University of Groningen

Genetic influences on baroreflex sensitivity during rest and mental stress

Riese, Harriette; Rijdsdijk, Fruhling V.; Ormel, Johan; van Roon, Arie M.; Neeleman, Jan; Rosmalen, Judith G. M.

Published in:
Journal of Hypertension

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Riese, H., Rijdsdijk, F. V., Ormel, J., van Roon, A. M., Neeleman, J., & Rosmalen, J. G. M. (2006). Genetic influences on baroreflex sensitivity during rest and mental stress. *Journal of Hypertension*, 24(9), 1779-1786.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Genetic influences on baroreflex sensitivity during rest and mental stress

Harriëtte Riese^a, Frühling V. Rijdsdijk^b, Johan Ormel^{a,e}, Arie M. van Roon^c, Jan Neeleman^{a,d} and Judith G.M. Rosmalen^{a,e}

Objective Baroreflex sensitivity (BRS) is a predictor of cardiovascular mortality and an indicator of sympathetic and parasympathetic autonomic regulation. Although the BRS is influenced by genetic factors, the evidence is limited, and it is unknown whether contributions of genes and environment to individual variation in BRS differ during rest and mental stress conditions.

Design and methods In 250 female twins, electrocardiogram and continuous finger blood pressure (BP) were assessed during two rest and two mental stress conditions. BRS was calculated as the mean modulus between inter-beat-interval and systolic BP. Genetic model fitting was used to investigate the relative contribution of genetic and environmental influences to individual differences in the BRS measures.

Results Familial resemblance for all conditions was found which was clearly mainly due to genetic contributions. A trend was found for higher genetic influences in the mental stress conditions (42 and 45%) compared to rest conditions (14 and 22%), and higher shared environmental effects in rest conditions (14 and 16%) compared to mental stress conditions (0.5 and 1%). Although their magnitude differed, the same genetic and shared environmental factors affected individual differences in BRS in all four conditions.

Conclusion Genetic influences explained up to 45% of the individual variation in BRS. This considerable proportion of genetic variance would make BRS an

useful candidate trait for future association and linkage studies in the search for genes influencing autonomic regulation and cardiovascular disease risk. *J Hypertens* 24:1779–1786 © 2006 Lippincott Williams & Wilkins.

Journal of Hypertension 2006, 24:1779–1786

Keywords: autonomic nervous system, baroreflex, genetics, twins

^aDepartment of Psychiatry, and Graduate School of Behavioral and Cognitive Neurosciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ^bSocial, Genetic and Developmental Psychiatry (SGDP) Research Centre, Institute of Psychiatry, Kings College, London, UK; ^cDepartment of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen; ^dJulius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht and ^eGraduate School for Experimental Psychopathology, The Netherlands

Correspondence and requests for reprints to Dr H. Riese, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, POBox 30.001, 9700 RB Groningen, The Netherlands
Tel: +31 50 3610171; fax: +31 50 3619722; e-mail: H.Riese@med.umcg.nl

Sponsorship: This research is part of the Twin Interdisciplinary Neuroticism Study (TWINS) in cooperation with the Study of Allostatic Load as a Unifying Theme (SALUT). TWINS was supported by the Netherlands Organization for Health Research and Development (ZonMw 904-57-130) and the UK–Netherlands Partnership Program in Science (BR 56-481 and BR 96-229) which is jointly run and financed by the British Council and the Netherlands Organization for Scientific Research (NWO). SALUT is a collaboration between various departments of the University Medical Center Groningen and the University Medical Center Utrecht, The Netherlands. SALUT is financially supported by the Netherlands Organization for Scientific Research (Pionier 900-00-002) and by the participating centres.

Received 15 September 2005 **Revised** 24 January 2006
Accepted 21 April 2006

Introduction

The baroreflex loop is an important cardiovascular control mechanism for short-term blood pressure (BP) regulation. Baroreflex sensitivity (BRS) can be defined as the transfer function between heart rate (HR) and BP changes [1]. Spontaneous BRS is clinically relevant as a predictor of cardiovascular mortality [2], and physiologically as an indicator of sympathetic and parasympathetic autonomic regulation, for example, in patients with diabetes [3]. Therefore, the identification of the relevant sources of dysfunctional BRS is important. However, there is a poor understanding of the determinants of spontaneous BRS. Impaired BRS in hypertensive patients has been suggested to be in part genetically determined [4]. The relative contribution of genetic influences to individual variation in BRS can be estimated in a twin design.

