRV is susceptible to several factors; thus, it is possible that variables that have not been collected in this study might have a greater influence on the HRV than the observed variables have. Fourth, the questionnaires measure psychosocial traits by using self-reporting; therefore, self-reported bias might affect the study. Despite these limitations, this study adds to a growing body of psychophysiological research by demonstrating the link between HRV and particular aspects of psychosocial factors in healthy individuals.

5. CONCLUSION

When measuring CVR to stress, an efficient stress paradigm is obligatory for drawing valid conclusions for psychophysiological processes. This study, therefore, validated the new paradigm (G-CEST) by investigating cardiovascular changes during the main time points of rest, anticipation, stress, and recovery in a healthy population setting. One of the most important findings emerging from this study is that the G-CEST is appropriate for providing an easy and effective way to induce moderate stress, irrespective of age and sex in healthy individuals. Thus, the application of G-CEST covers a variety of research hypotheses. Taken together, these findings extend the knowledge of validated paradigm in psychophysiological research.

Further, this study examines how mental health, varying facets of perceived stress and coping as well as emotional competence, controlled for sociodemographic factors, predict tonic and phasic HRV. Despite the limitations, the present study is a valuable contribution to the evidence for HRV and its association with coping and emotional competence, as the study indicates that self-reported psychosocial factors might modulate physiological states. Also, this study adds to a growing body of psychophysiological research and serves to deepen the understanding of HRV and its association with mental health, perceived stress as well as coping, and with emotional competence by showing that lower HRV reflects lower self-reported coping and lower emotional competence in the perception of one's own emotions. Further, the results indicate that emotional competence in the perception of others' emotions is linked to lower vagus-mediated HRV. This leads to the conclusion that high competence in the perception of others' emotions seems to come at a physiological cost. Considering the cardiovascular system, it can be summed up with the saying: *'Knowing me knowing you, but don't put yourself in others' shoes' – because you will end up with more than just stinky feet.*

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APPENDICES

APPENDIX A: CASE REPORT FORM

Cardiovascular reactivity in emotion regulation (CavareER)

Datum (TT/MM/JJJJ) ____ / ____ / _____

STAMMDATENBLATT

Familienname/Vorname(n) _____

Geburtsdatum _____

Maße:

Körpergröße:	cm	Körpergewicht:	kg
Bauchumfang:	cm	Taillenumfang:	cm

Bitte füllen Sie vor der Vergabe der Probanden-ID die Ein- und Ausschlusskriterien aus

Probanden-ID: _____

Termine	Datum/Uhrzeit	**Kontaktdaten**	
1.Termin	_____	Telefon	_____
		Email	_____
		Adresse	_____

Version 01/2016, vom 16.06.2016 Seite 1 von 3

Cardiovascular reactivity in emotion regulation (CavareER)

Ein- und Ausschlusskriterien		
Einschlusskriterien:	**Ja**	**Nein**
Alter ≥ 20	☐	☐
Alter ≤ 75	☐	☐
Gesund (60+ Blutdruck ≤ 150/95 mmHg)	☐	☐
BMI ≤ 35 kg/m²	☐	☐
Sprachfähigkeit (deutsch)	☐	☐
Schriftliche Einverständniserklärung	☐	☐

Ausschlusskriterien:	**Ja**	**Nein**
Medikamenteneinnahme	☐	☐
Schwangerschaft	☐	☐
Körperliche oder psychische Erkrankungen	☐	☐
LeistungssportlerIn	☐	☐

Sonstige Fragen:

	Ja	**Nein**
Rauchen Sie?	☐	☐
Wenn ja, wann die Letzte?	_____	
Haben Sie heute koffeinhaltige Getränke konsumiert?	☐	☐
Wenn ja, wann das Letzte?	_____	

Höchste abgeschlossene Ausbildung:

☐ Pflichtschule ☐ Lehre ☐ Matura ☐ FH/Universität

Händigkeit:

☐ Rechtshänder ☐ Linkshänder

Anamnese (Allergien, frühere Erkrankungen)

Aktuelle Erkrankung (Erkältung, Kopfschmerzen oä.)

Sonstige Bemerkungen

APPENDIX B: PARTICIPANT INFORMATION SHEETS AND CONSENT FORM

PatientInneninformation und Einwilligungserklärung zur Teilnahme an der Beobachtungsstudie

Kardiovaskuläre Reaktionsdynamik[1] bei der Emotionsregulation

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten Beobachtungsstudie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen Gespräch.

Ihre Teilnahme an dieser Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Sie oder Ihre medizinische Betreuung.

Beobachtungsstudien sind Studien, bei denen in der Regel nur Daten aufgezeichnet und ausgewertet werden, die im Rahmen von nicht belastenden Untersuchungen oder Befragungen erhoben werden. Beobachtungsstudien sind notwendig, um zusätzliche Erkenntnisse über bereits bewährte medizinische Verfahren zu gewinnen.

Unverzichtbare Voraussetzung für die Durchführung einer Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Zu dieser Beobachtungsstudie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck dieser Studie?

Der Zweck dieser Beobachtungsstudie ist es, in einer kurzen, genau definierten Untersuchung, die Reaktion des Herz-Kreislaufsystems unter Ruhe bzw. bei einfachen mentalen Belastungen wie z.B. bei einer Gedächtnisübung, zu untersuchen. Da die

[1] Herz-Kreislaufanpassung in bestimmten Situationen (z.B. bei leichten mentalen Aufgaben)

Reaktionsfähigkeit des Herz-Kreislaufsystems das Potenzial hat, ein wichtiger Prognosefaktor für das zukünftige Herz-Kreislauferkrankungsrisiko darzustellen, ist es wichtig, ein einfaches und vom Alter unabhängiges Messverfahren zu testen, um es anschließend in der klinischen Praxis einsetzen zu können. Aus diesem Grund richtet sich diese Studie ausschließlich an gesunde Männer und Frauen im Alter von 20-75 Jahren.

2. Wie läuft die Beobachtungsstudie ab?

Diese Studie wird an mehreren Orten durchgeführt und es werden insgesamt etwa 120 Personen daran teilnehmen. Ihre Teilnahme wird voraussichtlich 1,5 Stunden dauern.

Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:
Zu Beginn der Studie werden Sie gebeten, mehrere Fragebögen auszufüllen. In weiterer Folge werden Elektroden am Nacken und im Bereich des unteren Rippenbogens geklebt (zur Messung der Flüssigkeitsverschiebungen im Brustkorbbereich). Zusätzlich werden die Elektroden für die EKG-Messung (Aufnahme der elektrischen Aktivität der Herzmuskelzellen) angebracht und es wird der Blutdruck automatisch mittels Manschette am Oberarm und Sensoren an den Fingern während einer Abfolge von Ruhephasen und mentalen Aufgaben (z.B. einfache Gedächtnisübungen) gemessen. Der gesamte Versuch findet in sitzender Position statt und dauert etwa 90 Minuten.

Für die Untersuchung werden Sie gebeten, ans Institut zu kommen. Insgesamt ist ein Besuch im Ausmaß von etwa 90 Minuten notwendig.

