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Individual Differences in Cross-System Physiological Activity at Rest and in Response to Acute Social Stress

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ABSTRACT

Objective: Individual differences in long-term cardiovascular disease risk are related to physiological responses to psychological stress. However, little is known about specific physiological response profiles in young adults that may set the stage for long-term increased cardiovascular disease risk. We investigated individual differences in profiles of resting cardiovascular physiology and stress reactivity, combining parasympathetic, sympathetic, and hemodynamic measures.

Methods: Participants (n = 744, 71% women, mean [standard deviation] age = 20.1 [2.4] years) underwent the Trier Social Stress Test, while blood pressure (systolic blood pressure, diastolic blood pressure), electrocardiograms (interbeat interval), and impedance cardiograms (preejection period, left ventricular ejection time) were recorded. Respiratory sinus arrhythmia was derived from the combination of the electrocardiogram and the impedance cardiogram. A three-step latent profile analysis (LPA) was performed on resting and reactivity values to derive clusters of individual physiological profiles. We also explored demographic and health behavioral correlates of the observed latent clusters.

Results: For resting physiology, LPA revealed five different resting physiology profiles, which were related to sex, usual physical activity levels, and body mass index. Five cardiovascular stress reactivity profiles were identified: a reciprocal/moderate stress response (Cr1; 29%), and clusters characterized by high blood pressure reactivity (Cr2: 22%), high vagal withdrawal (Cr3; 22%), autonomic coactivation (parasympathetic nervous system and sympathetic nervous system; Cr4; 13%), and overall high reactivity (Cr5; 12%). Men were more likely to belong to the high reactivity (Cr5) cluster, whereas women were more likely to have autonomic coactivation (Cr4).

Conclusions: We identified five cardiovascular physiological reactivity profiles, with individuals displaying generalized hyperreactivity, predominant vagal withdrawal, autonomic coactivation, or blood pressure–specific hyperreactivity. Longitudinal studies are needed to determine whether these profiles are useful in early detection of individuals at high risk for cardiovascular disease.

Key words: autonomic nervous system activity, blood pressure, stress reactivity, impedance cardiography, psychophysiology.

INTRODUCTION

The sympathetic and parasympathetic branches of the autonomic nervous system (ANS) and related hemodynamic processes are essential components of the physiological response to environmental challenges. The balance of activation among these primary stress response subsystems can vary considerably across individuals, both in resting-state and in mental stress–induced reactivity. This is of high physiological relevance, as the resting-state and response profiles regulate variation in a wide range of adaptive processes and behaviors that are involved in many functions in life, such as threat appraisal and response regulation (1). Despite extensive recognition that these response systems are biologically well coordinated and play a role as individual risk markers in the cardiovascular reactivity hypothesis (2), surprisingly little empirical attention has been given to determine how the systems actually interact with each other and interplay in the face of exposure to stressors.

Attempts to advance the understanding of these individual differences in stress reactivity have resulted in models describing specific patterns of physiological (re)activity. In the 1990s, Berntson and colleagues (3) proposed the model of autonomic space. Important target organs involved in stress reactivity (i.e., the heart, lungs, and vascular system) are dually innervated, and the pattern of activation for these organs is not organized along one continuum of parasympathetic dominance to sympathetic dominance, but rather as a function of two independently operating branches of the ANS, referred to as a two-dimensional autonomic space (3). The balance

ACM = Adaptive Calibration Model, **AIC** = Akaike information criterion, **ANOVA** = analysis of variance, **ANS** = autonomic nervous system, **BIC** = Bayesian information criterion, **BMI** = body mass index, **DBP** = diastolic blood pressure, **ECG** = electrocardiogram, **IBI** = interbeat interval, **ICG** = impedance cardiogram, **LPA** = latent profile analysis, **LVET** = left ventricular ejection time, **PEP** = preejection period, **RSA** = respiratory sinus arrhythmia, **SBP** = systolic blood pressure, **TSST** = Trier Social Stress Test

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of parasympathetic and sympathetic cardiac regulation is relevant to health, as it has been shown that too little autonomic regulation (coinhibition of both ANS branches) is associated with poorer health status, prior myocardial infarction, and the presence of type 2 diabetes (4). In addition to the adverse consequences of ANS coinhibition, evidence also suggests that ANS coactivation may be detrimental (i.e., increases the risk of cardiac arrhythmias (5)). Coactivation of the sympathetic and parasympathetic nervous systems has been associated with stimulation of brain areas involved in the intense startle and defense response (6).

Another, more recent psychophysiological model describes four different physiological reactivity profiles that take into account the functional developmental changes that occur under stressful conditions and environments (i.e., the Adaptive Calibration Model [ACM]) (1). The model discriminates between four profiles based on the Biological Sensitivity to Context theory by Ellis and Boyce (7), including a "sensitive" profile (low stress, protective environment; high stress responsivity), a "vigilant" profile (highly stressful environments, high reactivity), an "unemotional" profile (low or absent stress reactivity), and a "buffered" profile (moderately stressful environments, moderate stress reactivity) (1). Several recent studies have investigated these profiles in data from youths (8) and adolescents (9). Although the study in youths (8) only investigated the activation of parasympathetic (respiratory sinus arrhythmia [RSA]) and sympathetic nervous system (skin conductance), the study in adolescents also examined hypothalamus-pituitary-adrenal axis activity and included boys only (9). In the latter study, three of four adolescents were in the normative buffered profile, growing up in normative environments with moderate exogenous stress levels. This profile is likely to be associated with a reduced risk of developing cardiovascular disease. This study also examined demographic and behavioral correlates of the revealed clusters; however, it found little relationships because of low statistical power. A further study examining reactivity profiles reported the presence of six distinctive profiles, with the majority of children again fitting in a pattern of cross-system moderate reactivity. Smaller groups showed parasympathetic-specific reactivity, high multisystem reactivity, hypothalamus-pituitary-adrenal axis–specific reactivity, and unresponsiveness. These groups of children significantly differed in socioeconomic status, family adversity, and age (10). These studies indicate that substantial individual differences exist that already develop in early life, which may influence long-term cardiovascular health outcomes.

There have been several other studies examining within-person profiles of stress reactivity. One study using a variable-centered clustering approach examined the summary measures heart rate and blood pressure, and arrived at high, medium, and blunted reactivity solutions (11), showing that the exaggerated reactivity group was associated with a 5-year increased risk of hypertension. Another recent but relatively underpowered analysis used machine learning to arrive at specific clusters and analyzed sympathetic autonomic arousal and summary measures (cardiac output, preejection period [PEP], left ventricular ejection time [LVET], skin conductance), showing that there were two reactivity profiles characterized by a different size of reactivity and one nonresponsive profile (12).