The only twin study available on BRS reported heritabilities (standardized genetic contribution) between 0.36 and 0.44 for spontaneous BRS, but this heritability was calculated for BRS measured in rest conditions only [5]. At rest, the BRS is predominantly a measure of cardiac vagal regulation [6], whereas, in general, under mental stress conditions the contribution of sympathetic activity increases. Different BRS levels due to shifts in sympathetic/parasympathetic balance in rest versus mental stress conditions have been reported before [1,7,8] and shown to be reproducible [9]. It can thus be hypothesized that the heritability of BRS differs across conditions. It is unclear, however, whether the magnitude of genetic and environmental influences on BRS variance differs during resting and mental stress conditions. In this paper we study the genetic influences on individual

differences in spontaneous BRS assessed during two rest and two mental stress conditions. Different techniques (e.g. pharmacologically, spectral analysis, sequence method) are available to quantify baroreflex gain. In the current study the gain of the transfer function between HR and BP changes is used to calculate BRS. Using multivariate genetic model fitting, we also examined the underlying genetic and environmental factor structure of these measures.

Methods

Subjects

This study is part of a larger project named the Twin Interdisciplinary Neuroticism Study (TWINS) in which the genetic and environmental origins of neuroticism are explored. The sample for the TWINS study was selected from the Groningen Twin Register (GTR). To establish the GTR, nine municipalities with more than 31 000 inhabitants in the north of The Netherlands were requested to provide addresses of inhabitants born between 1972 and 1992, from the same mother with an identical date of birth. All GTR participants filled out a survey, which included, among others, a zygosity questionnaire [10]. In total 125 female twin pairs visited our psychophysiological laboratory. Zygosity of this target group was determined using 10 microsatellite markers. Due to technical failures, zygosity of three twin pairs could not be determined by DNA genotyping; for these pairs survey data on zygosity were used instead. Status of medication use was assessed upon arrival in our laboratory, and subjects were categorized as non-users, anti-hypertensive users, and users of other medication. Body weight and height were measured for body mass index (BMI) calculation. The Ethics Committee of the University Medical Center Groningen approved the study, and all subjects gave written consent prior to participation. Table 1 shows the general characteristics of our study population.

Protocol and measurements

Subjects were measured in the sitting position during four conditions: a rest condition (rest1), a mental stress

condition with visual feedback (stress1), a mental stress condition with auditory feedback (stress2), and a second rest condition (rest2). In the stress conditions, subjects performed a mental stressing, modified version of the 'emotion face dot-probe' task [11]. On each trial of the task, a pair of faces [12] was presented for 19 ms, immediately followed by a mask for 50 ms, and then in the location previously occupied by the two masked faces dots appeared: 11 dots on one side, and 3 or 4 dots on the other side. Subjects indicated whether 3 or 4 dots appeared by button response as quickly as possible, while avoiding errors. Although the two stress tasks were essentially the same, in the second auditory feedback task subjects were 'punished' for a wrong answer by exposing them to white noise of 100 dB for 0.5 s. Such a quite invasive feedback method can be expected to affect the way subjects respond to a second mental stress task. For this reason, the test sequence of the conditions was not randomized. Cardiovascular measurements started after the subjects had relaxed in the sitting position for at least 10 min, and each condition lasted for about 5 min. Immediately after the final rest condition an armcuff was fixed around the upper arm to assess clinical BP (Omron M1 semi-automatic BP monitor; OMRON Healthcare Europe BV, Hoofddorp, The Netherlands). BP was measured twice within 2 min; a mean value was calculated and used in further analyses.

The Portapres device continuously recorded spontaneous fluctuations in beat-to-beat finger BP (FMS Finapres Medical Systems BV, Amsterdam, The Netherlands) [13,14]. A cuff was fixed around the middle phalanx of the third finger on the right hand, which was kept at heart level. HR was measured by a three-lead electrocardiogram (ECG). Changes in thoracic respiration signal were measured with a flexible band fixed around the upper part of the thorax. Respiration signals were filtered online with a high-pass filter with a time constant of 20 s. R-peak arrival was measured with an accuracy of 1 ms. Respiration and BP were sampled with a frequency of 100 Hz using the same computer clock that controlled R-peak triggering.

Measurements were regarded unsuitable when adequate signal recording failed. Detected artefacts for HR and BP were corrected by means of linear interpolation of four data points surrounding the artefact. Visual inspection of the BP and inter-beat-interval (IBI) signals yielded 976 (97.6%) measurements suitable for BRS calculation; 244 in rest1 ($N_{\text{twin1}}/N_{\text{twin2}} = 121/123$), 245 in stress1 ($N_{\text{twin1}}/N_{\text{twin2}} = 121/124$), 245 in stress2 ($N_{\text{twin1}}/N_{\text{twin2}} = 121/124$), and 242 ($N_{\text{twin1}}/N_{\text{twin2}} = 119/123$) in rest2. The CARSPAN spectral analysis program was used for BRS calculation [15,16]. This method for BRS calculation has been applied before [1,3,17,18]. The program allows for discrete Fourier transformation of non-equidistant systolic BP and IBI series. The analysed time series

