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Review

Genetic influences on cardiovascular stress reactivity

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ABSTRACT

Individual differences in the cardiovascular response to stress play a central role in the reactivity hypothesis linking frequent exposure to psychosocial stress to adverse outcomes in cardiovascular health. To assess the importance of genetic factors, a meta-analysis was performed on all published twin studies that assessed heart rate (HR) or blood pressure (BP) reactivity to the cold pressor test or various mental stress tasks. For reactivity to mental stress, the pooled heritability estimate ranged from 0.26 to 0.43. Reactivity to the cold pressor test yielded heritability estimates from 0.21 to 0.55. An ensuing review of genetic association studies revealed a number of genes, mostly within the sympathoadrenal pathway, that may account for part of the heritability of cardiovascular stress reactivity. Future progress in gene finding, that should include measures of sympathetic and vagal stress reactivity, may help uncover the molecular pathways from genetic variation to stress reactivity.

Contents

1. Introduction

Twin research has suggested a clear-cut genetic contribution to cardiovascular disease (CVD). These studies typically compare the concordance rates for cardiovascular morbidity or mortality in monozygotic (MZ) twins to those in dizygotic (DZ) twins. MZ twins, with a few rare exceptions (Martin et al., 1997), share all of their genotypes, whereas DZ twins on average share only half of the genotypes segregating in the family. Therefore, a larger concordance for CVD in MZ than in DZ twins means that genetic variation contributes to the risk for CVD. A landmark paper was published by twin researchers in Sweden (Marenberg et al., 1994). They searched the National Death Registry for death certificates on ∼21,000 twins born in Sweden between 1886 and 1925, where both twins within a pair still lived within the country in 1961. Survival analysis in males showed that the relative hazard of death from coronary heart disease when one's twin died of coronary heart disease before the age of 55 years, as compared with the hazard when one's twin did not die before 55, was 8.1 for monozygotic twins and 3.8 for male dizygotic twins. Among the women, when one's twin died of coronary heart disease before the age of 65 years, the relative hazard was 15.0 for monozygotic twins and 2.6 for dizygotic twins. Re-analysis using a correlated frailty model, which translates discrete yes/no traits into a continuously distributed latent liability, yielded a heritability to die from coronary heart disease of 57% in males and 38% in females (Zdravkovic et al., 2002, 2004).

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The genetic contribution to cardiovascular disease endpoints most likely results from the joint effects of risk genes on the classical biological and behavioral risk factors that impact on the atherosclerotic process. These include smoking (Li et al., 2003; Vink et al., 2005), physical inactivity (Stubbe et al., 2006; Beunen and Thomis, 1999), body mass index (Schousboe et al., 2003; Silventoinen et al., 2003) diabetes (Poulsen et al., 1999), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Evans et al., 2003; Kupper et al., 2005b), and plasma LDL-C and HDL-C levels (Beekman et al., 2002). Heritability estimates for these established risk factors are 50% or higher in most adult twin samples and these estimates remain remarkably similar across the adult life span (Hottenga et al., 2005, 2006; Snieder et al., 1999). Population variance in a number of other suspected risk factors, including insulin resistance (Poulsen et al., 2001; Liu et al., 2009; Simonis-Bik et al., 2008), inflammation (Worns et al., 2006; Su et al., 2008), hemostasis (de Lange et al., 2006; Peetz et al., 2004), cardiac autonomic control (Wang et al., 2009; Kupper et al., 2005a, 2006), type A (Rebollo and Boomsma, 2006) or type D (Kupper et al., 2007) personality, and depression (Sullivan et al., 2000) has also shown substantial genetic variation.

In addition to the above risk factors, cardiovascular reactivity to mental and emotional stressors has long been regarded to be a potential contributor to individual differences in cardiovascular disease risk (Treiber et al., 2003b; Kamarck and Lovallo, 2003). A propensity towards exaggerated reactivity combined to frequent exposure to stress may lead to allostatic changes in many of the regulatory systems important in CVD and identified above, e.g. blood pressure regulation, lipid and insulin metabolism, inflammation, and hemostasis. Cardiovascular stress reactivity is typically assessed by comparing baseline levels of heart rate (HR), SBP, and DBP to the levels attained during deliberate exposure to a painful stimulus like the cold pressor test or to mentally demanding tasks that are made stressful by adding performance-contingent reward or punishment (electric shock, loud noise). Apart from HR, SBP, and DBP additional measures are sometimes assessed as well to establish the relative contribution of the sympathetic versus the parasympathetic nervous system or vascular versus cardiac responses to the observed changes in HR and BP. These measures include venous or arterial catecholamine levels, pre-ejection period (PEP), heart rate variability (HRV), stroke volume, and total peripheral resistance (Berntson et al., 2008; Lawler et al., 2001; Sherwood et al., 1990).

Psychometric studies have established satisfactory temporal stability of the commonly used cardiovascular reactivity measures, particularly when aggregated over multiple stressors (Kamarck et al., 1992; Swain and Suls, 1996). Individual differences in cardiovascular reactivity to laboratory stress have been shown to translate well to naturalistic settings (Kamarck et al., 2003) and prospective studies have shown that these individual differences predict future hypertension (Light et al., 1999; Flaa et al., 2008; Moseley and Linden, 2006; Matthews et al., 2004; Newman et al., 1999) and atherosclerosis (Kamarck et al., 1997; Matthews et al., 2006). Obvious next questions are to what extent these individual differences in cardiovascular reactivity to stress are heritable and which genes may be involved. Identifying the genetic factors influencing stress reactivity may greatly improve the precision of epidemiological studies linking psychosocial stress to disease outcome (Yusuf et al., 2004). By lumping together subjects who are genetically susceptible to the effects of psychosocial stressors with those subjects that are less susceptible, many previous studies in the field may even have underestimated the significance of negative health effects in the former susceptible group.

Already more than a decade ago, Turner and Hewitt (1992; Hewitt and Turner, 1995) reviewed a number of early twin studies that explored the genetic and environmental origins of individual differences in HR and BP reactivity to psychological challenge. Their conclusion was that HR and BP reactivity are substantially heritable. Additional twin studies of cardiovascular reactivity have since confirmed heritability of HR and BP reactivity, but estimates for DBP, SBP and HR reactivity have been very different across studies for the same task or, within the same study, across different tasks, and have ranged from 0.00 to 0.85 (Ditto, 1993; Lensvelt-Mulders and Hettema, 2001; Smith et al., 1987; Carmelli et al., 1991; McIlhany et al., 1975; de Geus et al., 2007; Li et al., 2001; McCaffery et al., 2002).

