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The genetic relationship between neuroticism and autonomic function in female twins

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ABSTRACT

Background. Neuroticism is widely used as an explanatory concept in etiological research of psychopathology. In order to clarify what neuroticism actually represents, we investigated the genetic association between neuroticism and cardiovascular measures.

Method. In 125 female twin pairs (18–30 years), electrocardiogram and continuous finger blood pressure were assessed during two rest and two mental stress conditions. Mean values for baroreflex sensitivity (BRS), heart rate variability (HRV) and inter-beat interval (IBI) were calculated for each condition. Neuroticism was assessed by multiple questionnaires. Multivariate genetic model-fitting analyses were used to investigate the genetic correlation between latent neuroticism and the cardiovascular autonomic nervous system (ANS) measures.

Results. Neuroticism was negatively correlated to BRS and HRV. Neuroticism was not correlated to IBI. For BRS, this phenotypical relation was entirely determined by shared genetic influences. For HRV, the genetic contribution to the phenotypical correlation was not significant, but the proportions of explained covariance showed a trend of more genetic than environmental influences on the phenotypical relationship.

Conclusions. High neuroticism is associated with a deregulated ANS. Pleiotropic genetic effects may be partly responsible for this effect.

INTRODUCTION

The personality trait neuroticism is an important marker of vulnerability for emotional disorders. This is indicated by the predictive value of neuroticism scores on onset, duration, and outcome of mild and severe depression and anxiety (Clark *et al.* 1994; Ormel *et al.* 2004). In addition, neuroticism scores seem to influence exposure to stressful situations (Kendler *et al.* 2003), and to modify the effect of stressors on well-being and risk of depression (Ormel *et al.*

2001). Behavioral genetic studies have indicated considerable genetic influences on neuroticism, depression and anxiety (Heath *et al.* 1989; Kendler *et al.* 1993; Boomsma *et al.* 2000; Hettema *et al.* 2001); a strong relationship between neuroticism and the genetic risk of depression (Kendler *et al.* 1993); genetic influences on the association between neuroticism and depression (Jardine *et al.* 1984), and genetic influences on the association between neuroticism and anxiety (Hettema *et al.* 2006). In spite of this, neuroticism largely remains a non-informative marker of limited use as an explanatory concept in etiological theory and research of psychopathology (Ormel *et al.* 2004).

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What could be the pathway by which neuroticism implies risk for emotional disorders? Neuroimaging studies have related individual differences in neuroticism to brain activity in the left temporal lobe, the frontal lobe and amygdala (Canli *et al.* 2001; Wright *et al.* 2006), and a decreased resting regional cerebral glucose metabolism in the insular cortex (Deckersbach *et al.* 2006). These brain structures, in particular the anterior cingulate cortex (located on the frontal lobe), are also known to be involved in the peripheral adjustments of the autonomic nervous system (ANS) in reaction to (anticipated) stress (Gianaros *et al.* 2004, 2005; Matthews *et al.* 2004; Critchley, 2005; Critchley *et al.* 2005). Thus, neuroticism and ANS function share at least part of their anatomical basis.

Three commonly used cardiovascular peripheral indices of the ANS are inter-beat-interval (IBI), heart rate variability (HRV) in the high-frequency spectral band (also referred to as respiratory sinus arrhythmia or vagal tone), and baroreflex sensitivity (BRS). These ANS measures have been shown to be heritable traits (Singh *et al.* 1999; Tank *et al.* 2001; Ditto, 1993; Martin *et al.* 2004; Riese *et al.* 2006). Although BRS and HRV are highly correlated, BRS might be a better indicator of ANS function since it is influenced by both the sympathetic and the parasympathetic branches of the ANS, whereas HRV is only influenced by the parasympathetic branch of the ANS (Virtanen *et al.* 2003). Still, both HRV and BRS have been shown to be useful indicators of autonomic deregulation in patients with depression or anxiety symptoms, with and without cardiac disease (Piccirillo *et al.* 1997; Watkins *et al.* 1998; Watkins & Grossman, 1999; Virtanen *et al.* 2003; Lavoie *et al.* 2004; Broadley *et al.* 2005). Poor vagal tone has also been related to neuroticism in selected populations (Haug *et al.* 1994). The relation between neuroticism and IBI has been often studied, resulting in inconsistent findings. Individuals high on neuroticism were occasionally found to have relatively long IBIs (i.e. lower heart rate) (LeBlanc *et al.* 2004), but more often no relation was found (Burdick *et al.* 1982; Roger & Jamieson, 1988; Knyazev *et al.* 2002; Vassend & Knardahl, 2005). Based on previous findings we expected highly neurotic subjects to have a deregulated ANS, as

indicated by decreased BRS and HRV, and no differences in IBI.

