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ORIGINAL RESEARCH

Perceived Stress has Genetic Influences Distinct from Neuroticism and Depression

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Abstract The present study investigated whether the genetic determinants of neuroticism and depressive symptoms differ from those underlying perceived psychological stress. Multivariate structural equation models, which included age and sex as modifiers, were fitted to the total sample of 798 adolescents and young adults (female, $n = 459$; mean age 15.5 years). The sample included 139 monozygotic and 241 dizygotic twin pairs. Stress was measured using item response theory (IRT) scores, as derived from the Perceived Stress Scale and/or the Daily Life and Stressors Scale. Neuroticism was measured using the Neo-Five Factor Inventory or the Junior Eysenck Personality Questionnaire, depending on the age of the participant. Depressive symptoms were assessed using the IRT-scores of the Somatic and Psychological Health Report. The results suggest that the genetic effects underlying perceived psychological stress are largely shared with those that influence neuroticism and liability to depressive symptoms. However, separate genetic effects for perceived psychological stress that are not shared with neuroticism and depressive symptoms were also identified. The source of the identified trait specific effects requires further investigation.

Keywords Heritability · Twin study · Genetics

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Introduction

Numerous factors contribute to the development of depressive disorders. Major risk factors include genetic predisposition, stress, and a high score on the personality dimension "neuroticism" (de Kloet et al. 2005; Kendler et al. 2006a, b). The diathesis–stress-model assumes that depression results from the effects of a combination of genetic and environmental factors. According to this model, individuals inherit a genetic tendency (diathesis) and the impact of environmental stimuli, e.g. stress, upon this diathesis results in the development of depression. However, transactional stress concepts propose that stress does not result purely from a 'passive' perception of exposure to given environmental stimuli in a given situation; rather stress occurs as a function of 'a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being' (Lazarus and Folkman 1984). In a previous study we have shown in a smaller independent sample ($N = 360$), that the perception of stress seems to be a partly inherited trait (Federenko et al. 2006) and therefore could play an important role in the diathesis of depressive symptoms.

Previous authors have argued (e.g. Kendler et al. 2006b) that the depression diathesis is indexed by the stable personality trait neuroticism. This trait is defined by the inclination to worry, and the tendency towards being insecure, self-conscious, and temperamental. Research has shown that neuroticism is moderately heritable (Rettew et al. 2006; Lake et al. 2000), and shares strong genetic variance with symptoms of depression (Duggan et al. 1990; Hansell et al. 2012; Kendler et al. 1993; Kirk et al. 2000). Furthermore, individuals with high neuroticism scores perceive life events and daily problems as being more stressful than individuals with lower scores (Gunthert et al. 1999). Consequently, and in accordance with a transactional perspective, perceived stress is not solely environmental but is influenced by the degree of neuroticism. Thus, the genes that predispose to neuroticism may also be implicated in perceived stress.

Nevertheless, three issues remain unclear: (i) whether the genetic and environmental components that contribute to neuroticism and depressive symptoms are implicated in the perception of stress; (ii) whether there are common genetic or environmental influences on stressful life events and depression independent of neuroticism and (iii) to what extent perceived stress is an independent heritable risk factor. The present study investigated these three questions through the multivariate genetic analysis of twins assessed for neuroticism, depressive symptoms, and perceived stress.

Materials and methods

Subjects

The present sample comprised 798 adolescent or young adult twins who had taken part in either the Brisbane Longitudinal Twin Study (BLTS; Wright and Martin 2004), or the Twin Imaging Study (TIMS; Blokland et al. 2008) between 2009 and 2012. In the BLTS, psychiatric symptoms are assessed at ages 12, 14, 16, and 21 years. The TIMS is a follow-up study of the BLTS cohort, which involves investigation of twins aged >18 years. Zygosity was determined by a combination of standard questions (Martin and Martin 1975), a photograph of the twin pairs, and in most pairs by extensive genotyping. The sample consisted of 139 monozygotic (MZ) and 241 dizygotic (DZ) complete twin pairs and 38 individual twins. Table 1 shows the composition of the sample according to the different sex/zygosity groups. In both the MZ and DZ groups, female twin pairs were predominant. The mean age of the total sample was 15.5 years ($sd = 2.74$). Due to the presence of one twin aged 29 years, the age range was 12–29 years. All other twins were between 12 and 23 years old. To avoid distributional problems, age was z-transformed for further analysis.