Table 1 General characteristics of the twin sample; means (SD) and number of individuals are given

	Twins	
	Monozygotic (<i>N</i> = 148)	Dizygotic (<i>N</i> = 102)
Number of pairs	74	51
Age in years (SD)	23.4 (3.7)	23.5 (3.2)
BMI in kg/m ² (SD)	22.6 (3.9)	23.1 (3.2)
SBP in mmHg (SD)	124.5 (14.4)	123.7 (17.4)
DBP in mmHg (SD)	68.4 (6.7)	69.4 (7.9)
Medication users		
No medication at all (<i>N</i>)	133	70
Antihypertensive (<i>N</i>)	1	2
Other medication (<i>N</i>)	14	30

N, number of individuals; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

were corrected for artefacts and checked for stationarity. BRS was defined as the mean modulus between systolic BP and IBI in the 0.07–0.14 Hz frequency band with a coherence of 0.3 or higher, and expressed in ms/mmHg. The gain in the 0.07–0.14 Hz frequency band is influenced by both branches of the autonomic system, as is shown in several blockade studies [19–21]. It has been shown previously that the narrow band around 0.10 Hz is a valid band for determining changes in short-term blood pressure regulation [16,22], in particular when studying effects of mental stress [23,24]. For respiration, spectral power values were calculated, which were used in the BRS quality check procedure [23].

After BRS calculation, the quality of the dataset was assured by exclusion of:

- (1) 20 BRS values that were based on less than three frequency points;
- (2) 13 BRS values that were based on measurements of which more than 10% of the BP signal had been corrected by CARSPAN and/or contained too many artefacts (that is, showing signal gaps of more than 5 s of IBIs and/or more than 10 s in systolic BP signals);
- (3) 9 BRS values that were based on measurements lasting less than 100 s; and
- (4) 19 BRS values based on unreliable IBI spectral power values due to power influences from the respiration signal in the 0.07–0.14 Hz band, caused by slow breathing (during normal breathing the respiration peak can be expected around 0.25 Hz).

Two subjects were excluded because of supraventricular extrasystoles (8 BRS values), and 31 BRS values were excluded because of other reasons, e.g. talking, coughing during the measurement, or IBI power in the 0.15–0.50 Hz band instead of the 0.07–0.14 Hz band. In all, we obtained 876 (87.6%) measurements that met our quality criteria and were thus included in our final data set. So we had 12.4% unobtainable BRS values, which is better than those obtained in previous studies using spectral analysis where between 19 and 37% unobtainable BRS values were reported [17,25,26]. Individuals from whom no reliable BRS values were obtained were comparable to subjects with reliable values regarding age, BMI and clinical BP.

Statistical analyses

Analyses were applied on three types of BRS scores: on uncorrected BRS data; BRS data corrected for the effects of age, BMI and medication-use; and on data corrected for the effects of age, BMI, medication-use, systolic and diastolic BP. Status of medication use was entered into the regression procedure as dummy variables. The effect of medication use was marginal, so we decided to regress out any possible effects rather than to exclude individuals. The effects of the other possible confounders were

also very small, but to make our results comparable to the results reported by Tank *et al.* [5], they were also regressed out prior to genetic modelling. Genetic modelling was performed on the unstandardized residuals of the autonomic function measures after the confounding effects were regressed out in SPSS (Version 12.0.2; SPSS Inc., Chicago, Illinois, USA). Since the univariate analyses on the three types of BRS scores, which can be obtained upon request, were essentially the same, only the results on the BRS data corrected for the effects of age, BMI, medication-use, systolic and diastolic BP are reported in the current paper and used in subsequent multivariate analyses.

Genetic model fitting

In the classical twin model the differences between monozygotic (MZ) and dizygotic (DZ) covariances on a trait are used to investigate the relative contribution of genetic and environmental influences to individual differences in a trait. The observed variances/covariances of twin data are expressed as a function of latent genetic and environmental factors. The variance components considered are additive genetic variation (A); shared environmental variation (C) and a unique environmental component (E) that is not shared by family members and includes measurement error. For MZ and DZ twins reared together C correlates perfectly, whereas A correlates 1 in MZ twins and 0.5 in DZ twins since MZ twins share all their genes and DZ pairs 50% on average. The total variance of a trait for each individual is the sum of A, C and E. The effect and significance of these factors are inferred by fitting the observed covariances of the data for MZ and DZ pairs to their predicted covariances of the hypothesized model (ACE, AE, CE or E). The structural equation modelling program Mx (Version 1.3.65) was used to estimate model parameters by minimizing a goodness-of-fit statistic between observed and predicted covariances [27]. We used the raw maximum likelihood analyses, which automatically handle many missing data problems.