3. Worin liegt der Nutzen einer Teilnahme an der Beobachtungsstudie?

Es ist nicht zu erwarten, dass Sie aus Ihrer Teilnahme an dieser Studie einen unmittelbaren gesundheitlichen Nutzen ziehen werden, es werden aber Erkenntnisse über u.a. Ihren aktuellen Blutdruck sowie der Herzfrequenz bzw. deren Veränderung während der Untersuchung (kardiovaskulärer Status) ermittelt und Sie erhalten auf Wunsch eine daraus ableitbare mündliche Beratung.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Es können die im Rahmen dieser Studie durchgeführten Maßnahmen in äußerst seltenen Fällen zu einer geringfügigen Hautreizung durch die EKG-Elektroden oder einem leichten

Druckschmerz durch die Platzierung einer Druckmanschette am Oberarm oder an den Fingern, welche den Blutfluss für kurze Zeit unterbindet, entstehen.

5. Zusätzliche Einnahme von Arzneimitteln?

Nein.

6. Hat die Teilnahme an der Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Bei Teilnahme an der Studie werden Sie gebeten, auf den Konsum von alkoholischen Getränken ab dem Vorabend der Untersuchung sowie auf den Konsum von Kaffee, koffeinhaltigen Getränken o.ä. bzw. Tabakkonsum ab zwei Stunden vor der Untersuchung zu verzichten.

7. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrer Studienleiterin mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

8. Wann wird die Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der Studie ausscheiden ohne dass Ihnen dadurch Nachteile entstehen.

Ihre Studienleiterin wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese Studie bekannt werden und für Sie wesentlich werden könnten, umgehend informieren. Es ist aber auch möglich, dass Ihre Studienleiterin entscheidet, Ihre Teilnahme an der Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Ein möglicher Grund hierfür könnte sein:

a) Sie können den Erfordernissen der Studie nicht entsprechen

9. In welcher Weise werden die im Rahmen dieser Beobachtungsstudie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Studienleiterin und deren Mitarbeiter und Mitarbeiterinnen Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden („personenbezogene" Daten). Weiteres können ggf. Beauftragte von in- und ausländischen Gesundheitsbehörden, der zuständigen Ethikkommission und Personen, die von der Studienleiterin und/oder Auftraggeber und Auftraggeberin der Studie mit der Kontrolle der Datenqualität beauftragt wurden, Einsicht in diese Daten nehmen, um die Richtigkeit der Aufzeichnungen zu überprüfen. Diese Personen sind zur Verschwiegenheit verpflichtet.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos nicht namentlich genannt. Auch in etwaigen wissenschaftlichen Veröffentlichungen der Daten dieser Studie werden Sie nicht namentlich genannt.

Die Bestimmungen des Datenschutzgesetzes in der geltenden Fassung werden eingehalten.

10. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser Studie entstehen für Sie keine zusätzlichen Kosten. Ein Kostenersatz bzw. allfällige Vergütungen für die Teilnahme an dieser Studie sind nicht vorgesehen.

11. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser Studie stehen Ihnen die Studienleiterin und ihre Mitarbeiter und Mitarbeiterinnen gerne zur Verfügung.

Name der Kontaktperson: **Kathrin Hilgarter**, BSc, MSc

Ständig erreichbar unter: **0650/ 731 52 89**

12. Einwilligungserklärung

Name (Patienten/ Patientin) in Druckbuchstaben: .....

Geb. Datum: ..... Code: .....

Ich habe dieses Informationsblatt gelesen und verstanden und wurde darüber hinaus von Frau Kathrin Hilgarter, BSc, MSc ausführlich und verständlich über diese Studie aufgeklärt. Alle meine Fragen wurden beantwortet und ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den Anweisungen, die für die Durchführung der Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit beenden zu können, ohne dass mir daraus Nachteile entstehen.

Mit meiner persönlich datierten Unterschrift gebe ich hiermit freiwillig mein Einverständnis, dass meine Daten gespeichert und ohne direkten Personenbezug für wissenschaftliche Zwecke verwendet werden dürfen. Mir ist bekannt, dass zur Überprüfung der Richtigkeit der Datenaufzeichnung Beauftragte der zuständigen Behörden und der Ethikkommission, sowie mit der Kontrolle der Datenqualität beauftragte Personen Einblick in meine personenbezogenen Krankheitsdaten nehmen dürfen. Ich weiß, dass ich diese Zustimmungen jederzeit und ohne Angabe von Gründen widerrufen kann.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt bei der Studienleiterin.

.....

(Datum und Unterschrift des Patienten)

.....

(Datum, Name und Unterschrift der verantwortlichen Studienleiterin)

(Der Patient/die Patientin erhält eine unterschriebene Kopie der PatientInneninformation und Einwilligungserklärung, das Original verbleibt im Studienordner der Studienleiterin.)

