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A tale of two mechanisms: A meta-analytic approach toward understanding the autonomic basis of cardiovascular reactivity to acute psychological stress

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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 (n = 113) and/or parasympathetic activity (n = 73). 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

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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; Ehrenthal, 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, Willhelm, 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, & Gorma, 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) 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; Kasprowicz, 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** (Figure1). 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). 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 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.).

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Data Extraction and Synthesis

Several *a priori* data extraction criteria were established for included studies: 1. if there were ≥ 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 1 shows the number of studies at each stage of the review process.

[Insert Figure 1 about here]

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, measure the capture vagal activity related to respiration (Grossman & Taylor, 2007). Thus, parasympathetic indices were reduced to frequency and time domain indices.

[Insert Figure 2 about here]

Results

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Blood Pressure and Heart Rate Stress Reactivity

Figure 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, $F(2,479) = 5.04$, $p = .007$.

[Insert Figure 3 about here]

Sympathetic Nervous System Reactivity

A total of 83 studies were included in the present analysis. Table 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 3).

[Insert Table 1 about here]

Sympathetic Blockade of Cardiovascular Reactivity

Thirty studies evaluated the effects of sympathetic blockade on cardiovascular reactivity (Table 2). A significant reduction in overall cardiovascular function (H_g = -0.339 [-0.417- -0.260]; $p < .001$), SBP (H_g = -0.218 [-0.321- -0.116]; $p < .001$), and HR (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 4).

[Insert Table 2 and Figure 4 about here]

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 (β) and beta-1 (β_1) specific antagonists significantly attenuated overall cardiovascular reactivity, drugs targeting alpha-1 (α_1) receptors failed to influence stress reactions (Figure 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 5). Analyses of individual sympathetic antagonists were carried out (data not shown) but these analyses failed to uncover any significant differences between individual drugs.

[Insert Figure 5 about here]

Parasympathetic Nervous System Reactivity

A total of 76 studies were included in this meta-analysis. Table 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 3).

[Insert Table 3 about here]

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)

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 6).

[Insert Figure 6 about here]

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 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 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.

[Insert Figure 7 about here]

[Insert Figure 8 about here]

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.

[Insert Figure 9 about here]

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).

Correlation Analysis of Effect Sizes

An exploratory correlation analysis of effect sizes was conducted to assess the relatedness of effects sizes (Table 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 ($p < .01$).

[Insert Table 4 about here]

Sensitivity Analysis

When study quality scores were regressed onto aggregate effects, significant relationships emerged for HR, β= -.22, t = -3.19, $p = .002$, $\Delta R^2 = .047$, PEP, β= .30, t = 2.68, $p = .009$, $\Delta R^2 = .091$, and DBP blockade, β= .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.

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 chrontropic and inotropic properties of the heart, primarily through the activation of β_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 β_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 β_1 and β_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 β_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 α-receptors that when left unopposed by β_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 (Andrén & Hansson, 1981; Schmieder, Rueddel, Neus, Messerli, & VonEiff, 1987; Ulrych, 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, & Nakamua, 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, Cunnigham, 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.

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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; Ehrenthal 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 (β-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.

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Authors Notes

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Table 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[1]		
Heart rate	81	97.59
Systolic blood pressure	56	67.46
Diastolic blood pressure	55	66.26
Sympathetic indices measured[1]		
Plasma epinephrine	42	50.60
Plasma norepinephrine	44	53.01
Pre-ejection period	45	54.21
Stress tasks[2]		
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[2]		
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	

[1]Categorical sums are > 84 because of studies capturing multiple cardiovascular and sympathetic measures

[2]Study designs utilized multiple stress paradigms and samples hence categorical sums > 84

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Table 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[1]		
Heart rate	30	100.00
Systolic blood pressure	26	86.67
Diastolic blood pressure	24	80.00
Pharmacological blockade[1]		
Alpha-1	5	16.67
Non-selective beta	17	56.67
Beta-1	17	56.67
Stress tasks[2]		
Mental arithmetic	15	50.00
Stroop task	6	20.00
Reaction time task	2	6.67
Other tasks	9	30.00
Sample characteristics[2]		
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[2]		
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	

[1]Categorical sums are > 30 because of studies capturing multiple cardiovascular measures and using multiple pharmacological agents

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Table 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[1]		
Heart rate	72	100.00
Systolic blood pressure	39	54.17
Diastolic blood pressure	33	45.83
Parasympathetic indices measured[1]		
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[2]		
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[2]		
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[2]		
Healthy	71	98.61
Hypertensive	3	4.17
Study quality		
Mean quality score	8.06	
Range	4.00 – 12.00	

[1]Categorical sums are > 72 because of studies capturing multiple cardiovascular and parasympathetic measures

[2]Study designs utilized multiple stress paradigms and samples hence categorical sums > 72

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Table 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.