Although the previously described profiles all involve the size of stress reactivity, large individual differences exist in resting physiology as well (13). The resting, prestress level of cardiovascular activity may be related to the magnitude of cardiovascular response, which has been formulated in the "law of initial values." Wilder (14) defined this concept such that when the resting output of an organ increases, the size of its response to a given stimulus diminishes. Moreover, allostatic load theory (15,16) suggests that the chronic presence of stressors and their biological responses results in allostatic load on various organs and biological systems, such as the cardiovascular system. Allostatic load possibly results in gradually increasing resting levels (e.g., blood pressure and heart rate), eventually becoming pathophysiological. Both theories highlight the importance of investigating profiles of *baseline* levels of cardiovascular functioning, in addition to profiles of stress reactivity.

Information on profiles of baseline autonomic and hemodynamic arousal and profiles of stress reactivity in adults is relatively scarce. As the brain is still maturing and prefrontal control over reactivity still increases substantially after adolescence, different patterns may arise from those previously observed in children and young adolescents (8–10). We therefore aimed to identify latent profiles of the cardiovascular resting state, as well as profiles of stress reactivity of parasympathetic (RSA), sympathetic (PEP, LVET, interbeat interval [IBI] as a net measure of autonomic activation), and hemodynamic (systolic blood pressure [SBP], diastolic blood pressure [DBP]) response systems in healthy young adults and examine whether demographic and life-style factors are associated with these profiles, as they may be related to changes in health (4).

METHODS

Sample

The overall aim of this investigation, the "PHysiological and EMOtional stress Reactivity" (PHEMORE) study, is to examine the role of individual differences related to personality and mood in predicting reactivity to mental stress among young adults. In total, a convenience sample of 744 undergraduate students from Tilburg University, the Netherlands (71% women, mean [standard deviation] age = 20.1 [2.4] years) was included in the PHEMORE study. Participants took part in the study in exchange for course credits. Data were collected from January 2011 to June 2016. Exclusion criteria were a history of heart disease, epilepsy, or conditions preventing the participant to wear a blood pressure device or electrodes. Twenty of the 744 participants took part in a nonstress control Trier Social Stress Test (TSST), and for these participants, only baseline data were used in the current analyses. The Ethics Review Board Social and Behavioral Sciences of Tilburg University approved the study protocol. All participants gave informed consent before participating and were debriefed afterward.

Procedure

Participants were instructed to refrain from smoking and coffee consumption for 2 hours before testing as well as not to ingest more than three alcoholic beverages during the 24 hours before testing. Upon arrival at the Behavioral Physiology Lab (GO-LAB), all participants were asked to read and sign the informed consent form. Then, they were asked to complete a questionnaire, inquiring about demographics (age, sex, partner status), health behaviors (weekly physical activity habits, daily smoking, weekly alcohol consumption, daily coffee consumption), body composition (height and weight), and medication use. Subsequently, participants were fitted with the cardiovascular measurement equipment. Participants were examined in a sitting position throughout the protocol. After a 10-min resting period, during which we recorded a physiological baseline, participants took part in a 5-minute cognitive task not related to the present analyses and a recovery period (5 minutes). Participants fully recovered from the nonstressful task during this in-between period (rank-order correlations

with resting values: $r = 0.79–0.97$; mean differences with resting values: ΔDBP = 1.3 mm Hg, ΔSBP = −0.13 mm Hg, ΔIBI = 9 milliseconds, ΔPEP = −0.08 milliseconds, ΔLVET = 0.21, ΔRSA = 0.80 milliseconds). The stress-inducing part of the protocol then started using a slightly adapted version of the TSST, followed by a 5-minute recovery period. Participants filled out a second questionnaire at the end of the protocol. The present article reports on the results pertaining to the 10-minute resting phase and the physiological responses to active stressors of the TSST (math and speech).

Stress Manipulation Using the TSST

The TSST is a social stressor during which a participant is asked to perform a math task and to give a prepared speech (17). We adapted the original protocol of the TSST in two ways (1). We asked participants to remain seated throughout the entire procedure, as this is critical for obtaining reliable hemodynamic measures (standing up results in a sympathetic nervous system response that is not related to the social stress component of the TSST) (2). Instead of a job interview, participants were instructed to discuss their own (positive and negative) social skills. Mental arithmetic and speech tasks were performed in front of a two-person audience like in the original design. Previous research has shown that the original TSST procedure (18), as well as our slightly adapted TSST (19,20), produces a significant cardiovascular stress response. Furthermore, we randomized a task order, such that half of the participants first performed the speech task and the other half started with the math task.

Measures

Hemodynamic Variables

SBP and DBP were assessed using an ambulatory blood pressure monitor (ABP monitor type 90207; Spacelabs Healthcare Ltd., Issaquah, Washington). Blood pressures were obtained every 5 minutes during rest (three measurements), one measurement during TSST speech preparation, and every 90 seconds during speech, arithmetic, and recovery (three measurements for each phase). Averages of blood pressure were calculated for each experiment phase. We allowed for a maximum of two missing values each phase (i.e., rest, speech, and arithmetic), meaning that per variable, up to 10% of the cases, we based the average level of a phase on one blood pressure measurement only.

Cardiac Variables

The Vrije Universiteit Ambulatory Monitoring System (VU-AMS 4.6; Vrije Universiteit Amsterdam, the Netherlands) was used to record a continuous electrocardiogram (ECG) and impedance cardiogram (ICG) (21) using a seven-electrode configuration (three for the ECG and four for the ICG: http://www.vu-ams.nl/support/tutorials/hardware/electrodes/) and nonwoven, liquid gel AgCl electrodes (Kendall, Medcat, the Netherlands). The event button on the device was used to indicate start and end times of the phases of the experimental protocol.

VU-AMS software was used to automatically detect all R-peaks in the ECG, and all R-peak markers were visually checked and adjusted when necessary. The signal was visually checked for artifacts (e.g., premature atrial or ventricular contractions), which were removed before scoring the ECG and ICG data. The software automatically marks the starting points of inspiration and expiration derived from the ICG, which were scored for each breath and checked manually for the presence of signal artifacts before analyses (22).