We aim to study mechanisms via which neuroticism influences the risk for emotional disorders. Defining neuroticism as an emotional and autonomic function as a physiological equivalent of arousability suggests that they (partly) share etiological influences. Since both traits were found to be heritable, we aim to investigate the genetic overlap between neuroticism and autonomic function. Since ANS measures can be influenced by mental tasks, ANS function measures were assessed during two rest and two mental stress tasks. We hypothesized that (i) neuroticism and ANS function measures are heritable; (ii) a high neuroticism score is associated with a deregulated ANS (as described above); (iii) the phenotypical relationships between neuroticism and ANS measures are partly determined by shared genetic effects.

METHOD

Subjects

This study is part of a larger project named Twin Interdisciplinary Neuroticism Study (TWINS) in which the genetic and environmental origins of neuroticism are explored. The sample for the TWINS study was a selection from the Groningen Twin Register (GTR). To establish the GTR, in 2001 nine municipalities 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. The twins identified in this way all received an invitation to participate in the GTR. In 2002 (T1), 1047 participants of the GTR participated in a survey. The survey included, among others, personality questionnaires and a zygosity questionnaire (Nichols & Bilbro, 1966) to determine whether the twin pair were monozygotic (MZ) or dizygotic (DZ). From the GTR, 207 female twin pairs between 18 and 30 years old were eligible for the TWINS study. Survey data of 206 twin pairs were used in the statistical analyses of the current study. A group of 125 female twin pairs between 18 and 30 years from the GTR participated in TWINS in 2003/2004 (T2). Invited twin pairs who did not enroll in TWINS did so for various reasons, but mainly because they found the

Table 1. General characteristics of the twin sample

	Monozygotic	Dizygotic
T1 Number of twin pairs	115	91
Neuroticism		
Neo N-scale survey	34.1 (7.1)	34.5 (6.9)
Age (years)	22.6 (4.2)	23.1 (5.3)
T2 Number of twin pairs	74	51
Neuroticism		
Neo N-scale	30.4 (7.3)	31.3 (6.6)
EPQ N-scale	4.5 (2.9)	4.7 (2.7)
Neo N-scale sib	31.6 (6.7)	30.3 (7.3)
Age (years)	23.4 (3.7)	23.5 (3.2)
BMI (kg/m ²)	22.6 (3.9)	23.1 (3.2)
SBP (mmHg)	124.5 (14.4)	123.7 (17.4)
DBP (mmHg)	68.4 (6.7)	69.4 (7.9)

Numbers represent means (s.d.) unless indicated otherwise.

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

psychophysiological experiment too time-consuming/demanding, or had work obligations. TWINS participants did not differ from the other eligible women of the GTR, in age or neuroticism as assessed at T1. Zygosity of TWINS participants was determined using 10 microsatellite markers. For three twin pairs zygosity could not be determined using DNA and zygosity questionnaire data were used instead. At T2, status of medication use was assessed, and subjects were categorized as non-users, antihypertensive users, and users of other medication. In addition, bodyweight and height were measured for body mass index calculation (BMI). The study was approved by the Ethics Committee of the University Medical Center Groningen, and all subjects gave written consent prior to participation. Table 1 shows general characteristics of our sample.

Neuroticism

At T1, neuroticism was evaluated with the neuroticism dimension from the NEO-FFI inventory (Hoekstra *et al.* 1996), which consists of 12 statements that are rated on a five-point scale ranging from 'strongly disagree' to 'strongly agree'. At T2 neuroticism was evaluated again with the NEO-FFI inventory, and additionally with the Eysenck Personality Questionnaire (EPQ), consisting of 12 dichotomous items (Sanderman *et al.* 1991). To control for self-report bias neuroticism of a subject was also evaluated at T2 by the co-twin sister, again

using the neuroticism dimension from the NEO-FFI. In total four neuroticism measures were available for each subject.