To improve on statistical power, we analysed the repeated measurements of the two BRS conditions in multivariate genetic models, rather than each one separately. The first genetic model fitted was a basic Cholesky decomposition in which the maximum number of A, C and E factors (as many as there are observed variables) are specified. We compared the fit of this model to that of two more parsimonious factor models; an Independent Pathway (IP) and a Common Pathway (CP) model. In addition to the ACE factor structure, trait specific A (A_{sp}), C (C_{sp}) and E (E_{sp}) factors are specified in the IP and CP models (Fig. 1).

Results

Table 2 presents the untransformed means and standard deviations for BRS for each of the four conditions

Fig. 1

The Cholesky model, the Independent Pathway (IP) and the Common Pathway (CP) models. Subscript sp, specific; A, additive genetic variation; C, shared environmental variation; E, unique environmental variation; L, latent; Rest1, baroreflex sensitivity (BRS) during the first

separately. We found that BRS values during both mental stress conditions did not differ from each other ($\Delta\chi^2(1) = 2.6, P = 0.11$), and BRS values during the first rest were higher than during the second rest ($\Delta\chi^2(1) = 10.6, P = 0.001$). Moreover, values during the first rest were higher than during the mental stress conditions ($\Delta\chi^2(1) = 7.6, P = 0.006$), whereas values at the second rest were comparable to the values during the stress conditions ($\Delta\chi^2(1) = 0.1, P = 0.76$). So, compared to the initial rest condition, BRS was reduced during mental stress, and did not recover to its initial level in the second rest. In these analyses we did not assume that means would differ across individuals within a twin pair.

Indeed, the means for BRS were equal across individuals in MZ twin pairs; however, due to small sample fluctuations, small differences for some means were found across twins in DZ pairs and all means were specified as free parameters in further analyses. Means for BRS in all conditions did not differ between MZ and DZ twin pairs. The correlations within a twin cross traits for BRS measurements are also given in Table 2, and twin correlations within traits for MZs and DZs separately are given in Table 3 (correlations cross traits are available upon request). All MZ correlations within traits are more than twice the DZ correlations, suggesting non-additive (dominance) genetic effects. However, given the lack of power to detect non-additive genetic effects due to small sample size, we explore only models with shared environmental effects.

Genetic model fitting

We first looked at the heritability estimates of each of the tasks separately (univariate analyses). The general pattern that emerged was that A and C could be dropped individually from the ACE model, but not together (i.e. the E model showed a significant decline in fit). This means that we only had power to show significant effects of familial resemblance (A+C) for all conditions. That these effects should be attributed to lack of power instead of non-existent genetic effects was reflected in the large 95% confidence intervals (CIs) that often included the 0 value. The estimates for familial resemblance were 41% in the first rest, 39% in the mental stress task with visual feedback, 37% in the mental stress task with auditory feedback, and 17% in the second rest.

Fig. 1 (continued)

rest condition; Stress1, BRS during the first mental stress condition; Stress2, BRS during the second mental stress condition; Rest2, BRS during the second rest condition. Models are depicted for one twin only. For simplicity, for the Cholesky model the C factors were omitted. Note that in the IP model a single A, C and E factor independently influence the observed BRS values in addition to trait-specific A (A_{sp}), C (C_{sp}) and E (E_{sp}) factors, and that in a CP model the four observed BRS values load on a latent (L) BRS construct which is influenced by one A, C and E factor.

Table 2 Correlations [95% confidence interval] within a twin cross traits and means (SD) for baroreflex sensitivity (BRS) values (corrected for the effects of age, body mass index, medication-use, systolic and diastolic blood pressure) obtained in two rest and two mental stress conditions

	BRS rest1	BRS stress1	BRS stress2	BRS rest2
BRS rest1	1			
BRS stress1	0.67 [0.59–0.74]	1		
BRS stress2	0.66 [0.57–0.73]	0.78 [0.72–0.83]	1	
BRS rest2	0.76 [0.70–0.81]	0.67 [0.59–0.74]	0.64 [0.56–0.77]	1
N (twin1/twin2)	109/108	109/113	111/110	107/109
Mean BRS (SD) (ms/mmHg)	9.26 (3.64)	8.55 (3.33)	8.93 (3.61)	8.69 (3.65)

N, number of individuals. The within a twin cross trait correlations are constrained cross zygosity groups and twins in a pair to get one set of six correlations.