From the corrected ECG signal, period averages were calculated for heart period (IBI). RSA was derived from the combined ECG/ICG signal and averaged per period. Although respiratory behavior and transduction factors in the SA node may affect RSA (23), RSA (using the peak-to-trough method (24)) is recommended as the best noninvasive measure of parasympathetic cardiac activation to date (23,24). From the ICG, we derived systolic time intervals (PEP, LVET), which are considered to index sympathetic cardiac activation (25). The PEP is defined as the time interval between the onset of electromechanical systole (ECG Q-wave onset) and the onset of left ventricular ejection at the opening of the aortic valves, that is, S wave offset, or B-point), and reflects sympathetic influence on cardiac contractility (inotropy). LVET is defined as the time between the opening and closing of the aortic valves (T-wave offset, or X point) (25), and also is a measure of inotropy. PEP and LVET were manually scored from ensemble averages of the ICG of each protocol period by an experienced scorer of ICG signals (N.K.) using the VU-AMS interactive scoring software. Scoring procedures for impedance cardiography have been published previously (26,27). Averages were calculated based on the continuous VU-AMS data for each of the experiment phases.

Demographic and Behavioral Measures

Demographic and behavioral measures were obtained using self-report questionnaires that contained dedicated questions on demographics (age, sex, partner status [yes/no]), health behaviors (physical activity [weekly sports activities; yes, hours per week/no], smoking [yes, amount per day/no], weekly alcohol consumption [glasses], daily coffee consumption [cups]), body composition (height, weight), and medication use (string variable).

Statistical Analysis

Resting levels of the cardiovascular physiology measures were calculated as the mean of the resting period at the start of the experiment session. Reactivity levels were calculated by subtracting the resting level from the average stress level (average response to speech and math). We excluded the preparation phase, as anticipating a stressor is a passive stressor, whereas speech and math are active stressors, which we were interested in. First, a manipulation check was performed, testing whether stress values differed significantly from resting values by inspecting the within-subject effects of time using repeated-measures analysis of variance (ANOVA) with two time levels: rest − stress (average of the TSST math and speech tasks). In addition, we correlated each baseline measure with each reactivity measure and provided a supplemental table (Table S3, http://links.lww.com/PSYMED/A707).

To answer the main research questions, a three-step latent profile analysis (LPA) was applied to the resting data and to the reactivity data using the LatentGold software package (LatentGOLD 5.1; Statistical Innovations, Belmont, Massachusetts). LPA is a form of finite mixture modeling (ML based) used to identify the potential unobserved subgroups of individuals (or *clusters*) among the set of indicators (28). All available physiological data were included in the analyses. Possible covariates of retrieved clusters were tested in a separate step using the three-step option, consistent with recommendations for LPA modeling (29). Specifically, the three-step LPA was performed using the following steps:

In the first step, we tested which of the models with increasing numbers of classes (1–8) provided the best fit for the data. In LatentGOLD, differences in patterning and the level of activation may result in differences between classes. The latent class analyses were done separately for resting-state and reactivity values, and included PEP, LVET, RSA, IBI, SBP, and DBP. Cases were assigned to latent classes, and each model was evaluated by three fit indices: the Akaike information criterion (AIC), the AIC3, and the Bayesian information criterion (BIC), for all of which lower values indicate the better fit. It is important to point out that LPA takes classification inaccuracy into account, and hence, every individual receives a probability score of belonging to each class. When the best-fitting model was known and chosen, we ran that model again (step 2), to export the posteriors (i.e., probabilities for class membership for all classes and all individuals) to the original data file. Each participant received a likelihood of belonging score for each profile ranging from 0.00 to 1.00. Sensitivity analysis were used to examine whether the same profiles would emerge when pulling two random selections of the main sample and when splitting the file by sex, task order, and calculating separate reactivity values for the separate components of the TSST (math and speech).

The association of demographic variables and health behaviors (sex, age, smoking, physical activity, body mass index [BMI]) with class membership was estimated in the third step, examining these associations in one model. The magnitude of association of each class with demographics and health behaviors was estimated using logistic regression coefficients,

with the largest class as reference. These logistic regression coefficients were translated into class membership probabilities (i.e., odds ratios and 95% confidence interval) to simplify interpretation. For comparison purposes, in the supplemental materials, we also provide the standard Pearson/Spearman correlations between the demographic and health behaviors with the individual physiological measures on which the profiles are based (traditional variable-centered approach). The continuous probability scores for resting and reactivity profiles were then related to each other using Pearson correlations to examine whether a higher score of belonging to a certain resting profile was associated with a higher likelihood of belonging to a certain reactivity profile.

To examine the relationship between the resting-state profiles with subsequent individual measures of autonomic cardiac reactivity (RSA, IBI, PEP, LVET) and blood pressure reactivity (SBP, DBP) measures, ANOVA was used with the resting cluster as between-subject variable. Effect sizes of the ANOVA models are presented as η^2. NB. For the figures, we used heart rate instead of IBI, for presentation purposes. All analyses were conducted using Latent GOLD 5.1 (30) and SPSS v.24.0 (IBM Corp., Armonk, New York).

RESULTS

Sample Characteristics and Manipulation Check

Table 1 shows the sample characteristics. The study included 744 physically healthy individuals, of which 71% were female, and the mean (standard deviation) age was 20.1 (2.4) years. Participants had a mean (standard deviation) BMI of 21.8 (2.8) kg/m^2, the majority engaged in regular physical activity, and 15% were current smokers (Table 1).

TABLE 1. Sample Characteristics

	Values
Demographics	
Female sex	525 (71%)
Age, y	20.1 (2.4)
Single	401 (55%)
Health behaviors	
BMI, kg/m^2	21.8 (2.8)
Smoking (current)	108 (15%)
Regular exercise, y	482 (66%)
Resting physiology	
RSA, ms	85.0 (41.5)
PEP, ms	90.1 (10.6)
SBP, mm Hg	123.0 (10.1)
DBP, mm Hg	74.9 (7.4)
LVET, ms	290.3 (22.8)
IBI, ms	831.7 (111.9)
Reactivity to stress	
ΔRSA, ms	−16.6 (34.6)
ΔPEP, ms	−5.9 (5.4)
ΔSBP, mm Hg	17.8 (9.5)
ΔDBP, mm Hg	13.9 (7.3)
ΔLVET, ms	−17.1 (20.7)
ΔIBI, ms	−149.6 (89.1)

SD = standard deviation; BMI = body mass index; RSA = respiratory sinus arrhythmia; PEP = preejection period; SBP = systolic blood pressure; DBP = diastolic blood pressure; LVET = left ventricular ejection time; IBI = interbeat interval.

Values are presented as *n* (%) or mean (SD).

