Psychological Medicine (2012), **42**, 1249–1260. © Cambridge University Press 2011
doi:10.1017/S0033291711002431

ORIGINAL ARTICLE

Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins

N. K. Hansell[1]*, M. J. Wright[1], S. E. Medland[1], T. A. Davenport[2], N. R. Wray[1], N. G. Martin[1] and I. B. Hickie[2]

[1] *Genetic Epidemiology, Queensland Institute of Medical Research, Brisbane, Australia*
[2] *Brain and Mind Research Institute, University of Sydney, Sydney, Australia*

Background. Genetic studies in adults indicate that genes influencing the personality trait of neuroticism account for substantial genetic variance in anxiety and depression and in somatic health. Here, we examine for the first time the factors underlying the relationship between neuroticism and anxiety/depressive and somatic symptoms during adolescence.

Method. The Somatic and Psychological Health Report (SPHERE) assessed symptoms of anxiety/depression (PSYCH-14) and somatic distress (SOMA-10) in 2459 adolescent and young adult twins [1168 complete pairs (35.4% monozygotic, 53% female)] aged 12–25 years (mean = 15.5 ± 2.9). Differences between boys and girls across adolescence were explored for neuroticism, SPHERE-34, and the subscales PSYCH-14 and SOMA-10. Trivariate analyses partitioned sources of covariance in neuroticism, PSYCH-14 and SOMA-10.

Results. Girls scored higher than boys on both neuroticism and SPHERE, with SPHERE scores for girls increasing slightly over time, whereas scores for boys decreased or were unchanged. Neuroticism and SPHERE scores were strongly influenced by genetic factors [heritability (h^2) = 40–52%]. A common genetic source influenced neuroticism, PSYCH-14 and SOMA-10 (impacting PSYCH-14 more than SOMA-10). A further genetic source, independent of neuroticism, accounted for covariation specific to PSYCH-14 and SOMA-10. Environmental influences were largely specific to each measure.

Conclusions. In adolescence, genetic risk factors indexed by neuroticism contribute substantially to anxiety/depression and, to a lesser extent, perceived somatic health. Additional genetic covariation between anxiety/depressive and somatic symptoms, independent of neuroticism, had greatest influence on somatic distress, where it was equal in influence to the factor shared with neuroticism.

Received 26 July 2011; Revised 21 September 2011; Accepted 26 September 2011; First published online 4 November 2011

Key words: Adolescents, anxiety, depression, heritability, somatic distress, SPHERE, twins.

Introduction

There is consistent evidence that genes influence individual variation in the personality trait of neuroticism, as well as internalizing disorders such as anxiety and depression, and somatization syndromes (most commonly presenting as prolonged fatigue or chronic pain). In adolescents, these measures are moderately heritable [i.e. ~30–60% (Gillespie *et al*. 2004; Rettew *et al*. 2006; Lamb *et al*. 2010; Bartels *et al*. 2011)], consistent with that for adults (e.g. Kendler *et al*. 2007; Vassend *et al*. 2011). Genetic covariation has been shown between neuroticism and anxiety and/or depression (Boomsma *et al*. 2000; Hettema *et al*. 2004, 2006; Kendler *et al*. 2007), neuroticism and somatic health (Vassend *et al*. 2011), anxiety and depression (Gillespie *et al*. 2000; Kendler *et al*. 2007) and anxiety, depression and somatic syndromes (Hickie *et al*. 1999*b*; Gillespie *et al*. 2000; Kato *et al*. 2009). However, it remains unclear if the genetic overlap between anxiety and depression symptoms and common somatic complaints such as prolonged fatigue and pain is due largely to their relationship with neuroticism.

Extensive co-morbidity between depression and somatoform symptoms is frequently reported (e.g.