Table 1 Age, sex and zygosity composition of the sample

	MZ females	MZ males	DZ females	DZ males	DZ opposite sex
N of pairs (Ind.)	79 (166)	60 (125)	91 (189)	60 (123)	90 (195)
Mean age (years)	15.77	14.83	15.28	15.30	15.75
SD age	2.91	2.56	2.76	2.29	2.89
Age range	12–23	12–21	12–23	12–21	12–29

SD standard deviation, *ind.* number of individuals for each zygosity group

Measures

Perceived stress and neuroticism were assessed using age-appropriate questionnaires. For participants aged 12 and 14 years, perceived stress was measured using the 10-item *Perceived Stress Scale* (PSS; Cohen and Mermelstein 1983), and neuroticism was measured using the *Junior Eysenck Personality Questionnaire* (JEPQ; Eysenck 1972); 24-item scale for neuroticism). For participants aged 16 years or older, perceived stress was measured using the 30-item *Daily Life and Stressors Scale* (DLSS; Kearney et al. 1993), and neuroticism was measured using the *NEO-Five Factor Inventory* revised version (Neo-FFI-R; McCrae and Costa 2004) 12-item scale for neuroticism. In all participants, depressive symptoms were assessed using the 34-item *Somatic and Psychological Health Report* (SPHERE; Hickie et al. 2001).

To compare neuroticism scores between participants, the neuroticism sum-scores of the NEO-FFI and the JEPQ-scores were separately z-transformed and then combined. For the assessment of perceived stress and depressive symptoms, item response theory (IRT) analyses were performed (Wray et al. 2008). One advantage of IRT models is that the difficulty and discriminability of each item is taken into account by modeling a normally distributed liability based on the responses to the individual questionnaire items. It is thus superior to a simple sum score that assumes that all items have the same discriminating ability with respect to the underlying liability being measured. It is particularly useful if raw scores are markedly non-normal (as for depression), or widely different scales are being combined (as here for perceived stress). IRT analysis was carried out using: (i) all 10 items, each with 5 categories for the PSS; and (ii) all 30 items each with 5 categories for the DLSS questionnaire. A total of 129 subjects completed both the PSS and DLSS questionnaire at the same time-point. This overlapping information enabled items from

Table 2 Maximum likelihood estimates of age and sex effects (95 % CI) for neuroticism, depressive symptoms and perceived stress

	N = m/f	Sex β	Age β
Neuroticism	459/339	−0.2 (−0.35, −0.06)	−0.01 (−0.09, 0.07)
Depression	444/334	−0.07 (−0.19, 0.04)	0.00 (−0.07, 0.05)
Stress	452/334	−0.02 (−0.11, 0.06)	−0.10 (−0.06, 0.16)

Negative values for the sex effect implies lower scores in males. MLE adjust for relatedness of twins

CI confidence interval, *N* number of individuals, *m* male, *f* female

both the PSS and the DLSS for all participants to be placed on the same scale of liability values (θ-scores). IRT models were implemented in the WinBugs program (Lunn et al. 2000), which applies a Bayesian Markov Chain Monte Carlo method for parameter estimation. Chains were generated with 7,000 iterations after an initial burn-in of 3,000 iterations. For the assessment of depressive symptoms, IRT analysis was applied to the SPHERE-data according to the procedure used for the stress-data. All 34 items of the SPHERE questionnaire, each of which had three categories (0 = sometimes/never; 1 = often; 2 = most of the time), were used for analysis. IRT θ-scores of depressive symptoms and perceived stress were used for further analysis. All scores showed approximately normal *N(0,1)* distributions. IRT scores were not produced for neuroticism because raw scores were nicely normal and little would have been gained by further transformation.

Model fitting

Structural equation models (SEM) were fitted using the full information maximum likelihood (FIML) method. This allowed use of data from all individual twins, including those without co-twins, and from participants with missing outcome measures. The degrees of freedom and twice the log-likelihood were computed using MX (Neale et al. 2003). Details of the twin design and analytical methods, including assumption testing, are described elsewhere (Neale and Cardon 1992).