A manipulation check using repeated-measures ANOVA, with time (baseline rest, stress) as an independent variable, confirmed that the TSST was successful in inducing a physiological stress response for all autonomic and hemodynamic measures (SBP: $F(1,674) = 2372.13$, $p < .001$; DBP: $F(1,675) = 2478.58$, $p < .001$; IBI: $F(1,606) = 1711.13$, $p < .001$; RSA: $F(1,593) = 137.10$, $p < .001$; PEP: $F(1,579) = 691.42$, $p < .001$; LVET: $F(1,580) = 394.92$, $p < .001$). Table 1 displays the average resting and reactivity values for each of the measures.

Resting Physiological Profiles

An LPA including all cases with resting baseline data was used to explore the presence of latent autonomic and hemodynamic resting-state profiles. Table 2 reports the fit statistics of the subsequent models with increasing numbers of clusters in the upper panel. Results showed that a five-cluster model (in bold) fit the data best, as larger models had a worse (i.e., higher) BIC.

Sensitivity analysis (performing the same cluster analysis on two random selections of the main sample) rendered the same solution. In addition, the same held for sex, meaning that a five-cluster solution was the best-fitting model for both men and women, although specific physiological characteristics of the components differed for men versus women (data not shown), suggesting a role for sex as a covariate. We analyzed sex as a possible determinant of the latent profiles in subsequent analyses. Figure 1 depicts the averages of the measures included in the five profiles derived from the total sample.

As shown in Figure 1, the largest cluster (*C1: sympathovagal balance, normative BP*) comprised 30% ($n = 248$) of the sample, showing a profile of sympathovagal balance and normative blood pressure. Cluster 2 (*C2: high parasympathetic*) comprised 26% ($n = 193$) of the sample and was characterized by an elevated resting activation of the parasympathetic nervous system and accordingly a slower heart rate, otherwise comparable to cluster 1. Cluster 3 (*C3: high SBP*) included 16% ($n = 119$) of the sample and was characterized by high blood pressure, whereas sympathovagal balance showed trends toward parasympathetic dominance. The fourth cluster (*C4: low parasympathetic*) comprised 15% ($n = 112$) of the sample, in which individuals were characterized by a low parasympathetic tone and high sympathetic activation and, as a consequence, high heart rate. In addition, SBP was elevated. The final cluster (*C5: active PNS, PEP/LVET balance favoring contractility*) consisted of 13% ($n = 97$) of the sample, and individuals in this cluster were characterized by high contractility (LVET) and high parasympathetic activity, with all other variables being moderately activated, except PEP, which was less active than average.

Demographic and Health Behavior Correlates of the Resting Profiles

Table 3 shows the prevalence and means of the tested class determinants, as well as the estimates (odds ratio [95% confidence interval]) for each demographic or health behavior factor for class membership. Results showed that in the demographic model, men were four times as likely to be in the high SBP cluster (C3) and twice as likely to be in the high contractility cluster (C5). Individuals who engaged less often in regular physical activity were more likely to be in the low vagal cluster (C4), and a higher

TABLE 2. Fit Statistics for Subsequent Models With Increasing Number of Classes for Baseline Arousal (Upper Panel) and Stress Reactivity (Lower Panel)

			BLRT			
	Model	LL	−2LL Diff	Bootstrapped *p* Value	BIC	NPar
Baseline arousal	1 profile	−16,479.0	—		33,037.01	12
	2 profiles	−16,236.8	484.37	<.001	32,638.25	25
	3 profiles	−16,129.1	215.36	<.001	32,508.27	38
	4 profiles	−16,038.3	181.67	<.001	32,412.42	51
	5 profiles	**−15,969.9**	**136.74**	**<.001**	**32,361.28**	**64**
	6 profiles	−15,930.4	79.08	<.001	32,367.80	77
	7 profiles	−15,890.2	80.37	<.001	32,373.04	90
	8 profiles	−15,867.8	44.82	.010	32,413.82	103
Stress reactivity	1 profile	−15,560.3	—		31,199.67	12
	2 profiles	−15,199.7	721.30	<.001	30,563.97	25
	3 profiles	−15,119.3	160.75	<.001	30,488.81	38
	4 profiles	−15,048.5	141.54	<.001	30,432.87	51
	5 profiles	**−14,984.3**	**128.50**	**<.001**	**30,389.98**	**64**
	6 profiles	−14,951.1	66.28	<.001	30,409.30	77
	7 profiles	−14,925.4	51.50	<.001	30,442.40	90
	8 profiles	−14,902.2	46.39	.004	30,482.63	103

LL = log likelihood; BLRT = Bootstapped likelihood ratio test, BIC = Bayesian information criterion; NPar = number of parameters.
The best-fitting model is indicated in boldface.

BMI was characteristic of the high SBP cluster (C3). We also examined the bivariate correlations between the demographic and health behaviors with the baseline physiological measures (Supplemental Table S1, http://links.lww.com/PSYMED/A707), which revealed a consistent pattern of results.

Profiles of Cross-System Physiological Stress Reactivity

We investigated the clustering of physiological measures in response to social stress (cardiovascular reactivity measures), which is qualitatively different from predicting individual, univariate reactivity measures, as these current analyses reveal clustering in the within-person reactivity *profiles*. The lower panel of Table 2 shows the model fits of eight subsequent cluster analyses, with increasing number of clusters. The lowest BIC and therefore the best-fitting, most parsimonious model included five clusters.

Sensitivity analysis using two random selections of the main sample, and although splitting by sex, showed the stability of this five-cluster solution. Moreover, repeating the analysis for math and speech reactivity separately arrived at the same conclusion, with similar levels of physiological activation. With respect to task order, a five-cluster solution with similar profiles was present in participants who did the speech task first. In participants who did the math task first, however, cluster 2 was not present very clearly, and therefore, a four-cluster solution was better. The other profiles were present with similar averages in this latter analysis (see online supplement for the data, http://links.lww.com/PSYMED/A707). Figure 2 visualizes the cardiovascular reactivity profiles for the clusters that emerged from the LPA. The first cluster (C1: "balanced"), comprising 29% (n = 216) of the sample, shows a moderate stress response, with moderate increases in blood pressure and

