

PERIPHERAL PHYSIOLOGICAL MECHANISMS OF CARDIOVASCULAR STRESS  
REACTIVITY

by

Ryan C. Brindle

A thesis submitted to the University of Birmingham  
for the degree of  
DOCTOR OF PHILOSOPHY

School of Sport, Exercise and Rehabilitation Sciences

University of Birmingham

October 2015

UNIVERSITY OF  
BIRMINGHAM

**University of Birmingham Research Archive**

**e-theses repository**

This unpublished thesis/dissertation is copyright of the author and/or third parties. The intellectual property rights of the author or third parties in respect of this work are as defined by The Copyright Designs and Patents Act 1988 or as modified by any successor legislation.

Any use made of information contained in this thesis/dissertation must be in accordance with that legislation and must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the permission of the copyright holder.

---

## **Abstract**

---

This thesis aimed to increase understanding of the underlying physiological sources of the substantial inter-individual variability in heart rate (HR) and blood pressure (BP) reactions to acute psychological stress. This aim was achieved using a multi-method approach that included meta-analysis, laboratory studies, and prospective secondary analysis of epidemiological data. Chapter 2 implicated beta-adrenergic sympathetic activation and parasympathetic withdrawal in the cardiovascular stress response and showed that autonomic changes vary as a function of stress task, age, and sex. Chapter 3 demonstrated that individual differences in a unique HR complexity marker accounted for a significant amount of the observed variance in HR reactivity and that this effect was independent of task performance and changes in autonomic activity and respiration. Chapter 4 revealed that individual differences in resting physiological allostatic load related to HR reactivity such that higher allostatic load indicated lower reactivity. Finally, in Chapter 5, multivariate cluster analysis of HR, systolic and diastolic BP reactivity resolved a large sample into four homogenous clusters, each displaying significantly different reactivity patterns and risk of hypertension at 5-year follow-up. The research reported in this thesis confirms already suspected physiological sources of individual difference but also reveals novel sources that deserve further inquiry.

---

## Acknowledgments

---

I must thank many people for their help in my PhD completion. First and foremost, I must thank my supervisors: Dr Anna C. Phillips, Dr Annie T. Ginty, and Professor Doug Carroll. Over the last three years you have not only fueled my passion and curiosity in research but have also instilled in me the valuable skills to succeed in science; all while making it enjoyable, exciting, and fun. Thank you for being so professionally and personally generous to me.

I have also been fortunate to work with many talented individuals without whom my PhD experience would not have been so rich. My gratitude goes to Dr Sam Lucas for teaching me trans-cranial Doppler sonography, Dr James Fisher for aiding me in carrying out experimentally rigorous physiological measurements, Dr Jet Veldhuijzen van Zanten for teaching me forearm blood flow and hematocrit measurement techniques, Dr Dave McIntyre for helping on numerous occasions handle data processing issues, Professor Janet Lord, Hema Chahal, and Dr Jon Hazeldine for teaching me flow cytometry, Dr Susanne R. de Rooij and Tessa Roseboom for granting me access to the Dutch Famine Birth Cohort dataset, and Dr Adam Bibbey for not only being a valuable research (and conference) partner but also a lot of fun. Also, I must thank all those individuals in the Behavioural Medicine Group for listening to my talks and presentations and supplying truly informative feedback.

A special thanks goes to Professor Sarah Conklin for inspiring me to achieve more than I thought possible. Upon entering Allegheny College I did not know the world of research existed but with her contagious passion for Psychophysiology she inspired me to take on research and constantly push myself beyond my comfort zone. Without your help, confidence, and passion I would not have applied to Birmingham and would not be where I am today.

Outside of the PhD I am blessed to have a wonderful family, without whom I would have never gotten this far. In particular, I would like to thank my Grandparent, Ann Butyn, and the Micai family for their energetic support of my PhD journey. A special thanks must go to Martina Micai for being so supportive during my PhD. I cannot express how much your support, your open-mind, and at times, your patience, has helped me along the way. You've enriched my PhD experience academically, personally, and culturally.

Finally, to my brother Chris and sister Alyssa, thank you so much for being there to talk to me. The many laughs, movie quotes, and memories always made me feel at home. Lastly, to my parents Chris and Wendy, you laid the foundation for this success by fostering in me passion, curiosity, work ethic, creativity, and love. For this I will always be eternally grateful.

---

## Publications and conference presentations produced during the PhD

---

**This thesis comprises the following four original empirical papers:**

1. **Brindle, R.C.**, Ginty, A.T., Phillips, A.C., & Carroll, D. (2014). A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress. *Psychophysiology*, *51*, 964-976.
2. **Brindle, R.C.**, Ginty, A.T., Phillips, A.C., Fisher, J.P., McIntyre, D., & Carroll, D. (accepted). Heart rate complexity: A novel approach to assessing cardiac stress reactivity. *Psychophysiology*
3. **Brindle, R.C.**, Ginty, A.T., Carroll, D., & Phillips, A.C. (under review). High physiological allostatic load relates to blunted cardiac reactivity to acute mental stress.
4. **Brindle, R.C.**, Ginty, A.T., Jones, A., Phillips, A.C., Roseboom, T.J., Carroll, D., Painter, R.C., & de Rooij, S.R. (under review). Cardiovascular reactivity patterns and pathways to hypertension: A multivariate cluster analysis.

**During the period of postgraduate study at the University of Birmingham, the following papers were also published/submitted:**

1. Bibbey, A., Ginty, A.T., **Brindle, R.C.**, Phillips, A.C., & Carroll, D. (under review). Blunted cardiac stress reactors exhibit relatively high levels of behavioral impulsivity.
2. Ginty, A.T., **Brindle, R.C.**, & Carroll, D. (2015). Cardiac stress reactions and perseverance: Diminished reactivity is associated with study non-completion. *Biological Psychology*, *109*, 200-205.
3. **Brindle, R.C.**, Ginty, A.T., & Conklin, S.C. (2013). Is the association between depression and blunted cardiovascular stress reactions mediated by perceptions of stress? *International Journal of Psychophysiology*, *90*, 66-72.

**During the period of postgraduate study at the University of Birmingham, the following conference presentations/posters were made**

1. **Brindle, R.C.**, Ginty, A.T., Phillips, A.C., Bibbey, A., & Carroll, D. (2014). Blunted systolic blood pressure responses to acute psychological stress are related to measures of behavioural perseverance. [Abstract, Poster] 13<sup>th</sup> International Congress of Behavioral Medicine, Groningen, Netherlands
2. **Brindle, R.C.**, Ginty, A.T., Phillips, A.C., & Carroll, D. (2014). A tale of two mechanisms: A meta-analysis of the autonomic basis of cardiovascular stress reactivity. [Abstract, Poster] 72<sup>nd</sup> Meeting of the American Psychosomatic Society, San Francisco, CA. Psychosomatic Medicine, 76, 3, A48.
3. Ginty, A.T., Williams, S.E., **Brindle, R.C.**, Bibbey, A., Phillips, A.C., & Carroll, D. (2014). Do you listen to your head or your heart? Dissociation between psychological and physiological systems. 13<sup>th</sup> International Congress of Behavioral Medicine, Groningen, Netherlands, (Invited Symposium), *International Journal of Behavioral Medicine*, 21 (suppl. 1), S59.
4. **Brindle, R.C.**, Ginty, A.C., Phillips, A.C., & Carroll, D. (2014). A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity. 11<sup>th</sup> Annual Psychology, Health and Medicine Conference, (Symposium), *The Psychological Society of Ireland*.
5. **Brindle, R.C.**, Ginty, A.T., & Conklin. (2013). Symptoms of depression and cardiovascular stress reactivity: The role of stressor type, stress exposure, and stress perception. [Abstract, Poster] 71st Meeting of the American Psychosomatic Society, Miami, FL. Psychosomatic Medicine, 75, 3.
6. **Brindle, R.C.**, Ginty, A.T., & Conklin. (2013). Symptoms of depression and cardiovascular stress reactivity: The role of stressor type, stress exposure, and stress perception. [Abstract, Poster] Midlands Health Psychology Network, Birmingham, UK

---

## Table of Contents

---

<b>Chapter 1</b>	<b>General introduction</b>	<b>Page</b>
	The Cardiovascular Response to Exercise and Mental Stress	1
	Exaggerated Reactivity is related to Adverse Health Outcomes	1
	Blunted Reactivity is related to Adverse Health and Behavioural Outcomes	2
	Sources of Individual Differences in Cardiovascular Stress Reactivity	4
	The Autonomic Basis of Cardiovascular Stress Reactivity	4
	Cardiovascular Stress Reactivity and HR Complexity	6
	Cardiovascular Stress Reactivity and Baseline Allostatic Load	7
	Multivariate Individual Differences in Cardiovascular Reactivity	9
	Present Thesis	11
	My Contributions to the Studies in this Thesis	11
	References	14
<b>Chapter 2</b>	<b>A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress</b>	
	Abstract	33
	Introduction	34
	Methods	37
	Results	45
	Discussion	59
	References	67
<b>Chapter 3</b>	<b>Heart rate complexity: A novel approach to assessing cardiac stress reactivity</b>	
	Abstract	82
	Introduction	83
	Methods (Study 1)	86
	Results (Study 1)	88
	Summary (Study 1)	91
	Methods (Study 2)	91
	Results (Study 2)	93
	Summary (Study 2)	96
	Discussion	96
	References	102

**Chapter 4      High allostatic load is associated with blunted cardiac reactivity to acute mental stress**

Abstract	115
Introduction	116
Methods	119
Results	124
Discussion	127
References	131

**Chapter 5      Cardiovascular reactivity patterns and pathways to hypertension: A multivariate cluster analysis**

Abstract	137
Introduction	138
Methods	140
Results	144
Discussion	147
References	154

**Chapter 6      General discussion**

Summary of Results	160
Autonomic Basis of Cardiovascular Stress Reactivity	160
Cardiovascular Stress Reactivity and HR Complexity	161
Cardiovascular Stress Reactivity and Allostatic Load	161
Multivariate Individual Differences in Cardiovascular Reactivity	162
Implications	163
Peripheral Physiology	164
Context of Stress	165
Person Factors	166
Limitations	167
Strengths	169
Future Directions	169
Conclusion	172
References	174

**Appendices**

1. References Contained in Meta-Analysis (Chapter 2)	185
2. Chapter 3 Supplementary Tables (3.6 & 3.7)	205
3. Chapter 4 Supplementary Tables (4.2 & 4.3)	206



---

## List of Figures

---

<b>Chapter 2</b>	<b>A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress</b>	<b>Page</b>
Figure 2.1:	Flow diagram of sympathetic nervous system systematic review.	43
Figure 2.2:	Flow diagram of parasympathetic nervous system systematic review.	44
Figure 2.3:	Cardiovascular, sympathetic, and parasympathetic reactivity to acute psychological stress.	47
Figure 2.4:	Cardiovascular stress reactivity in response to sympathetic blockade.	50
Figure 2.5:	Subgroup analysis of the influence of sympathetic blockade on individual cardiovascular variables.	51
Figure 2.6:	Subgroup analysis of stress task.	54
Figure 2.7:	Subgroup analysis of age group.	55
Figure 2.8:	Subgroup analysis of age group for sympathetic blockade.	56
Figure 2.9:	Subgroup analysis of sex.	57
Figure 2.10:	Autonomic reactivity to acute psychological stress in studies measuring both sympathetic and parasympathetic reactivity simultaneously.	58
<b>Chapter 4</b>	<b>High allostatic load is associated with blunted cardiac reactivity to acute mental stress</b>	
Figure 4.1:	Relationship between allostatic load and heart rate reactivity to the PASAT.	126
<b>Chapter 5</b>	<b>Cardiovascular reactivity patterns and pathways to hypertension: A multivariate cluster analysis</b>	
Figure 5.1:	Cluster mean (SE) for systolic (SBP), diastolic (DBP), and heart rate (HR) reactivity for overall sample and clusters.	145
Figure 5.2:	Relative risk of hypertension by cluster membership.	151

---

## List of Tables

---

<b>Chapter 1</b>	<b>General introduction</b>	Page
Table 1.1:	Summary of HR Complexity Measures and Acute Psychological Stress	13
<b>Chapter 2</b>	<b>A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress</b>	
Table 2.1:	Characteristics of included studies for the meta-analyses of sympathetic indices	48
Table 2.2:	Characteristics of included studies for meta-analysis of sympathetic blockade	49
Table 2.3:	Characteristics of included studies for meta-analysis of parasympathetic indices	52
Table 2.4:	Correlation analysis of effect sizes	59
<b>Chapter 3</b>	<b>Heart rate complexity: A novel approach to assessing cardiac stress reactivity</b>	
Table 3.1:	Cardiac descriptive statistics Study 1	89
Table 3.2:	Predictors of heart rate reactivity Study 1	90
Table 3.3:	Cardiac descriptive statistics Study 2	94
Table 3.4:	Individual predictors of heart rate reactivity Study 2	95
Table 3.5:	Full regression model of heart rate reactivity Study 2 (n = 162)	95
<b>Chapter 4</b>	<b>High allostatic load is associated with blunted cardiac reactivity to acute mental stress</b>	
Table 4.1:	Sample Characteristics	125
<b>Chapter 5</b>	<b>Cardiovascular reactivity patterns and pathways to hypertension: A multivariate cluster analysis</b>	
Table 5.1:	General Study Parameters of Clusters 2002-2004 Wave (N = 671)	147
Table 5.2:	General Study Parameters of Clusters 2008-2009 Wave (N = 439)	149

---

## List of Abbreviations

---

ANOVA	Analysis of Variance
ApEn	Approximate Entropy
BMI	Body Mass Index
BP	Blood Pressure
CO	Cardiac Output
CRF	Cardio-Respiratory Fitness
D2	Correlation Dimension
DBP	Diastolic Blood Pressure
DF $\alpha$ 1	Detrended Fluctuation Analysis Short Term
DF $\alpha$ 2	Detrended Fluctuation Analysis Long Term
ECG	Electrocardiography
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
FITC	Fluorescein Isothiocyanate
HADS	Hospital Anxiety and Depression Scale
HF-HRV	High-frequency Heart Rate Variability
Hg	Hedge's G Effect Size
HR	Heart Rate
INT	Sympathetic-Parasympathetic Interaction Term
I <sup>2</sup>	Higgin's Heterogeneity Statistic
ISEI-92	International Socioeconomic Index-92
METS	Metabolic Equivalents
OR	Odds Ratio
PASAT	Paced Auditory Serial Addition Task
PBMC	Peripheral Blood Mononuclear Cells
PEP	Pre-ejection Period
PNS	Overall Parasympathetic Activity
RMSSD	Root Mean Square of Successive Differences
RSA	Respiratory Sinus Arrhythmia
SA	Sino-atrial Node
SBP	Systolic Blood Pressure
SD1	Standard Deviation of Poincaré Plot Short Term
SD2	Standard Deviation of Poincaré Plot Long Term
SES	Socio-Economic Status
SNS	Overall Sympathetic Activity
SV	Stroke Volume
TPR	Total Peripheral Resistance

---

## Chapter 1

---

### General Introduction

## **The Cardiovascular Response to Exercise and Mental Stress**

In response to physical exercise, heart rate (HR) and blood pressure (BP) increase in precise proportion to augmented metabolic demand. In a highly coordinated physiological cascade, blood flow is diverted to working muscle groups and increases in cardiac output (CO) and BP assure adequate tissue perfusion, regulate body temperature, and remove metabolic waste (McArdle, Katch, & Katch, 2001). From a metabolic perspective, such a physiological reaction is appropriate, necessary, and healthy (Astrand, Cuddy, Saltin, & Stenberg, 1964). However, similar increases in HR, BP, and CO are observed in response to numerous psychological stress tasks despite only minimal changes in metabolic demand (Balanos et al., 2010; Carroll, Turner, & Prasad, 1986a; Carroll, Turner, & Hellawell, 1986b; Carroll, Phillips, & Balanos, 2009a; Sherwood, Allen, Obrist, & Langer, 1986; Turner & Carroll, 1985). Similar cardiovascular adjustments are also seen in novice parachutists preceding jumping (Stromme, Wikeby, Blix, & Ursin, 1978) and in helicopter pilots during difficult flights (Blix, Stromme, & Ursin, 1974). In such cases, metabolically uncoupled increases in HR, BP, and CO challenge homeostasis as the heart is working harder than the rest of the body. This notion formed the foundation for the reactivity hypothesis which considers that individuals who mount large magnitude cardiovascular responses to acute mental stress are at increased risk of cardiovascular disease (Obrist, 1981).

## **Exaggerated Reactivity is related to Adverse Health Outcomes**

The reactivity hypothesis (Obrist, 1981) has fueled over 30 years of research examining the health consequences of exaggerated cardiovascular reactions to acute psychological stress. Support has come from laboratory studies and several large-scale prospective studies that have established links between large magnitude cardiovascular reactions and future blood pressure

status (Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, Smith, Shipley, Steptoe, Brunner, & Marmot, 2001; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Matthews, Woodall, & Allen, 1993; Newman, McGarvey & Steele, 1999; Treiber, Turner, Davids, & Strong, 1997), hypertension (Borghi, Costa, Boschi, Mussi, & Ambrosioni, 1986; Everson, Kaplan, Goldberg, & Salonen, 1996; Markovitz, Matthews, Kannel, Cobb, & D'Agostino, 1993; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998), systemic markers of atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews, Owens, Kuller, Sutton-Tyrrell, Lassila, & Wolfson, 1998; Roemmich et al., 2011; Roemmich, Lobarinas, Joseph, Lambiase, & Archer, 2009), increased left ventricular mass (Georgiades, Lemne, De Faire, Lindvall, & Fredrikson, 1997; Kapuku, Treiber, Davis, Harshfield, Cook, & Mensah, 1999), and ventricular wall thickness (al'Absi et al., 2002; al'Absi et al., 2006) and increased cardiovascular disease mortality (Carroll et al., 2012). Qualitative reviews (Gerin et al., 2000; Schwartz et al., 2003; Taylor, Kamarck, & Dianzumba, 2003; Treiber et al., 2003) and a meta-analysis (Chida & Steptoe, 2010) also support this contention.

### **Blunted Reactivity is related to Adverse Health and Behavioural Outcomes**

As a corollary of the reactivity hypothesis and its empirical support, low or blunted cardiovascular reactions to acute stress were assumed to be benign or even protective (Carroll, Lovallo, & Phillips, 2009b). From a metabolic standpoint, this reasoning makes sense since little metabolic change occurs in response to acute psychological stress (Balanos et al., 2010; Carroll et al., 2009a). However, recent evidence has begun to show this line of reasoning to be faulty as blunted reactivity has been linked to a host of adverse health and behavioural outcomes (Carroll et al., 2009b; Lovallo, 2011; Phillips, Ginty, & Hughes, 2013). Specifically, evidence from two

independent large-scale epidemiological studies, the West of Scotland Twenty-07 Study and Dutch Famine Birth Cohort Study, have shown blunted cardiovascular and cortisol reactions to acute psychological stress relate cross-sectionally to negative life events (Carroll, Phillips, Ring, Der, & Hunt, 2005; Phillips, Carroll, Ring, Sweeting, & West, 2005), obesity (Carroll, Phillips, & Der, 2008; Phillips, Roseboom, Carroll, & de Rooij, 2012), depressive symptomatology (Carroll, Phillips, Hunt, & Der, 2007; de Rooij, Schene, Phillips, & Roseboom, 2010), low cognitive function (Ginty, Phillips, Der, Deary, & Carroll, 2011a; Ginty, Phillips, Roseboom, Carroll, & de Rooij, 2012), and poor self-reported health (de Rooij & Roseboom, 2010; Phillips, Der, & Carroll, 2009a) and prospectively predict increased likelihood of becoming obese (Carroll et al., 2008; Phillips et al., 2012), suffering from cognitive decline (Ginty, Phillips, Der, Deary, & Carroll, 2011b), developing depressive symptomatology (Phillips, Hunt, Der, & Carroll, 2011; Phillips, 2011), and reporting poor health (Phillips et al., 2009a). It should be noted that these two studies employed different stress tasks in independent populations.

Supportive evidence comes from smaller lab-based studies as well; blunted stress reactions have been linked to increased depressive symptomatology (Brindle, Ginty, & Conklin, 2013; Ehrental, Herrmann-Linge, Fey, & Shauenburg, 2010; Salomon, Bylsma, White, Panaite, & Rottenberg, 2013; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; York et al., 2007), smoking status (al'Absi, Hatsukami, & Davis, 2005; al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Ginty et al., 2014; Girdler, Jamner, Jarvki, Soles, & Shapiro, 1997; Kirchbaum, Strasburger, & Langkrar, 1993; Phillips, Der, Hunt, & Carroll, 2009b; Roy, Steptoe, & Kirschbaum, 1994), substance abuse (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002; Sorocco, Lovallo, Vincent, & Collins, 2006), disordered eating (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012; Koo-Loeb, Pedersen, &

Girdler, 1998), and exercise dependency (Heaney, Ginty, Carroll, & Phillips, 2011). Thus it would appear that cardiovascular reaction profiles located at either end of the reactivity spectrum are disadvantageous for health (Lovallo, 2011).

### **Sources of Individual Differences in Cardiovascular Stress Reactivity**

As the two preceding sections demonstrate, HR and BP reactivity have proven to be relatively reliable indicators of adverse health and behavioural outcomes. Admittedly though, measurements of HR and BP alone can hide large amounts of inter-individual variability that could be potentially useful from a research or clinical perspective (Lovallo, 2005; Lovallo & Gerin, 2003; Manuck, 1994). This is because both HR and BP are multiply determined cardiovascular endpoints that are controlled by numerous upstream cardioregulatory processes (e.g., autonomics, hemodynamics, local tissue processes, central command, etc., Kasprowicz, Manuck, Malkoff, & Krantz, 1990; Sherwood, Dolan, & Light, 1990). Hence, it may be time to alter the approach taken with regard to the reactivity hypothesis so that we may continue to use HR and BP reactivity as biomarkers of future health. One way in which this could be accomplished is to focus on the up-stream physiological individual differences that contribute to the large amount of observed inter-individual variability in HR and BP stress reactivity.

### **The Autonomic Basis of Cardiovascular Stress Reactivity**

Although the heart possesses intrinsic automaticity, regulation of HR results primarily from dual innervation by the parasympathetic and sympathetic nervous systems (Katona, McLean, Dighton, & Guz, 1982). The parasympathetic nervous system innervates both the sino-atrial (SA) and atrio-ventricular nodes and through acetylcholinergic mechanisms decreases HR; the sympathetic nervous system innervates the SA node and myocardium and increases HR and myocardial contractility primarily through norepinephrine release (Pappano, 2013). Peripheral



vasculature on the other hand is singly innervated by the postganglionic sympathetic fibers that induce vasoconstriction through norepinephrine release and activation of alpha-adrenergic receptors (Sparks & Rooke, 1987). Given the cardioregulatory role of the autonomic nervous system, there potentially exists a large amount of inter-individual differences in the autonomic response to acute psychological stress that cannot be fully captured by measuring HR alone.

A substantial number of studies have measured and reported indices of autonomic function (e.g., Mezzacappa, Kelsey, & Katkin, 2001; Mills, Dimsdale, Ziegler, Berry, & Bain, 1990; Willemsen, Ring, Carroll, Evans, Clow, & Hucklebridge, 1998) within the acute stress reactivity paradigm and several quantitative (Mills & Dimsdale, 1991; Stemmler, Grossman, Schmid, & Foerster, 1991) and qualitative reviews (Berntson, Cacioppo, & Quigley, 1991, 1993a, 1993b) have attempted to outline the role of the autonomic nervous system in responding to acute psychological stress. Currently, studies have implicated vagal withdrawal (Berntson, Cacioppo, Binkley, Uchino, Quigley, & Fieldstone, 1994; Grossman, Stemmler, & Meinhardt, 1990; Grossman, Watkins, Wilhelm, Manolakis, & Low, 1996; Sloan, Korten, & Myers, 1991) and sympathetic activation (Cacioppo, Berntson, Binkley, Quigley, Uchino, & Fieldstone, 1994a; Mills & Dimsdale, 1991; Mills, Dimsdale, Nelesen, Jasiewicz, Ziegler, & Kennedy, 1994; Winzer, Ring, Carroll, Willemsen, Drayson, & Kendall, 1999) in driving cardiovascular stress responses. Despite this effort, the autonomic basis of cardiovascular reactivity remains somewhat equivocal, mainly due to small sample size, *post-hoc* analyses, and a lack of studies specifically designed to probe autonomic stress reactivity. Hence, there is a need to more firmly establish the autonomic basis of cardiovascular stress reactivity; this was the aim of Chapter 2 of this thesis. If either/both branches of the autonomic nervous system are firmly implicated in the cardiovascular stress response further research could explore how individual differences in

autonomic activation translate into individual differences in HR and BP reactivity, and ultimately disease risk (Cacioppo, Uchino, & Berntson, 1994b).

### **Cardiovascular Stress Reactivity and HR Complexity**

The regulation of HR is complex. The brain (Wager, Waugh, Lindquist, Noll, Fredrickson, & Taylor, 2009a; Wager, van Ast, Hughes, Davidson, Lindquist, & Ochsner, 2009b), peripheral autonomic nervous system (Katona et al., 1982), hormonal and cellular mechanisms (Marsland, Manuck, Wood, Rabin, Muldoon, & Cohen, 1995; Mills, Dimsdale, Ziegler, Berry, & Bain, 1990), and hemodynamic processes (Pappano, 2013; Spaker & Rooke, 1987) have all been extensively characterised in the context of HR. Needless to say, it is not surprising that HR data appears extremely complex and chaotic (Persson, 1996). This observation has motivated the development and application of HR complexity measures to HR data. These measures differ from the more conventional HR variability measures derived from linear spectral analysis and their time-domain analogs in that they are based on nonlinear dynamics and chaos theory and are designed to quantify the nonlinear, dynamical, and chaotic properties of HR data that are not easily captured using linear spectral methods (Beckers, Verheyden, & Aubert, 2005). Some commonly utilised HR complexity measures are contained in Table 1.1 at the end of this chapter.

Researchers have contended that the more regulatory processes an organism has, the greater its ability to functionally adapt to environmental stimuli. Put another way, the more regulatory elements an organism has the greater its degrees of freedom (Beckers et al., 2006; Goldberg, Peng, & Lipsitz, 2002; Lipsitz, 2002; Schubert Lambertz, Nelesen, Bardwell, Choi, & Dimsdale, 2009). In line with this notion, researchers have begun to explore how HR complexity measures change in response to acute psychological stress. However, not many studies exist that

have rigorously utilised HR complexity measures in the context of acute psychological stress and as a result there is a large amount of inconsistency in its reported relationship with acute psychological stress (Table 1.1). Also, there are many outstanding questions regarding the application of HR complexity measures to the stress reactivity paradigm. Are changes in HR complexity measures independent of changes in parasympathetic and sympathetic activity? Are HR complexity measures influenced by changes in respiration? Do changes in HR complexity relate to changes in HR? Since HR complexity measures may represent an unexplored pool of individual differences that could advance our understanding of the cardiovascular stress response (Anishchenko, Igosheva, Yakusheva, Glushkovskaya-Semyachkina, Khokhlova, 2001a), Chapter 3 aimed to systematically address these questions with regard to correlation dimension, a HR complexity measure that has been shown to decrease in response to mental stress both in the field (Melillo, Bracale, & Pecchia, 2011) and in the laboratory (Schubert et al., 2009).

### **Cardiovascular Stress Reactivity and Baseline Allostatic Load**

Allostatic load has been recently discussed as a candidate mechanism through which chronic stress influences future cardiovascular responding to acute psychological stress (Danese & McEwen, 2011; Gallo, Jiménez, Shivpuri, de los Monteros, & Mills, 2011; Gleib, Goldman, Chuang, & Weinstein, 2007). Despite some evidence linking trauma to exaggerated cardiovascular and cortisol stress reactions reactivity (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Heim, et al., 2000; Heim, Newport, Wagner, Wilcox, Miller, & Nemeroff, 2002; Leucke, 2000), emerging evidence suggests that individuals who report suffering from chronic or having experienced significant child trauma display blunted cardiovascular and cortisol reactions to acute psychological stress. Specifically, from the childhood trauma literature, those having reported experiencing childhood trauma displayed blunted cardiovascular

and cortisol responses to acute stress later in life (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011; Elzinga, Roelofs, Tollenaar, Bakvis, van Pelt, & Spinhoven, 2008; Feldman, Vengrober, Eidelman-Rothman, & Zagoory-Sharon, 2013; Lovallo, Farag, Sorocco, Cohon, & Vincent, 2012; MacMillan et al., 2009; Voellmin, et al., 2015). Moreover those reporting trauma in adulthood (DePierro, D'Adnrea, & Pole, 2013) or a greater number of negative life events also appear to mount blunted cardiovascular stress responses (Carroll et al., 2005; Musante, Treiber, Kapuku, Moore, Davis, & Strong, 2000; Phillips et al., 2005). Finally, a large meta-analysis also provided qualified support for the link between high levels of chronic stress and blunted BP reactivity (Chida & Hamer, 2008). Based on this, the allostatic load model may provide a unique mechanism through which to explore how individual differences in past experience, influence basal physiology, and result in individual differences in cardiovascular stress reactivity.

Unlike the traditional concept of homeostasis, where physiology is tightly regulated via negative feedback around an immovable set point (Gross, 1998), allostasis emphasises flexible regulation where physiology is constantly passing through different allostatic states, each of which has a different set point (Sterling, 2012). However, whereas allostasis is acutely adaptive, some allostatic states are not ideal and can comprise functionally should they be maintained indefinitely; this is the central tenet of the allostatic load model (McEwen, 1998a,b). The prototypical example of this process is hypercortisolism. Acutely, cortisol secretion is necessary to deal with stress, however, prolonged secretion negatively impacts on the glucocorticoid receptors located in the hippocampus, and over time erodes the negative feedback branch of the cortisol regulatory cycle leading to more cortisol secretion (Logan & Barksdale, 2008). In this case, the result of allostatic load would be a state of heightened basal activity, but, other

functional phenotypes have been outlined (McEwen, 1998b), of which, hypoactivation is particularly relevant to the discussion of chronic stress and blunted cardiovascular stress reactivity. However, no study has directly tested the relationship between individual differences physiological allostatic load and cardiovascular stress reactivity in healthy sample free of disease processes. This was the aim of Chapter 4 of this thesis.

### **Multivariate Individual Differences in Cardiovascular Reactivity**

Physiology is inherently complex; HR is controlled by, among other factors, autonomic, hemodynamic, cellular, and humoral regulatory processes (Klabunde, 2005) and BP is controlled by autonomic, hemodynamics, and local metabolic and myogenic influences, to name a few (Pappano, 2013; Spaker & Rooke, 1987). Moreover, HR and BP regulate each other through changes in CO and by activation/deactivation of the baroreflex (Persson, 1996). How physiology relates to disease is also complex. For example, the development of hypertension has been linked to changes in autonomics, hemodynamics, and the renin-angiotensin system (Oparil, Zaman, & Calhoun, 2003; Persson, 1996). Consequently, a case can be made that the univariate statistics commonly employed to test the reactivity hypothesis are not entirely appropriate as they do not properly model the complexity of physiology, or its relationship to disease. This oversimplification of end-point physiology and the use of univariate statistics have been cited as a possible source of inconsistency in and underestimation of the link between stress reactivity and hypertension (Pickering & Gerin, 1990). As a result, some have advocated examining individual differences in multivariate patterns of cardiovascular reactivity (Lawler et al., 2001; Llabre, Klein, Saab, McCalla, & Schneiderman, 1998).

Initial support for such an approach dates from the 1950s when Wolf and colleagues (1951, 1955) noted that additional inter-individual difference existed when, instead of BP

reactivity, the patterns of CO and total peripheral resistance (TPR) modulation in response to a stress interview were considered. It was not until later that the terms *cardiac* and *vascular* reactors emerged to describe individuals who reliably increased BP under stress by augmenting CO or TPR, respectively (Kasprowicz et al., 1990). Numerous other classifications, loosely based on this original conception emerged thereafter (Allen, Boquet, & Shelley, 1991; Kline et al., 2002; Lawler et al., 2001; Light, Turner, Hinderliter, Girdler, & Sherwood, 1994; Llabre et al., 1998; McCaffery, Muldoon, Backen, Jennings, & Manuck, 2000). With regard to disease, classifying individuals based on multivariate patterns of reactivity appeared initially successful. It was observed that cardiac reactors were significantly more likely to be currently classified as mildly hypertensive and had increased ambulatory BP (Light, Turner, Hinderliter, & Sherwood, 1993; Llabre et al., 1998). However, others have reported evidence that increased vascular reactivity may confer greater hypertension risk (Kline et al., 2002). Despite initial success and the recognised value of exploring individual differences in multivariate stress reactivity patterns (Kline, 2002), this approach was not fully embraced and remains underutilised (Llabre et al., 1998). This is probably because BP and HR alone can be easily measured and it is harder to establish a reactivity pattern as a dispositional trait compared to establishing a single variable (Manuck, 1994). Further, there is no standard classification scheme and external criterion validity, that is the ability of reactivity patterns to predict future disease, has not been established (Llabre, 1998). In response to some of these criticisms it was the final aim of this thesis (Chapter 5) to explore multivariate inter-individual patterns of HR and BP reactivity in a large sample and prospectively relate them to future hypertension risk.

## **Present Thesis**

The present thesis is comprised of one meta-analysis, two experimental studies, and one secondary analysis of epidemiological data that yielded four papers that explore inter-individual difference in the context of cardiovascular reactivity to acute psychological stress. The first paper aimed to summarise the existing literature concerning the autonomic basis of cardiovascular stress reactivity. It was hypothesised that the parasympathetic and sympathetic nervous systems would both be perturbed by acute psychological stress and related to HR and BP reactivity. The second paper aimed to determine if measures of HR complexity represented a novel source of individual difference with regard to HR reactivity. It was hypothesised that individual differences in HR complexity would relate to individual differences in HR reactivity and withstand adjustment for changes in parasympathetic and sympathetic activity, the sympathetic-parasympathetic interaction, and respiration. The third paper aimed to determine if individual differences in resting physiological allostatic load, measured across cardiovascular, neuroendocrine, and anthropometric domains, related to individual differences in cardiovascular stress reactivity. It was hypothesised that cumulative allostatic load would relate to cardiovascular stress responses. The fourth paper examined, using clustering algorithms, multivariate patterns of HR, SBP, and DBP and how individual differences in reactivity patterns related prospectively to future hypertension diagnosis. It was hypothesised that several homogenous clusters of individuals would be identified and that they would carry significantly different risk of hypertension diagnosis.

## **My Contributions to the Studies in this Thesis**

The idea for Paper 1 was mine. The meta-analysis was jointly designed by all four authors. I undertook the collection and screening of articles and the extraction of data with

reliability checks by DC. I undertook the statistical analyses with input from all authors. All authors contributed to the final version of the manuscript. Study 1 of Paper 2 was jointly designed by all authors. I carried out the recruitment of participants and data collection and processing. I undertook the statistical analyses with input from all authors. Study 2 of Paper 2 was designed by ATG. I helped in data collection and conceived of the idea to look at HR complexity. The statistical analyses were conducted with input from all authors. The manuscript was written under the supervision of DC and all authors contributed to the final version. The study design for Paper 3 was mine with input from all authors. The idea to look at allostatic load was prompted by ATG. Technical aspects of the protocol, including the ELISA and cellular assays were carried out under the supervision of ACP. I received substantial help from Dr Jon Hazeldine, Professor Janet Lord, and Hema Chahal (not authors) in flow cytometry. Statistical analyses were performed by me with input from ATG. I initially drafted the manuscript and all authors contributed to the final version. The idea for Paper 4 was jointly discussed among me, ATG, ACP, and DC. I was granted access to the Dutch Famine Birth Cohort dataset with thanks to SDR and TJR, with whom DC, ACP, and ATG have a collaboration. Statistical analyses were conducted under the supervision of DC. The initial manuscript was drafted with input from DC and all authors contributed to the final version.



**Table 1.1** Summary of HR complexity measures and acute psychological stress

Complexity Measure	Meaning	Response to Mental Stress	Stress Task	References
Correlation Dimension (D2)	Characterises the number of attractors in a time series	D2 ↓	University Exam	Melillo et al., 2011
		↓	Speech Task	Schubert et al., 2009
Standard Deviations of Poincaré Plot (SD1, SD2)	Describes the short term (SD1) and long term (SD2) correlation between successive RR intervals in a time series	SD1 ↓	Driving Stress	Brisinda et al., 2015
		↓	Mental Arithmetic	Saperova et al., 2015
		SD2 ↓	Driving Stress	Brisinda et al., 2015
Detrended Fluctuation Analysis ( $\alpha_1$ , $\alpha_2$ )	Measures the short term ( $\alpha_1$ ) and long term ( $\alpha_2$ ) correlation <i>within</i> a time series	$\alpha_1$ ↓	Driving Stress	Brisinda et al., 2015
		↑	Mental Arithmetic	Saperova et al., 2015
		$\alpha_2$ ↑	Driving Stress	Brisinda et al., 2015
		↑	Mental Arithmetic	Saperova et al., 2015
Entropy	Measures irregularity in a time series	↔	Mental Arithmetic, Driving Stress	Anishchenko et al., 2001b, Brisinda et al., 2015
		↓	University Exam	Anishchenko et al., 2001a
		↓	Performance Stress	Williamon et al., 2013
		↓	Mental Arithmetic	Saperova et al., 2015

## References

- al'Absi, M., Devereux, R.B., Lewis, C.E., Kitzman, D.W., Rao, D.C., Hopkins, P., et al. (2002). Blood pressure responses to acute stress and left ventricular mass (The Hypertension Genetic Epidemiology Network Study). *American Journal of Cardiology*, 89, 536-540.
- al'Absi, M., Wittmers, L.E., Erickson, J., Hatsukami, D., & Crouse, B. (2003). Attenuated adrenocortical and blood pressure responses to psychological stress in ad libitum and abstinent smokers. *Pharmacology, Biochemistry, and Behavior*, 74, 401-410.
- al'Absi, M., Hatsukami, D., & Davis, G. L. (2005). Attenuated adrenocorticotrophic responses to psychological stress are associated with early smoking relapse. *Psychopharmacology (Berl)*, 181, 107-117
- al'Absi, M., Devereux, R.B., Rao, D.C., Kitzman, D., Oberman, A., Hopkins, P., et al. (2006). Blood pressure stress reactivity and left ventricular mass in a random community sample of African-American and Caucasian men and women. *American Journal of Cardiology*, 15, 240-244.
- Allen, M.T., Boquet Jr., A.J., & Shelley, K.S. (1991). Cluster analysis of cardiovascular responsivity to three laboratory stressors. *Psychosomatic Medicine*, 53, 272-288.
- Anishchenko, T., Igosheva, N., Yakusheva, T., Glushkovskaya-Semyachkina, O., & Khokhlova, O. (2001a). Normalized entropy applied to the analysis of interindividual and gender-related differences in the cardiovascular effects of stress. *European Journal of Applied Physiology*, 85, 287-298.
- Anishchenko, T., Igosheva, N.B., Pavlov, A.N., Khovanov, A., & Yakusheva, T.A. (2001b). Comparative analysis of methods for classifying the cardiovascular system's states under stress. *Critical Reviews in Biomedical Engineering*, 29, 462-481.

- Ashman, S.B., Dawson, G., Panagiotides, H., Yamada, E., & Wilkinson, C.W. (2002). Stress hormone levels of children of depressed mothers. *Development and Psychopathology*, 14, 333-349.
- Astrand, P.O., Cuddy, T.E., Saltin, B., & Stenberg, J. (1964). Cardiac output during submaximal and maximal work. *Journal of Applied Physiology*, 19, 268-274.
- Balanos, G.M., Phillips, A.C., Frenneaux, M.P., McIntyre, D., Lykidis, C., Griffin, H.S., et al. (2010). Metabolically exaggerated cardiac reactions to acute psychological stress: The effects of resting blood pressure status and possible underlying mechanisms. *Biological Psychology*, 85, 104-111.
- Barnett, P. A., Spence, J. D., Manuck, S. B., & Jennings, J. R. (1997). Psychological stress and the progression of carotid artery disease. *Journal of Hypertension*, 15, 49-55.
- Beckers, F., Verheyden, B., & Aubert, A.E. (2005). Aging and nonlinear heart rate control in a healthy population. *American Journal of Physiology*, 290, H2560-H2570.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1991). Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. *Psychological Review*, 98, 459-487.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993a). Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. *Psychological Bulletin*, 114, 296-322.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993b). Autonomic space and psychophysiological response. *Psychophysiology*, 31, 44-61.
- Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., & Fieldstone, A. (1994). Autonomic cardiac control III. Psychological stress and cardiac response in

- autonomic space as revealed by pharmacological blockade. *Psychophysiology*, 31, 599-608.
- Blix, A.S., Stromme, S.B., & Ursin, H. (1974). Additional heart rate: An indicator of psychological activation. *Aerospace Medicine*, 45, 1219-1222.
- Borghi, C., Costa, F.V., Boschi, S., Mussi, A., & Ambrosioni, E. (1986). Predictors of stable hypertension in young borderline subjects: A five year follow-up study. *Journal of Cardiovascular Pharmacology*, 8, S138-S141.
- Brisinda, D., Fioravanti, F., Sorbo, A.R., Venuti, A., & Fenici, R. (2015). Psychophysiological assessment of acute stress induced by high-pressure law-enforcement driving: A pilot study. *Psychology and Social Behavior Research*, 2, 36-50.
- Brindle, R.C., Ginty, A.T., & Conklin, S.M. (2013). Is the association between depression and blunted cardiovascular stress reactions mediated by perceptions of stress? *International Journal of Psychophysiology*, 90, 66-72.
- Cacioppo, J.T., Berntson, G.G., Binkley, P.F., Quigley, K.S., Uchino, B.N., & Fieldstone, A. (1994a). Autonomic cardiac control. II. Noninvasive indices and basal response as revealed by autonomic blockade. *Psychophysiology*, 31, 586-598.
- Cacioppo, J.T., Uchino, B.N., & Berntson, G.G. (1994b). Individual differences in the autonomic origins of heart rate reactivity: The psychometrics of respiratory sinus arrhythmia and pre-ejection period. *Psychophysiology*, 31, 412-419.
- Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., et al. (2007). Decreased ACTH and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, 15, 1080-1087.

- Carpenter, L.L., Shattuck, T.T., Tyrka, A.R., Geraciotti, T.D., & Price, L.H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology (Berl)*, 214, 367-375.
- Carroll, D., Turner, J.R., & Prasad, R. (1986a). The effects of level of difficulty on mental arithmetic challenge on heart rate and oxygen consumption. *International Journal of Psychophysiology*, 4, 167-173.
- Carroll, D., Turner, J.R., & Hellawell, J.C. (1986b). Heart rate and oxygen consumption during active psychological challenge: The effects of level of difficulty. *Psychophysiology*, 23, 174-181.
- Carroll, D., Davey Smith, G., Sheffield, D., Shipley, M.J., & Marmot, M.G. (1995). Pressor reactions to psychological stress and prediction of future blood pressure: Data from the Whitehall II Study. *British Medical Journal*, 310, 771-776.
- Carroll, D., Smith, G.D., Shipley, M.J., Stptoe, A., Brunner, E.J., & Marmot, M.G. (2001). Blood pressure reactions to acute psychological stress and future blood pressure status: A 10-year follow-up of men in the Whitehall II study. *Psychosomatic Medicine*, 63, 737-743.
- Carroll, D., Ring, C., Hunt, K., Ford, G., & Macintyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: Effects of sex, age, and socioeconomic position. *Psychosomatic Medicine*, 65, 1058-1064.
- Carroll, D., Phillips, A.C., Ring, C., Der, G., & Hunt, K. (2005). Life events and hemodynamics stress reactivity in the middle-aged and elderly. *Psychophysiology*, 42, 269-276.
- Carroll, D., Phillips, A.C., Hunt, K., & Der, G. (2007). Symptoms of depression and cardiovascular reactions to acute psychological stress: Evidence from a population study. *Biological Psychology*, 75, 68-74.

- Carroll, D., Phillips, A.C., & Der, G. (2008). Body mass index, abdominal adiposity, obesity, and cardiovascular reactions to psychological stress in a large community sample. *Psychosomatic Medicine*, 20, 653-660.
- Carroll, D., Phillips, A.C., & Balanos, G.M. (2009a). Metabolically exaggerated cardiac reactions to acute psychological stress revisited. *Psychophysiology*, 46, 270-275.
- Carroll, D., Lovallo, W.R., & Phillips, A.C. (2009b). Are large physiological reactions to acute psychological stress always bad for health? *Social and Personality Psychology Compass*, 3, 725-743.
- Carroll, D., Ginty, A.T., Der, G., Hunt, K., Benzeval, M., & Phillips, A.C. (2012). Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. *Psychophysiology*, 49, 1444-1448.
- Chida, Y., & Hamer, M. (2008). Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: A quantitative review of 30 years of investigation. *Psychological Bulletin*, 134, 829-885.
- Chida, Y. & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension*, 55, 1026-1032.
- Danese, A., & McEwen, B.S. (2011). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, 106, 29-39.
- DePierro, J., D'Andrea, W., & Pole, N. (2013). Attention biases in females survivors of interpersonal violence: Relationship to trauma-related symptoms and physiology. *European Journal of Psychotraumatology*, 4, 19135-19144.

- de Rooij, S.R., Schene, A.H., Phillips, D.I., & Roseboom, T.J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology*, 35, 866-877.
- de Rooij S.R. & Roseboom, T.J. (2010). Further evidence for an association between self-reported health and cardiovascular as well as cortisol reactions to acute psychological stress. *Psychophysiology*, 47, 1172-1175.
- Ehrenthal, J.C., Herrmann-Linge, C., Fey, M., & Shauenburg, H. (2010). Altered cardiovascular adaptability in depressed patients without heart disease. *World Journal of Biological Psychiatry*, 11, 586-593.
- Elzinga, B.M., Roelofs, K., Tollenaar, M.S., Bakvis, P., van Pelt, J., & Spinhoven, P. (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: A study among healthy young subjects. *Psychoneuroendocrinology*, 33, 227-237.
- Everson, S.A., Kaplan, G.A., Goldberg, D.E., & Salonen, J.T. (1996). Anticipatory blood pressure responses to exercise predict future high blood pressure in middle-aged men. *Hypertension*, 27, 1059-1064.
- Everson, S. A., Lynch, J. W., Chesney, M. A., Kaplan, G. A., Goldberg, D. E., Shade, S. B., et al. (1997). Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: Population based study. *British Medical Journal*, 314, 553-558.
- Feldman, R., Vengrober, A., Eidelman-Rothman, M., & Zagoory-Sharon, O. (2013). Stress reactivity in war-exposed young children with and without posttraumatic stress disorders: Relations to maternal stress hormones, parenting, and child emotionality and regulation. *Development and Psychopathology*, 25, 943-955.