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Figure 1. Flow diagram of sympathetic nervous system systematic review.

Figure 2. Flow diagram of parasympathetic nervous system systematic review.

Figure 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. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate. *indicates $p < .05$.

Figure 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 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

Figure 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

Figure 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

Figure 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

Figure 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

Figure 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.

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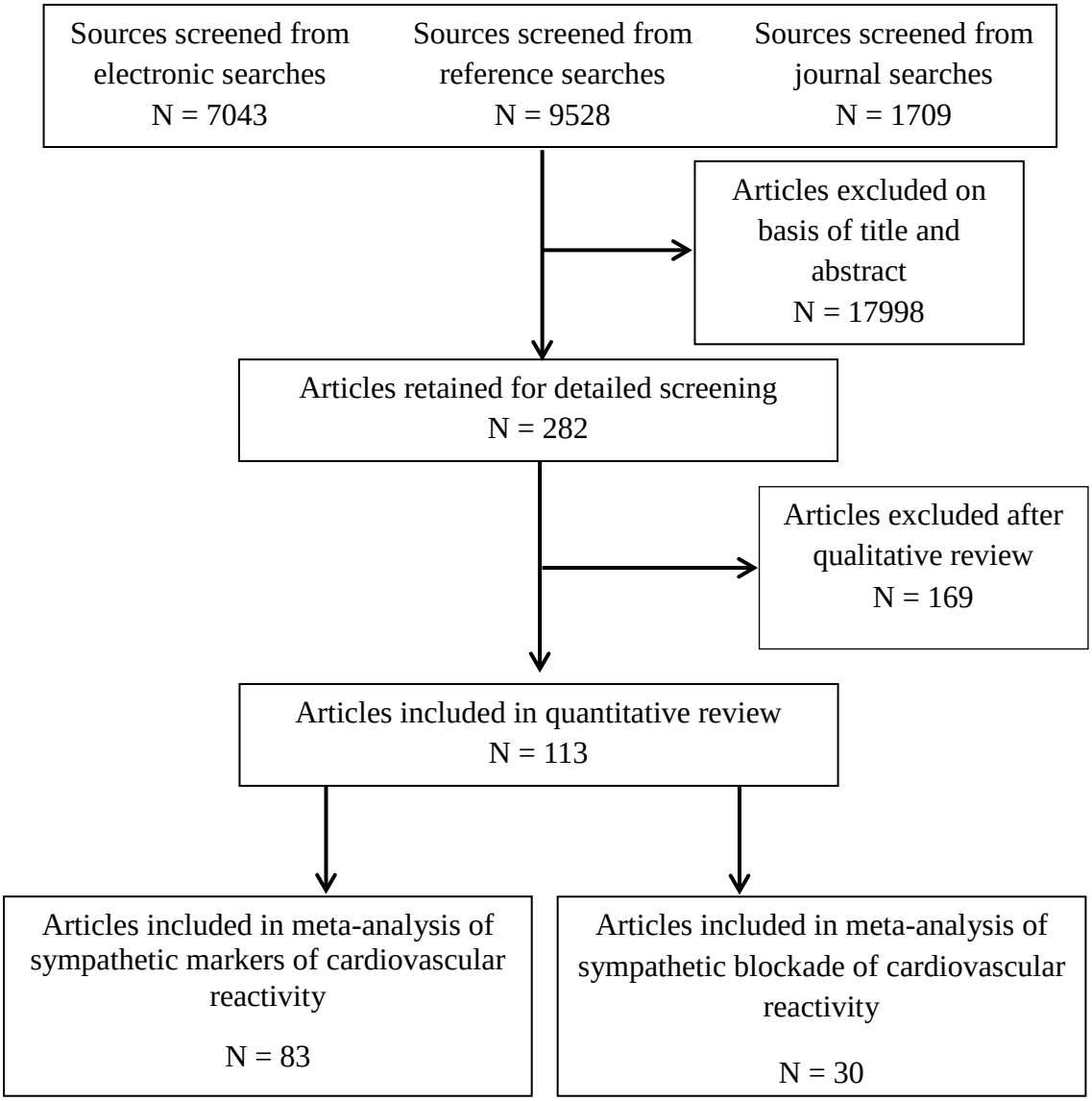

