

Neuroticism and Morning Cortisol Secretion: Both Heritable, But No Shared Genetic Influences

Harriëtte Riese,¹ Frühling V. Rijsdijk,² Judith G. M. Rosmalen,¹ Harold Snieder,¹ and Johan Ormel¹

¹University Medical Center Groningen, University of Groningen

²King's College London

ABSTRACT Neuroticism is widely used as an explanatory concept in etiological research of psychopathology. To clarify what neuroticism actually represents, we investigated the phenotypic and genetic relationship between neuroticism and the morning cortisol secretion. In the current classic twin study, 125 female twin pairs (74 monozygotic and 51 dizygotic pairs) participated. For each participant, 4 different neuroticism scores were available to calculate a neuroticism composite score that was used in the statistical analyses. The morning cortisol secretion was assessed by 4 salivary samples in the 1st hour after awakening. Significant genetic influences for the neuroticism composite score (55%), and each of the 4 cortisol samples (52%–69%) were found. There was no phenotypic or genotypic relationship between neuroticism and morning cortisol secretion. Although neuroticism and cortisol were both heritable traits, they did not share any genetic influences.

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Correspondence concerning this article should be addressed to Harriëtte Riese, Interdisciplinary Center for Psychiatric Epidemiology (ICPE), Department of Psychiatry and Unit of Genetic Epidemiology & Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001 (CC72), 9700 RB Groningen, The Netherlands. E-mail: H.Riese@med.umcg.nl.

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Neuroticism features in all the major personality models (e.g., Cloninger, 1986; Eysenck & Eysenck, 1985; McCrae & Costa, 1997). It is moderately heritable (e.g., Boomsma et al., 2000; Eaves et al., 1999; Flint, 2004; Heath, Jardine, Eaves, & Martin, 1989; Loehlin, 1992; Plomin, 1994) and is regarded as an important marker of (genetic) “vulnerability” for emotional disorders such as depression and anxiety (Clark, Watson, & Mineka, 1994; Ormel, Rosmalen, & Farmer, 2004). However, neuroticism is of limited use as an explanatory concept in etiological theory and research of psychopathology, because consistent evidence regarding (neuro)physiological and (social-) cognitive correlates of neuroticism is lacking (Ormel et al., 2004). Its explanatory value will increase if the mechanisms underlying the associations between neuroticism and psychopathology are clarified. Defining neuroticism as “a person’s characteristic level of distress over a protracted period of time” (Ormel et al., 2004, p. 906) suggests that alterations in the hypothalamic–pituitary–adrenocortical (HPA) axis function may be involved in such an association (Miller, Chen, & Zhou, 2007). Previous studies in small heterogenous samples indeed suggest the existence of a positive relationship between neuroticism and cortisol, the major end product of the HPA axis, although findings are inconsistent (Chan, Goodwin, & Harmer, 2007; Portella, Harmer, Flint, Cowen, & Goodwin, 2005; Wirtz et al., 2007).

Just like neuroticism, HPA axis dysfunction has been found to be associated with affective disorders (Holsboer, 2000). Several studies indicate that cortisol is influenced by genetic factors, although the magnitude of the heritability estimate varies. In 11 reviewed twin studies, a large variation in cortisol heritability (namely, 0%–84%) was reported (Bartels, van den Berg, Sluyter, Boomsma, & De Geus, 2003). The variation was considered due to differences in the method of data collection (blood, saliva, or urine) and frequency and timing of sample collection. Combining five comparable twin studies in a simultaneous analysis resulted in a heritability estimate of 62% for basal cortisol levels. In a sample of 12-year-old twins (Bartels, De Geus, Kirschbaum, Sluyter, & Boomsma, 2003), heritability for salivary cortisol levels was 22%–24% at awakening and 56%–59% approximately 45 min after awakening. In an adult twin sample the heritability for cortisol levels was 34% at awakening and 32% 30 min after awakening (Kupper et al., 2005). In their model, no additional heritability for the cortisol awakening response was found. In contrast, Wüst, Federenko, Hellhammer, and Kirschbaum

(2000) reported heritability estimates of 40% for the mean cortisol increase in the first hour after awakening and 48% for the area under the cortisol response curve but no heritability for the awakening level. In summary, findings are difficult to compare across studies but do suggest genetic influences on individual differences in the morning cortisol secretion.