- Gallo, L.C., Jiménez, J.A., Shivpuri, de los Monteros, K.E., & Mills, P.J. (2011). Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. *Annals of Behavioral Medicine*, 41, 21-31.
- Georgiades, A., Lemne, C., de Faire, U., Lindvall, K., & Fredrikson, M. (1997). Stress-induced blood pressure measurements predict left ventricular mass over three years among borderline hypertensive men. *European Journal of Clinical Investigation*, 27, 733-739.
- Gerin, W., Pickering, T. G., Glynn, L., Christenfeld, N., Schwartz, A., Carroll, D., & Davidson, K. (2000). An historical context for behavioral models of hypertension. *Journal of Psychosomatic Research*, 48, 369-377.
- Ginty, A.T., Phillips, A.C., Der, G., Deary, I.J., and Carroll, D. (2011a). Cognitive ability and simple reaction time predict cardiac reactivity in the West of Scotland Twenty-08 Study. *Psychophysiology*, 48, 1022-1027.
- Ginty, A.T., Phillips, A.C., Der, G., Deary, I.J., Carroll, D. (2011b). Heart rate reactivity is associated with future cognitive ability and cognitive change in a large community sample. *International Journal of Psychophysiology*, 82, 167-174.
- Ginty, A.T., Phillips, A.C., Roseboom, T.J., Carroll, D., and de Rooij, S.R. (2012). Cardiovascular and cortisol reactions to acute psychological stress and cognitive ability in Dutch Famine Birth Cohort Study. *Psychophysiology*, 49, 391-400.
- Ginty, A.T., Phillips, A.C., Higgs, S., Heaney, J.L.J., & Carroll, D. (2012). Disordered eating behavior is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, 37, 715-724.



- Ginty, A.T., Jones, A., Carroll, D., Roseboom, T.J., Phillips, A.C., Painter, R., et al. (2014). Neuroendocrine and cardiovascular reactions to acute psychological stress are attenuated in smokers. *Psychoneuroendocrinology*, 48, 87-97.
- Girdler, S.S., Jamner, L.D., Jarvik, M., Soles, J.R. & Shapiro, D. (1997). Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. *Psychosomatic Medicine*, 59, 294-306.
- Glei, D.A., Goldman, N., Chuang, Y.L., Weinstein, M. (2007). Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. *Psychosomatic Medicine*, 69, 769-776.
- Goldberg, A.L., Peng, C.K., & Lipsitz, L.A. (2002). What is physiologic complexity and how does it change with aging and disease. *Neurobiology of Aging*, 23, 23-26.
- Gross, C.G. (1998). Claude Bernard and the constancy of the internal environment. *Neuroscientist*, 4, 380-385.
- Grossman, P., Stemmler, G., & Meinhardt, E. (1990). Paces respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. *Psychophysiology*, 27, 404-416.
- Grossman, P., Watkins, L.L., Wilhelm, F.H., Manolakis, D., & Lown, B. (1996). Cardiac vagal control and dynamic responses to psychological stress among patients with coronary artery disease. *The American Journal of Cardiology*, 78, 1424-1427.
- Heaney, J.L.J., Ginty, A.T., Carroll, D., & Phillips, A.C. (2011). Preliminary evidence that exercise dependence is associated with blunted cardiac and cortisol reactions to acute psychological stress. *International Journal of Psychophysiology*, 79, 323-329.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M.M., Bonsall, R., et al. (2000).

Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *284*, 592-597.

Heim, C., Newport, D.J., Wagner, D., Wilcox, M.M., Miller, A.H., & Nemeroff, C.B. (2002).

The role of early adverse experiences and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depression and Anxiety*, *15*, 117-125.

Kapuku, G. K., Treiber, F. A., Davis, H. C., Harshfield, G. A., Cook, B. B., & Mensah, G. A.

(1999). Hemodynamic function at rest, during acute stress, and in the field: Predictors of cardiac structure and function 2 years later in youth. *Hypertension*, *34*, 1026-1031.

Kasprowicz, A.L., Manuck, S.B., Malkoff, S.B., & Krantz, D.S. (1990). Individual differences in

behaviorally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology*, *27*, 605-619.

Katona, P.G., McEan, M., Dighton, D.H., & Guz, A. (1982). Sympathetic and parasympathetic

cardiac control in athletes and nonathletes at rest. *Journal of Applied Physiology*, *52*, 1652-1657.

Klabunde RE. (2005) *Cardiovascular Physiology Concepts*. New York: Lippincott Williams &

Wilkins.

Kline, K.A., Saab, P.G., Llabre, M.M., Spitzer, S.B., Evans, J.D., McDonald, P.A.G., et al.

(2002). Hemodynamic response patterns: Responder type differences in reactivity and recovery. *Psychophysiology*, *39*, 739-746.

Kirschbaum, C., Strasburger, C.J., & Langkrar, J. (1993). Attenuated cortisol responses to psychological stress but not to CRH or ergometry in young habitual smokers.

*Pharmacology, Biochemistry, and Behaviour*, 44, 527-531.

Koo-Loeb, J.H., Pedersen, C., & Girdler, S.S. (1998). Blunted cardiovascular and catecholamine stress response reactivity in women with bulimia nervosa. *Psychiatry Research*, 80, 13-27.

Lawler, K.A., Kline, K.A., Adlin, R.F., Wilcox, Z.C., Craig, F.W., Krishnomoorthy, J.S., et al. (2001). Psychophysiological correlates of individual differences in patterns of hemodynamic reactivity. *International Journal of Psychophysiology*, 40, 93-107.

Light, K.C., Turner, J.R., Hinderliter, A.L., & Sherwood, A. (1993). Race and gender comparisons: II. Predictions of work blood pressure from laboratory baseline and cardiovascular reactivity measures. *Health Psychology*, 12, 366-375.

Light, K.C., Turner, J.R., Hinderliter, A.L., Girdler, S.S., & Sherwood, A. (1994). Comparison of cardiac versus vascular reactors and ethnic groups in plasma epinephrine and norepinephrine responses to stress. *International Journal of Behavioral Medicine*, 1, 229-246.

Lipsitz, L.A. (2002). Dynamics of stability: The physiologic basis of functional health and frailty. *Journal of Gerontology: Biological Sciences*, 57, 115-125.

Llabre, M.M., Klein, B.R., Saab, P.G., McCalla, J.B., & Schneiderman, N. (1998). Classification of individual differences in cardiovascular responsivity: The contribution of reactor type controlling for race and gender. *International Journal of Behavioral Medicine*, 5, 213-229.

- Logan, J.G., & Barksdale, D.J. (2008). Allostasis and allostatic load: Expanding the discourse on stress and cardiovascular disease. *Journal of Nursing and Healthcare of Chronic Illness*, 17, 201-208.
- Lovallo, W.R., Dickensheets, S.L., Myers, D., Thomas, T.L., & Nixon, S.J. (2000). Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcoholism: Clinical and Experimental Research*, 24, 651-658.
- Lovallo, W.R., & Gerin, W. (2003). Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. *Psychosomatic Medicine*, 65, 36-45.
- Lovallo, W.R. (2005). Cardiovascular reactivity: Mechanisms and pathways to cardiovascular disease. *Biological Psychology*, 58, 119-132.
- Lovallo, W.R. (2011). Do low levels of stress reactivity signal poor states of health? *Biological Psychology*, 86, 121-128.
- Lovallo, W.R., Farag, N.H., Sorocco, K.H., Cohoon, A.J., & Vincent, A.S. (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma Family Health Patterns Project. *Biological Psychiatry*, 71, 344-349.
- Luecken, L.J. (2000). Parental caring and loss during childhood and adult cortisol responses to stress. *Psychology and Health*, 15, 841-851.
- Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health*, 88, 389-394.

MacMillan, H.L., Georgiades, K., Duku, E.K., Shea, A., Steiner, M., Niec, A., et al. (2009).

Cortisol response to stress in female youths exposed to childhood maltreatment: Results of the Youth Mood Project. *Biological Psychiatry*, 66, 62-68.

Manuck, S.B. (1994). Cardiovascular reactivity in cardiovascular disease: 'Once more unto the breach.' *International Journal of Behavioral Medicine*, 1, 4-27.

Markovitz, J.H., Matthews, K.A., Kannel, W.B., Cobb, J.L., & D'Agostino, R.B. (1993).

Psychological predictors of hypertension in the Framingham Study. *JAMA*, 270, 2439-2443.

Markovitz, J.H., Racynski, J.M., Wallace, D., Chettur, V., & Chesney, M.A. (1998).

Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: The CARDIA study. *Psychosomatic Medicine*, 60, 186-191.

Marsland, A.L., Manuck, S.B., Wood, P., Rabin, B.S., Muldoon, M.F., & Cohen, S. (1995).

B<sub>2</sub>-Adrenergic receptor density and cardiovascular response to mental stress. *Physiology & Behavior*, 57, 1163-1167.

Matthews, K. A., Woodall, K. L., & Allen, M. T. (1993). Cardiovascular reactivity to stress predicts future blood pressure status. *Hypertension*, 22, 479-485.

Matthews, K. A., Owens, J. F., Kuller, L. H., Sutton-Tyrrell, K., Lassila, H. C., & Wolfson, S. K.

(1998). Stress-induced pulse pressure change predicts women's carotid atherosclerosis. *Stroke*, 29, 1525-1530.

McArdle, W.D., Katch, F.I., & Katch, V.L. (2001). *Exercise Physiology: Energy, nutrition, and human performance* (5<sup>th</sup> ed). New York, New York, Lippincott, Williams, & Wilkins.

McCaffery, J.M., Muldoon, M.F., Bachen, E.A., Jennings, J.R., & Manuck, S.B. (2000).

Behaviorally-evoked plasma catecholamine response and 24-hour excretion of urinary catecholamines among cardiac and vascular reactors. *Biological Psychology*, 52, 53-69.

McEwen, B.S. (1998a). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, 1, 33-44.

McEwen, B.S. (1998b). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338, 171-179.

Melillo, P., Bracale, M., & Pecchia, L. (2011). Nonlinear heart rate variability features for real-life stress detection. Case study: Students under stress due to university examination. *Biomedical Engineering Online*, 10, 1-13.

Mezzacappa, E.S., Kelsey, R.M., Katkin, E.S. (2001). Vagal rebound and recovery from psychological stress. *Psychosomatic Medicine*, 63, 650-657.

Mills, P.J., Dimsdale, J.E., Ziegler, M.G., Berry, C.C., & Bain, R.D. (1990). Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. *Psychosomatic Medicine*, 52, 621-623.

Mills, P.J., & Dimsdale, J.E. (1991). Cardiovascular reactivity to psychosocial stressor: A review of the effects of beta-blockade. *Psychosomatics*, 32, 209-220.

Mills, P.J., Dimsdale, J.E., Nelesen, R.A., Jasiewicz, J., Ziegler, M.G., & Kennedy, B. (1994). Patterns of adrenergic receptors and adrenergic agonists underlying cardiovascular responses to a psychological challenge. *Psychosomatic Medicine*, 56, 70-76.

Musante, L., Triber, F.A., Kapuku, G., Moore, D., Davis, H., & Strong, W. (2000). The effects of life events on cardiovascular reactivity to behavioral stressors as a function of socioeconomic status, ethnicity, and sex. *Psychosomatic Medicine*, 62, 760-767.

- Newman, J. D., McGarvey, S. T., & Steele, M. S. (1999). Longitudinal association of cardiovascular reactivity and blood pressure in Samoan adolescents. *Psychosomatic Medicine*, 61, 243-249.
- Obrist, P. (1981). *Cardiovascular Psychophysiology: A perspective*. New York, New York: Plenum Press.
- Oparil S, Zaman MA, Calhoun DA. (2003) Pathogenesis of hypertension. *Annals of Internal Medicine*, 139,761-776.
- Panknin, T.L., Dickensheets, S.L., Nixon, S.J., & Lovallo, W.R. (2002). Attenuated heart rate responses to public speaking in individuals with alcohol dependence. *Alcoholism, Clinical and Experimental Research*, 26, 841-847.
- Pappano, A.J. (2013). *Cardiovascular physiology* (10<sup>th</sup> ed). Philadelphia, PA: Elsevier.
- Persson, P.B. (1996). Modulation of cardiovascular control mechanism and their interaction. *Physiological Reviews*, 76, 193-244.
- Phillips, A.C., Carroll, D., Ring, C., Sweeting, H., & West, P. (2005). Life events and acute cardiovascular reactions to mental stress: A cohort study. *Psychosomatic Medicine*, 67, 384-392.
- Phillips, A.C., Der, G., & Carroll, D. (2009a). Self-reported health and cardiovascular reactions to psychological stress in a large community sample: Cross-sectional and prospective associations. *Psychophysiology*, 46, 1020-1027.
- Phillips, A.C., Der, G., Hunt, K., & Carroll, D. (2009b). Haemodynamic reactions to acute psychological stress and smoking status in a large community sample. *International Journal of Psychophysiology*, 73, 273-278.

- Phillips, A.C. (2011). Blunted cardiovascular reactivity relates to depression, obesity, and self-reported health. *Biological Psychology*, 86, 106-113.
- Phillips, A.C., Hunt, K., Der, G., & Carroll, D. (2011). Blunted cardiac reactions to acute psychological stress predict symptoms of depression five years later: Evidence from a large community study. *Psychophysiology*, 48, 142-148.
- Phillips, A.C., Roseboom, T.J., Carroll, D., & de Rooij, S.R. (2012). Cardiovascular and cortisol reactions to acute psychological stress and adiposity: Cross-sectional and prospective associations in the Dutch Famine Birth Cohort study. *Psychosomatic Medicine*, 74, 699-710.
- Phillips, A.C., Ginty, A.T., & Hughes, B. (2013). The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90, 1-7.
- Pickering, T.G., & Gerin, W. (1990). Cardiovascular reactivity in the laboratory and the role of behavioral factors in hypertension: A critical review. *Annals of Behavioral Medicine*, 12, 3-16.
- Roemmich, J.N., Lobarinas, C.L., Joseph, P.N., Lambiase, M.J., Archer, F.D., et al. (2009). Cardiovascular reactivity to psychological stress and carotid intima-media thickness in children. *Psychophysiology*, 46, 293-299.
- Roemmich, J.N., Feda, D.M., Seelbinder, A.M., Lambiase, M.J., Kala, G.K., & Dorn, J. (2011). Stress-induced cardiovascular reactivity and atherosclerosis in adolescents. *Atherosclerosis*, 215, 465-470.



- Roy, M.P., Steptoe, A., & Kirschbaum, C. (1994). Association between smoking status and cardiovascular and cortisol stress responsivity in healthy young men. *International Journal of Behavioral Medicine*, 1, 264-283.
- Salomon, K., Clift, A., Karlsdottir, M., & Rottenberg, J. (2009). Major depressive disorder is associated with attenuated cardiovascular reactivity and impaired recovery among those free of cardiovascular disease. *Health Psychology*, 28, 157-165.
- Salomon, K., Bylsma, L.M., White, K.E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependent? A comparison of major depressive disorder remitted depression and health controls. *International Journal of Psychophysiology*, 90, 50-57.
- Saperova, E., & Dimitriev, D. (2015). Heart rate variability as a measure of autonomic regulation of cardiac activity during mental stress. *The FASEB Journal*, 29, 799.12.
- Schubert, C., Lambertz, M., Nelesen, R.A., Bardwell, W., Choi, J. B., & Dimsdale, J.E. (2009). Effects of stress on heart rate complexity- A comparison between short-term and chronic stress. *Biological Psychology*, 80, 325-332.
- Schwartz, A.R., Gerin, W., Davidson, K.W., Pickering, T.G., Brosschot, J.F., Brosschot, J.F., Thayer, J.F., et al. (2003). Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. *Psychosomatic Medicine*, 65, 22-35.
- Sherwood, A., Allen, M.T., Obrist, P.A., & Langer, A.W. (1986). Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. *Psychophysiology*, 23, 89-104.
- Sherwood, A., Dolan, C.A., & Light, K.C. (1990). Hemodynamics of blood pressure responses during active and passive coping. *Psychophysiology*, 27, 656-668.

- Sloan, R.P., Korten, J.B., & Myers, M.M. (1991). Components of heart rate reactivity during mental arithmetic with and without speaking. *Physiology and Behavior*, 50, 1039- 1045.
- Sorocco, K. H., Lovallo, W. R., Vincent, A. S., & Collins, F. L. (2006). Blunted hypothalamic-pituitary-adrenocortical axis responsivity to stress in persons with a family history of alcoholism. *International Journal of Psychophysiology*, 59, 210-217.
- Sparks, H.V., & Rooke, T.W. (1987). Essentials of cardiovascular physiology. Minneapolis: University of Minnesota Press.
- Stemmler, G., Grossman, P., Schmid, H., & Foerster, F. (1991). A model of cardiovascular activation components for studies using autonomic receptor antagonists. *Psychophysiology*, 28, 367-382.
- Sterling, P. (2012). Allostasis: A model of predictive regulation. *Physiology and Behavior*, 106, 5-15.
- Stromme, S.B., Wikeby, P.C., Blix, A.S., & Ursin, H. (1978). Additional heart rate. In Ursin, H., Baade, E., & Levine, S. (Eds.), *Psychobiology of stress* (pp83-89). London: Academic Press
- Taylor, T. R., Kamarck, T. W., & Dianzumba, S. (2003). Cardiovascular reactivity and left ventricular mass: An integrative review. *Annals of Behavioral Medicine*, 26, 182-193.
- Treiber, F. A., Turner, J. R., Davis, H., & Strong, W. B. (1997). Prediction of resting cardiovascular functioning in youth with family histories of essential hypertension: A 5-year follow-up. *International Journal of Behavioral Medicine*, 4, 278-291.
- Treiber, F. A., Kamarck, T., Schneiderman, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular Reactivity and Development of Preclinical and Clinical Disease States. *Psychosomatic Medicine*, 65, 46-62.

- Turner, J.R., & Carroll, D. (1985). Heart rate and oxygen consumption during mental arithmetic, a video game, and graded exercise: Further evidence of metabolically-exaggerated cardiac adjustments? *Psychophysiology*, 22, 261-267.
- Voellmin, A., Winzeler, K., Hug, E., Wilhelm, F.H., Schaefer, V., Gaab, J., et al. (2015). Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity. *Psychoneuroendocrinology*, 51, 58-67.
- Wager, T.D., Waugh, C.E., Lindquist, M., Noll, D.C., Fredrickson, B.L., & Taylor, S.F. (2009a). Brain mediators of cardiovascular responses to social threat: Part I: Reciprocal dorsal and central sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*, 47, 821-835.
- Wager, T.D., van Ast, V.A., Hughes, B.L., Davidson, M.L., Lindquist, M.A., & Ochsner, K.N. (2009b). Brain mediators of cardiovascular responses to social threat, Part II: Prefrontal-subcortical pathways and relationship with anxiety. *Neuroimage*, 47, 836- 851.
- Willemsen, G., Ring, C., Carroll, D., Evans, P., Clow, A., & Hucklebridge, F. (1998). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic and cold pressor. *Psychophysiology*, 35, 252-259.
- Williamon, A., Aufegger, L., Wasley, D., Looney, D., & Mandic, D.P. (2013). Complexity of physiological responses decreases in high stress musical performance. *Journal of the Royal Society Interface*, 10, 1-6.
- Winzer, A., Ring, C., Carroll, D., Willemsen, G., Drayson, M., Kendall, M. (1999). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of beta-adrenergic blockade. *Psychophysiology*, 36, 591- 601.

- Wolf, S., & Wolff, H.G. (1951). A summary of experimental evidence relating life stress to pathogenesis of essential hypertension in man. In E.T., Bell (Ed.), *Hypertension: A Symposium* (pp.288-322). Minneapolis: University of Minnesota Press.
- Wolf, S., Cardon, P.V., Shepard, E.M., & Wolff, H.R. (1955). *Life Stress and Essential Hypertension*. Baltimore: Williams and Wilkins.
- York, K.M., Hassan, M., Li, Q., Li, H., Fillingim, R.B., & Sheps, D.S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine*, 69, 521-528.

---

## Chapter 2

---

### A Tale of Two Mechanisms: A Meta-Analytic Approach Toward Understanding the Autonomic Basis of Cardiovascular Reactivity to Acute Psychological Stress

This chapter has been published under the following reference:

Brindle, R.C., Ginty, A.T., Phillips, A.C., & Carroll, D. (2014). A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress. *Psychophysiology*, 51, 964-976.

### **Abstract**

A series of meta-analyses was undertaken to determine the contributions of sympathetic and parasympathetic activation to cardiovascular stress reactivity. A literature search yielded 186 studies of sufficient quality that measured indices of sympathetic and/or parasympathetic activity. A range of psychological stressors perturbed blood pressure and heart rate. There were comparable aggregate effects for sympathetic activation, as indexed by increased plasma epinephrine and norepinephrine, and shortened pre-ejection period, and parasympathetic deactivation, as indexed by heart rate variability measures. Effect size varied with stress task, sex, and age. In contrast to alpha-adrenergic blockade, beta-blockade attenuated cardiovascular reactivity. Cardiovascular reactivity to acute psychological stress would appear to reflect both beta-adrenergic activation and vagal withdrawal to a largely equal extent.

**Keywords:** Cardiovascular Reactivity; Meta-analysis; Parasympathetic; Stress; Sympathetic

## Introduction

During exercise a metabolically driven increase in heart rate (HR) and blood pressure (BP) is observed. Within a highly coordinated physiological cascade blood flow is diverted to working muscles and increases in HR and BP assure that oxygen demands are met, temperature is regulated, and metabolic waste is removed (McArdle, Katch, & Katch, 2001). Similar cardiovascular adjustments are seen in response to acute psychological stress despite an absence of augmented metabolic demand. This has led researchers to suggest that, when uncoupled from metabolic demand, large magnitude increases in HR and BP are detrimental to health (Obrist, 1981).

Indeed, research has shown that exaggerated physiological stress responses are associated with future hypertension (Borghi, Costa, Boschi, Mussi, & Ambrosioni, 1986; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Chida & Steptoe, 2010a; Everson, Kaplan, Goldberg, & Salonen, 1996; Jennings, et al., 2004; Markovitz, Racynski, Wallace, Chettur, & Chesney, 1998; Markovitz, Matthews, Kannel, Cobb, & D'Agostino, 1993), atherosclerosis (Everson et al., 1997; Roemmich et al., 2011; Roemmich, Lobarinas, Joseph, Lambiase, & Archer, 2009) and increased cardiovascular disease mortality (Carroll et al., 2012). By logical extension, small magnitude stress responses were previously assumed to be, not only more appropriate from a metabolic perspective, but also indicative of positive health. However, recent research has shown this line of reasoning to be flawed as blunted HR and BP responses have been linked with depression (Brindle, Ginty, & Conklin, 2013; Carroll, Phillips, Hunt, & Der, 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; Ehrental, Herrmann-Linge, Fey, & Shauenburg, 2010; Phillips, Hunt, Der, & Carroll, 2010; Salomon, Bylsma, White, Panaite, & Rottenberg, 2013; Salomon, Clift, Karlsdottir, &

Rottenberg, 2009; York et al., 2007), obesity (Phillips, Roseboom, Carroll, & de Rooij, 2012; Phillips, 2011; Singh & Shen, 2013), disordered eating (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012; Koo-Loeb, Pedersen, & Girdler, 1998), and cognitive decline (Ginty, Phillips, Der, Deary, & Carroll, 2011). Consequently, it would appear that reactions that fall within the normative range are indicative of functional homeostatic regulation and that extreme (i.e., blunted or exaggerated) cardiovascular responses to psychological stress signal system dysregulation that can lead to adverse health and behavioural outcomes (Lovallo, 2011).

At the present however, the results of research focused on elucidating the underlying physiological determinants of the cardiovascular stress response remain somewhat equivocal. Some research has suggested that the cardiovascular stress response is primarily the result of sympathetic mechanisms (Marsland et al., 1995; Mills, et al., 1994; Mills & Dimsdale, 1991; Mills, Dimsdale, Ziegler, Berry, & Bain, 1990; Pacák et al., 1989) while others implicate the vagal system (Grossman, Watkins, Wilhelm, Manolakis, & Lown, 1996; Hjortskov et al., 2004; Jiang et al., 1993; Sloan, Korten, & Myers, 1991) in driving stress reactions. Still others implicate interactions between the two autonomic nervous system branches (Allen & Crowell, 1989; Berntson et al., 1994a; Cacioppo, Uchino, & Berntson, 1994; Gianaros, Quigley, Mordkoff, & Stern, 2001; Lane, Adcock, & Burnett, 1992), fluctuations in baroreflex sensitivity (Duscheck, Dietel, Schandry, & Reyes del Paso, 2008; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012; Steptoe & Sawada, 1989) and peripheral tissue influences in cardiovascular stress reactions (Lovallo, 2005; Lovallo & Gerin, 2003; Shapiro, Sloan, Bagiella, Bigger, & Gorman, 1996; Sloan, Shapiro, & Gorman, 1990).

Consequently, research focus on the physiological mechanisms responsible for HR and BP responses to psychological stress is warranted for three reasons. First, a large amount of



inter-individual variability exists with respect to HR and BP stress responses (Wager et al., 2009). However, given that HR and BP are both multiply determined cardiovascular endpoints, the physiological mechanisms responsible for HR and BP potentially represent a novel physiological level at which to assess cardiovascular stress responses. At this level, individual differences could exist in hemodynamic regulation, autonomic activation (both central and peripheral), and peripheral tissue and end target organ effects; individual differences that are missed if only HR and BP responses are assessed (Llabre, Klein, Saab, McCalla, & Schneiderman, 1998; Lovallo, 2005; Lovallo & Gerin, 2003; Manuck, 1994). Second, inter-individual variability at the physiological level more proximal to HR and BP could potentially carry disproportionate health risk (Kline et al., 2002; Llabre et al., 1998). For example, HR can increase as a result of parasympathetic withdrawal, sympathetic activation, or an interaction of the two autonomic branches (Berntson et al., 1994a; Berntson, Cacioppo, Quigley, & Fabro, 1994b; Berntson, Cacioppo, & Quigley, 1991). Likewise, BP is modulated by both cardiac (HR, cardiac output, and stroke volume) and vascular (total peripheral resistance; TPR) parameters. Consequently, any single HR or BP stress reaction could be caused by a number of physiological mechanisms. Given that hypertension is a vascular pathology linked with enhanced sympathetic activity, it is possible that a stress response driven by sympathetic activation or enhanced vascular reactivity could carry disproportionate risk for hypertension (Kline et al., 2002). Further, research has shown that individual response patterns remain relatively stable across stressors, lending more support to the notion that individual response stereotypy can potentially have pathogenic consequences (Hassellund, Flaa, Sandvik, Kjeldsen, & Rostrup, 2010; Hawkley et al., 2001; Kasprovicz, Manuck, Malkoff, & Krantz, 1990; Kline et al., 2002; Sherwood, Dolan, & Light, 1990a; Sherwood, Turner, Light, & Blumenthal, 1990b). Third, if extreme

cardiovascular reactivity is conceptualized as a biomarker of underlying pathology then exploration of the physiological mechanisms responsible for the cardiovascular stress responses could inform research focused on the negative health outcomes associated with such reactions (Chida & Steptoe 2010b; Chida & Steptoe, 2010c ; Lane et al., 2009a; Lane et al., 2009b).

For these reasons, a series of meta-analyses was conducted to assess the autonomic basis of cardiovascular stress reactions. Summary effects of stress reactivity of both sympathetic and parasympathetic indices are reported, as well as the combined effects of pharmacological autonomic blockade on cardiovascular reactivity. The value of such an analysis lies in the aggregation of a large body of literature, deploying a variety of experimental procedures to address the same question; in this case, what are the autonomic contributions to cardiovascular reactivity? In addition, subgroup analysis allowed for a comprehensive examination of physiological and non-physiological factors (i.e., sex, age, stress task, receptor type) that may influence stress reactivity.

## **Method**

### **Data Sources**

The protocol for data searching was based on approaches described previously (Counsell, 1997; Higgins & Green, 2011; Meade & Richardson, 1997) and the results are reported in line with the guidelines contained in the PRISMA Statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA group 2009). Electronic searches of the following databases were performed: Google Scholar, MedLine, PubMed, and PsycINFO, ProQuest Dissertation and Theses, ProQuest COS Conference Paper Index, Index to Theses, and Open Grey. Theses, conference proceedings, and grey literature searches were undertaken to minimize the effect of publication bias (Tak, Meijer,

Manoharan, de Jonge, & Rosmalen, 2010). The search strategy for sympathetic meta-analyses consisted of connecting a single primary (cardiovascular reactivity **OR** cardiovascular reactions) and secondary word (sympathetic nervous system **OR** sympathetic activation **OR** sympathetic agonist **OR** sympathetic antagonist **OR** agonist **OR** antagonist **OR** beta adrenergic **OR** alpha adrenergic **OR** sympathetic blockade **OR** blockade) using the Boolean operator **AND** (Figure 2.1). Searches for parasympathetic reports consisted of the same primary words connected to the following secondary words (parasympathetic nervous system **OR** blockade **OR** atropine **OR** respiratory sinus arrhythmia (RSA) **OR** high-frequency heart rate variability (HF-HRV) **OR** root mean square of successive differences (RMSSD)) with the Boolean operator **AND** (Figure 2.2). Dates of searches were restricted from 1967 to January 2013 to allow comparison with an earlier systematic review of sympathetic blockade studies (Mills & Dimsdale, 1991). Relevant online journals were searched using the criteria outlined above, i.e., search terms and Boolean operators, and the reference sections of articles retained for detailed inspection were manually screened.

### **Study Selection and Quality Assessment**

Due to the heterogeneity of definitions of the term “acute psychological stress” (Chida & Steptoe, 2010a) we defined, for the purposes of this review, acute psychological stress as an active, but metabolically undemanding, time-limited psychological task performed in a laboratory under controlled conditions. Specific focus was given to cardiovascular reactions to psychological stress because of the long established association between individual differences in stress reactions and health risk. In this context, understanding the underlying autonomic mechanisms is crucial to more fully characterise these relationships. For inclusion, studies had to meet the following criteria: 1. scientific report in the English language, i.e., peer-reviewed

articles, dissertations, abstracts, conference proceedings, 2. measured cardiovascular and sympathetic reactions to a task that was consistent with the definition of acute psychological stress provided above, 3. the stress task must have elicited a statistically significant increase in cardiovascular activity as indexed by a faster heart rate, and/or increased systolic (SBP) and diastolic blood pressure (DBP), 4. in the case of observational studies there must be at least one measure of sympathetic nervous system function (pre-ejection period (PEP), plasma epinephrine or norepinephrine), 5. in the case of intervention studies, there must be at least one measure of cardiovascular function (HR, SBP, or DBP). 6. in the case of observational studies, cardiovascular function must be measured at baseline prior to stress exposure, 7. for intervention studies, there must be a control element in the form of a within subjects crossover design or a between groups design with a no-treatment group, and 8. when results from the same sample appeared in separate publications, publications registering either a lower quality score or having a smaller sample size were excluded (Chida & Steptoe, 2010a). PEP has been validated, using pharmacological blockade, as a marker of beta-adrenergic activity (Harris, Schoenfeld, & Weissler, 1967; Mezzacappa, Kelsey, & Katkin, 1999; Winzer et al., 1999) and may represent a superior measure of sympathetic activity as it does not require indirect derivation or calculation used to estimate stroke volume (SV) and TPR (Newlin, & Levenson, 1979; Newman, & Callister, 1999). Only studies reporting statistically significant increases in HR or BP were included because the aim of the study was to examine the underlying mechanisms of cardiovascular reactions to mental stress and only in these studies could significant perturbation of the cardiovascular system and possible upstream autonomic mechanisms be assured. Sources selected for detailed review were screened using an 11-item quality assessment guide designed for the present study (Meade & Richardson, 1997). The purpose of the guide was to

screen prospective sources in a standardized fashion that would, if included, yield a quality score that could be used to highlight potential bias resulting from heterogeneous study quality. Quality scores did not factor into the decisions regarding inclusion. Examples of details included in the guide are variables measured, variables controlled for (e.g., body mass index (BMI), medical history), pharmacological techniques (i.e., agent, dose), cardiovascular impact of stress task, data handling techniques (i.e., artefact screening), and study design details (i.e., task counterbalancing, blinding procedures). A corresponding scoring key was created that was scored from 0 to 16. For eight of the questions, a score of 1 point was awarded if the study design element was present and 0 points if it was absent (e.g., task counterbalancing). Two questions regarding confounding variables had a scale of 0-3 and awarded points based on how many variables were controlled for. The final question was concerned with data processing and had a scale of 0-2 and awarded points based on how many steps were taken to assure quality data (i.e., screening for artifacts). Although results of each study had to be read in order to complete the quality assessment, no information regarding the study findings were recorded at this stage in an effort to eliminate inclusion bias. For included studies a separate data extraction sheet was completed. Manuscript screening and study quality assessment was carried out by one author (R.C.B). To verify inclusion and study assessment 20% of the retained reports were randomly reviewed by an additional author (D.C.).

### **Data Extraction and Synthesis**

Several *a priori* data extraction criteria were established for included studies: 1. if there were  $\geq 2$  measures of cardiovascular or sympathetic function in a single study each measure was analysed independently, 2. if  $> 1$  distinct, i.e., separated by a rest period, acute psychological stress task was used in a single study, each stress task was analysed independently, and 3. when

separate data were available for sex or age group, each subsample was analysed separately. Data were extracted from included studies in the form of means, standard deviations, and reactivity change scores, calculated as the difference between stress and baseline means. Where necessary, the author(s) of a study were contacted for additional data.

### **Meta-Analysis Procedures**

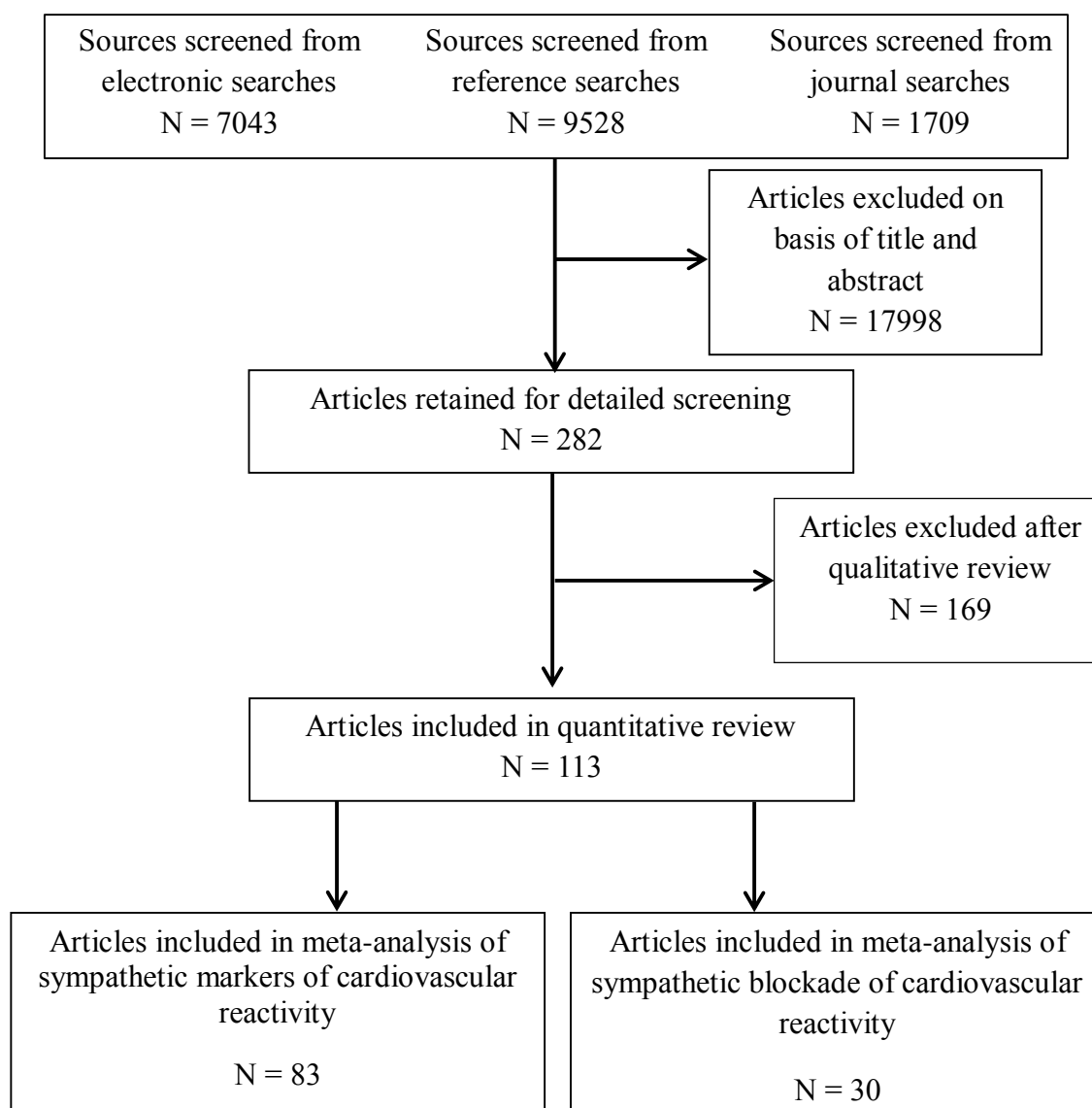
Random effects modelling was employed in the present study according to procedures outlined by Hunter and Schmidt (2004) and Lipsey and Wilson (2001). For observational studies, means and standard deviations for baseline and stress phases were used to calculate effect sizes. In the case of blockade studies, effect size was calculated from derived reactivity change scores (stress - baseline) pre- and post-blockade. Hedge's  $g$  ( $H_g$ ) was chosen as it improves on Cohen's  $d$  by correcting for small sample sizes and provides a more conservative estimate of aggregate effects (Borenstein, Hedges, Higgins, & Rothstein, 2009). Where data were presented only in figures, means and standard deviations were abstracted using an open source Web plot digitizer (<http://arohatgi.info/WebPlotDigitizer>) designed specifically for abstracting raw data from published figures. Overall effect sizes were calculated by weighting studies using the inverse variance method (Lipsey and Wilson, 2001) which gives more weight to studies with greater precision.

We employed Higgin's  $I^2$  statistic to quantify the percentage of total variance due to heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Publication bias was quantitatively assessed using Egger's unweighted regression asymmetry test (Egger, Davey Smith, Schneider, & Minder, 1997) and Rosenthal's Fail-safe  $N$  (Rosenberg, 2005; Rosenthal, 1979). Study quality bias was assessed by regressing study quality scores onto effect sizes.

Subgroup analyses on unweighted effect sizes were conducted for cardiovascular and autonomic variables to test for variations in effect size with stress task, age, sex, pharmacological agent, and receptor target using one-way ANOVAs. Stress task subgroup analyses were restricted to the following tasks as these were the only stress exposures reported in sufficient studies to make meta-analysis appropriate: mental arithmetic, Stroop, reaction time, and speech tasks. All analyses were performed using MIX 2.0 meta-analysis software (Bax, 2011) and SPSS version 20 (SPSS Inc. Chicago, Illinois, USA).

### **Sympathetic Meta-analyses**

Two separate, yet complimentary, meta-analyses were carried out to assess the role of sympathetic activation in cardiovascular reactivity. First, the overall ability of acute psychological stress tasks to elicit a sympathetic response, indexed by peripheral sympathetic markers, was addressed. Next, studies were aggregated that examined the effectiveness of sympathetic pharmacological blockade in attenuating HR and BP responses to acute mental stress. Conducting two meta-analyses on experimentally distinct bodies of literature that utilise different empirical methods to the same end allowed for the most comprehensive assessment of the role of sympathetic activation in cardiovascular reactivity. Figure 2.1 shows the number of studies at each stage of the review process.



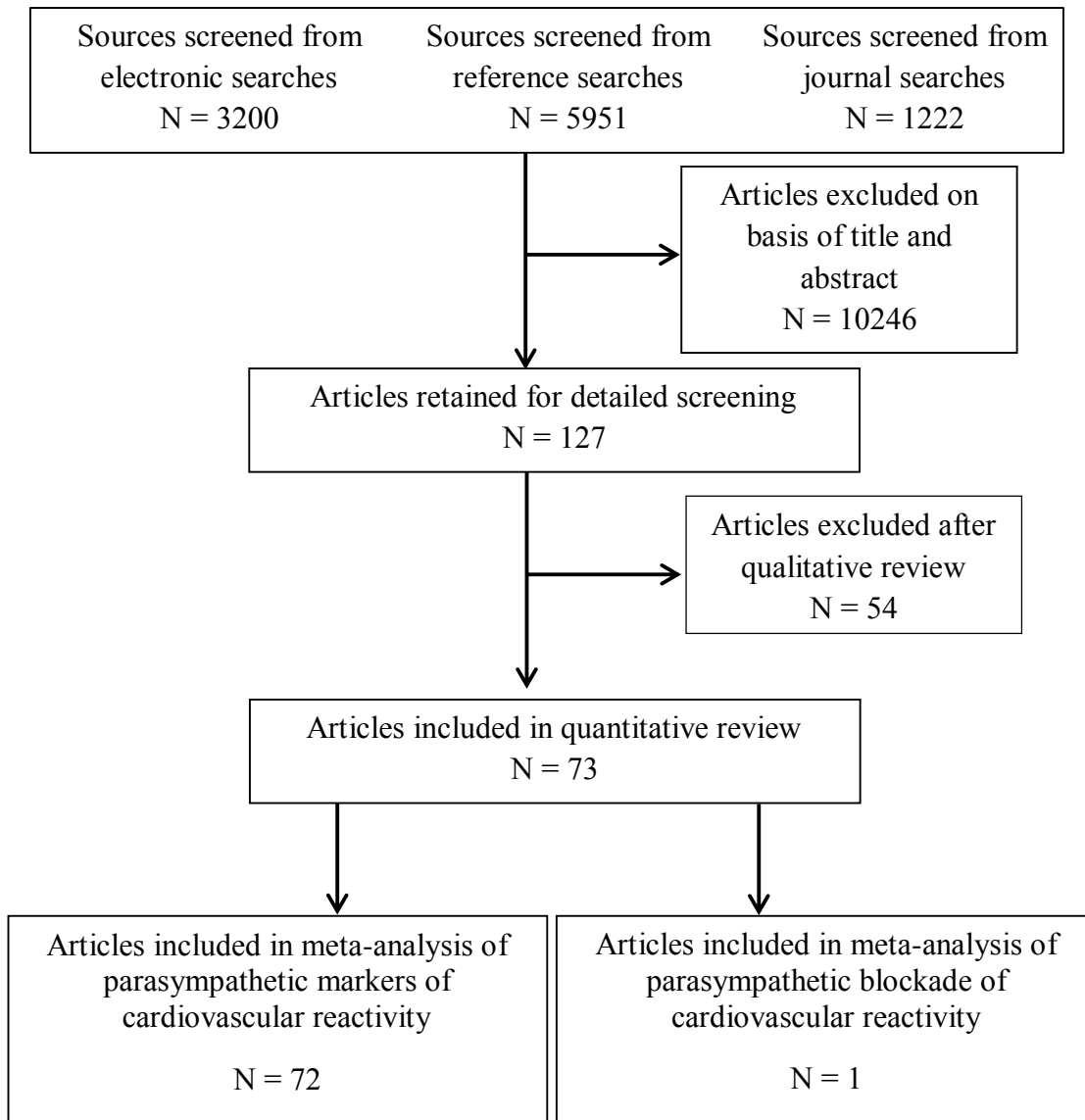
**Figure 2.1** Flow diagram of sympathetic nervous system systematic review.

### Parasympathetic Meta-Analyses

Two additional meta-analyses, focused on assessing the role of the parasympathetic nervous system in cardiovascular reactivity to acute psychological stress, were carried out using an identical protocol to the above. The inclusion criteria were the same as applied above, save that in this case, studies had to include at least one measure of parasympathetic activity defined as HF-HRV, RMSSD, or RSA. For the purpose of this analysis studies reporting RSA or HF-



HRV were collapsed as both, in theory, capture vagal activity related to respiration (Grossman & Taylor, 2007). Thus, parasympathetic indices were reduced to frequency and time domain indices. Figure 2.2 shows the number of studies at each stage of the review process.



**Figure 2.2** Flow diagram of parasympathetic nervous system systematic review.

## Results

### Blood Pressure and Heart Rate Stress Reactivity

Figure 2.3 shows that a range of acute psychological stress tasks reliably perturbed overall cardiovascular activity ( $H_g = 1.119$  [1.068-1.170];  $p < .001$ ), SBP ( $H_g = 1.249$  [1.151-1.348];  $p < .001$ ), DBP ( $H_g = 1.130$  [1.036-1.224];  $p < .001$ ), and HR ( $H_g = 1.021$  [0.946-1.095];  $p < .001$ ). In each case hemodynamic function increased with exposure to psychological stress. The effects of acute stress were greater for SBP reactivity than HR reactivity,  $F(2,479) = 5.04$ ,  $p = .007$ .

### Sympathetic Nervous System Reactivity

A total of 83 studies were included in the present analysis. Table 2.1 outlines the summary characteristics of the included studies. Acute psychological stress produced significant increases in overall sympathetic activity ( $H_g = 0.551$  [0.497-0.605];  $p < .001$ ), plasma epinephrine ( $H_g = 0.620$  [0.528-0.712];  $p < .001$ ), plasma norepinephrine ( $H_g = 0.452$  [0.360-0.545];  $p < .001$ ), and PEP ( $H_g = -0.574$  [-0.668 - -0.481];  $p < .001$ ). Subgroup analyses revealed no significant differences between the effect sizes for the different sympathetic variables (Figure 2.3).

### Sympathetic Blockade of Cardiovascular Reactivity

Thirty studies evaluated the effects of sympathetic blockade on cardiovascular reactivity (Table 2.2). A significant reduction in overall cardiovascular reactivity ( $H_g = -0.339$  [-0.417- -0.260];  $p < .001$ ), SBP reactivity ( $H_g = -0.218$  [-0.321- -0.116];  $p < .001$ ), and HR reactivity ( $H_g = -0.670$  [-0.830- -0.509];  $p < .001$ ) was observed. Subgroup analyses revealed significant differences between reductions in HR, SBP, and DBP reactivity,  $F(2,149) = 16.43$ ,  $p < .001$ . HR

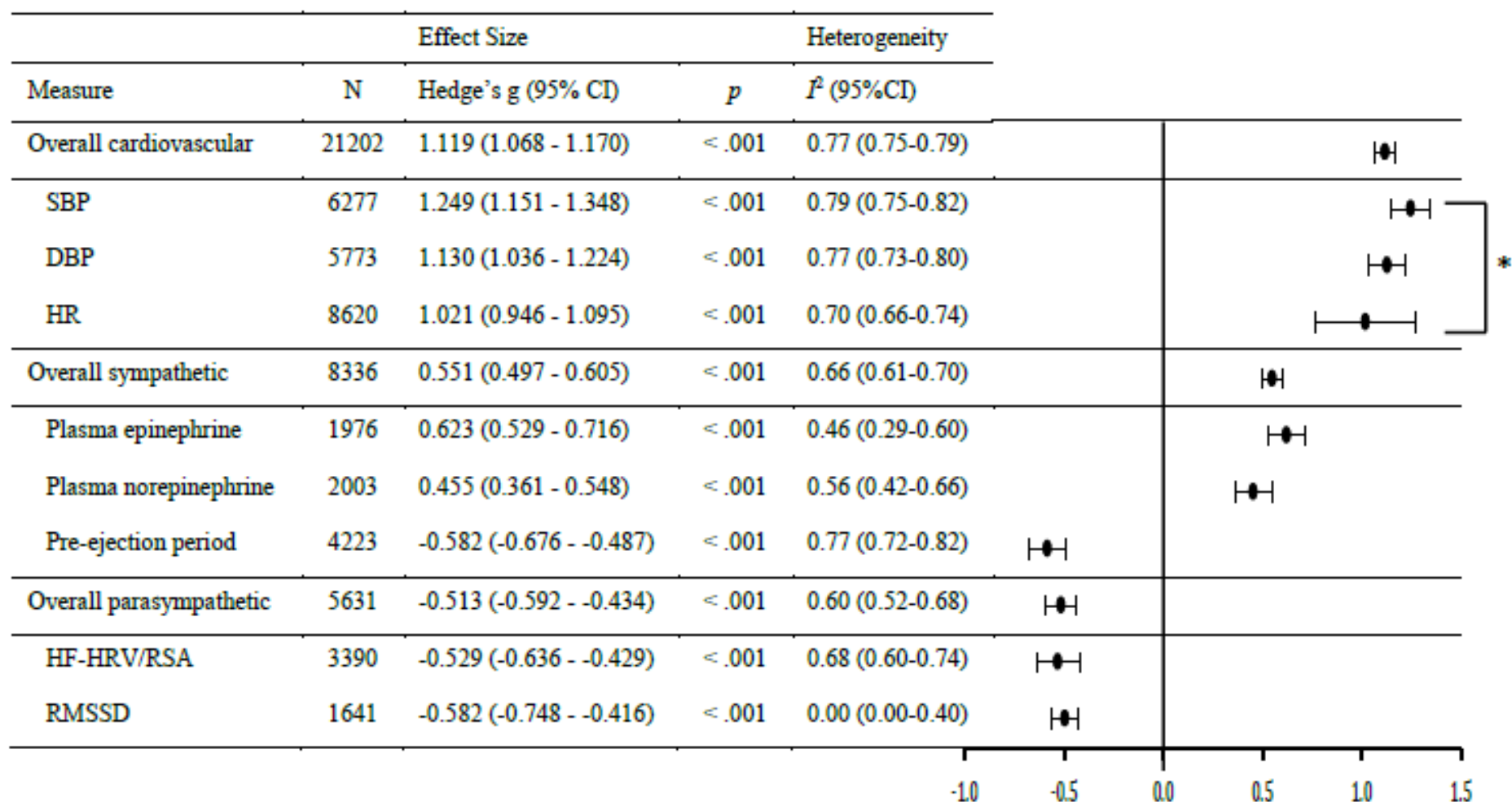
reactivity was attenuated significantly more than SBP or DBP reactivity by sympathetic blockade (Figure 2.4).