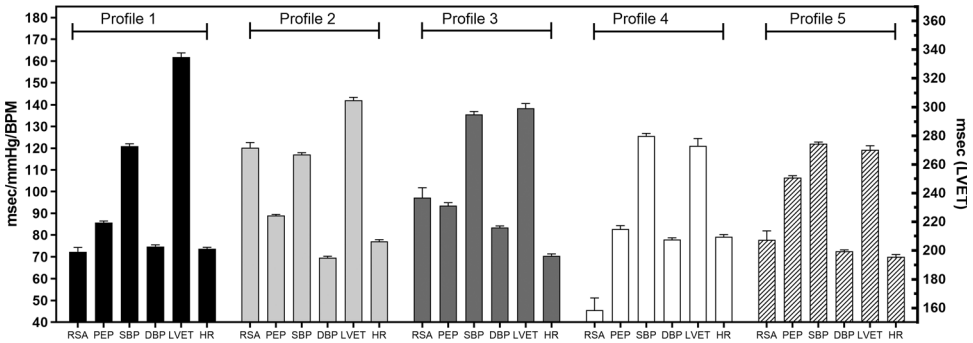

FIGURE 1. Baseline arousal profiles. RSA = respiratory sinus arrhythmia (assessed with the peak-to-valley method; in milliseconds); PEP = preejection period (in milliseconds); SBP = systolic blood pressure (in millimeters of mercury); DBP = diastolic blood pressure (in millimeters of mercury); LVET = left ventricular ejection time (in milliseconds); HR = heart rate (in beats per minute). Right *y*-axis is the scale for LVET. Error bars denote 1 standard error of the mean.

TABLE 3. Demographic and Health Behavior Correlates of Physiological Baseline Profiles

	Cluster 1 "SV Balance – Normative BP"		Cluster 2 "High Vagal"		Cluster 3 "High SBP"		Cluster 4 "Low Vagal"		Cluster 5 "Active PNS, PEP/LVET Balance Favoring Contractility"			
Class size, %	31		26		16		15		13			
	M/%	Ref.	M/%	OR (95% CI)	M/%	OR (95% CI)	M/%	OR (95% CI)	M/%	OR (95% CI)	Wald	*p*
Sex (men)	19%	1	25%	1.33 (0.70–2.52)	**50%**	**4.16 (2.09–8.29)**	26%	1.82 (0.80–4.12)	**31%**	**2.25 (1.09–4.64)**	**20.53**	**<.001**
Age, y	20.0	1	20.1	0.98 (0.89–1.09)	20.7	0.99 (0.88–1.11)	19.9	0.91 (0.74–1.13)	19.7	0.90 (0.73–1.11)	1.45	.84
Smoking (yes)	12%	1	19%	1.69 (0.81–3.51)	16%	1.13 (0.46–2.8)	14%	1.08 (0.41–2.83)	11%	0.93 (0.31–2.77)	3.05	.55
Exercise (yes)	65%	1	73%	1.51 (0.86–2.64)	67%	0.99 (0.51–1.91)	**39%**	**0.31 (0.17–.59)**	**74%**	1.45 (0.69–3.07)	**28.63**	**<.001**
BMI, kg/m^2	21.3	1	22.1	1.12 (0.99–1.25)	**23.0**	**1.22 (1.08–1.39)**	21.8	1.11 (0.97–1.26)	21.2	1.11 (0.86–1.14)	**13.32**	**.010**

SV = sympathovagal; BP = blood pressure; SBP = systolic blood pressure; PNS = peripheral nervous system; PEP = preejection period; LVET = left ventricular ejection time; M = mean; OR = odds ratio; CI = confidence interval; BMI = body mass index.

Values in bold refer to group differences with $p < .05$

heart rate, and autonomic balance characterized by relatively more parasympathetic than sympathetic change in response to the TSST. The second profile (C2: "high BP reactivity") is characterized by high SBP and DBP reactivity, as well as reciprocal ANS activation (withdrawing parasympathetic and increasing sympathetic cardiac drive) and comprised 22% ($n = 164$) of the sample. The third profile ("high parasympathetic reactivity") was characterized by reduction of RSA, whereas other measures displayed moderate reactivity (22%; $n = 164$). Cluster 4 ("blunted, ANS coactivation") was characterized by low autonomic coactivation and a relatively moderate blood pressure reactivity, and virtually no heart rate and contractility (LVET) response (13%; $n = 97$). The fifth cluster ("high contractility and parasympathetic reactivity") was, similar to cluster 3, characterized by a large parasympathetic withdrawal. In this fifth cluster though, this was paired with disproportionately high blood pressure responses and a large increase in heart rate. The LVET reduction was also largest in this fifth cluster (12%; $n = 89$).

Demographic and Health Behavior Correlates of the Reactivity Profiles

Table 4 displays the demographic and health behavioral correlates of the five reactivity clusters. As for demographics, men were twice as likely to be in cluster 5, characterized by exaggerated autonomic responding and high SBP reactivity, as compared with the "reciprocal ANS response & moderate BP" cluster 1 (i.e., reference). Women were more likely to be in cluster 4, characterized by a relatively blunted response and ANS coactivation. Participants in this fourth cluster also were inclined to be older. Smoking, performing regular physical activity, and BMI were unrelated to the clusters. As with the baseline measures, we examined the bivariate correlations between the demographic and health behaviors with the physiological responses (Supplemental Table S1, http://links.lww.com/PSYMED/A707), which revealed a consistent pattern of results.

Correspondence Between Latent Resting and Reactivity Clusters

Resting-state profiles were associated with *individual* physiological reactivity measures (Supplemental Table S2, http://links.lww.com/PSYMED/A707). ANOVA analyses revealed significant associations of cluster membership during rest with subsequent RSA reactivity ($\eta^2 = 0.16$), IBI reactivity ($\eta^2 = 0.16$), PEP reactivity ($\eta^2 = 0.07$), and LVET reactivity ($\eta^2 = 0.04$), but not for SBP reactivity ($\eta^2 = 0.01$) or DBP reactivity ($\eta^2 = 0.02$).