Firstly, univariate model fitting was performed separately for each of the three variables (neuroticism, depressive symptoms, and perceived stress) in order to partition the variation into: an additive genetic factor (A); a non-additive genetic factor (D); a common environmental factor (C); and an unshared environmental factor (E). Submodels with only two factors (AE and CE models) were compared with the three-factor models in which they were nested by likelihood ratio Chi square tests. For multivariate analysis a Cholesky decomposition for an ACE model was compared with an AE and a CE Cholesky decomposition. The aim of the analyses was to determine whether genetic influences specific to perceived stress exist after neuroticism and depressive symptoms have been accounted for. Therefore, neuroticism was used as the first, depressive symptoms as the second, and perceived stress as the third latent factor. The fit of each model was assessed by the differences in log likelihood between the sub and the full models. The most parsimonious model was chosen for data interpretation. Outliers were checked using the %P option in MX (Neale et al. 2003) for univariate and multivariate analysis. No outlier was removed. For all models, sex and z-score of age were fitted as fixed effects.

Results

Sex and age effects for neuroticism, depressive symptoms, and perceived stress

Table 2 shows the regression coefficients for age and sex and the corresponding confidence intervals. No significant effects were found for age, although this may reflect the narrow age range of the sample. Although males showed slightly lower scores for all three variables, the difference was only significant for neuroticism.

Twin correlations

As shown in Table 3, the following correlations were observed: (1) higher within-trait correlations between MZ-twins compared with DZ-twins for all variables (bold), which is consistent with an additive genetic effect for these variables; (2) significant intra-individual correlations between the three variables in both MZ and DZ twins, which indicates that these variables are related; (3) higher cross-twin cross-trait correlations for MZ twins than for DZ twins, which indicates a common genetic effect for these three variables.

Model fitting

Univariate model fitting was carried out for all three variables. Table 4 shows the goodness-of-fit and the parameter estimates for the ACE, the CE, and the AE models for neuroticism, depressive symptoms, and perceived stress respectively. For two of the three variable the MZ

Table 3 Pearson-correlations between variables in MZ and DZ twins (MZ in lower, DZ in upper triangle) corrected for age and sex

	Twin 1			Twin 2		
	Neuroticism	Depression	Stress	Neuroticism	Depression	Stress
Twin 1						
Neuroticism	1	0.59	0.60	0.21	0.21	0.15
Depression	0.58	1	0.63	0.06	0.24	0.11
Stress	0.58	0.51	1	0.06	0.17	0.19
Twin 2						
Neuroticism	0.53	0.33	0.38	1	0.54	0.59
Depression	0.31	0.48	0.31	0.57	1	0.55
Stress	0.40	0.47	0.54	0.52	0.47	1

Table 4 Model-fitting results for univariate models of z-transformed neuroticism-scores and θ-scores of depressive symptoms and perceived stress

		Goodness-of-fit-index						Parameter estimates (CI = 95 %)		
Model	Descrip	-2LL	df	AIC	ΔX^2	Δdf	*p*	A	C	E
Stress										
1	ACE	1442.02	792	141.98	–	–	–	0.52 (0.34, 0.62)	0 (0, 0.12)	0.48 (0.38, 60)
2	CE	1457.76	793	128.26	15.74	1	<0.00	–	0.30 (0.21, 0.39)	0.7 (0.61, 0.79)
3	**AE**	**1442.02**	**793**	**143.98**	**0**	**1**	**1**	**0.52 (0.39, 0.62)**	**–**	**0.48 (0.38, 0.61)**
Neuroticism										
1	ACE	2123.16	772	579.16	–	–	–	0.48 (0.17, 0.58)	0.0 (0.00, 0.24)	0.52 (0.42, 0.64)
2	CE	2131.74	773	585.74	8.58	1	<0.00	–	0.34 (0.25, 0.43)	0.66 (0.57, 0.75)
3	**AE**	**2123.16**	**773**	**577.16**	**0**	**1**	**1**	**0.48 (0.37, 0.58)**	**–**	**0.52 (0.42, 0.63)**
Depression										
1	ACE	1811.12	780	251.11	–	–	–	0.37 (0.02, 0.55)	0.07 (0.00, 0.34)	0.56 (0.45, 0.69)
2	CE	1815.40	781	253.40	4.28	1	0.04	–	0.34 (0.24, 0.43)	0.66 (0.58, 0.76)
3	**AE**	**1811.42**	**781**	**249.42**	**0.30**	**1**	**0.58**	**0.46 (0.34, 0.55)**	**–**	**0.54 (0.44, 0.66)**