To improve on power to show heritable differences, we analysed the four conditions where BRS was measured simultaneously (multivariate analyses, Table 4). We first looked at different nested models within the three different genetic models (Cholesky, IP, CP). In the Cholesky model A and C effects could be dropped one at a time (model 1a and 1b) and simultaneously (model 1c) without a significant decline in fit, i.e. this model shows no significant familial effects. In the IP model, the effects of test-specific A and C influences were non-significant (model 2a), but the effects of the shared A and C factor were significant [$\Delta\chi^2(4 \text{ df}) = 18.5$ and 10.0 , respectively]. In the CP model, again the effects of test-specific A and C influences were non-significant (model 3a). The effects of C on the latent BRS phenotype was non-significant, whereas the effects of A was just significant [$\Delta\chi^2(1 \text{ df}) = 0.0$ and 4.0 , respectively]. Using the Akaike's Information Criterion (AIC) [28], the best-fitting sub-model within the Cholesky, IP and CP models were model 1b (AIC = -53.4), model 2a (AIC = -50.2) and model 3c (AIC = -38.5), respectively.

To pick an overall best-fitting model we examined these AIC values. The CP model clearly fits the data less well than the Cholesky decomposition and the IP model. The difference in AIC values between the Cholesky and the IP model was quite small and we therefore selected the most parsimonious IP model (model with fewer parameters) as the best-fitting model (model 2a). This model showed a very good fit to the data ($P = 0.27$). The results of the IP model are in contrast with the Cholesky model, which showed no significant familial effects

(model 1c). The reason for this is because in the Cholesky model only the first genetic factor loadings are high and significant (comparable to the IP model). Thus, relative to the large number of dropped A and C parameters (which were mostly non-significant), the difference in χ^2 is low and the total test will result in a non-significant decline in fit.

The final model, thus, included one shared A, C and E factor and four specific E factors (model 2a). This means that the same genetic and environmental factors were found to influence individual differences in BRS during rest and mental stress conditions, although their magnitude differed. In Table 5, the standardized variance components of this model are given. We found higher heritabilities (a^2) in the two mental stress conditions compared to the rest conditions, and higher shared environment effects (c^2) in the two rest conditions compared to the mental stress conditions. However, these effects were not significant since the CIs of the estimates overlapped.

Discussion

The main goal of the present study was to estimate the magnitude of the contribution of genetic and environmental influences on inter-individual variation in BRS measured during rest and mental stress conditions. In agreement with the univariate analyses, the multivariate analyses revealed significant familial resemblance, which was clearly mainly due to genetic contributions. Genetic effects were slightly higher after correction for age, BMI, medication-use, and additional adjustment for systolic

Table 3 Twin correlations [95% confidence interval] within traits and means (SD) for baroreflex sensitivity (BRS) values (corrected for the effects of age, body mass index, medication-use, systolic and diastolic blood pressure) obtained in two rest and two mental stress conditions within MZ and DZ twin pairs

	BRS rest1	BRS stress1	BRS stress2	BRS rest2
MZ	0.41 [0.20 to 0.58]	0.40 [0.18 to 0.57]	0.45 [0.25 to 0.62]	0.31 [0.08 to 0.50]
DZ	0.07 [−0.26 to 0.38]	0.09 [−0.27 to 0.42]	0.04 [−0.31 to 0.37]	0.09 [−0.22 to 0.38]
Mean _{MZ} BRS (SD) (ms/mmHg)	9.17 (3.60)	8.21 (2.91)	8.58 (3.29)	8.66 (3.78)
N _{MZ} (twin1/twin2)	63/65	65/68	64/66	63/55
Mean _{DZ} BRS (SD) (ms/mmHg)	9.29 (3.68)	8.98 (3.86)	9.29 (4.0)	8.63 (3.43)
N _{DZ} (twin1/twin2)	46/43	44/45	47/44	44/44

MZ, monozygotic twin pairs. DZ, dizygotic twin pairs. N, number of individuals. Confidence intervals including zero indicate non-significance.

Table 4 Multivariate genetic model-fitting results of the baroreflex sensitivity measures (corrected for the effects of age, body mass index, medication-use, systolic and diastolic blood pressure) obtained in two rest and two mental stress conditions