* Address for correspondence: Dr N. K. Hansell, Genetic Epidemiology, Queensland Institute of Medical Research, Post Office, Royal Brisbane Hospital, Queensland, Australia 4029.
(Email: Narelle.Hansell@qimr.edu.au)

Goldberg, 1996; Vaccarino *et al*. 2009). Previous work, particularly in health care settings, has indicated the extent to which the two syndromes can be distinguished cross-sectionally and, more importantly, longitudinally (Hickie *et al*. 1997, 1999*c*; Gillespie *et al*. 1999; van der Linden *et al*. 1999). Both syndromes appear to have relatively early ages of onset, with some subjects largely only ever developing one or other form of illness. Our previous genetic analyses (Hickie *et al*. 1999*b*; Gillespie *et al*. 2000) also showed that, while significant genetic risk is shared between measures of psychological and somatic distress, there were also independent genetic and environmental risk factors influencing somatic health. This has also been shown in a large Swedish study exploring somatic syndromes in women (Kato *et al*. 2009). A variety of different psychosocial and neurobiological paths have been proposed to explain both the common and distinctive aspects of the two syndromes (Rief *et al*. 2010).

Boomsma *et al*. (2000) found that genetic covariance between measures of anxiety, depression, somatic anxiety and neuroticism could be attributed to a common genetic source in adolescents. However, studies in young adults suggest that genetic covariation between anxiety and depression measures and somatic health may exceed that due to the relationship with neuroticism. Gillespie *et al*. (2000) showed that 67% of the genetic variance in somatic distress was due to sources that also influence measures of depression and phobic anxiety, whereas Vassend *et al*. (2011) showed recently that only 35–48% of the genetic variance in somatic health appears due to a source influencing neuroticism.

Adolescence is the peak age of onset for all of the major adult psychiatric phenotypes, with the emergence of depressive disorders post-puberty being of greatest significance (Merikangas *et al*. 2010). Of prime importance in clinical psychiatry is the identification of the earliest phenotypes that emerge during this key developmental period and the extent to which they predict transition to the major anxiety, mood and psychotic disorders in adult life. Such work lies at the heart of current international efforts to promote earlier intervention (Hetrick *et al*. 2008; Hamilton *et al*. 2011; McGorry *et al*. 2011) or 'pre-emptive' psychiatry (McGorry, 2011). Characterization of key genetic or environmental risks (and the extent to which they are shared or unique) during the same period has the capacity to inform both the type and timing of more relevant preventive and early intervention strategies. Other modelling of risks to depression based on twin studies in the teenage and early adult years indicate the extent to which there are likely to be both multiple relevant time points and changing patterns of both genetic and environmental risk (Kendler *et al*. 2008).

In the current study, we explore these relationships in a primarily adolescent population sample comprising twins from the Brisbane Longitudinal Twin Study (Wright & Martin, 2004). Measures of anxiety/depression and somatic distress, as well as a measure of overall mental health and well-being were assessed by self-report using the Somatic and Psychological Health Report (SPHERE) questionnaire (Hickie *et al*. 2001*a*). The instrument was developed specifically to explore these types of relationships in those with common forms of psychological distress, but particularly those with affective syndromes. The subscales measure somatic and psychological symptoms independently (van der Linden *et al*. 1999; Wijeratne *et al*. 2006) and characterize symptomatology (mood and behavioural features) as continuous dimensional traits, so are advantageous for genetic modelling in a population sample (i.e. twin studies have greater power to resolve sources of familial resemblance when using continuous compared with binary or ordinal data; Neale *et al*. 1994).

Given the variations in prevalence and age of onset of depressive disorders between boys and girls in the post-pubertal period, we tested for potential differences in SPHERE scores by gender and explored differences across adolescence to young adulthood (12–25 years). Using a trivariate twin design, we then investigated the relationship of neuroticism, which captures trait-based anxiety present from early childhood and is likely to be indicative of genetic risk factors (Kotov *et al*. 2010), to the co-morbidity found between anxiety/depression and somatic distress.

Method

Sample

The sample comprised 2459 adolescents and young adult twins [1168 complete pairs, 35.4% monozygotic (MZ), 53% female], mean age 15.5±2.9, range 12.0–25.6 years. Participants are typical of the South East Queensland adolescent and young adult population on a range of traits and had taken part in one or more studies (Fig. 1). Written, informed consent was obtained from all participants and a parent or guardian for those aged <18 years. The study was approved by the Human Research Ethics Committee at the Queensland Institute of Medical Research.