Although both neuroticism and cortisol are heritable, it is currently unknown if and to what extent their genetic influences are shared. The aim of the present classical twin study is to investigate whether there is a genetic relationship between neuroticism and HPA axis function. We hypothesize that neuroticism is related to the morning cortisol secretion and that part of the phenotypical relationship between neuroticism and cortisol is determined by shared genetic influences.

METHOD

Participants

This study is part of the Twin Interdisciplinary Neuroticism Study (TWINS) in which the genetic and environmental origins of neuroticism are explored. For this purpose, in 2002 (T1) the Groningen Twin Register (GTR) was established. The study was limited to females for two main reasons: (a) optimization of power and (b) higher neuroticism scores and much higher incidence of emotional disorders in women. In 206 female twin pairs from the GTR, we collected neuroticism data in the T1 assessment wave. A subgroup of 125 pairs participated in TWINS in 2003/2004 (T2), in which additional neuroticism data and cortisol were assessed. These twins did not differ in age or neuroticism scores from the main sample of the GTR (T1) (Riese et al., 2007). Mean age of the subgroup that completed the T2 measurements was 23.4 years ($SD = 3.5$). One hundred twenty-four (49.6%) participants were students, 106 (42.4%) were employed, and 16 (6.4%) were unemployed or ran the family household; data of 4 (1.6%) participants were missing. Forty-one (16.4%) participants lived alone, 74 (29.6%) with parents, 22 (8.8%) with partner and children, 46 (18.4%) with partner, 3 (1.2%) with children, and 64 (25.6%) had a different living situation, for example, student accommodation. All participants reported to be in good physical and mental health during the intake. Three participants reported current use of antihypertensive medication, and 11 reported current use of medication for psychiatric disorders. Zygosity was assessed by questionnaire (Nichols & Bilbro, 1966) and DNA samples. A full description of the sample selection and procedures has been published (Riese et al., 2006, 2007).

The study was approved by the Ethics Committee of the University Medical Center Groningen, and all participants gave written consent prior to participation.

Neuroticism

At T1, neuroticism was measured in 206 participants with the neuroticism subscale of the NEO-Five Factor Inventory (NEO-FFI) inventory (Costa & McCrae, 1992; Hoekstra, Ormel, & De Fruyt, 1996). At T2, neuroticism was measured again in 125 pairs in three different ways: (a) self-report using the short form of the Eysenck Personality Questionnaire (Sanderman, Eysenck, & Arrindell, 1991), (b) self-report using the NEO-FFI inventory (Costa & McCrae, 1992; Hoekstra et al., 1996), and (c) co-twin report using the NEO-FFI inventory (Costa & McCrae, 1992; Hoekstra et al., 1996) in order to adjust for self-report bias in neuroticism. Thus, twins participating at T1 only had one measure of neuroticism, whereas twins who participated at both T1 and T2 had four measures of neuroticism (descriptive data for these scales have been published previously; Riese et al., 2007). To simplify present analyses while maximizing the usefulness of available information, for each individual a composite score was generated by the LAVASE program (Campbell, Rijdsdijk, & Sham, 2007) using the correlational structure of the four neuroticism scales accounting for both rater bias and zygosity misclassification of twin pairs (Riese et al., 2007). Comparable models have shown a substantial decrease in variance attributed to individual-specific environment (including measurement error) and a proportional increase in heritability of liability for major depression, generalized anxiety disorder, alcohol dependence, and adult antisocial behavior (Kendler, Prescott, Jacobson, Myers, & Neale, 2002). The neuroticism composite score (Ncomp) was available for 206 pairs (115 monozygotic [MZ] and 91 dizygotic [DZ] pairs). The mean value of the Ncomp measure is -0.0001 , $SD = 0.86$, $range = -2.44$ to 2.44 , $skewness = 0.20$, $kurtosis = -0.02$.

Saliva Collection

Four morning saliva samples were collected at home using the Salivette sampling device (Rommelsdorf, Germany). Participants collected one evening sample at 10:30 p.m. (or earlier when going to bed; CORT22:30), the first morning sample immediately after waking up (still lying in bed; CARTawk), and subsequently 30 (CORT30), 45 (CORT45), and 60 (CORT60) minutes after awakening. The current study only reports on the morning samples, that is, CORTawk, CORT30, CORT45, and CORT60.