Model	χ^2 (df)	P value	AIC	Compared to	χ^2 (df)	P value
1. CholACE	49.0 (42)	0.21	-35.0	—	—	—
1a. Drop A	54.4 (52)	0.38	-49.6	model 1	5.4 (10)	0.86
1b. Drop C	50.6 (52)	0.53	-53.4	model 1	1.6 (10)	0.99
1c. Drop A+C	75.3 (62)	0.12	-48.7	model 1	26.4 (20)	0.15
2. IP ACE	61.6 (48)	0.09	-34.4	—	—	—
2a. IP2 ACE *	61.8 (56)	0.27	-50.2	model 2	0.2 (8)	0.99
2b. IP2 Drop A	80.2 (60)	0.04	-39.8	model 2a	18.5 (4)	0.001
2c. IP2 Drop C	71.8 (60)	0.14	-48.2	model 2a	10.0 (4)	0.04
2d. IP2 Drop A+C	107.1 (64)	0.006	-20.9	model 2a	45.3 (8)	<0.001
3. CP ACE	82.8 (54)	0.007	-25.2	—	—	—
3a. CP2 ACE	87.5 (62)	0.02	-36.5	model 3	4.7 (8)	0.79
3b. CP2 Drop A	91.5 (63)	0.01	-34.5	model 3a	4.0 (1)	0.046
3c. CP2 Drop C	87.5 (63)	0.02	-38.5	model 3a	0.0 (1)	1.00
3d. CP2 Drop A+C	107.1 (64)	0.0006	-20.9	model 3a	19.6 (2)	<.001

CholACE, Cholesky. IP, Independent Pathway model. IP2, Independent Pathway model without A- and C-specific factors. CP, Common Pathway model. CP2 ACE, Common Pathway model without A- and C-specific factors. χ^2 (df), fit of the model calculated as differences in likelihoods between each of the genetic models and a perfect fitting (saturated) model. AIC, Akaike's Information Criterion = $\chi^2 - 2 \times \text{df}$ (lower AIC indices indicate a better fit). *, best fitting model assessed by likelihood ratio χ^2 test and AIC, which takes into account both the goodness of fit and the parsimony of the model and can be used to compare non-nested models. The fit of a reduced model will be better (i.e. the dropped parameter will be non-significant) if the difference in χ^2 does not exceed the critical value (at the 0.05 level) for that number of degrees-of-freedom (e.g. 3.84 for 1 df).

and diastolic BP. This increase, however, was marginal, and may be attributed to more homogeneous BRS data after correction for these known confounders.

Multivariate analyses indicated that the same genetic and shared environmental factors affected individual differences in BRS in all four experimental conditions. This finding suggests a stability of genetic and environmental influences across conditions. We were unable to conclude significant heritable and shared environmental effects on their own, due to lack of power (small sample and effect size). For all conditions, however, familial resemblance was found, which was clearly mainly due to genetic

contributions. The trend for higher genetic effects in mental stress conditions (42 and 45%) compared to rest conditions (14 and 22%), and higher shared environment effects in rest conditions (14 and 16%) compared to mental stress conditions (0.5 and 1%) is remarkable. This differential balance between genetic and shared environmental influences for rest and mental stress conditions is in agreement with findings on BP. In a laboratory study of adolescents, essentially the same genetic and shared environmental influences affected individual differences in BP during rest and during mental stress; higher heritabilities were found during mental stress compared to rest conditions, and some evidence was found for a small contribution of shared environmental factors especially under rest conditions [29].

Most evidence suggests that BRS is partly influenced by genetic factors [4], and indeed previously identified polymorphisms seem to explain part of the variance in BRS [30,31]. However, until now only one study reported on the heritability of BRS, in that case obtained from 5-min measurements during a rest condition [5]. The magnitude of the genetic effects in their rest condition (around 40%) is comparable to the genetic effects in the mental stress, but not to the genetic effects in the rest conditions of our study. Since both studies have comparable sample sizes and MZ/DZ ratios, these discrepancies in findings may be attributed to BRS measurements in different postures (semi-supine versus sitting body position), the inclusion of both sexes or only female twin pairs, differences in applied methodology, or a wider age range in Tank *et al.*'s study.

Limitations of our study are, as mentioned before, the relatively small sample size. This limitation might also have affected the heritability estimate, as reported in

Table 5 Standardized variance component and 95% confidence interval (CI) of the best-fitting multivariate model (= model 2a; IP2 ACE in Table 4) for the baroreflex sensitivity (corrected for the effects of age, body mass index, medication-use, systolic and diastolic blood pressure) measures obtained in two rest and two mental stress conditions

Parameters	Estimates [95%CI]
a^2 BRS rest1	0.22 [0.00–0.54]
a^2 BRS stress1	0.42 [0.00–0.58]
a^2 BRS stress2	0.45 [0.0001–0.61]
a^2 BRS rest2	0.14 [0.00–0.45]
c^2 BRS rest1	0.16 [0.00–0.44]
c^2 BRS stress1	0.01 [0.00–0.38]
c^2 BRS stress2	0.005 [0.00–0.36]
c^2 BRS rest2	0.14 [0.00–0.39]
e^2 BRS rest1	0.36 [0.20–0.56]
e^2 BRS stress1	0.33 [0.19–0.53]
e^2 BRS stress2	0.30 [0.16–0.49]
e^2 BRS rest2	0.48 [0.27–0.70]
e_{sp}^2 BRS rest1	0.26 [0.18–0.36]
e_{sp}^2 BRS stress1	0.25 [0.17–0.34]
e_{sp}^2 BRS stress2	0.25 [0.17–0.35]
e_{sp}^2 BRS rest2	0.24 [0.14–0.36]

a^2 , heritability; c^2 , shared environmental variation; e^2 , unique environmental variation; e_{sp}^2 , specific unique environmental variation; BRS, baroreflex sensitivity. Note that per condition (e.g. BRS rest1) a^2 , c^2 , e^2 and e_{sp}^2 add up to 1.