Here we performed a meta-analysis on all published studies in twins that assessed HR or BP reactivity to the cold pressor or mental stress tasks. In the discussion, we briefly review the heritability estimates of a number of other cardiovascular measures for which sufficient numbers were not yet available to do a meta-analysis. We further review the first attempts to find genetic associations with reactivity measures in molecular genetic studies.

2. Methods

2.1. Search strategy

We identified articles on cardiovascular stress reactivity in twins through a systematic search of the MEDLINE (Pubmed) database and inspection of reference lists of selected articles up to July 1st 2009. The following terms were used for the MEDLINE search ("Blood Pressure"[Mesh] OR "heart rate"[Mesh]) AND "Twin"[All Fields] AND "Heritability"[All Fields] AND ("reactivity"[All Fields] OR "response"[All Fields] OR "stress"[All Fields]). No language restriction was applied for searching and study inclusion.

We only included the articles that reported the sample size and separate correlations for monozygotic (MZ) and dizygotic (DZ) twins for SBP, DBP or HR reactivity to the cold pressor test or to mentally demanding tasks. Three articles by Busjahn et al. (1996), Snieder et al. (1997) and Carmelli et al. (1985) were preliminary reports of the same studies as reported in Li et al. (2001), de Geus et al. (2007) and Carmelli et al. (1991), respectively. The initial reports were removed as duplicates because the latter articles reported larger sample sizes. We further excluded literature reviews and three older studies in which the sample size was less than 80 twin pairs (Shapiro et al., 1968; Carroll et al., 1985; Turner et al., 1986). If the results from multiple independent samples ($\geq$80 pairs) were included in a single paper, these were treated as separate studies (e.g. adolescent and middle-aged twin samples in de Geus et al., 2007). For the cold pressor test, we also included the study by Snieder et al. (1997; van Doornen et al., 1998) for which the twin correlations have not been published previously. For each included study, we listed authors, publication year, and extracted information on ethnicity, sample size, mean age with standard deviation and age range, stressors and twin correlations for SBP, DBP, and HR (see Tables 1 and 4).

2.2. Meta-analysis

Meta-analysis was done separately for reactivity to mental stress and the cold pressor test. In studies that used multiple mental stressors, we used the aggregated reactivity measures across all mental stressors. Two studies already reported on aggregated mental stress only (McCaffery et al., 2002; de Geus et al., 2007). In a third study (Ditto, 1993) we aggregated the two mental stress tasks by estimating a single twin correlation across these tasks during the pooling procedure described below.

Structural equation modeling (SEM) in Mx software (Neale et al., 2006) was used to estimate five pooled twin correlations across all studies for five zygosity-by-sex groups: MZ males (MZM), DZ males (DZM), MZ females (MZF), DZ females (DZF) and dizygotic opposite sex (DOS). Two studies originally reported sample size and twin correlations in only two zygosity groups (MZ and DZ)

Table 1
Description of twin correlations of SBP, DBP and HR reactivity to mental stress.

Investigator	Ethnicity	Sample size (pairs)	Age		Stressors	Twin correlations		
			Mean ± SD	Range		SBP	DBP	HR
Smith et al. (1987)	Caucasians	82 MZM 88 DZM	35.0 ± n.a.	21.0–61.0	MA	R_{MZM}: 0.24 R_{DZM}: -0.06[a]	R_{MZM}: 0.30 R_{DZM}: 0.04	R_{MZM}: 0.07 R_{DZM}: 0.21
Carmelli et al. (1991)	Caucasians	47 MZM 54 DZM	62.4 ± n.a.	59.0–69.0	MA	R_{MZM}: 0.71 R_{DZM}: 0.31	R_{MZM}: 0.56 R_{DZM}: 0.23	R_{MZM}: 0.46 R_{DZM}: 0.17
Ditto (1993)	Caucasians	20 MZM 20 MZF 20 DZM 20 DZF 20 DOS	20.0 ± 5.0	12.0–44.0	Aggregated 1. MA 2. CT	R_{MZM}: 0.32 R_{DZM}: -0.08 R_{MZF}: 0.23 R_{DZF}: 0.16 R_{DOS}: 0.19	R_{MZM}: 0.65 R_{DZM}: 0.03 R_{MZF}: 0.19 R_{DZF}: 0.20 R_{DOS}: 0.19	R_{MZM}: 0.59 R_{DZM}: 0.07 R_{MZF}: 0.50 R_{DZF}: 0.12 R_{DOS}: 0.15
Lensvelt-Mulders and Hettema (2001)	Caucasians	57 MZF 43 DZF	31.5 ± n.a.	18.0–47.0	Film evoked emotion	R_{MZF}: 0.44 R_{DZF}: 0.27	R_{MZF}: 0.27 R_{DZF}: 0.23	n.a.
Li et al. (2001)	Caucasians	82 MZM 42 MZF 37 DZM 13 DZF 24 DOS	30.0 ± 12.0	n.a.	MA	R_{MZM}: 0.05 R_{DZM}: 0.21 R_{MZF}: 0.53 R_{DZF}: 0.18 R_{DOS}: 0.39	R_{MZM}: 0.20 R_{DZM}: 0.20 R_{MZF}: 0.38 R_{DZF}: 0.003 R_{DOS}: 0.33	R_{MZM}: 0.53 R_{DZM}: 0.28 R_{MZF}: 0.61 R_{DZF}: 0.42 R_{DOS}: 0.36
McCaffery et al. (2002)	Caucasians	54 MZM 47 MZF 22 DZM 22 DZF	21.1 ± 2.8	18.0–30.0	Aggregated 1. Stroop 2. MA	R_{MZM}: 0.43 R_{DZM}: -0.19 R_{MZF}: 0.24 R_{DZF}: 0.20	R_{MZM}: 0.37 R_{DZM}: -0.19 R_{MZF}: 0.24 R_{DZF}: -0.09	R_{MZM}: 0.56 R_{DZM}: -0.05 R_{MZF}: 0.49 R_{DZF}: 0.46
de Geus et al. (2007)	Adolescent Caucasians	35 MZM 35 MZF 31 DZM 30 DZF 29 DOS	16.7 ± 2.0	13.0–22.0	Aggregated 1. RT 2. MA	R_{MZM}: 0.56 R_{DZM}: 0.24 R_{MZF}: 0.24 R_{DZF}: 0.41 R_{DOS}: 0.04	R_{MZM}: 0.12 R_{DZM}: 0.11 R_{MZF}: 0.15 R_{DZF}: 0.27 R_{DOS}: -0.06	R_{MZM}: 0.37 R_{DZM}: 0.01 R_{MZF}: 0.50 R_{DZF}: 0.26 R_{DOS}: 0.27
	Middle-aged Caucasians	45 MZM 49 MZF 37 DZM 39 DZF 39 DOS	44.2 ± 6.7	34.0–63.0	Aggregated 1. RT 2. MA	R_{MZM}: 0.38 R_{DZM}: -0.19 R_{MZF}: 0.25 R_{DZF}: -0.16 R_{DOS}: 0.39	R_{MZM}: 0.14 R_{DZM}: 0.11 R_{MZF}: 0.27 R_{DZF}: -0.06 R_{DOS}: 0.07	R_{MZM}: 0.45 R_{DZM}: 0.45 R_{MZF}: 0.44 R_{DZF}: 0.11 R_{DOS}: 0.15