Participants recorded the actual times of saliva collection and indicated any deviations from the instructions. Saliva samples were taken to

our laboratory by the participants themselves. Participants were requested to refrain from intense physical exercise on the day preceding and time before arrival in the laboratory. In addition, participants were requested to refrain from eating, drinking, and smoking after 10:00 p.m. on the day prior to the laboratory visit and to brush their teeth after collecting the last saliva sample.

Sampling-time variation of the morning samples was limited because all participants arrived at the laboratory at approximately 8:30 a.m. Saliva was immediately extracted from the salivettes and stored at -20°C until analysis.

Cortisol Analysis

Samples of all participants were analyzed with the same reagent. In each batch, 60 samples (5 samples \times 6 twin pairs) were assayed in duplicate. Thus, all samples from one participant were assayed in a single batch and twin pairs were assayed together. Cortisol was measured directly in duplicate in 100 μl saliva using an in-house radioimmunoassay (RIA) applying a polyclonal rabbit cortisol antibody and 1,2,6,7 ^3H Cortisol (Amersham) as tracer. After incubation for 30 mins at 60°C the bound and free fractions were separated using activated charcoal. The intra-assay and inter-assay coefficient of variation were between 4.1% and 8.2%, and between 5.6% and 12.6%, respectively. Of the 250 participants, 3 did not return their salivettes or some salivettes contained not enough saliva for cortisol determination. The following number of cortisol values could be obtained for each sample point: 224 for the CORT22:30, 215 for the CORTawk, 224 for the CORT30, 226 for the CORT45, and 226 for the CORT60 sample. The quality of the data set was assured by exclusion of (a) 6 participants using corticosteroid-containing medication and (b) excluding cortisol values that were 3 *SD* above the mean for a particular time point to reduce the impact of outliers: 3 for CORTawk, 1 for the CORT30, 2 for CORT45, and 2 for CORT60. After these exclusions, cortisol values approached a normal distribution. (c) Noncompliance, that is, reporting to not have taken the cortisol sample within 30 min of the requested sampling time (Kudielka, Broderick, & Kirschbaum, 2003), resulted in removing one CORT60 sample. All other saliva samples were reported to be taken within 15 min of the requested sampling time, a delay considered to be acceptable (Dockray, Bhattacharyya, Molloy, & Step-toe, 2008), except for one sample that was taken 17 min past the requested sampling time of 60 min after awakening. In total, we obtained 1,072 (85.8%) cortisol samples that met our quality criteria and were thus included in our analyses: 214 for the CORT22:30, 206 for the CORTawk, 217 for the CORT30, 218 for the CORT45, and 217 for the CORT60 sample.

Data Preparation

The primary statistical analyses as reported in the current paper were performed on cortisol data of participants who had a positive cortisol awakenings response (CAR) because previous studies have shown that a nonpositive CAR might indicate noncompliance (Kupper et al., 2005). For 89.7% of the participants the CAR was positive, which was comparable to percentages reported by others; 76.8% (Wüst, Wolf, et al., 2000) and 89% (Kupper et al., 2005). Because a nonpositive CAR may sometimes reflect a physiological feature of a person rather than an indicator of noncompliance (Dockray et al., 2008), statistical analyses were repeated after inclusion of participants with a nonpositive CAR. In the analyses, variables were adjusted for age. This is a common procedure in twin analyses because age can spuriously introduce a shared environmental effect if there is a significant correlation between the phenotype and age, because twins are always of the same age. Other potential confounders of the relationship between cortisol measures and psychological variables as previously reported in the literature (e.g., Rosmalen et al., 2005) were also measured in the current study: body mass index (BMI), smoking habits, phase of reproductive cycle, oral contraceptive use, sleep quality, and season of sampling. In our data set, the cortisol samples were influenced by sleep duration, oral contraceptive use, BMI, and smoking status. Thus, analyses were repeated while additionally adjusting for these confounders. Finally, the four morning cortisol samples were used for calculating area-under-curve (AUC) measures (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003): AUC with respect to the ground (a total output measure; AUCg) and AUC with respect to increase (a measure of time-dependent change; AUCi).