APPENDIX C: SUPPLEMENTAL FIGURES AND TABLE

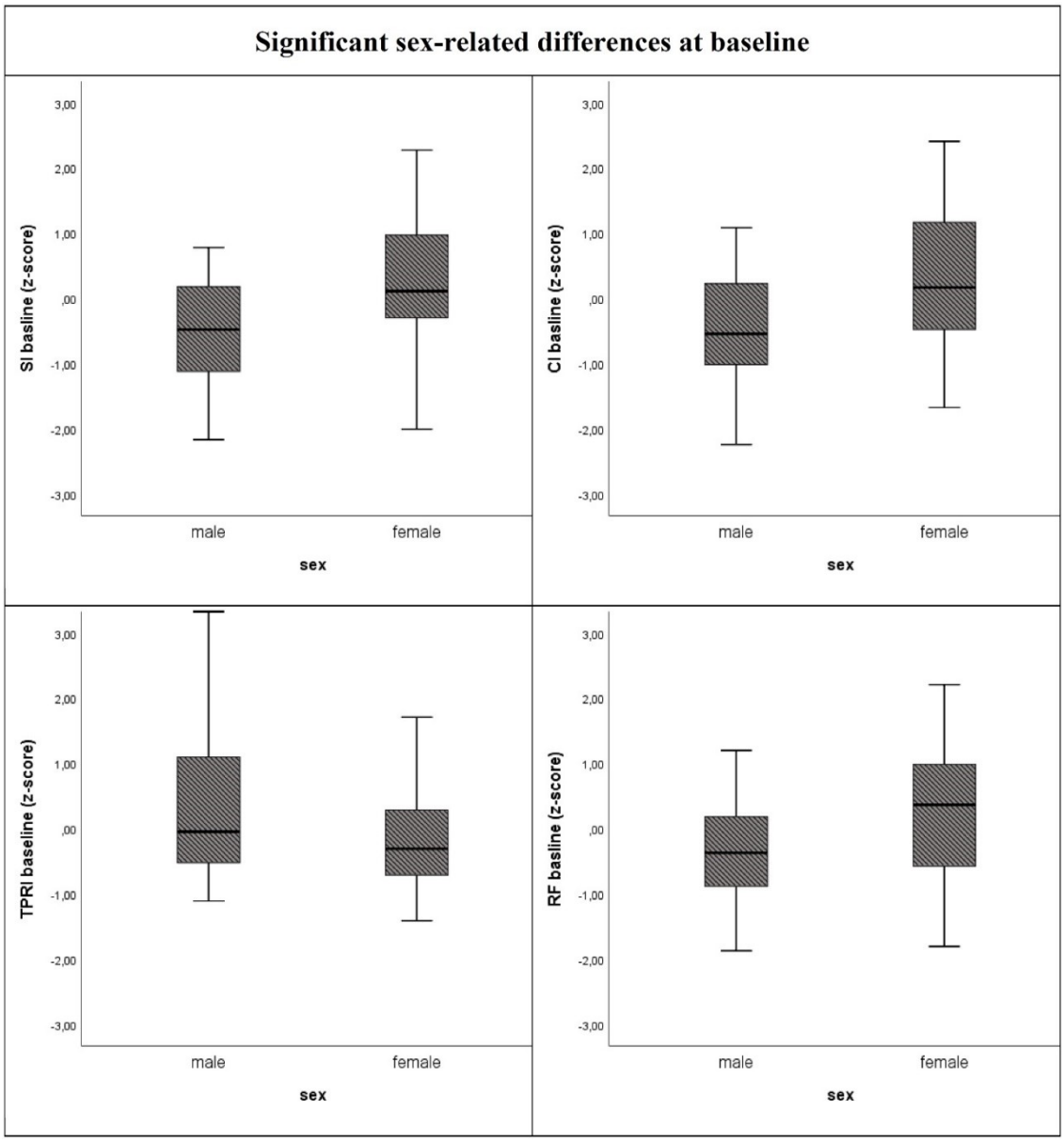

Figure A.1: Visualization of significant cardiovascular differences at baseline

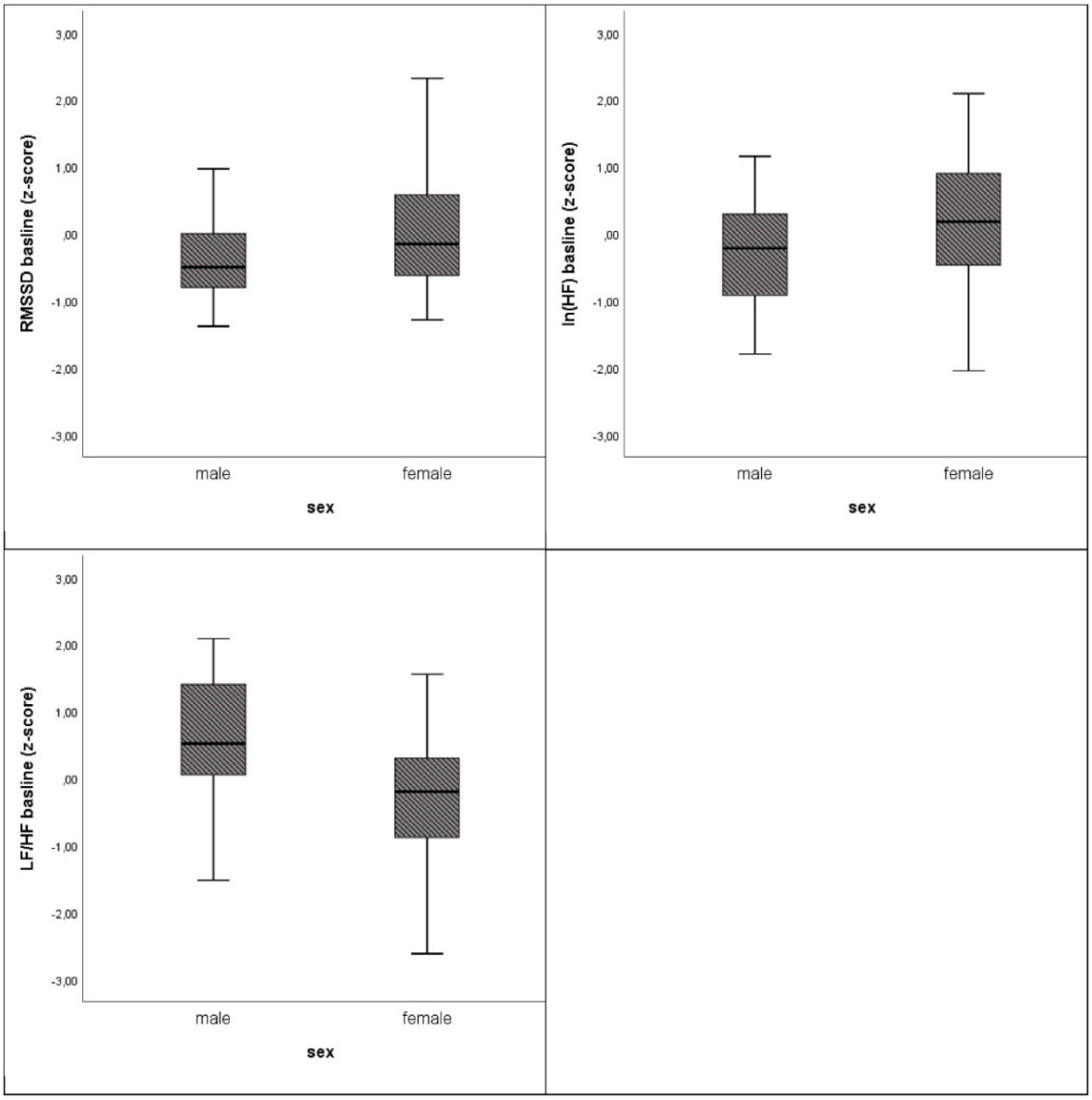

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

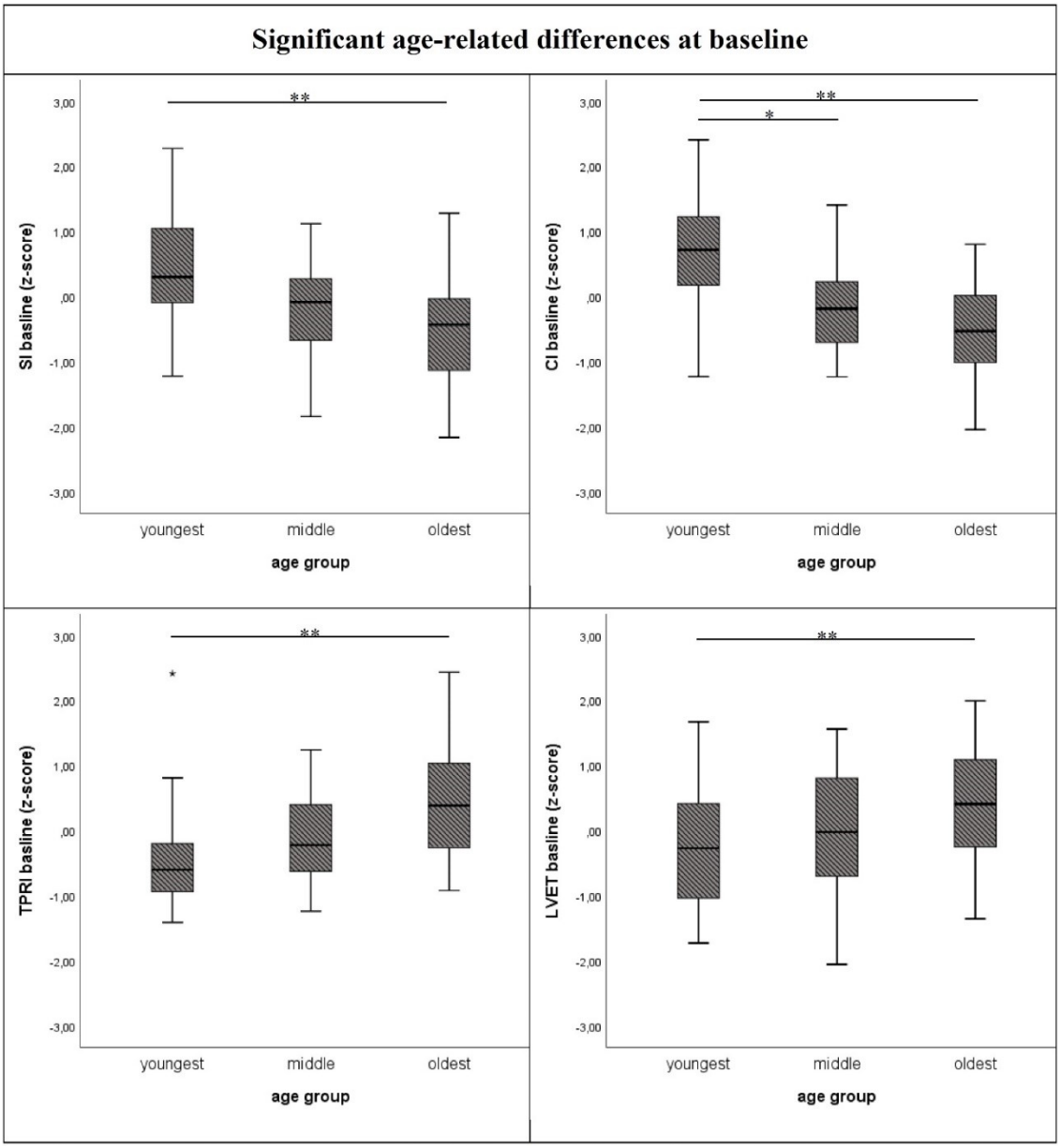