RT: reaction time task; MA: mental arithmetic task; CT: concept task; Stroop: color-word conflict task; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MZM: monozygotic males; DZM: dizygotic males; MZF: monozygotic females; DZF: dizygotic females; DOS: dizygotic opposite sex; n.a.: data not given in the article.

[a] The minus sign was incorrectly omitted in the original article as indicated by Turner and Hewitt (1992).

rather than five zygosity-by-sex groups (Li et al., 2001; McCaffery et al., 2002). We contacted the authors of these two studies, and both groups were willing and able to revisit their original dataset and provide us with the correlations for each zygosity-by-sex group.

For each zygosity-by-sex group, heterogeneity of the twin correlations across studies was tested by comparing the model that fixed the correlations to be equal across studies to the full model that estimated the twin correlations separately for each study. The degrees of freedom for this test is the number of the studies available for pooling minus one. Taking SBP reactivity to mental stress as an example (Table 1), MZM and DZM correlations were set equal across seven studies (there were only females in the study of Lensvelt-Mulders and Hettema (2001), MZF and DZF correlations across six studies (there were only males in studies of Smith et al. (1987) and Carmelli et al. (1991), and DOS correlations across three studies (Ditto, 1993 and adolescent and middle-aged twins in de Geus et al., 2007). To test for heterogeneity the fit of these models was then compared to the full models, with degrees of freedom of 6, 5, and 2 respectively.

2.2.1. *Genetic modeling and sex differences*

In a next step, SEM of the pooled twin correlations was used to estimate the genetic and environmental sources of individual differences (i.e. variance components) in BP and HR reactivity to mental stress and the cold pressor test. The sample size for each zygosity-by-sex group was equal to the sum of the sample sizes of all included studies. The full model allows for additive genetic (A), either common environmental (C) or dominant genetic (D) influences as well as unique environmental (E) influences on SBP, DBP and HR reactivity. The total variance was constrained to be equal to one in these models. More parsimonious models then leave out individual genetic or environmental components and we tested the loss of fit to the observed data by calculating the change in χ^2 ($\Delta\chi^2$) against the gain of degrees of freedom (Δdf).

The existence of sex differences in the influences of genetic and environmental factors on the phenotype can take several forms (Reynolds and Hewitt, 1995). Sex differences were examined by comparing a full model in which parameter estimates were allowed to differ in magnitude between males and females, with a reduced model in which parameter estimates are constrained to be equal across the sexes. In addition, models were tested in which genetic or common environmental influences differ in kind between males and females. In this case, correlations in DOS twin pairs between the latent genetic (r_g) or common environmental (r_c) factors will be smaller than the normal values of 0.5 and 1, respectively.

3. Results

We identified a total of 20 potentially relevant articles through our searches, but excluded 12 for the reasons listed in Fig. 1. In the remaining eight articles, we identified nine published studies that met our inclusion criteria and added one previously unpublished analysis of cold pressor data in one of our own samples. Eight studies could be used in the meta-analysis of cardiovascular (CV) reactivity to mental stress (Table 1), and five could be used in the meta-analysis of cardiovascular reactivity to the cold pressor test (Table 4).

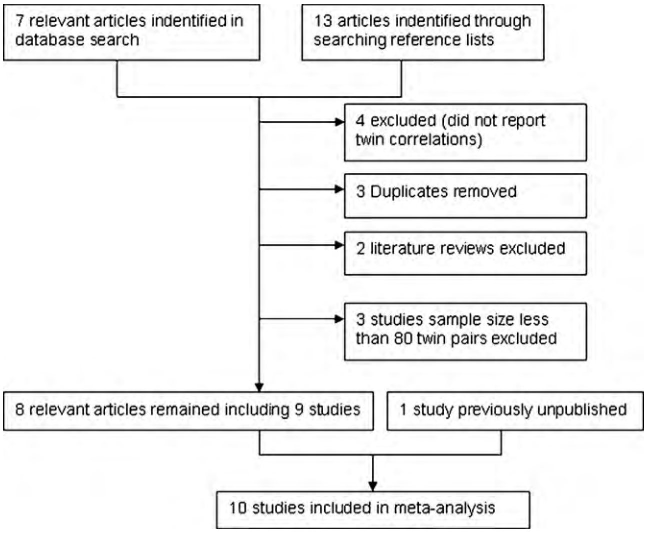

Fig. 1. Selection tree for the studies included in the meta-analysis. The database search identified articles up to July 1, 2009.

3.1. Cardiovascular reactivity to mental stress

Table 2 shows the total sample size and the pooled twin correlations for each zygosity-by-sex group. MZ correlations are consistently higher than DZ correlations for SBP, DBP as well as HR reactivity to mental stress, indicating an important contribution of genetic factors. Models that set twin correlations equal across studies in the five zygosity-by-sex groups did not have a significant worse fit (p's > 0.01) than the full model, with the exception of SBP reactivity in the MZ males ($p = 0.001$). This indicates heterogeneity in the MZM twin correlations across these studies. The main source of this heterogeneity was the study of Carmelli et al. (1991). Recomputing the pooled MZM correlation without this study changed the correlation estimate from 0.36 (0.26–0.45) to 0.29 (0.18–0.39).

Table 3 presents the genetic and environmental parameter estimates and 95% confidence intervals of the best fitting models for SBP, DBP and HR reactivity to mental stress. For SBP reactivity an AE model with sex differences in heritability provided the best fit. Heritabilities were 0.26 and 0.38 for SBP reactivity in males and females, respectively. Excluding the data of Carmelli et al. (1991) from the pooled MZM correlation decreased SBP reactivity in males to 0.19 (0.17–0.21).