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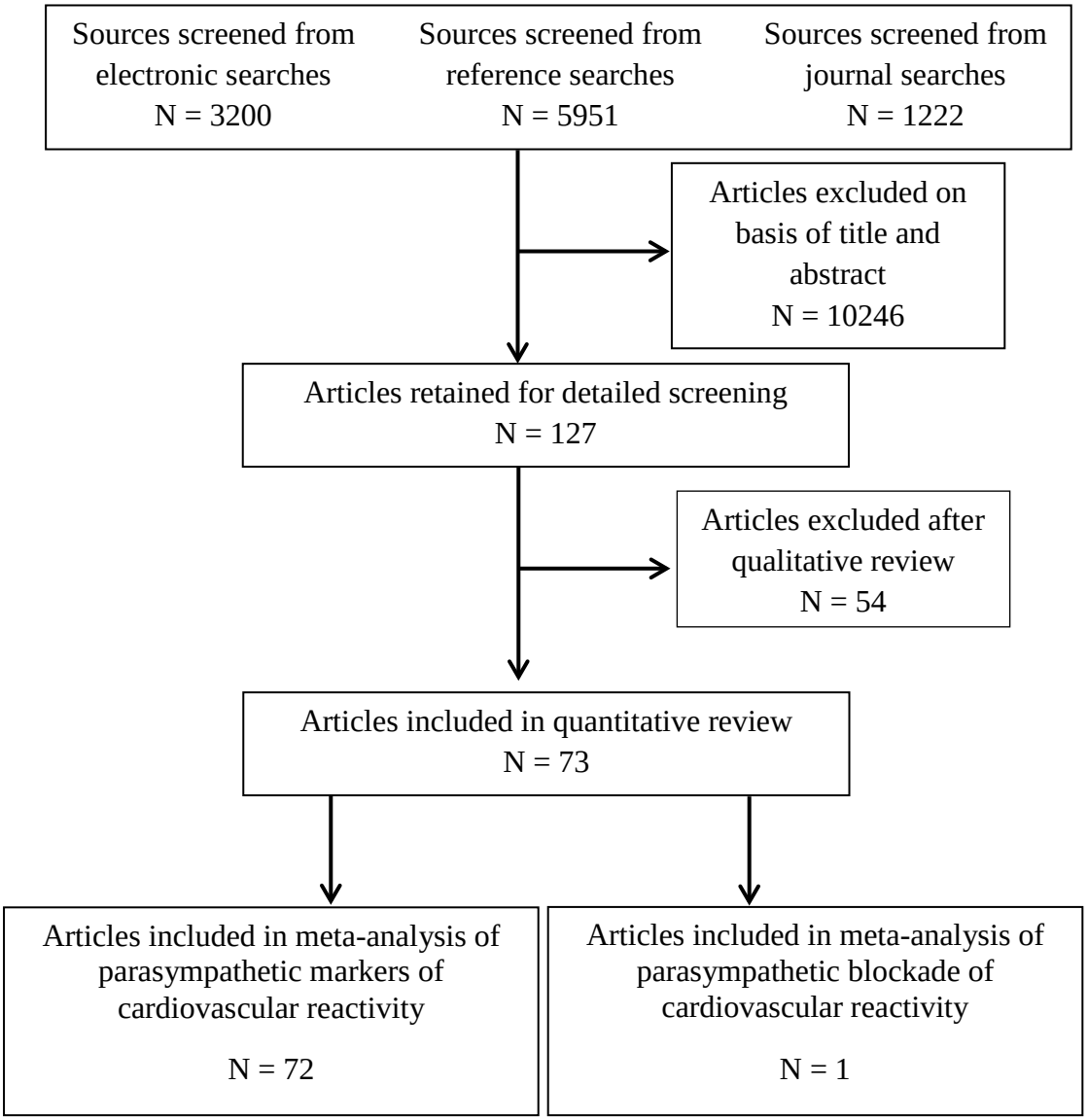