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

The difference between the groups is significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

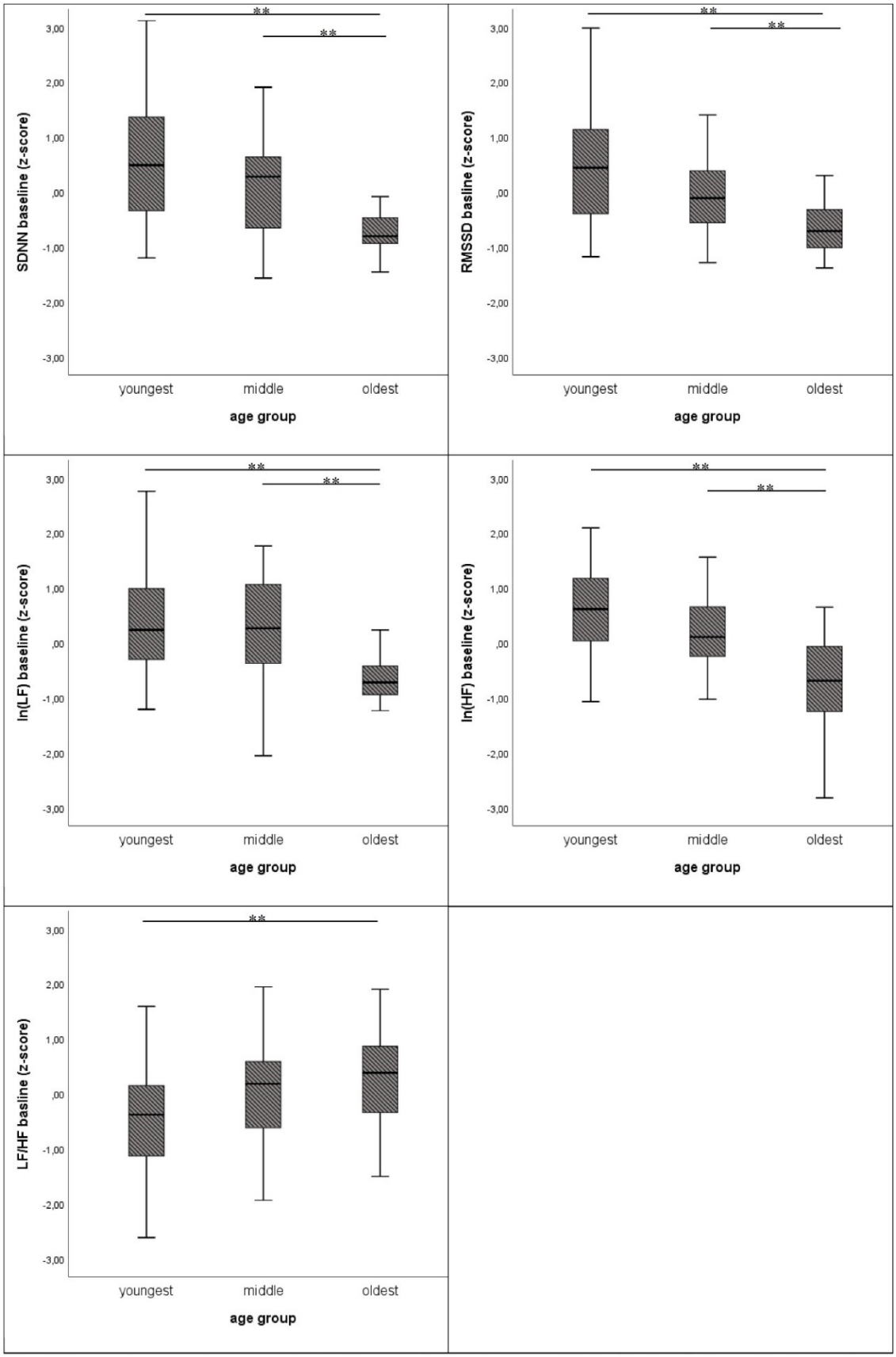

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

The difference between the groups is significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