For DBP reactivity, in addition to additive genetic effect (0.14), we also observed dominant genetic effects (0.15). There was no significant sex difference in the genetic and environmental estimates for DBP and HR.

3.2. Cardiovascular reactivity to the cold pressor test

Table 5 shows the total sample size and the pooled twin correlations for each zygosity-by-sex group. MZ correlations are higher than DZ correlations for SBP, DBP as well as HR reactivity, indicating an important contribution of genetic factors. Models that set twin correlations equal across studies in the five zygosity-by-sex groups did not fit significantly worse than the full model (p's > 0.01), with the exception of DBP reactivity in MZ males ($p = 2.0 \times 10^{-6}$) and HR reactivity in MZ females ($p = 3.6 \times 10^{-8}$). For DBP reactivity in MZ males, heterogeneity was mainly due to two studies (McIlhany et al., 1975; Ditto, 1993) that reported very high MZM correlations. Recomputing the pooled MZM correlations without these studies changed the DBP correlation estimate from 0.60 (0.50–0.68) to 0.48 (0.36–0.59). HR reactivity in MZ females was due to the study by Li et al. (2001). Excluding this study increased the pooled MZM correlation from 0.47 (0.30–0.62) to 0.68 (0.53–0.79).

Table 6 presents the genetic and environmental parameter estimates and the 95% confidence intervals of best fitting models for SBP, DBP and HR reactivity to the cold pressor test. For SBP reactivity, males and females showed significantly different heritabilities (0.21 versus 0.33). No sex differences were found for DBP and HR reactivity that showed heritabilities of 0.55 and 0.45, respectively. For HR reactivity, the r_g estimate was close to zero, indicating clear qualitative differences in the genetic influence on cold pressure reactivity in males and females. Excluding the most outlying data from the pooled twin correlations in the MZM group for DBP reactivity and in the MZF group for HR reactivity did not greatly affect the heritability estimates (data not shown).

Table 2
Pooled twin correlation estimates (95% CI) for five zygosity-by-sex groups for SBP, DBP and HR reactivity to mental stress.

	Sample size (pairs) MZM/DZM/MZF/DZF/DOS	MZM	DZM	MZF	DZF	DOS
SBP	365/289/250/167/112	0.36 (0.26, 0.45)[a]	0.05 (−0.07, 0.17)	0.34 (0.22, 0.45)	0.17 (0.02, 0.32)	0.27 (0.09, 0.44)
DBP	365/289/250/167/112	0.31 (0.21, 0.40)	0.10 (−0.02, 0.21)	0.26 (0.14, 0.37)	0.11 (−0.05, 0.26)	0.12 (−0.08, 0.30)
HR	365/289/193/124/112	0.42 (0.32, 0.50)	0.20 (0.08, 0.31)	0.51 (0.39, 0.61)	0.25 (0.07, 0.41)	0.23 (0.04, 0.40)

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MZM: monozygotic males; DZM: dizygotic males; MZF: monozygotic females; DZF: dizygotic females; DOS: dizygotic opposite sex.

[a] MZM correlation showed significant heterogeneity across studies ($p < 0.01$).

Table 3
Genetic and environmental parameter estimates (95% CI) of best fitting models for SBP, DBP and HR reactivity to mental stress.

	Best fitting models	A (95% CI)	D (95% CI)	E (95% CI)
SBP	AE sex difference: male	0.26 (0.23–0.29)	–	0.74 (0.71–0.77)
	AE sex difference: female	0.38 (0.33–0.43)	–	0.62 (0.57–0.67)
DBP	ADE no sex difference	0.14 (0.08–0.20)	0.15 (0.07–0.24)	0.71 (0.68–0.74)
HR	AE no sex difference	0.43 (0.40–0.47)	–	0.57 (0.53–0.60)

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CI: confidence interval; A: additive genetic influence; D: dominant genetic influence; E: unique environmental influence

Table 4
Description of twin correlations of SBP, DBP and HR reactivity to the cold pressor test.

Investigator	Ethnicity	Sample size (pairs)	Age		Twin correlations		
			Mean ± SD	Range	SBP	DBP	HR
McIlhany et al. (1975)	Caucasians and African Americans	40 MZM 47 MZF 32 DZM 36 DZF 45 DOS	14.0 ± 6.5	5.0–50.0	R_{MZM}: 0.58 R_{DZM}: 0.39 R_{MZF}: 0.55 R_{DZF}: 0.05 R_{DOS}: 0.09	R_{MZM}: 0.82 R_{DZM}: 0.46 R_{MZF}: 0.62 R_{DZF}: 0.39 R_{DOS}: 0.38	n.a.
Carmelli et al. (1991)	Caucasians	47 MZM 54 DZM	62.4 ± n.a.	59.0–69.0	R_{MZM}: 0.51 R_{DZM}: 0.42	R_{MZM}: 0.26 R_{DZM}: 0.34	R_{MZM}: 0.31 R_{DZM}: −0.04
Ditto et al. (1993)	Caucasians	20 MZM 20 MZF 20 DZM 20 DZF 20 DOS	20.0 ± 5.0	12.0–44.0	R_{MZM}: 0.65 R_{DZM}: 0.18 R_{MZF}: 0.38 R_{DZF}: 0.07 R_{DOS}: 0.04	R_{MZM}: 0.84 R_{DZM}: 0.19 R_{MZF}: 0.37 R_{DZF}: −0.08 R_{DOS}: 0.10	R_{MZM}: 0.50 R_{DZM}: 0.31 R_{MZF}: 0.78 R_{DZF}: 0.08 R_{DOS}: −0.04
Li et al. (2001)	Caucasians	82 MZM 41 MZF 37 DZM 13 DZF 22 DOS	30.0 ± 12.0	n.a.	R_{MZM}: 0.37 R_{DZM}: 0.37 R_{MZF}: 0.32 R_{DZF}: −0.28 R_{DOS}: 0.35	R_{MZM}: 0.49 R_{DZM}: 0.48 R_{MZF}: 0.45 R_{DZF}: 0.13 R_{DOS}: 0.03	R_{MZM}: 0.58 R_{DZM}: 0.38 R_{MZF}: −0.07 R_{DZF}: 0.32 R_{DOS}: 0.00
Snieder et al. (data collected in 1994) Previously unpublished	Caucasians	46 MZM 50 MZF 37 DZM 40 DZF 40 DOS	48.3 ± 6.6	30.0–58.0	R_{MZM}: 0.43 R_{DZM}: 0.36 R_{MZF}: 0.35 R_{DZF}: 0.29 R_{DOS}: 0.14	R_{MZM}: 0.65 R_{DZM}: 0.16 R_{MZF}: 0.54 R_{DZF}: 0.19 R_{DOS}: 0.15	R_{MZM}: 0.43 R_{DZM}: 0.42 R_{MZF}: 0.64 R_{DZF}: 0.09 R_{DOS}: −0.02

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MZM: monozygotic males; DZM: dizygotic males; MZF: monozygotic females; DZF: dizygotic females; DOS: dizygotic opposite sex.
n.a.: data not given in the article.