A additive genetic factors, *AIC* Akaike's information criterion, *C* common environmental factors, *CI* confidence interval, *df* degrees of freedom, *E* unique environmental factors, −2LL twice negative log-likelihood, ΔX^2 difference in X^2 to saturated model, Δ*df* difference in degrees of freedom to saturated model. Bold values indicates best fitting model

correlation is more than twice the DZ correlation indicating, at least directionally, the presence of non-additive genetic (D) effects. However, in all cases the estimate of D was non-significant—not surprisingly given the huge sample sizes required to detect significant D (data not shown). Since a major interest is whether our twin correlations could possibly be accounted for by shared family environment, we therefore focus on the results of fitting the ACE model which enables us to estimate the upper 95 % confidence interval for the influence of C on these variables. This ranges from 12 % of variance for stress and 24 % for neuroticism to 34 % for depression. Not surprisingly, no significant worsening of the fit of the ACE models was observed when C was fixed to zero. In contrast, A could not be dropped from the model without significant worsening of fit. Therefore the AE model was the best fitting and most parsimonious model accounting for around half of the variance for all three variables.

Multivariate analysis was performed using Cholesky decomposition of the three variables in the order neuroticism, depressive symptoms, and perceived stress. The first latent factor loaded on all three variables (neuroticism, depressive symptoms, and perceived stress), the second latent factor loaded on depressive symptoms and stress, and the third latent factor loaded on perceived stress only, for A, C, and E respectively. The C matrix could be dropped from the model without worsening fit ($\Delta X^2_6 = 3.18$, $p = 0.79$), while all A (drop $\Delta X^2_6 = 25.9$, $p = 0.0002$) and E covariance components ($\Delta X^2_3 = 91.5$, $p = 10^{-19}$) were essential to maintain fit. Thus, the best fitting model was an AE model, with six pathways for each of A and E as shown in Fig. 1.

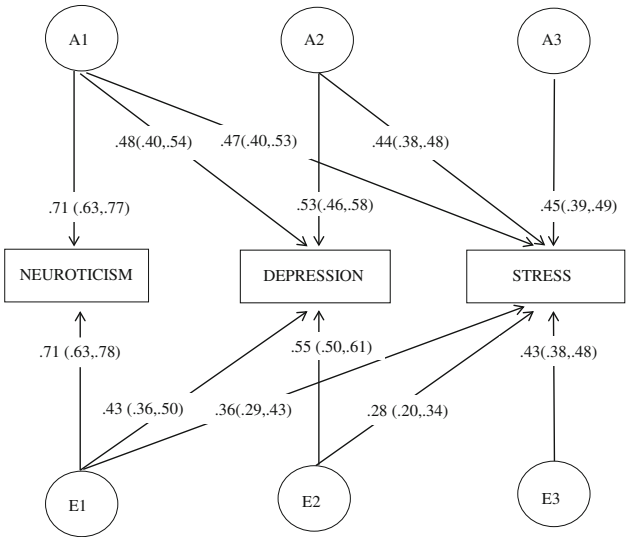

Fig. 1 Cholesky decomposition for latent variables. Latent factor loadings are standardized to unit variance (95 % CI). *A1–A3* additive genetic factors, *E1–E3* unique environmental factors

Table 5 Additive genetic and unshared environmental correlations between z-score neuroticism, θ-score depressive symptoms, and θ-score perceived stress corrected for age and sex (CI = 95 %)

	Environmental		
	Neuroticism	Depression	Stress
Genetic			
Neuroticism	–	0.50 (0.39,0.6)	0.44 (0.31,0.55)
Depression	0.64 (0.50,0.75)	–	0.32 (0.18,0.44)
Stress	0.72 (0.59,0.82)	0.78 (0.66,0.89)	–

CI confidence interval

The first genetic factor (A_1), which loaded primarily on neuroticism and accounted for 50 % of its variance, also accounted for 23 % of the variance in depressive symptoms and 22 % of the variance in perceived stress. The second genetic factor (A_2), which loaded primarily on depressive symptoms (28 %), also accounted for 19 % of the variance in perceived stress. This left a specific genetic contribution (A_3) to perceived stress that accounted for 20 % of its variance. Since the primary question of interest was whether perceived stress was influenced by specific genetic factors independent of neuroticism and depressive symptoms, the significance of A_3 was tested by dropping it from the model. This caused a highly significant worsening of fit ($\Delta X_1^2 = 15.35$, $p < 0.001$). Interestingly, the genetic path from the depression factor (A_2) to stress was also highly significant (drop $\Delta X_1^2 = 21.33$, $p = 10^{-6}$), whereas the equivalent path for environment was not (drop $\Delta X_1^2 = 3.03$, $p = 0.08$).