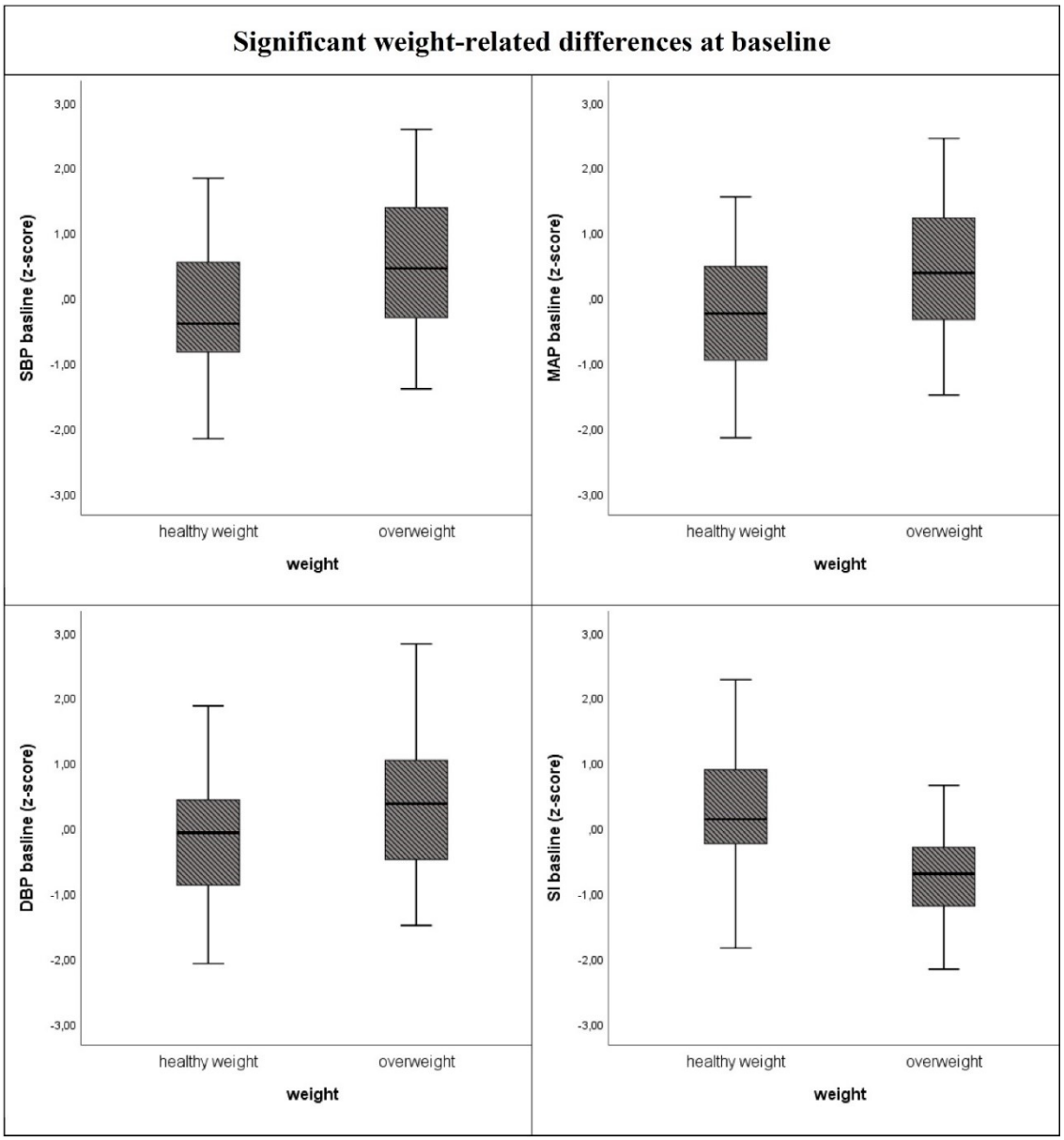

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

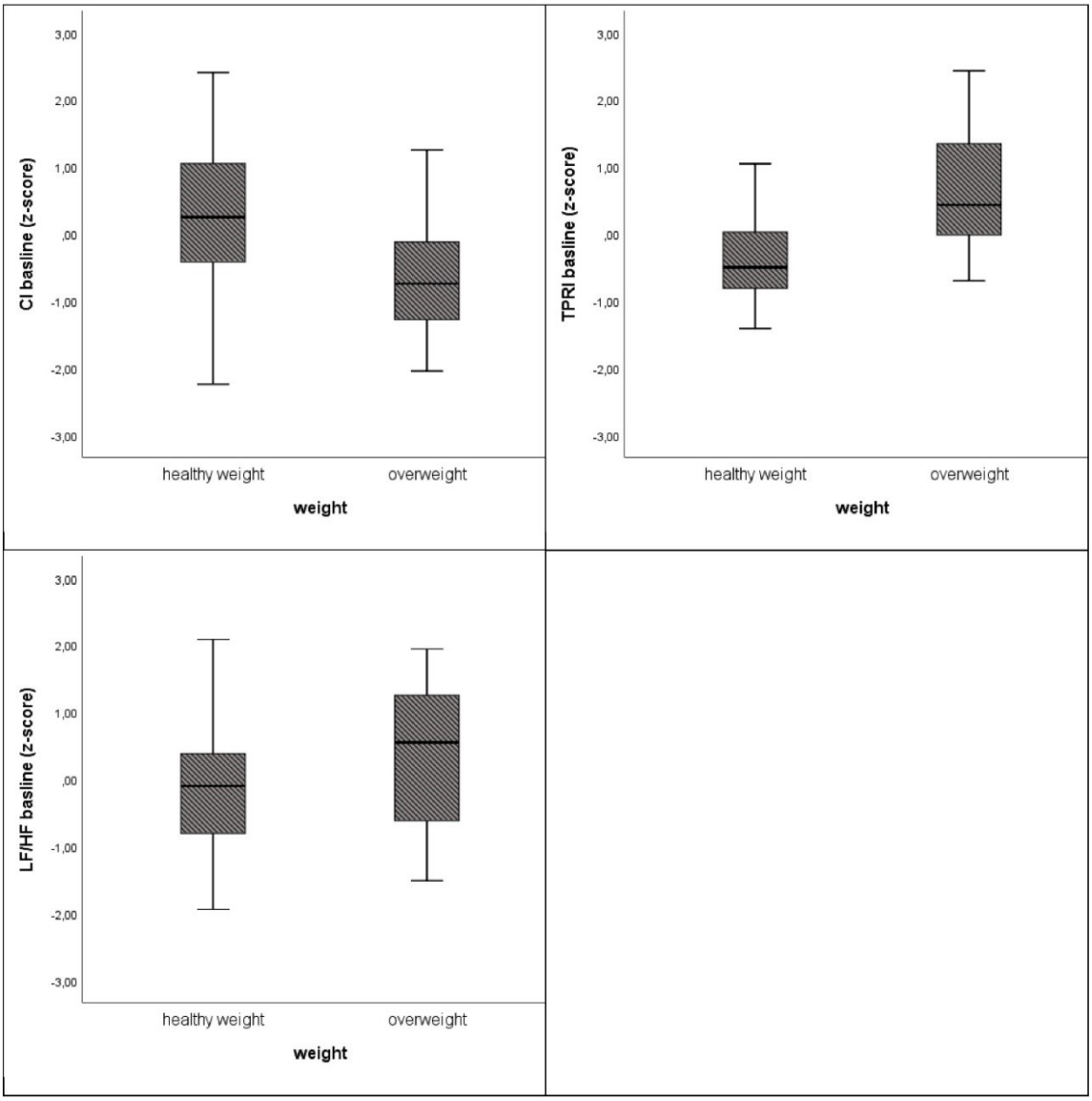

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

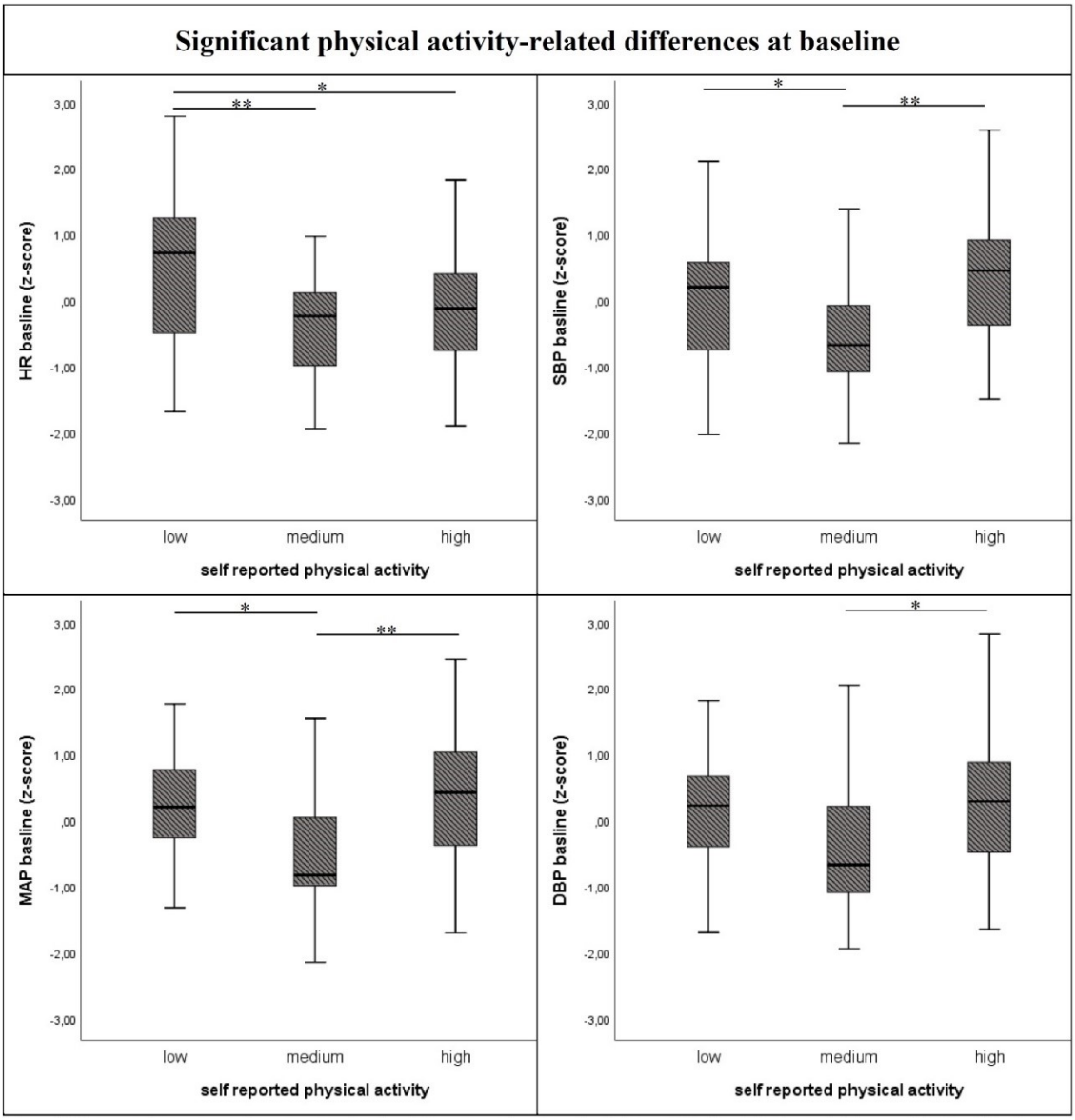