Table 5
Pooled twin correlation estimates (95% CI) for five zygosity-by-sex groups for SBP, DBP and HR reactivity to the cold pressor test.

	Sample size (pairs) MZM/DZM/MZF/DZF/DOS	MZM	DZM	MZF	DZF	DOS
SBP	235/180/158/109/127	0.47 (0.37, 0.57)	0.37 (0.23, 0.49)	0.41 (0.27, 0.53)	0.11 (−0.09, 0.29)	0.14 (−0.03, 0.31)
DBP	235/180/158/109/127	0.60 (0.50, 0.68)[a]	0.34 (0.20, 0.47)	0.52 (0.40, 0.63)	0.21 (0.01, 0.38)	0.21 (0.03, 0.37)
HR	195/148/111/73/82	0.48 (0.36, 0.58)	0.24 (0.07, 0.39)	0.47 (0.30, 0.62)[a]	0.13 (−0.11, 0.35)	−0.02 (−0.24, 0.20)

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MZM: monozygotic males; DZM: dizygotic males; MZF: monozygotic females; DZF: dizygotic females; DOS: dizygotic opposite sex.

[a] Correlation showed significant heterogeneity across studies ($p < 0.01$).

Table 6
Genetic and environmental parameter estimates (95% CI) of best fitting models for SBP, DBP and HR reactivity to the cold pressor test.

	Best fitting models	A (95% CI)	C (95% CI)	E (95% CI)	r_g[a]
SBP	ACE sex difference: male	0.21 (0.04–0.35)	0.26 (0.15–0.41)	0.53 (0.45–0.60)	
	ACE sex difference: female	0.33 (0.28–0.40)	–	0.67 (0.60–0.72)	
DBP	AE no sex difference	0.55 (0.50–0.61)	–	0.45 (0.39–0.50)	
HR	AE no sex difference, r_g estimated	0.45 (0.40–0.51)	–	0.55 (0.49–0.60)	0.01

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CI: confidence interval; A: additive genetic influence; C: common environmental influence; E: unique environmental influence.

[a] r_g is the correlation between additive genetic factors for DOS twins.

4. Discussion

Individual differences in the cardiovascular response to stress play a central role in the reactivity hypothesis linking frequent exposure to psychosocial stress to adverse outcomes in cardiovascular health (Treiber et al., 2003b; Kamarck et al., 2003). Here we used meta-analysis of twin resemblance in SBP, DBP and HR reactivity to show that cardiovascular stress reactivity to mental stressors and the cold pressor test are heritable traits. For SBP reactivity to the mental stressors, the pooled heritability across all studies ranged from 0.26 (males) to 0.38 (females). SBP reactivity to the cold pressor test yielded comparable heritability estimates ranging from 0.21 (males) to 0.33 (females). For DBP reactivity, heritability to the cold pressor test was higher (0.55) than that to mental stress even after including dominance variation (broad heritability of 0.29). Heritability estimates for HR reactivity to mental stress (0.43) and the cold pressor test (0.45) were very similar.

Formal testing revealed only mild heterogeneity in the twin correlation estimates across studies on mental stress, but confidence intervals around the pooled estimates for the twin correlations were fairly large and often included zero in the DZ groups. In view of the many ways in which a mental stress-testing experiment can be set up, even when using comparable stressors (task difficulty, amount of feedback, trial by trial reward/punishment, competing against a criterion or competition with visible scores of others, etc.) this variation between studies in twin correlation estimates should be expected.

The major novel finding to arise from the meta-analysis was that the heritability of stress reactivity shows quantitative and qualitative sex differences. SBP reactivity to both mental stress and to the cold pressor test was more heritable in females than in males. In the studies reporting opposite sex twin pair correlations, these correlations were often comparable to the same-sex DZ twin pair correlations. A notable exception, however, was the very low DOS correlation for HR reactivity to the cold pressor test, suggesting that different genes affect this HR reactivity in males and females. Inspection of Tables 1 and 4 further suggest a possible decrease in heritability from adolescence to middle-age but we did not have sufficient data points to robustly test this hypothesis.

In the time frame of the mental stress tasks used (5–10 min) HR and BP reactivity are largely governed by the effects of the sympathetic and parasympathetic nervous system on cardiac output and vascular resistance. No study to date has addressed the heritability of cardiac output or peripheral resistance changes in response to stress. The latter is unfortunate because the patterning of vascular versus cardiac reactivity may be highly relevant to the type of disease outcome (Lawler et al., 2001; Sherwood and Turner, 1995). A few twin studies did test the effects of stress on parasympathetic nervous system reactivity, assessed as changes in heart rate variability in the respiratory frequency range or RSA (Grossman et al., 1990; Goedhart et al., 2007). In 208 middle-aged Dutch twin pairs RSA was measured during a rest period and a number of stress tasks (de Geus et al., 2007; Snieder et al., 1997). Heritability of the RSA decreases during a tone avoidance task was 0.24 and 0.33 in males and females, respectively (Snieder et al., 1997). However, no significant heritability was found for RSA decreases during an RT or MA task (de Geus et al., 2007). In 427 European American and 308 African American adolescent twins, Wang et al. (2009) measured RSA at rest and during three mental stressors. Heritability of the aggregated RSA decrease was 0.49. Significant heritability of aggregated RSA reactivity across two mental stressors was also found in 320 Dutch adolescent twins, albeit with a more modest heritability estimate of 0.09 (de Geus et al., 2007).