Cardiovascular autonomic function

At T2, cardiovascular autonomic function was assessed by BRS, HRV and IBI, during four standardized conditions: a rest condition (rest1), a stress condition with visual feedback (stress1), a stress condition with auditory feedback (stress2), and a second rest condition (rest2). Mental stress is expected to induce a shift in cardiac sympathetic/parasympathetic balance due to vagal withdrawal and increased sympathetic autonomic activity, which is known to induce a reduction of BRS, HRV and IBI (e.g. Mulder *et al.* 1993; van Roon *et al.* 2004). In the stress conditions, subjects performed a modified version of the 'emotion face dot-probe' task (Mogg & Bradley, 1999; Riese *et al.* 2006). On each trial of the task, a pair of faces (Ekman & Friesen, 1976) was presented for 19 ms, immediately followed by a mask for 50 ms. Subsequently, dots appeared in the location previously occupied by the two masked faces: 11 dots on one side, and three or four dots on the other side. Subjects indicated whether three or four dots appeared by button response as quickly as possible, while avoiding errors. Compared to the original task (Mogg & Bradley, 1999) only the response frame was adjusted: subjects had to respond to three or four dots instead of a horizontal or vertical plotted semi-colon. The two stress tasks were essentially the same, but 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. Cardiovascular measurements started after the subjects had relaxed in sitting position for at least 10 min, and each condition lasted for about 5 min. Immediately after the last rest condition, clinical blood pressure (BP) was measured (Omron M1 semi-automatic BP monitor; OMRON Healthcare Europe BV, Hoofddorp, The Netherlands) 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) (Peñáz, 1973; Wesseling *et al.* 1982). A three-lead

electrocardiogram (ECG) was applied for registering heart rate by disposable electrodes [3M™ Red Dot™ Ag/AgCl electrodes (3M, St Paul, MN, USA) for single use]. Changes in thoracic respiration signal were measured with a flexible band fixed around the upper part of the thorax. Respiration and BP were sampled with a frequency of 100 Hz using the same computer clock that controlled R-peak triggering.

Measurements were rejected when adequate signal recording failed. Detected artefacts, viz. outliers and missing values, for continuous BP and heart rate were corrected by means of linear interpolation of four data-points surrounding the artefact. Visual inspection of BP and IBI signals yielded 976 (=97.6%) measurements suitable for BRS calculation in the CARSPAN spectral analysis program (Robbe *et al.* 1987; Mulder, 1988). BRS was defined as the mean modulus between spectral values of IBI variability and systolic BP variability in the 0.07–0.14 Hz frequency band. BRS is expressed in ms/mmHg. For respiration, spectral power values were calculated, which were used in the BRS quality check procedure. After BRS calculation, the quality of the dataset was assured by exclusion of 124 (12.4%) measurements that did not meet criteria which are described in detail elsewhere (Riese *et al.* 2006). The main reasons for exclusion were too many artefacts in the BP signal, and supraventricular extra systoles. Subjects for whom no reliable BRS values were obtained were excluded in analyses regarding IBI and HRV. HRV measurements of two subjects (eight measurements) deviated more than 3 s.d. from the mean for that task condition and were additionally excluded.

Statistical analyses

Genetic modeling was performed on the unstandardized residuals of the autonomic function measures after the effects of age, BMI, medication-use, systolic BP and diastolic BP were regressed out in SPSS version 12.0.2 (SPSS Inc., Chicago, IL, USA). Three subjects used antihypertensives; 44 subjects used other medication with no known effects on the autonomic measures. The effect of medication use was marginal, so we decided to regress out any possible effects rather than to exclude individuals (see also Riese *et al.* 2006). Regressing out

possibly confounding influences on the autonomic function measures is a way to take these influences into account without losing power in the statistical analyses because of multiple co-variates.

Model-fitting procedure

To improve on statistical power, we analyzed the relation between latent factors for neuroticism and each of the ANS measures in multivariate models. The models included a latent neuroticism factor, determined by the twin's self-reported neuroticism (three measures) and the co-twin's report of the twin's neuroticism (L_N); latent BRS, HRV and IBI factors, each determined by two rest and two stress condition (L_{BRS} , L_{HRV} and L_{IBI}) (see Fig. 1). ANS measures obtained in the four experimental conditions were modeled loading onto a single latent factor, since we previously showed that the same genetic and shared environmental factors affected individual differences in BRS in all four conditions (Riese *et al.* 2006). In addition, for the neuroticism variables, a 'rater-bias' component was modeled, because the scoring of a co-twin on, for example, depression status has been shown to be more informative of a twin's own depression state (Kendler *et al.* 2002). The rater-bias component takes into account the additional covariance between a subject's own self-reports and what is reported for the co-twin, and enables the separation of rater bias and unreliability from the underlying latent factors.