The Twin Model

Classical twin analysis allows estimation of the effects of (unobserved or latent) genetic and environmental factors on the variance of an observed trait. The power to estimate these variance components is derived by the differential predictions of the covariance (or correlation) of the trait among MZ and DZ twin pairs. MZ pairs correlate 1 for the additive genetic component (A), whereas DZ pairs correlate 0.5, as they share, on average, only 50% of their genes. However, both MZ and DZ pairs correlate 1 for the shared environmental component (C) and both are uncorrelated for the unshared environmental component (E), which also includes measurement error. Assuming that MZ and DZ twins experience the same degree of similarity in their environments, a higher MZ than DZ twin correlation is interpreted as caused by the greater proportion of genes shared by MZ twins allowing estimation of A. An estimate for C is

given by the difference in MZ correlation and the estimated effect of A. Because the phenotypic differences between MZ twins can only be due to unique environmental influences, this gives an estimate for E. When measuring multiple traits in each twin, significant phenotypic correlations between traits within twins suggest a common etiology. The ratio of the MZ and DZ cross-trait cross-twin correlations indicates to what extent the common etiology is genetic or environmental in origin: a 2:1 ratio suggests the effects of A, whereas a 1:1 ratio suggests the effects of C. Nonsignificant cross-trait cross-twin correlations suggest that the common etiology is due to E (Neale & Cardon, 1992).

Model Fitting Analyses

Twin correlations as well as maximum likelihood estimates of the A, C, and E components were obtained by the Mx program (Neale, Boker, Xie, & Maes, 2003) using raw data analyses. To simplify estimated patterns of twin correlations, equality constraints were imposed on those correlations that are not expected to be different, either due to symmetry or the assumptions of the ACE model. This constrained model estimates (a) one set of phenotypic correlations between neuroticism and cortisol (regardless of twin order and zygosity); (b) a set of MZ and DZ within-trait, cross-twin correlations (within-pair twin resemblance on a single variable, e.g., Ncomp); and (c) a set of MZ and DZ cross-trait cross-twin correlations (e.g., Ncomp measured in one member of a twin pair and CARTawk measured in the other twin).

For the genetic modeling, a Cholesky decomposition was fitted to the multivariate twin data (Neale & Cardon, 1992). A Cholesky decomposition provides a saturated description of the multivariate data; the first factor influences all measures, the second factor only influences the second and subsequent measures, the third factor only influences the third and subsequent measures, and so forth (for simplicity the model presented in Figure 1 contains only A factors). In this full (or saturated) model there are as many factors as variables for each A, C, and E component. This means that the phenotypic correlation between any two variables can be decomposed in genetic and environmental pathways. The standardized solution gives the genetic and environmental factor correlations between all variables. The fit of submodels (dropping A or C parameters) from the full model was assessed by the χ^2 difference test (Neale & Cardon, 1992) and the Akaike's Information Criterion ($AIC = \chi^2 - 2df$; Akaike, 1987). Confidence intervals of parameter estimates were obtained by maximum likelihood (Neale & Miller, 1997).

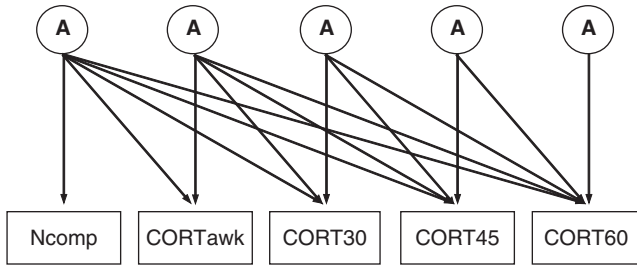


Figure 1

Simplified schematic presentation of the full Cholesky model. For simplicity, the model is presented for only one member of a twin pair and only contains additive (A) genetic factors.

RESULTS

In Table 1, the descriptives are given for MZ and DZ pairs separately. The means and variances of the neuroticism composite score and the cortisol measures were not significantly different between MZ and DZ pairs. In Table 2, the within-trait cross-twin (twin correlations) and the cross-trait cross-twin correlations are presented for MZ and DZ pairs. The twin correlations were higher for MZ

Table 1

Means (Standard Deviations) of the Neuroticism Composite Score and the Cortisol Awakenings Response Samples for Monozygotic and Dizygotic Twins Separately