A limitation of most twin studies performed so far, and hence of the meta-analysis based on these studies, is that they analyzed reactivity as a change score. That way, the heritability estimates will reflect an inseparable mix of newly emerging genetic or environmental influences during stress and an amplification or dampening of genetic or environmental influences already present at rest. Emerging genes are genes that are truly expressed only during stress. They contribute to the heritability of a cardiovascular trait only when it is measured under stressful conditions. Amplified genes are genes that have an effect on individual differences in a cardiovascular trait at rest, but these effects become stronger under stress. As shown by de Geus et al. (2007) for RSA and DBP reactivity, significant amplification may occur even when change scores (reactivity) are not heritable. To explicitly test for emergence and amplification, bivariate analysis of resting and aggregated stress levels are needed and we reinforce the plea of de Geus et al. (2007) that future studies should use bi- or multivariate (in case of combined mental and physical stressors) designs.

Taken together, the results of our meta-analysis convincingly show that cardiovascular reactivity to an acute mental challenge or cold pressor test is substantially heritable. The obvious next question is which genes might be responsible for this heritability. A comprehensive list of potential pathways and candidate genes is given by Imumorin et al. (2005) and Table 7 lists the available studies to date that have tested the association of candidate genes with BP and HR reactivity to stress.

Table 7
Summary of studies testing genetic associations with stress reactivity of SBP, DBP and HR.

Investigators	Ethnicity and sample size	Analysis methods	Stressors	Genes	SNPs	Reactivity in the genotype groups and significance of the test used by the investigators to compare the genotype groups (see under analysis methods)		
	Mean age ± SD(range)					SBP (mmHg)	DBP (mmHg)	HR (bpm)
Li et al. (2001)	332 Caucasians from 100 MZ and 66 DZ twin pairs Age: 30.1 ± 12.0	ANOVA testing an effect of genotype on the change scores	1. MA 2. CP	*ADRB2*	Arg16Gly	NS	MA 10.0 Arg/Arg 8.0 Arg/Gly 7.5 Gly/Gly ($p < 0.05$) CP 8.4 Arg/Arg 7.0 Arg/Gly 7.0 Gly/Gly ($p < 0.05$)	NS
					Gln27Glu	NS	NS	NS
					Thr164Ile	NS	NS	NS
					−47C>T	NS	NS	NS
McCaffery et al. (2002)	309 Caucasians including 101 MZ and 44 DZ twin pairs Age: 21.1 ± 2.8 (18–30)	Regression of the baseline-adjusted change scores on genotype	1. Stroop 2. MA	*ADRA1B*	Ile178Ile	NS	NS	NS
					Gly183Gly	NS	NS	NS
				ADRA2A	−1291C>G	NS	NS	NS
				ADRB1	Ser49Gly	NS	NS	NS
					Gly386Arg	NS	Stroop and MA: 7.0 Gly/Gly and Gly/Arg 4.8 Arg/Arg ($p < 0.01$)	NS
				ADRB2	Arg16Gly	NS	NS	NS
					Gln27Glu	NS	NS	NS

Table 7 (*Continued*)

Investigators	Ethnicity and sample size	Analysis methods	Stressors	Genes	SNPs	Reactivity in the genotype groups and significance of the test used by the investigators to compare the genotype groups (see under analysis methods)		
	Mean age ± SD(range)					SBP (mmHg)	DBP (mmHg)	HR (bpm)
Liu et al. (2006)	47 Caucasians; Asian-American Hispanic/Latino East Indian individuals: 23 males and 24 females Age: 21–49	ANOVA testing the interaction of genotype and condition (rest vs. task period)	Stroop	*ADRB2*	Arg16Gly	MAP: NS		NS
					Gln27Glu	MAP: NS		NS
Poole et al. (2006)	228 African Americans and 222 Caucasians Age: 18.5 ± 2.7	MANOVA testing effect of haplotype on change scores with baseline levels as covariates	1. Video game 2. CP	*ADRB2*	Gly16Arg	NS	NS	n.a.
					Gln27Glu	NS	NS	n.a.
Hassan et al. (2008)	148 African American and Caucasian CAD patients: 103 males and 45 females Age: 64.0 ± 9.0	MANOVA testing an interaction of genotype and condition (rest vs. stress) with baseline level as a covariate	Public-speaking task	*ADRB1*	Ser49Gly	NS	NS	NS
					Gly389Arg	NS	NS	NS
				ADRB2	Gly16Arg	NS	NS	NS
					Gln27Glu	NS	NS	NS
					523C>A	NS	NS	NS
Kurnik et al. (2008)	40 African Americans and 39 Caucasians Age: 25.7 ± 5.3	Regression of the baseline-adjusted change scores on genotype	CP	*ADRA2C*	del322–325	28.6 del/del 18.8 del/ins and ins/ins ($p = 0.016$)	19.7 del/del 13.9 del/ins and ins/ins ($p = 0.058$)	30.9 del/del 13.4 del/ins and ins/ins ($p = 0.004$)
				GNB3	825C>T	NS	NS	20.4 T/T 12.1 C/T and C/C ($p = 0.003$)
Zhang et al. (2004)	294 Caucasians: 21 MZM, 8 DZM, 82 MZF, 30 DZF, and 7 DOS Age: 42.0 ± 1.0 (15–84)	SOLAR based regression of genotype on the change scores	CP	*TH*	Repeat polymorphism: two most common (TCAT)*n* alleles, (TCAT)6 and (TCAT)10i	NS	NS	NS
Rao et al. (2008)	172 Caucasians: 119 MZ and 53 DZ Age: 15–84	SOLAR based regression of genotype on the change scores	CP	*TH*	−824C>T	18.4 T/T 15.1 T/C 10.5 C/C	15.4 T/T 11.9 T/C 7.9 C/C	NS
					−801G>C	NS	NS	NS
					−581A>G	NS	NS	NS
					−494G>A	NS	NS	NS
Treiber et al. (2003a,b)	161 African Americans 213 Caucasians Age: 18.6 ± 2.7	ANCOVA testing an effect of genotype on change scores with baseline level as a covariate	1. Video game (VG) 2. Forehead cold	*ET-1*	Lys198Asn	VG in low SES subgroup 15.5 Asn/Asn; 13.1 Asn/Lys and Lys/Lys ($p < 0.05$)	VG in Obese subgroup 13.0 Asn/ASn 10.0 Asn/Lys and Lys/Lys[a] ($p_{\text{interaction}} < 0.04$)	NS