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

The difference between the groups is significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

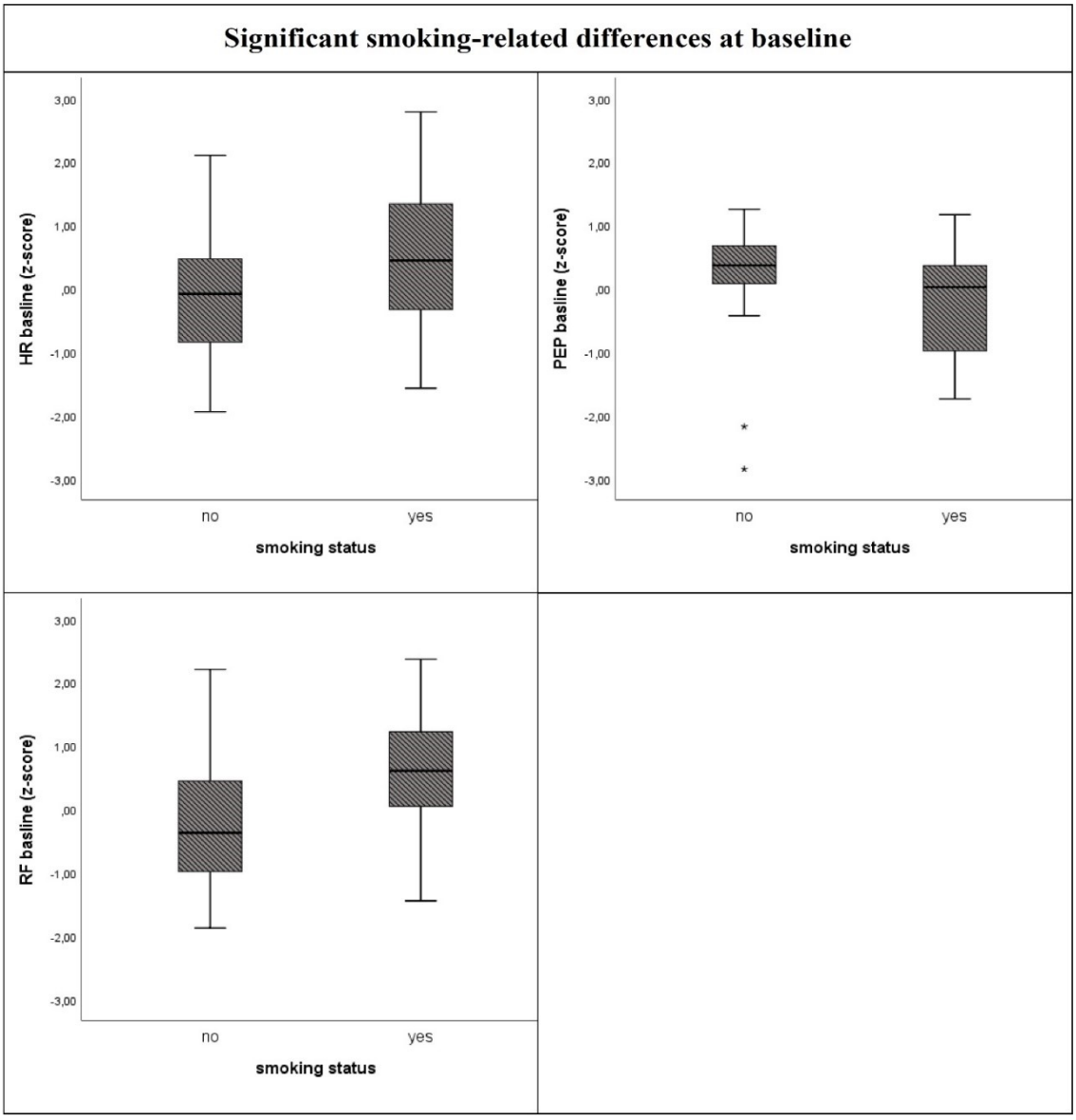

Figure A.1: Visualization of significant cardiovascular differences at baseline (continued)