Tank *et al.* [5], although their results did not include any formal model fitting tables nor CIs around reported twin correlations. However, when accepting the laboratory session as being rather demanding for volunteers, and the data-analysing procedure quite time consuming, one should appreciate the number of valid measurements obtained. Moreover, by using an experimental repeated measurement design, selecting a relatively homogeneous group of young, healthy female participants and performing multivariate analyses, we largely worked around this disadvantage. The recovery of the mean BRS after the stress-induced reduction of BRS was not as pronounced as expected. The inclusion of a longer rest period in future studies might be advisable for complete recovery to initial BRS level. However, the comparable estimates for genetic and environmental influences for both rest conditions suggest that a prolonged recovery period would not have altered the current results. Furthermore, it should be noted that the technique for BRS estimation used in the current paper is not the only technique available for BRS estimation. It is in our opinion, however, the most appropriate choice to study the differences in genetic and environmental influences on BRS during rest and mental stress, since the BRS determined by the gain of the transfer function between HR and BP in the 0.07–0.14 Hz band is particularly sensitive for mental stress. And finally, since only young women were included in the study, we could not test for possible gender differences.

To conclude, familial resemblance for BRS in all conditions was found, which was clearly mainly due to genetic contributions. The same genetic and shared environmental factors affected individual differences in BRS in all four experimental conditions. This finding suggests a stability of genetic and environmental influences across conditions, although the magnitude of genetic influence differed across tasks. The present paper is only the second paper showing a heritable influence on BRS, and the first to show a trend for an increase in genetic influences under mental stress, a pattern previously found for BP. Genetic influences explained up to 45% of the individual variation in BRS. Since BRS was shown to have a considerable proportion of genetic variance, it would make an useful candidate trait for future association and linkage studies in the search for genes influencing autonomic regulation and cardiovascular disease risk.

Acknowledgements

Dr A.J. Oldehinkel and Dr S. Sytema, Department of Psychiatry, University Medical Center Groningen, University of Groningen, are acknowledged for their efforts to establish the Groningen Twin Register (GTR). The technical department, Instrumentatie Dienst Psychologie (Department head: Dr J.B.P. Veldman), of the Faculty of Behavioural and Social Sciences, University of Groningen is acknowledged for technical support.