### **Sympathetic Blockade Subgroup Analyses**

Subgroup analyses of pharmacological receptor targets revealed significant differences in the attenuation of overall cardiovascular reactivity,  $F(2,146) = 4.63$ ,  $p = .011$ . Where non-selective beta ( $\beta$ ) and beta-1 ( $\beta_1$ ) specific antagonists significantly attenuated overall cardiovascular reactivity, drugs targeting alpha-1 ( $\alpha_1$ ) receptors failed to influence stress reactions (Figure 2.4). When the effect of drug intervention on individual cardiovascular variables was examined, ANOVAs revealed a significant drug effect for HR reactivity,  $F(2,52) = 6.82$ ,  $p = .002$ . Non-selective beta blockers attenuated reactivity significantly more than alpha-1 blockers which was actually associated with a slight increase in heart rate reactions (Figure 2.5). Analyses of individual sympathetic antagonists were carried out (data not shown) but these analyses failed to uncover any significant differences between individual drugs.

### **Parasympathetic Nervous System Reactivity**

A total of 76 studies were included in this meta-analysis. Table 2.3 outlines the summary characteristics of the included studies. Significant overall vagal withdrawal was observed in response to psychological stress ( $H_g = -0.513$  [-0.592 - -0.434];  $p < .001$ ). Subgroup analyses of individual parasympathetic indices revealed significant effects for HF-HRV/RSA ( $H_g = -0.529$  [-0.636 - -0.429];  $p < .001$ ), RMSSD ( $H_g = -0.582$  [-0.748 - -0.416];  $p < .001$ ), but failed to show any significant differences between the indices (Figure 2.3).



**Figure 2.3** Cardiovascular, sympathetic, and parasympathetic reactivity to acute psychological stress. Results of meta-analysis and subgroup and sensitivity analyses. Overall reactivity variables represent an aggregate effect of each variable's three respective sub-variables. HR-HRV = high frequency heart rate variability, RSA = respiratory sinus arrhythmia, RMSSD = root mean square of successive differences \*indicates  $p < .05$ .

**Table 2.1** Characteristics of included studies for the meta-analyses of sympathetic indices

Characteristic	Included studies	
	Number	Percentage
Total studies	83	100.00
Average sample size	41	
Range	5– 902	
Cardiovascular variables measured <sup>1</sup>		
Heart rate	81	97.59
Systolic blood pressure	56	67.46
Diastolic blood pressure	55	66.26
Sympathetic indices measured <sup>1</sup>		
Plasma epinephrine	42	50.60
Plasma norepinephrine	44	53.01
Pre-ejection period	45	54.21
Stress tasks <sup>2</sup>		
Mental arithmetic	37	44.05
Stroop task	20	23.81
Reaction time task	7	8.33
Speech	17	20.24
Other tasks	16	19.05
Sample characteristics <sup>2</sup>		
Male only	46	54.76
Female only	16	19.28
Mixed sex	26	30.95
Average age	32.19	
Age range (years)	9.60 – 68.50	
Sample health		
Healthy	77	92.77
Hypertensive	6	7.14
Study quality		
Mean quality score	8.16	
Range	2.00 – 12.00	

<sup>1</sup>Categorical sums are > 84 because of studies capturing multiple cardiovascular and sympathetic measures

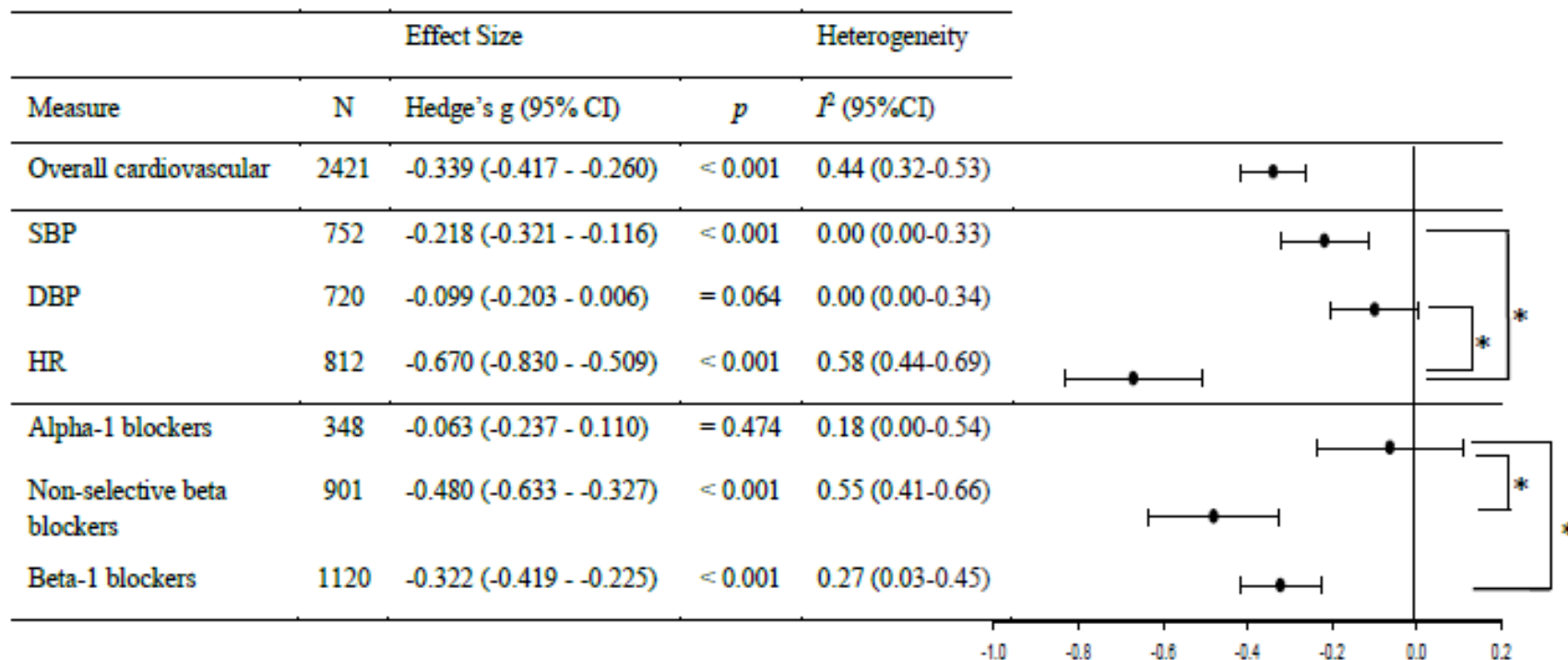
<sup>2</sup>Study designs utilized multiple stress paradigms and samples hence categorical sums > 84

**Table 2.2** Characteristics of included studies for meta-analysis of sympathetic blockade

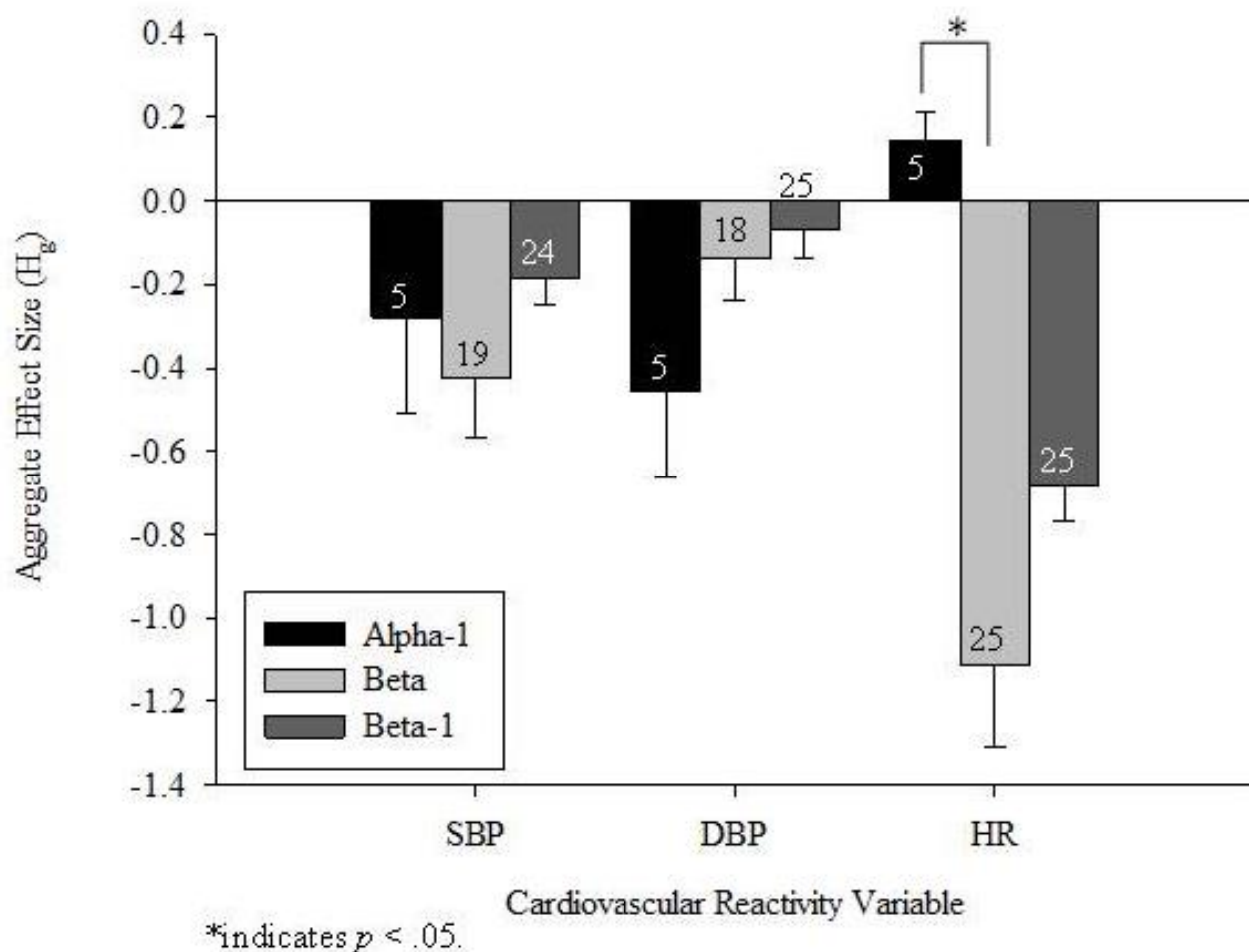
Characteristic	Included Studies	
	Number	Percentage
Total studies	30	100.00
Average sample size	15	
Range	5– 48	
Cardiovascular variables measured <sup>1</sup>		
Heart rate	30	100.00
Systolic blood pressure	26	86.67
Diastolic blood pressure	24	80.00
Pharmacological blockade <sup>1</sup>		
Alpha-1	5	16.67
Non-selective beta	17	56.67
Beta-1	17	56.67
Stress tasks <sup>2</sup>		
Mental arithmetic	15	50.00
Stroop task	6	20.00
Reaction time task	2	6.67
Other tasks	9	30.00
Sample characteristics <sup>2</sup>		
Male only	14	46.67
Female only	0	0.00
Mixed sex	17	56.67
Average age	37.90	
Age range (years)	23.00 – 60.00	
Sample health <sup>2</sup>		
Healthy	15	50.00
Hypertensive	13	43.33
Cardiovascular disease	1	3.33
Post myocardial infarction	2	6.67
Study quality		
Mean quality score	6.29	
Range	1.00 – 12.00	

<sup>1</sup>Categorical sums are > 30 because of studies capturing multiple cardiovascular and sympathetic measures

<sup>2</sup>Study designs utilized multiple stress paradigms and samples hence categorical sums > 30



**Figure 2.4** Cardiovascular stress reactivity in response to sympathetic blockade. Results of meta-analysis, and subgroup and sensitivity analyses. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate



**Figure 2.5** Subgroup analysis of the influence of sympathetic blockade on individual cardiovascular variables. Numbers in bars denote number of studies in each subgroup. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate \*indicates  $p < .05$ .

### Parasympathetic Blockade of Cardiovascular Reactivity

Since only one study was uncovered that fulfilled the inclusion criteria no meta-analytic analysis was carried out. Cardiovascular stress reactivity was not directly assessed but changes in heart period suggest that despite a large increase in baseline, stress reactivity was mildly attenuated, albeit not as much as under beta-blockade (Reyes del Paso, Langewitz, Robles, & Pérez, 1996).



**Table 2.3** Characteristics of included studies for meta-analysis of parasympathetic indices

Characteristic	Included Studies	
	Number	Percentage
Total studies	72	100.00
Average sample size	34.64	
Range	6 – 218	
Cardiovascular variables measured <sup>1</sup>		
Heart rate	72	100.00
Systolic blood pressure	39	54.17
Diastolic blood pressure	33	45.83
Parasympathetic indices measured <sup>1</sup>		
High frequency heart rate variability	39	54.17
Root mean square of successive differences	17	23.61
Respiratory sinus arrhythmia	20	27.78
Stress tasks <sup>2</sup>		
Mental arithmetic	28	38.89
Stroop task	9	12.50
Reaction time task	7	9.72
Speech	12	16.67
Other tasks	24	33.33
Sample characteristics <sup>2</sup>		
Male only	29	40.28
Female only	23	31.97
Mixed sex	31	43.06
Average age	32.17	
Age range (years)	9.00 – 82.50	
Sample health <sup>2</sup>		
Healthy	71	98.61
Hypertensive	3	4.17
Study quality		
Mean quality score	8.06	
Range	4.00 – 12.00	

<sup>1</sup>Categorical sums are > 72 because of studies capturing multiple cardiovascular and sympathetic measures

<sup>2</sup>Study designs utilized multiple stress paradigms and samples hence categorical sums > 72

## Subgroup Analyses

### Stress task.

Subgroup analysis of stress tasks indicated that effect sizes varied with task for SBP,  $F(3,111) = 4.22, p = .007$ , DBP,  $F(3,102) = 6.79, p < .001$ , and overall sympathetic,  $F(3,158) = 3.18, p = .026$ , and parasympathetic activity,  $F(3,77) = 3.58, p = .018$ . Post-hoc analyses revealed that speech tasks were significantly more provocative than mental arithmetic. Speech tasks also provoked larger DBP reactions than reaction time tasks. Sympathetic activation was greater for reaction time tasks than mental arithmetic and greater parasympathetic withdrawal for Stroop than for speech tasks also emerged (Figure 2.6).

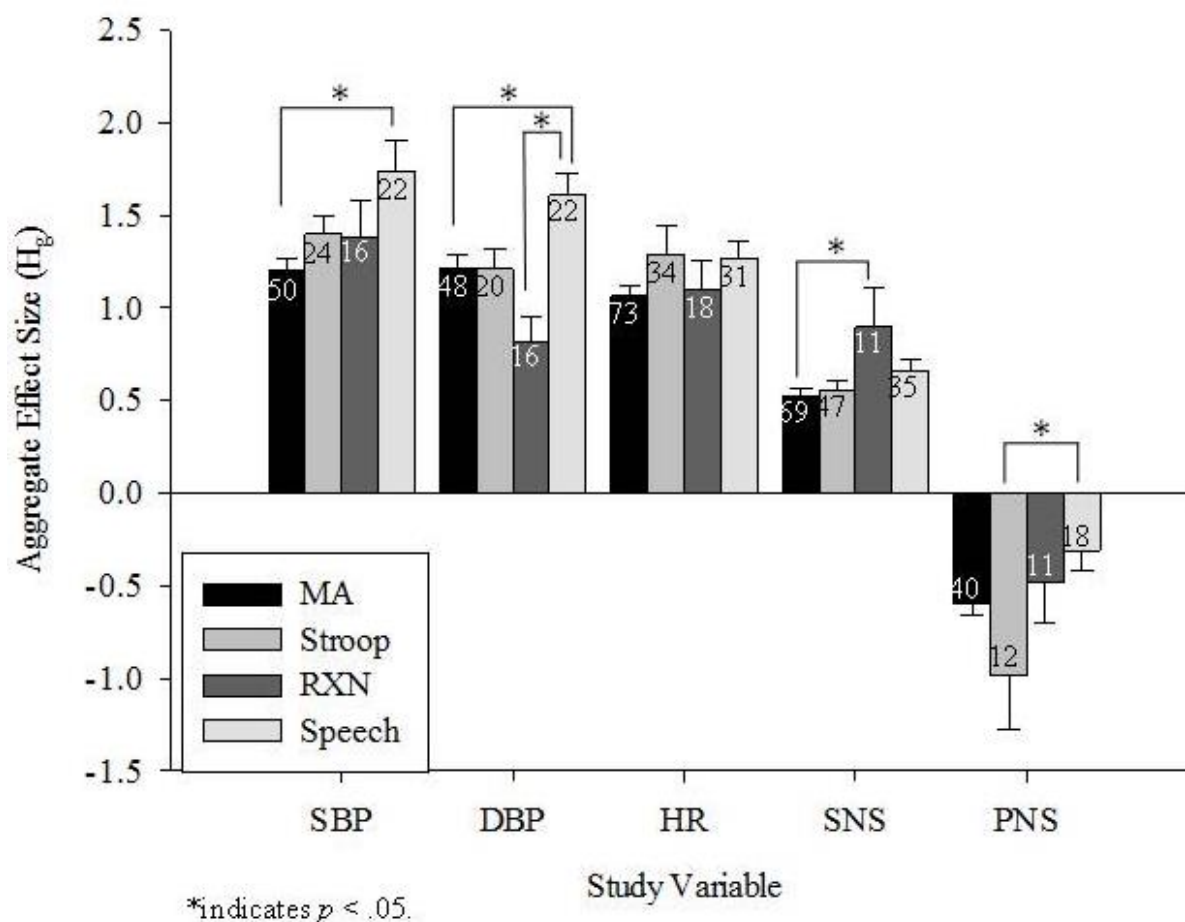
### Age group.

Study samples were divided into three groups (18-30, 31-49, 50+ years). One-way ANOVA revealed that effect sizes for HR varied with age,  $F(2,190) = 3.57, p = .030$ , as did overall sympathetic reactivity,  $F(2,200) = 9.62, p < .001$  (Figure 2.7). Post hoc analysis confirmed that the youngest age group exhibited the largest HR reactions and the greatest overall sympathetic nervous system reactions. Significant age variations in effect size were also found for plasma norepinephrine,  $F(2,68) = 4.88, p = .010$ , and PEP,  $F(2,64) = 6.65, p = .002$ . In both cases, effect sizes decreased with age.

Subgroup analysis for sympathetic blockade revealed significant effect size variations with age for SBP,  $F(2,45) = 5.19, p = .009$ , and HR,  $F(2,52) = 4.52, p = .016$ , reactivity (Figure 2.8). In both cases, greater attenuation of reactivity was observed in the 18-30 age group compared to the 31-49 age group. No significant differences were observed between the 50+ age group and the other age groups on any cardiovascular measure.

### Sex.

Subgroup analysis for sex revealed effect size differences in SBP,  $F(1,105) = 16.89$ ,  $p < .001$ , DBP,  $F(1,101) = 5.38$ ,  $p = .022$ , and overall sympathetic reactivity,  $F(1,147) = 6.21$ ,  $p = .014$  (Figure 9). In all cases, males were characterized by larger effect sizes.

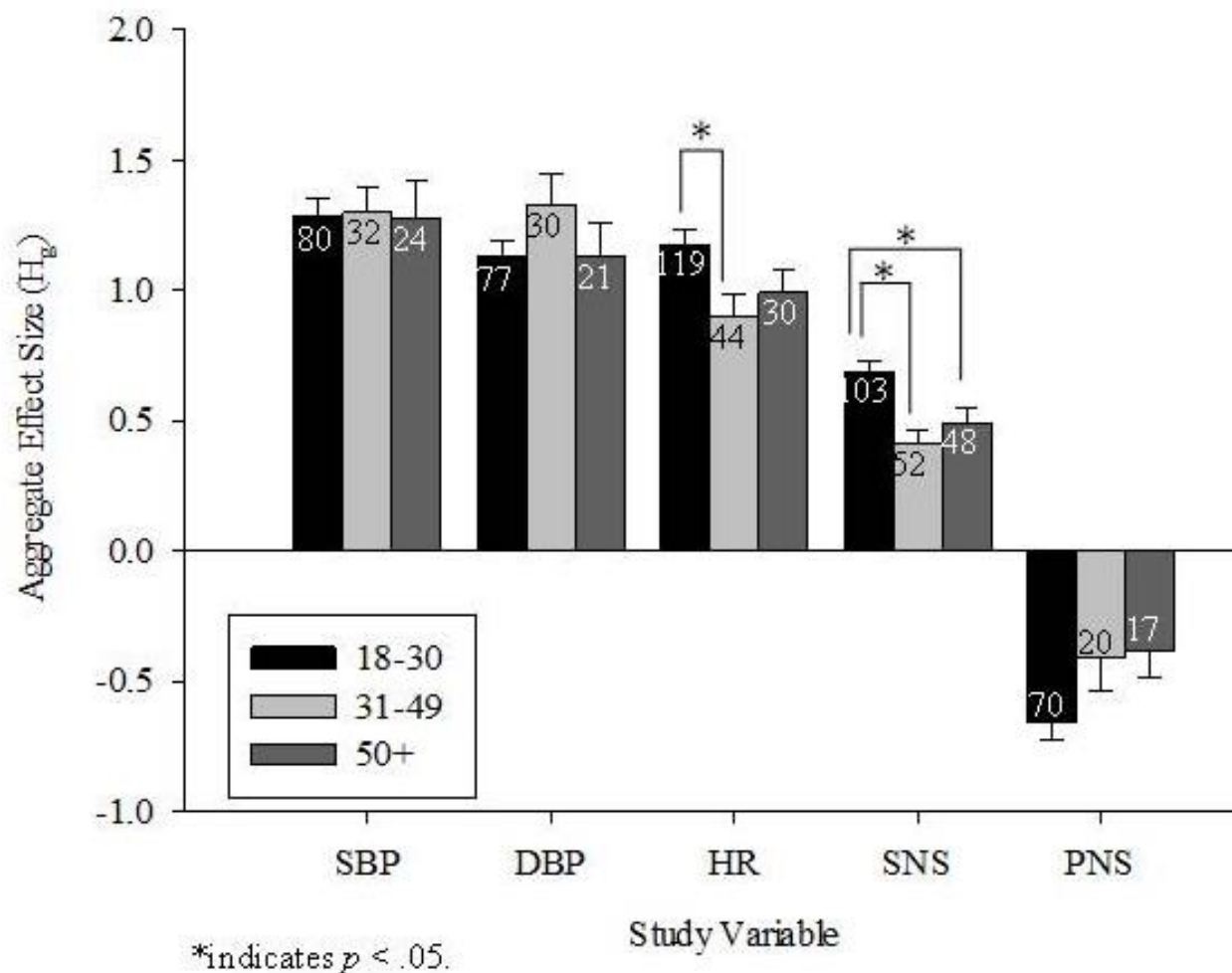


**Figure 2.6** Subgroup analysis of stress task. Numbers in bars denote number of studies in each subgroup. MA = mental arithmetic task, RXN = reaction time task, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SNS = overall sympathetic reactivity, PNS = overall parasympathetic withdrawal

### Studies with Simultaneous Sympathetic and Parasympathetic Measurement

Twenty seven studies included in the above analyses reported markers of both sympathetic and parasympathetic reactivity. Due to the possibility of task selection bias in separate studies of sympathetic and parasympathetic reactivity, analyses restricted to these 27

studies were undertaken. The aggregate effect sizes for sympathetic ( $H_g = 0.585$  [0.436 -0.735];  $p < .001$ ) and parasympathetic ( $H_g = -0.530$  [-0.655 - -0.406];  $p < .001$ ) reactivity were virtually identical to those that emerged from the original analyses (Figure 10).

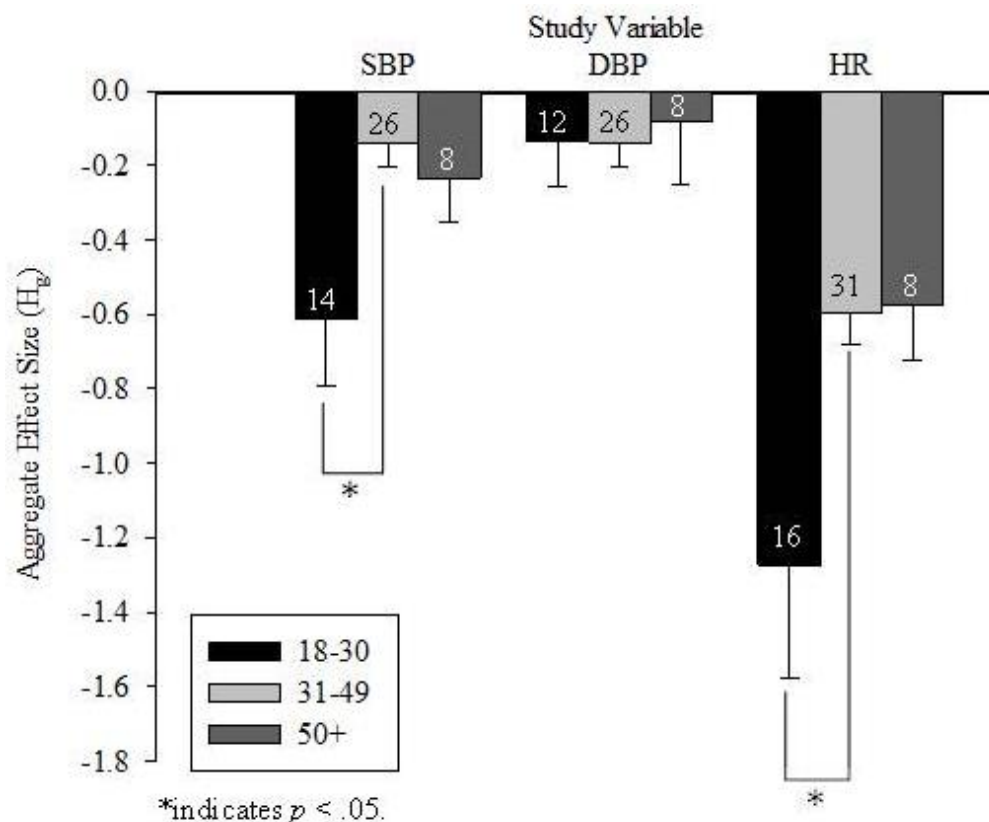


**Figure 2.7** Subgroup analysis of age group. Numbers in bars denote number of studies in each subgroup. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SNS = overall sympathetic reactivity, PNS = overall parasympathetic withdrawal \*indicates  $p < .05$ .

### Correlation Analysis of Effect Sizes

An exploratory correlation analysis of effect sizes was conducted to assess the relatedness of effects sizes (Table 2.4). Briefly, all cardiovascular variables were significantly correlated (all  $p < .05$ ). Plasma epinephrine was significantly related to SBP and HR (all  $p < .05$ ) while PEP

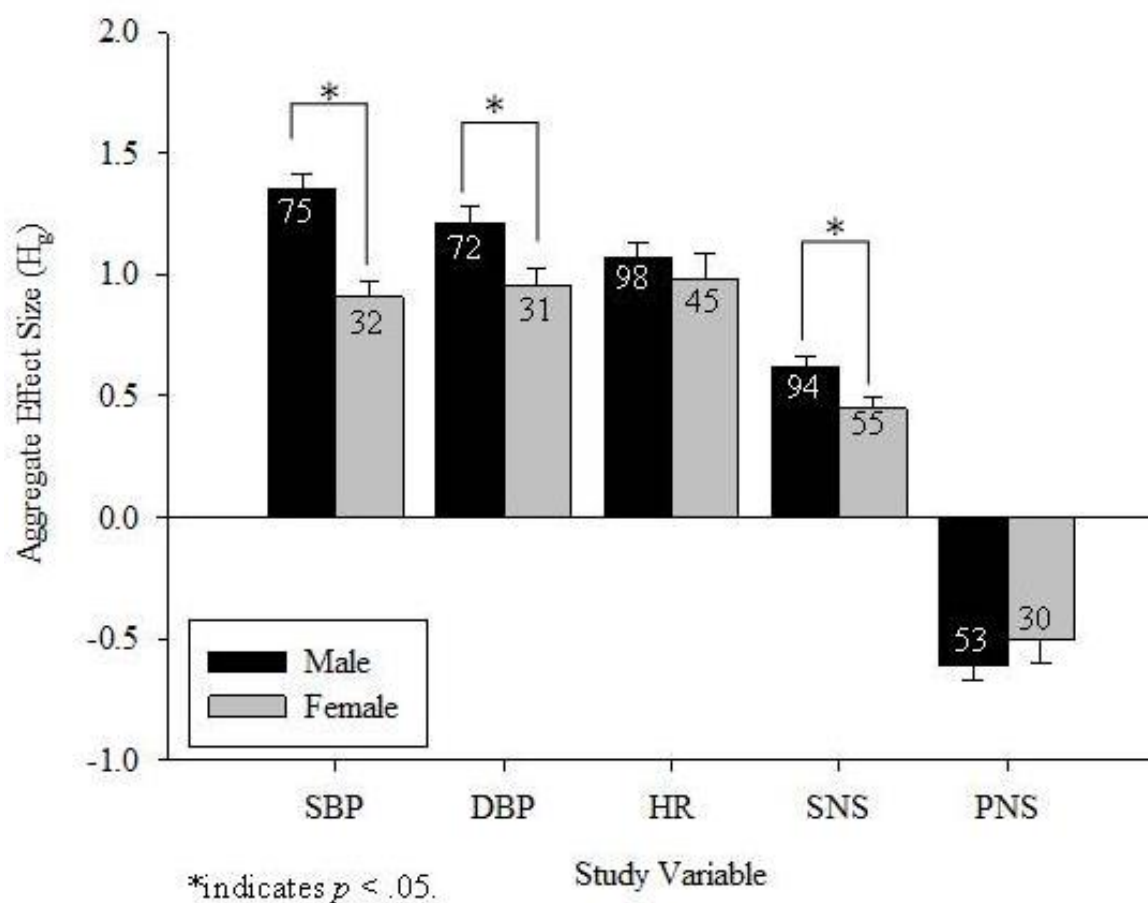
was also significantly correlated with HR ( $p < .01$ ). Overall sympathetic activation and parasympathetic withdrawal were associated with HR (all  $p < .05$ ) but not with each other ( $p = .081$ ). Finally, PEP was directly related to overall vagal withdrawal ( $p < .01$ ).



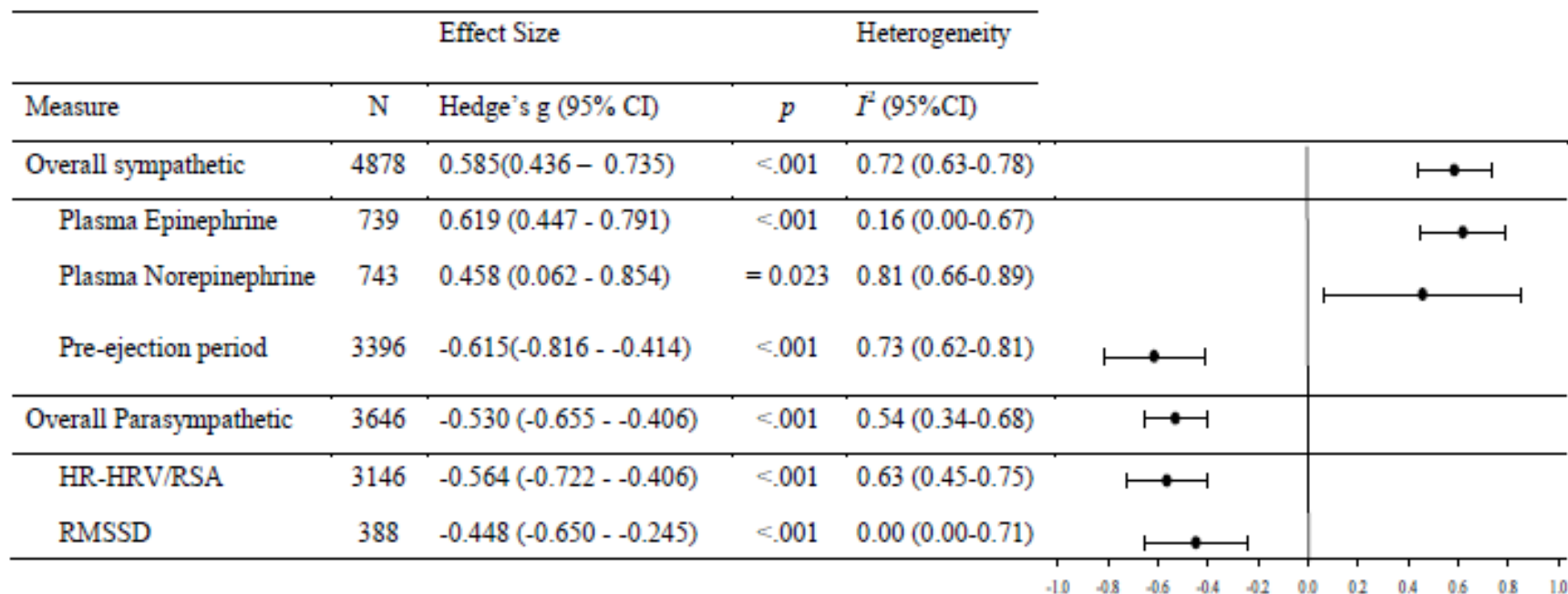
**Figure 2.8** Subgroup analysis of age group for sympathetic blockade. Numbers in bars denote number of studies in each subgroup. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate \*indicates  $p < .05$ .

### Sensitivity Analysis

When study quality scores were regressed onto aggregate effects, significant relationships emerged for HR,  $\beta = -.22$ ,  $t = -3.19$ ,  $p = .002$ ,  $\Delta R^2 = .047$ , PEP,  $\beta = .30$ ,  $t = 2.68$ ,  $p = .009$ ,  $\Delta R^2 = .091$ , and DBP blockade,  $\beta = .39$ ,  $t = 2.88$ ,  $p = .006$ ,  $\Delta R^2 = .155$ . Publication bias analysis of all meta- and subgroup analyses with Rosenthal's Failsafe N produced a range of values from 84-21645.



**Figure 2.9** Subgroup analysis of sex. Numbers in bars denote number of studies in each subgroup. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SNS = overall sympathetic reactivity, PNS = overall parasympathetic withdrawal \*indicates  $p < .05$ .



**Figure 2.10** Autonomic reactivity to acute psychological stress in studies measuring both sympathetic and parasympathetic reactivity simultaneously (27 studies). Results of meta-analysis and subgroup analysis. Overall reactivity variables represent an aggregate effect of each variable's three respective sub-variables.

**Table 2.4** Correlation analysis of effect sizes

	1.	2.	3.	4.	5.	6.	7.	8.
1. SBP	1							
2. DBP	.641**	1						
3. HR	.545**	.338**	1					
4. EPI	.312*	.080	.304*	1				
5. NE	.331*	.215	.198	.441**	1			
6. PEP	.069	-.037	-.424**	-.307	-.583	1		
7. SNS	.065	.046	.178*	-	-	-	1	
8. PNS	-.111	-.468*	-.316*	.141	.143	.520**	.247	1

Notes: SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, EPI = plasma epinephrine, NE = plasma norepinephrine, PEP = pre-ejection period, SNS = overall sympathetic activation, PNS = overall vagal withdrawal. Values represent Pearson Product Moment Correlations. \* =  $p < 0.05$ , \*\* =  $p < 0.01$ . Since SNS was derived from EPI, NE, and PEP values no correlation analysis was carried out.

## Discussion

Despite a substantial number of studies reporting indices of autonomic function within the stress reactivity paradigm, the autonomic basis of cardiovascular stress reactions has remained largely unclear due to small sample sizes, the *post-hoc* nature of the analysis of autonomic indices in some instances, and the relative scarcity of studies designed specifically to probe autonomic reactivity. Consequently, the present study used meta-analytic techniques to aggregate the current literature in an attempt to help clarify the autonomic basis of cardiovascular stress reactivity. Overall, the analyses revealed a pattern of autonomic activity during acute stress exposure that involved both beta-adrenergic sympathetic activation and vagal withdrawal to a roughly equal extent. When the analyses were restricted to just those studies that had



included both sympathetic and parasympathetic indices, in order to avoid task selection bias, a virtually identical result was obtained.

Subgroup analyses revealed several significant differences in effect size among cardiovascular and autonomic reactivity with regard to variations in stress task, sex, and age. Speech tasks appeared to provoke larger overall BP responses than the other exposures whereas HR reactions remained fairly constant across stress paradigms despite reaction time tasks eliciting a significantly stronger overall sympathetic response. Advancing age was associated with a decrease in sympathetic activation under stress; a finding that was mirrored by a decrease in HR reactivity with increasing age. Finally, men appeared to mount significantly higher BP and sympathetic responses than women. At the very least, these outcomes suggest that researchers should pay heed to the sex and age characteristics of their sample.

The present results are consistent with the notion that sympathetic activation and vagal withdrawal contribute in relatively equal magnitudes to cardiovascular stress reactivity. Significant sympathetic activation, indexed by PEP, a measure of myocardial contractility, and plasma epinephrine suggest that increases in HR are mediated by beta-adrenergic mechanisms, a finding in line with several studies that examined the relationship between beta-receptor physiology and reactivity (Marsland et al., 1995; Mills et al., 1994; Mills et al., 1990; Pacák et al., 1989). Under stress, PEP decreased (contractility increased) and epinephrine increased and both measures were highly correlated with HR. Pharmacological blockade studies have established PEP as a reliable indicator of cardiac beta-adrenergic activity (Harris, Schoenfeld, & Weissler, 1967; Mezzacappa, Kelsey, & Katkin, 1999; Newlin, & Levenson, 1979; Winzer et al., 1999), whereas epinephrine increases the chronotropic and inotropic properties of the heart, primarily through the activation of  $\beta_1$  receptors located on the myocardium (Klabunde, 2005; van

Zwieten, 1988; van Zwieten, 1986). The combination of these effects results in an increased HR and cardiac output under stress. This in turn contributes to increased BP given the vascular system is a closed circuit. Aggregate effects of blockade studies support the role of beta-adrenergic mechanisms in stress reactivity. Omnibus analysis of all sympathetic blockers revealed significant attenuation of both HR and SBP reactivity. However, subgroup analysis of drug class revealed that only non-selective and  $\beta_1$ -blockers significantly reduced HR, with the non-selective blockers being more effective. This finding accords with the results of an earlier review of pharmacological blockade in cardiovascular stress reactivity (Mills & Dimsdale, 1991). It is an outcome that makes good sense as the myocardium hosts both  $\beta_1$  and  $\beta_2$  receptors (Brodde, Zerkowski, Borst, Maier, & Michel, 1989; Summers et al., 1989) and both regulate HR in a similar direction; accordingly, selective blockade that fails to inhibit  $\beta_2$  receptors will necessarily have a less profound effect on HR. Beta blockade exerted only modest non-significant effects on SBP reactivity and failed to influence DBP stress reactions. This may be due to the presence of vascular  $\alpha$ -receptors that when left unopposed by  $\beta_2$  receptors act to constrict vessels (Klabunde, 2005). Alternatively, this may suggest that regulation of phasic changes in BP is paramount (Julius, 1988) as several studies have shown that stress-induced changes in BP, which in most cases are triggered by an increase in cardiac output and decrease in vascular resistance, are instead initiated by increased vascular resistance under beta-blockade (Andr n & Hansson, 1981; Schmieder, Rueddel, Neus, Messerli, & VonEiff, 1987; Urych, 1969). Significant increases in plasma norepinephrine were also observed but its role is less clear as the aggregate effect was relatively small compared to that of PEP and epinephrine and correlated only with SBP reactivity. Given that norepinephrine has a larger affinity for alpha-

adrenergic receptors relative beta-receptors, norepinephrine may primarily act to modulate vascular tone (Sherwood, Klandorf, & Yancey, 2005; Stanfield & Germann, 2008).

A significant withdrawal of cardiac vagal tone, as indexed by HF-HRV, RMSSD, and RSA was also observed. This result has been found by several others (Grossman et al., 1996; Hjortskov et al., 2004; Jiang et al., 1993; Sloan et al., 1991) and suggests that increases in HR with exposure to acute psychological stress is also a function of a release of the vagal brake on the heart which could, via an increase in cardiac output, increase BP. No meta-analysis was conducted on articles reporting parasympathetic blockade as only one report was found that met inclusion criteria (Reyes del Paso et al., 1996). In this study, atropine had a small effect on heart period changes to stress compared to the no drug condition. It is impossible to draw conclusions from a single study with a single psychological stress task and a small sample (N=9). In contrast, several studies have employed blockade with atropine and glycopyrrolate to probe parasympathetic control of cardiac reactions to physical exercise (Fisher et al., 2006; Kahler, Gaffney, & Braunwald, 1962; Martin et al., 1973; Ogoh et al., 2005; Robinson, Epstein, Beiser, & Braunwald, 1966; Seifert et al., 2010). On the whole, results from these studies and those using beta-blockade (Epstein, Robinson, Kahler, & Braunwald, 1965; Kahler et al., 1962; Martin et al., 1973; Robinson et al., 1966) have suggested that the initial HR increase to exercise is primarily vagal in nature with sympathetic activation occurring only at more intense levels of exertion (Yamamoto, Highson, & Nakamura, 1992; Yamamoto, Hughson, & Peterson, 1991). This would suggest that the autonomic control of cardiovascular activation during physical activity and psychological stress differ somewhat. It is clear that additional parasympathetic blockade studies are necessary to completely confirm the role of the parasympathetic nervous system in stress reactivity. Such studies would optimally include multiple psychological

stressors within a repeated measures design and could potentially take advantage of the differing lipophilic properties of atropine and glycopyrrolate; the former crosses the blood brain barrier whereas the latter remains in the periphery.

Sympathetic and parasympathetic influences may not be independent, however, as several models of cardiovascular regulation exist that incorporate interactions between the autonomic branches. The accentuated antagonism model suggests that background autonomic tone may moderate transient changes in sympathetic or vagal activity. For example, sympathetic HR effects have been shown to decrease with increasing levels of background vagal tone while vagal effects become augmented in states of high background sympathetic activity (Uijtdehaage & Thayer, 2000). The autonomic space model places the autonomic branches within a bivariate space, rather than a single linear spectrum, such that each branch can change independently allowing for a range of stress responses from co-activation to co-inhibition in addition to reciprocal changes (Berntson, Cacioppo, & Quigley, 1993). Finally, the baroreflex, which has been shown to modulate both sympathetic and vagal efferents (Chapleau, Cunningham, Sullivan, Wachtel, & Abboud, 1995; Lanfranchi & Somers, 2002), may represent the node at which cortical activity and cardiovascular afferents integrate to modulate cardiovascular responses to mental stress (Duschek, Werner, & Reyes del Paso, 2013). The outcome of the present correlational analyses is consistent with the autonomic space model as the effects size for PEP, a marker of cardiac beta-adrenergic activity, was indirectly related to overall parasympathetic effect size suggesting reciprocity in the patterning of sympathetic activation and vagal withdrawal on the heart. However, this does not preclude the possibility that the other models hold merit as moderation analysis was not possible given statistical constraints and baroreflex was not assessed in the present study.

A vast literature supports the notion that extreme cardiovascular reactions to stress (i.e. blunted and exaggerated) are associated with adverse health such as hypertension (Borghi et al., 1986; Carroll et al., 1995; Carroll et al., 2003; Chida & Steptoe, 2010a; Everson et al., 1996; Jennings et al., 2004; Markovitz et al., 1998; Markovitz et al., 1993), atherosclerosis (Everson et al., 1997; Roemmich et al., 2011; Roemmich et al., 2009), and depression (Brindle et al., 2013; Carroll et al., 2007; de Rooij et al., 2010; Ehrental et al., 2010; Phillips et al., 2010; Salomon et al., 2013; Salomon et al., 2009; York et al., 2007). This, in part, undoubtedly reflects the ease and inexpensiveness of HR and BP measurement. Substantially less attention has been paid to the somewhat more demanding measurement of their upstream physiological determinants, particularly in the context of health outcomes. It has been suggested that a shift in focus may greatly facilitate translational psychophysiology in treatment development (Lane et al., 2009a; Lane et al., 2009b). To that end, several directions for future research are provided. First, the psychophysiological field has seen in recent years the incorporation of relatively novel research methodologies (fMRI, Doppler echocardiography, sympathetic nerve microneurography) that have allowed researchers to more directly measure basic physiological responses under stress (Carter & Ray, 2009; Duschek & Schandry, 2003; Ginty et al., 2012; Sheu, Jennings, & Gianaros, 2012). Such methodologies, in conjunction with other basic measures (i.e., end-organ catecholamines, receptor physiology measures) permit the impact of acute psychological stress to be analysed at multiple upstream physiological levels. This will allow for a more comprehensive characterization of the basic physiology and physiological interactions responsible for end organ measures such as HR or BP. Second, research should aim to examine the relationship between more upstream physiological measures and disease. Given that HR and BP are multiply-determined endpoints, variations in upstream reactions are unlikely to be entirely co-linear with

variations in HR and BP and may provide stronger predictions of health outcomes. Finally, given that cardiovascular reactivity has been shown to relate to distinct psychological constructs such as personality (Howard, Hughes, & James, 2011; Krantz & Manuck, 1984; Vitaliano, Russo, Bailey, Young, & McCann, 1993) and psychopathology (Carroll et al., 2007; Ginty et al., 2012), research assessing the relationship between psychological factors and physiological mechanisms would be informative.