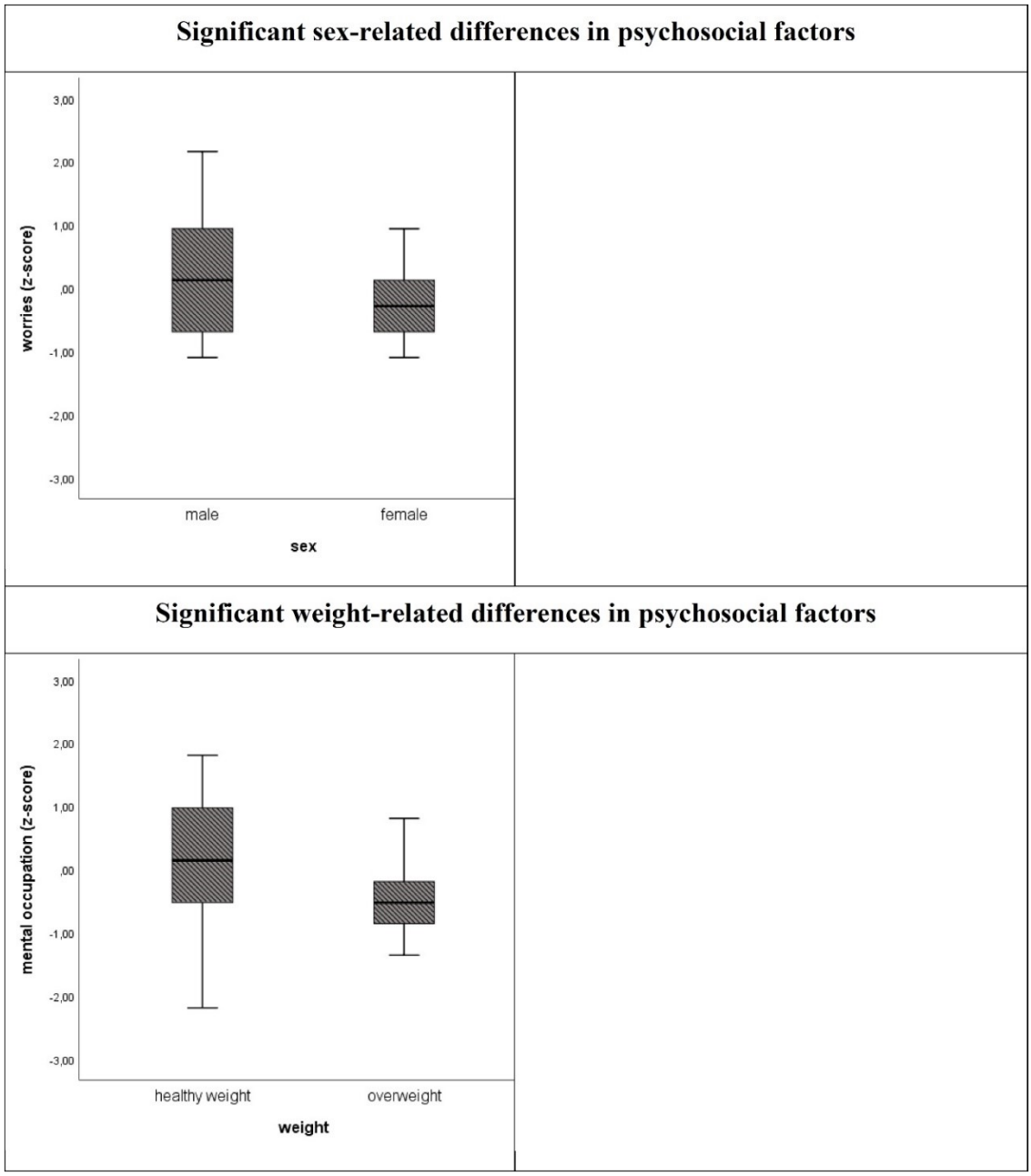

Figure A.2: Visualization of significant differences in psychosocial factors

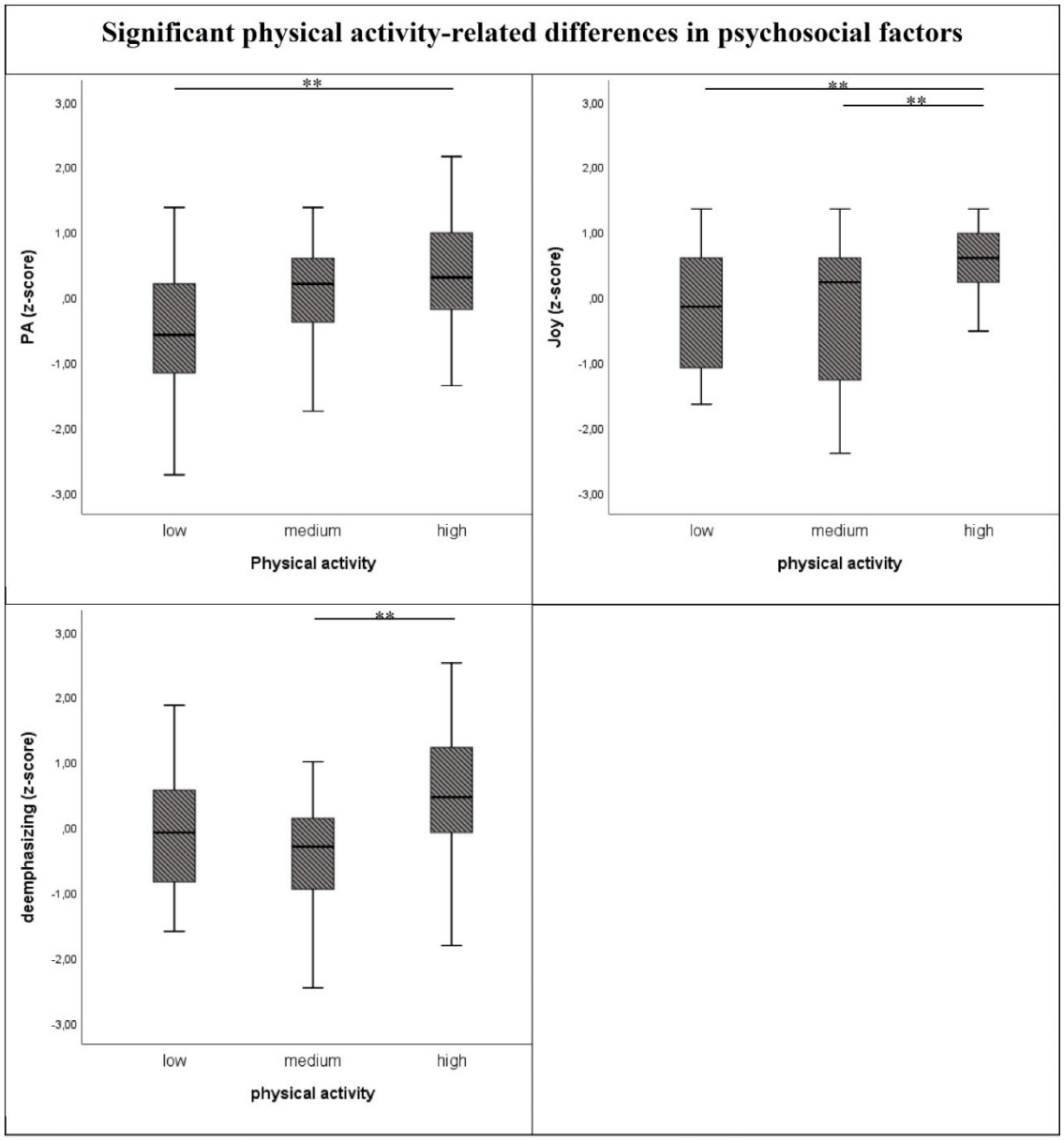

Figure A.2: Visualization of significant differences in psychosocial factors (continued)

The difference between the groups is significant at the level of * p <.05 (2-sided) and ** *p* <.01 (2-sided).