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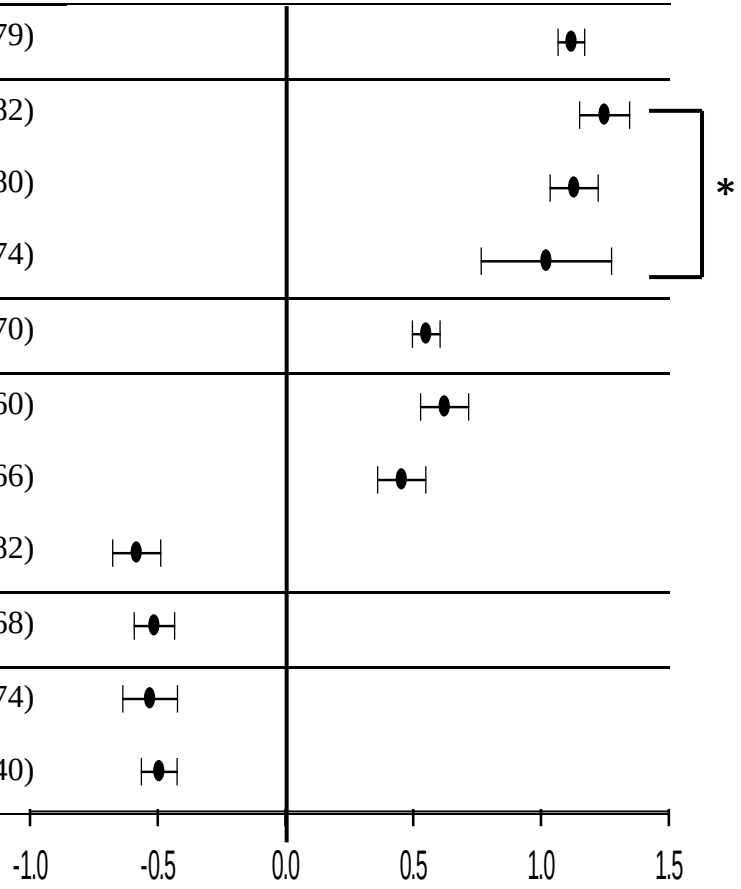
		Effect Size		Heterogeneity
Measure	N	Hedge's g (95% CI)	*p*	I^2 (95%CI)
Overall cardiovascular	21202	1.119 (1.068 - 1.170)	< .001	0.77 (0.75-0.79)
SBP	6277	1.249 (1.151 - 1.348)	< .001	0.79 (0.75-0.82)
DBP	5773	1.130 (1.036 - 1.224)	< .001	0.77 (0.73-0.80)
HR	8620	1.021 (0.946 - 1.095)	< .001	0.70 (0.66-0.74)
Overall sympathetic	8336	0.551 (0.497 - 0.605)	< .001	0.66 (0.61-0.70)
Plasma epinephrine	1976	0.623 (0.529 - 0.716)	< .001	0.46 (0.29-0.60)
Plasma norepinephrine	2003	0.455 (0.361 - 0.548)	< .001	0.56 (0.42-0.66)
Pre-ejection period	4223	-0.582 (-0.676 - -0.487)	< .001	0.77 (0.72-0.82)
Overall parasympathetic	5631	-0.513 (-0.592 - -0.434)	< .001	0.60 (0.52-0.68)
HF-HRV/RSA	3390	-0.529 (-0.636 - -0.429)	< .001	0.68 (0.60-0.74)
RMSSD	1641	-0.582 (-0.748 - -0.416)	< .001	0.00 (0.00-0.40)



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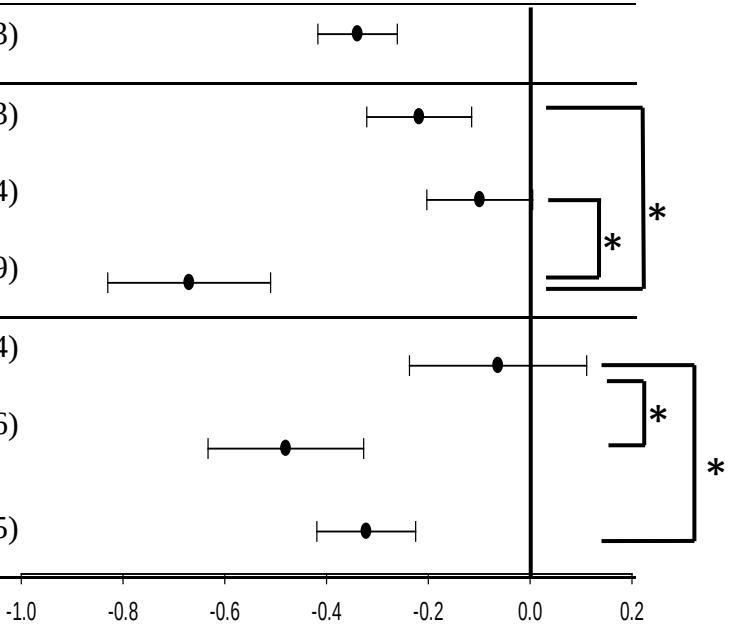
		Effect Size		Heterogeneity
Measure	N	Hedge's g (95% CI)	*p*	I^2 (95%CI)
Overall cardiovascular	2421	-0.339 (-0.417 - -0.260)	< 0.001	0.44 (0.32-0.53)
SBP	752	-0.218 (-0.321 - -0.116)	< 0.001	0.00 (0.00-0.33)
DBP	720	-0.099 (-0.203 - 0.006)	= 0.064	0.00 (0.00-0.34)
HR	812	-0.670 (-0.830 - -0.509)	< 0.001	0.58 (0.44-0.69)
Alpha-1 blockers	348	-0.063 (-0.237 - 0.110)	= 0.474	0.18 (0.00-0.54)
Non-selective beta blockers	901	-0.480 (-0.633 - -0.327)	< 0.001	0.55 (0.41-0.66)
Beta-1 blockers	1120	-0.322 (-0.419 - -0.225)	< 0.001	0.27 (0.03-0.45)