Maximum likelihood estimates of the parameters were obtained by the Mx program (Neale *et al.* 2003), using raw data analyses. This means that the goodness of fit of all models (χ^2 statistic) was measured relative to a saturated model. The overall goodness of fit of a model was assessed by the Akaike's Information Criterion [AIC, $\chi^2 - 2$ df (Akaike, 1987)] and χ^2 statistic. The AIC assesses the fit of the model (χ^2) relative to the number of parameters, reflecting the goodness of fit and parsimony, to accept or reject nested models (a lower AIC indices indicate a better fit). The fit of sub-models was assessed by χ^2 difference test (Neale & Cardon, 1992). Confidence intervals of parameter estimates were obtained by maximum likelihood (Neale & Miller, 1997).

The low accuracy of the zygosity questionnaires compared with DNA marker data

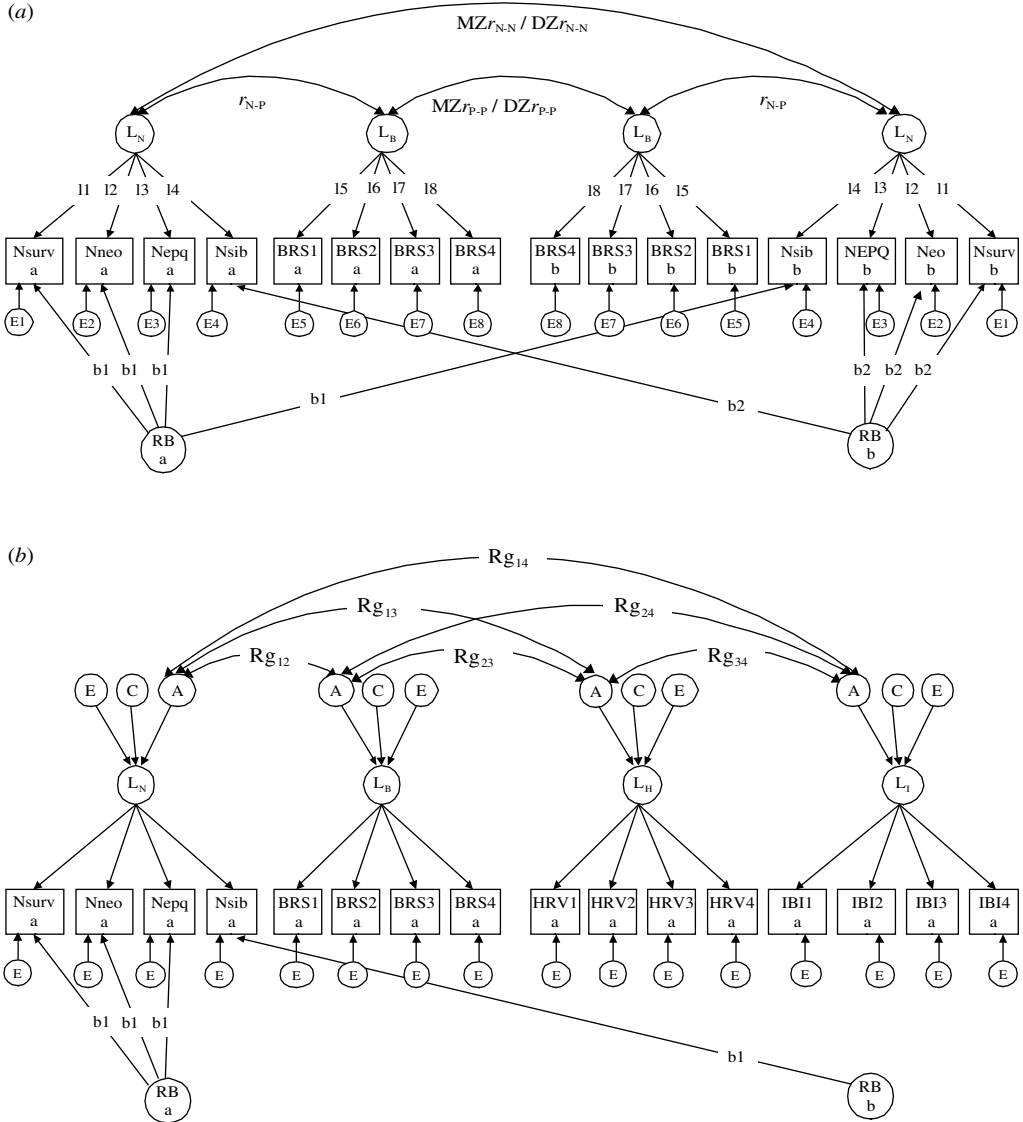


FIG. 1. (a) The Phenotypic Common Pathway Model (including a rater bias component) for neuroticism and baroreflex sensitivity (BRS) (for a twin pair). For simplicity, the observed heart rate variability (HRV) and inter-beat interval (IBI) were omitted in this graphical representation. (b) The genetic Common Pathway Model (including a rater bias component) for neuroticism, BRS, HRV, IBI (for an individual, twin a). Nsurv, NEO neuroticism scale assessed during the survey; Nneo, NEO neuroticism scale assessed during the stress reactivity experiment; Nepq, Eysenck neuroticism scale assessed during the stress reactivity experiment; Nsib, NEO neuroticism scale filled in by twin sister assessed during the stress reactivity experiment; a: refers to twin a in a pair; b: refers to twin b in a pair; BRS1 to BRS4, observed baroreflex sensitivity in the four experimental conditions (these four experimental conditions are: first rest condition, first mental stress condition, second mental stress condition, second rest condition.); HRV1 to HRV4, observed HRV (IBI power in the 0.07–0.14 Hz frequency band) in the four experimental conditions; IBI1 to IBI4, observed inter-beat interval in the four experimental conditions; MZr_{N-N}/DZr_{N-N} , MZ and DZ twin correlations for latent neuroticism; MZr_{P-P}/DZr_{P-P} , MZ and DZ twin correlations for the latent physiological factors; r_{N-P} : phenotypic correlation between latent neuroticism and latent physiological factors; L_N , latent neuroticism factor; L_P , latent physiological factor; 11 to 18, loadings on the pathway from latent neuroticism to observed neuroticism; E1 to E8, error term for the observed variables; b1, b2, loadings on the pathway from latent rater bias to observed neuroticism; RB: latent rater bias factor for each subject in a twin pair (a, b); A: additive genetic variation; C: shared environmental variation; E: unique environmental variation; Rg_{12} , Rg_{13} and Rg_{14} , genetic correlation between latent neuroticism and latent BRS, HRV and IBI, respectively; Rg_{23} , genetic correlation between latent BRS and latent HRV; Rg_{24} , genetic correlation between latent BRS and latent IBI; Rg_{34} , genetic correlation between latent HRV and latent IBI.