The present study suffers from several limitations. First, with exception of the sympathetic blockade data, all other data are cross-sectional making it impossible to draw causal inferences. Second, due to software constraints subgroup-analyses were carried out using unweighted effect sizes. This is not optimal as each study is treated with equal weight when larger studies should be given a heavier weight since, in theory, these studies should be more precise (Lipsey & Wilson, 2001). However, weighted and unweighted effect sizes were qualitatively compared and generally were similar in magnitude. Finally, several overall and subgroup analyses indicated significant publication bias. Where positive publication bias was observed Rosenthal's Failsafe N was calculated (Rosenthal, 1979; Rosenberg, 2005). This statistic represents that number of manuscripts reporting null results that are needed to counter the observed significant effect size. Results ranged from 84 (PEP) to 21645 (overall cardiovascular reactivity) studies indicating that a substantial number of null results must exist in the "file drawer" to negate the present results.

The present study is the first quantitative review of cardiovascular reactivity focusing on the underlying autonomic basis of HR and BP stress reactions. The results implicate both the sympathetic ( $\beta$ -adrenergic) and parasympathetic nervous systems in stress-induced cardiovascular reactivity to a roughly similar extent. Understanding the mechanisms

underpinning reactions to acute psychological stress is essential if psychophysiological research is to progress our understanding of its links to behaviour and disease.

## References

- Andrén, L., Hansson, L., & Björkman, M. (1981). Haemodynamic effects of noise exposure before and after  $\beta_1$ -selective and non-selective  $\beta$ -adrenoceptor blockade in patients with essential hypertension. *Clinical Science*, 61, 89s-91s.
- Allen, M.T., & Crowell, M.D. (1989). Patterns of autonomic response during laboratory stressors. *Psychophysiology*, 26, 603-614.
- Bax, L. (2011). Professional software for meta-analysis in Excel. Version 2.0.1.4. [Computer software]. BiostatXL.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1991). Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. *Psychological Review*, 98, 459-487.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993). Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. *Psychological Bulletin*, 114, 296-322.
- Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., & Fieldstone, A. (1994a). Autonomic cardiac control III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockade. *Psychophysiology*, 31, 599-608.
- Berntson, G.G., Cacioppo, J.T., Quigley, K.S., & Fabro, V.T. (1994b). Autonomic space and psychophysiological response. *Psychophysiology*, 31, 44-61.
- Borenstein, M., Hedges, L.V., Higgins, J.P.T., & Rothstein, H.R. (2009). Introduction to meta-analysis. West Sussex, UK: John Wiley & Sons Ltd.



- Borghi, C., Costa, F.V., Boschi, S., Mussi, A., & Ambrosioni, E. (1986). Predictors of stable hypertension in young borderline subjects: A five year follow-up study. *Journal of Cardiovascular Pharmacology*, 8, S138-S141.
- Brindle, R.C., Ginty, A.T., & Conklin, S.M. (2013). Is the association between depression and blunted cardiovascular stress reactions mediated by perceptions of stress? *International Journal of Psychophysiology*, 90, 66-72.
- Brodde, O.E., Zerkowski, H.R., Borst, H.G., Maier, W., & Michel, M.C. (1989). Drug- and disease-induced changes in human cardiac  $\beta_1$ - and  $\beta_2$ -adrenoceptors. *European Heart Journal*, 10, 38-44.
- Cacioppo, J.T., Uchino, B.N., & Berntson, G.G. (1994). Individual differences in the autonomic origins of heart rate reactivity: The psychometrics of respiratory sinus arrhythmia and pre-ejection period. *Psychophysiology*, 31, 412-419.
- Carroll, D., Ginty, A.T., Der, G., Hunt, K., Benzeval, M., & Phillips, A.C. (2012). Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. *Psychophysiology*, 49, 1444-1448.
- Carroll, D., Phillips, A.C., Hunt, K., & Der, G. (2007). Symptoms of depression and cardiovascular reactions to acute psychological stress: Evidence from a population study. *Biological Psychology*, 75, 68-74.
- Carroll, D., Ring, C., Hunt, K., Ford, G., & Macintyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: Effects of sex, age, and socioeconomic position. *Psychosomatic Medicine*, 65, 1058-1064.

- Carroll, D., Davey Smith, G., Sheffield, D., Shipley, M.J., & Marmot, M.G. (1995). Pressor reactions to psychological stress and prediction of future blood pressure: data from the Whitehall II Study. *British Medical Journal*, 310, 771-776.
- Carter, J.R., & Ray, C.A. (2009). Sympathetic neural responses to mental stress: Responders, nonresponders and sex differences. *American Journal of Physiology*, 296, H847- H853.
- Chapleau, M.W., Cunningham, J.T., Sullivan, M.J., Wachtel, R.E., & Abboud, F.M. (1995). Structural versus functional modulation of the arterial baroreflex. *Hypertension*, 26, 341-347.
- Chida, Y., & Steptoe, A. (2010a). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status. *Hypertension*, 55, 1026-1032.
- Chida, Y., & Steptoe, A. (2010b, May). Response to stress reactivity and its association with increased cardiovascular risk: A role for the sympathetic nervous system? [Letter to the Editor]. *Hypertension*, 55.
- Chida, Y., & Steptoe, A. (2010c, July). Response to mental stress, arterial stiffness, central pressures, and cardiovascular risk [Letter to the Editor]. *Hypertension*, 56.
- Counsell, C. (1997). Formulating questions and locating primary studies for inclusion in systemic reviews. *Annals of Internal Medicine*, 127, 380-387.
- de Rooij, S.R., Schene, A.H., Phillips, D.I., & Roseboom, T.J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology*, 35, 866-877.
- Duschek, S., & Schandry, R. (2003). Functional transcranial Doppler sonography as a tool in psychophysiology research. *Psychophysiology*, 40, 436-454.

- Duscheck, S., Dietel, A., Chandry, R., & Reyes del Paso, G. (2008). Increased baroreflex sensitivity and reduced cardiovascular reactivity in individuals with chronic low blood pressure. *Hypertension Research*, *31*, 1873-1878.
- Duscheck, S., Werner, N.S., & Reyes del Paso, G.A. (2013). The behavioral impact of baroreflex function: A review. *Psychophysiology*, *50*, 1183-1193.
- Ehrenthal, J.C., Herrmann-Linge, C., Fey, M., & Shauenburg, H. (2010). Altered cardiovascular adaptability in depressed patients without heart disease. *World Journal of Biological Psychiatry*, *11*, 586-593.
- Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*, *315*, 629-634.
- Epstein, S.E., Robinson, B.F., Kahler, R.L., & Braunwald, E. (1965). Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *Journal of Clinical Investigation*, *44*, 1745-1753.
- Everson, S.A., Lynch, J.W., Chesney, M.A., Kaplan, G.A., Goldberg, D.E., Shade, S.B., et al. (1997). Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: Population based study. *British Medical Journal*, *314*, 553-558.
- Everson, S.A., Kaplan, G.A., Goldberg, D.E., & Salonen, J.T. (1996). Anticipatory blood pressure responses to exercise predict future high blood pressure in middle-aged men. *Hypertension*, *27*, 1059-1064.
- Fisher, J.P., Ogoh, S., Dawson, E.A., Fadel, P.J., Secher, N.H., Raven, P.B., & White, M.J. (2006). Cardiac and vasomotor components of the carotid baroreflex control of arterial blood pressure during isometric exercise in human. *Journal of Physiology*, *572*, 869-880.

- Gianaros, P.J., Onyewuenyi, I.C., Sheu, L.K., Christie, I.C., & Critchley, H.D. (2012). Brain systems for baroreflex suppression during stress in humans. *Human Brain Mapping*, 33, 1700-1716.
- Gianaros, P.J., Quigley, K.S., Mordkoff, J.T., & Stern, R.M. (2001). Gastric myoelectrical and autonomic cardiac reactivity to laboratory stressors. *Psychophysiology*, 38, 642-652.
- Ginty, A.T., Phillips, A.C., Higgs, S., Heaney, J.L.J., & Carroll, D. (2012). Disordered eating behavior is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, 37, 715-724.
- Ginty, A.T., Phillips, A.C., Der, G., Deary, I.J., & Carroll, D. (2011). Heart rate reactivity is associated with future cognitive ability and cognitive change in a large community sample. *International Journal of Psychophysiology*, 82, 167-174.
- Grossman, P., & Taylor, E.W. (2007). Toard understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology*, 74, 263-285.
- Grossman, P., Watkins, L.L., Willhelm, F.H., Manolakis, D., & Lown, B. (1996). Cardiac vagal control and dynamic responses to psychological stress among patients with coronary artery disease. *The American Journal of Cardiology*, 78, 1424-1427.
- Harris, W.S., Schoenfeld, C.D., & Weissler, A.M. (1967). Effects of adrenergic receptor activation and blockade on the systolic preejection period, heart rate, and arterial pressure in man. *The Journal of Clinical Investigation*, 46, 1704-1714.

- Hassellund, S.S., Flaa, A., Sandvik, L., Kjeldsen, S.E., & Rostrup, M. (2010). Long-term stability of cardiovascular and catecholamine responses to stress tests: An 18-year follow-up study. *Hypertension*, 55, 131-136.
- Hawkey, L.C., Burleson, M.H., Poehlmann, K.M., Berntson, G.G., Malarkey, W.B., & Cacioppo, J.T. (2001). Cardiovascular and endocrine reactivity in older females: Intertask consistency. *Psychophysiology*, 38, 863-872.
- Higgins, J.P.T., & Green, S. (2011). Cochrane handbook for systematic reviews of interventions (5.1.0 ed.). The Cochrane Collaboration.
- Higgins, J.P.T., Thompson, Deeks, J.J. & Altman, D.G. (2003). Measuring inconsistency in meta-analysis. *British Medical Journal*, 327, 557-560.
- Hjortskov, N., Rissén, D., Blangsted, A.K., Fallentin, N., Lundberg, U., & Sogaard, K. (2004). The effect of mental stress on heart rate variability and blood pressure during computer work. *European Journal of Applied Physiology*, 92, 84-89.
- Howard, S., Hughes, B.M., James, J.E. (2011). Type D personality and hemodynamic reactivity to laboratory stress in women. *International Journal of Psychophysiology*, 80, 96-102.
- Hunter, J.E., and Schmidt, F.L. (2004). Methods of meta-analysis: Correcting error and bias in research findings. Thousand Oaks, California: Sage Publications.
- Jennings, R.J., Kamarck, T.W., Everson-Rose, S.A., Kaplan, G.A., Manuck, S.B., & Salonen, J.T. (2004). Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation*, 110, 2198-2203.

- Jiang, W., Hayano, J., Coleman, E.R., Hanson, M.W., Frid, D.J., O'Conno, C., et al. (1993). Relations of cardiovascular responses to mental stress and cardiac vagal activity in coronary artery disease. *The American Journal of Cardiology*, 72, 551-554.
- Julius, S. (1988). The blood pressure seeking properties of the central nervous system. *Journal of Hypertension*, 6, 177-185.
- Kahler, R.L., Gaffney, T.E., & Braunwald, E. (1962). The effects of autonomic nervous system inhibition on the circulatory response to muscular exercise. *Journal of Clinical Investigation*, 41, 1981-1987.
- Kasprowicz, A.L., Manuck, S.B., Malkoff, S.B., & Krantz, D.S. (1990). Individual differences in behaviourally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology*, 27, 605-619.
- Klabunde, R.E. (2005). *Cardiovascular Physiology Concepts*. New York, New York, Lippincott Williams & Wilkins.
- Kline, K.A., Saab, P.G., Llabre, M.M., Spitzer, S.B., Evans, J.D., Green McDonald, P.A., & Schneiderman, N. (2002). Hemodynamic response patterns: Responder type and difference in reactivity and recovery. *Psychophysiology*, 39, 739-746.
- Koo-Loeb, J.H., Pedersen, C., & Girdler, S.S. (1998). Blunted cardiovascular and catecholamine stress response reactivity in women with bulimia nervosa. *Psychiatry Research*, 80, 13-27.
- Krantz, D.S., & Manuck, S.B. (1984). Acute psychophysiologic reactivity and risk of cardiovascular disease: A review and methodological critique. *Psychological Bulletin*, 96, 435-464.

- Lane, R.D., Waldstein, S.R., Chesney, M.A., Jennings, J.R., Lovallo, W.R., Kozel, P.J., et al. (2009a). The rebirth of neuroscience in psychosomatic medicine, Part I: Historical context, methods, and relevant basic science. *Psychosomatic Medicine*, 71, 117-134.
- Lane, R.D., Waldstein, S.R., Critchley, H.D., Derbyshire, S.W.G., Drossman, D.A., Wager, T.D., et al. (2009b). The rebirth of neuroscience in psychosomatic medicine, Part II: Clinical applications and implications in research. *Psychosomatic Medicine*, 71, 135-151.
- Lane, J.D., Adcock, R.A., & Burnett, R.E. (1992). Respiratory sinus arrhythmia and cardiovascular responses to stress. *Psychophysiology*, 29, 461-470.
- Lanfranchi, P.A., & Somers, V.K. (2002). Arterial baroreflex function and cardiovascular variability: Interactions and implications. *American Journal of Physiology*, 283, R815-R826.
- Lipsey, M.W., and Wilson, D.B. (2001). Practical meta-analysis. Thousand Oaks, California: Sage Publications.
- Llabre, M.M., Klein, B.R., Saab, P.G., McCalla, J.B., & Schneiderman, N. (1998). Classification of individual differences in cardiovascular responsivity: The contribution of reactor type controlling for race and gender. *International Journal of Behavioral Medicine*, 5, 213-229.
- Lovallo, W.R., & Gerin, W. (2003). Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. *Psychosomatic Medicine*, 65, 36-45.
- Lovallo, W.R. (2005). Cardiovascular reactivity: Mechanisms and pathways to cardiovascular disease. *International Journal of Psychophysiology*, 58, 119-132.
- Lovallo, W.R. (2011). Do low levels of stress reactivity signal poor states of health? *Biological Psychology*, 86, 121-128.

- Manuck, S.B. (1994). Cardiovascular reactivity in cardiovascular disease: "Once more unto the breach." *International Journal of Behavioral Medicine*, 1, 4-31.
- Markovitz, J.H., Racynski, J.M., Wallace, D., Chettur, V., & Chesney, M.A. (1998). Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: the CARDIA study. *Psychosomatic Medicine*, 60, 186-191.
- Markovitz, J.H., Matthews, K.A., Kannel, W.B., Cobb, J.L., & D'Agostino, R.B. (1993). Psychological predictors of hypertension in the Framingham Study. *JAMA*, 270, 2439-2443.
- Marsland, A.L., Manuck, S.B., Wood, P., Rabin, B.S., Muldoon, M.F., & Cohen, S. (1995). B<sub>2</sub>-Adrenergic receptor density and cardiovascular response to mental stress. *Physiology & Behavior*, 57, 1163-1167.
- Martin, C.W., Shaver, J.A., Leon, D.F., Thompson, M.E., Reddy, P.S., & Leonard, J.J. (1973). Autonomic mechanisms in hemodynamic responses to isometric exercise. *Journal of Clinical Investigation*, 54, 104-115.
- McArdle, W.D., Katch, F.I., & Katch, V.L. (2001). *Exercise Physiology: Energy, nutrition, and human performance* (5<sup>th</sup> ed). New York, New York, Lippincott, Williams, & Wilkins.
- Meade, M.O., & Richardson, W.S. (1997). Selecting and apprising studies for a systematic review. *Annals of Internal Medicine*, 127, 531-537.
- Mezzacappa, E.S., Kelsey, R.M., & Katkin, E.S. (1999). The effects of epinephrine administration on impedance cardiographic measures on cardiovascular function. *International Journal of Psychophysiology*, 31, 189-196.



Mills, P.J., Dimsdale, J.E., Nelesen, R.A., Jasiewicz, J., Ziegler, M.G., & Kennedy, B. (1994).

Patterns of adrenergic receptors and adrenergic agonists underlying cardiovascular responses to a psychological challenge. *Psychosomatic Medicine*, 56, 70-76.

Mills, P.J., & Dimsdale, J.E. (1991). Cardiovascular reactivity to psychosocial stressor: A review of the effects of beta-blockade. *Psychosomatics*, 32, 209-220.

Mills, P.J., Dimsdale, J.E., Ziegler, M.G., Berry, C.C., & Bain, R.D. (1990). Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. *Psychosomatic Medicine*, 52, 621-623.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6, 1-6.

Newlin, D.B., & Levenson, R.W. (1979). Pre-ejection period: Measuring beta-adrenergic influences upon the heart. *Psychophysiology*, 16, 546-553.

Newman, D.G., & Callister, R. (1999). The non-invasive assessment of stroke volume and cardiac output by impedance cardiography: A review. *Aviation, Space, and Environmental Medicine*, 70, 780-790.

Obrist, P. (1981). *Cardiovascular Psychophysiology: A perspective*. New York, New York, Plenum Press.

Ogoh, S., Fisher, J.P., Dawson, E.A., White, M.J., Secher, N.H., & Raven, P.B. (2005). Autonomic nervous system influence on arterial baroreflex control of heart rate during exercise in humans. *Journal of Physiology*, 566, 599-611.

Pacák, K., Nedvidková, J., Horváth, M., Frantík, E., Husek, P., & Pacovský, V. (1989). High cardiovascular reactivity to psychological challenge associated alternatively with high

density of beta-adrenergic receptors or with high resting levels of catecholamines.

*Activitas Nervosa Superior*, 31, 96-99.

Phillips, A.C., Roseboom, T.J., Carroll, D., & de Rooij, S.R. (2012). Cardiovascular and cortisol reactions to acute psychological stress and adiposity: Cross-sectional and prospective associations in the Dutch Famine Birth Cohort Study. *Psychosomatic Medicine*, 74, 699-710.

Phillips, A.C. (2011). Blunted cardiovascular reactivity related to depression, obesity, and self-reported health. *Biological Psychology*, 86, 106-113.

Phillips, A.C., Hunt, K., Der, G., & Carroll, D. (2010). Blunted cardiac reactions to acute psychological stress predict symptoms of depression five years later: Evidence from a large community sample. *Psychophysiology*, 48, 142-148.

Reyes del Paso, G.A., Langewitz, W., Robles, H., & Pérez. (1996). A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. *International Journal of Psychophysiology*, 22, 163-171.

Robinson, B.F., Epstein, S.E., Beiser, G.D., & Braunwald, E. (1966). Control of heart rate by the autonomic nervous system. *Circulation Research*, 19, 400-411.

Roemmich, J.N., Feda, D.M., Seelbinder, A.M., Lambiase, M.J., Kala, G.K., & Dorn, J. (2011). Stress-induced cardiovascular reactivity and atherosclerosis in adolescents. *Atherosclerosis*, 215, 465-470.

Roemmich, J.N., Lobarinas, C.L., Joseph, P.N., Lambiase, M.J., Archer, F.D., et al. (2009). Cardiovascular reactivity to psychological stress and carotid intima-media thickness in children. *Psychophysiology*, 46, 293-299.

- Rosenberg, M. (2005). The file-drawer problem revisited: A general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution*, 59, 464-468.
- Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin*, 86, 638-641.
- Salomon, K., Bylsma, L.M., White, K.E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependent? A comparison of major depressive disorder remitted depression and health controls. *International Journal of Psychophysiology*, 90, 50-57.
- Salomon, K., Clift, A., Karlsdottir, M., & Rottenberg, J. (2009). Major depressive disorder is associated with attenuated cardiovascular reactivity and impaired recovery among those free of cardiovascular disease. *Health Psychology*, 28, 157-165.
- Schmieder, R.E., Rueddel, H., Neus, H., Messerli, F.H., & von Eiff, A.W. (1987). Disparate hemodynamic responses to mental challenge after antihypertensive therapy with beta blockers and calcium entry blockers. *The American Journal of Medicine*, 82, 11-16.
- Seifert, T., Fisher, J.P., Young, C.N., Hartwich, D., Ogoh, S., Raven, P.B., et al. (2010). Glycopyrrolate abolishes the exercise-induced increase in cerebral perfusion in humans. *Experimental Physiology*, 95, 1016-1025.
- Shapiro, P.A., Sloan, R.P., Bagiella, A., Bigger Jr, J.T., & Gorman, J.M. (1996). Heart rate reactivity and heart period variability throughout first year after heart transplantation. *Psychophysiology*, 33, 54-62.
- Sherwood, L., Klandorf, H., & Yancey, P.H. (2005). *Animal Physiology: From Genes to Organisms*. Belmont, California, Thomson Brooks Cole.

- Sherwood, A., Dolan, C.A., & Light, K.C. (1990a). Hemodynamics of blood pressure responses during active and passive coping. *Psychophysiology*, 27, 656-668.
- Sherwood, A., Turner, J.R., Light, K.C., & Blumenthal, J.A. (1990b). Temporal stability of the hemodynamics of cardiovascular reactivity. *International Journal of Psychophysiology*, 10, 95-98.
- Sheu, L.K., Jennings, J.R., & Gianaros, P.J. (2012). Test-retest reliability of an fMRI paradigm for studies of cardiovascular reactivity. *Psychophysiology*, 49, 873-884.
- Singh, K., & Shen, B. (2013). Abdominal obesity and chronic stress interact to predict blunted cardiovascular reactivity. *International Journal of Psychophysiology*, 90, 73-79.
- Sloan, R.P., Korten, J.B., & Myers, M.M. (1991). Components of heart rate reactivity during mental arithmetic with and without speaking. *Physiology and Behavior*, 50, 1039- 1045.
- Sloan, R.P., Shapiro, P.A., & Gorman, J.M. (1990). Psychophysiological reactivity in cardiac transplant recipients. *Psychophysiology*, 27, 187-194.
- Stanfield, C.L., & Germann, W.J. (2008). *Principals of Human Physiology*. New York, New York, Pearson.
- Step toe, A., & Sawada, Y. (1989). Assessment of baroreceptor reflex function during mental stress and relaxation. *Psychophysiology*, 26, 140-147.
- Summers, R.J., Molnaar, P., Russell, F., Elnatan, J., Jones, C.R., Buxton, B.F., et al. (1989). Coexistence and localization of  $\beta_1$ - and  $\beta_2$ -adrenoceptors in the human heart. *European Heart Journal*, 10, 11-21.
- Tak, L.M., Meijer, A., Manoharan, A., de Jonge, P., & Rosmalen, J.G.M. (2010). More than the sum of its parts: Meta-analysis and its potential to discover sources of heterogeneity in psychosomatic medicine. *Psychosomatic Medicine*, 72, 253-265.

- Uijtdehaage, S.H.J., & Thayer, J.F. (2000). Accentuated antagonism in the control of human heart rate. *Clinical Autonomic Research*, 10, 107-110.
- Ulrych, M. (1969). Changes in general hemodynamics during stressful mental arithmetic and non-stressing quiet conversation and modification of the latter by beta-adrenergic blockade. *Clinical Science*, 36, 453-461.
- van Zwieten, P.A. (1988). The role of adrenoceptors in circulatory and metabolic regulation. *The American Heart Journal*, 116, 1384-1392.
- van Zwieten, P.A. (1986). Interaction between  $\alpha$ - and  $\beta$ -adrenoceptor-mediated cardiovascular effects. *Journal of Cardiovascular Pharmacology*, 8, S21- S28.
- Vitaliano, P.P., Russo, J., Bailey, S.L., Young, H.M., & McCann, B.S. (1993). Psychosocial factors associated with cardiovascular reactivity in older adults. *Psychosomatic Medicine*, 55, 164-177.
- Wager, T.D., Waugh, C.E., Linquist, M., Noll, D.C., Frederickson, B.L., & Taylor, S.F. (2009). Brain mediators of cardiovascular responses to social threat: Part I: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*, 47, 821-835.
- Winzer, A., Ring, C., Carroll, D., Willemsen, G., Drayson, M., Kendall, M. (1999). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of beta-adrenergic blockade. *Psychophysiology*, 36, 591-601.
- Yamamoto, Y., Hughson, R.L., & Nakamura, Y. (1992). Autonomic nervous system response to exercise in relation to ventilator threshold. *CHEST*, 101, 206-210.

- Yamamoto, Y., Hughson, R.L., & Peterson, J.C. (1991). Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. *Journal of Applied Physiology*, *71*, 1136-1442.
- York, K.M., Hassan, M., Li, Q., Li, H., Fillingim, R.B., & Sheps, D.S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine*, *69*, 521-528.

---

## Chapter 3

---

### Heart Rate Complexity: A Novel Approach to Assessing Cardiac Stress Reactivity

This chapter has been accepted to *Psychophysiology* under the following citation:

Brindle, R.C., Ginty, A.T., Phillips, A.C., Fisher, J.P., McIntyre, D., & Carroll, D. (accepted).

Heart rate complexity: A novel approach to assessing cardiac stress reactivity. *Psychophysiology*.

### **Abstract**

Correlation dimension (D2), a measure of heart rate complexity, has been shown to decrease in response to acute mental stress and relate to adverse cardiovascular health. However, the relationship between stress-induced change in D2 and HR has yet to be established. The present studies aimed to assess this relationship systematically while controlling for changes in respiration and autonomic activity. In Study 1 (N = 25) D2 decreased during stress and predicted heart rate reactivity even after adjusting for changes in respiration rate, and cardiac vagal tone. This result was replicated in Study 2 (N = 162) and extended by including a measure of cardiac sympathetic activity; D2 remained an independent predictor of HR reactivity in a hierarchical linear model containing measures of cardiac parasympathetic and sympathetic activity and their interaction. These results suggest that D2 may provide additional information regarding cardiac stress reactivity above that provided by traditional measures of cardiac autonomic function.

**Keywords:** Correlation dimension; stress; heart rate; pre-ejection period; heart rate variability



## Introduction

It is now a widely accepted that individuals differ markedly in the magnitude of their cardiovascular reactions to acute psychological stress and that such individual differences have implications for both health and behavior (Chida & Steptoe, 2010; Phillips, Ginty, & Hughes, 2013; Treiber et al., 2003). Understanding the physiological determinants of cardiovascular stress reactions thus becomes an important area of inquiry. Although a recent large-scale meta-analysis implicated both the parasympathetic and sympathetic nervous systems in cardiovascular responses to acute mental stress (Brindle, Ginty, Phillips, & Carroll, 2014), characterizing individual differences in autonomic activity is difficult as the activity of the cardiac autonomic nerves must be assessed indirectly in humans, and due to their inaccessibility it is not plausible to make intra-neural recordings. Hence, researchers have had to rely on indirect measures of autonomic activity.

Measures of HR variability, namely the spectral analysis variable of high-frequency variability and its time domain analogue root mean square of successive differences (RMSSD), have allowed researchers to gauge changes in cardiac vagal activity induced by acute mental stress. On the whole, acute withdrawal of cardiac vagal influence has been observed during stress leading to increased HR and augmented cardiac output (Brindle et al., 2014). However, beta-adrenergic sympathetic activation has also been directly implicated in cardiac output augmentation. Using pre-ejection period, a measure of myocardial contractility that can be accurately captured using impedance cardiography or Doppler ultrasonography (Cacioppo, Uchino, Berntson, 1994), studies have shown that cardiac reactivity to psychological stress is also the result of beta-adrenergic sympathetic activation (Brindle et al., 2014). Focusing on adaptation to recurrent stressors Kelsey and colleagues (2001, 2004) showed when evaluation

observation disrupted the adaptation process the rebound in HR reactivity was accompanied by a resurgence of beta-adrenergic activation. In addition, in a series of studies examining challenge and threat appraisals to mental stress it was found that challenge appraisals were often characterized by augmented heart rate and pre-ejection (PEP) reactions, further implicating the beta-adrenergic sympathetic nervous system in cardiovascular reactivity (Tomaka, Blascovich, Kelsey, & Leitten, 1993; Tomaka, Blascovich, Kibler, & Ernst, 1997).

However, a notable amount of inter-individual variability in cardiovascular reactivity remains unaccounted for; variability that could potentially lend insight into stress-disease associations. Emerging evidence suggests that cardiac pacemaker cells in the sino-atrial node can operate in a seemingly non-linear or chaotic manner due to the convergence of autonomic, hormonal, and hemodynamic influences (Hagerman, Berglund, Lorin, Nowak, & Sylvén, 1996; Lipsitz, 1995; Wagner, & Persson, 1998) and this has prompted some researchers to examine the effect of acute stress on measures of HR complexity. This class of cardiac measures, based on nonlinear dynamics and chaos theory, characterize the dynamic properties of the HR generating system (for reviews please refer to Acharya, Joseph, Kannathal, Lim, & Suri, 2006; Goldberger et al., 2002a; Goldberger, Peng, & Lipsitz, 2002b, Hagerman et al., 1996; Wagner & Persson, 1998).

Although various HR complexity measures have been shown to be perturbed by acute stress (Anishchenko, Igosheva, Yakusheva, Glushkovskaya-Semyachkina, & Khoklova, 2001; Brisinda, Fioravanti, Sorbo, Venuti, & Fenici, 2015; Melillo, Bracale, & Pecchia, 2011), the correlation dimension (D2) appears to be particularly relevant in the context of mental stress. First, studies have shown D2 to decrease during acute mental stress episodes. A study by Schubert and colleagues (2009) observed a significant decrease in D2 during an acute socially

evaluative speech task and reported a negative association between baseline D2 and a self-reported measure of chronic stress. In the field, D2 derived from ambulatory ECG traces was significantly lower during a university exam compared to a holiday period (Melillo, et al., 2011). Taken together, these data support the notion that D2 is sensitive to mental stress and to some extent generalizes outside the laboratory. Second, clinical research has shown D2 to be particularly relevant in the context of myocardial ischemia and ventricular fibrillation, conditions also associated with increased mental stress and mental stress induced sudden cardiac death (Kamarck & Jennings, 1991; Lampert, Joska, Burg, Batsford, McPherson, & Jain, 2002; Lane et al., 2005). D2 has been reported to significantly decrease in response to myocardial ischemia and hours to minutes before ventricular fibrillation in animals (Skinner, Carpeggiani, Landisman, & Fulton, 1991) and humans (Skinner, Pratt, & Vybiral, 1993) as well as predict the onset of ventricular fibrillation in prefibrillation heart rate data of arrhythmia patients (Kroll & Fulton, 1991).

Although D2 has been shown to decrease under mental stress, no study has addressed the relationship between stress-induced changes in HR and D2. Two studies are reported that address this relationship. The aims of the studies were two-fold. First, they were concerned with determining if D2 reactivity related to stress-induced changes in HR and whether controlling for changes in RMSSD and respiration rate influenced the relationship. Second, the studies attempted to determine whether changes in D2 withstood further adjustment for changes in PEP and the interaction between RMSSD and PEP.

## Study 1

### Methods

#### Participants and Experimental Design

Twenty five healthy individuals (Mean age (SD) = 19.77 (3.86); 50% female) were recruited for the present study. Potential participants were excluded if they reported having a history of cardiovascular or metabolic disease or had previously participated in the psychological stress protocol. All participants were required to refrain from alcohol and vigorous exercise 12 h, caffeine 2 h, and food and drinks other than water 1 h before testing. They received participation credit and the study was approved by the University of Birmingham Ethics Committee.

Upon arrival to the laboratory anthropometric measures were completed and participants sat quietly while being instrumented. Participants then completed a standardized 8-min adaptation period before data was obtained during a formal 8-min baseline and an 8-min Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). During the baseline period, participants were asked to remain seated and rest quietly, while during the PASAT participants were required to consecutively add single digit numbers, presented via CD recording, while remembering the most recent number so that it may then be added to the next number presented. Participants answered via a keypad and numbers were presented at increasing speeds beginning with an inter-number interval of 4.0 seconds that decreased by 0.5 seconds every two mins. The PASAT was chosen in the present study as it has been shown to reliably perturb cardiac activity (Mathias, Stanford, & Houston, 2004; Ring, Burns, & Carroll, 2002), through both vagal withdrawal (Brindle et al., 2014; Mezzacappa, Kelsey, Katikin, & Sloan, 2001) and beta-adrenergic sympathetic activation (Kelsey et al., 2000; Rousselle et al., 1995; Winzer, Ring,

Carroll, Willemsen, Drayson, & Kendall, 1999), and demonstrate acceptable test-retest reliability (Ginty, Gianaros, Derbyshire, Phillips, & Carroll, 2013; Willemsen et al., 1998). Participants completed a brief questionnaire (Knafner et al., 2011) immediately upon completion of the task, which required them to rate task stressfulness on a standard Likert scale ranging from 1-10 anchored by “not at all stressful” to “extremely stressful.” PASAT score, an index of task performance, was calculated by subtracting 5 points for every wrong or unanswered question from a starting value of 1000.

### **Physiological Measurements**

Heart rate and respiration rate were measured continuously during all task phases via three-lead ECG and a leak-free respiratory mask and gas analyzer (ML206; ADInstruments, Bella Vista, NSW, Australia), respectively. All data were continuously sampled at 200 Hz using an analogue-digital converter (PowerLab, ADInstruments) and analyzed offline using LabChart software (Version 7, ADInstruments). Continuous data from each phase (i.e., baseline, stress) was used to calculate phase means for HR, respiration rate, and HR variability and complexity measures. Reactivity was defined as the difference between stress and baseline phase means.

### **Cardiac Data Processing**

Raw ECG data was visually inspected for artifacts. Following removal of artifacts, RR interval data was subjected to analysis using Kubios HRV 2.0, a software suite specifically designed for the analysis of human HRV and complexity (Tarvainen & Niskanen, 2008). RMSSD of the RR intervals was used as an index of cardiac parasympathetic activity as it has been shown to capture high frequency changes in HR variability which positively relate to cardiac parasympathetic control (Kleiger et al., 1991; Task Force of the ESC and NAPE, 1996). D2 was calculated using the algorithms outlined by Tarvainen & Niskanen (2008).

## Statistical Analysis

Repeated-measures (baseline, stress) ANOVAs were used to confirm that the acute stress exposure significantly perturbed HR and other HR measures. Individual simple linear regressions were used to assess the associations between D2 and RMSSD change scores and HR reactivity. Next, individual hierarchical regressions were undertaken to control for respiration rate, BMI, PASAT score and baseline HR as these measures have been shown to influence HR reactivity (Carroll et al., 2000; Carroll, Phillips, & Der, 2008; Ginty, Phillips, Roseboom, Carroll, & de Rooij, 2012b). HR reactivity was again the outcome variable, changes in respiration rate and other control variables were entered at step 1 and D2 or RMSSD were then entered at step 2. Finally, all remaining significant cardiac autonomic predictor variables were then entered into a single regression model to assess their independent contributions to HR reactivity. Differences in participant number as noted in the tables reflect occasional missing data.

## Results

### Participants

The mean (SD) BMI was 22.46 (3.20) kg/m<sup>2</sup>. Participants achieved a mean score of 878.15 (86.98) on the PASAT and reported an average task stressfulness of 5.08 (1.98).

### Cardiovascular, Autonomic, and Respiratory Reactions to Acute Stress

Repeated measures (baseline, stress) ANOVA revealed a significant increase in HR,  $F(1,25) = 27.08, p < .001, \eta^2 = .520$ , respiration rate,  $F(1,25) = 37.09, p < .001, \eta^2 = .597$ , and a significant decrease in D2,  $F(1,24) = 9.06, p = .006 .001, \eta^2 = .274$  and RMSSD,  $F(1,24) = 8.77, p = .007 .001, \eta^2 = .268$  (Table 3.1).

**Table 3.1** Cardiac descriptive statistics Study 1

	Mean (SD)	
	Baseline	Stress
HR (beats/min)	73.19 (10.99)	80.40 (12.90)
RMSSD (ms)	63.43 (36.66)	49.58 (45.79)
Correlation Dimension (ms)	3.41 (1.11)	2.65 (1.56)
Respiration Rate (breaths/min)	16.46 (2.22)	20.78 (4.06)

### Autonomic Correlates of Heart Rate Reactivity

Both RMSSD,  $r = -.688$ ,  $p < .001$ , and D2,  $r = -.563$ ,  $p = .003$ , significantly correlated with HR reactivity. Changes in respiration rate did not significantly relate to HR reactivity ( $p = .64$ )

### Autonomic Predictors of Heart Rate Reactivity

Unadjusted regression models revealed that D2,  $\beta = -.56$ ,  $p = .003$ ,  $\Delta R^2 = .317$  and RMSSD,  $\beta = -.69$ ,  $p < .001$ ,  $\Delta R^2 = .473$ , were significant predictors of HR reactivity (Table 3.2). In all cases, decreases in each cardiac autonomic variable were associated with increased HR reactivity. In models that were adjusted for changes in respiration rate and other confounders, D2 and RMSSD both continued to predict HR reactivity. When both autonomic predictors were included in a single model, with changes in respiration rate, both measures independently predicted HR reactivity (Table 3.2).

**Table 3.2** Predictors of heart rate reactivity Study 1

	$\beta$	$t$	$p$	$\Delta R^2$
Individual Models				
RMSSD (n = 25)				
Unadjusted	-.69	-4.54	<.001	.473
Adjusted	-.69	-4.00	=.001	.424
Correlation dimension (n = 25)				
Unadjusted	-.56	-3.27	=.003	.317
Adjusted	-.66	-3.65	=.002	.382
Full Model (n=25)				
RMSSD	-.57	-4.04	=.001	
Correlation Dimension	-.41	-2.78	=.011	.615

### Sensitivity Analysis: Other HR Complexity Measures

As several other HR complexity measures have been shown, in some circumstances, to be perturbed by acute mental stress (Anishchenko et al., 2001; Brisinda et al., 2015; Melillo et al., 2011) stress-induced change scores were also derived for SD1, SD2, Df $\alpha$ 1, Df $\alpha$ 2, and ApEn using previously outlined algorithms (Tarvainen & Niskanen, 2008). Pearson's correlations were undertaken to assess the relationship between stress-induced changes in these measure and HR reactivity. Df $\alpha$ 1 ( $r = 0.599$ ,  $p = .002$ ), SD1 ( $r = -0.688$ ,  $p < .001$ ), and SD2 ( $r = -0.414$ ,  $p = .039$ ), were all related to HR reactivity; SD2 and ApEn were not (all  $p > .05$ ). Intercorrelations among HR variability and complexity measures were also undertaken (Appendix II Table 3.6).



## Summary

The PASAT significantly increased HR and decreased RMSSD and D2. RMSSD and D2 were predictors of HR reactivity when various control variables, including changes in respiration rate, were accounted for and both independently predicted HR reactivity when entered into a single linear model.

## Study 2

### Methods

#### Participants

Adolescent participants ( $N = 185$ ) were recruited from local high schools proximal to the University. Data from 9 participants were unusable due to signal acquisition problems resulting in a final sample of 176 participants (age,  $M = 18.04$ ,  $SD = 0.43$ ; 82% female). Exclusion criteria included history of cardiovascular or metabolic disease and participants were required to refrain from alcohol and vigorous exercise 12h, caffeine 2h, and food and drinks other than water 1h before testing. All participants and legal guardians, if participants were under 18, gave informed consent. Participants received £10 for study participation. The study was approved by the University Ethics Committee.

#### Procedure

Height and weight were measured on arrival at the laboratory and body mass index (BMI) calculated. Participants were then asked to recline in a lateral decubitus position while ECG electrodes were attached and the Doppler probe positioned. After a 10-min adaptation

period, participants were asked to rest quietly for a 10-min formal baseline period, followed by a 10-min stress phase, in which participants undertook the PASAT. Afterwards, participants completed a brief questionnaire regarding task stressfulness. Participants responded on a standard Likert scale ranging from 0-6 anchored by “not at all” and “extremely” (Khanfer, Carroll, Lord, & Phillips, 2012).

### **Acute Psychological Stress Task**

A similar PASAT was used to that of Study 1 with some modifications to enhance task stressfulness. The PASAT was 10 min in length and was presented at a faster speed beginning at 2.5 sec intervals and shortening 0.5s every 2 mins. In addition, an experimenter overtly recorded every answer, and participants were informed that in response to wrong answers or hesitation, they would hear brief bursts of loud aversive noise. Participants were required to watch themselves in a mirror and were videotaped so that “body language experts” could assess anxiety levels. In reality, participants were not videotaped and were given a standardized number of noise bursts which were administered every 10 numbers, coinciding with wrong answers or hesitation where possible (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012a).

### **Cardiovascular Measures**

Continuous ECG data, digitized at 1000Hz was collected during the same task phases as Study 1 using Grass amplifier (Grass P511, Grass Instruments, USA), CED Power1401 and Spike 2 software (Cambridge Electronic Design, Cambridge, UK). Using the same protocol as Study 1 HR, D2, and RMSSD were derived from the ECG trace. PEP was measured using a Philips Sonos 7500 ultrasound machine with a S3 two dimensional transducer (1-3MHz). Digital images of spectral waveforms were recorded for offline processing. For each measurement point averages were obtained from 3 or more recorded waveforms; phase means were derived from the

measurement point averages in each phase. An apical five-chamber view was used to identify blood flow through the aortic valve during systole. The velocity profile of aortic flow was captured immediately below the orifice of the aortic valve (2.0mm sample volume) using pulsed-wave spectral mode at a screen sweep speed of 100mm/s. PEP was quantified using the velocity time integral and overlaid ECG trace to measure the elapsed time between the onset of ventricular depolarization (beginning of QRS complex) and ventricular ejection (beginning of velocity profile). Relatively high correlations have been reported between measures of PEP derived from echo- and impedance cardiography (Carvalho et al., 2010; Cybulski, Michalak, Koźluk, Piątkowska, & Niewiadomski, 2004). Finally, to account for interactions between the parasympathetic and sympathetic branches of the autonomic nervous system an interaction term (INT) was created using the mean-centered change scores of RMSSD and PEP.

### **Statistical Analysis**

The same statistical analyses were carried out as in Study 1.

## **Results**

### **Participants**

The mean (SD) BMI was 23.40 (4.51) kg/m<sup>2</sup>. Participants achieved a mean score of 600.20 (177.65) on the PASAT and reported an average task stressfulness of 4.42 (1.12).

### **Cardiovascular and Autonomic Reactions to Acute Stress**

Repeated measures (baseline, stress) ANOVA revealed that the PASAT significantly increased HR,  $F(1,160) = 427.66, p < .001, \eta^2 = .728$ . Significant decreases in D2,  $F(1,160) = 55.26, p < .001, \eta^2 = .257$ , RMSSD,  $F(1,160) = 122.56, p < .001, \eta^2 = .434$ , and PEP,  $F(1,160) =$

223.15,  $p < .001$ ,  $\eta^2 = .582$ , were also observed in response to stress (for summary statistics see Table 3.3). No main effect of stress was observed for the INT,  $F(1,160) = 0.01$ ,  $p = .92$ ,  $\eta^2 = < .001$ .

**Table 3.3** Cardiac descriptive statistics Study 2

	Mean (SD)	
	Baseline	Stress
HR (beats/min)	74.52 (12.09)	90.70 (14.78)
RMSSD (ms)	64.31 (42.96)	34.60 (26.51)
PEP (ms)	0.091 (0.012)	0.077 (0.015)
INT	0.07 (0.49)	0.09 (1.79)
Correlation dimension	3.09 (1.38)	2.05 (1.53)

### Autonomic Predictors of Heart Rate Reactivity

Unadjusted regression models revealed that D2,  $\beta = -.40$ ,  $p < .001$ ,  $\Delta R^2 = .163$ , RMSSD,  $\beta = -.36$ ,  $p < .001$ ,  $\Delta R^2 = .126$ , PEP,  $\beta = -.63$ ,  $p < .001$ ,  $\Delta R^2 = .392$ , and INT,  $\beta = -.17$ ,  $p = .03$ ,  $\Delta R^2 = .028$ , were all significant predictors of HR reactivity (Table 3.4). All measures were negatively related to HR reactivity. In models that were adjusted for HR baseline, BMI, PASAT score, and gender, D2, RMSSD, PEP, and INT all continued to predict HR reactivity. When all autonomic predictors were included in a full single model only RMSSD, PEP, and D2 independently predicted HR reactivity (Table 3.5).

**Table 3.4** Individual predictors of heart rate reactivity Study 2

	$\beta$	$t$	$p$	$\Delta R^2$
RMSSD (n = 176)				
Unadjusted	-.36	-4.79	<.001	.126
Adjusted	-.34	-4.56	<.001	.099
PEP (n = 162)				
Unadjusted	-.63	-10.12	<.001	.392
Adjusted	-.63	-10.04	<.001	.350
INT (n = 162)				
Unadjusted	-.17	-2.16	.03	.028
Adjusted	-.28	-2.97	.003	.048
Correlation dimension (n = 176)				
Unadjusted	-.40	-5.57	<.001	.163
Adjusted	-.41	-5.78	<.001	.149

**Table 3.5** Full regression model of heart rate reactivity Study 2 (n = 162)

	$\beta$	$t$	$p$	$\Delta R^2$
RMSSD	-.27	-4.93	<.001	.339
PEP	-.51	-8.89	<.001	.107
INT	-.11	-1.78	.076	-.017
Correlation dimension	-.28	-4.91	<.001	.108
Full Model				.537

### **Sensitivity Analysis: Other HR Complexity Measures**

As in Study 1, DFa1 ( $r = 0.369$ ,  $p < .001$ ), SD1 ( $r = -0.358$ ,  $p < .001$ ), and SD2 ( $r = -0.246$ ,  $p = .001$ ) were related to HR reactivity. In contrast to Study 1, DFa2 ( $r = 0.509$ ,  $p < .001$ ), and ApEn ( $r = -0.639$ ,  $p < .001$ ), were also related to HR reactivity. Intercorrelations among HR variability and complexity measures were also undertaken (Appendix II Table 3.7).

### **Summary**

Results from Study 2 are consistent with Study 1. A significant decrease in D2 was again observed in response to acute mental stress and D2 independently predicted HR reactivity even after controlling for several cardiac and non-cardiac confounders. The results also extend the findings of Study 1 by showing that D2 remained an independent predictor of HR reactivity to mental stress when both cardiac parasympathetic and sympathetic activity and the interaction between the autonomic branches were taken into account.

### **Discussion**

With the present study we sought to examine whether D2, a measure of HR complexity, accounted for a significant portion of the variance in HR reactivity to acute psychological stress when measures of cardiac sympathetic and parasympathetic activity, indexed by PEP and RMSSD, respectively, were accounted for. In the Study 1 it was demonstrated that D2 predicted HR reactivity above and beyond RMSSD, even when changes in respiration rate were taken into account. This finding is consistent with those of Schubert and colleagues (2009) who reported that stress-induced changes in D2 withstood adjustment for respiratory activity. Study 2 included a measure of cardiac beta-adrenergic activity and results showed that D2 still accounted

for a unique portion of the variation in HR reactivity when RMSSD, PEP, and their interaction term were included in a single regression model.