We specifically examined the correspondence between the five resting physiology profiles (C1 through C5) with the five cardiovascular reactivity profiles (Cr1 through Cr5; Table 5). The correlations between the resting profiles and reactivity profiles showed that there were only modest associations between the profiles, suggesting that baseline patterns determine reactivity patterns only in a limited manner. The observed correlations were physiologically fitting though, as the high resting blood pressure cluster was less likely to occur together with the high blood pressure reactivity profiles. Similarly, the high vagal activity profile at rest was associated with two reactivity profiles characterized by large parasympathetic withdrawal reactivity in response to the acute stressors. The normative resting profile was unrelated to the balanced moderate

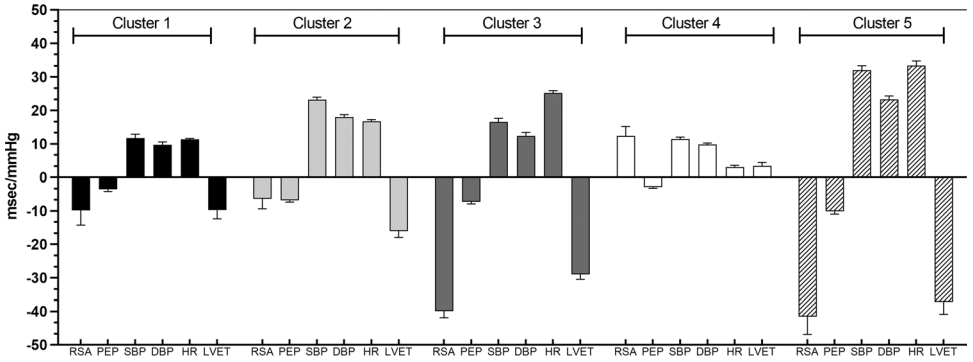

FIGURE 2. Profiles of cardiovascular reactivity. Reactivity values stratified by profile. RSA = respiratory sinus arrhythmia (assessed with the peak-to-valley method; in milliseconds); PEP = preejection period (in milliseconds); SBP = systolic blood pressure (in millimeters of mercury); DBP = diastolic blood pressure (in millimeters of mercury); LVET = left ventricular ejection time (in milliseconds); HR = heart rate in (beats/minute). Error bars denote 1 standard error of the mean.

reactivity profile, nor was any other resting profile associated with the adaptive reactivity profile (Table 5).

For comparison purposes, we also present the bivariate correlations between the baseline physiological measures and the corresponding physiological reactivity measures (Supplemental Table S3, http://links.lww.com/PSYMED/A707). The overall results of these correlations indicate that in general the intercorrelation of the specific physiological measures is higher than the correlations across measures. The data also indicate negative correlations between resting levels and reactivity (Δ) measures at the variable level. These data indicate that the associations between resting physiology and cardiovascular stress reactivity are complicated and support the unique additive value of the cluster-based approach based on LPA presented in Table 5.

DISCUSSION

The current study evaluated the presence of latent clustering in the cardiovascular resting state, as well as cardiovascular reactivity in young adults. We also investigated demographic and health behavior correlates of the physiological resting and reactivity profiles and predicted the magnitude of individual cardiovascular reactivity measures from the resting-state profiles. The results support three general conclusions. First, five distinctive cardiovascular resting profiles were identified that differed in autonomic balance and the level of resting SBP. Second, results indicate that men were twice as likely to be in profiles with higher resting blood pressure and increased sympathetic cardiac drive. Furthermore, five distinctive reactivity profiles were extracted that differed in autonomic balance and blood pressure reactivity. Sex and age were associated with these profiles. The resting profiles were significantly related to individual cardiovascular reactivity measures, particularly reactivity of the ANS, heart rate, and cardiac contractility. However, the five baseline profiles corresponded only modestly with the five reactivity profiles, suggesting that both individual cardiovascular measures and their within-person profile may provide unique information about long-term cardiovascular risk.

The observed variation in the profiles of autonomic balance, chronotropic, and inotropic measures during rest is in concordance with the autonomic space model developed by Berntson and colleagues (3). However, this comprehensive theory of autonomic control does not discriminate between resting physiology and reactivity and assumes that resting autonomic balance will influence the phasic stress response. The correlations between resting and reactivity profiles show that this may not always be the case. Autonomic regulation functions within several autonomic constraints, one of which is the "law of initial values," which among others

TABLE 4. Demographic and Health Behavior Correlates of Physiological Reactivity Profiles

	Cluster 1 "Reciprocal ANS Response + Moderate BP"		Cluster 2 "High BP"		Cluster 3 "High PNS & HR Reactivity"		Cluster 4 "Blunted, ANS Coactivation"		Cluster 5 "High Parasympathetic and Hemodynamic Reactivity"		Wald	*p*
Class size, %	29		22		22		13		12			
	M/%	Ref.	M/%	OR (95% CI)	M/%	OR (95% CI)	M/%	OR (95% CI)	M/%	OR (95% CI)	Wald	*p*
Sex (men)	26%	1	33%	1.78 (0.96–3.31)	28%	1.29 (0.66–2.54)	14%	**0.31 (0.10–1.00)**	**39%**	**2.27 (1.18–4.37)**	**16.81**	**.002**
Age, y	20.1	1	19.8	0.95 (0.83–1.09)	19.9	0.96 (0.82–1.11)	21.1	**1.19 (1.00–1.42)**	20.0	0.95 (0.82–1.10)	**10.23**	**.037**
Smoking (yes)	19%	1	9%	0.45 (0.18–1.09)	14%	0.68 (0.31–1.51)	18%	0.95 (0.35–2.56)	12%	0.54 (0.22–1.32)	5.034	.28
Exercise (yes)	67%	1	62%	0.70 (0.40–1.22)	67%	0.97 (0.53–1.78)	61%	0.82 (0.40–1.67)	65%	0.79 (0.42–1.47)	1.94	.75
BMI, kg/m^2	21.8	1	21.5	0.98 (0.87–1.09)	21.9	1.03 (0.94–1.13)	22.4	1.05 (0.94–1.18)	21.7	1.00 (0.89–1.12)	1.47	.83

ANS = autonomic nervous system; BP = blood pressure; PNS = peripheral nervous system; M = mean; Ref. = reference; HR = heart rate; OR = odds ratio; confidence interval; BMI = body mass index.