(90%) could potentially result in biased estimates (underestimation of genetic variance) of the T1 survey neuroticism questionnaire. Misclassification of twin pairs was accounted for by a mixture distribution approach using weighted likelihood (Neale, 2003). In this method, the data are entered twice in the analyses, once as MZ and once as DZ pairs, with probability weights according to the estimated accuracy in the sample. Note that this method is only relevant for the neuroticism questionnaire collected in the total sample. We observed slightly higher heritabilities (and smaller c^2) for the L_N factor using this method, and therefore a slight increase in power to detect a genetic correlation between L_N and L_{BRS} , L_{HRV} , or L_{IBI} , respectively.

The phenotypic common pathway model

The phenotypic common pathway model was used to derive the twin correlations between the latent phenotypes (Fig. 1a). To simplify interpretation, we applied some constraints to this model in order to obtain: (i) one set of within-twin cross-trait correlations between L_N , L_{BRS} , L_{HRV} and L_{IBI} , regardless of twin order or zygosity group; and (ii) one set of cross-twin cross-trait correlations for MZ and DZ pairs separately, but independent of twin order (e.g. $L_{Ntwin1} - L_{BRStwin2} = L_{Ntwin2} - L_{BRStwin1}$). The MZ/DZ cross-twin within-trait correlations (e.g. $L_{Ntwin1} - L_{Ntwin2}$) were free to vary across zygosity groups.

Genetic models

Based on biometrical genetic principals, the MZ/DZ ratio of the cross-twin within-trait correlations provides the power to decompose the variances of each latent factor into additive genetic effect (A), shared (or common) environmental effects (C) and non-shared (or individual-specific) environmental effects (E). The association between neuroticism and ANS factors, if significant, implies common etiological influences. The power to distinguish between different sources of variance causing the correlation is derived from the cross-twin cross-trait correlations: (a) significant cross-trait cross-twin correlations (e.g. $L_{Ntwin1} - L_{BRStwin2}$) imply that the common etiological influences are familial, but whether they are genetic or environmental in origin is indicated by the

MZ/DZ ratio of these correlations. A 2:1 ratio is indicative of A, whereas a 1:1 ratio suggests influences of C in inducing a correlation between the latent variables; (b) non-significant cross-trait cross-twin correlations imply that the common etiological influences are due to E.