Decomposition of the nonshared environmental covariance showed that the first factor (E_1) accounted for 50 % of the variance for neuroticism and also accounted for 18 % of the variance in depressive symptoms and 13 % of the variance in perceived stress. The second factor (E_2), which loaded on depressive symptoms (30 %), also accounted for 8 % of the variance in perceived stress. The specific nonshared environmental contribution to perceived stress (E_3) accounted for 18 % of its variance. The genetic and environmental standardized path coefficients between the three variables, derived from the trivariate Cholesky analyses, are shown in Table 5.

Discussion

The present study investigated the extent to which genetic and environmental determinants of neuroticism and depressive symptoms are shared with those underlying perceived stress, and whether an independent genetic effect exists for the perception of stress. To our knowledge, this is the first study to dissect the genetic and environmental associations between these three variables.

The results of the univariate analyses showed that for perceived stress, neuroticism, and depressive symptoms, around 50 % of the variance was explained by additive genetic effects. This is broadly consistent with previous findings (Federenko et al. 2006; Rettew et al. 2006; Lunn et al. 2000; Sullivan et al. 2000). In addition, substantial genetic overlap was observed between neuroticism and depressive symptoms, consistent with previous findings (e.g. Jardine et al. 1984; Fanous et al. 2002) and, unsurprisingly, with perceived stress.

A novel and interesting finding of the present study was that even when the genetic influences that perceived stress shared in common with neuroticism and depressive symptoms were taken into account, a substantial and highly significant genetic influence specific to perceived stress was observed, accounting for 20 % of its total variance. Furthermore, our results show that there are common genetic (but not environmental) influences on perceived stress and depression after their common genetic influences with neuroticism have been accounted for. To our knowledge, no previous study has investigated or reported these effects.

Stress is a complex phenotype, and can be conceptualized in terms of the influence of objectively measurable stress factors such as traumatic life events, work overload, social rejection, and low social-economic status. Nonetheless, the individual's appraisal and perception of the relevance of such events or processes is influenced by a variety of factors. Thus the same life event (e.g. the death of a relative) can result in varying degrees of stress between individuals, depending on, for example, the individual's appraisal of the situation and their coping

strategies (Dumont and Provost 1999). Previous authors have therefore argued that the individual's appraisal of the event itself, rather than objectively measurable stressful events, should be considered when assessing stress as a risk factor for depression and other psychiatric disorders (Shrout et al. 1989). Perceived stress, on the other hand, may not be an independent risk factor but may instead be substantially influenced by other risk factors for depression such as personality. Research has indeed demonstrated a high correlation between perceived stress and neuroticism, the latter being an established risk factor for depression. It has therefore been suggested that both may in fact measure the same phenomenon (McCrae 1990).

The present data show that despite the strong overlap in genetic influences between all three variables there are also common genetic effects for depressive symptoms and perceived stress that are not shared with neuroticism. Furthermore, there are substantial specific genetic influences on perceived stress that are not shared with depressive symptoms or neuroticism.

Our results suggest that perceived stress is not a mere proxy for the personality trait neuroticism and that is has genetic overlap with depression independent of neuroticism.

A further interesting finding was the mainly independent influence of nonshared environmental factors on depressive symptoms and perceived stress. This may be of relevance for future studies of environmental factors. Nonetheless, the possibility that our findings may have been influenced by idiosyncratic reactions to puberty (which many of our subjects were experiencing), or short term influences on the day of testing, cannot be excluded.

Limitations of the present study include our relatively modest sample size, and the potential heterogeneity of the instruments used to measure perceived stress and neuroticism. To overcome this problem for the stress scales, use of overlapping information from the 129 participants who completed both the PSS and DLSS questionnaire at the same time-point enabled items from both instruments, as well as liability values (θ-scores) for all participants, to be placed on the same scale. A further limitation was the lack of data concerning factors such as stressful life events and social support, which would have allowed interesting further analyses. We plan to strengthen our data through the addition of objective measures of stress, as indexed by hair cortisol concentrations (Staufenbiel et al. 2013).

Disentangling the differential genetic and nonshared environmental influences on neuroticism, perceived stress, and depressive symptoms will facilitate the identification of biological and environmental risk markers in future studies. Large scale genome wide association studies (GWAS) are now underway to map genes influencing neuroticism and depressive symptoms, and it will be intriguing to see what influence these have on measures of perceived stress.

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