	Monozygotic Twins	Dizygotic Twins
Ncomp	0.00 (0.87)	0.00 (0.85)
CORTawk (in nmol/L)	8.35 (4.46)	9.27 (4.96)
CORT30 (in nmol/L)	18.21 (8.43)	18.98 (8.60)
CORT45 (in nmol/L)	21.57 (10.54)	21.28 (8.71)
CORT60 (in nmol/L)	21.94 (9.42)	21.27 (7.88)

Note. “Ncomp” is the neuroticism composite score obtained from the neuroticism scale of the NEO-FFI inventory (assessed twice within 1 to 2 years), the neuroticism scale of the Eysenck Personality Questionnaire, and the co-twin report on the neuroticism scale of the NEO-FFI inventory. The Ncomp score controls for possible rater bias and zygosity misclassification of twin pairs (Campbell et al., 2007). Descriptive data for the four neuroticism scales have been published previously (Riese et al., 2007). Salivary cortisol samples were taken at awakening (CORTawk) and 30 (CORT30), 45 (CORT45), and 60 (CORT60) min after awakening.

Table 2

Within-Trait Cross-Twin Correlations (95% CI) for the Neuroticism Composite Score and the Cortisol Measures (Upper Panel), the Phenotypic Cross-Trait Correlations (r_{ph} ; 95% CI), and Cross-Trait Cross-Twin Correlations for Monozygotic and Dizygotic Twin Pairs Separately (Lower Panel)

Within-Trait		Cross-Twin (MZ Pairs)	Cross-Twin (DZ Pairs)
Ncomp	—	0.88 [0.83 to 0.91]	0.60 [0.46 to 0.70]
CORTawk	—	0.55 [0.33 to 0.70]	0.27 [−0.09 to 0.54]
CORT30	—	0.71 [0.57 to 0.81]	0.23 [−0.19 to 0.54]
CORT45	—	0.70 [0.54 to 0.80]	0.28 [−0.13 to 0.57]
CORT60	—	0.53 [0.33 to 0.68]	0.20 [−0.22 to 0.51]
Cross-Trait	Within-Twins (r_{ph})	Cross-Twin (MZ Pairs)	Cross-Twin (DZ Pairs)
Ncomp-CORTawk	−0.02 [−0.17 to 0.14]	−0.02 [−0.17 to 0.14]	0.01 [−0.17 to 0.19]
Ncomp-CORT30	0.01 [−0.14 to 0.16]	0.03 [−0.13 to 0.18]	0.05 [−0.13 to 0.23]
Ncomp-CORT45	−0.04 [−0.19 to 0.11]	−0.05 [−0.20 to 0.11]	−0.01 [−0.19 to 0.17]
Ncomp-CORT60	−0.03 [−0.18 to 0.12]	−0.06 [−0.21 to 0.09]	−0.05 [−0.23 to 0.14]

Note. “MZ pairs” are the monozygotic twin pairs. “DZ pairs” are the dizygotic twin pairs. “Ncomp” is the neuroticism composite score. Salivary cortisol samples were taken at awakening (CORTawk) and 30 (CORT30), 45 (CORT45), and 60 (CORT60) min after awakening. The CIs of the phenotypic correlations include the value 0, which indicates that the correlations are nonsignificant.

pairs compared to DZ pairs for the neuroticism composite score and all four cortisol samples, suggesting that these traits are heritable. There were no significant phenotypic or cross-trait cross-twin correlations between the neuroticism composite score and any of the cortisol variables. Thus, genetic and environmental decomposition of these correlations are not shown any further. We only report here the heritability estimates of the neuroticism composite score and the cortisol measures.

Compared to the full genetic multivariate ACE Cholesky decomposition, $\chi^2(df) = 86.91 (65)$, $p = .04$, $AIC = -43.09$, a reduced ACE model, where C effects for the neuroticism composite score were allowed and C effects for all four cortisol measures were set to zero, $\chi^2(df) = 87.86 (79)$, $p = .23$, $AIC = -70.14$, did not fit significantly worse and was the most parsimonious model to describe the data. However, to account for the lack of power in small samples to detect small effects of common environment and to prevent artificial inflation of heritability estimates, we report standardized parameter estimates and confidence intervals for A, C, and E derived from the full ACE model (Table 3). The significant drop in fit of the model dropping both A and C influences, $\Delta\chi^2(df) = 286.88 (30)$, $p < .001$, indicates that the observed covariance could not be explained solely by unique environmental factors.