The genetic Cholesky decomposition. This baseline model contains 16 A, C and E factors; the first A, C and E factors influence all neuroticism and ANS variables. The second A, C and E factors influence the second and following variables, and so on. The last A, C and E factors influence only the last variable. This genetically saturated decomposition was compared with a theoretical genetic common pathway model, using their AIC indices.

The genetic common pathway model. In this model the correlational structure of the four latent phenotypes (L_N , L_{BRS} , L_{HRV} and L_{IBI}) was modeled as a function of four latent A, C and E factors specified in a triangular decomposition, with common A_1 , C_1 and E_1 factors influencing all four corresponding latent factors, A_2 , C_2 and E_2 influencing the second, third and fourth latent factors, A_3 , C_3 and E_3 the third and fourth, and A_4 , C_4 and E_4 only the fourth latent factor. The standardized solution of this model is expressed in correlated factors: six for the A, C and E factors, depicted in Fig. 1b (only the A correlations are shown). The higher the correlation, the more likely the influences on the two latent phenotypes are similar.

In addition, the extent to which the latent A factors contribute to the phenotypic correlation between any two latent phenotypes can be obtained by multiplying the square roots of the standardized estimates (h^2) of the latent phenotypes with their corresponding genetic correlation (r_g). A similar procedure is followed to get the contribution of the C and E to the phenotypic correlation. The A, C and E contributions to the phenotypic correlation will sum up to the total phenotypic correlation.

RESULTS

Table 1 presents the four neuroticism scores for MZ and DZ twins separately. Except for the EPQ N-scale for MZ twin pairs [$\Delta\chi^2(1) = 5.4$, $p = 0.02$], mean neuroticism scores did not differ

Table 2. Means (s.d.) for IBI, HRV, and BRS measures obtained in the four experimental conditions

	Laboratory condition			
	rest1	stress1	stress2	rest2
Autonomic function				
BRS (ms/mmHg)	9.21 (3.65)	8.60 (3.44)	9.00 (3.58)	8.68 (3.71)
HRV ln (ms ²)	6.86 (0.95)	6.66 (0.88)	6.72 (0.88)	6.78 (0.94)
IBI (ms)	772.49 (107.25)	757.82 (110.10)	751.37 (109.70)	757.95 (104.30)

For calculation of mean values (s.d.) only those individuals were included who had values available for all four conditions ($n = 191$).

BRS, Baroreflex sensitivity; HRV, IBI power in the 0.07–0.14 Hz frequency band; ln, transformed by natural logarithm; IBI, inter-beat interval.

Table 3. Phenotypic correlations (95% CI) between latent neuroticism and latent physiological measures (BRS, HRV and IBI); cross-twins and cross-trait correlations presented separately for MZ and DZ pairs

Latent factors	r_{ph}	r_{MZ}	r_{DZ}
N-N		0.83 (0.66 to 0.95)	0.51 (0.21 to 0.77)
BRS-BRS		0.55 (0.35 to 0.70)	0.06 (–0.32 to 0.43)
HRV-HRV		0.54 (0.34 to 0.68)	0.13 (–0.23 to 0.46)
IBI-IBI		0.58 (0.41 to 0.70)	0.05 (–0.28 to 0.40)
N-BRS	–0.26 (–0.41 to –0.09)	–0.32 (–0.47 to –0.14)	–0.14 (–0.39 to 0.14)
N-HRV	–0.26 (–0.41 to –0.10)	–0.30 (–0.46 to –0.12)	–0.24 (–0.47 to 0.03)
N-IBI	–0.13 n.s. (–0.29 to 0.03)	–0.15 (–0.31 to 0.03)	–0.23 (–0.46 to 0.05)

Correlations are derived from the Phenotypic Common Pathway model.

r_{ph} , phenotypic correlation; N, latent Neuroticism factor; BRS, latent baroreflex sensitivity factor; HRV, latent heart rate variability factor; IBI, latent inter-beat-interval factor; n.s., non-significant.

across individuals within a twin pair or across zygosity groups. Table 2 presents the means and standard deviations for BRS, HRV and IBI for each of the four conditions. The means were equal across individuals in MZ twin pairs. However, due to small-sample fluctuations, small differences between certain subgroups (across twins in a pair and across zygosity groups) were found. Therefore, all means were specified as free parameters in further analyses.