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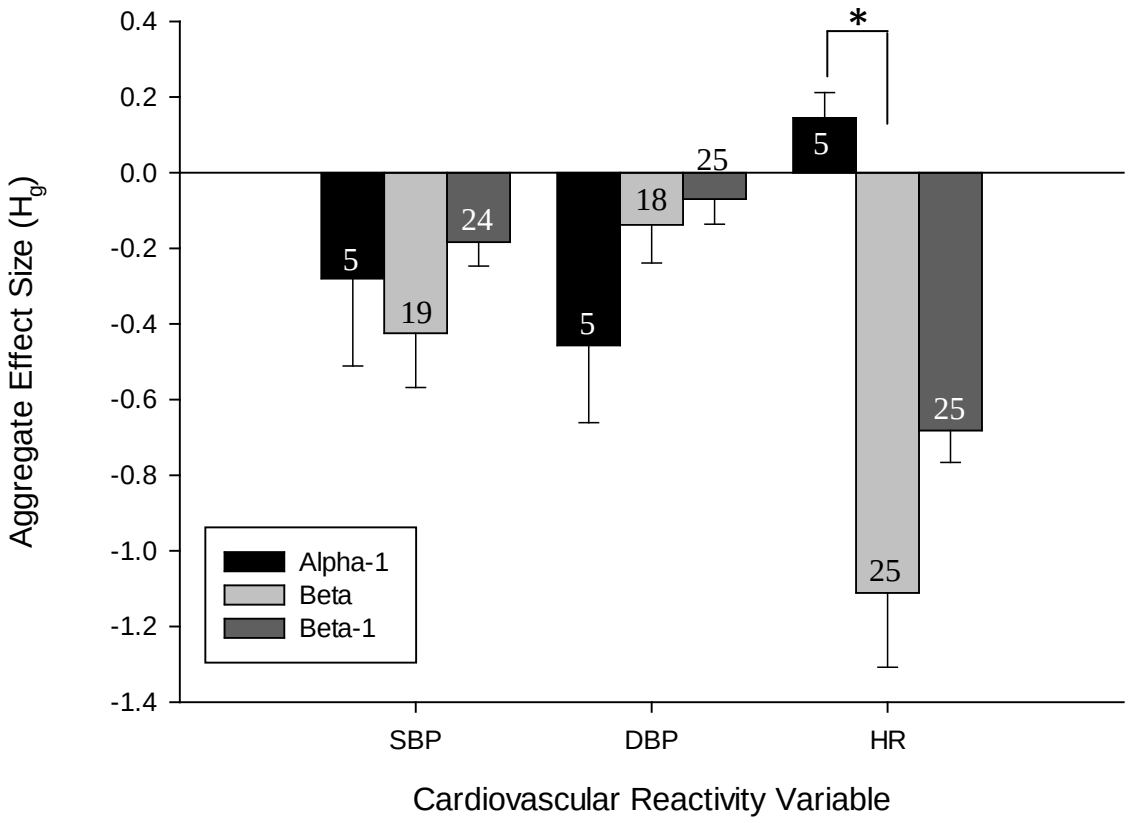

*indicates $p < .05$.