Table 3
Standardized Parameter Estimates (95% CI) of the Contribution of Genetic (a^2), Shared Environmental (c^2) and Nonshared Environmental (e^2) Influences on the Neuroticism Composite Score and the Four Cortisol Measures

	a^2	c^2	e^2
Ncomp	0.55 [0.34 to 0.81]	0.33 [0.06 to 0.53]	0.13 [0.09 to 0.17]
CORTawk	0.46 [0.06 to 0.70]	0.09 [0.00 to 0.47]	0.45 [0.30 to 0.65]
CORT30	0.69 [0.26 to 0.80]	0.01 [0.00 to 0.41]	0.30 [0.20 to 0.44]
CORT45	0.69 [0.19 to 0.80]	0.004 [0.00 to 0.45]	0.31 [0.20 to 0.46]
CORT60	0.52 [0.03 to 0.67]	0.005 [0.00 to 0.45]	0.48 [0.33 to 0.68]

Note. All estimates were derived from the full ACE Cholesky decomposition. "Ncomp" is the neuroticism composite score. Salivary cortisol samples were taken at awakening (CORTawk) and 30 (CORT30), 45 (CORT45), and 60 (CORT60) min after awakening.

Fifty-five percent of individual differences in the neuroticism composite score were explained by genetic influences, 33% by shared environmental influences, and 13% by nonshared environmental influences. The individual differences in the four cortisol samples were explained by genetic (range 46%–69%) and nonshared environmental influences (range 30%–48%) only. The heritabilities derived from the reduced ACE model gave comparable estimates (indicated by overlapping confidence intervals): for CORTawk (56%), CORT30 (70%), CORT45 (70%), and CORT60 (52%).

Adjusting for potential confounders, including different sets of participants (both positive and negative CAR), or using the cortisol area-under-curve measures (AUCg and AUCi) instead of individual cortisol samples in the analysis did not change our major finding on the absence of a phenotypic or genotypic relationship between neuroticism and morning cortisol secretion. The heritability estimate of AUCg was 64% (95% CI = 0.14–0.80), and the heritability estimate of AUCi was not significant (33%; 95% CI = 0.00–0.72). Finally, we tested whether the correlation between neuroticism and cortisol changed as a function of the level of neuroticism (Purcell, 2002). No such interaction was found.

DISCUSSION

We found substantial genetic influences on both neuroticism (55%) and salivary cortisol levels during the first hour after awakening (between 46% and 69%). Comparable heritability estimates for neuroticism have been reported previously (e.g., Boomsma et al., 2000). Other studies, however, have not found the somewhat unusual shared environmental influences of 33% of the neuroticism composite score, which might be due to small-sample fluctuations. Compared to previous studies the point estimates for the heritabilities for the four cortisol measures seem to be higher (Bartels, De Geus, et al., 2003; Kupper et al., 2005). However, because the 95% CIs of the cortisol measures in both previous studies and our study largely overlap, these “differences” cannot be considered significant.

We did not find any phenotypic or genetic correlations between neuroticism and cortisol. To the best of our knowledge, the present study is the largest sample in which this phenotypic relationship was tested and the first in which the genetic relationship was tested.

Using a homogenous female population has its benefits because the results cannot be confounded by gender or a wide age range. However, studies in men and older women are needed to test whether the current results can be more widely generalized. Our findings are largely in line with previous reports of smaller studies. In two publications on the relationship between neuroticism and morning cortisol secretion, no relationship (Chan et al., 2007) and a “statistically non-significant positive correlation” (Wirtz et al., 2007) were reported. An earlier study by Portella and colleagues (2005) reported a positive relationship between neuroticism and morning cortisol secretion, but they had selected participants who scored extremely high or low on a neuroticism scale. Moreover, dichotomization of continuous variables may generate spurious findings (Babyak, 2004). This makes the Portella et al. results difficult to generalize to the population at large. These previous and our current findings suggest that there is no phenotypical relationship between neuroticism, defined as a broad domain of personality, and morning cortisol secretion.

In addition to the phenotypical relationship, the current classic twin study also allowed for studying the genetic relationship between neuroticism and cortisol. We did not find a genetic association. This means that neuroticism and cortisol do not share any of their genetic influences in spite of the well-established genetic relationship between neuroticism and depression (see introduction) and the genetic relationship between HPA axis dysfunction and depression (Holsboer, 2000; Jabbi et al., 2007). Our findings suggest that two important risk markers for depression, namely, neuroticism and HPA axis dysfunction, are phenotypically and genetically independent. That is, they may be part of separate pathways underlying depression.