The phenotypic common pathway model was used to derive the correlations between the latent neuroticism factor and the three autonomic function factors (see Table 3). This model fitted the data well. Latent neuroticism was negatively correlated with BRS [$r = -0.26$, $\Delta\chi^2(1) = 9.1$, $p = 0.003$], and HRV [$r = -0.26$, $\Delta\chi^2(1) = 9.8$, $p = 0.002$]. The correlation with IBI was also negative but not significant [$r = -0.13$, $\Delta\chi^2(1) = 2.6$, $p = 0.11$]. Twin correlations within and across traits for MZ and DZ twins separately are also given in Table 3. All MZ correlations within traits are more than twice the DZ correlations, suggesting non-additive (or

dominance) genetic effects in addition to additive genetic effects. However, given the lack of power to detect dominance (D) genetic effects due to small sample size we explored only models with shared environmental (C) effects. Fitting an ADE model instead of an ACE model would not have changed the conclusions of this paper since we are mainly interested in the genetic correlation between neuroticism and autonomic function measures.

To obtain a $\chi^2(df)$ statistic, the saturated model ($-2 \text{ Log L} = 14231.8$, $df = 3169$) was compared to the phenotypic common pathway model [$\chi^2(df) = 958.0$ (485), $p < 0.001$, $AIC = -12.0$]; the genetic Cholesky decomposition [$\chi^2(df) = 368.2$ (136), $p < 0.001$, $AIC = 96.2$]; and the genetic common pathway model [$\chi^2(df) = 961.5$ (485), $p < 0.001$, $AIC = -8.6$]. The modeling procedure showed that the genetic common pathway model fitted the data well. The parameter estimates derived from this model are summarized in Table 4. The genetic correlation with latent neuroticism was only significant for latent BRS [$r_g = -0.71$, $\Delta\chi^2(1) = 4.97$, $p = 0.03$],

Table 4. Upper panel: standardized parameter estimates (95% CI). Lower panel: the phenotypical correlations (95% CI) and the proportions (95% CI) of A, C and E variance explaining the phenotypical correlations (r_{ph}). All derived from the best-fitting multivariate model (=genetic common pathway model; see Results section)

Latent factor		a^2	c^2	e^2
Neuroticism		0.52 (0.12 to 0.90)	0.31 (0.00 to 0.68)	0.16 (0.05 to 0.33)
BRS		0.53 (0.12 to 0.69)	0.01 (0.00 to 0.37)	0.46 (0.31 to 0.66)
HRV		0.51 (0.01 to 0.67)	0.02 (0.00 to 0.46)	0.48 (0.32 to 0.67)
IBI		0.51 (0.14 to 0.68)	0.05 (0.00 to 0.37)	0.44 (0.31 to 0.61)
		Part of r_{ph} due to		
Phenotypical correlation (r_{ph})		a^2	c^2	e^2
N-BRS	-0.26 (-0.41 to -0.10)	-0.38 (-0.56 to -0.05)	0.06 n.s. (-0.22 to 0.22)	0.05 n.s. (-0.06 to 0.16)
N-HRV	-0.27 (-0.42 to -0.11)	-0.23 n.s. (-0.52 to 0.09)	-0.08 n.s. (-0.35 to 0.17)	0.04 n.s. (-0.08 to 0.15)
N-IBI	-0.14 n.s. (-0.30 to 0.02)	-0.04 n.s. (-0.34 to 0.23)	-0.12 n.s. (-0.34 to 0.14)	0.02 n.s. (-0.09 to 0.12)

BRS, Baroreflex sensitivity; HRV, IBI power in the 0.07–0.14 Hz frequency band; IBI, inter-beat-interval; n.s., non-significant.

but neither for HRV [$r_g = -0.44$, $\Delta\chi^2(1) = 1.89$, $p = 0.17$] nor IBI [$r_g = -0.07$, $\Delta\chi^2(1) = 0.05$, $p = 0.82$]. In Table 4, we report the proportions of the phenotypic correlations between latent neuroticism and the three latent ANS measures as determined by shared A, C and E influences. These values are better interpretable, since in addition to r_g , r_c and r_e , they also depend on the magnitude of the heritability, c^2 and e^2 of the two latent variables. For both the relationship between neuroticism and BRS and the relationship between neuroticism and HRV, the proportion of explained covariance was predominantly accounted for by genetic influences, although the genetic correlation reached significance only for BRS.