The finding of reduced HR complexity under stress accords with others who have reported decreased HR complexity in response to acute mental (Melillo et al., 2011; Schubert et al., 2009), performance (Williamon et al., 2013), and physical (Butler, Yamamoto, & Highson, 1994; Hagerman et al., 1996; Osaka, Saitoh, Atarashi, & Hayakawa, 1993) stress. Presently, the basic physiological meaning of transient stress-induced reductions in HR complexity remains unclear. However, the clinical significance of D2 is better established and may provide some insight into the physiological underpinnings of D2. For example, D2 appears to be related to the electrical stability of the heart. Both environmental and acute stresses have been shown in animals and humans to modulate the electrical stability of the heart. In rats, a social defeat model of stress produced a significant increase in isolated ventricular premature beats (Sgoifo et al., 1999), whereas in dogs, a restraint model of stress significantly reduced the stimulation threshold for repetitive extrasystole (Verrier & Lown, 1984). In humans, mental stress (for review see Taggart, Boyett, Logantha, & Lambiase, 2011) has been reported to significantly increase the presence T-wave alternans (Kop et al., 2004, Lampert et al., 2005), a marker of cardiac electrical instability, increase ventricular premature beats (Lown & DeSilva, 1978), and cause myocardial ischemia (Strike & Steptoe, 2003), which can compromise cardiac electrical stability through changes in ion concentration and tissue conduction (Opie, 1985; James, Taggart, McNally, Newman, Sproton, & Hardman, 2000). Also, a substantial body of literature exists showing an association between stress and sudden cardiac death from ventricular arrhythmia, a clinical condition with etiological roots in the electrical stability of the heart (Kamarck & Jennings, 1991; Lampert, Joska, Burg, Batsford, McPherson, & Jain, 2002; Lane et

al., 2005). Consistent with the notion of D2 relating to cardiac electrical stability, D2 has been reported to decrease significantly in response to myocardial ischemia and before ventricular fibrillation in animals (Skinner, Carpeggiani, Landisman, & Fulton, 1991) and humans (Skinner, Pratt, & Vybiral, 1993) as well as predict the onset of ventricular fibrillation in prefibrillation heart rate data of arrhythmia patients (Kroll & Fulton, 1991).

Efforts have been made to determine the physiological underpinning of HR generation under stress and there are currently two prominent models of HR stress reactivity. Based on data collected using single and double pharmacological blockades Stemmler and colleagues (1991) advanced a theoretical 6-variable quantitative model of HR reactivity that accounted for the influence of basal HR,  $\alpha$ - and  $\beta$ -adrenergic activity, cholinergic influence, as well as interactive effects, and residual effects which they defined as local tissue influences (i.e., metabolic effects). However, when employed to analyze blockade data, a restrictive model was employed that omitted interaction and residual terms. This model was expanded upon by Berntson and colleagues (1991, 1993, 1994) who developed the concept of autonomic space to account for the origins of cardiac reactions to acute psychological stress. This model positioned sympathetic and parasympathetic cardiac control in a 2-dimensional space where changes in HR reactivity could result from a number of autonomic changes ranging from independent changes in a single autonomic branch to co-activation, or reciprocal activation of the autonomic branches. Although this model represented an advance in that it formally acknowledged and accounted for the possibility that the sympathetic and parasympathetic nervous systems may interact, it took no account of the possibility of non-linear influences on HR generation during acute stress exposure. In the present study, D2 continued to predict HR reactivity even when RMSSD, PEP,



and INT were accounted for suggesting that a fuller account of the origins of HR stress reactivity should also include measures of complexity such as D2.

A few examples of non-linear physiological mechanisms, that have been shown to be relevant in the context of behavioral stress, include accentuated antagonism, baroreflex function, and central processing. Accentuated antagonism is the autonomic interaction by which increases in sympathetic activity have a lesser chronotropic influence at higher levels of parasympathetic activity and increases in parasympathetic activity have greater chronotropic influence at high levels of sympathetic activity (Levy, & Zieske, 1969; Warner, & Russell, 1969). This interaction was shown in a small study to be relevant in the context of behavioral stress as a significant interaction between left ventricular ejection time and respiratory sinus arrhythmia, indicators of sympathetic (McCubbin, Richardson, Langer, Kizer, & Obrist, 1983; Schächinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001) and parasympathetic function, respectively, was found to contribute, alongside sympathetic and parasympathetic influences, to the chronotropic response to a battery of behavioral stressors (Uijtdehaage, & Thayer, 2000). D2, in the current study, continued to predict HR reactivity even when this autonomic interaction, modelled using INT, was taken into account. Similarly, the baroreflex, which modulates HR in response to acute changes in blood pressure (Chapleau, Cunningham, Sullivan, Wachtel, & Abboud, 1995; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012; Head, & McCarty, 1987), has been implicated in cardiovascular reactions to acute psychological stress (Forsman, & Lindblad, 1983; Sleight, Fox, Lopez, & Brooks, 1978; Stephenson, 1984; Steptoe, & Sawada, 1989). Finally, cortical and subcortical brain regions have been directly implicated in the modulation of HR in response to stress with some regions exerting positive and others negative chronotropic influence (Wager, et al., 2009a; Wager, et al., 2009b). It should be noted that these are just a few of the

possible non-linear cardiac influences and that other modulators (e.g., receptor physiology; Marsland et al., 1995; Mills & Dimsdale, 1991; Mills, Dimsdale, Ziegler, Berry, & Bain, 1990; Pacák et al., 1989) may impact HR under behavioral stress but remain to be more fully characterized in this context.

Our overall study is not without limitations. First, respiratory parameters were not measured in Study 2 and, accordingly, the influence of changes in respiration rate during stress on the D2 response could not be assessed. However, previous studies of D2 and respiration have produced mixed results (Kanters, et al., 1997; Mangin, et al., 2008; Schubert et al., 2009), and in Study 1 we found that D2 predicted changes in HR even when changes in respiration rate were controlled for. Second, no clinical endpoints were included in these studies, as they focused on young healthy participants. Accordingly, the relationship between changes in D2 and clinical outcomes could not be assessed. As decreases in D2 have been shown to precipitate adverse cardiac events and stress was found in both studies to decrease D2, further research, using large epidemiological datasets, should be undertaken to assess the relationship between stress-induced changes in D2 and clinical outcomes. Third, an argument could be made that multicollinearity exists between RMSSD and D2. However, in neither study were RMSSD and D2 significantly correlated (Study 1  $r = .286$ ,  $N = 25$ ; Study 2  $r = -.010$ ,  $N = 176$ ).

The advent of HR complexity measures has made possible further progress in characterizing HR generation during acute stress exposure by facilitating quantification of cardiac influences not captured by traditionally used measures (e.g., RMSSD, PEP, RMSSD x PEP interaction). D2 quantifies the number of underlying functional components responsible for a HR time series and may, accordingly, provide insight into stress-induced cardiac change above that gained by measures of cardiac sympathetic and parasympathetic activation. However,

current models of cardiac reactivity have largely neglected HR complexity variables. As stress-induced decreases in D2 significantly predicted HR reactivity and remained an independent predictor when measures of cardiac sympathetic and parasympathetic activity and their interaction were controlled for, this study provides evidence to support the inclusion of such measures in models of cardiac stress reactivity. In addition, since decreases in D2 have been shown to predict adverse cardiac events linked to altered electrical stability of the heart future research should aim to evaluate if stress-induced changes in D2 hold clinical value.

## References

- Acharya, U.R., Joseph, K.P., Kannathal, N., Lim, C.M., & Suri, J.S. (2006). Heart rate variability: A review. *Medical and Biological Engineering and Computing*, 44, 1031-1051.
- Anishchenko, T., Igosheva, N., Yakusheva, T., Glushkovskaya-Semyachkina, O., & Khokhlova, O. (2001). Normalized entropy applied to the analysis of interindividual and gender-related differences in the cardiovascular effects of stress. *European Journal of Applied Physiology*, 85, 287-298.
- Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., & Fieldstone, A. (1994). Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockade. *Psychophysiology*, 31, 599-608.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993). Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. *Psychological Bulletin*, 114, 296-322.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1991). Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. *Psychological Review*, 98, 459-487.
- Brindle, R.C., Ginty, A.T., Phillips, A.C., & Carroll, D. (2014). A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress. *Psychophysiology*, 51, 964-976.

- Brisinda, D., Fioravanti, F., Sorbo, A.R., Venuti, A., & Fenici, R. (2015). Psychophysiological assessment of acute stress induced by high-pressure law-enforcement driving: A pilot study. *Psychology and Social Behavior Research*, 2, 36-50.
- Butler, G.C., Yamamoto, Y., & Highson, R.L. (1994). Fractal nature of short-term systolic BP and HR variability during lower body negative pressure. *American Journal of Physiology*, 267, R26-R33.
- Cacioppo, J.T., Uchino, B.N., Berntson, G.G. (1994). Individual differences in the autonomic origins of heart rate reactivity: The psychometrics of respiratory sinus arrhythmia and preejection period. *Psychophysiology*, 31, 412-419.
- Carroll, D., Phillips, & Der, G. (2008). Body mass index, abdominal adiposity, obesity and cardiovascular reactions to psychological stress in a large community sample. *Psychosomatic Medicine*, 70, 653-660.
- Carroll, D., Harrison, L., Johnston, D., Ford, G., Hunt, K., Der, G., & West, P. (2000). Cardiovascular reactions to psychological stress: The influence of demographics variables. *Journal of Epidemiology and Community Health*, 54, 876-877.
- Carvalho, P., Piava, R.P., Couceiro, R., Henriques, J., Antunes, M., Quintal, I., et al. (2010). Comparison of systolic time interval measurement modalities for portable device. *Proceedings from the IEEE EMBS*, 606-609.
- Chapleau, M.W., Cunningham, J.T., Sullivan, M.J., Wachtel, R.E., & Abboud, F.M. (1995). Structural versus functional modulation of the arterial baroreflex. *Hypertension*, 26, 341-347.
- Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status. *Hypertension*, 55, 1026-1032.

- Chu Duc, H., Nguyen Phan, K., Nguyem Viet, D. (2013). A review of heart rate variability and its applications. *Procedia APCBEE*, 7, 80-85.
- Cokkinos, D.V., Heimonas, E.T., Demopoulos, J.N., Haralambakis, A., Tsartsalis, G., & Gardikas, C.D. (1974). Influence of heart rate increase on uncorrected pre-ejection period/left ventricular ejection time (PEP/LVET) ratio in normal individuals. *British Heart Journal*, 38, 683-388.
- Cybulski, G., Michalak, E., Koźluk, E., Piątkowska, A., & Niewiadomski, W. (2004). Stroke volume and systolic time intervals: Beat-to-beat comparison between echocardiography and ambulatory impedance cardiography in supine and tilted positions. *Medical & Biological Engineering & Computing*, 42, 707-711.
- Duschek, S., Dietel, A., Schandry, R., & Reyes del Paso, G.A. (2008). Increased baroreflex sensitivity and reduced cardiovascular reactivity in individuals with chronic low blood pressure. *Hypertension Research*, 31, 1873-1878.
- Elbert, T., Ray, W.J., Kowalik, Z.J., Skinner, J.E., Graf, K.E., Birbaumer, N. (1994). Chaos and physiology: Deterministic chaos in excitable cells. *Physiological Reviews*, 74, 1-47.
- Elbert, T., Lutzenberger, W., Rockstroh, B., Berg, P., & Cohen, R. (1992). Physical aspects of the EEG in schizophrenics. *Biological Psychology*, 32, 595-606.
- Forsman, L., & Lindblad, L.E. (1983). Effect of mental stress on baroreceptor-mediate changes in blood pressure and heart rate and on plasma catecholamines and subjective responses in health men and women. *Psychosomatic Medicine*, 45, 435-445.

- Gianaros, P.J., Onyewuenyi, I.C., Sheu, L.K., Christie, I.C., & Critchley, H.D. (2012). Brain systems for baroreflex suppression during stress in humans. *Human Brain Mapping*, 33, 1700-1716.
- Gianaros, P.J., & Sheu, L.K. (2009). A review of neuroimaging studies of stressor-evoked blood pressure reactivity: Emerging evidence for a brain-body pathway to coronary heart disease risk. *Neuroimage*, 47, 922-936.
- Ginty, A.T., Gianaros, P.J., Derbyshire, S.W.G., Phillips, A.C., & Carroll, D. (2013). Blunted cardiac stress reactivity related to neural hypoactivation. *Psychophysiology* 50, 219-229.
- Ginty, A.T., Phillips, A.C., Higgs, S., Heaney, J.L.J., & Carroll, D. (2012a). Disordered eating behavior is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, 37, 715-724.
- Ginty, A.T., Phillips, A.C., Roseboom, T.J., Carroll, D., & de Rooij, S.R. (2012b). Cardiovascular and cortisol reactions to acute psychological stress and cognitive ability in the Dutch Famine Birth Cohort Study. *Psychophysiology*, 49, 391-400.
- Goldberger, A.L., Amaral, L.A.N., Hausdorff, J.M., Ivanov, P.C., Peng, C.K., & Stanley, H.E. (2002a). Fractal dynamics in physiology: Alterations with disease and aging. *Proceedings of the National Academy of Sciences*, 99, 2466-2472.
- Goldberger, A.L., Peng, C.K., & Lipsitz, L.A. (2002b). What is physiologic complexity and how does it change with aging and disease? *Neurobiology of Aging*, 23, 23-26.
- Grassberger, P., & Procaccia, I. (1983). Measuring the strangeness of strange attractors. *Physica D*, 9, 189-208.
- Gronwall, D.M.A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, 44, 367-373.

- Grossman, P.J., & Kollai, M. (1993). Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: Within- and between-individual relations. *Psychophysiology*, 30, 486-495.
- Grossman, P., Stemmler, G., & Meinhardt, E. (1990). Paced respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. *Psychophysiology*, 27, 404-416.
- Hagerman, I., Berglund, M., Lorin, M., Nowak, J., & Sylvén, C. (1996). Chaos-related deterministic regulation of heart rate variability in time and frequency domains: Effects of autonomic blockade and exercise. *Cardiovascular Research*, 31, 410-418.
- Harris, W.S., Schoenfeld, C.D., & Weissler, A.M. (1967). Effects of adrenergic receptor activation and blockade on the systolic preejection period, heart rate, and arterial pressure in man. *The Journal of Clinical Investigation*, 46, 1704-1714.
- Head, G.A., & McCraty, R. (1987). Vagal and sympathetic components of the heart rate range and gain of the baroreceptor-heart rate reflex in conscious rats. *Journal of the Autonomic Nervous System*, 21, 203-213.
- James, P.R., Taggart, P., McNally, S.T., Newman, S.P., Sproton, S.C., & Hardman, S.M. (2000). Acute psychological stress and the propensity to ventricular arrhythmias: Evidence for a linking mechanism. *European Heart Journal*, 21, 1023-1028.
- Kanters, J.K., Hojgaard, M.V., Agner, E., Holstein-Rathlou, N.H. (1997). Influence of forced respiration on nonlinear dynamics in heart rate variability. *American Journal of Physiology*, 272, R1149-R1154.
- Kelsey, R.M., Soderlund, K., & Arthur, C.M. (2004). Cardiovascular reactivity and adaptation to recurrent psychological stress: Replication and extension. *Psychophysiology*, 41, 924-934.



Kelsey, R.M., Blascovich, J., Leitten, C.L., Schneider, T.R., Tomaka, J., & Weins, S. (2000).

Cardiovascular reactivity and adaptation to recurrent psychological stress: The moderating effects of evaluative observation. *Psychophysiology*, 37, 748-756.

Kent, K.M., Epstein, S.E., Cooper, T., & Jacobowitz, D.M. (1974). Cholinergic innervation of the canine and human ventricular conducting system. *Circulation*, 50, 948-955.

Khanfer, R., Carroll, D., Lord, J.M., Phillips, A.C. (2012). Reduced neutrophil superoxide production among healthy older adults in response to acute psychological stress. *International Journal of Psychophysiology* 86, 238-244.

Kleiger, R.E., Bigger, J.T., Bosner, M.S., Chung, M.K., Cook, J.R., Rolnitzky, L.M.,..., Fleis, J.L. (1991). Stability over time of variables measuring heart rate variability in normal subjects. *The American Journal of Cardiology*, 68, 626-630.

Kop, W.J., Krantz, D.S., Nearing, D., Gottdiener, J.S., Quigley, J.F., O'Callahan, M., et al. (2004). Effects of acute mental stress and exercise on T-wave alternans in patients with implantable cardioverter defibrillators and controls. *Circulation*, 109, 1864-1869.

Kroll, M.W., & Fulton, K.W. (1991). Slope filtered pointwise correlation dimension algorithm and its evaluation with prefibrillation heart rate data. *Journal of Electrocardiology*, 24, 97-101.

Lampert, R., Shusterman, V., Burg, M.M., Lee, F.A., Earley, C., Goldberg, A., et al. (2005). Effects of psychological stress on repolarization and relationship to autonomic and hemodynamic factors. *Journal of Cardiovascular Electrophysiology*, 16, 1-6.

Levy, M.N., & Zieske, H. (1969). Autonomic control of cardiac pacemaker activity and atrioventricular transmission. *Journal of Applied Physiology*, 27, 465-470

- Lown, B., & DeSilva, R.A. (1978). Roles of psychological stress and autonomic nervous system changes in provocation of ventricular premature complexes. *The American Journal of Cardiology*, 41, 979-985.
- Lipsitz, L.A. (1995). Age-related changes in the “complexity” of cardiovascular dynamics: A potential marker of vulnerability to disease. *Chaos*, 5(1), 102-109.
- Lipsitz, L.A., & Goldberger, A.L. (1992). Loss of ‘complexity’ and aging. *JAMA*, 267(13), 1806-1809.
- Mangin, L., Fiamma, M.N., Straus, C., Derenne, J.P., Zelter, M., Clerici, C., & Similowski, T. (2008). Sources of human ventilator chaos: Lessons from switching controlled mechanical ventilation to inspiratory pressure support in critically ill patients. *Respiratory Physiology and Neurobiology*, 161, 189-196.
- Marsland, A.L., Manuck, S.B., Wood, P., Rabin, B.S., Muldoon, M.F., & Cohen, S. (1995). B<sub>2</sub>-Adrenergic receptor density and cardiovascular response to mental stress. *Physiology & Behavior*, 57, 1163-1167.
- Mathias, C.W., Stanford, M.S., & Houston, R.J. (2004). The psychological experience of the paced auditory serial addition task (PASAT): Does the PASAT induce autonomic arousal? *Archives of Clinical Neuropsychology* 19, 543-554.
- McCubbin, J.A., Richardson, J.E., Langer, A.W., Kizer, J.S., & Obrist, P.A. (1983). Sympathetic neuronal function and left ventricular performance during behavioral stress in humans: The relationship between plasma catecholamines and systolic time intervals. *Psychophysiology*, 20, 102-110.

- Melillo, P., Bracale, M., & Pecchia, L. (2011). Nonlinear heart rate variability features for real-life stress detection. Case study: students under stress due to university examination. *Biomedical Engineering Online*, 10, 1-13.
- Mezzacappa, E.S., Kelsey, R.M., & Katkin, E.S. (1999). The effects of epinephrine administration on impedance cardiographic measures on cardiovascular function. *International Journal of Psychophysiology*, 31, 189-196.
- Mezzacappa, E.S., Kelsey, R.M., Katkin, E.S., & Sloan, R.P. (2001). Vagal rebound and recovery from psychological stress. *Psychosomatic Medicine*, 63, 650-657.
- Mills, P.J., & Dimsdale, J.E. (1991). Cardiovascular reactivity to psychosocial stressor: A review of the effects of beta-blockade. *Psychosomatics*, 32, 209-220.
- Mills, P.J., Dimsdale, J.E., Ziegler, M.G., Berry, C.C., & Bain, R.D. (1990). Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. *Psychosomatic Medicine*, 52, 621-623.
- Nahshoni, E., Adler, E., Laniado, S., & Keren, G. (1998). Fractal organization of the pointwise correlation dimension of the heart rate. *Medical Hypotheses*, 51, 367-376.
- Newlin, D.B., & Levenson, R.W. (1979). Pre-ejection period: Measuring beta-adrenergic influences upon the heart. *Psychophysiology*, 16, 546-553.
- Opie, L.H. (1985). Products of myocardial ischemia and electrical instability of the heart. *Journal of the American College of Cardiology*, 5, 162-165.
- Osaka, M., Saitoh, Atarashi, H., & Hayakawa, H. (1993). Correlation dimension of heart rate variability: A new index of human autonomic function. *Frontiers of Medical and Biological Engineering*, 5, 289-300.

- Pacák, K., Nedvidková, J., Horváth, M., Frantík, E., Husek, P., & Pacovský, V. (1989). High cardiovascular reactivity to psychological challenge associated alternatively with high density of beta-adrenergic receptors or with high resting levels of catecholamines. *Activitas Nervosa Superior*, 31, 96-99.
- Penttälä, J., Kuusela, T., & Scheinin, H. (2005). Analysis of rapid heart rate variability in the assessment of anticholinergic drug effects in humans. *European Journal of Clinical Pharmacology*, 61, 559-565.
- Penttälä, J., Helminen, A., Jartti, T., Kuusela, T., Huikuri, H.V., Tulppo, M.P., et al. (2001). Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: Effects of various respiratory patterns. *Clinical Physiology*, 21, 365-376.
- Phillips, A.C., Ginty, A.T., & Hughes, B.M. (2013). The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90, 1-7.
- Pincus, S.M. (2001). Assessing serial irregularity and its implications for health. *Annals of the New York Academy of Sciences*, 954, 245-267.
- Reyes del Paso, G.A., Langewitz, W., Robles, H., & Pérez, N. (1996). A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. *International Journal of Psychophysiology*, 22, 163-171.
- Richman, J.S., & Moorman, J.R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology*, 278, H2039-2049.
- Ring, C., Burns, V.E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology* 39, 585-590.

- Rousselle, J.G., Blascovich, J., & Kelsey, R.M. (1995). Cardiorespiratory response under combined psychological and exercise stress. *International Journal of Psychophysiology*, 20, 49-58.
- Schächinger, H., Weinbacher, M., Kiss, A., Ritz, R., & Langeqitz, W. (2001). Cardiovasuclar indices of peripheral and central sympathetic activation. *Psychosomatic Medicine*, 63, 788-796.
- Scheinin, H., Helminen, A., Huhtala, S., Grönroos, P., Bosch, J.A., Kuusela, T., et al. (1999). Spectral analysis of heart rate variability as a quantitative measure of parasympatholytic effect-integrated pharmacokinetics and pharmacodynamics of three anticholinergic drugs. *Therapeutic Drug Monitoring*, 21, 141-151.
- Schipke, J.D., Pelzer, M., & Arnold, G. (1999). Effect of respiration rate on short-term heart rate variability. *Journal of Clinical and Basic Cardiology*, 2, 92-95.
- Schubert, C., Lambertz, M., Nelesen, R.A., Bardwell, W., Choi, J. B., & Dimsdale, J.E. (2009). Effects of stress on heart rate complexity- A comparison between short-term and chronic stress. *Biological Psychology*, 80, 325-332.
- Sgoifo, A., Koolhaas, J., De Boer, S., Musso, E., Stilli, D., Buwalda, B., et al. (1999). Social stress, autonomic neural activation, and cardiac activity in rats. *Neuroscience and Biobehavioral Reviews*, 23, 915-923.
- Shaffer, F., McCraty, R., & Zerr, C.L. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, 5, 1-18.

- Skinner, J.E., Pratt, C.M., & Vybiral, T. (1993). A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. *American Heart Journal*, 125, 731-743.
- Skinner, J.E., Carpeggiani, C., Landisman, C.E., & Fulton, K.W. (1991). Correlation dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia. *Circulation Research*, 68, 966-976.
- Sleight, P., Fox, P., Lopez, R., & Brooks, D.E. (1978). The effect of mental arithmetic on blood pressure variability and baroreflex sensitivity in man. *Clinical Science and Molecular Medicine*, 4, 381s-382s.
- Stemmler, G., Grossman, P., Schmid, H., & Foerster, F. (1991). A model of cardiovascular activation components for studies using autonomic receptor antagonists. *Psychophysiology*, 28, 367-382.
- Stephenson, R.B. (1984). Modification of reflex regulation of blood pressure by behavior. *Annual Reviews of Physiology*, 46, 133-142.
- Stephoe, A., & Sawada, Y. (1989). Assessment of baroreceptor reflex function during mental stress and relaxation. *Psychophysiology*, 26, 140-147.
- Strike, P.C., & Steptoe, A. (2003). Systematic review of mental stress-induced myocardial ischaemia. *European Heart Journal*, 24, 690-703.
- Taggart, P., Boyett, M.R., Logantha, S.J.R.J., & Lambiase, P.D. (2011). Anger, emotion, and arrhythmias: From brain to heart. *Frontiers in Physiology*, 2, 67-77.
- Tarvainen, M.P., & Niskanen, J. (2008). Kubios HRV version 2.0 users guide.

- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards, of measurement, physiological interpretation, and clinical use. *Circulation*, 93, 1043-1065.
- Tomaka, J., Blascovich, J., Kibler, J., & Ernst, J.M. (1997). Cognitive and physiological antecedents of threat and challenge appraisal. *Journal of Personality and Social Psychology*, 73, 63-72.
- Tomaka, J., Blascovich, J., Kelsey, R.M., & Leitten, C.L. (1993). Subjective, physiological, and behavioral effects of threat and challenge appraisal. *Journal of Personality and Social Psychology*, 65, 248-260.
- Treiber, F.A., Kamarck, T., Schneidermann, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine*, 65, 46-62.
- Uijtdehaage, S.H.J., & Thayer, J.F. (2000). Accentuated antagonism in the control of human heart rate. *Clinical Autonomic Research*, 10, 107-110.
- Vaillancourt, D.E., & Newell, K.M. (2002). Changing complexity in human behaviour and physiology through aging and disease. *Neurobiology of Aging*, 23, 1-11.
- Verrier, R.L., & Lown, B. (1984). Behavioral stress and cardiac arrhythmias. *Annual Reviews of Physiology*, 46, 155-176.
- Warner, H.R., & Russell, R.O. (1969). Effect of combined sympathetic and vagal stimulation on heart rate in the dog. *Circulation Research*, 24, 567-573.
- Wager, T.D., Waugh, C.E., Lindquist, M., Noll, D.C., Fredrickson, B.L., & Taylor, S.F. (2009a). Brain mediators of cardiovascular responses to social threat: Part I:

- Reciprocal dorsal and central sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*, 47, 821-835.
- Wager, T.D., van Ast, V.A., Hughes, B.L., Davidson, M.L., Lindquist, M.A., & Ochsner, K.N. (2009b). Brain mediators of cardiovascular responses to social threat, Part II: Prefrontal-subcortical pathways and relationship with anxiety. *Neuroimage*, 47, 836- 851.
- Wagner, & Persson, P.B. (1998). Chaos in the cardiovascular system: An update. *Cardiovascular Research*, 40, 257-264.
- Willemsen, G., Ring, C., Carroll, D., Evans, P., Clow, A., & Hucklebridge, F. (1998). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic and cold pressor. *Psychophysiology* 35, 252-259.
- Williamon, A., Aufegger, L., Wasley, D., Looney, D., & Mandic, D.P. (2013). Complexity of physiological responses decreases in high stress musical performance. *Journal of the Royal Society Interface*, 10, 1-6.
- Winzer, A., Ring, C., Carroll, D., Willemsen, G., Drayson, M., & Kendall, M. (1999). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of beta-adrenergic blockade. *Psychophysiology*, 36, 591-601.



---

## Chapter 4

---

High Allostatic Load is Associated with Blunted Cardiac Reactivity to Acute Mental Stress

This chapter is under review under the following citation:

Brindle, R.C., Ginty, A.T., Carroll, D., & Phillips, A.C. (under review). High allostatic load is associated with blunted cardiac reactivity to acute mental stress.

### Abstract

Allostatic load has been discussed as a possible mechanism linking chronic stress to blunted cardiovascular stress reactivity later in life. However, no study has directly tested the relationship between measured allostatic load and cardiovascular reactivity. In fifty-four participants baseline physiological allostatic load was computed using: baseline measures of heart rate, systolic and diastolic blood pressures, epinephrine and norepinephrine,  $\beta_2$ -adrenergic receptor density, waist-hip ratio, body-mass index, and estimated cardiorespiratory fitness. Participants completed acute mental arithmetic and cold pressor stress tasks while heart rate and blood pressure were measured. Allostatic load score was significantly related to heart rate reactivity to mental arithmetic only; the greater the allostatic load, the lower the cardiac stress reactivity. This relationship remained significant after controlling for task engagement and performance, and symptoms of depression. These results are consistent with the notion that blunted stress reactivity is a marker of physiological dysregulation and provides unique support for the idea of allostatic load as a candidate mechanism linking chronic stress to blunted stress reactivity later in life.

**Keywords:** Allostatic load, cardiovascular reactivity, mental stress, cold pressor

## Introduction

Accumulating evidence suggests that chronic stress is associated with atypical physiological responses to acute stress later in life. For example, although some reports exist that link childhood trauma to exaggerated cardiovascular and cortisol reactivity (Heim, et al., 2000; Leucken, 2000), emerging evidence from both laboratory based studies (Carpenter et al., 2007; MacMillan et al., 2009) and epidemiological datasets (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012) appears to support the notion that blunted cardiovascular and cortisol responses to acute psychological stress are characteristic of individuals who report having experienced childhood trauma. Similar evidence exists also for trauma experienced in adulthood (DePierro, D'Andrea, & Pole, 2013). Moreover, reporting a high number of number of negative life events also appears to be associated with blunted cardiovascular stress reactivity in adults (Phillips, Carroll, Ring, Sweeting, & West, 2005). Finally, a recent meta-analysis of over 700 studies provided evidence that high levels of general life stress and job stress relate to blunted blood pressure (BP) reactivity, although sub-group analyses tended to produce mixed results (Chida & Hamer, 2008).

The allostatic load model has been discussed in the context of chronic stress (Gallo, Jiménez, de los Monteros, & Mills, 2011) and childhood trauma (Danese & McEwen, 2011) and may offer insight into the mechanism by which chronic stress and childhood trauma impact on acute stress responding. The model, which is grounded in Selye's "paradox of stress" (1936), does not emphasize the traditional notion of homeostasis and negative feedback regulation, but rather views physiology through the lens of allostasis (Sterling & Eyer, 1988). Accordingly, instead of regulating biological systems up or down relative to an unchangeable set point (i.e., homeostasis), biological systems instead, induced by environmental stimuli, constantly shift

between allostatic states that have different set points, thus allowing an organism to more readily cope with environmental demands (Sterling, 2012). However, whereas allostasis is acutely adaptive, repeated or prolonged allostasis, as in the case of traumatic events or chronic stress, can induce a state of allostatic load in which functionality is compromised (McEwen, 1998). Particularly relevant to the current discussion, McEwen (1998) pointed out that one functional phenotype indicative of allostatic load is that of an *inadequate stress response* or *hypoactivation*.

The allostatic load model has been shown to be robust in predicting adverse health outcomes. In practice, due to the model's multisystem approach, biological markers from various domains (cardiovascular, neuroendocrine, metabolic, anthropometric, immune, etc.) are measured and a single composite score is computed such that a higher score is indicative of greater allostatic load (Juster, McEwen, & Lupien, 2010). Using this method, high levels of allostatic load have been shown to predict physical and cognitive decline (Seeman, McEwen, Rowe, & Singer, 2001) and all-cause mortality (Karlman, Singer, & Seeman, 2006); all of which, with the exception of mortality, have also been linked to blunted cardiovascular stress reactivity (Bennett, Blissett, Carroll, & Ginty, 2014; Phillips, Ginty, & Hughes, 2013).

Given that chronic stress increases allostatic load, and relates to blunted stress reactivity, and both allostatic load and blunted reactivity relate to similar health and behavioral outcomes, it is reasonable to speculate that blunted cardiovascular reactivity may relate to increased allostatic load. Two studies provide reason to believe such a relationship should exist. First, in a sample of over 200 adolescents, a social allostatic load index, computed from various social domains (e.g., housing conditions, family dynamics, exposure to violence), was inversely related to cardiovascular reactivity, such that higher social allostatic load predicted blunted cardiovascular stress reactivity (Evans, Kim, Ting, Tesher, & Shannis, 2007). Second, in a case-controlled

study, patients with diabetes, in response to mental stress, displayed blunted cardiovascular and cortisol reactivity and were also characterized by higher levels of life stress, and higher daily interleukin-6 and cortisol compared to healthy controls. The authors interpreted such stress reactions as a manifestation of augmented allostatic load in the diabetic sample (Steptoe, Hackett, Lazzarino, Bostock, Marca, & Carvalho, 2014). However, no formal allostatic load index was computed.

Consequently, the present study aimed to examine directly the relationship between physiological allostatic load and cardiovascular stress reactivity in a sample of healthy young adults; this sample being chosen as the basic mechanisms of allostatic load are likely to be minimally confounded by disease processes. An allostatic load index was computed from nine biomarkers in the cardiovascular (resting systolic (SBP) and diastolic (DBP) blood pressure, resting heart rate (HR), and estimated cardiorespiratory fitness), neuroendocrine (resting norepinephrine, epinephrine and  $\beta_2$ -adrenergic cell receptor density) and anthropometric (waist-hip ratio and BMI) domains and cardiovascular reactivity was recorded in response to two acute stress tasks: mental arithmetic and cold pressor. These two tasks were chosen specifically to examine whether the relationship between allostatic load and cardiovascular stress reactivity varied as a function of task type, the former being an active stressor and the latter a passive stressor (Salomon, Bylsma, White, Panaite, & Rottenberg, 2013). Some evidence suggests that blunted cardiovascular reactivity only manifests in response to active stressors (Salomon et al., 2013; Schwerdtfeger & Rosenkaimer, 2011). Hence, based on the available evidence it was hypothesized that high allostatic load would relate to blunted cardiovascular reactivity to the mental arithmetic stressor but not the cold pressor.

## **Methods**

### **Participants**

Fifty-four participants were recruited for the present study from around the University community. Participants were required to refrain from alcohol and vigorous exercise 12h, caffeine 2h, and food and drinks other than water 1h before testing. Participants with a history of cardiovascular or metabolic disease were excluded. Participants received coursework credit and the study was approved by the University of Birmingham Ethics Committee.

### **Procedure**

Upon arrival to the laboratory, anthropometric measures were taken and participants completed the Hospital Anxiety and Depression Scale (HADS) and the physical activity assessment. Participants were then asked to sit quietly while a cannula was inserted into the antecubital vein for blood sampling and blood pressure cuff was attached. After establishing the cannula, participants sat quietly for a standard 20-min adaptation period before engaging in two acute stress tasks: the Paced Auditory Serial Addition Task (PASAT) or cold pressor task, counterbalanced across participants. Each task was self-contained in that each task had its own baseline and stress phase and an additional standard 10-min rest period separated the tasks. During the baseline phase participants were asked to sit quietly and during each stress phase they completed the PASAT or cold pressor tasks. After task completion, participants completed a brief questionnaire about the task.

### **Questionnaire**

The HADS (Zigmond & Snaith, 1983) is an established 14-item scale comprising 7-items measuring depression, with emphasis on anhedonia, not somatic manifestations, and 7-items

measuring anxiety. In the current study the Cronbach alpha coefficient was .68. Following the conclusion of each stress task, participants rated task stressfulness and engagement on standard Likert scales ranging from 1-10 and 1-6, respectively, both anchored by “not at all” and “extremely.”

### **Acute Psychological Stress Tasks**

The present version of the Paced Auditory Serial Arithmetic Test (PASAT; Gronwall, 1977) is a 10-min socially evaluative mental arithmetic task that has been shown to reliably perturb cardiovascular function through both parasympathetic and sympathetic mechanisms (Ginty, Gianaros, Derbyshire, Phillips, & Carroll, 2013; Ring, Burns, & Carroll, 2002). Single digit numbers were presented via CD player and participants were required to add consecutive integers while retaining the most recent number in memory so that it could be added to the next number presented. In order to enhance task stressfulness, during the task, an experimenter overtly scored the participants performance and provided a standard number of aversive noise bursts that the participant was told corresponded to wrong answers. In addition, participants were required to continuously watch themselves on a television screen and were told that they were being recorded for body language analysis and that they were competing against other participants whose scores were displayed on a scoreboard in front of the participant. PASAT score, an index of task performance, was calculated by subtracting 5 points for every wrong or unanswered question from a starting value of 1000.

The cold pressor task (Hines & Brown, 1936) required participants to immerse one hand, up to the wristfold, in 0-1°C water for 2min. This task has been shown to reliably elicit a cardiovascular response (Allen, Sherwood, Obrist, Crowell, & Grange, 1987), mainly though

alpha-adrenergic mechanisms and peripheral vasoconstriction (Ring, Harrison, Winzer, Carroll, Drayson, & Kendall, 2000). The tasks were counterbalanced across participants.

### **Cardiovascular Measures**

HR, SBP, and DBP were measured discretely at 2-min intervals during the baseline and stress phases using a semi-automated sphygmomanometer (Critikon Inc., Tampa, FL) and blood pressure cuff placed over brachial artery on the non-dominant arm. Four measurements (minutes 1, 3, 5, and 7) were taken during the baseline and stress phases of the PASAT and two measurements (minutes 0 and 2) were taken during the baseline and stress phases of the cold pressor task. Phase measures were averaged to create baseline and stress phase means for each task. Stress reactivity was defined as the difference between stress and baseline phase means.

### **Allostatic Load Index**

An allostatic load composite index score was calculated using nine variables spanning three commonly measured biological domains (Juster, McEwen, & Lupien, 2010): neuroendocrine, cardiovascular, and anthropometric. All these measures were standardized to z-scores and cardiorespiratory fitness (CRF) was multiplied by -1 to keep scaling across the variables consistent. The sum of the nine standardized factors constituted the allostatic load index. This method is commonly used to derive allostatic load and cardiometabolic risk and is scaled such that higher scores indicate higher allostatic load (Jennings, Heim, Kuan, Gianaros, Muldoon, & Manuck, 2013; Juster et al., 2010). In addition, this method has been recommended in the context of allostatic load, as it preserves the continuous properties of biological data and allows for the assessment of outcomes at both the high and low ends of the allostatic load spectrum (Seplaki, Goldman, & Gleit, 2005).



**Neuroendocrine Domain.**

Measures of epinephrine, norepinephrine and  $\beta_2$ -adrenergic cell receptor density were undertaken to assess allostatic load in the neuroendocrine domain. Venous blood was collected in EDTA vacutainers (BD Bioscience, Franklin Lakes, USA) before stress testing, at the end of the 20-min adaptation period. Samples were immediately placed on ice, centrifuged for 15min at 4°C. Samples were then stored at -80°C before being analyzed, in duplicate, using a commercially available ELISA (IBL International, Germany). The assay is based on the sandwich principle. In a preparation step, sample catecholamines were extracted, acylated, and derivitized. During the ELISA an unknown concentration of derivitized catecholamine is bound to a goat anti-rabbit detection antibody on the surface of a micro titer plate. An enzyme-linked secondary antibody is then added that forms a sandwich around the bound catecholamines. After the substrate reaction, detectable color develops in proportion to the amount of bound catecholamine. The ELISA simultaneously tested plasma norepinephrine and epinephrine levels and has been shown to correlate highly with high-performance liquid chromatography methods (Westermann, Hubl, Kaiser, & Salewski, 2002). For epinephrine intra- and inter-assay mean coefficients of variation were 28% and 15.2%, respectively, while the same values for norepinephrine were 22% and 12.5%. Mean values were calculated from duplicate samples.

For analysis of baseline  $\beta_2$ -adrenergic cell receptor density, venous blood was again collected before stress testing, at the end of the 20-min adaptation period, but in heparinized vacutainers.  $\beta_2$ -adrenergic cell receptor density was quantified on peripheral blood mononuclear cells (PBMCs), as evidence has shown that  $\beta_2$ -adrenergic cell receptors located on PBMCs and on the myocardium are structurally and functionally similar (Brodde, Beckeringh, & Mchel, 1987). Approximately  $4 \times 10^6$  PBMCs were isolated on the same day using the previously

described Ficoll Paque gradient method (Böyum, 1968) and stored at  $-80^{\circ}\text{C}$  in freezing medium (90% fetal calf serum/10% DMSO; Sigma Aldrich, Missouri, USA). Before flow cytometry analysis, two separate samples of approximately  $2 \times 10^6$  PBMCs were prepared. The first sample was stained with a rabbit non-specific FITC-conjugated IgG isotype control antibody (Biorbyt, Cambridge, UK; dilution 1:50) and the second sample with a rabbit FITC-conjugated  $\beta_2$ -adrenergic cell receptor antibody (Biorbyt, Cambridge, UK; dilution 1:50). The IgG non-specific antibody was used to quantify non-specific binding. Median fluorescence of both samples was measured with a flow cytometer and CFlow Plus software (Accuri, Cambs, UK).  $\beta_2$ -adrenergic cell receptor density was quantified by subtracting median fluorescence of the  $\beta_2$ -adrenergic cell receptor antibody sample from that of the IgG sample.

### **Cardiovascular Domain.**

Baseline measures of HR, SBP, and DBP and estimated cardio-respiratory fitness were used to assess allostatic load in the cardiovascular domain. As each task had a separate baseline, measures of HR, SBP, and DBP from the baseline of the PASAT were used. The choice to use baseline PASAT values instead of baseline cold pressor values was based on 1) results from independent paired-samples t-tests that showed no significant difference between baseline values across the tasks (all  $p$ 's  $> .27$ ) and 2) the fact that baseline means from the PASAT were derived from four measures while baseline cold pressor mean were derived from two measures; the former being more reliable (LLabre, Ironson, Spitzer, Gellman, Weidler, & Schneiderman, 1988). To estimate CRF, participants were asked to report their level of physical activity on a scale of 1-5: 1 = inactive, 5 = 3+ hours of aerobic exercise/week. Scores of 1, 2, 3, 4, and 5, were then recoded with into physical activity scores with values of 0, 0.32, 1.06, 1.76, and 3.03, respectively. CRF in METS was estimated using the following algorithm: (Gender (female = 0,

male = 1) x 2.77) - (age in years x 0.10) - (BMI x 0.17) - (resting HR x 0.3) + (physical activity score) + 18.07 (Jurca et al., 2005).

### **Anthropometric Domain.**

Height and weight were measured using a portable stadiometer and Seca scale and BMI was calculated as  $\text{kg/m}^2$ . Measures of waist and hip circumference were taken below the last palpable rib and at the top of the iliac crest, respectively (World Health Organization, 2008). BMI and waist-hip ratio were used as allostatic load makers of the anthropometric domain.

### **Statistical Analysis**

Repeated-measures (baseline, stress) ANOVAs were used to confirm significant perturbation of the cardiovascular system (BP and HR) by both stress tasks. Descriptive bivariate correlations between allostatic load and cardiovascular reactivity variables were followed by unadjusted linear regressions. Adjusted multiple regression models predicting cardiovascular stress reactivity contained task engagement rating and performance, and HADS depression score in the first step and allostatic load in step two. Subjective task engagement and measured task performance were inserted as covariates to discount the possibility that differences in cardiovascular stress reactivity resulted from individual differences in task effort (Phillips et al., 2013). HADS depression score was inserted as a covariate as compelling evidence links high levels of depression to increased allostatic load (McEwen, 2000) and blunted stress reactivity (de Rooij et al., 2010; Salomon et al., 2013). Small discrepancies in degrees of freedom reflect occasional missing data.

## Results

Participant characteristics are shown in Table 4.1. One participant was four standard deviations outside the mean for HR reactivity to the PASAT and was excluded from analyses.

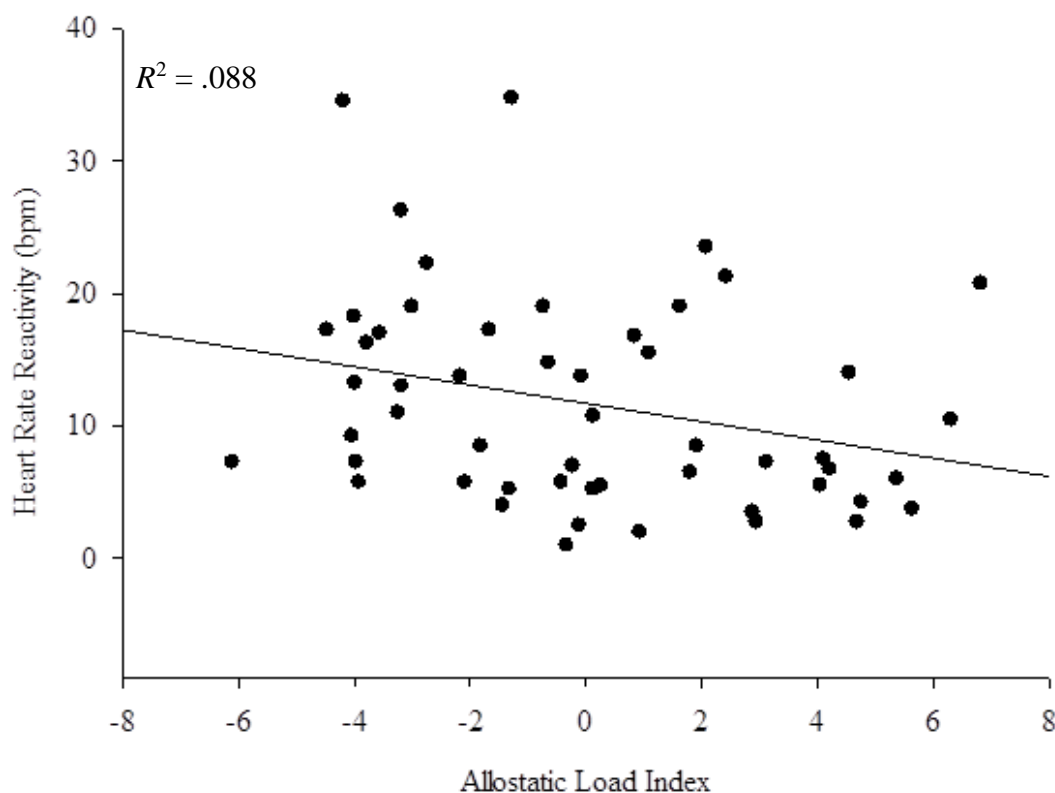
**Table 4.1** Sample characteristics

	Mean (SD)	
Gender (% female)	45.3	
Age (years)	20.9 (3.40)	
BMI	22.6 (2.59)	
Waist/Hip Ratio	0.8 (0.06)	
Estimated Cardiorespiratory Fitness (METS)	14.1 (1.74)	
HADS Depression Score	2.1 (2.19)	
Allostatic Load Index	0.0 (3.29)	
	Baseline	Stress
Norepinephrine (ng/ml)	341.5 (141.56)	-
Epinephrine (ng/ml)	560.7 (468.10)	-
$\beta_2$ -adrenergic receptors/cell	204.6 (93.46)	-
PASAT		
Heart Rate (bpm)	63.8 (11.11)	75.5 (13.38)*
Systolic Blood Pressure (mmHg)	104.3 (11.71)	119.9 (15.21)*
Diastolic Blood Pressure (mmHg)	60.6 (7.63)	69.8 (8.38)*
Self-reported Engagement	-	4.5 (1.12)
Self-reported Stressfulness	-	6.8 (1.86)
Task performance (score)	-	665.1 (160.67)
Cold Pressor		
Heart Rate (bpm)	64.1 (10.84)	68.8 (12.77)*
Systolic Blood Pressure (mmHg)	105.3 (12.14)	121.9 (16.02)*
Diastolic Blood Pressure (mmHg)	60.3 (7.44)	72.3 (11.08)*
Self-reported Stressfulness	-	5.8 (2.64)

\* denotes significant ( $p < .05$ ) increase from baseline

### Cardiovascular Reactions to PASAT and Cold Pressor Tasks

The mean (SD) reactivity to the PASAT was 15.6 (9.56) mmHg, 9.3 (5.27) mmHg, and 11.7 (7.89) bpm for SBP, DBP and HR, respectively. For the cold pressor, the analogous averages were 16.7 (11.82) mmHg, 12.0 (8.92) mmHg, and 4.6 (5.38) bpm. Repeated measures ANOVAs revealed highly significant differences between baseline and stress task cardiovascular values: for the PASAT, HR,  $F(1,52) = 116.35, p < .001, \eta^2 = .69$ , SBP,  $F(1,52) = 141.81, p < .001, \eta^2 = .73$ , and DBP,  $F(1,52) = 163.66, p < .001, \eta^2 = .76$ , and for the cold pressor, HR,  $F(1,51) = 38.34, p < .001, \eta^2 = .43$ , SBP,  $F(1,51) = 103.20, p < .001, \eta^2 = .67$ , and DBP,  $F(1,51) = 94.16, p < .001, \eta^2 = .65$ . Phase means are presented in Table 4.1. BP and HR reactivity to the PASAT and cold pressor were not correlated (all  $p$ 's  $> .30$ ).