An explanation for our current finding could be that the neuroticism construct is too broad and heterogeneous to find a relationship with the cortisol measures. Future studies should focus on more specific lower order facets of neuroticism (e.g., anxiety, angry hostility; Costa & McCrae, 1995) or temperamental aspects related to negative affect (e.g., anxious distress, irritable distress; Rothbart & Bates, 1998). We cannot exclude that lower order facets of neuroticism have counteracting relationships with morning cortisol secretion and that combining such facets into a higher order neuroticism construct obscures such relationships.

In conclusion, there is no phenotypic relationship between neuroticism and morning cortisol secretion in a young population-based female sample. Although neuroticism and cortisol are both heritable traits, they do not share any genetic influences.

REFERENCES

- Akaike, H. (1987). Factor-analysis and AIC. *Psychometrika*, *52*, 317–332.
- Babyak, M. A. (2004). What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic Medicine*, *66*, 411–421.
- Bartels, M., De Geus, E. J. C., Kirschbaum, C., Sluyter, F., & Boomsma, D. I. (2003). Heritability of daytime cortisol levels in children. *Behavior Genetics*, *33*, 421–433.
- Bartels, M., van den Berg, M., Sluyter, F., Boomsma, D. I., & De Geus, E. J. C. (2003). Heritability of cortisol levels: Review and simultaneous analysis of twin studies. *Psychoneuroendocrinology*, *28*, 121–137.
- Boomsma, D. I., Beem, A. L., van den Berg, M., Dolan, C. V., Koopmans, J. R., Vink, J. M., et al. (2000). Netherlands twin-family study of anxious depression (NETSAD). *Twin Research*, *3*, 323–334.
- Campbell, D. D., Rijdsdijk, F. V., & Sham, P. C. (2007). Computation of individual latent variable scores from data with multiple missingness patterns. *Behavior Genetics*, *37*, 408–422.
- Chan, S. W., Goodwin, G. M., & Harmer, C. J. (2007). Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine*, *37*, 1281–1291.
- Clark, L. A., Watson, D., & Mineka, S. (1994). Temperament, personality, and the mood and anxiety disorders. *Journal of Abnormal Psychology*, *103*, 103–116.
- Cloninger, C. R. (1986). A unified biosocial theory of personality and its role in the development of anxiety-states. *Psychiatric Developments*, *4*, 167–226.
- Costa, P. T., & McCrae, R. R. (1992). *Revised NEO Personality Inventory (NEO-PI-R) and the Five Factor Inventory (NEO-FFI): Professional manual*. Odessa, FL: Psychological Assessment Resources.
- Costa, P. T., Jr., & McCrae, R. R. (1995). Domains and facets: Hierarchical personality assessment using the revised NEO personality inventory. *Journal of Personality Assessment*, *64*, 21–50.
- Dockray, S., Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A. (2008). The cortisol awakening response in relation to objective and subjective measures of waking in the morning. *Psychoneuroendocrinology*, *33*, 77–82.
- Eaves, L., Heath, A., Martin, N., Maes, H. H., Neale, M., Kendler, K., et al. (1999). Comparing the biological and cultural inheritance of personality and social attitudes in the Virginia 30,000 study of twins and their relatives. *Twin Research*, *2*, 62–80.