DISCUSSION

The heritability estimates of the best-fitting multivariate model were around 50% for neuroticism, BRS, HRV, and IBI. These estimates are comparable to estimates for neuroticism, BRS and HRV reported before (Havlik *et al.* 1980; Ditto, 1993; Heath *et al.* 1994; Voss *et al.* 1996; Russell *et al.* 1998; Singh *et al.* 1999; Boomsma *et al.* 2000; Tank *et al.* 2001), and slightly higher than those reported for IBI (Martin *et al.* 2004). Multivariate analyses indicated that high scores on neuroticism were associated with a deregulated ANS as indicated by a less favorable ANS profile, namely lower BRS and HRV levels. Neuroticism was not correlated with IBI. The phenotypic relationship

between neuroticism and BRS could be entirely explained by shared genetic influences. For HRV, the genetic contribution to the phenotypic correlation was not significant, but the proportions of explained covariance showed a trend towards more genetic than environmental influences on the phenotypic relationship. Presumably due to the small sample size, the power was just short on picking up a significant genetic correlation between neuroticism and HRV.

Our findings suggest that a single genetic vulnerability might confer risk for both high neuroticism scores and an unfavorable ANS profile. Since our study should be considered a cross-sectional study, the causal chain of events that give rise to the common genetic factor remains unknown. Several explanations are possible. First, genetic vulnerability initially may have expressed itself in ANS deregulation in the pre-morbid state, which over time causes an increase in neuroticism. Findings in the prospective ‘Munich vulnerability study’ showed that healthy subjects who had a first-degree relative with an affective disorder had a comparable physiological endophenotype as their affected relative (Modell *et al.* 2005). Alternatively, genetic vulnerability may have expressed itself first in high neuroticism, which may increase an individual’s daily experienced level of distress (Ormel *et al.* 2004). Frequent long-lasting adaptation to daily stress may lead to persistent alterations in ANS regulation (McEwen & Wingfield, 2003). Furthermore, the common

genetic factor may also reflect pleiotropic genes that influence each of the traits without causal effects between the traits. Such common genetic vulnerability is recently illustrated in a review regarding depressive symptoms and coronary artery disease (McCaffery *et al.* 2006). Finally, as recently suggested to be the most likely scenario, the outlined possible explanations may co-exist (De Geus, 2006).

Different polymorphisms were found to explain part of the variance in BRS (Ylitalo *et al.* 2000; Milan *et al.* 2005), HRV (Neumann *et al.* 2005), or vulnerability for affective disorders (Hariri *et al.* 2005; Pezawas *et al.* 2005). Pleiotropic genetic influences on these traits warrant further research. For example, a variant in the ACE receptor gene has been found to explain variation in both panic disorder (Olsson *et al.* 2004), and HRV (Busjahn *et al.* 1998). Furthermore, evidence has been found for an association between a functional serotonin transporter promoter polymorphism (5-HTT LPR) and neuroticism and other anxiety-related personality traits (Lesch *et al.* 1996; Sen *et al.* 2004). Although the exact mechanisms still need to be unraveled, the 5-HTTLPR polymorphism has also been related to cardiovascular reactivity to mental stress (Williams *et al.* 2001; McCaffery *et al.* 2003). Gender differences in this latter relation (McCaffery *et al.* 2003), but also in neuroticism and cardiovascular reactivity in general, imply that the findings of the current study obtained in women may not be generalizable to men.

Cardiac vagal tone has been proposed as a marker of the ability of emotion regulation, viz. lower resting vagal tone has been presumed to reflect deficient emotion regulation (Porges *et al.* 1994). Thayer and colleagues describe how autonomic imbalance, and decreased parasympathetic tone in particular, may indicate deficient self-regulation (Thayer & Lane, 2000; Thayer & Brosschot, 2005). They underline that chronic withdrawal of parasympathetic inhibitory action can be pathogenic (negative affective states and somatic ill health). Given our results, it is tempting to speculate that both high neuroticism scores and ANS dysregulation are markers of ineffective emotional regulation mechanisms.

In conclusion, neuroticism is negatively associated with BRS and HRV. The phenotypic

relationship between neuroticism and BRS could be entirely explained by shared genetic influences. The phenotypic relationship between neuroticism and HRV showed a trend of more shared genetic than environmental influences. These genetic correlations may reflect a pleiotropic genetic basis for less effective emotion regulation mechanisms.

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DECLARATION OF INTEREST

None.

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