**Figure 4.1** Relationship between allostatic load and heart rate reactivity to the PASAT.

### **Allostatic Load and Stress Reactivity**

The mean (SD) allostatic load score was 0.0 (3.29). Correlation analysis revealed a significant relationship between allostatic load and HR reactivity to the PASAT. Indeed, an unadjusted linear model revealed that those with higher allostatic load registered smaller HR responses,  $\beta = -.29$ ,  $t = -2.15$ ,  $p = .04$ ,  $\Delta R^2 = .083$ . This relationship withstood adjustment for PASAT engagement and performance, as well as HADS depression score,  $\beta = -.30$ ,  $t = -2.20$ ,  $p = .03$ ,  $\Delta R^2 = .088$  (Figure 4.1). No such association was evident for HR reactions to the cold pressor. In addition, there were no significant associations between allostatic load and SBP or DBP reactivity to either stress task. Supplementary analysis using a new allostatic load score defined as the Zsum of resting DBP,  $\beta$ -receptors, and waist-hip ratio can be found in Appendix III (Tables 4.2 and 4.3).

### **Discussion**

In a sample of healthy young adults, allostatic load was negatively correlated with HR reactivity to the PASAT. High allostatic load was associated with diminished HR reactions to acute stress. This association remained significant after controlling for PASAT engagement and performance, and symptoms of depression. This is consistent with the notion that blunted HR reactivity is a marker of physiological dysregulation (Carroll, Lovallo, & Phillips, 2009).

These are the first data, to our knowledge, to demonstrate a relationship between a measured physiological allostatic load index and cardiovascular reactions to acute psychological stress. However, our results resonate with previous findings in that physical and cognitive decline, obesity, and impulsivity have all been independently linked to blunted cardiac reactivity and increased allostatic load (Bennett, et al., 2014; Evans, 2003; Karlamangla, et al., 2006; Phillips et al., 2013; Seeman et al., 2001). Further, our findings are in line with two previous

studies showing that a social allostatic load score was associated with blunted stress reactivity (Evans et al., 2007) and that diabetic patients exhibiting signs of increased allostatic load (elevated interleukin-6, cortisol, and life stress) were characterised by blunted cardiovascular reactivity to acute mental stress (Steptoe et al., 2014). Finally, the present data positively reinforce the candidacy of allostatic load as a mechanism linking chronic stress to blunted stress reactivity later in life.

It is notable that allostatic load related to HR reactivity to the PASAT only. This is not the first time such a result has been reported; in two independent studies, individuals with depression, or those reporting high levels of depressive symptomatology exhibited blunted HR reactivity to a public speech stressor but not to a cold pressor task (Salomon et al., 2013; Schwerdtfeger & Rosenkaimer, 2011). Taken together, these results not only underscore the preserved cardiovascular capacity of individuals with depression, or in the current study high allostatic load, to react to a stressor but also highlight the unique nature of stressors involving motivated behavior, or active coping, as these appear to be where blunted reactivity profiles manifest. In terms of stress reactivity, this notion formed the basis for the theory of central motivational dysregulation, which suggests that blunted cardiovascular reactivity is a marker of dysregulation in the cortical substrates that support motivated behavior (Carroll et al., 2009; Carroll, Phillips, & Lovallo, 2011); several sub-regions of the cingulate cortex, insula, and amygdala have been implicated in neuroimaging studies directly comparing blunted and exaggerated cardiovascular stress responders (Gianaros, May, Siegle, & Jennings, 2005; Ginty et al., 2013). Interestingly, allostatic load research in humans and animals has found that similar regions, namely, the amygdala, hippocampus, cingulate, and prefrontal cortex, are perhaps the most vulnerable to allostatic load accumulation (Ganzel, Morris, & Wetherington, 2010). For

example, in a large study of Australian men and women the number of adverse childhood events negatively related to anterior cingulate cortex size (Cohen et al., 2006) and in children from “risky families” blunted amygdala activation was observed in response to a facial emotion task (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). Finally, acute stress-induced activation of the core visceral stress-response circuit, which includes the subgenual anterior cingulate cortex, bed nucleus of the stria terminalis, amygdala, and paraventricular nucleus of the hypothalamus, was found to negatively correlate with both the emotional and physical abuse subscales of the Childhood Trauma Questionnaire (Banihashemi, Sheu, Midei, & Gianaros, 2015). Hence, it may be the central nervous system where the effects of allostatic load manifest ultimately leading to dysregulated peripheral physiology (i.e., blunted cardiovascular stress reactivity) and disease.

Interestingly, allostatic load score did not correlate with blood pressure reactivity to either task. This could possibly be explained by the fact that blood pressure is a multiply determined cardiovascular variable; changes in BP represent the net effect of changes in cardiac output and vascular resistance, the latter being modulated, to a large extent, by local myogenic and metabolic activity (Pappano & Wier, 2013). It may be that such mechanisms are less susceptible to the accumulation of allostatic load. A corollary of such logic, though, is that HR reactivity is vulnerable to the accumulation of allostatic load. Given that changes in HR are primarily the result of autonomic nervous system modulation, both centrally and peripherally (Pappano & Wier, 2013), this perhaps illustrates a particular susceptibility of the autonomic nervous system to the toxic effects of high allostatic load.

The present results should be interpreted within the context of several limitations. First, blunted reactivity has been discussed in the past as simply being a marker of low task



engagement (Phillips et al., 2013). However, this does not appear to have influenced the present results as the relationship between allostatic load and HR reactivity withstood adjustment for self-reported task engagement and objective task performance. Second, although the theoretical grounds for the present study were developed within the context of early childhood trauma and chronic stress, no measures of trauma or chronic stress were included in the present study. This was because the aim of the present study was to examine the association between physiological allostatic load and acute stress reactivity and an *a priori* decision was made to use a young adult sample free from confounding disease processes. Consequently, no conclusions can be drawn as to the cause of the observed allostatic load or its accumulation or relationship to stress reactivity over the course of time. Such questions provide motivation for future research including assessments of early life trauma and chronic stress.

In conclusion, we observed a negative association between a physiological allostatic load score and cardiac reactivity to acute mental stress. As allostatic load is a marker of physiological dysregulation, these results are consistent with the notion that blunted stress reactivity is a marker of maladaptive physiological functioning. Further, these results support the idea of allostatic load as a candidate mechanism linking early childhood trauma and chronic stress to blunted stress reactivity later in life

## References

- Allen, M.T., Sherwood, A., Obrist, P.A., Crowell, M.D., & Grange, L.A. (1987). Stability of cardiovascular reactivity to laboratory stressors: A 2 ½ year follow-up. *Journal of Psychosomatic Research*, 31, 639-645.
- Banihashemi, L., Sheu, L.K., Midei, A.J., & Gianaros, P.J. (2015). Childhood physical abuse predicts stressor-evoked activity within the central visceral control regions. *Social Cognitive and Affective Neuroscience*, 10, 474-485.
- Bennett, C., Blissett, J., Carroll, D., & Ginty, A.T. (2014). Rated and measured impulsivity in children is associated with diminished cardiac reactions to acute psychological stress. *Biological Psychology*, 102, 68-72.
- Böyum, A. (1968). Isolation of mononuclear cells and granulocytes from human blood. *Scandinavian Journal of Clinical Laboratory Investigation*, 97, 77-89.
- Brodde, O., Beckeringh, J.J., & Michel, M.C. (1987). Human heart  $\beta$ -adrenoceptors: A fair comparison with lymphocyte  $\beta$ -adrenoceptors. *Trends in Pharmacological Science*, 8, 403-407.
- Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., et al. (2007). Decreased ACTH and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, 15, 1080-1087.
- Carroll, D., Lovallo, W.R., & Phillips, A.C. (2009). Are large physiological reactions to acute psychological stress always bad for health? *Social Personality and Psychology Compass*, 3, 725-743.
- Carroll, D., Phillips, A.C., & Lovallo, W.R. (2011). The behavioural and health corollaries of blunted physiological reactions to acute psychological stress: revising the reactivity

hypothesis, in: Wright, R.A., Gendolla, G.H.E. (Eds.). *Motivation Perspectives of Cardiovascular Response*. APA Press, Washington, DC, pp. 243-263.

Chida, Y., & Hamer, M. (2008). Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: A quantitative review of 30 years of investigation. *Psychological Bulletin*, *134*, 829-885.

Cohen, R.A., Grieses, S., Hoth, K.F., Paul, R.H., Sweet, L., Tate, D., et al. (2006). Early life stress and morphometry of the adult cingulate cortex and caudate nuclei. *Biological Psychiatry*, *15*, 975-982.

Danese, A., & McEwen, B.S. (2011). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, *106*, 29-39.

DePierro, J., D'Andrea, W., & Pole, N. (2013). Attention biases in females survivors of interpersonal violence: Relationship to trauma-related symptoms and physiology. *European Journal of Psychotraumatology*, *4*, 19135-19144.

de Rooij, S.R., Schene, A.H., Phillips, D.I., & Roseboom, T.J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology*, *35*, 866-877.

Evans, G.W. (2003). A multimethodological analysis of cumulative risk and allostatic load among rural children. *Developmental Psychology*, *39*, 924-933.

Evans, G.W., Kim, P., Ting, A.H., Tesher, H.B., & Shannis, D. (2007). Cumulative risk, maternal responsiveness, and allostatic load among young adolescents. *Developmental Psychology*, *43*, 341-351.

- Gallo, L.C., Jiménez, J.A., Shivpuri, de los Monteros, K.E., & Mills, P.J. (2011). Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. *Annals of Behavioral Medicine*, 41, 21-31.
- Ganzel, B.L., Morris, P.A., & Wethington, E. (2010). Allostasis and the human brain: Integrating models of stress from social and life sciences. *Psychological Review*, 117, 134-174.
- Gianaros, P.J., May, C.J., Siegle, G.J., & Jennings, J.R. (2005). Is there a functional neural correlate of individual differences in cardiovascular reactivity? *Psychosomatic Medicine*, 67, 31-39.
- Ginty, A.T., Gianaros, P.J., Derbyshire, S.W., Phillips, A.C., & Carroll, D. (2013). Blunted cardiac stress reactivity relates to neural hypoactivation. *Psychophysiology*, 50, 219-229.
- Gronwall, D.M.A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perception and Motor Skills*, 44, 367-373.
- Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M.M., Bonsall, R., et al. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*, 284, 592-597.
- Hines, E.A., & Brown, G.E. (1936). The cold pressor test for measuring the reactivity of the blood pressure: Data concerning 571 normal and hypertensive subjects. *American Heart Journal*, 11, 1-9.
- Jennings, J.R., Heim, A.F., Kuan, D.C., Gianaros, P.J., Muldoon, M.F., & Manuck, S.B. (2013). Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. *Stroke*, 44, 2480-2485.

- Jurca, R., Jackson, A.S., LaMonte, M.J., Morrow Jr., J.R., Blair, S.N., Wareham, N.J., et al. (2005). Assessing cardiorespiratory fitness without performing exercise testing. *American Journal of Preventative Medicine*, 29, 185-193.
- Juster, R.P., McEwen, B.S., & Lupien, S.J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, 35, 2-16.
- Karlamangla, A.S., Singer, B.H., & Seeman, T.E. (2006). Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging. *Psychosomatic Medicine*, 68, 500-507.
- Llabre, M.M., Ironson, G.H., Spitzer, S.B., Gellman, M.D., Weidler, D.J., & Schneiderman, N. (1988). How many blood pressure measurements are enough? An application of generalizability theory to the study of blood pressure reliability. *Psychophysiology*, 25, 97-106.
- Lovallo, W.R., Farag, N.H., Sorocco, K.H., Cohoon, A.J., & Vincent, A.S. (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma Family Health Patterns Project. *Biological Psychiatry*, 71, 344-349.
- Luecken, L.J. (2000). Parental caring and loss during childhood and adult cortisol responses to stress. *Psychology and Health*, 15, 841-851.
- MacMillan, H.L., Georgiades, K., Duku, E.K., Shea, A., Steiner, M., Niec, A., et al. (2009). Cortisol response to stress in female youths exposed to childhood maltreatment: Results of the Youth Mood Project. *Biological Psychiatry*, 66, 62-68.
- McEwen, B.S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, 1, 33-44.
- McEwen, B.S. (2000). Mood disorders and allostatic load. *Biological Psychiatry*, 54, 200-207

- Pappano, A.J. & Wier, W.G. (2013). *Cardiovascular Physiology*, tenth ed. Elsevier, Philadelphia.
- Phillips, A.C., Carroll, D., Ring, C., Sweeting, H., & West, P. (2005). Life events and acute cardiovascular reactions to mental stress: A cohort study. *Psychosomatic Medicine*, 67, 384-392.
- Phillips, A.C., Ginty, A.T., & Hughes, B., 2013. The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90, 1-7.
- Ring, C., Harrison, L.K., Winzer, A., Carroll, D., Drayson, M., & Kendall, M. (2000). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of alpha-adrenergic blockade. *Psychophysiology*, 37, 634-643.
- Ring, C., Burns, V.E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology*, 39, 585-590.
- Salomon, K., Bylsma, L.M., White, K.E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependent? A comparison of major depressive disorder, remitted depression and health controls. *International Journal of Psychophysiology*, 90, 50-57.
- Schwerdtfeger, A., & Rosenkaimer, A.K.. (2011). Depressive symptoms and attenuated physiological reactivity to laboratory stressors. *Biological Psychology*, 87, 430-438.
- Seeman, T.E., McEwen, B.S., Rowe, J.W., & Singer, B.H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences*, 98, 4770-4775.
- Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature*, 138, 32-32.

- Seplaki, C.L., Goldman, N., & Gleib, D., & Weinstein, M. (2005). A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Experimental Gerontology*, 40, 438-449.
- Steptoe, A., Hackett, R.A., Lazzarino, A.I., Bostock, S., La Marca, R., Carvalho, et al. (2014). Disruption of multisystem responses to stress in type 2 diabetes: Investigating the dynamics of allostatic load. *Proceedings of the National Academy of Sciences*, 111, 15693-15698.
- Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology, in: Fisher, S. & Reason, J. (Eds.), *Handbook of Life stress, Cognition, and Health* (629-649), Wiley, New York.
- Sterling, P. (2012). Allostasis: A model of predictive regulation. *Physiology and Behavior*, 106, 5-15.
- Taylor, S.E., Eisenberger, N.I., Saxbe, D., Lehman, B.J., & Lieberman, M.D. (2006). Neural responses to emotional stimuli are associated with childhood family stress. *Biological Psychiatry*, 60, 296-301.
- Westermann, J., Hubl, W., Kaiser, N., & Salewski, L. (2002). Simple, rapid and sensitive determination of epinephrine and norepinephrine in urine and plasma by non-competitive enzyme immunoassay, compared with HPLC method. *Clinical Laboratory*, 48, 61-71.
- World Health Organization. (2008). *Waist circumference and waist-hip ratio*. WHO Press, Geneva.
- Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67, 361-370.

---

## Chapter 5

---

### Cardiovascular Reactivity Patterns and Pathways to Hypertension: A Multivariate Cluster Analysis

This chapter is under review under the following citation:

Brindle, R.C., Ginty, A.T., Jones, A., Phillips, A.C., Roseboom, T.J., Carroll, D., Painter, R.C.,  
& de Rooij, S.R. Cardiovascular reactivity patterns and pathways to hypertension: A multivariate  
cluster analysis (under review).



### Abstract

Substantial evidence links exaggerated mental stress induced blood pressure reactivity to future hypertension but the results for heart rate reactivity are less clear. For this reason multivariate cluster analysis was carried out to examine the relationship between heart rate and blood pressure reactivity *patterns* and hypertension in a large prospective cohort (age range 55-60 years). Four clusters emerged with statistically different systolic and diastolic blood pressure and heart rate reactivity. Cluster 1 was characterised by a relatively robust blood pressure and heart rate response while the blood pressure and heart rate responses of cluster 2 were relatively modest. Cluster 3, characterised by relatively blunted cardiovascular stress reactivity overall and cluster 4, by exaggerated systolic and diastolic blood pressure reactivity only, showed an increased risk for hypertension at five year follow-up. Body mass index was revealed as a mediator of the increased hypertension risk seen in cluster 3. These results provide novel evidence of a potential pathway linking blunted reactivity to hypertension and support the already established direct link between exaggerated blood pressure reactivity and hypertension.

**Keywords:** Psychological Stress, Multivariate Cluster Analysis, Hypertension, Blood Pressure, Heart Rate, Body Mass Index

## Introduction

The association between exaggerated blood pressure (BP) reactions to acute psychological stress and hypertension is well established. Supporting evidence comes from several independent epidemiological datasets that have shown exaggerated systolic (SBP) and/or diastolic (DBP) BP reactivity to acute psychological stress to be linked with increased resting BP at 5- and 12-year follow-up (Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Markovitz, Racynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993) and to predict hypertension diagnosis at 4-, 5-, 13-, and 20-year follow-up (Borghi, Costa, Boschi, Mussi, & Ambrosioni, 1986; Carroll, Ginty, Painter, Roseboom, Phillips, & de Rooij, 2012; Everson, Kaplan, Golderberg, & Salonen, 1996; Matthews, Katholi, McCreath, Whooley, Williams, Zhu, et al., 2004; Ming, Adler, Kessler, Fogg, Matthews, Herd, et al., 2004). In addition, being “high risk” for developing hypertension based on parental history or having elevated resting BP are associated with exaggerated BP stress reactivity (al’Absi, Everson, & Lovallo, 1995; Sausen, Lovallo, & Wilson, 1991; Tuomisto, 1997). Importantly, a large meta-analysis also has also established a positive association between BP stress reactivity and hypertension (Chida & Steptoe, 2010).

In contrast, the relationship between stress-induced heart rate (HR) reactivity and hypertension remains equivocal. Relatively increased HR reactivity has been observed among individuals with parental history of hypertension (Hastrup, Light, & Obrist, 1982) and several small scale studies have reported a positive association between HR stress reactivity and increased 1-year ambulatory SBP (von Eiff, Gogolin, Jacobs, & Neus, 1985) and incident mild hypertension (Vrijkotte, van Doomen, & de Geus, 2000). However, a relationship between HR

reactivity and elevated BP has failed to emerge from epidemiological studies (Matthews et al., 2004; Ming et al., 2004) or meta-analysis (Chida & Steptoe, 2010). Further complexity is added by findings of negative associations between HR stress reactivity and hypertension risk factors such as obesity and the use of addicting substances such as alcohol and tobacco. In each case, the obese (Carroll, Phillips, & Der, 2008; Jones, McMillan, Jones, Kowalik, Steeden, Deanfield, et al., 2012; Phillips, Roseboom, Carroll, & de Rooij, 2012), smokers (Evans, Greaves-Lord, Euser, Tulen, Franken, & Huizink, 2012; Ginty, Hones, Carroll, Roseboom, Phillips, Painter, & de Rooij, 2014; Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; Phillips, Der, Hunt, & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994; Straneva, Hinderliter, Wells, Lenahan, & Girdler, 2000), and those dependent on alcohol (Panknin, Dickensheets, Nixon, & Lovallo, 2002) all exhibited blunted rather than exaggerated HR responses to acute psychological stress. Hence, it is possible that blunted HR reactivity may be implicated in the development of hypertension, although in an indirect fashion. Alternatively, it is also possible that obesity and behavioural dependencies may relate to both blunted HR stress reactivity and hypertension through unrelated pathways. Accordingly, it may be timely to take a more nuanced look at the relationship between cardiovascular stress reactivity and hypertension.

It has been suggested that focusing on a single cardiovascular reactivity variable may be limiting in scope, as evidence has shown that different patterns of end-organ responses have differential risk for disease (Manuck, 1994) and that focusing on multivariate patterns of stress reactivity may be more informative (Ring, Burns, & Carroll, 2002). With regard to BP and HR this makes sense given that these variables are not independent but, in fact, profoundly influence each other; increases in cardiac output increase BP and changes in BP influence HR via baroreceptor mechanisms (Klabunde, 2005). However, the wide interindividual variation in

normal patterns of HR and BP stress responses makes it challenging to define homogeneous groups of subjects. Cluster analysis offers a solution to this problem by assigning subjects from a single large cohort into clusters based on their statistical similarity in a set of variables defined *a priori*. This approach was undertaken with two goals: 1) to identify clusters of individuals who exhibit significantly different patterns of BP and HR stress reactivity, and 2) assess whether membership to a particular cluster conferred increased/decreased risk of hypertension diagnosis at 5-year follow-up.

## Methods

### Participants

Participants were from the Dutch Famine Birth Cohort, which comprised 2414 men and women born in Amsterdam during 1943-1947. The selection procedures and loss to follow-up have been described in detail elsewhere (Painter, Roseboom, Bossuyt, Osmond, Barker, & Bleker, 2005; Ravelli, van der Meulen, Michels, Osmond, Berker, Hales, et al., 1998). All 1423 members of the cohort who lived in the Netherlands on September 1, 2002 were invited to the clinic to undergo stress testing; 740 attended. The study was approved by the local Medical Ethics Committee, carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

### General Study Parameters

On arrival to the clinic, research nurses undertook anthropometric measurements and collected socioeconomic status (SES), education, and lifestyle data during a standardized interview. Height was measured twice using a fixed or portable stadiometer and weight was measured twice using Seca and portable Tefal scales. Body mass index (BMI) was calculated as

weight (kg)/height (m<sup>2</sup>) from the averages of the two height and weight measures. SES was defined according to the International Socio-Economic Index (ISEI)-92, which is based on the participant's or their partner's occupation, whichever has the higher status (Bakker & Seiben, 1992). Values on the ISEI-92 range from 16 (low status) to 87. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression (Zigmond & Snaith, 1983). Education level was measured on a 10-point scale (1 = primary education not completed, 10 = university completed). Alcohol consumption was recorded as the number of units consumed per week; one unit was defined as one glass of an alcoholic beverage. On the basis of self-report, participants were characterized as current, ex, or never smokers and also indicated whether or not they were currently taking anti-hypertensive medication. In the 2008-2009 follow-up interviews, participants reported whether or not they had ever received a diagnosis of hypertension from a physician. The mean (SD) temporal lag between this assessment and stress testing was 5.5 (0.60) years. Dropout between stress testing and hypertension diagnosis determination was 34.6%.

### **Psychological Stress Protocol**

Stress testing was carried out in the afternoon between the hours of 12:00-14:00 following a light lunch. A formal 20-minute baseline was followed by three psychological stress exposures: Stroop, mirror-tracing, and a speech task. Each task lasted 5 minutes and was separated by 6-minute between-task intervals; a 30-minute recovery phase followed the final stress task. The Stroop task was a computerised version of the classic Stroop colour-word conflict task. After instruction, participants were allowed to practise until they fully grasped the requirements of the task. During the task, a mistake or response over the time limit (5s) triggered a beep. The mirror-tracing task required participants to trace a star that could only be

seen in a mirror image (Lafayette Instruments Corp., Lafayette, IN, USA). Participants were allowed to practice one circuit. They were told to give priority to accuracy over speed and that most people could perform five circuits without diverging from the line. Every divergence from the line induced a short beep. Prior to the speech task, participants listened to a pre-recorded scenario in which they were told to imagine that they were falsely accused of pick-pocketing. Participants were instructed to give a 3-minute response to the accusation and were given 2 minutes to prepare a response. The responses were recorded on video and participants were told that the number of repetitions, the eloquence and the persuasiveness of their performance would be marked by a team of communication-experts and psychologists.

Continuous measures of BP and HR were made during the stress test protocol using a Finometer or Portapres Model-2 (Finapres Medical Systems, Amsterdam, the Netherlands). There was no difference in reactivity as a function of the two different measurement instruments. Four 5-minute blocks were defined as follows: baseline (final 5 minutes in baseline period), Stroop, mirror-tracing, and speech task (including preparation time). Mean SBP, DBP, and HR were calculated for each period.

### **Statistical Analysis**

Baseline SBP, DBP, and HR were the averages of measures recorded during the 5-minute period 15 minutes into the formal baseline. The three stress tasks were considered as a single stress period. Hence, SBP, DBP, and HR were averaged across this period to obtain stress phase values. Stress reactivity was defined as the difference between stress and baseline averages for SBP, DBP, and HR. A repeated-measures ANOVA, comparing baseline and stress task values, was carried out to confirm that the stress tasks perturbed cardiovascular activity. Partial eta squared is reported as the measure of effect size.

Cluster analysis was carried out using Ward's method in SPSS version 22 (IBM, Chicago, USA) (Ward, 1963). Raw reactivity scores for SBP, DBP, and HR were converted to z-scores to ensure that the cluster analysis was not influenced by the scale of individual variables. Ward's method begins with the same number of clusters as cases. In each subsequent step, cases are combined, forming one less cluster than before. For each cluster, a within-cluster sum of the squared Euclidean distances between individual scores and the mean of each variable in that cluster is calculated; the smaller the sum of squares, the greater the similarity between individuals in the cluster. A total sum of squares is then calculated across all clusters. Ward's method determines which two clusters will produce the smallest increase in the total sum of squares when they are merged. Eventually, the merger of two dissimilar clusters will cause a substantial increase in the total sum of squares. The state of the clusters just prior to this point is considered the "natural solution" to the clustering process. Follow-up one-way ANOVAs were carried out to determine whether clusters differed significantly on mean SBP, DBP, and HR reactivity. Between cluster differences in general study parameters were tested with one-way ANOVAs and Chi-squared analysis. Binary logistic regression was used to assess whether cluster membership in 2002-2004 predicted the development of hypertension at the 2008-2009 follow-up. Following tests of unadjusted models, models were adjusted for education, SES, BMI, sex, age, HADS-depression score, smoking status, and alcohol consumption, and self-reported anti-hypertension medication use at stress-testing to assess the influence of potential confounders.

## Results

### Study Population

Of the 740 cohort members, 721 completed the stress protocol. Cardiovascular data were unavailable for four participants. Incomplete cardiovascular data due to technical problems, and participant exclusion, due to significant arrhythmia, determined during cardiovascular data processing left an effective sample size of 671.

### Stress Reactivity

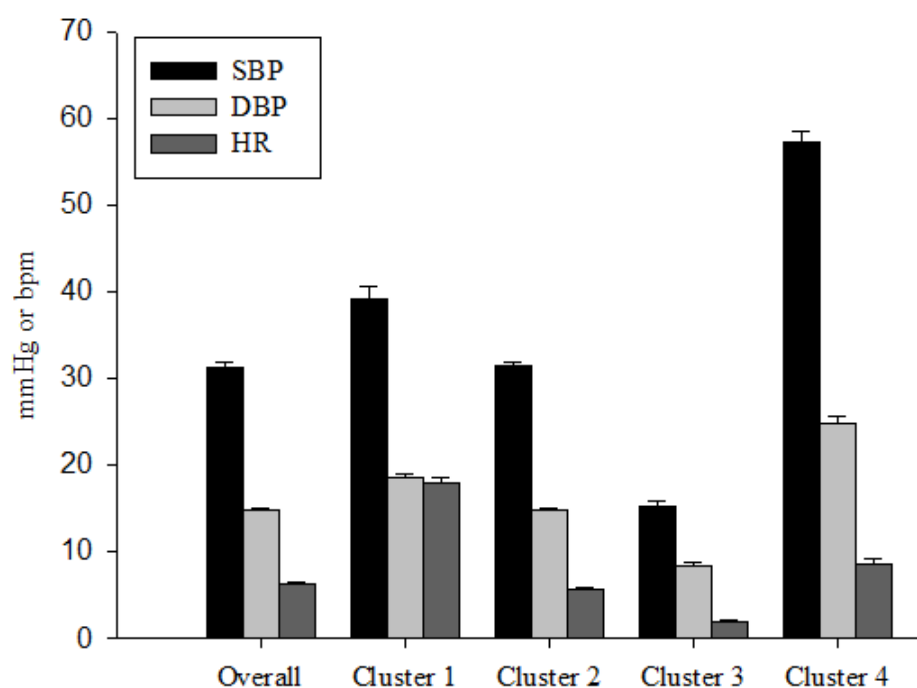
The stress task battery significantly perturbed SBP,  $F(1, 670) = 2378.91, p < .001, \eta^2 = .78$ , DBP,  $F(1, 670) = 583.97, p < .001, \eta^2 = .47$ , and HR,  $F(1, 670) = 168.19, p < .001, \eta^2 = .20$ ; in all cases cardiovascular activity increased in response to stress. The overall magnitude of the cardiovascular perturbations is shown in Figure 5.1.

### Cluster Analysis

Based on the criterion discussed for selecting the appropriate number of clusters, SBP, DBP, and HR reactions to the stress task battery were found to resolve to four distinct clusters. The means and standard errors for SBP, DBP, and HR reactivity for each cluster can be found in Figure 5.1. Results of independent one-way ANOVAs and *post-hoc* analyses showed that all the clusters were significantly different from each other on all cardiovascular variables ( $p < .001$ ). Whereas cluster 2 was characterised by reactivity values most in line with the sample average, the other clusters were different in several respects. Individuals in cluster 1 registered notably high HR responses while individuals in cluster 3 exhibited an overall blunted reactivity profile. Finally, individuals in cluster 4 mounted a large SBP and DBP response but only a modest HR response.



Analysis of general study parameters revealed several significant differences between the clusters (Table 5.1). Significant between-cluster differences ( $p < .05$ ) were found for education, SES, BMI, HADS-depression score, baseline SBP, and smoking status. There were no significant cluster differences in age, gender, alcohol consumption, dropout, and hypertension medication use at the time of stress testing.



**Figure 5.1** Cluster mean (SE) for systolic (SBP), diastolic (DBP), and heart rate (HR) reactivity for overall sample and clusters. All variables are significantly different across all clusters.

### Cluster Risk for Hypertension

Hypertension status was recorded for 439 participants in 2008-2009. There was no significant difference in HR or BP stress reactivity between those who participated in the follow-up and those who did not. Analysis of general 2002-2004 study parameters in the follow-up sample revealed significant differences between the clusters in education, SES, BMI, HADS-depression score, and smoking status; age, gender, and alcohol consumption did not significantly

vary across clusters (Table 5.2). In all, 211 (48%) reported having received a diagnosis of hypertension from a physician. Binary logistic regression confirmed a relationship between cluster membership and hypertension status, OR = 1.55, 95% CI, 1.25-1.94,  $p < .001$ . This relationship persisted when additionally adjusting for hypertension medication use at the time of stress testing, OR = 1.41, 95%CI, 1.08-1.86,  $p = .01$ . Sensitivity analyses with cluster 1 as a reference cluster showed that clusters 3, OR = 2.03, 95% CI, 1.00-4.13,  $p = .05$ , and 4, OR = 3.79, 95% CI, 1.72-8.33,  $p = .001$ , had significantly increased risk of hypertension whereas the relative risk for cluster 2, OR = 1.41, 95% CI, 0.71-2.80,  $p = .33$ , was non-significant (Figure 5.2).

Analyses were undertaken comparing clusters 1 and 4 only to probe contributing factors to the increased hypertension risk. When general study parameters (education, SES, BMI, HADS-depression score, and smoking status) were entered into the model at step 1, and cluster membership at step 2, the significantly increased risk of hypertension for those in cluster 4 persisted, OR = 3.20, 95% CI, 1.30-7.89,  $p = .01$ . When the same general study parameters were entered in the model comparing clusters 1 and 3 only, the relative risk of hypertension was abolished, OR = 1.66, 95% CI, 0.71-3.91,  $p = .25$ . Inspection of the general study parameters revealed that BMI was the only significant predictor of hypertension risk in this model. When only BMI was entered at step 1 and cluster membership at step 2, cluster membership was not significantly related to hypertension risk, OR = 1.53, 95% CI, 0.73-3.23,  $p = .26$ .

**Table 5.1** General study parameters of clusters 2002-2004 wave (N = 671)

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	( N = 66)	( N = 305)	( N = 198)	( N = 102)
Education	5.3 (2.4) †	4.6 (2.2)	4.1 (2.1)*	4.8 (2.1)
SES	56.3 (11.7)# †	49.7 (14.1)*	47.3 (14.5)*	50.7 (13.4)
BMI (kg/m <sup>2</sup> )	27.0 (3.7) †	28.6 (4.6)	29.3 (5.1)*	28.7 (4.3)
HADS-Depression	2.3(2.3) †	3.1 (2.9)	3.8 (3.3)* ‡	2.8 (2.7) †
Smoking (% smokers) <sup>a</sup>	6.1	19.3	39.1	16.7
Hypertension Medication Use <sup>b</sup>	19.7%	20.0%	25.8%	29.4%
Sex (% female)	50.0%	48.5%	59.1%	50.9%
Age	58.4 (0.9)	58.2 (0.9)	58.2 (1.0)	58.3 (0.9)
Alcohol	9.0 (9.8)	10.2 (13.8)	8.7 (12.7)	11.2 (17.4)
Dropout <sup>c</sup>	33.3%	37.1%	34.9%	27.5%
Baseline SBP	135.1 (23.0) †‡	127.9 (19.6)	127.2 (20.5)*	126.0 (22.0)*
Baseline DBP	70.3 (11.5)	66.1 (11.3)	66.9 (12.0)	65.9 (14.6)
Baseline HR	74.6 (9.6)	73.0 (10.3)	74.9 (10.8)	75.0 (11.3)

Note: Values are reported as Mean (SD). \*different from Cluster 1, #different from Cluster 2, †different from Cluster 3, ‡different from Cluster 4

<sup>a</sup> denotes significant Chi-Square ( $p < .05$ )

<sup>b</sup> denotes those reporting medication usage

<sup>c</sup> denote percent not returning in 2008-2009

## Discussion

Using multivariate cluster analysis, four homogenous clusters of individuals with statistically different SBP, DBP, and HR stress reactivity were identified. Further, cluster membership was found to predict increased risk of hypertension at 5 year follow-up, a result that

withstood adjustment for hypertension medication use at time of stress testing. Specifically, two clusters, one characterised by a relatively blunted reactivity profile across all cardiovascular parameters, and the other by exaggerated SBP and DBP reactivity, were found to confer increased risk for subsequent hypertension. Upon further examination, the increased risk for the blunted cluster was mediated by BMI whereas the risk associated with the exaggerated blood pressure cluster withstood adjustment for various behavioural and socio-demographic variables. This finding provides critical support for the already established link between exaggerated BP reactivity and hypertension (Chida & Steptoe, 2010) and uniquely demonstrates a potential pathway by which blunted stress reactivity may be associated to hypertension risk.

That the blunted cluster registered the highest BMI was not surprising since other studies have demonstrated a link between measures of adiposity and attenuated HR reactions to stress (Carroll et al., 2008; Jones et al., 2012; Phillips et al., 2012). Also, the finding that increased BMI was associated with increased risk of hypertension diagnosis underscores the accepted status of obesity as a hypertension risk factor (El-Atat, Aneja, Mcfarlane, & Sowers, 2003). However, the novelty lies in the increased risk of hypertension among blunted responders and the role BMI may play in the increased risk. When BMI was controlled for in the logistical regression, the previously significant increase in hypertension risk for blunted responders was abolished, suggesting that BMI mediates any increase in the risk for hypertension associated with blunted stress reactions. This finding not only supports the emerging evidence contending that blunted cardiovascular reactivity is disadvantageous for health (Phillips, Ginty, & Hughes, 2013) but, to the authors' knowledge, this is the first identification of a potential pathway linking blunted cardiovascular reactivity to hypertension. Alternatively, increased BMI may lead to both blunted cardiovascular reactivity and hypertension. However, we have previously shown in this

cohort (Phillips et al., 2012) as well as in a different cohort (Carroll et al., 2008) that blunted HR stress reactivity is associated with an increased risk of becoming obese during follow-up, suggesting that attenuated HR reactions may indeed precede the development of obesity.

**Table 5.2** General study parameters of clusters 2008-2009 wave (N = 439)

	Cluster 1 ( N = 44)	Cluster 2 ( N = 192)	Cluster 3 ( N = 129)	Cluster 4 ( N = 74)
Education	5.4 (2.2) †	4.7 (2.2) †	3.9 (1.9)*# ‡	4.8 (2.0) †
ISEI-92	56.1 (10.2) †	51.1 (14.0)	47.1 (14.0)*	50.9 (13.4)
BMI (kg/m <sup>2</sup> )	26.8 (3.3) †	28.7 (4.8)	29.2 (5.2)*	28.7 (4.1)
HADS-Depression	2.1 (1.9) †	3.0 (2.9)	3.8 (3.4)*	2.5 (2.7) †
Smoking (% smokers) <sup>a</sup>	4.6	18.8	38.3	17.6
Sex (% female)	52.3%	49.5%	58.1%	51.4%
Age	58.4 (1.0)	58.2 (0.9)	58.2 (0.9)	58.3 (0.9)
Alcohol	8.3 (7.7)	10.0 (15.3)	9.5 (14.1)	10.6 (17.4)
Baseline SBP	133.9 (21.2)	127.7 (19.0)	126.5 (20.1)	127.6 (20.2)
Baseline DBP	69.9 (10.6)	66.7 (11.3)	66.8 (12.5)	66.9 (12.2)
Baseline HR	74.3 (8.7)	73.1 (9.7)	74.3 (10.6)	74.8 (11.3)
Hypertension Medication Use <sup>ab</sup>	15.9%	19.3%	29.5%	31.1%
Physician Diagnosed Hypertension <sup>ac</sup>	34.1%	42.0%	51.2%	66.2%

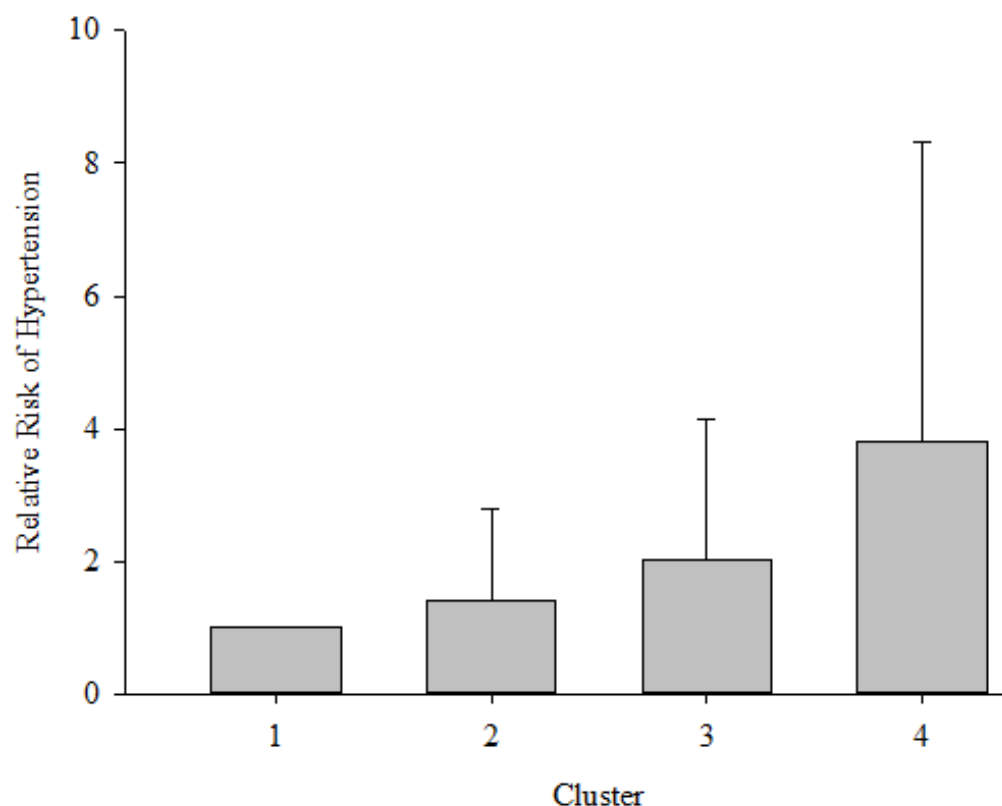
Note: Values are reported as Mean (SD). Differences denote  $p < .05$  \*different from Cluster 1, #different from Cluster 2, †different from Cluster 3, ‡different from Cluster 4

<sup>a</sup> denotes significant Chi-Square ( $p < .05$ )

<sup>b</sup> denotes those reporting medication usage

<sup>c</sup> denotes percent with physician diagnosis of hypertension

Individuals with exaggerated SBP and DBP reactivity had the greatest risk of hypertension. Moreover, this relationship withstood adjustment for several anthropometric and socio-demographic factors. Although mediation by some other unanalysed factor is possible, it is unlikely, as previous studies have shown the association between exaggerated BP stress reactivity and hypertension withstood statistical adjustment for other variables such as age, gender, and baseline BP (Matthews et al., 2004). What is more likely is that repeated large magnitude surges in BP, induced by mental stress, engage local BP regulatory mechanisms and lead over time to upward structural resetting of the peripheral vasculature (Folkow, 1990; Obrist, 1981). Specifically, elevated resting BP results from a positive feedback cycle in which frequent acute surges in BP promote vascular hypertrophy which decreases lumen diameter and increases vessel stiffness, in turn, amplifying future BP fluctuations. Evidence of such processes lies in the reported association of exaggerated BP reactivity with increased carotid intima-media thickness in children (Roemmich, Lobarinas, Joseph, Archer III, & Dorn, 2009), adolescents (Lambiase, Dorn, & Roemmich, 2012; Roemmich, Feda, Seelbinder, Lambiase, Kala, & Dorn, 2011), and adults (Jennings, Kamarck, Everson-Rose, Kaplan, Manuck, & Salonen, 2004; Kamarck, Everson, Kaplan, Manuck, Jennings, Salonen, et al., 1997), and with increased vascular stiffness (Lipman, Grossman, Bridges, Hamner, & Taylor, 2002) as well as the propensity for BP reactivity to increase with age (Uchino, Birmingham, & Berg, 2010). It is likely that such physiological processes underlie the development of hypertension in those displaying exaggerated BP responses to mental stress (Borghi et al., 1986; Carroll et al., 2012; Matthews et al., 2004; Ming et al., 2004).



**Figure 5.2** Relative risk of hypertension by cluster membership.

An unexpected finding was that the cluster of individuals carrying the least risk of hypertension did not have reactivity values located at the mean but instead had the largest HR reaction and second largest BP reaction. One possible interpretation, focusing specifically on BP, researchers have argued that, between individuals, similar BP reactions could result from significantly different changes in cardiac output and total peripheral resistance; individuals mounting large increases in cardiac output were classified as *cardiac reactors* and individuals whose BP rose primarily as a result of vasoconstriction fell into the *vascular reactor* category. Moreover, it has been suggested that not only is the magnitude of reactivity significant in the context of disease but that different underlying mechanisms may carry differential disease risk (Folkow, 1990). The present results accord with this framework as the individuals in the highest

risk cluster registered the highest BP reaction despite only a modest increase in HR, whereas the clusters carrying the least amount of risk mounted the second largest BP response but also recorded a HR reaction almost 3x larger than the sample mean. With such differences in cardiac activity between the clusters, it may be that individuals in the cluster with the least risk increased BP by augmenting cardiac output while the high-risk cluster increased BP primarily through vasoconstriction. Hence, these data suggest that not only is the magnitude with which an individual responds to mental stress significant in the context of disease, but also underlying hemodynamic mechanisms carry differential risk and should be considered.

The current study is not without limitations. First, it could be argued that an element of subjectivity exists in choosing the final number of reactivity profile clusters. This is an issue with all forms of cluster analysis. We accepted four clusters for two reasons: a substantial increase in total sum of squares was observed during the iteration decreasing the sample from five clusters to four, and outputs with five or three clusters either had very small clusters with extreme individuals or large, heterogeneous clusters, respectively. Second, the effect sizes in the current study are small. However, they are consistent in magnitude with those observed in other studies (Ming et al., 2004), and this is not unexpected as hypertension is multiply determined, having etiological roots in the vascular, autonomic, genetic, and metabolic domains (Oparil, Zaman, & Calhoun, 2003). Third, although we have statistically modelled the data such that BMI mediated the hypertension risk for the Cluster 3, the possibility does exist that BMI may independently relate to blunted cardiovascular reactivity and hypertension. Finally, the possibility exists that famine exposure *in utero* could influence the present results. However, chi square analysis revealed that famine exposure did not differ across the clusters ( $p = .25$ ) nor did it relate to hypertension diagnosis ( $p = .17$ ).



In conclusion, using multivariate cluster analysis, four distinct HR and BP reactions patterns were identified that differed in relative risk of hypertension diagnosis at 5 year follow-up. A profile characterised by exaggerated BP and relatively modest HR changes conferred the greatest risk whereas a relatively blunted reaction pattern also carried risk, but through its association with BMI. These results provide novel evidence for a potential pathway linking blunted stress reactivity to hypertension, as well as offering additional support that exaggerated BP reactivity is implicated in hypertension.

## References

- al'Absi, M., Everson, S.A., Lovallo, W.R. (1995). Hypertension risk factors and cardiovascular reactivity to mental stress in young men. *International Journal of Psychophysiology*, 20, 155-160.
- Bakker, B., & Seiben, I. (1992). Maten voor prestige, social-economische status en sociale klasse voor de standard beroepenclassificatie. *Sociale Wetenschappen*, 40, 1-22.
- Borghi, C., Costa, F.V., Boschi, S., Mussi, A., & Ambrosioni, E. (1986). Predictors of stable hypertension in young borderline subjects: a five-year follow-up study. *Journal of Cardiovascular Pharmacology*, 8(suppl. 5), S138-S141.
- Carroll, D., Smith, G.D., Sheffield, D., Shipley, M.J., & Marmot, M.G. (1995). Pressor reactions to psychological stress and prediction of future blood pressure: Data from the Whitehall II study. *British Medical Journal*, 310, 771-776.
- Carroll, D., Ring, C., Hunt, K., Ford, G., & Macintyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: effects of sex, age, and socioeconomic position. *Psychosomatic Medicine*, 65, 1058-1064.
- Carroll, D., Phillips, A.C., & Der, G. (2008). Body mass index, abdominal adiposity, obesity, and cardiovascular reactions to psychological stress in a large community sample. *Psychosomatic Medicine*, 70, 653-660.
- Carroll, D., Phillips, A.C., Der, G., Hunt, K., & Benzeval, M. (2011). Blood pressure reactions to acute mental stress and future blood pressure status: data from the 12-year follow-up of the West of Scotland study. *Psychosomatic Medicine*, 73, 737-742.
- Carroll, D., Ginty, A.T., Painter, R.C., Roseboom, T.J., Phillips, A.C., & de Rooij, S.R. (2012). Systolic blood pressure reactions to acute stress are associated with future hypertension

- status in the Dutch Famine Birth Cohort study. *International Journal of Psychophysiology*, 85, 270-273.
- Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension*, 55, 1026-1032.
- El-Atat, F., Aneja, A., Mcfarlane, S., & Sowers, J. (2003). Obesity and hypertension. *Endocrinology and Metabolism Clinics of North America*, 32, 823-854.
- Evans, B.E., Greaves-Lord, K., Euser, A.S., Tulen, J.H.M., Franken, I.H.A., & Huizink, A.C. (2012). Alcohol and tobacco use and heart rate reactivity to a psychosocial stressor in an adolescent population. *Drug and Alcohol Dependence*, 126, 296-303.
- Everson, S.A., Kaplan, G.A., Goldberg, D.E., & Salonen, J.T. (1996). Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. *Hypertension*, 27, 1059-1064.
- Folkow B. (1990). "Structural factors" in primary and secondary hypertension. *Hypertension*, 16, 89-101.
- Ginty, A.T., Jones, A., Carroll, D., Roseboom, T.J., Phillips, A.C., Painter, R., & de Rooij, S.R. (2014). Neuroendocrine and cardiovascular reactions to acute psychological stress are attenuated in smokers. *Psychoneuroendocrinology*, 48, 87-97.
- Girdler, S.S., Jamner, L.D., Jarvik, M., Soles, R.J., & Shapiro, D. (1997). Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. *Psychosomatic Medicine*, 59, 294-306.
- Hastrup, J.L., Light, K.C., Obrist, P.A. (1982). Parental hypertension and cardiovascular responses to stress in healthy young adults. *Psychophysiology*, 19, 615-622.