TABLE 5. Correlations (95% Confidence Interval) Between the Latent Cardiovascular Resting Clusters and Latent Cardiovascular Reactivity Clusters

	Reactivity Cluster 1 "Reciprocal ANS Response + Moderate BP"	Reactivity Cluster 2 "High BP"	Reactivity Cluster 3 "High PNS & HR Reactivity"	Reactivity Cluster 4 "Blunted, ANS Coactivation"	Reactivity Cluster 5 "High PNS and Hemodynamic Reactivity"
Resting cluster 1 "SV balance, normative BP"	0.05 (−0.02 to 0.12)	.09 (0.01 to 0.17)*	**−0.20 (−0.26 to −0.13)*** **	0.09 (0.01 to 0.17)*	−0.03 (−0.11 to 0.05)
Resting cluster 2 "high vagal tone, low HR"	−0.01 (−0.08 to 0.07)	**−0.19 (−0.25to −0.13)*** **	*0.20 (0.12 to 0.29)****	**−0.17 (−0.22 to −0.11)*** **	*0.15 (0.07 to 0.23)****
Resting cluster 3 "high SBP"	0.02 (−0.06 to 0.11)	**−0.13 (−0.19 to −0.06)****	*0.19 (0.10 to 0.28)****	**−0.09 (−0.14 to −0.04)***	−0.01 (−0.08 to 0.06)
Resting cluster 4 "low vagal tone, increased HR"	−0.04 (−0.11 to 0.03)	*0.16 (0.07 to 0.23)****	**−0.17 (−0.21 to −0.11)*** **	*0.17 (0.07 to 0.25)****	**−0.10 (−0.15 to −0.04)****
Resting cluster 5 "active PNS, PEP/LVET balance favoring contractility"	−0.04 (−0.11 to 0.04)	*0.10 (0.02 to 0.17)**	−0.03 (−0.10 to 0.05)	0.02 (−0.06 to 0.10)	−0.05 (−0.11 to 0.02)

ANS = autonomic nervous system; BP = blood pressure; PNS = peripheral nervous system; HR = heart rate; SV = sympathovagal; SBP = systolic blood pressure; PEP = preejection period; LVET = left ventricular ejection time.
Presented are Pearson correlations and bootstrapped 95% confidence intervals. $n = 724$ for all correlations, as all participants received a likelihood of belonging score for each cluster, ranging from 0.00 to 1.00.
Values that are less likely to occur together are in bold, and those that are more likely to occur together are in italics.
*$p < .05$.
**$p < .01$.
***$p < .001$.

describes that the size of the phasic response is dependent on the baseline (14). This perspective is exemplified in our analyses where the resting profiles predicted the distal individual reactivity measures: resting profiles 2 and 3, in which parasympathetic tone is high, were predictive of high (phasic) parasympathetic withdrawal stress reactivity (Supplemental Table S3, http://links.lww.com/PSYMED/A707). However, this only held for individual measures and not so much for the association between resting and reactivity profiles as presented in Table 5. This means that the tuning of the different central and ANS processes that drive the cardiovascular system during rest and stress reflects different aspects of cardiovascular physiology that may be relevant to long-term health and disease outcomes.

In autonomic coactivation, the net result of autonomic regulation on the heart is highly dependent on the relative dominance of sympathetic and parasympathetic nervous systems (3). In our coactivated reactivity profile (Cr4), this is visualized by the relatively large vagal activation and relatively small sympathetic activation, resulting in the net effect of small heart period and blood pressure responses. This finding is in accordance with prior research (6), and variation in this balance suggests a role for genetic influences. Reciprocal modes of autonomic control yield the largest dynamic range of reactivity and a high degree of stability in the heart's response (3). In the present data, there were three reactivity profiles with reciprocal autonomic regulation, one almost uncoupled profile with hardly any sympathetic activation at all and one coactivation profile. These findings are largely in concordance with Berntson's autonomic space model.

Our results also correspond with selected aspects of the ACM developed in young adolescents and children. One a priori difference is that we analyzed resting physiology separate from reactivity because of methodological and content-related considerations. Furthermore, in the ACM studies (1,7,8), the clusters were mostly based on predetermined cutoffs and associations with the stressfulness of the context children grew up in. Our baseline results concurred reasonably well with results from a latent class analysis of the ACM (9), as we observed three of the four baseline variations (all except the low sympathetic *and* parasympathetic tone) in the present study. Because we based our profiles on hemodynamic data as well, we found two additional profiles that were specifically characterized by individual differences in resting blood pressure. With respect to reactivity, our profiles showed some similarities in terms of autonomic balance (9) but were more specific as well, showing that profiles with a similar autonomic balance differentiated on blood pressure and cardiac contractility. However, we did not relate the observed clusters to early life adversity, and we can therefore not compare our findings with such previous reports. Another study examining profiles of sympathetic autonomic arousal and summary measures was in concordance with our profiles to the extent that sympathetic arousal tends to differ between profiles (12). The current study is broader, though, in showing that the same level of sympathetic arousal may be coupled with differential parasympathetic and hemodynamic activation levels.

There have been some studies relating resting-state cardiovascular physiology to demographic and health behavioral characteristics. With respect to sex differences, meta-analytic evidence shows that women generally have a higher heart rate but also higher parasympathetic modulation compared with men (31). In the current LPA, we examined the prevalence of combinations of

cardiovascular physiological measures. Women were substantially more likely to be in the reference profile than any of the other resting physiology profiles. The reference profile was characterized by autonomic balance and normative blood pressure, normal BMI, and reasonably good health behaviors. With respect to reactivity, men were in general more likely to be in other than adaptive reactivity profiles. Women were also overrepresented in reactivity profile 4, characterized by coactivation of both branches of the ANS, and a blunted heart rate and blood pressure response. In this fourth profile, individuals—all young adults—were relatively older and characterized by lower parasympathetic activation. In the Midlife in the United States daily activities study, parasympathetic heart rate variability was inversely associated with age. Heart rate variability was lower in men (trend) and non-Whites, and higher in smokers (32). In our study, none of the profiles were significantly associated with smoking. The resting "high blood pressure" profile (with exaggerated parasympathetic cardiac tone and low sympathetic cardiac drive) was significantly associated with increased BMI. Prior research shows that a higher BMI was associated with lower parasympathetic tone (33), which is in contrast with our findings. Elevated BMI has been frequently associated with increased blood pressure though (34–36), which is fitting with our findings.

It should be noted that the balance between different measures of the cardiovascular system ultimately determines output and potential physiological burden. In studies that use cardiovascular measures as predictors of incident heart disease or hypertension (e.g., Ref. (37)) and in studies examining cardiovascular responses to stress and exercise (38), (a range of) individual physiological measures are used instead of profiles of these measures. LPA, as used in the present study, enables researchers to focus on the system response, thereby gaining knowledge on the physiological context of the individual measures, and the relative importance of patterning these measures in predicting a distal health outcome. This is especially valuable because our findings suggest that individual measures, as commonly used in stress studies, render different correlations between cardiovascular rest and stress levels from the within-person profiles. It should be noted, however, that LPA-based findings as reported here are hypothesis generating, and both replication studies and longitudinal analyses are needed to document the validity and predictive value of the observed profiles for hard medical outcomes.