References

- 1 Van Roon AM, Mulder LJM, Althaus M, Mulder G. Introducing a baroreflex model for studying cardiovascular effects of mental workload. *Psychophysiology* 2004; **41**:961–981.
- 2 La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; **351**:478–484.
- 3 Lefrandt JD, Hoogenberg K, Van Roon AM, Dullaart RP, Gans RO, Smit AJ. Baroreflex sensitivity is depressed in microalbuminuric type I diabetic patients at rest and during sympathetic manoeuvres. *Diabetologia* 1999; **42**:1345–1349.
- 4 Parmer RJ, Cervenka JH, Stone RA. Baroreflex sensitivity and heredity in essential hypertension. *Circulation* 1992; **85**:497–503.
- 5 Tank J, Jordan J, Diedrich A, Stoffels M, Franke G, Faulhaber HD, *et al.* Genetic influences on baroreflex function in normal twins. *Hypertension* 2001; **37**:907–910.
- 6 Kaushal P, Taylor JA. Inter-relations among declines in arterial distensibility, baroreflex function and respiratory sinus arrhythmia. *J Am Coll Cardiol* 2002; **39**:1524–1530.
- 7 Mulder LJM, Veldman JBP, Van Der Veen FM, Van Roon AM, Rudel H, Schachinger H, *et al.* On the effects of mental task performance on heart rate, blood pressure and its variability measures. In: Di Rienzo M, Marcia G, Parati G, Pedotti A, Zanchetti A, editors. *Blood pressure and heart rate variability*. Amsterdam: IOS Press; 1993, pp. 153–166.
- 8 Van Roon AM. Short-term cardiovascular effects of mental tasks [PhD thesis]. Groningen, The Netherlands: University of Groningen; 1998 (see <http://irs.uib.rug.nl/ppn/165987529> for an electronic version).
- 9 Iellamo F, Legramante JM, Raimondi G, Castrucci F, Massaro M, Peruzzi G. Evaluation of reproducibility of spontaneous baroreflex sensitivity at rest and during laboratory tests. *J Hypertens* 1996; **14**:1099–1104.
- 10 Nichols R, Bilbro W. Diagnosis of twin zygosity. *Acta Genet* 1966; **16**:265–275.
- 11 Mogg K, Bradley BP. Orienting of attention to threatening facial expressions presented under conditions of restricted awareness. *Cogn Emot* 1999; **13**:713–740.
- 12 Ekman P, Friesen WV. Measuring facial movement. *Environ Psychol Nonverbal Behav* 1976; **1**:56–75.
- 13 Peñáz J. Photoelectric measurement of blood pressure, volume and flow in the finger. *Digest of the International Conference on Medicine and Biological Engineering Dresden: Conference Committee of the Xth International Conference on Medicine and Biological Engineering* [abstract] 1973; 104.
- 14 Wesseling KH, De Wit B, Settels JJ, Klaver WH. On the indirect registration of finger blood pressure after Peñáz. *Funkt Biol Med* 1982; **1**:245–250.
- 15 Mulder LJM. Assessment of cardiovascular reactivity by means of spectral analysis [PhD thesis]. Groningen, The Netherlands: University of Groningen; 1988.
- 16 Robbe HW, Mulder LJM, Ruddle H, Langewitz WA, Veldman JBP, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension* 1987; **10**:538–543.
- 17 Dietrich A, Riese H, van Roon AM, Van Engelen K, Ormel J, Neeleman J, *et al.* Spontaneous baroreflex sensitivity in (pre)adolescents. *J Hypertens* 2006; **24**:345–352.
- 18 Althaus M, Van Roon AM, Mulder LJM, Mulder G, Aarnoudse CC, Minderaa RB. Autonomic response patterns observed during the performance of an attention-demanding task in two groups of children with autistic-type difficulties in social adjustment. *Psychophysiology* 2004; **41**:893–904.
- 19 Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol Heart Circ Physiol* 1985; **249**:H867–H875.
- 20 Hayano J, Sakakibara Y, Yamada M, Mukai S, Fujinami T, Yokoyama K, *et al.* Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol* 1991; **67**:199–204.
- 21 Weise F, Heydenreich F, Runge U. Contributions of sympathetic and vagal mechanisms to the genesis of heart rate fluctuations during orthostatic load: a spectral analysis. *J Auton Nerv Syst* 1987; **21**:127–134.
- 22 Wesseling K, Settels J. Baromodulation explains short-term blood pressure variability. In: Orlebeke J, Mulder G, Van Doornen L, editors. *The psychophysiology of cardiovascular control*. New York: Plenum Press; 1985.
- 23 Jorna P. Spectral analysis of heart rate and psychological state: a review of its validity as a workload index. *Biol Psychol* 1992; **34**:237–257.
- 24 Mulder G, Mulder LJM. Information processing and cardiovascular control. *Psychophysiology* 1981; **18**:392–402.
- 25 Veerman DP, Imholz BPM, Wieling W, Karemaker JM, Vanmontfrans GA. Effects of aging on blood-pressure variability in resting conditions. *Hypertension* 1994; **24**:120–130.

- 26 Pitzalis MV, Mastropasqua F, Passantino A, Massari F, Ligurgo L, Forleo C, *et al.* Comparison between noninvasive indices of baroreceptor sensitivity and the phenylephrine method in post-myocardial infarction patients. *Circulation* 1998; **97**:1362–1367.
- 27 Neale MC, Boker SM, Xie G, Maes HH. *Mx: Statistical modeling*, 6th ed. Richmond VA: Department of Psychiatry, VCU; 2003.
- 28 Akaike H. Factor-analysis and AIC. *Psychometrika* 1987; **52**:317–332.
- 29 Boomsma DI, Snieder H, De Geus EJC, Van Doornen LJP. Heritability of blood pressure increases during mental stress. *Twin Research* 1988; **1**:15–25.
- 30 Milan A, Mulatero P, Williams TA, Carra R, Schiavone D, Martuzzi R, *et al.* Bradykinin B-2 receptor gene (–58T/C) polymorphism influences baroreflex sensitivity in never-treated hypertensive patients. *J Hypertens* 2005; **23**:63–69.
- 31 Ylitalo A, Airaksinen KEJ, Hautanen A, Kupari M, Carson M, Virolainen J, *et al.* Baroreflex sensitivity and variants of the renin angiotensin system genes. *J Am Coll Cardiol* 2000; **35**:194–200.