- Jennings, J.R., Kamarck, T.W., Everson-Rose, S.A., Kaplan, G.A., Manuck, S.B., & Salonen, J.T. (2004). Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation*, *110*, 2198-2203.
- Jones, A., McMillan, M.R., Jones, R.W., Kowalik, G.T., Steeden, J.A., Deanfield, J.E., et al. (2012). Adiposity is associated with blunted cardiovascular neuroendocrine and cognitive responses to acute mental stress. *PLoS ONE*, *7*, e39143.
- Kamarck, T.W., Everson, S.A., Kaplan, G.A., Manuck, S.B., Jennings, J.R., Salonen, R., et al. (1997). Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation*, *96*, 3842-3848.
- Klabunde, R.E. (2005). *Cardiovascular Physiology Concepts*. New York: Lippincott Williams & Wilkins.
- Lambiase, M.J., Dorn, J., Roemmich, J.N. (2012). Metabolic and cardiovascular adjustments during psychological stress and carotid artery intima-media thickness in youth. *Physiology and Behavior*, *105*, 1140-1147.
- Lipman, R.D., Grossman, P., Bridges, S.E., Hamner, J.W., & Taylor, J.A. Mental stress responses, arterial stiffness, and baroreflex sensitivity in healthy aging. *Journal of Gerontology A Biological Sciences*, *57*, B279-B284.
- Manuck, S.B. (1994). Cardiovascular reactivity in cardiovascular disease: “once more unto the breach.” *International Journal of Behavioral Medicine*, *1*, 4-31.

- Markovitz, J.H., Raczynski, J.M., Wallace, D., Chettur, V., & Chesney, M.A. (1998). Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: the CARDIA study. *Psychosomatic Medicine*, 60, 186-191.
- Matthews, K.A., Woodall, K.L., & Allen, M.T. (1993). Cardiovascular reactivity to stress predicts future blood pressure status. *Hypertension*, 22, 479-485.
- Matthews, K.A., Katholi, C.R., McCreath, H., Whooley, M.A., Williams, D.R., Zhu, S., & Markovitz, J.H. (2004). Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation*, 110, 74-78.
- Ming, E.E., Adler, G.K., Kessler, R.C., Fogg, L.F., Matthews, K.A., Herd, A.J., & Rose, R.M. (2004). Cardiovascular reactivity to work stress predicts subsequent onset of hypertension: the Air Traffic Controller Health Change study. *Psychosomatic Medicine*, 66, 459-465.
- Obrist P. (1981). Cardiovascular Psychophysiology: a perspective. New York: Plenum Press.
- Oparil, S., Zaman, M.A., & Calhoun, D.A. (2003). Pathogenesis of hypertension. *Annals of Internal Medicine*, 139, 761-776.
- Painter, R.C., Roseboom, T.J., Bossuyt, P.M., Osmond, C., Barker, D.J., & Bleker, O.P. (2005). Adult mortality at age 57 after prenatal exposure to the Dutch famine. *European Journal of Epidemiology*, 20, 673-679.
- Panknin, T.L., Dickensheets, S.L., Nixon, S.J., & Lovallo, W.R. (2002). Attenuated heart rate responses to public speaking in individuals with alcohol dependence. *Alcoholism Clinical and Experimental Research*, 26, 841-847.

- Phillips, A.C., Der, G., Hunt, K., & Carroll, D. (2009). Haemodynamic reactions to acute psychological stress and smoking status in a large community sample. *International Journal of Psychophysiology*, 73, 273-278.
- Phillips, A.C., Roseboom, T.J., Carroll, D., & de Rooij, S.R. (2012). Cardiovascular and cortisol reactions to acute psychological stress and adiposity: Cross-sectional and prospective associations in the Dutch Famine Birth Cohort Study. *Psychosomatic Medicine*, 74, 699-710.
- Phillips, A.C., Ginty, A.C., & Hughes, B.M. (2013). The other side of the coin: blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90, 1-7.
- Ravelli, A.C.J., van der Meulen, J.H.P., Michels, R.P.J., Osmond, C., Berker, D.J.P., Hales, C.N., & Bleker, O.P. (1998). Glucose tolerance in adults after prenatal exposure to famine. *Lancet*, 351, 173-177.
- Ring, C., Burns, V.E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology*, 39, 585-590.
- Roemmich, J.N., Lobarinas, C.L., Joseph, P.N., Lambiase, M.J., Archer III, F.D., & Dorn J. (2009). Cardiovascular reactivity to psychological stress and carotid intima-media thickness in children. *Psychophysiology*, 46, 293-299.
- Roemmich, J., Feda, D.M., Seelbinder, A.M., Lambiase, M.J., Kala, G.K., & Dorn, J. (2011). Stress-induced cardiovascular reactivity and atherogenesis in adolescents. *Atherosclerosis*, 215, 465-470.

- Roy, M.P., Steptoe, A., & Kirschbaum, C. (1994). Association between smoking status and cardiovascular and cortisol stress responsivity in health young men. *International Journal of Behavioral Medicine*, 1, 264-283.
- Sausen, K.P., Lovallo, W.R., & Wilson, M.F. (1991). Heart rate reactivity, behavior pattern, and parental hypertension as predictors of cardiovascular activity during cognitive challenge. *Psychophysiology*, 28, 639-647.
- Straneva, P., Hinderliter, A., Wells, E., Lenahan, H., & Girdler, S. (2000). Smoking, oral contraceptives, and cardiovascular reactivity to stress. *Obstetrics and Gynecology*, 95, 78-83.
- Tuomisto, M. (1997). Intra-arterial blood pressure and heart rate reactivity to behavioral stress in normotensive, borderline, and mild hypertensive men. *Health Psychology*, 16, 554-565.
- Uchino, B.N., Birmingham, W., & Berg, C.A. (2010). Are older adults less or more physiologically reactivity? a meta-analysis of age-related differences in cardiovascular reactivity to laboratory tasks. *Journal of Gerontology Psychological Sciences*, 65B, 154-162.
- von Eiff, A.W., Gogolin, E., Jacobs, U., & Neus, H. (1985). Heart rate reactivity under mental stress as a predictor of blood pressure development in children. *Journal of Hypertension*, 3, S89-S91.
- Vrijkotte, T.G.M., van Doornen, L.J.P., de Geus, E.J.C. (2000). Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. *Hypertension*, 35, 880-886.
- Ward, J.H. (1963). Hierarchical grouping to optimise an objective function. *Journal of the American Statistics Association*, 58, 236-244.

Zigmond, A.S., & Snaith, R.P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, 67, 361-370.



---

## **Chapter 6**

---

General Discussion

The overall aim of this thesis was to better understand the substantial inter-individual variability observed in HR and BP reactivity to acute psychological stress. This aim was achieved by using a range of methods that included meta-analysis, laboratory studies, and a secondary analysis of epidemiological data.

## **Summary of Results**

### **The Autonomic Basis of Cardiovascular Stress Reactivity**

The aim of Chapter 2 was to summarise the existing literature concerning the autonomic nervous system response to acute psychological stress to better establish the autonomic basis of cardiovascular stress reactivity. One hundred and eighty-six studies of sufficient quality were identified. Four independent mixed-effects meta-analyses were undertaken; two concerned peripheral markers of sympathetic or parasympathetic activity and two concerned pharmacological blockade of the sympathetic or parasympathetic nervous system, all within the acute psychological stress paradigm. Aggregate effects showed that, on the whole, both the sympathetic and parasympathetic nervous systems are perturbed by acute psychological stress to much the same degree in terms of effect size and both sympathetic activation and parasympathetic withdrawal contribute to cardiovascular stress reactivity. This same result emerged when analyses were confined to studies measuring both autonomic branches simultaneously, and suggested that task selection bias was not an influencing factor. Analysis of blockade studies revealed that beta-adrenergic sympathetic blockade attenuated cardiovascular reactivity; no analysis was carried out on parasympathetic blockade studies as too few were available, making this a clear focus for future research. Subgroup analyses revealed that sympathetic and parasympathetic aggregate effects significantly varied across age, sex, and

stress task: speech tasks were most provocative, sympathetic activation decreased with age and was greater in men than women.

### **Cardiovascular Stress Reactivity and HR Complexity**

Chapter 3 explored the relationship between correlation dimension (D2), a measure of HR complexity, and HR reactivity to acute psychological stress across 2 studies. It aimed to determine if correlation dimension 1) was related to HR reactivity, 2) related to HR reactivity independent of changes in sympathetic and parasympathetic activity, indexed by pre-ejection period (PEP), and root mean square of successive difference (RMSSD), respectively, and 3) was influenced by changes in respiration. In Study 1 (N = 25) D2, HR, RMSSD, and respiration rate were measured in response to an acute mental arithmetic stressor. HR and respiration rate significantly increased, and D2 and RMSSD significantly decreased, in response to stress. Stress-induced changes in D2 were significantly related to HR; a result that withstood adjustment for RMSSD and respiration rate reactivity. In Study 2 (N = 162) HR, PEP, and RMSSD were measured in response to acute mental arithmetic stress. To account for the interaction between the parasympathetic and sympathetic nervous systems, an interaction term was computed. In response to the stress task, HR increased and PEP and RMSSD decreased. In a regression model entering reactivity values for D2, RMSSD, PEP and the interaction term, as predictors of HR reactivity, D2, RMSSD, and PEP all emerged as independent predictors.

### **Cardiovascular Stress Reactivity and Allostatic Load**

Chapter 4 focussed on the relationship between physiological allostatic load, measured at rest, and cardiovascular reactivity to mental arithmetic and cold pressor stress tasks in a healthy sample. An allostatic load index was computed from nine biomarkers in the cardiovascular (resting SBP, DBP, HR, and estimated cardiorespiratory fitness), neuroendocrine (resting

norepinephrine, epinephrine and  $\beta_2$ -adrenergic cell receptor density) and anthropometric (waist-hip ratio and BMI) domains, and SBP, DBP, and HR reactivity was recorded. Allostatic load was significantly negatively related to HR reactivity, but only to mental arithmetic, such that higher allostatic load was related to lower HR reactivity. Given that task engagement and performance have been suggested to relate to reactivity (Phillips, Ginty, & Hughes, 2013), and depressive symptomatology has been linked to both reactivity and allostatic load (Carroll, Phillips, Hunt, & Der, 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; McEwen, 2000, 2003; Phillips, Hunt, Der, Carroll, 2010; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; Salomon, Bylsma, White, Panaite, & Rottenberg, 2013; York, Hassan, Li, Fillingim, & Sheps, 2007), this analysis was revisited adjusting for self-reported task engagement, task performance, and self-reported depressive symptomatology; allostatic load still significantly negatively related to HR reactivity. No relationships were observed between allostatic load and BP reactivity to either task or HR reactivity to the cold pressor task.

### **Multivariate Individual Differences in Cardiovascular Reactivity**

Chapter 5 aimed to explore, using a large epidemiological dataset, multivariate individual differences in patterns of cardiovascular reactivity to acute psychological stress and their prospective association with physician-diagnosed hypertension. Multivariate cluster analysis was carried out on individuals from the Dutch Famine Birth Cohort dataset (N =671) which measured SBP, DBP, and HR reactions to a battery of stress tasks. The sample resolved to four homogenous clusters: Cluster 1 was characterised by a relatively robust SBP, DBP, and HR responses; Cluster 2 registered modest increases in all three parameters; Cluster 3 was relatively non-responsive and exhibited blunted SBP, DBP, and HR responses; and Cluster 4 mounted large SBP and DBP responses but only a modest HR increase. Prospective analysis was then

undertaken to examine if cluster membership predicted hypertension diagnosis in 439 participants at five year follow-up. Clusters 3 and 4 conferred significantly increased risk for hypertension five years later. For Cluster 3, BMI was found to abolish the increased risk when inserted as a covariate. The increased risk for hypertension characteristic of those with a Cluster 4 response pattern survived statistical adjustment for a host of socio-demographic and anthropometric variables, as well as for anti-hypertensive medication use at the time of stress testing.

## **Implications**

The reactivity hypothesis (Obrist, 1981) has been the foundation of over 30 years of research examining the physiological response to stress and how stress impacts health. Exaggerated cardiovascular responses to acute psychological stress have been linked to increased risk of cardiovascular diseases (Chida & Steptoe, 2010) and recently, blunted reactions have also been found to relate to adverse health and behavioural outcomes (Phillips et al., 2013). However, HR and BP are multiply determined cardiovascular endpoints that are controlled by numerous upstream cardioregulatory processes (e.g., autonomics, hemodynamics, local tissue processes, central command, etc., (Kasprowicz, Manuck, Malkoff, & Krantz, 1990; Sherwood, Dolan, & Light, 1990), and to ignore them is to ignore a large amount of potentially insightful inter-individual variability (Lovallo, 2005; Lovallo & Gerin, 2003; Manuck, 1994). This perspective gave rise to the key aim of this thesis, that it would be informative to focus research effort on examining the individual differences in physiology that contribute to the observed inter-individual variability in HR and BP stress reactivity. This thesis is timely in that it resonates with others who have maintained a similar contention, emphasising the elucidation of “pathways to the stress response” that capture individual differences in brain activation, psychological

processing, and cardiovascular reactivity (Critchley et al., 2003; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Gianaros, & Sheu, 2009; Gianaros, & Wager, 2015; Lovallo, 2005; Lovallo & Gerin, 2005; Wager, Waugh, Linquist, Noll, Fredrickson, & Talyor, 2009a; Wager, van Ast, Hughes, Davidson, Lindquist, & Ochsner, 2009b), and is novel in that it focuses on peripheral sources of inter-individual differences in cardiovascular stress reactivity. Specifically, this thesis identifies three general areas in which individual differences have the potential to impact on cardiovascular stress responses: peripheral physiology, the context of stress, and person factors.

### **Peripheral Physiology**

Lovallo (2005) proposed a three level stress response model in which Level I included the limbic system and prefrontal cortex and was responsible for mediating the psychological stress response, Level II included the hypothalamus and brainstem regions that translate top-down inputs into bodily responses, the area between Levels II and III accounted for the autonomic and endocrine outputs to the periphery, and Level III incorporated the structure and function of peripheral tissues. Results from this thesis provide support for this model as individual differences were documented in the area between Level II and III (Chapters 2 and 3), in Level III (Chapter 4), and in the resultant cardiovascular response (Chapter 5).

The role of the autonomic nervous system in cardiovascular reactions to acute psychological stress has been appreciated for a long time, evidenced by its central role in early models of cardiac reactivity (Berntson, Cacioppo, & Quigley, 1991; Bernston, Cacioppo, & Quigley, 1993; Berntson, Cacioppo, Binkley, Uchino, Quigley, & Fieldstone, 1994; Stemmler, Grossman, Schmid, Foerster, 1991). Chapter 2 provides supportive evidence for these models as it implicated both the sympathetic and parasympathetic nervous system branches in the

cardiovascular response, especially the HR response. HR is not only controlled by the autonomic nervous system, but rather is subject to other influences (e.g., haemodynamic, humoral) that potentially can interact and form linear and non-linear cardioregulatory loops (Hagerman, Berglund, Lorin, Nowak, & Sylvén, 1996; Lipsitz, 1995; Wagner, & Persson, 1998). Chapter 3 showed that individual differences in correlation dimension, a HR complexity measure that is designed to quantify the number of functional inputs responsible for a given time series (Table 1.1), was related to HR reactivity across two studies. More importantly, it should be noted that this relationship was independent of respiration, sympathetic, parasympathetic, and sympathetic-parasympathetic interaction effects, suggesting that other individual differences in cardiac regulation, not captured by traditional autonomic markers exist that potentially impact HR reactivity.

The stress response does not occur in a vacuum but rather against the backdrop of basal physiological conditions. Thus, if individual differences exist at baseline then it is possible that individual differences in reactivity will be observed (Jennings, Kamarck, Stewart, Eddy, & Jonson, 1992). Results from Chapter 4 resonate with this notion as resting allostatic load, which included resting measures from cardiovascular, anthropometric, and neuroendocrine domains related to HR reactivity such that higher allostatic load predicted lower reactivity. Finally, in Chapter 5 a large amount of individual difference was observed in the multivariate pattern of reactivity.

### **The Context of Stress**

It has been long recognized that stress tasks *per se* and their characteristics (e.g., duration, social evaluation) are a source of individual difference (Dickerson, & Kemeny, 2004; Kamarck & Lovallo, 2003; Krantz & Manuck, 1984). Tasks have been characterised as physical vs.

psychological (Sherwood, Allen, Obrist, & Langer, 1986), passive vs. active (Isowa, Ohira, & Murashima, 2004; Sherwood et al., 1990), alpha-adrenergic vs. beta-adrenergic (Willemsen, Ring, Carroll, Evans, Clow, & Hucklebridge, 1998), and social vs. non-social (Ewart & Kolodner, 1993; Prkachin, Mills, Zwaal, & Husted, 2001), of which, along these demarcations lie differences in cardiovascular reactions, underlying physiological mechanisms, and the ability to predict disease outcomes (Fredrickson & Matthews, 1990). Results of this thesis support this notion, as in Chapters 2 and 4 individual differences with respect to stress tasks were observed. Subgroup analyses of the meta-analyses (Chapter 2) revealed that speech tasks provoked greater BP responses compared to the other tasks (mental arithmetic, reaction time, and Stroop), reaction time tasks elicited a stronger sympathetic response than mental arithmetic stressors, and the Stroop prompted a notably larger parasympathetic withdrawal compared to speech tasks. In Chapter 4 two stress tasks were employed, mental arithmetic and cold pressor; allostatic load only related to reactivity to the mental arithmetic, which is a known active stressor with social evaluation, while the cold pressor is passive with minimal social evaluation (Schwerdtfeger & Rosenkaimer, 2011; Sherwood et al., 1990). Moreover, reactivity values from the two tasks and self-report ratings of task stressfulness (analysis not in Chapter 4) were uncorrelated across the sample suggesting that individuals react differently to different tasks, both physically and psychologically. Taken together, these findings underscore the need to consider the nature of stress tasks in experimental design as a source of individual difference.

### **Person Factors**

Results from several of the chapters in this thesis were also consistent with the notion that individual differences in cardiovascular stress reactivity are also affected by non-physiological factors unique to each participant (e.g., sex, age, etc., Herd, 1991). For example, a meta-analysis



of 31 laboratory studies (Uchino, Birmingham, & Berg, 2009) showed that increasing age was associated with lower HR reactivity but greater SBP reactivity. Results from Chapter 2 provide qualified support as HR reactivity was statistically greater in the younger samples; perhaps attributable to the significantly greater sympathetic activation, as evidenced by enhanced efficacy of beta-adrenergic blockade in this age group. No relationship between age and SBP reactivity was observed. It was also observed that males displayed greater SBP, DBP, and sympathetic activation which falls in line with findings reported elsewhere (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Light, Turner, Hinderliter, & Sherwood, 1993; Steptoe, Fieldman, Evans, & Perry, 1996). Finally, examination of socio-demographic parameters across cardiovascular reactivity clusters in Chapter 5 revealed several significant differences: educational attainment, socioeconomic status, body mass index, depressive symptomatology, and smoking status, all of which have been already identified as personal factors that contribute to the inter-individual variability observed in HR and BP reactivity.

### **Limitations**

This thesis is not without limitations. The specific limitations of each study are outlined in the Discussion sections of each chapter. Thus, only limitations that are common across chapters will be discussed here. First, although the studies in this thesis orient physiological individual differences as causes of individual differences in stress reactivity, direction of causation cannot be firmly established. An exception here is the case of the sympathetic blockade. The meta-analysis contained in Chapter 2, in which pharmacological blockade of the beta-adrenergic sympathetic nervous system significantly reduced HR reactivity to acute mental stress, and thus provided corroboration of the findings of the more observational studies. What is also possible is that stress reactions and their precursors impact each other in reciprocal ways.

For example, large magnitude increases in BP engage local BP regulatory mechanisms that over time lead to vascular hypertrophy, a process called upward structural resetting (Folkow, 1990). The decreased lumen diameter and increased vascular stiffness caused by hypertrophy then leads to increased resting BP and augmented future BP responses to stress. In such a circumstance it can become hard to disentangle the direction of causality. Second is the problem of generalisation; Chapters 3 and 4 were both conducted in young, otherwise healthy, participants. Although the samples contained both males and females, generalisation to older populations remains to be determined. Regarding Chapter 3, a loss of HR complexity has been documented with increasing age (Kaplan, Furman, Pincus, Ryan, Lipsoitz, & Goldberger, 1991; Lipsitz & Goldberger, 1992). Hence, it still remains possible that the finding of reduced HR complexity under stress would generalise to an older population. Alternatively, a lower HR complexity at baseline may restrict further decreases (i.e., floor effect). In relation to Chapter 4, evidence would suggest that the relation found in this study would generalise to other populations as reactivity has been shown to be relatively stable over months (Kasprowicz et al., 1990) and years (Allen, Sherwood, Obrist, Crowell, & Grange, 1987; Bursleson et al., 2003), and to have a strong genetic component (Carroll, Hewitt, Last, Turner, & Sims, 1985; Sims, Hewitt, Kelly, Carroll, & Turner, 1986; Turner, Carroll, Sims, Hewitt, & Kelly, 1986; Wu, Snieder, De Geus, 2010), and, by definition, allostatic load accumulates over time (McEwen, 1998). Thus, if reactivity remains relatively consistent and allostatic load increases one could expect the relationship to grow stronger or at the very least remain stable. Finally, it is always possible that the observational associations reported here are, to some extent, influenced by possible confounding from some unmeasured or poorly measured variable (Christenfeld, Sloan, Carroll, & Greenland, 2004). However, all studies adjusted for many possible confounders.

## **Strengths**

This thesis also has several strengths. First, a range of methodologies were deployed. The meta-analysis (Chapter 2) comprised cross-sectional studies and pharmacological experiments, Chapters 3 and 4 were cross-sectional experimental studies, and Chapter 5 was a secondary analysis of the Dutch Famine Birth Cohort and allowed for cluster and prospective analysis. Second, this thesis contains research on multiple age populations. Chapters 3 and 4 focused on young adults, Chapter 5 comprised a longitudinal study of late middle-aged adults, and Chapter 2 included studies with participant samples of all age groups. Finally, perhaps the greatest strength, is the wide array of objective physiological measures included in this thesis: standard blood pressure cuff (Chapters 2-4), portapres/finometer (Chapters 3 and 5), electrocardiography (Chapters 2 and 3), plasma catecholamines (Chapters 2 and 4), pre-ejection period derived from impedance cardiography (Chapter 2) and Doppler echocardiography (Chapter 3), heart rate variability (Chapters 2 and 3) and complexity (Chapter 3),  $\beta_2$ -adrenergic cell receptor density (Chapter 4), pharmacological blockade (Chapter 2), and respiration (Chapter 3). In addition, meta-analysis (Chapter 2) and cluster analysis (Chapter 5) were applied to physiological data in a novel manner.

## **Future Directions**

Research could proceed in various directions based on the research contained in this thesis. First, large datasets that contain physiological data and disease endpoints should be revisited with a focus put on identifying multivariate individual differences (Chapter 5). This could be accomplished by applying clustering algorithms (Allen, Boquet, & Shelley, 1991), factor analysis (McCaffery, Marslan, Strohacker, Muldoon, & Manuck, 2012), structural

equation modelling (Whiteman, Deary, Fowkes, & Gerald, 2000), and machine-learning techniques (Jang, Park, Kim, & Sohn, 2012; Sharma & Gedeon, 2012) to identify 1) physiological and psychological patterns that underlie the cardiovascular stress response and, 2) individuals who display particular patterns of stress reactivity that are particularly pathogenic. Such an approach would compliment the strong research already present in the field. For example, a previous examination of the Dutch Famine Birth Cohort study found that SBP reactivity to a battery of stress tasks was significantly related to hypertension risk at 5 year follow-up,  $OR = 1.014$ , 95% CI (1.002-1.26),  $p = .02$  (Carroll, Ginty, Painter, Roseboom, Phillips, & de Rooij, 2012). A re-analysis of the same data, adjusting for similar confounders, using cluster analysis (Chapter 5) not only confirmed this previous finding, as cluster membership was predictive of hypertension risk, but made it more specific by showing that large magnitude SBP reactions, relative to the sample mean, may only be pathogenic when a robust HR response is absent (for full discussion see Chapter 5). Hence, previously published findings relating cardiovascular reactivity to disease may potentially be revised for specificity (as in this example) if the datasets are revisited with a focus on exploring multivariate individual differences.

A second direction for future research is to begin disentangling directions of causality with respect to the development of extreme stress reactivity (i.e., blunted or exaggerated). Directly, building off the findings in Chapter 4, a longitudinal study exploring the accumulation of allostatic load and the dynamics of cardiovascular reactivity over time would begin to disentangle (but, not fully establish) the direction of causality. Current evidence suggests that childhood trauma (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011; Lovallo, Farag, Sorocco, Cohon, & Vincent, 2012) and negative life events (Carroll, Phillips,

Ring, Der, & Hunt, 2005; Phillips, Carroll, Ring, Sweeting, & West, 2005) play a role in the development of blunted stress reactions later in life, however, the findings are inconsistent with some reporting exaggerated reactivity (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Heim, et al., 2000; Heim, Newport, Wagner, Wilcox, Miller, & Nemeroff, 2002; Leucken, 2000). However, dynamics of such developments are not established. For example, does blunted reactivity directly develop from such traumatic experiences or is it the end result of a process that perhaps begins with exaggerated reactivity and through allostatic mechanisms stresses the body (e.g., wear and tear), ultimately resulting in the inability to physiologically respond to stress. Presently it is not known (Danese & McEwen, 2011), but perhaps longitudinal analysis could begin to establish these patterns.

Finally, the overall goal of this thesis was to identify individual differences that impact upon cardiovascular stress reactivity. Based on this, future research could proceed by identifying novel sources and further exploring already known pools of individual difference. One such example includes individual differences in genes. Compared to other underlying physiological processes (e.g., autonomic and hemodynamic), genetic effects have received relatively little attention in the context of acute stress responding (for reviews see De Geus, Kuppers, Boomsma, & Snieder, 2007; Wu et al., 2010). Despite this, a meta-analysis of twin studies found strong evidence of heritability of HR and BP reactivity to acute mental and cold pressor stress tasks with pooled heritability estimates for each task ranging from 0.26 - 0.43 and 0.21 to 0.55, respectively (Wu et al., 2010). However, the results were tempered by the finding that studies exploring candidate genetic variants responsible for the heritable component of stress reactivity are largely inconsistent (Wu et al., 2010). For example Li et al. (2001), reported increased DBP reactivity to mental arithmetic and cold pressor stress among Arg/Arg homozygotes for the

ADRB2 Arg16Gly polymorphism but this effect has yet to be replicated (Liu et al., 2006; McCaffery, Pogue-Geile, Ferrell, Petro, & Manuck, 2002; Poole, Snieder, Davis, & Treiber, 2006). Similar discordant findings exist for the 5-HTTLPR genetic variant (McCaffery, Bliel, Pogue-Geile, Ferrell, & Manuck, 2003; Williams et al., 2001; Williams et al., 2008). Other candidate genetic variants include: ADRA2C (Kurnik et al., 2008), tyrosine hydroxylase (Rao et al., 2008), NOS3 (Malhotra et al., 2004), OXTR (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), and endothelin-1 (Treiber et al., 2003). Continued research in this area, particularly exploring how gene variability impacts the underlying mechanisms of HR and BP reactivity and disease risk, is sure to advance current knowledge related to the stress response.

## **Conclusion**

In conclusion, this thesis used a multi-method approach of meta-analysis, laboratory testing, and secondary analysis of epidemiological data to further probe the individual differences that contribute to high degree of observed inter-individual variability in cardiovascular reactivity to acute psychological stress. Both branches of the autonomic nervous system were implicated in stress reactions and individual differences in a novel measure of HR complexity were found to account for a significant portion of unexplained inter-individual variance in HR reactivity. Individual differences in resting allostatic load, computed from cardiovascular, anthropometric, and neuroendocrine domains, were negatively related to HR reactivity. Finally, it was shown that multivariate individual differences, captured using cluster analysis, prospectively related to hypertension diagnosis. Overall, this thesis outlines several sources of individual difference with respect to cardiovascular stress and demonstrates that novel sources of individual differences relate to disease risk. Building on the established success of the univariate reactivity hypothesis, given the findings presented in this thesis and in the research

field, perhaps it is fitting to conclude that further research concerning the reactivity hypothesis would benefit from a focus on individual differences more broadly in addition to those simply observed in HR and BP reactivity.

## References

- Ashman, S.B., Dawson, G., Panagiotides, H., Yamada, E., & Wilkinson, C.W. (2002). Stress hormone levels of children of depressed mothers. *Development and Psychopathology*, 14, 333-349.
- Allen, M.T., Sherwood, A., Obrist, P.A., Crowell, M.D., & Grange, L.A. (1987). Stability of cardiovascular reactivity to laboratory stressors: A 2 ½ year follow-up. *Journal of Psychosomatic Research*, 31, 639-645.
- Allen, M.T., Boquet, A.J., & Sheeley, K.S. (1991). Cluster analyses of cardiovascular responsiveness to three laboratory stressors. *Psychosomatic Medicine*, 53, 272-288.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1991). Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. *Psychological Review*, 98, 459-487.
- Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993). Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. *Psychological Bulletin*, 114, 296-322.
- Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., & Fieldstone, A. (1994). Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockade. *Psychophysiology*, 31, 599-608.
- Burleson, M.H., Poehlmann, K.M., Hawkey, L.C., Ernst, J.M., Berntson, G.G., Malarkey, W.B., et al. (2003). Neuroendocrine and cardiovascular reactivity to stress in mid-aged and older women: Long-term temporal consistency of individual differences. *Psychophysiology*, 40, 358-369.



Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., et al. (2007).

Decreased ACTH and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, 15, 1080-1087.

Carpenter, L.L., Shattuck, T.T., Tyrka, A.R., Geraciotti, T.D., & Price, L.H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology (Berl)*, 214, 367-375.

Carroll, D., Hewitt, J.K., Last, K.A., Turner, J.R., & Sims, J. (1985). A twin study of cardiac reactivity and its relationship to parental blood pressure. *Physiology and Behavior*, 34, 103-106.

Carroll, D., Ring, C., Hunt, K., Ford, G., & McIntyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: Effects of sex, age, and socioeconomic position. *Psychosomatic Medicine*, 65, 1058-1064.

Carroll, D., Phillips, A.C., Ring, C., Der, G., & Hunt, K. (2005). Life events and hemodynamics stress reactivity in the middle-aged and elderly. *Psychophysiology*, 42, 269-276.

Carroll, D., Phillips, A.C., Hunt, K., & Der, G. (2007). Symptoms of depression and cardiovascular reactions to acute psychological stress: Evidence from a population study. *Biological Psychology*, 75, 68-74.

Carroll, D., Ginty, A.T., Painter, R.C., Roseboom, T.J., Phillips, A.C., & de Rooij, S.R. (2012). Systolic blood pressure reactions to acute stress are associated with future hypertension status in the Dutch Famine Birth Cohort Study. *International Journal of Psychophysiology*, 85, 270-273.

- Chida. Y. & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension*, 55, 1026-1032.
- Christenfeld, N.J.S., Sloan, R.P., Carroll, D., & Greenland, S. (2004). Risk factors, confounding, and the illusion of statistical control. *Psychosomatic Medicine*, 66, 868-875.
- Critchley, H.D., Corfield, D.R., Chandler, M.P., Mathias, C.J., & Dolan, R.J. (2000). Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. *The Journal of Physiology*, 523, 259-270.
- Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., et al. (2003). Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. *Brain*, 126, 2139-2152.
- Danese, A., & McEwen, B.S. (2011). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, 106, 29-39.
- De Geus, E.J.C., Kupper, N., Boomsma, D.I., & Snieder, H. (2007). Bivariate genetic modeling of cardiovascular stress reactivity: Does stress uncover genetic variance? *Psychosomatic Medicine*, 69, 356-364.
- de Rooij, S.R., Schene, A.H., Phillips, D.I., & Roseboom, T.J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology*, 35, 866-877.
- Dickerson, S.S., & Kemeny, M.E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, 130, 355-391.

- Ewart, C.K., & Kolodner, K.B. (1993). Predicting ambulatory blood pressure during school: Effectiveness of social and nonsocial reactivity tasks in black and white adolescents. *Psychophysiology*, 30, 30-38.
- Falkow, B. (1990). "Structural factors" in primary and secondary hypertension. *Hypertension*, 16, 89-101.
- Fredrickson, M., & Matthews K.A. (1990). Cardiovascular responses to behavioral stress and hypertension: A meta-analytic review. *Annals of Behavioral Medicine*, 12, 30-39.
- Gianaros, P.J., & Sheu, L.K. (2009). A review of neuroimaging studies of stress-evoked blood pressure reactivity: Emerging evidence for a brain-body pathway to coronary heart disease risk. *Neuroimage*, 47, 922-936.
- Gianaros, P.J., & Wager, T.D. (2015). Brain-body pathways linking psychological stress and physical health. *Current Directions in Psychological Science*, 24, 313-321.
- Hagerman, I., Berglund, M., Lorin, M., Nowak, J., & Sylvén, C. (1996). Chaos-related deterministic regulation of heart rate variability in time and frequency domains: Effects of autonomic blockade and exercise. *Cardiovascular Research*, 31, 410-418.
- Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M.M., Bonsall, R., et al. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. 284, 592-597.
- Heim, C., Newport, D.J., Wagner, D., Wilcox, M.M., Miller, A.H., & Nemeroff, C.B. (2002). The role of early adverse experiences and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depression and Anxiety*, 15, 117-125.
- Herd, J.A. (1991). Cardiovascular response to stress. *Physiological Reviews*, 71, 305-330.

- Isowa, T., Ohira, H., Murashima, S. (2004). Reactivity of immune, endocrine, and cardiovascular parameters to active and passive acute stress. *Biological Psychology*, 65, 101-120.
- Jang, E.H., Park, B.J., Kim, S.H., & Sohn, J.H. (2012). Discrimination of negative emotions by machine learning algorithms. *IEEEExplore*, 283-288.
- Jennings, J.R., Kamarck, T., Stewart, C., Eddy, M., & Johnson, P. (1992). Alternate cardiovascular baseline assessment techniques: Vanilla or resting baseline. *Psychophysiology*, 29, 742-750.
- Kaplan, D.T., Furman, M.I., Pincus, S.M., Ryan, S.m., Lipsitz, L.A., & Goldberger, A.L. (1991). Aging and the complexity of cardiovascular dynamics. *Biophysical Journal*, 59, 945-949.
- Kamarck, T.W., & Lovallo, W.R. (2003). Cardiovascular reactivity to psychological challenge: Conceptual and measurement considerations. *Psychosomatic Medicine*, 65, 9-21.
- Kasprowicz, A.L., Manuck, S.B., Malkoff, S.B., & Krantz, D.S. (1990). Individual differences in behaviorally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology*, 27, 605-619.
- Krantz, D.S., & Manuck, S.B. (1984). Acute psychophysiological reactivity and risk of cardiovascular disease: A review and methodologic critique. *Psychological Bulletin*, 96, 435-464.
- Kurnik, D., Friedman, E.A., Muszkat, M., Sofowora, G.G., Xie, H.G., Dupont, W.D., et al. (2009). Genetic variants in the  $\alpha_{2C}$ -adrenoceptor and G-protein contribute to ethnic differences in cardiovascular stress response. *Pharmacogenetics and Genomics*, 18, 743-750.

- Li, G.H., Faulhaber, H.D., Rosenthal, M., Schuster, H., Jordan, J., Timmermann, B., et al. (2001).  $\beta$ -2 adrenergic receptor gene variations and blood pressure under stress in normal twins. *Psychophysiology*, 38, 485-489.
- Light, K.C., Turner, J.R., Hinderliter, A.L., & Sherwood, A. (1993). Race and gender comparison: I. Hemodynamic responses to a series of stressors. *Health Psychology*, 12, 354-365.
- Lipsitz, L.A., & Golderberger, A.L. (1992). Loss of 'Complexity' and aging. *JAMA*, 267, 1806-1809.
- Lipsitz, L.A. (1995). Age-related changes in the "complexity" of cardiovascular dynamics: A potential marker of vulnerability to disease. *Chaos*, 5(1), 102-109.
- Liu, Z., Barnes, S.A., Sokolnicki, L.A., Snyder, E.M., Johnson, B.D., Turner, S.T., et al. (2006). Beta-2 adrenergic receptor polymorphisms and the forearm blood flow response to mental stress. *Clinical Autonomic Research*, 16, 105-112.
- Lovallo, W.R., & Gerin, W. (2003). Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. *Psychosomatic Medicine*, 65, 36-45.
- Lovallo, W.R. (2005). Cardiovascular reactivity: Mechanisms and pathways to cardiovascular disease. *International Journal of Psychophysiology*, 58, 119-132.
- Lovallo, W.R., Farag, N.H., Sorocco, K.H., Cohoon, A.J., & Vincent, A.S. (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma Family Health Patterns Project. *Biological Psychiatry*, 71, 344-349.
- Luecken, L.J. (2000). Parental caring and loss during childhood and adult cortisol responses to stress. *Psychology and Health*, 15, 841-851.

- Malhotra, S., Poole, J., Davis, H., Dong, Y., Pollock, J., Snieder, H., et al. (2004). Effects of NOS3 Glu298Asp polymorphism on hemodynamic reactivity to stress: Influences of ethnicity and obesity. *Hypertension*, 44, 866-871.
- Manuck, S.B. (1994). Cardiovascular reactivity in cardiovascular disease: 'Once more unto the breach.' *International Journal of Behavioral Medicine*, 1, 4-27.
- McCaffery, J.M., Pogue-Geile, M.F., Ferrell, R.E., Petro, N., & Manuck, S.B. (2002). Variability within  $\alpha$ - and  $\beta$ -adrenoreceptor genes as a predictor of cardiovascular function at rest and in response to mental challenge. *Journal of Hypertension*, 20, 1105-1114.
- McCaffery, J.M., Bleil, M., Pogue-Geile, M.F., Ferrell, R.E., & Manuck, S.B. (2003). Allelic variation in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cardiovascular reactivity in young adult male and female twins of European-American descent. *Psychosomatic Medicine*, 65, 721-728.
- McCaffery, J.M., Marsland, A.L., Strohacker, K., Muldoon, M.F., & Manuck, S.B. (2012). Factor structure underlying components of allostatic load. *PLOSOne*, 7, e47246.
- McEwen, B.S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, 1, 33-44.
- McEwen, B.S. (2000). Mood disorders and allostatic load. *Biological Psychiatry*, 54, 200-207
- McEwen, B.S. (2003). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology*, 22, 108-124.
- Obrist, P. (1981). *Cardiovascular Psychophysiology: A perspective*. New York, New York: Plenum Press.

- Phillips, A.C., Carroll, D., Ring, C., Sweeting, H., & West, P. (2005). Life events and acute cardiovascular reactions to mental stress: A cohort study. *Psychosomatic Medicine*, 67, 384-392.
- Phillips, A.C., Hunt, K., Der, G., & Carroll, D. (2010). Blunted cardiac reactions to acute psychological stress predict symptoms of depression five years later: Evidence from a large community sample. *Psychophysiology*, 48, 142-148.
- Phillips, A.C., Ginty, A.T., & Hughes, B. (2013). The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90, 1-7.
- Poole, J.C., Snieder, H., Davis, H.C., & Treiber, F.A. (2006). Anger suppression and adiposity modulate association between ADRB2 haplotype and cardiovascular stress reactivity. *Psychosomatic Medicine*, 68, 207-212.
- Prkachin, K.M., Mills, D.E., Zwaal, C., & Husted, J. (2001). Comparison of hemodynamic responses to social and nonsocial stress: Evaluation of an anger interview. *Psychophysiology*, 38, 879-885.
- Rao, F., Zhang, L., Wessell, J., Zhang, K., Wen, G., Kennedy, B.P., et al. (2009). Adrenergic polymorphism and the human stress response. *Annals of the New York Academy of Sciences*, 1148, 282-296.
- Rodrigues, S.M., Saslow, L.R., Garcia, N., John, O.P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences*, 106, 21437-21441.

- Salomon, K., Clift, A., Karlsdottir, M., & Rottenberg, J. (2009). Major depressive disorder is associated with attenuated cardiovascular reactivity and impaired recovery among those free of cardiovascular disease. *Health Psychology, 28*, 157-165.
- Salomon, K., Bylsma, L.M., White, K.E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependent? A comparison of major depressive disorder remitted depression and health controls. *International Journal of Psychophysiology, 90*, 50-57.
- Schwerdtfeger, A., & Rosenkaimer, A.K.. (2011). Depressive symptoms and attenuated physiological reactivity to laboratory stressors. *Biological Psychology, 87*, 430-438.
- Sharma, N., & Gedeon, T. (2012). Objective measures, sensors and computational techniques for stress recognition and classification: A survey. *Computer Methods and Programs in Biomedicine, 108*, 1287-1301.
- Sherwood, A., Allen, M.T., Obrist, P.A., & Langer, A.W. (1986). Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustment to physical and psychological stress. *Psychophysiology, 23*, 89-104.
- Sherwood, A., Dolan, C.A., & Light, K.C. (1990). Hemodynamics of blood pressure responses during active and passive coping. *Psychophysiology, 27*, 656-668.
- Sims, J., Hewitt, J.K., Kelly, K.A., Carroll, D., & Turner, J.R. (1986). Familial and individual influences on blood pressure. *Acta Geneticae Medicae et Gemellologiae, 35*, 7-21.
- Stemmler, G., Grossman, P., Schmid, H., & Foerster, F. (1991). A model of cardiovascular activation components for studies using autonomic receptor antagonists. *Psychophysiology, 28*, 367-382.



- Steptoe, A., Fieldman, G., Evans, O., & Perry, L. (1996). Cardiovascular risk and responsivity to mental stress: The influence of age, gender, and risk factors. *European Journal of Preventative Cardiology*, 3, 83-93.
- Treiber, F.A., Barbeau, P., Harshfield, G., Kang, H.S., Pollock, D.M., Pollock, J.S., et al. (2003). Endothelin-1 gene Lys198ASN polymorphism and blood pressure reactivity. *Hypertension*, 42, 494-499.
- Turner, J.R., Carroll, D., Sims, J., Hewitt, J.K., & Kelly, K.A. (1986). Temporal and inter-task consistency of heart rate reactivity during active psychological challenge: A twin study. *Physiology and Behavior*, 38, 641-644.
- Uchino, B.N., Birmingham, W., & Berg, C.A. (2009). Are older adults less or more physiologically reactive? A meta-analysis of age-related differences in cardiovascular reactivity to laboratory tasks. *Journal of Gerontology: Psychological Sciences*, 65B, 154-162.
- Wager, T.D., Waugh, C.E., Lindquist, M., Noll, D.C., Fredrickson, B.L., & Taylor, S.F. (2009a). Brain mediators of cardiovascular responses to social threat: Part I: Reciprocal dorsal and central sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*, 47, 821-835.
- Wager, T.D., van Ast, V.A., Hughes, B.L., Davidson, M.L., Lindquist, M.A., & Ochsner, K.N. (2009b). Brain mediators of cardiovascular responses to social threat, Part II: Prefrontal-subcortical pathways and relationship with anxiety. *Neuroimage*, 47, 836- 851.
- Wagner, & Persson, P.B. (1998). Chaos in the cardiovascular system: An update. *Cardiovascular Research*, 40, 257-264.

- Whiteman, M.C., Deary, I.J., Fowkes, F., & Gerald, R.F. (2000). Personality and social predictors of atherosclerotic progression: Edinburgh Artery Study. *Psychosomatic Medicine*, 62, 703-714.
- Willemsen, G., Ring, C., Carroll, D., Evans, P., Clow, A., & Hucklebridge, F. (1998). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic and cold pressor. *Psychophysiology*, 35, 252-259.
- Williams, R.B., Marchuk, D.A., Gadde, K.M., Barefoot, J.C., Grichnik, K., Helms, M.J., et al. (2001). Central nervous system serotonin function and cardiovascular responses to stress. *Psychosomatic Medicine*, 63, 300-305.
- Williams, R.B., Marchuk, D.A., Siegler, I.C., Barefoot, J.C., Helms, M.J., Brummet, B.H., et al. (2008). Childhood socioeconomic status and serotonin transporter gene polymorphism enhance cardiovascular reactivity to mental stress. *Psychosomatic Medicine*, 70, 32-39.
- Wu, T., Snieder, H., & de Geus, E. (2010). Genetic influences on cardiovascular stress reactivity. *Neuroscience and Biobehavioral Reviews*, 35, 58-68.
- York, K.M., Hassan, M., Li, Q., Li, H., Fillingim, R.B., & Sheps, D.S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine*, 69, 521-528.

---

## Appendix I: References Contained in Meta-Analysis

---

### Meta-analysis of peripheral sympathetic markers\*

\*Bolded studies measured both sympathetic and parasympathetic markers

1. Åkerstedt, T., Gillberg, M., Hjemdahl, P., Sigurdson, K., Gustavsson, I., Daleskog, M., & Pollare, T. (1983). Comparison of urinary and plasma catecholamine responses to mental stress. *Acta Physiologica Scandinavica*, 117, 19-26.
2. Al' Absi, M., Bongard, S., Buchanan, T., Pincomb, G.A., Licinio, J., & Lovallo, W.R. (1997). Cardiovascular and neuroendocrine adjustment to public speaking and mental arithmetic stressors. *Psychophysiology*, 34, 266-275.
3. Allen, M.T., Obrist, P.A., Sherwood, A., & Crowell, M.D. (1987). Evaluation of myocardial and peripheral vascular responses during reaction time, mental arithmetic, and cold pressor tasks. *Psychophysiology*, 24, 648-656.
4. Allen, M.T., & Crowell, M.D. (1990). The effects of paced respiration on cardiopulmonary responses to laboratory stressors. *Journal of Psychophysiology*, 4, 357-368.
5. Allen, M.T., Stoney, C.M., Owens, J.F., & Matthews, K.A. (1993). Hemodynamic adjustments to laboratory stress: The influence of gender and personality. *Psychosomatic Medicine*, 55, 505-517.
6. Atterhög, J.H., Eliasson, K., & Hjemdahl, P. (1981). Sympathoadrenal and cardiovascular responses to mental stress, isometric handgrip, and cold pressor test in asymptomatic young men with primary T wave abnormalities in the electrocardiogram. *British Heart Journal*, 46, 311-319.
7. Barnes, R.F., Raskind, M., Gumbrecht, G., & Halter, J.B. (1982). The effects of age on the plasma catecholamine response to mental stress in man. *Journal of Clinical Endocrinology and Metabolism*, 54, 64-69.