Malhotra et al. (2004)	235 African Americans 262 Caucasians Age: 18.5 ± 2.6	ANCOVA testing an effect of genotype on change scores with baseline level as a covariate	Video game	*NOS3*	Glu298Asp	NS	African Americans non-Obese 13.5 Glu/Glu 9.4 Asp/Glu and Asp/Asp ($p_{\text{interaction}} < 0.04$) European Americans, Obese 13.3 Glu/Glu 9.4 Asp/Glu and Asp/Asp ($p_{\text{interaction}} < 0.04$)	NS
Boomsma et al. (1991)	160 Caucasian twin pairs and their parents Age Twins: 16.7 (14–20) Fathers: 48.0 Mothers: 46.0	MANOVA using genotype by condition (rest, stressors)	1. RT 2. MA	*PI*	M, S/Z	Fathers, MA 12.8 MM 9.2 Non-MM ($p = 0.021$)	NS	n.a.
Williams et al. (2001)	30 Caucasians 24 African Americans 36 males and 18 females Age: 18–49	ANOVA using genotype by condition (rest, stress)	Anger and sadness recall	*5-HTT*	short (*s*) and long (*l*) alleles	MAP 2.3 *s*/*s* 9.1 *s*/*l* + *l*/l[a] ($p < 0.0001$)		Effects not reported but significant at $p < 0.05$
McCaffery et al. (2003)	382 Caucasians 131 MZ and 60 DZ twin pairs Age: 21.0 ± 2.8	ANOVA on genetically independent subset using genotype by task (Stroop, MA) on baseline-adjusted change scores	1. Stroop 2. MA	*5-HTT*	Short (*s*) and long (*l*) alleles	NS	NS	Females (MA + Stroop) 14.9 *s*/*s* 6.7 *l*/*s* 9.0 *l*/*l* ($p < 0.01$)
Williams et al. (2008)	94 African Americans and 71 Caucasians; 94 males and 71 females Age: 35.1 (18–50)	Regression of the baseline-adjusted change scores on genotype	Anger and sadness recall	*5-HTT*	Short (*s*) and long (*l*) alleles	11.4 *l*/*l* 9.9 *l*/*s* 7.2 *s*/*s* ($p < 0.047$)	8.6 *l*/*l* 7.2 *l*/*s* 4.3 *s*/*s* ($p < 0.0001$)	8.7 *l*/*l* 8.5 *l*/*s* 5.5 *s*/*s* ($p < 0.033$)

ADRB1: adrenergic receptor-β1; ADRB2: adrenergic receptor-β2; ADRA1B: adrenergic receptor-α1b; ADRA2A: adrenergic receptor-α2a; ADRA2C: adrenergic receptor-α2c; TH: tyrosine hydroxylase; ET-1: endothelin-1; NOS3: nitric oxide synthase 3; PI: protease inhibitor; 5-HTT: serotonin transporter; CP: cold pressor test; MA: mental arithmetic task; Stroop: color-word interference task; RT: reaction time task; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MAP: Mean arterial pressure; TPR: total peripheral resistance; BMI: body mass index; CAD: coronary artery disease; SES: socioeconomic status; MZM: monozygotic males; DZM: dizygotic males; MZF: monozygotic females; DZF: dizygotic females; DOS: dizygotic opposite sex.

n.a.: data not given in the article.

NS: non-significant association.

[a] Effect sizes were extracted from figures in articles.

Heritable individual differences in BP and HR reactivity may arise from variation in genes that code for elements of the vagal and sympathoadrenal systems, including transmitter synthesis, release and reuptake, enzymatic degradation and receptor density and sensitivity. The β1- and β2-adrenergic receptors, for instance, play an important role in the cardiac response to neural and hormonal adrenergic stimulation as well as in the vasodilatory response (Brodde et al., 2006; Dishy et al., 2001). Non-synonymous variants in the genes coding for these receptors (*ADRB1* and *ADRB2*), i.e. variants that change an amino acid in the protein, have been associated with altered cardiac and vascular responses to various adrenergic agonists and are suspected to modulate cardiovascular disease risk (Brodde, 2008). In keeping, most association attempts have focused on variation in genes that code for these receptors.

In a study of healthy twins, higher DBP reactivity (+2.2 mmHg) was found in carriers of the Gly allele at position Gly386Arg of the *ADRB1* gene compared to Arg/Arg homozygotes (McCaffery et al., 2002). Although a study in cardiac patients failed to replicate this effect, patients that were homozygous for the Ser allele at position Ser49Gly in *ADRB1* gene were more likely to experience stress-induced myocardial ischemia (Hassan et al., 2008). Evidence to support a role for the *ADRB2* gene has been less compelling. In a study of Li et al. (2001) Arg/Arg homozygotes for the *ADRB2* Arg16Gly polymorphism had higher DBP reactivity to a mental arithmetic task (+2.5 mmHg) and a cold pressor test (+1.4 mmHg) than Gly/Gly homozygotes. Three other studies failed to replicate this finding (Liu et al., 2006; McCaffery et al., 2002; Poole et al., 2006) and no evidence was found for an effect of three other variants in this gene.

The most striking association result so far was found for the α_{2C}-adrenergic receptor (Kurnik et al., 2008). There is substantial evidence that α_{2C}-adrenergic mechanisms in the central nervous system affect the level of sympathetic drive to the heart and blood vessels. Noradrenergic activation of the α_{2C}-adrenergic receptor located on the presynaptic membrane acts to inhibit further release of noradrenaline from sympathetic nerves and adrenaline from the adrenal gland, whereas stimulation of the postsynaptic variant on vascular smooth muscle induces vasoconstriction. A common deletion of 12 base pairs that code for 4 amino acids (del322–325) in the *ADRA2C* gene causes a marked decrease in the response to adrenergic agonists (Small et al., 2000). Homozygotes for this deletion had higher HR (+17.5 bpm), SBP (9.8 mmHg) and DBP (+5.8 mmHg) reactivity to the cold pressor test than the combined heterozygote and insertion/insertion groups.

An additional SNP (C825T) in the gene coding the heterotrimeric guanine nucleotide-binding protein B3-subunit (*GNB3*) was also significantly associated with HR reactivity. Homozygous T-allele carriers increased their HR on average 8.3 bpm more during stress than non-T carriers. This makes sense since G-proteins mediate intracellular signaling transduction of adrenergic receptors, including the α_{2C}-adrenergic receptor. Importantly, the strong ethic differences in HR reactivity, with black participants responding more strongly than white participants, largely disappeared when the analysis accounted for the higher frequency of the deleterious variants of these genetic variants in black participants (Kurnik et al., 2008). Genetic variation in other α-adrenergic receptor subtypes (*ADRA1B* and *ADRA2A*) has been tested also (McCaffery et al., 2002), but no such clear associations with stress reactivity emerged as for *ADRA2C*.