The present findings provide indications for potential pathways by which cardiovascular stress responses may influence future health risk. Evidence indicates that exaggerated sympathetic activation is predictive of the incidence of hypertension (39,40), atrial fibrillation (41), and ventricular arrhythmias (42). In contrast, efferent parasympathetic activation is thought to be antiarrhythmic (41,42). Also, too little autonomic regulation is associated with poorer health status, prior myocardial infarction, and the presence of type 2 diabetes mellitus (4). Profiles with relative sympathetic dominance and accompanying high SBP and heart rate during rest and profiles with either autonomic withdrawal of both branches or large reactivity of the sympathetic branch may be at risk for developing cardiometabolic disease in the future. One previous longitudinal study examined the profiles based on heart rate and blood pressure and showed that a profile of overall exaggerated reactivity was associated with a 5-year increased risk of hypertension (11). With respect to the current data, we may conclude that individuals in resting clusters 3 and 4 (high blood pressure and sympathetic dominance [low parasympathetic tone], respectively) and reactivity profiles 2 and 4 (high BP reactivity and low responsiveness, respectively) seem at risk for cardiometabolic disorders, and this hypothesis requires evaluation in future research. The most important predictors of these clusters were lack of physical exercise and high BMI. This suggests that in these clusters we already may see allostatic load at work (15). Research findings suggest that autonomic balance may be restored by regular aerobic training, which is known to result in improvement of resting parasympathetic heart rate variability and a relatively smaller reactivity in response to moderate activation (43).

Future research is needed to replicate the observed clustering of cardiovascular resting and reactivity measures in general population samples and in clinical samples, as well as across time. As we suggest previously, our results advocate that the tuning of the various drives (parasympathetic, sympathetic nervous system, neuroendocrine) of the cardiovascular system is different during rest from that in response to stress. This should be further studied though, as we only give preliminary evidence. It would be very informative to find out whether there is a genetic underpinning to the physiological resting and reactivity clusters, as we previously found for individual cardiovascular measures relevant to the stress response (26,44,45). Furthermore, it would be interesting to find out to what extent the clusters are affected by environmental challenges such as early life stress, like is the case in the ACM study (9), or by current mood.

Statistically derived physiological clusters may not reflect physiologically (or clinically) relevant differences. We will know more about whether the observed profiles have significance, when using them as predictors for long-term cardiovascular outcomes. Future studies could therefore examine the prospective association of cardiovascular physiology activation clusters with incident hypertension or metabolic syndrome. Moreover, aging is an important factor in determining the profiles of autonomic control of the cardiovascular system. Studies show that across the adult age range, the average level of global autonomic regulation seems to decrease linearly with aging (46,47). Average parasympathetic control of heart rate, though, seems to follow a U-shaped curve, with a decreasing heart rate variability (root mean square of successive differences (RMSSD)) until 70 years of age and a gradually increasing variability in the decades thereafter (47). It is important to realize that these findings are based on cross-sectional studies in which by definition the between-subject effects and the within-subject changes are indiscriminately disentangled. The within-subject effect of aging on autonomic cardiac control is not known yet and should be subject to further study. This issue is very relevant when examining age-related changes in cardiovascular resting and reactivity profiles across the adult age range, and the effect on incidence of heart disease.

This study has limitations and strengths. The current study was limited by the fact that we were unable to assess the neurohormonal stress response, which is unfortunate and should be added in future studies all the more because the brain effector circuits related to neuroendocrine and ANS reactivity may in part function independently (48). Adding these might result in novel risk profiles during rest and in response to psychological stressors. Furthermore, we were unable to take measures of preload and afterload (thoracic fluid content, total peripheral resistance) into account, whereas they might affect the size of change in PEP in

response to mental stress (49). It will be important to establish whether indices of preload and afterload have additive value over and above measuring PEP and LVET when determining psychophysiological profiles of cardiovascular risk. Other limitations are our laboratory setting and our apparently healthy undergraduate student sample. Both characteristics interfere with the generalizability of the current findings to real-life settings and to clinical populations. Although the TSST is currently considered to be state-of-the-art for evoking multisystem stress reactivity and was successful in doing so in the present study, these responses still reflect an artificial context. The tasks used in the TSST involve "active coping" tasks (50), and it is possible that different profiles will emerge when other challenge tasks are used, such as passive stressors (e.g., mirror tracing or cold pressor test) or in case of the anticipation of stress (preparation period of the TSST). However, the TSST is potent in producing a fast acute cardiovascular response. Another possible limitation is that in our test protocol, a cognitive task (remembering a list of 15 words, or continuous performance) preceded the TSST, with a 5-minute resting period in between. Although these cognitive tasks are low-impact challenges and participants rested in between, there might have been carryover effects from these tasks to the TSST. We also did not repeat the task in participants, so we cannot conclude on the test-retest reliability of the cardiovascular resting and response profiles. We did do sensitivity analyses though, showing that the same profiles came out for two random subsamples, for women and men, for different task orders, and for reactivity to math and speech separately. The found that stability in the latent profile solution provides confidence in the reported outcome. Finally, we did not include emotional reactivity measures in this study. Studies generally show small associations between physiological stress reactivity and concurrent emotional activation (51,52), but we cannot rule out that emotional reactivity may relate to the resting and reactivity profiles. In addition, examining the relation of these profiles with personality traits would make sense, because of the substantial evidence linking personality to physiological responses, but fell out of the scope of the current article and thus is a recommended focus of future research. Strengths of the study include the large sample size, the novelty of using the three-step LPA, and the inclusion of PEP as a measure of sympathetic cardiac drive, which enabled us to look beyond summary measures such as heart rate and blood pressure.

In conclusion, the current study uncovered distinctive profiles of the physiological resting state and profiles in cardiovascular responses to acute stress. Both sets of profiles were related to demographic measures (i.e., sex, age) and health behavior–related factors (regular exercise, BMI). The current findings may have clinical implications in the field of cardiovascular disease prevention and risk prediction. We identified resting-state and reactivity profiles that were characterized by high blood pressure and sympathetic dominance, and individuals in these clusters were two to four times more likely to be male. It is well documented that high blood pressure under the age of 40 years is predictive of premature heart disease (53). The high SBP cluster also was associated with a higher BMI. Adolescent-increased BMI is a known risk factor for elevated cardiovascular disease risk later in life (54). In addition, sympathetic hyperactivity, portrayed by reduced PEP and/or reduced LVET, poses an elevated risk of hypertension and subsequent heart disease (55). Identifying clusters of resting-state cardiovascular physiology and cardiovascular stress reactivity profiles may help in personalized risk stratification and in prevention, with implications for pharmacotherapy, psychological, and health behavior interventions.

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