8. Becker, L.C., Pepine, C.J., Bonsall, R., Cohen, J.D., Goldberg, A.D., Coughlan, C., et al. (1996). Left ventricular, peripheral vascular, and neurohumoral responses to mental stress in normal middle-aged men and women. *Circulation*, 94, 2768-2777.
9. Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., & Fieldstone, A. (1994). Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockade. *Psychophysiology*, 31, 599-608.
10. Berntson, G.G., Cacioppo, J.T., & Fieldstone, A. (1996). Illusions, arithmetic, and the bidirectional modulation of vagal control of the heart. *Biological Psychology*, 44, 1-17.
11. Bosch, J.A., de Geus, E.J.C., Kelder, A., Veerman, E.C.I., Hoogstraten, J., & Amerongen, A.V.N. (2001). Differential effects of active versus passive coping on secretory immunity. *Psychophysiology*, 38, 836-846.
12. Bosch, J.A., de Geus, E.J.C., Veerman, E.C.I., Hoogstraten, J., & Amerongen, A.V.N. (2003). Innate secretor immunity in response to laboratory stressors that evoke distinct patterns of cardiac autonomic activity. *Psychosomatic Medicine*, 65, 245-258.
13. Bosch, J.A., Berntson, G.G., Cacioppo, J.T., Dhabhar, F.S., & Marucha, P.T. (2003). Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: A potential pathway linking immunologic reactivity to cardiovascular disease. *Brain, Behavior, and Immunity*, 17, 251-259.
14. Bosch, J.A., de Geus, E.J.C., Carroll, D., Goedhart, A.D., Anane, L.A., Veldhuizen van Zanten, J.J., et al. (2009). A general enhancement of autonomic and cortisol responses during social evaluative threat. *Psychosomatic Medicine*, 71, 877-885.
15. Boutcher, S.H., & Stocker, D. (1996). Cardiovascular response of young and older males to mental challenge. *Journal of Gerontology: Psychological Sciences*, 51B, P261-P267.
16. Boutcher, Y.N., & Boutcher, S.H. (2006). Cardiovascular response to Stroop: Effect of verbal response and task difficulty. *Biological Psychology*, 73, 235-241.
17. Burleson, M.H., Malarkey, W.B., Cacioppo, J.T., Poehlmann, K.M., Kiecolt-Glaser, J.K., Berntson, G.G., & Glaser, R. (1998). Postmenopausal hormone replacement:

- Effects on autonomic, neuroendocrine, and immune reactivity to brief psychological stressors. *Psychosomatic Medicine*, 60, 17-25.
18. Burleson, M.H., Poehlmann, K.M., Hawkley, L.C., Ernst, J.M., Berntson, G.G., Malarkey, W.B., et al. (2003). Neuroendocrine and cardiovascular reactivity to stress in mid-aged and older women: Long term temporal consistency of individual differences. *Psychophysiology*, 40, 358-369.
  19. Burns, V.E., Ring, C., Drayson, M., & Carroll, D. (2002). Cortisol and cardiovascular reactions to mental stress and antibody status following hepatitis B vaccination: A preliminary study. *Psychophysiology*, 39, 361-368.
  20. Burns, J.W., Ferguson, M.L., Fernquist, S.K., & Katkin, E.S. (1992). Test-retest reliability of inotropic and chronotropic measures of cardiac reactivity. *International Journal of Psychophysiology*, 12, 165-168.
  21. Cacioppo, J.T., Malarkey, W.B., Kiecolt-Glaser, J.K., Uchino, B.N., Sgoutas-Emch, S.A., Sheridan, J.F., et al. (1995). Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. *Psychosomatic Medicine*, 57, 154-164.
  22. Cacioppo, J.T., Burleson, M.H., Poehlmann, K.M., Malarkey, W.B., Kiecolt-Glaser, J.K., Berntson, G.G., et al. (2000). Autonomic and neuroendocrine responses to mild psychological stressors: Effects of chronic stress on older women. *Annals of Behavioral Medicine*, 22, 140-148.
  23. Cohen, S., Hamrick, N., Rodriguez, M.S., Feldman, P.J., Rabin, B.S., & Manuck, S.B. (2000). The stability of and intercorrelations among cardiovascular, immune, endocrine, and psychological reactivity. *Annals of Behavioral Medicine*, 22, 171-179.
  24. de Geus, E.J.C., van Doornen, L.J.P., de Visser, D.C., & Orlebeke, J.F. (1990). Existing and training induced differences in aerobic fitness: Their relationship to physiological response patterns during different types of stress. *Psychophysiology*, 27, 457-478.
  25. de Geus, E.J.C., Kupper, N., Boomsma, D.I., & Snieder, H. (2007). Bivariate genetic modelling of cardiovascular stress reactivity: Does stress uncover genetic variance? *Psychosomatic Medicine*, 69, 356-364.

26. Dimsdale, J.E., Young, D., Moore, R., & Strauss, H.W. (1987). Do plasma norepinephrine levels reflect behavioral stress? *Psychosomatic Medicine*, 49, 375-382.
27. Eisenhofer, G., Lambie, D.G., & Johnson, R.H. (1985).  $\beta$ -adrenoceptor responsiveness and plasma catecholamines as determinants of cardiovascular reactivity to mental stress. *Clinical Science*, 69, 483-492.
28. Eliasson, K., Hjemdahl, P., & Kahan, T. (1983). Circulatory and sympatho-adrenal responses to stress in borderline and established hypertension. *Journal of Hypertension*, 1, 131-139.
29. Farag, N.H., Bardwell, W.A., Nelesen, R.A., Dimsdale, J.E., & Mills, P.J. (2003). **Autonomic responses to psychological stress: The influence of menopausal status.** *Annals of Behavioral Medicine*, 26, 134-138.
30. Freyschuss, U., Fagius, J., Wallin, B.G., Bohlin, G., Perski, A., & Hjemdahl, P. (1990). Cardiovascular and sympathoadrenal responses to mental stress: A study of sensory intake and rejections reactions. *Acta Physiologica Scandinavica*, 139, 173-183.
31. Gianaros, P.J., Quigley, K.S., Mordkoff, J.T., & Stern, R.M. (2001). **Gastric myoelectrical and autonomic cardiac reactivity to laboratory stressors.** *Psychophysiology*, 38, 642-652.
32. Grossman, P., Brinkman, A., & de Vries, J. (1992). **Cardiac autonomic mechanisms associated with borderline hypertension under varying behavioral demands: Evidence for attenuated parasympathetic tone but not for enhanced beta-adrenergic activity.** *Psychophysiology*, 29, 698-711.
33. Halbrügge, T., Gerhardt, T., Ludwig, J., Heidbreder, E., & Graefe, K. (1988). Assay of catecholamine and dihydroxyphenylethyleneglycol in human plasma and its application in orthostasis and mental stress. *Life Sciences*, 43, 19-26.
34. Hawkey, L.C., Burleson, M.H., Poehlmann, K.M., Berntson, G.G., Malarkey, W.B., & Cacioppo, J.T. (2001). **Cardiovascular and endocrine reactivity in older females: Intertask consistency.** *Psychophysiology*, 38, 863-872.
35. Hjemdahl, P., & Eliasson, K. (1979). Sympatho-adrenal and cardiovascular response to mental stress and orthostatic provocation in latent hypertension. *Clinical Science*, 57, 189s-191s.

36. Hjemdahl, P., Freyschuss, U., Juhlin-Dannfelt, A., & Linde, B. (1984). Differentiated sympathetic activation during mental stress evoked by the Stroop test. *Acta Physiologica Scandinavica, Suppl. 527*, 25-29.
37. Hjemdahl, P., Fagius, J., Freyschuss, U., Wallin, B.G., Daleskog, M., Bohlin, G., & Perski, A. (1989). Muscle sympathetic activity and norepinephrine release during mental challenge in humans. *American Journal of Physiology*, 257, E654-E664.
- 38. Hoshikawa, Y., & Yamamoto, Y. (1997). Effects of Stroop color-word conflict test on the autonomic nervous system responses. *American Journal of Physiology*, 272, H1113-H1121.**
- 39. Houtveen, J.H., Rietveld, S., & de Geus, E.J.C. (2002). Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. *Psychophysiology*, 39, 427-436.**
40. Hull, E.M., Young, S.H., & Ziegler, M.G. (1984). Aerobic fitness affects cardiovascular and catecholamine responses to stress. *Psychophysiology*, 21, 353-360.
41. Jennings, J.R., Kamarck, T., Manuck, S.B., Everson, S.A., Kaplan, G., & Salonen, J.T. (1997). Aging or disease? Cardiovascular reactivity in Finnish men over the middle years. *Psychology and Aging*, 12, 225-238.
42. Jones, P.P., Spraul, M., Matt, K.S., Seals, D.R., Skinner, J.S., & Ravussin, E. (1996). Gender does not influence sympathetic neural reactivity to stress in healthy humans. *American Journal of Physiology*, 270, H350-H357.
43. Jørgensen, L.S., Christiansen, P., Raundahl, U., Østgaard, S., Christensen, J., Fenger, M., & Flach, H. (1990). Autonomic response to an experimental psychological stressor in health subjects: Measurement of sympathetic, parasympathetic, and pituitary-adrenal parameters: Test-retest reliability. *Scandinavian Journal of Clinical Laboratory Investigation*, 50, 823-829.
44. Kaji, Y., Ariyoshi, K., Tsuda, Y., Kanaya, S., Fujino, T., & Kuwabara, H. (1989). Quantitative correlation between cardiovascular and plasma epinephrine response to mental stress. *European Journal of Applied Physiology*, 59, 221-226.

45. Kamarck, T.W., Jennings, J.R., Stewart, C.J., & Eddy, M.J. (1993). Reliable responses to a cardiovascular reactivity protocol: A replication study in a biracial female sample. *Psychophysiology*, 30, 627-634.
46. Kasprowicz, A.L., Manuck, S.B., Malkoff, & Krantz, D.S. (1990). Individual differences in behaviourally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology*, 27, 605-618.
47. Kelsey, R.M. (1991). Electrodermal lability and myocardial reactivity to stress. *Psychophysiology*, 28, 619-631.
48. Kelsey, R.M., Blascovich, J., Leitten, C.L., Schneider, T.R., Tomaka, J., & Wiens, S. (2000). Cardiovascular reactivity and adaptation to recurrent psychological stress: The moderating effects of evaluative observation. *Psychophysiology*, 37, 748-756.
49. Kop, W.J., Weissman, N.J., Zhu, J., Bonsall, R.W., Doyle, M., Stretch, M.R., et al. (2008). Effects of acute mental stress and exercise on inflammatory markers in patients with coronary artery disease and healthy controls. *American Journal of Cardiology*, 101, 767-773.
50. Light, K.C., Turner, J.R., Hinderliter, A.L., Girdler, S.S., & Sherwood, A. (1994). Comparison of cardiac versus vascular reactors and ethnic groups in plasma epinephrine and norepinephrine responses to stress. *International Journal of Behavioral Medicine*, 1, 229-246.
51. Maier, K.J., Waldstein, S.R., & Synowski, S.J. (2003). Relations of cognitive appraisal to cardiovascular reactivity, affect, and task engagement. *Annals of Behavioral Medicine*, 26, 32-41.
52. Manhem, K., Jern, A., Pilhall, M., Shanks, G., & Jern, S. (1991). Haemodynamic responses to psychosocial stress during the menstrual cycle. *Clinical Science*, 81, 17-22.
53. Manuck, S.B., Cohen, S., Rabin, B.S., Muldoon, M.F., & Bachen, E.A. (1991). Individual differences in cellular immune response to stress. *Psychological Science*, 2, 111-115.
54. Manuck, S.B., Polefrone, J.M., Terrell, D.F., Muldoon, M.F., Kasprowicz, A.L., Waldstein, S.R.,..., Graham, R.E. (1996). Absence of enhanced sympathoadrenal activity and behaviourally evoked cardiovascular reactivity among offspring of hypertensives. *American Journal of Hypertension*, 9, 245-255.



55. Marsland, A.L., Manuck, S.B., Wood, P., Rabin, B.S., Muldoon, M.F., & Cohen, S. (1995).  $\beta_2$ -adrenergic receptor density and cardiovascular response to mental stress. *Physiology and Behavior*, 57, 1163-1167.
56. McCaffery, J.M., Muldoon, M.F., Bachen, E.A., Jennings, J.R., & Manuck, S.B. (2000). Behaviorally-evoked plasma catecholamine response and 24-hour excretion of urinary catecholamines among cardiac and vascular reactors. *Biological Psychology*, 52, 53-69.
57. McCann, B.S., Carter, J., Vaughan, M., Raskind, M., Wilkinson, C.W., & Veith, R.C. (1993). Cardiovascular and neuroendocrine responses to extended laboratory challenge. *Psychosomatic Medicine*, 55, 497-504.
58. McCubbin, J.A., Richardson, J.E., Langer, A.W., Kizer, J.S., & Obrist, P.A. (1983). Sympathetic neuronal function and left ventricular performance during behavioral stress in humans: The relationship between plasma catecholamines and systolic time intervals. *Psychophysiology*, 20, 102-110.
59. McGrath, J.J., & O'Brien, W.H. (2001). Pediatric impedance cardiography: Temporal stability and Intertask consistency. *Psychophysiology*, 38, 479-484.
- 60. Mezzacappa, E.S., Kelsey, R.M., Katkin, E.S., & Sloan, R.P. (2001). Vagal rebound and recovery from psychological stress. *Psychosomatic Medicine*, 63, 650-657.**
61. Mills, P.J., Berry, C.C., Dimsdale, J.E., Nelesen, R.A., & Ziegler, M.G. (1993). Temporal stability of task-induced cardiovascular, adrenergic, and psychological responses: The effects of race and hypertension. *Psychophysiology*, 30, 197-204.
62. Mills, P.J., Nelesen, R.A., Ziegler, M.G., Parry, B.L., Berry, C.C., Dillon, E., & Dimsdale, J.E. (1996). Menstrual cycle effects on catecholamine and cardiovascular responses to acute stress in black but not white normotensive women. *Hypertension*, 27, 962-967.
63. Musgrave, I.F., Bachmann, A.W., Saar, N., & Gordon, R.D. (1984). A comparison of cardiovascular and catecholamine responses to three stimuli in mild hypertension. *Metabolism*, 33, 718-723.
- 64. Nater, U.M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M.M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity-associations with adrenergic activity. *Psychoneuroendocrinology*, 31, 49-58.**

65. Noll, G., Wenzel, R.R., Schneider, M., Oesch, V., Binggeli, C., Shaw, S., et al. (1996). Increased activation of the sympathetic nervous system and endothelin by mental stress in normotensive offspring of hypertensive parents. *Circulation*, 93, 866-872.
66. Obrist, P.A., Light, K.C., James, S.A., & Strogatz, D.S. (1987). Cardiovascular responses to stress: I. Measures of myocardial response and the relationship to high resting systolic pressure and parental hypertension. *Psychophysiology*, 24, 65-78.
67. Ottaviani, C., Shapiro, D., Davydov, D.M., & Goldstein, I.B. (2008). Autonomic stress response modes and ambulatory heart rate level and variability. *Journal of Psychophysiology*, 22, 28-40.
68. Ring, C., Carroll, D., Willemsen, G., Cooke, J., Ferraro, A., & Drayson, M. (1999). Secretory immunoglobulin A and cardiovascular activity during mental arithmetic and paced breathing. *Psychophysiology*, 36, 602-609.
69. Ring, C., Burns, V.E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology*, 39, 585-590.
70. Saab, P.G., Llabre, M.M., Hurwitz, B.E., Frame, C.A., Reineke, L.J., Fins, A.I., et al. (1992). Myocardial and peripheral vascular response to behavioral challenges and their stability in black and white Americans. *Psychophysiology*, 29, 384-397.
71. Salomon, K., Bylsma, L.M., White, K.E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependant? A comparison of major depressive disorder remitted depression and healthy controls. *International Journal of Psychophysiology*, 90, 50-57.
72. Schneider, G.M., Jacobs, D.W., Gevirtz, R.N., & O'Connor, D.T. (2003). Cardiovascular haemodynamic response to repeated mental stress in normotensive subjects at genetic risk of hypertension: Evidence of enhanced reactivity, blunted adaptation, and delayed recovery. *Journal of Human Hypertension*, 17, 829-840.
73. Schommer, N.C., Hellhammer, D.H., & Kirschbaum, C. (2003). Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. *Psychosomatic Medicine*, 65, 450-460.
74. Sinyor, D., Schwartz, S.G., Peronnet, F., Brisson, G., & Seraganian, P. (1983). Aerobic fitness level and reactivity to psychosocial stress: Physiological, biochemical, and subjective measures. *Psychosomatic Medicine*, 45(3), 205-217.

75. Sinyor, D., Peronnet, F., Brisson, G., & Seraganian, P. (1988). Failure to alter sympathoadrenal responses to psychosocial stress following aerobic training. *Physiology and Behavior*, 42, 293-296.
76. Sothmann, M.S., Hart, B.A., & Horn, T.S. (1992). Sympathetic nervous system and behavioral responses to stress following exercise training. *Physiology and Behavior*, 51, 1097-1103.
77. Stoney, C.M., Matthews, K.A., McDonald, R.H., & Johnson, C.A. (1988). Sex differences in lipid, lipoprotein, cardiovascular, and neuroendocrine responses to acute stress. *Psychophysiology*, 25, 645-656.
78. Stoney, C.M., Hughes, J.W., Kuntz, K.K., West, S.G., & Thornton, L.M. (2002). Cardiovascular stress responses among Asian Indian and European American women and men. *Annals of Behavioral Medicine*, 24, 113-121.
- 79. Uchino, B.N., Cacioppo, J.T., Malarkey, W., & Glaser, R. (1995). Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. *Journal of Personality and Social Psychology*, 69, 736-743.**
80. Uchino, B.N., Uno, D., Holt-Lunstad, J., & Flinders, J.B. (1999). Age-related differences in cardiovascular reactivity during acute psychological stress in men and women. *The Journal of Gerontology*, 54B, P339-P346.
- 81. Vella, E.J., & Friedman, B.H. (2009). Hostility and anger in: Cardiovascular reactivity and recovery to mental arithmetic stressors. *International Journal of Psychophysiology*, 72, 253-259.**
82. Wennlund, A., Wahrenberg, E., Hagström-Toft, E., Bolinder, J., & Arner, P. (1994). Lipolytic and cardiac responses to various forms of stress in humans. *International Journal of Sports Medicine*, 15, 408-413.
83. Willemsen, G., Ring, C., Carroll, D., Evans, P., Clow, A., & Hucklebridge, F. (1998). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic stressors. *Psychophysiology*, 35, 252-259.

Meta-analysis of sympathetic blockade

1. Albus, M., Stahl, S., Müller-Spahn, F., & Engel, R.R. (1986). Psychophysiological differentiation of two types of anxiety and its pharmacological modification by minor tranquilizer and beta-receptor-blocker. *Biological Psychology*, 23, 39-51.
2. Albus, M., Zellner, A., Bondy, B., Müller-Spahn, F., Engel, R., & Ackenhell, M. (1989). Influence of CGP361A, propranolol, and diazepam on autonomous reactions to different stressors. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 13, 87-97.
3. Andrén, L., Hansson, L., & Björkman, M. (1981). Haemodynamic effects of noise exposure before and after  $\beta_1$ -selective and non-selective  $\beta$ -adrenoceptor blockade in patients with essential hypertension. *Clinical Science*, 61, 89s-91s.
4. Andrén, L., Hansson, L., Eggertsen, R., Hedner, T., & Karlberg, B.E. (1983). Circulatory effects of noise. *Acta Medica Scandinavica*, 213, 31-35.
5. Bairey, C.N., Krantz, D.S., DeQuattro, V., Berman, D.S., & Rozanski, A. (1991). Effect of beta-blockade on low heart rate-related ischemia during mental stress. *Journal of the American College of Cardiology*, 17, 1388-1395.
6. Benschop, R.J., Nieuwenhuis, E.S., Tromp, E.A.M., Godaert, G.L.R., Ballieux, R.E., & van Doornen, L.J.P. (1994). Effect of  $\beta$ -adrenergic blockade on immunological and cardiovascular changes induced by mental stress. *Circulation*, 89, 762-769.
7. Bonelli, J., Hörtnagl, H., Brücke, Th., Magometschnigg, D., Lochs, H., & Kaik, G. (1979). Effect of calculation stress on hemodynamics and plasma catecholamines before and after  $\beta$ -blockade with propranolol and mepindolol sulphate. *European Journal of Clinical Pharmacology*, 15, 1-8.
8. Bonelli, J. (1982). Stress, catecholamines and beta-blockade. *Acta Medica Scandinavica*, 660, 214-218.
9. Eliasson, K., Kahan, T., Hylander, B., & Hjemdahl, P. (1986). Reactivity to mental stress and cold provocation during long-term treatment with metoprolol, propranolol, or hydrochlorothiazide. *Journal of Hypertension*, 4, S263-S265.
10. Eliasson, K., Kahan, T., Hylander, B., & Hjemdahl, P. (1987). Responses to mental stress and physical provocations before and during long term treatment of hypertensive patients with  $\beta$ -adrenoceptor blockers or hydrochlorothiazide. *British Journal of Clinical Pharmacology*, 24, 1-14.

11. Emery, C.F., Blumenthal, J.A., Hauck, E.R., & Ekelund, L.G. (1994). Cardiovascular reactivity to mental stress in hypertensive patients receiving atenolol vs enalapril. *Journal of Cardiopulmonary Rehabilitation*, 14, 232-237.
12. Fauvel, J.P., Hadj-Aissa, A., Laville, M., Pozet, N., Bernard, N., Sassard, J., & Zech, P. (1990). Cardiovascular reactivity to and renal impact of stress and exercise: Effects of bisoprolol. *Journal of Cardiovascular Pharmacology*, 16, S19-S24.
13. Floras, J.S., Hassan, O., Jones, J.V., & Sleight, P. (1985). Cardiosensitive and nonselective beta-adrenoceptor blocking drugs in hypertension: A comparison of their effect on blood pressure during mental and physical activity. *Journal of the American College of Cardiology*, 6, 186-195.
14. François, B., Cahen, R., Gravejat, M.F., & Estrade, M. (1984). Do beta blockers prevent pressor responses to mental stress and physical exercise? *European Heart Journal*, 5, 348-353.
15. Freyschuss, U., Hjemdahl, Juhlin-Dannfelt, A., & Linde, B. (1988). Cardiovascular and sympathoadrenal responses to mental stress: Influence of  $\beta$ -blockade. *American Journal of Physiology*, 255, H1443-H1451.
16. Girard, A., Holand, S., Laude, D., & Elghozi, J. (2001). Antihypertensive monotherapy and cardiovascular responses to an acoustic startle stimulus. *Journal of Cardiovascular Pharmacology*, 37, 101-107.
17. Grillot, M., Fauvel, J.P., Cottet-Emard, J.M., Laville, M., Peyrin, L., Pozet, N., & Zech, P. (1995). Spectral analysis of stress-induced change in blood pressure and heart rate in normotensive subjects. *Journal of Cardiovascular Pharmacology*, 25, 448-452.
18. Guazzi, M., Fiorentini, C., Polese, A., Olivari, M.T., & Magrini, F. (1976). Antihypertensive action of propranolol in man: Lack of evidence for a neural depressive effect. *Clinical Pharmacology and Therapeutics*, 20, 304-309.
19. Heidbreder, E., Pagel, G. Röckel, A., & Heidland, A. (1978). Beta-adrenergic blockade in stress protection. Limited effect of Metoprolol in psychological stress reaction. *European Journal of Clinical Pharmacology*, 14, 391-398.
20. Krantz, D.S., Contrada, R.J., LaRiccia, P.J., Anderson, J.R., Durel, L.A., Dembroski, T.M., & Weiss, T. (1987). Effects of beta-adrenergic stimulation and blockade on

- cardiovascular reactivity, affect, and type A behaviour. *Psychosomatic Medicine*, 49, 146-158.
21. Lee, D., Lu, Z.W., & DeQuattro, V. (1996). Neural mechanisms in primary hypertension: Efficacy of  $\alpha$ -blockade with Doxazosin during stress. *American Journal of Hypertension*, 9, 47-53.
  22. Mazzuero, G., Galdangelo, F., Zotti, A.M., Bertolotti, G., & Tavazzi, L. (1987). Effects of propranolol, atenolol, and chlodesmethildiazepam on response to mental stress in patients with recent myocardial infarction. *Clinical Cardiology*, 10, 293-302.
  23. Miller, S.B., & Ditto, B. (1991). Exaggerated sympathetic nervous system response to extended psychological stress in offspring of hypertensives. *Psychophysiology*, 28, 103-112.
  24. Moriguchi, A., Otsuka, A., Kohara, K., Mikami, H., Katahira, K., Tsunetoshi, T., et al. (1992). Spectral change in heart rate variability in response to mental arithmetic before and after the beta-adrenoceptor blocker, carteolol. *Clinical Autonomic Research*, 2, 267-270.
  25. Nyberg, G., Graham, R.M., & Stokes, G.S. (1977). The effect of mental arithmetic in normotensive and hypertensive subjects and its modification by  $\beta$ -adrenergic receptor blockade. *British Journal of Clinical Pharmacology*, 4, 469-474.
  26. Olsson, G., Hjemdahl, P., & Rehnqvist, N. (1986). Cardiovascular reactivity to mental stress during gradual withdrawal of chronic postinfarction treatment with metoprolol. *European Heart Journal*, 7, 765-772.
  27. Reyes del Paso, G.A., Langewitz, W., Robles, H., & Pérez, N. (1996). A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. *International Journal of Psychophysiology*, 22, 163-171.
  28. Ring, C., Harrison, L.K., Winzer, A., Carroll, D., Drayson, M., & Kendall, M. (2000). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of alpha-adrenergic blockade. *Psychophysiology*, 37, 634-643.
  29. Schmieder, R.E., Rueddel, H., Neus, H., Messerli, F.H., & von Eiff, A.W. (1987). Disparate hemodynamic responses to mental challenge after antihypertensive therapy

with beta blockers and calcium entry blockers. *The American Journal of Medicine*, 82, 11-16.

30. Winzer, A., Ring, C., Carroll, D., Willemsen, G., Drayson, M., & Kendall, M. (1999). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of beta-adrenergic blockade. *Psychophysiology*, 36, 591-601.

#### Meta-analysis of peripheral parasympathetic markers

1. Allen, M.T., & Crowell, M.D. (1990). The effects of paced respiration on cardiopulmonary responses to laboratory stressors. *Journal of Psychophysiology*, 4, 357-368.
2. Altemus, M., Redwine, L.S., Leong, Y., Frye, C.A., Porges, S.W., & Carter, S. (2001). Responses to laboratory psychosocial stress in postpartum women. *Psychosomatic Medicine*, 63, 814-821.
3. Balanos, G.M., Phillips, A.C., Frenneaux, M.P., McIntyre, D., Lykidis, C., Griffin, H.S., & Carroll, D. (2010). Metabolically exaggerated cardiac reactions to acute psychological stress: The effects of resting blood pressure status and possible underlying mechanisms. *Biological Psychology*, 85, 104-111.
4. Barbosa, D.F., Prada, F.J.A., Glanner, M.F., Nóbrega, O.T., & Córdova, C. (2010). Cardiovascular response to Stroop test: Comparison between the computerized and verbal tests. *Brazilian Archives of Cardiology*, 94, 477-481.
5. Bernardi, L., Wdowczyk, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., & Sleight, P. (2000). Effects of controlled breathing, mental activity, and mental stress with or without verbalization on heart rate variability. *Journal of the American College of Cardiology*, 35, 1462-1469.
6. Berntson, G.G., Cacioppo, J.T., & Fieldstone, A. (1996). Illusions, arithmetic, and the bidirectional modulation of vagal control of the heart. *Biological Psychology*, 44, 1-17.
7. Bosch, J.A., de Geus, E.J.C., Kelder, A., Veerman, E.C.I., Hoogstraten, J., & Amerongen, A.V.N. (2001). Differential effects of active versus passive coping on secretory immunity. *Psychophysiology*, 38, 836-846.

8. Bosch, J.A., Berntson, G.G., Cacioppo, J.T., Dhabhar, F.S., & Marucha, P.T. (2003). Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: A potential pathway linking immunologic reactivity to cardiovascular disease. *Brain, Behavior, and Immunity*, 17, 251-259.
9. Bosch, J.A., de Geus, E.J.C., Veerman, E.C.I., Hoogstraten, J., & Amerongen, A.V.N. (2003). Innate secretor immunity in response to laboratory stressors that evoke distinct patterns of cardiac autonomic activity. *Psychosomatic Medicine*, 65, 245-258.
10. Bosch, J.A., de Geus, E.J.C., Carroll, D., Goedhart, A.D., Anane, L.A., Veldhuizen van Zanten, J.J.,..., Edwards, K.M. (2009). A general enhancement of autonomic and cortisol responses during social evaluative threat. *Psychosomatic Medicine*, 71, 877-885.
11. Boutcher, S.H., & Stocker, D. (1996). Cardiovascular response of young and older males to mental challenge. *Journal of Gerontology: Psychological Sciences*, 51B, P261-P267.
12. Boutcher, Y.N., & Boutcher, S.H. (2006). Cardiovascular response to Stroop: Effect of verbal response and task difficulty. *Biological Psychology*, 73, 235-241.
13. Burleson, M.H., Malarkey, W.B., Cacioppo, J.T., Poehlmann, K.M., Kiecolt-Glaser, J.K., Berntson, G.G., & Glaser, R. (1998). Postmenopausal hormone replacement: Effects on autonomic, neuroendocrine, and immune reactivity to brief psychological stressors. *Psychosomatic Medicine*, 60, 17-25.
14. Burleson, M.H., Poehlmann, K.M., Hawkey, L.C., Ernst, J.M., Berntson, G.G., Malarkey, W.B., et al. (2003). Neuroendocrine and cardiovascular reactivity to stress in mid-aged and older women: Long term temporal consistency of individual differences. *Psychophysiology*, 40, 358-369.
15. Burns, V.E., Ring, C., Drayson, M., & Carroll, D. (2002). Cortisol and cardiovascular reactions to mental stress and antibody status following hepatitis B vaccination: A preliminary study. *Psychophysiology*, 39, 361-368.
16. Cacioppo, J.T., Malarkey, W.B., Kiecolt-Glaser, J.K., Uchino, B.N., Sgoutas-Emch, S.A., Sheridan, J.F., et al. (1995). Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. *Psychosomatic Medicine*, 57, 154-164.
17. Cacioppo, J.T., Burleson, M.H., Poehlmann, K.M., Malarkey, W.B., Kiecolt-Glaser, J.K., Berntson, G.G., et al. (2000). Autonomic and neuroendocrine responses to mild



- psychological stressors: Effects of chronic stress on older women. *Annals of Behavioral Medicine*, 22, 140-148.
18. Chatkoff, D.K., Maier, K.J., Javaid, J., Hammoud, M.K., & Munkrishna, P. (2009). Dispositional hostility and gender differentially related to cognitive appraisal, engagement, and cardiovascular reactivity across cognitive and emotional laboratory tasks. *Personality and Individual Differences*, 47, 122-126.
  19. de Geus, E.J.C., van Doornen, L.J.P., de Visser, D.C., & Orlebeke, J.F. (1990). Existing and training induced differences in aerobic fitness: Their relationship to physiological response patterns during different types of stress. *Psychophysiology*, 27, 457-478.
  20. de Geus, E.J.C., Kupper, N., Boomsma, D.I., & Snieder, H. (2007). Bivariate genetic modelling of cardiovascular stress reactivity: Does stress uncover genetic variance? *Psychosomatic Medicine*, 69, 356-364.
  21. Delaney, J.P.A., & Brodie, D.A. (2000). Effects of short-term psychological stress on the time and frequency domains of heart rate variability. *Perceptual and Motor Skills*, 91, 515-524.
  22. Duschek, S., Werner, N., Kapan, N., & Reyes del Paso, G.A. (2007). Patterns of cerebral blood flow and systemic hemodynamics during mental arithmetic. *Journal of Psychophysiology*, 22, 81-90.
  23. Egizio, V.B., Jennings, J.R., Christie, I.C., Sheu, L.K., Matthews, K.A., & Gianaros, P.J. (2008). Cardiac vagal activity during psychological stress varies with social functioning in older women. *Psychophysiology*, 45, 1046-1054.
  24. Ehrental, J.C., Herrmann-Lingen, C., Fey, M., & Schauenburg, H. (2010). Altered cardiovascular adaptability in depressed patients without heart disease. *The World Journal of Biological Psychiatry*, 11, 586-593.
  25. Farag, N.H., Bardwell, W.A., Nelesen, R.A., Dimsdale, J.E., & Mills, P.J. (2003). Autonomic responses to psychological stress: The influence of menopausal status. *Annals of Behavioral Medicine*, 26, 134-138.
  26. Friedman, B.H., Thayer, J.F., & Tyrrell, R.A. (1996). Spectral characteristics of heart period variability during cold face stress and shock avoidance in normal subjects. *Clinical Autonomic Research*, 6, 147-152.

27. Gianaros, P.J., Quigley, K.S., Mordkoff, J.T., & Stern, R.M. (2001). Gastric myoelectrical and autonomic cardiac reactivity to laboratory stressors. *Psychophysiology*, 38, 642-652.
28. Gianaros, P.J., Salomon, K., Zhou, F., Owens, J.F., Edmundowicz, D., Kuller, L.H., & Matthews, K.A. (2005). A greater reduction in high-frequency heart rate variability to a psychological stressor is associated with subclinical coronary and aortic calcification in postmenopausal women. *Psychosomatic Medicine*, 67, 553-560.
29. Grillot, M., Fauvel, J.P., Cottet-Emard, J.M., Laville, M., Peyrin, L., Pozet, N., & Zech, P. (1995). Spectral analysis of stress-induced change in blood pressure and heart rate in normotensive subjects. *Journal of Cardiovascular Pharmacology*, 25, 448-452.
30. Grossman, P., Brinkman, A., & de Vries, J. (1992). Cardiac autonomic mechanisms associated with borderline hypertension under varying behavioral demands: Evidence for attenuated parasympathetic tone but not for enhanced beta-adrenergic activity. *Psychophysiology*, 29, 698-711.
31. Grossman, P., Wilhelm, F.H., Kawachi, I., & Sparrow, D. (2001). Gender differences in psychophysiological responses to speech stress among older social phobics: Congruence and incongruence between self-evaluative and cardiovascular reactions. *Psychosomatic Medicine*, 63, 765-777.
32. Guasti, L., Simoni, C., Mainardi, L., Crespi, C., Cimpanelli, M., Klersy, C., et al. (2005). Global link between heart rate and blood pressure oscillations at rest and during mental arousal in normotensive and hypertensive subjects. *Autonomic Neuroscience: Basic and Clinical*, 120, 80-87.
33. Hawkey, L.C., Burleson, M.H., Poehlmann, K.M., Berntson, G.G., Malarkey, W.B., & Cacioppo, J.T. (2001). Cardiovascular and endocrine reactivity in older females: Intertask consistency. *Psychophysiology*, 38, 863-872.
34. Hoshikawa, Y., & Yamamoto, Y. (1997). Effects of Stroop color-word conflict test on the autonomic nervous system responses. *American Journal of Physiology*, 272, H1113-H1121.
35. Houtveen, J.H., Rietveld, S., & de Geus, E.J.C. (2002). Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory

- frequency to respiratory sinus arrhythmia during mental stress and physical exercise. *Psychophysiology*, 39, 427-436.
36. Hughes, J.W., & Stoney, C.M. (2000). Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine*, 62, 796-803.
  37. Isowa, T., Ohira, H., & Murashima, S. (2006). Immune, endocrine and cardiovascular responses to controllable and uncontrollable acute stress. *Biological Psychology*, 71, 202-213.
  38. Keary, T.A., Hughes, J.W., & Palmieri, P.A. (2009). Women with posttraumatic stress disorder have larger decreases in heart rate variability during stress tasks. *International Journal of Psychophysiology*, 73, 257-264.
  39. Kimura, K., Isowa, T., Ohira, H., & Murashima, S. (2005). Temporal variation of acute stress responses in sympathetic nervous and immune systems. *Biological Psychology*, 70, 131-139.
  40. Kop, W.J., Synowski, S.J., Newell, M.E., Schmidt, L.A., Waldstein, S.R., & Fox, N.A. (2011). Autonomic nervous system reactivity to positive and negative mood induction: The role of acute psychological responses and frontal electrocortical activity. *Biological Psychology*, 86, 230-238.
  41. Lantelme, P., Milon, H., Gharib, C., Gayet, C., & Fortrat, J. (1998). White coat effect and reactivity to stress: Cardiovascular and autonomic nervous system responses. *Hypertension*, 31, 1021-1029.
  42. Madden, K., & Savard, G.K. (1995). Effects of mental state on heart rate and blood pressure variability in men and women. *Clinical Physiology*, 15, 557-569.
  43. Matthews, S.C., Nelesen, R.A., & Dimsdale, J.E. (2005). Depressive symptoms are associated with increased systemic vascular resistance to stress. *Psychosomatic Medicine*, 67, 509-513.
  44. Mezzacappa, E.S., Kelsey, R.M., Katkin, E.S., & Sloan, R.P. (2001). Vagal rebound and recovery from psychological stress. *Psychosomatic Medicine*, 63, 650-657.
  45. Miller, S.B. (1994). Parasympathetic nervous system control of heart rate responses to stress in offspring of hypertensives. *Psychophysiology*, 31, 11-16.
  46. Moriguchi, A., Otsuka, A., Kohara, K., Mikami, H., Katahira, K., Tsunetoshi, T., et al. (1992). Spectral change in heart rate variability in response to mental arithmetic before

- and after the beta-andrenoceptor blocker, carteolol. *Clinical Autonomic Research*, 2, 267-270.
47. Mueller, A., Strahler, J., Armbruster, D., Lesch, K., Brocke, B., & Kirschbaum, C. (2012). Genetic contributions to acute autonomic stress responsiveness in children. *International Journal of Psychophysiology*, 83, 302-308.
  48. Nater, U.M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M.M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity- associations with adrenergic activity. *Psychoneuroendocrinology*, 31, 49-58.
  49. Ottaviani, C., Shapiro, D., Davydov, D.M., & Goldstein, I.B. (2008). Autonomic stress response modes and ambulatory heart rate level and variability. *Journal of Psychophysiology*, 22, 28-40.
  50. Pagani, M., Rimoldi, O., Pizzinelli, P., Furlan, R., Crivellaro, W., Liberati, D., et al. (1991). Assessment of the neural control of the circulation during psychological stress. *Journal of the Autonomic Nervous System*, 35, 33-42.
  51. Pagani, M., Mazzuero, G., Ferrari, A., Liberati, D., Cerutti, S., Vaitl, D., et al. (1991). Sympathovagal interaction during mental stress. *Circulation*, 83, II43-II51.
  52. Ring, C., Carroll, D., Willemsen, G., Cooke, J., Ferraro, A., & Drayson, M. (1999). Secretory immunoglobulin A and cardiovascular activity during mental arithmetic and paced breathing. *Psychophysiology*, 36, 602-609.
  53. Ring, C., Burns, V.E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology*, 39, 585-590.
  54. Ruediger, H., Seibt, R., Scheuch, K., Krause, M., & Alam, S. (2004). Sympathetic and parasympathetic activation in heart rate variability in male hypertensive patients under mental stress. *Journal of Human Hypertension*, 18, 307-315.
  55. Schubert, C., Lambertz, M., Nelesen, R.A., Bardwell, W., Choi, J.B., & Dimsdale, J.E. (2009). Effects of stress on heart rate complexity- A comparison between short-term and chronic stress. *Biological Psychology*, 80, 325-332.
  56. Schwabe, L., Szinnai, G., Keller, U., & Schachinger, H. (2007). Dehydration does not influence cardiovascular reactivity to behavioural stress in young healthy humans. *Clinical Physiology and Functional Imaging*, 27, 291-297.

57. Sgoifo, A., Braglie, F., Costoli, T., Musso, E., Meerlo, P., Ceresini, G., & Troisi, A. (2003). Cardiac autonomic reactivity and salivary cortisol in men and women exposed to social stressors: Relationship with individual ethological profile. *Neuroscience and Biobehavioral Reviews*, 27, 179-188.
58. Shinba, T., Kariya, N., Matsui, Y., Ozawa, N., Matsuda, & Yamamoto, K. (2008). Decrease in heart rate variability response to task is related to anxiety and depressiveness in normal subjects. *Psychiatry and Clinical Neurosciences*, 62, 603-609.
59. Sloan, R.P., Korten, J.B., & Myers, M.M. (1991). Components of heart rate reactivity during mental arithmetic with and without speaking. *Physiology and Behavior*, 50, 1039-1045.
60. Sloan, R.P., Shapiro, P.A., Bagiella, E., Fishkin, P.E., Gorman, J.M., & Myers, M.M. (1995). Consistency of heart rate and sympathovagal reactivity across different autonomic contexts. *Psychophysiology*, 32, 452-459.
61. Sloan, R.P., Shapiro, P.A., Bagiella, E., Gorman, J.M., & Bigger Jr., J.T. (1995). Temporal stability of heart period variability during a resting baseline and in response to psychological challenge. *Psychophysiology*, 32, 191-196.
62. Sloan, R.P., Demeersman, R.E., Shapiro, P.A., Bagiella, E., Kuhl, J.P., Zion, A.S., et al. (1997). Cardiac autonomic control is inversely related to blood pressure variability responses to psychological challenge. *American Journal of Physiology*, 272, H2227-H2232.
63. Sloan, R.P., Bagiella, A., Shapiro, P.A., Kuhl, J.P., Chernikhova, D., Berg, J., & Myers, M.M. (2001). Hostility, gender, and cardiac autonomic control. *Psychosomatic Medicine*, 63, 434-440.
64. Spalding, T.W., Jeffers, L.S., Porges, S.W., & Hatfield, B.D. (2000). Vagal and cardiac reactivity to psychological stressors in trained and untrained men. *Medicine & Science in Sports & Exercise*, 32, 581-591.
65. Strahler, J., Mueller, A., Rosenlocher, F., Kirschbaum, C., & Rohleder, N. (2010). Salivary  $\alpha$ -amylase stress reactivity across different age groups. *Psychophysiology*, 47, 587-595.

66. Uchino, B.N., Cacioppo, J.T., Malarkey, W., & Glaser, R. (1995). Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. *Journal of Personality and Social Psychology*, 69, 736-743.
67. Uchino, B.N., Uno, D., Holt-Lundstad, J., & Flinders, J.B. (1999). Age-related differences in cardiovascular reactivity during acute psychological stress in men and women. *The Journals of Gerontology*, 54B, P339-P346.
68. Vella, E.J., & Friedman, B.H. (2009). Hostility and anger in: Cardiovascular reactivity and recovery to mental arithmetic stressors. *International Journal of Psychophysiology*, 72, 253-259.
69. de Vries-Bouw, M., Popma, A., Vermeiren, R., Doreleijers, T.A.H., van de Ven, P.M., Jansen, L.M.C. (2011). The predictive value of low heart rate and heart rate variability during stress for reoffending in delinquent male adolescents. *Psychophysiology*, 48, 1596-1603.
70. Wang, X., Ding, X., Su, S., Li, Z., Riese, H., Thayer, J.F., Trieber, F., & Snieder, H. (2009). Genetic influences on heart rate variability at rest and during stress. *Psychophysiology*, 46, 458-465.
71. Wood, R., Maraj, B., Lee, C.M., & Reyes, F. (2002). Short-term heart rate variability during a cognitive challenge in young and older adults. *Age and Aging*, 31, 131-135.
72. Wright, C.E., O'Donnell, K., Brydon, L., Wardle, J., & Steptoe, A. (2007). Family history of cardiovascular disease is associated with cardiovascular responses to stress in healthy young men and women. *International Journal of Psychophysiology*, 63, 275-282.

#### Meta-analysis of parasympathetic blockade

1. Reyes del Paso, G.A., Langewitz, W., Robles, H., & Pérez, N. (1996). A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. *International Journal of Psychophysiology*, 22, 163-171.

---

**Appendix II: Chapter 3 Supplementary Tables**


---

**Table 3.6.** HR Variability and Complexity Intercorrelations Study 1 (N = 25)

	1.	2.	3.	4.	5.	6.	7.	8.
1. HR	1							
2. RMSSD	-.688**	1						
3. D2	-.563**	.286	1					
4. DF $\alpha$ 1	.599**	-.452*	-.063	1				
5. DF $\alpha$ 2	.059	-.252	-.353	-.143	1			
6. SD1	-.688**	1.00**	.286	-.452*	-.252	1		
7. SD2	-.414*	.659**	.254	.063	-.068	.659**	1	
8. ApEn	-.098	-.278	.112	-.050	.307	-.278	-.395*	1

\* =  $p < 0.05$ , \*\* =  $p < 0.01$ .**Table 3.7.** HR Variability and Complexity Intercorrelations Study 1 (N = 176)

	1.	2.	3.	4.	5.	6.	7.	8.
1. HR	1							
2. RMSSD	-.360**	1						
3. D2	-.400**	-.010	1					
4. DF $\alpha$ 1	.369**	-.549**	-.246**	1				
5. DF $\alpha$ 2	.509**	-.382**	-.292**	.286**	1			
6. SD1	-.358**	1.00**	-.010	-.549**	-.382**	1		
7. SD2	-.246**	.733**	.090	-.263**	-.211**	.733**	1	
8. ApEn	-.639**	.113	.386**	-.445**	-.418**	.113	-.112	1

\* =  $p < 0.05$ , \*\* =  $p < 0.01$ .

---

**Appendix III: Chapter 4 Supplementary Tables**


---

**Table 4.2.** Correlations between Allostatic Load and Cardiovascular Reactivity (N = 53)

	1.	2.	3.	4.	5.	6.	7.
9. Allostatic Load	1						
<u>PASAT Reactivity</u>							
10. HR	-.362**	1					
11. SBP	-.220	.505**	1				
12. DBP	-.175	.363**	.805**	1			
<u>Cold Pressor Reactivity</u>							
13. HR	-.101	-.002	-.121	-.102	1		
14. SBP	-.102	-.069	.025	.069	.405**	1	
15. DBP	-.051	-.148	-.074	.012	.333**	.642**	1

\* =  $p < 0.05$ , \*\* =  $p < 0.01$ .Note: Allostatic Load defined as the sum of Z scores for resting DBP,  $\beta$ -receptors, and waist-hip ratio**Table 4.3** Allostatic Load as a Predictor of HR Reactivity to PASAT (N = 53)

	$\beta$	$t$	$p$	$\Delta R^2$
Unadjusted Model				
Allostatic Load	-.36	-2.77	=.008	.131
Adjusted Model				
PASAT Score	.02	.123	.902	
Self-reported Task Engagment	.19	1.20	.237	
HADS-Depression	-.16	-1.15	.258	.081
Allostatic Load	-.35	-2.60	=.013	.117