On the side of catecholamine synthesis, tyrosine hydroxylase (TH) has drawn most of the research attention. TH is the rate-limiting enzyme in the synthesis of the catecholamines. Testing a repeat polymorphism, Zhang et al. (2004) reported no effect of the number (TCAT) repeats on SBP, DBP and HR reactivity to the cold pressor test. Testing four SNPs in the promoter region of the gene in the same sample, however, revealed a significant positive association between the number of T alleles at base pair position −824 and SBP and DBP reactivity to the cold pressor test (Rao et al., 2008). Homozygous T-allele carriers had higher DBP (+7.6 mmHg) and SBP (+9.9 mmHg) than non-T carriers. Parallel effects were seen on catecholamine reactivity and the SNP accounted for 5.5% of the increases in plasma epinephrine and 1.5% of the increases in plasma norepinephrine.

A second system that responds fast enough to influence acute stress reactivity is the endothelial system that controls vascular smooth muscle function via production of vasoactive substances such as nitric oxide (NO), a potent vasodilator, and endothelin-1 (ET-1), a potent vasoconstrictor (Spieker et al., 2002). Researchers at the Medical College of Georgia tested the associations between non-synonymous SNPs in the ET-1 (Lys198Asn) and the NOS3 gene (Glu298Asp) and reactivity to a video game and forehead cold stimulus in a cross-sectional sample of African and European American normotensive young adults (Malhotra et al., 2004; Treiber et al., 2003a). Both polymorphisms showed associations with BP reactivity to the video game stressor in a complex pattern that depended upon obesity, ethnicity and SES. Among the obese, homozygote carriers of the ET-1 198 Asn allele had greater increases in DBP (+3.0 mmHg) than non-carriers. Homozygote Asn allele carriers who came from lower SES backgrounds exhibited higher SBP reactivity (+2.4 mmHg) than non-carriers. Carrier status for the NOS3 298Asp allele interacted with ethnicity and obesity status for diastolic BP reactivity such that in non-obese African Americans Glu/Glu homozygotes exhibited greater diastolic BP reactivity (+4.1 mmHg) compared to non-Glu allele carriers. Among obese European Americans, higher diastolic BP reactivity (+3.9 mmHg) was also found in the Glu/Glu homozygotes (Malhotra et al., 2004).

A further source of genetic differences in reactivity may be found in the central nervous system at the level of subjective perception of the stressor. Subjective feelings of threat are the core determinant of the generation of the autonomic responses underlying stress reactivity. Reactivity may be particularly sensitive to variation in serotonergic functioning, since selective serotonin reuptake inhibitors (SSRIs) that inhibit the serotonin transporter have been shown to reduce cardiovascular reactivity to mental stressors or emotion-inducing stimuli (Golding et al., 2005; Kemp and Nathan, 2004). Three studies have tested an association between a functional genetic variant in the linked polymorphic region (5-HTTLPR) of the serotonin transporter gene and cardiovascular stress reactivity. The results have been somewhat confusing, which parallels the fate of this genetic variant in psychiatric genetics at large (e.g. Caspi et al., 2003; Risch et al., 2009). Williams et al. (2001) reported that individuals carrying one or two long (*l*) alleles showed higher mean arterial pressure (MAP) reactivity (+6.8 mmHg) to a session of guided recall of moments of anger and sadness than *s*-allele homozygotes. This result was replicated and extended in a larger sample, where *l*-allele homozygotes had higher SBP (+4.2 mmHg), DBP (+4.3 mmHg), and HR (+3.2 bpm) reactivity compared to *s*-allele homozygotes (Williams et al., 2003). In sharp contrast, McCaffery et al. (2003) found a detrimental effect of the *s*-allele, particularly in females. Females with an *s*/*s* genotype exhibited aggregated HR reactivity across a Stroop and mental arithmetic task that was higher than that in males of the same genotype (+11.4 bpm) or females having either one (+8.2 bpm) or two long alleles (+5.9 bpm). In this study, no association between 5-HTTLPR genotype and SBP or DBP reactivity was found.

From the brief review above it is clear that, in spite of the significant heritability emerging from twin studies, independently and consistently replicated genetic variants that explain this heritability are still at large. This is not too surprising. As reactivity is likely to be influenced by multiple genes and interactions of small effect, the effect size for each gene is generally expected to be small. Standard power calculations show that up to 1000 participants are required to detect gene main effects (http://hydra.usc.edu/gxe/). As reviewed by McCaffery et al. (2007) the required sample size will be even larger if one of the alleles is rare (e.g. less than 5–10%) or a large number of markers is typed and the statistical criterion, typically set at 0.05 for two-tailed tests, has to be adjusted for multiple comparisons. Also, since our results show that different genes may be expressed in men and women and potentially across age, samples may be required that are either homogeneous for gender and age or large enough to allow testing in subsamples. Finally, a number of association studies have tested genotype effects on task minus resting baseline change scores, sometimes even correcting for baseline levels. As with twin studies on reactivity, a bi- or multivariate approach that uses genotype and condition (e.g. rest, mental stress, physical stress, pharmacological challenge, etc.) as factors may be the optimal approach. The interaction between genotype and condition captures both emergence and amplification, whereas using change scores corrected for baseline levels may fail to detect genes that influence both resting levels and reactivity. Such genes do exist as was shown by Boomsma et al. (1991) for the α-1-antitrypsin (*ATT*) gene. The two rare deficiency alleles of a highly polymorphic locus in this gene reduced both absolute SBP levels (−7.0 mmHg) and the SBP reactivity (−3.6 mmHg) to mental stress among adult males. Correcting for the gene effects on the baseline would likely have removed the evidence for its effect on reactivity.

The concerns voiced above in no way disqualify the pioneering studies listed in Table 7, nor their at times encouraging results as for the common polymorphisms in the *TH* and *ADRA2C* genes. On the contrary, they aim to constitute a call for continued efforts in this area to provide independent replication of these studies. Sufficient efforts by multiple laboratories will allow future meta-analysis on their combined association results as a way to separate false positives from truly causal gene variants.

In summary, twin studies find strong evidence for a genetic contribution to individual differences in cardiovascular reactivity to stress, which is a biomarker for CVD. Future progress in genetic association studies, that include measures of sympathetic and vagal reactivity, may help uncover the molecular pathways from genes to stress reactivity. The long term aim is improved identification of at-risk subjects and timely person-specific intervention.

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