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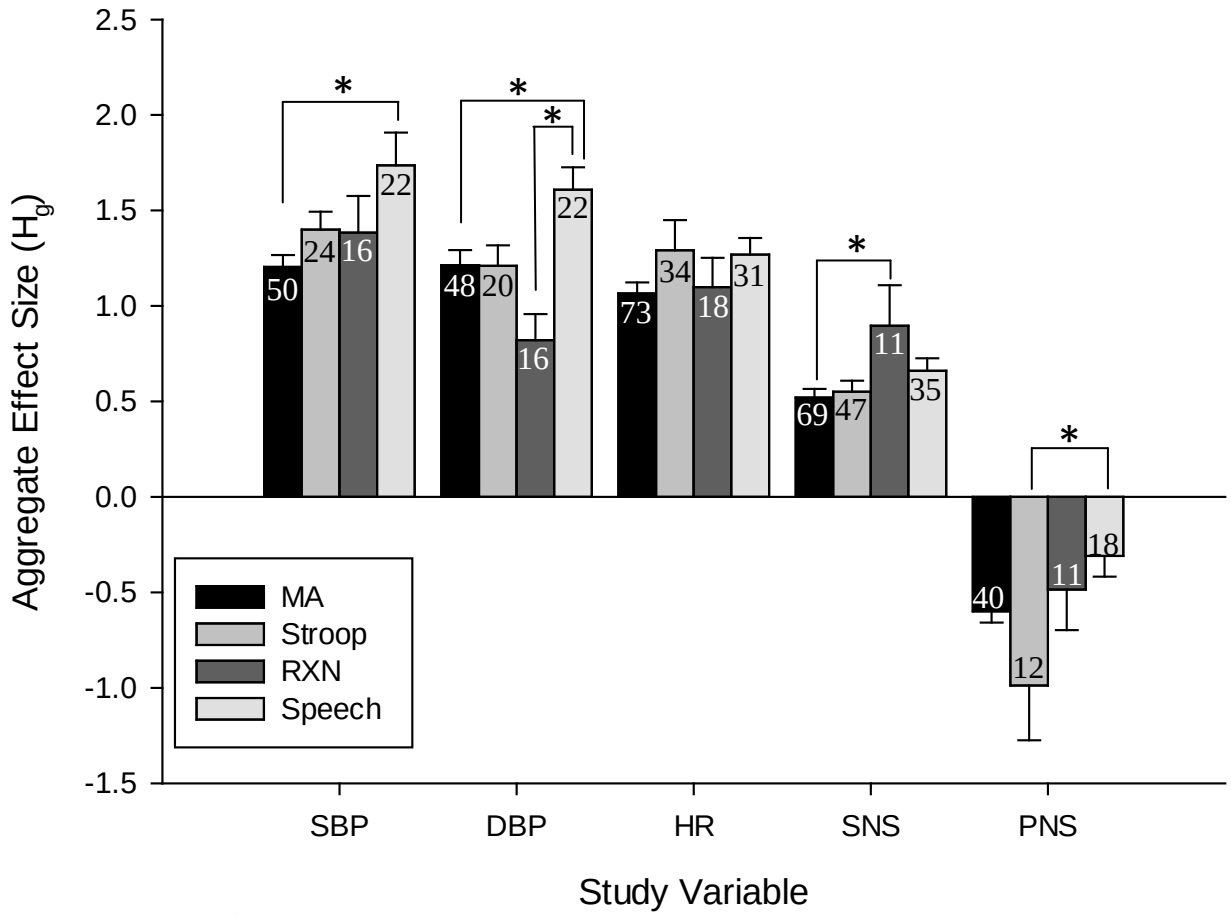