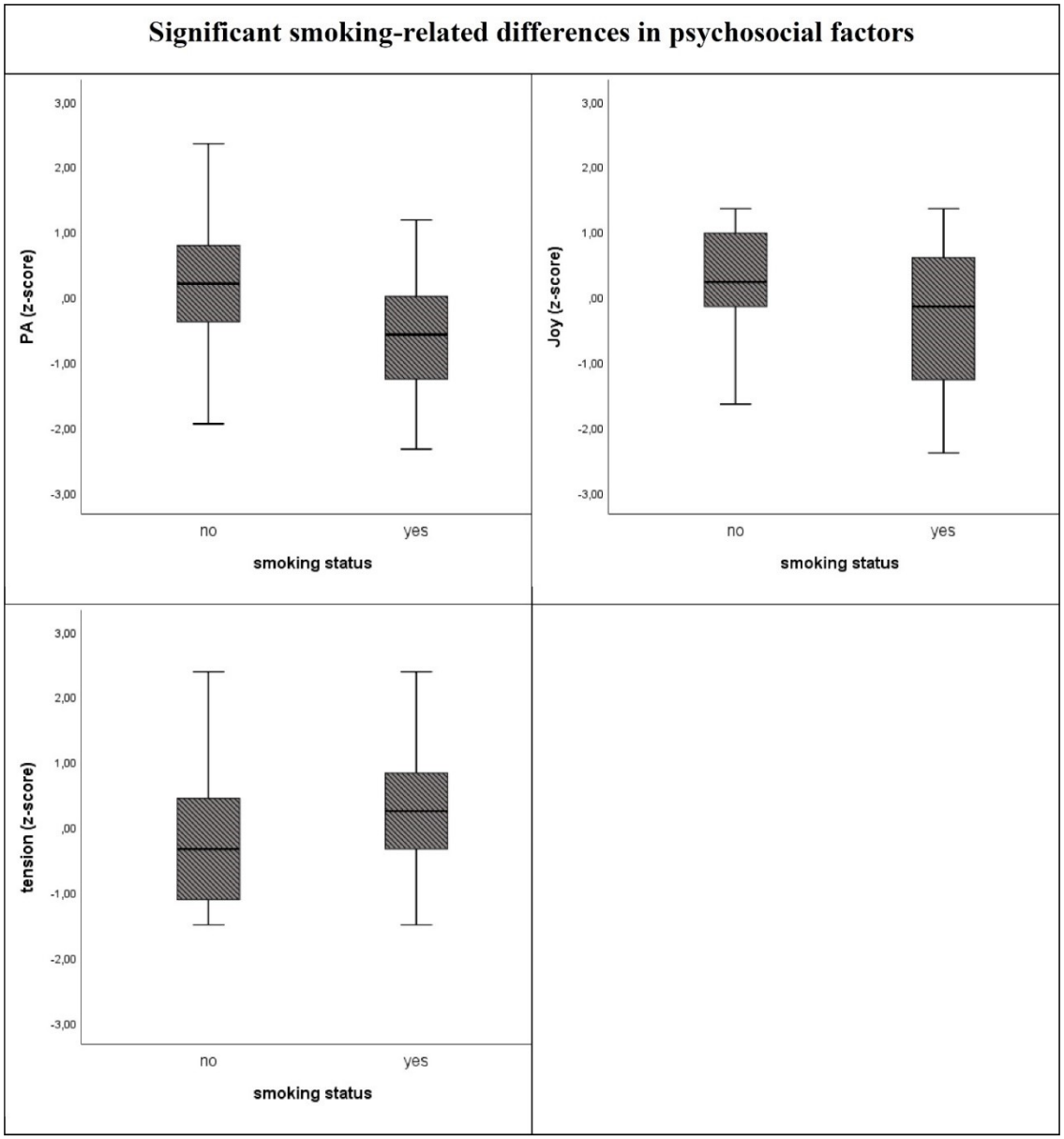

Figure A.2: Visualization of significant differences in psychosocial factors (continued)

Table A.1: Detailed Information of used questionnaires

Dimension	Scale	Subscale	Item ID		Cronbach α
Mental health	PANAS	Positive affect	PA1 PA 2 PA 4 PA 7 PA 9	PA 10 PA 12 PA 14 PA 18 PA 20	.81
		Negative affect	NA 3 NA 5 NA 6 NA 8 NA 11	NA 13 NA 15 NA 16 NA 17 NA 19	.84
	STAI-T		STAIT1 (-) STAIT2 STAIT3 STAIT4 STAIT5 STAIT6 (-) STAIT7 (-) STAIT8 STAIT9 STAIT10 (-)	STAIT11 STAIT12 STAIT13 (-) STAIT14 STAIT15 STAIT16 (-) STAIT17 STAIT18 STAIT19 (-) STAIT20	.86
	CES-D		CES-D1 CES-D2 CES-D3 CES-D4 (-) CES-D5 CES-D6 CES-D7 CES-D8 (-) CES-D9 CES-D10	CES-D11 CES-D12 (-) CES-D13 CES-D14 CES-D15 CES-D16 (-) CES-D17 CES-D18 CES-D19 CES-D20	.83
Perceived stress and coping I	PSQ-R	Worries	PSQ5 PSQ7 PSQ10	PSQ13 PSQ15	.77
		Tension	PSQ1 (-) PSQ6 (-) PSQ9	PSQ17 PSQ18	.71
		Joy	PSQ4 (-) PSQ8 (-) PSQ12 (-)	PSQ14 (-) PSQ16 (-)	.76
		Demands	PSQ2 PSQ3 PSQ11	PSQ19 (-) PSQ20	.74

Table A.1: Detailed Information of used questionnaires (continued)

Dimension	Scale	Subscale	Item ID		Cronbach α
Perceived stress and coping II	SVF-48	Deemphasizing	STAIT7 STAIT16 STAIT19	STAIT32 STAIT40 STAIT44	.86
		Distraction	STAIT8 STAIT13 STAIT21	STAIT27 STAIT38 STAIT46	.80
		Control of situations	STAIT5 STAIT9 STAIT18	STAIT31 STAIT36 STAIT47	.67†
		Positive self-instructions	STAIT3 STAIT15 STAIT22	STAIT28 STAIT30 STAIT43	.84
		Positive use of support	STAIT1 STAIT6 STAIT20	STAIT26 STAIT34 STAIT42	.87
		Escape	STAIT2 STAIT11 STAIT17	STAIT25 STAIT35 STAIT48	.89
		Mental occupation	STAIT4 STAIT12 STAIT23	STAIT29 STAIT37 STAIT41	.93
		Resignation	STAIT10 STAIT14 STAIT24	STAIT33 STAIT39 STAIT45	.81
Emotional competence	SEAS	Perception of one's own emotions (EE)	SEAS1 (-) SEAS5 (-) SEAS13 SEAS22 SEAS26 (-)	SEAS33 SEAS40 (-) SEAS45 (-) SEAS49 (-)	.73
		Perception of the emotions of others (AE)	SEAS3 SEAS9 SEAS24 SEAS28 SEAS30 SEAS36	SEAS37 SEAS43 SEAS44 SEAS46 SEAS48 (-)	.83
		Control over the expression of emotions (EC)	SEAS4 (-) SEAS6 (-) SEAS14 (-) SEAS17 (-)	SEAS23 (-) SEAS35 (-) SEAS41	.53†
		Masking of emotions (M)	SEAS7 SEAS10 (-) SEAS15 SEAS19	SEAS25 (-) SEAS31 SEAS38 SEAS42	.77

Table A.1: Detailed Information of used questionnaires (continued)

Dimension	Scale	Subscale	Item ID		Cronbach α
Emotional competence	SEAS	Regulation of one's own emotions (ER)	SEAS2	SEAS20 (-)	.67†
			SEAS11 (-)	SEAS27 (-)	
			SEAS16 (-)	SEAS32	
		Regulation of the emotions of others (AR)	SEAS8 (-)	SEAS29 (-)	.60†
			SEAS12	SEAS34 (-)	
			SEAS18 (-)	SEAS39 (-)	
			SEAS21 (-)	SEAS47	

(-) reverse coded; † $\alpha \leq .70$