- Eysenck, H. J., & Eysenck, M. W. (1985). *Personality and individual differences. A natural science approach*. New York: Plenum Press.
- Flint, J. (2004). The genetic basis of neuroticism. *Neuroscience and Biobehavioral Reviews*, **28**, 307–316.
- Heath, A. C., Jardine, R., Eaves, L. J., & Martin, N. G. (1989). The genetic structure of personality: II. Genetic item analysis of the EPQ. *Personality and Individual Differences*, **10**, 615–624.
- Hoekstra, H. A., Ormel, J., & De Fruyt, F. (1996). *NEO-PI-R NEO-FFI. Big Five Persoonlijkheidsvragenlijsten [NEO-PI-R NEO-FFI. Big Five Personality Inventory]*. Lisse, The Netherlands: Swets Test Service.
- Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, **23**, 477–501.
- Jabbi, M., Korf, J., Kema, I. P., Hartman, C., Van der Pompe, G., Minderaa, R. B., et al. (2007). Convergent genetic modulation of the endocrine stress response involves polymorphic variations of 5-HTT, COMT and MAOA. *Molecular Psychiatry*, **12**, 483–490.
- Kendler, K. S., Prescott, C. A., Jacobson, K., Myers, J., & Neale, M. C. (2002). The joint analysis of personal interview and family history diagnoses: Evidence for validity of diagnosis and increased heritability estimates. *Psychological Medicine*, **32**, 829–842.
- Kudielka, B. M., Broderick, J. E., & Kirschbaum, C. (2003). Compliance with saliva sampling protocols: Electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. *Psychosomatic Medicine*, **65**, 313–319.
- Kupper, N., De Geus, E. J. C., van den Berg, M., Kirschbaum, C., Boomsma, D. I., & Willemsen, G. (2005). Familial influences on basal salivary cortisol in an adult population. *Psychoneuroendocrinology*, **30**, 857–868.
- Loehlin, J. C. (1992). *Genes and environment in personality development*. London: Sage Publications.
- McCrae, R. R., & Costa, P. T. (1997). Personality trait structure as a human universal. *American Psychologist*, **52**, 509–516.
- Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, **133**, 25–45.
- Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2003). *Mx: Statistical modeling* (6th ed.). Richmond: Virginia Commonwealth University, Department of Psychiatry.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Publishers.
- Neale, M. C., & Miller, M. B. (1997). The use of likelihood-based confidence intervals in genetic models. *Behavior Genetics*, **27**, 113–120.
- Nichols, R., & Bilbro, W. (1966). Diagnosis of twin zygosity. *Acta Genetica et Statistica Medica*, **16**, 265–275.
- Ormel, J., Rosmalen, J., & Farmer, A. (2004). Neuroticism: A non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology*, **39**, 906–912.
- Plomin, R. (1994). *Genetics and experience. The interplay between nature and nurture*. London: Sage Publications.

- Portella, M. J., Harmer, C. J., Flint, J., Cowen, P., & Goodwin, G. M. (2005). Enhanced early morning salivary cortisol in neuroticism. *American Journal of Psychiatry*, **162**, 807–809.
- Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, **28**, 916–931.
- Purcell, S. (2002). Variance components models for gene–environment interaction in twin analysis. *Twin Research*, **5**, 554–571.
- Riese, H., Rijdsdijk, F. V., Ormel, J., van Roon, A. M., Neeleman, J., & Rosmalen, J. G. M. (2006). Genetic influences on baroreflex sensitivity at rest and during mental stress. *Journal of Hypertension*, **24**, 1779–1786.
- Riese, H., Rosmalen, J. G. M., Ormel, J., van Roon, A. M., Oldehinkel, A. J., & Rijdsdijk, F. V. (2007). The genetic relationship between neuroticism and autonomic function in female twins. *Psychological Medicine*, **37**, 257–267.
- Rosmalen, J. G. M., Oldehinkel, A. J., Ormel, J., De Winter, A. F., Buitelaar, J. K., & Verhulst, F. C. (2005). Determinants of salivary cortisol levels in 10–12 year old children: A population-based study of individual differences. *Psychoneuroendocrinology*, **30**, 483–495.
- Rothbart, M. K., & Bates, J. E. (1998). Temperament. In W. Damon & N. Eisenberg (Eds.), *Handbook of child psychology, Vol. 3: Social, Emotional, and Personality Development* (pp. 105–176). New York: Wiley.
- Sanderman, R., Eysenck, S. B. G., & Arrindell, W. A. (1991). Cross-cultural comparisons of personality: The Netherlands and England. *Psychological Reports*, **69**, 1091–1096.
- Wirtz, P. H., Elsenbruch, S., Emini, L., Rudisuli, K., Groessbauer, S., & Ehlert, U. (2007). Perfectionism and the cortisol response to psychosocial stress in men. *Psychosomatic Medicine*, **69**, 249–255.
- Wüst, S., Federenko, I., Hellhammer, D., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*, **25**, 707–720.
- Wüst, S., Wolf, J., Hellhammer, D. H., Federenko, I., Schommer, N., & Kirschbaum, C. (2000). The cortisol awakening response: Normal values and confounds. *Noise and Health*, **2**, 79–88.