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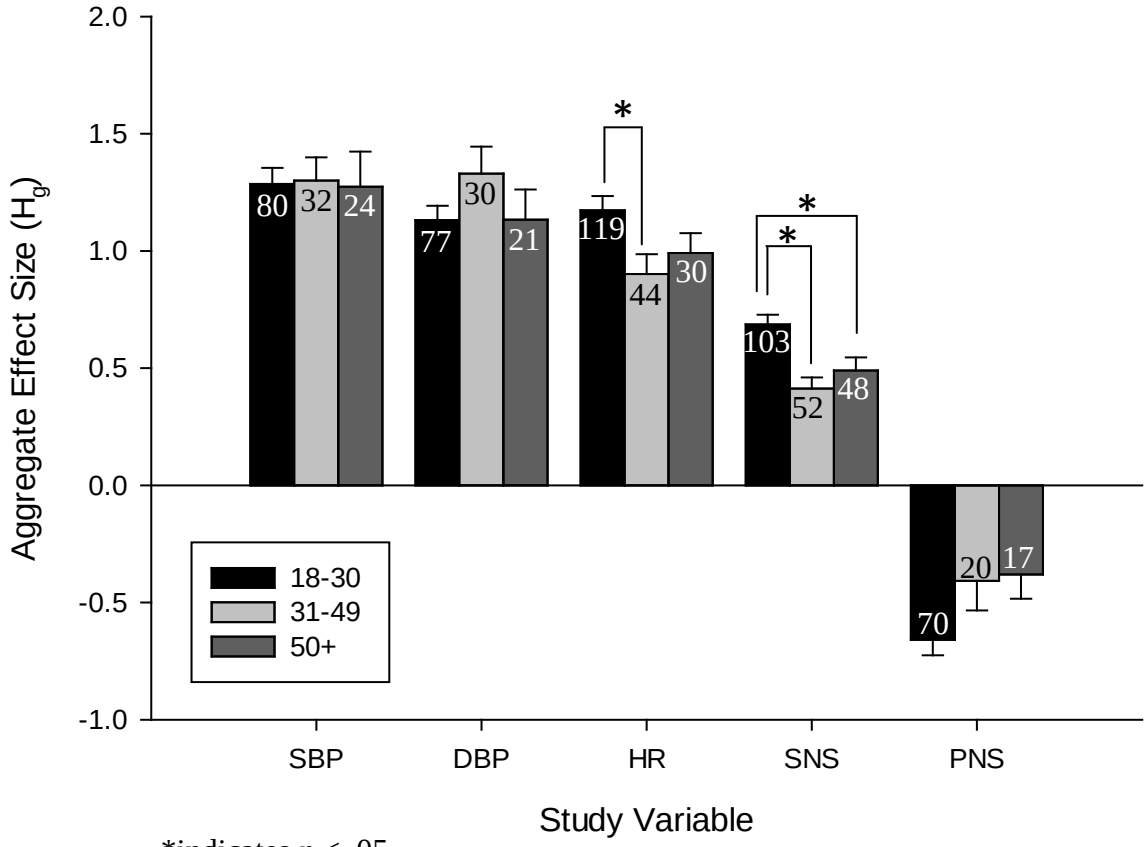

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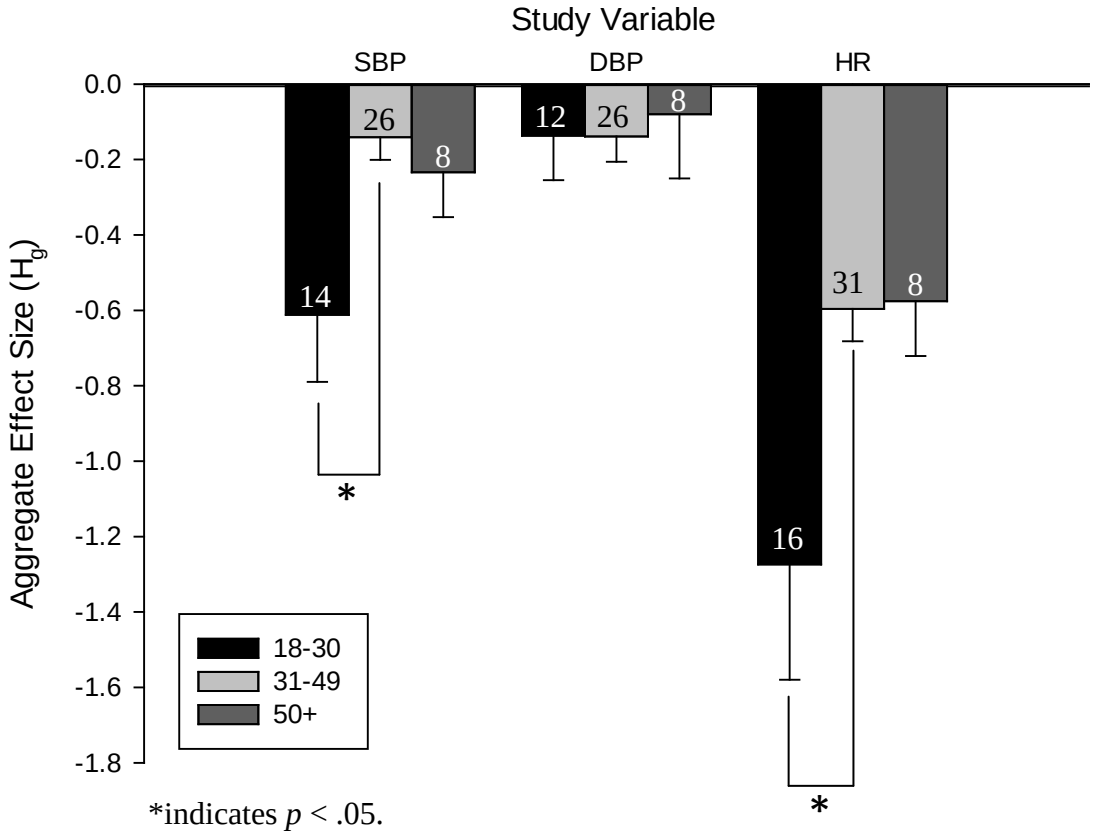

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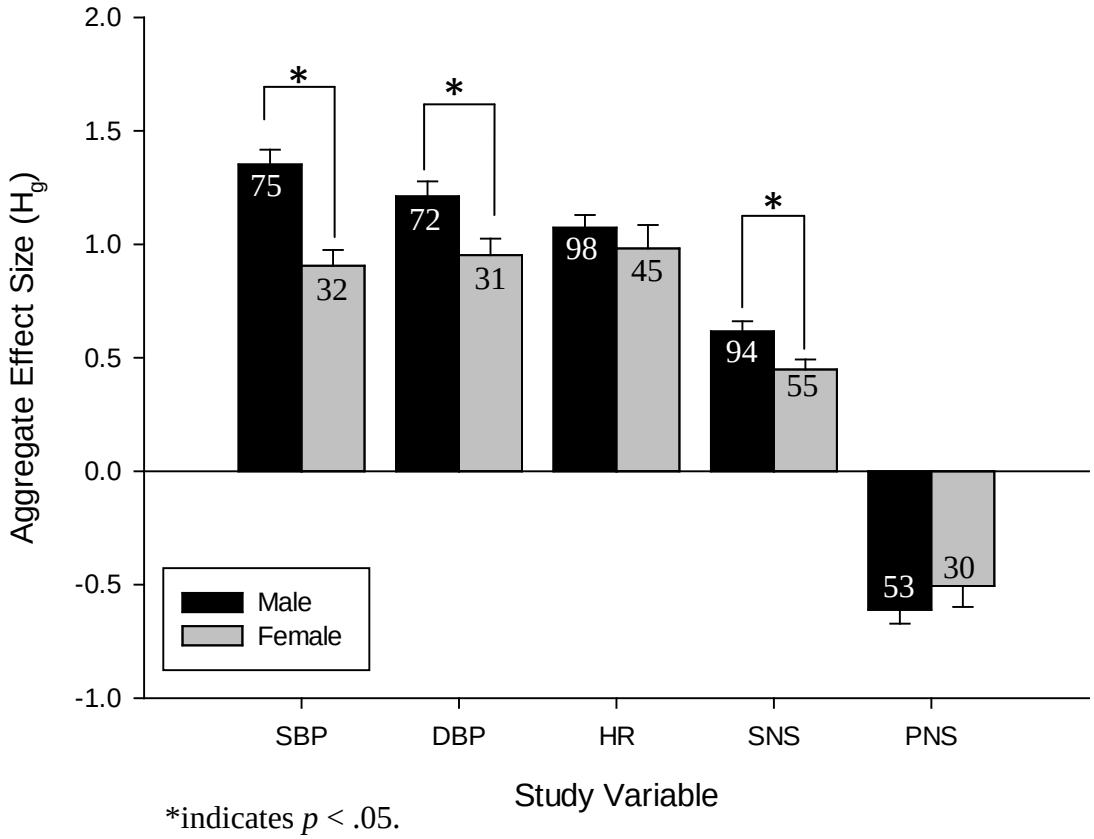

*indicates $p < .05$.

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		Effect Size		Heterogeneity
Measure	N	Hedge's g (95% CI)	*p*	I^2 (95%CI)
Overall sympathetic	4878	0.585(0.436 – 0.735)	<.001	0.72 (0.63-0.78)
Plasma Epinephrine	739	0.619 (0.447 - 0.791)	<.001	0.16 (0.00-0.67)
Plasma Norepinephrine	743	0.458 (0.062 - 0.854)	= 0.023	0.81 (0.66-0.89)
Pre-ejection period	3396	-0.615(-0.816 - -0.414)	<.001	0.73 (0.62-0.81)
Overall Parasympathetic	3646	-0.530 (-0.655 - -0.406)	<.001	0.54 (0.34-0.68)
HR-HRV/RSA	3146	-0.564 (-0.722 - -0.406)	<.001	0.63 (0.45-0.75)
RMSSD	388	-0.448 (-0.650 - -0.245)	<.001	0.00 (0.00-0.71)