Measures

SPHERE

Three measures were obtained from the 34-item SPHERE questionnaire (Hickie *et al*. 2001*a*, *b*). Participants indicated if they had been troubled by

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

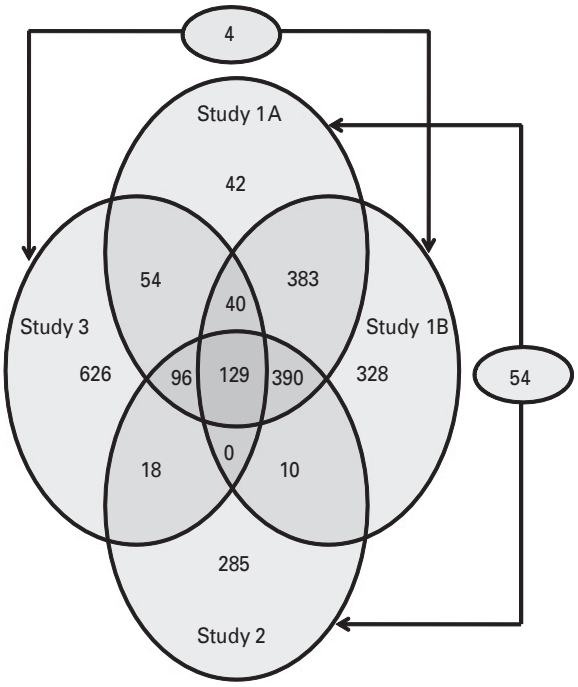

Fig. 1. Venn diagram showing study participation numbers for Somatic and Psychological Health Report (SPHERE) collection across three studies (Wright & Martin, 2004), with added components for participants in studies 1A and 2 only (54 participants) and studies 1B and 3 only (four participants). Data were collected once only for 1281 participants [52% of total sample ($n=2459$)], twice for 523 (21%), three times for 526 (21%), four times for 129 (5%). A measure of neuroticism was available for 84% of the sample. For approximately one-third of the sample a single assessment of neuroticism from the NEO was available, a further third were assessed on the Junior Eysenck Personality Questionnaire (JEPQ) (one to two occasions) and the remaining third were assessed on both the NEO (single occasion) and JEPQ (one to three occasions; JEPQ and NEO were collected at the same time point for 393 individuals, $r=0.71$). The summed scores for each neuroticism measure were standardized (Z-scores: mean $=0\pm1$) and averaged to produce a composite measure. For participants with multiple SPHERE measures, a mean measure (and mean age) was used in analyses. Studies 1 and 2 are ongoing in-person studies of melanocytic naevi (moles) at age 12 and 14 years (studies 1A and 1B) and cognition at 16 (Study 2). Study 3 was a mail and phone study of health and well-being targeting adolescent and young adult twins. Exclusion criteria for the cognition study at 16 were parental report of head injury, neurological or psychiatric illness, substance abuse/dependence or current use of psychoactive medication in either twin. Availability was the only criterion for the other studies. We determined zygosity from DNA using a commercial kit (AmpFlSTR Profiler Plus Amplification Kit; ABI, USA) and this was later confirmed for >80% of the sample genotyped on a genome-wide single nucleotide polymorphism (SNP) genotyping platform [610K Illumina; Illumina Inc., USA (Medland *et al*. 2009)].

symptoms over the past few weeks, making one of three response choices: sometimes/never (coded as zero); often; most of the time (each coded as 1). Items were summed to obtain scores for SPHERE-34 (all 34 items), PSYCH-14 (14 items tapping anxiety/depression), SOMA-10 (10 items, non-overlapping with PSYCH-14, tapping somatic distress). Internal consistency was good (Cronbach's $\alpha=0.89$ for SPHERE-34, 0.84 for PSYCH-14, 0.70 for SOMA-10). Items missing for 50 individuals (mean $=1.3\pm0.8$ items, ranging 1–6 items, <0.001% of the dataset) were imputed in PRELIS 2.30 (Scientific Software International, UK) based on sex, age and remaining items (i.e. 28–33 items).

SPHERE measures were collected on at least two occasions for just under half the sample (i.e. 48%; see Fig. 1). To increase test measurement reliability for this first analysis, we averaged the data collected on multiple occasions to give a single measure, together with an 'average age' at assessment. This decision was further supported by the subtleness and generally linear nature of change with age and the relative stability of the data over time (in a subsample of 91 individuals tested twice within 2–6 months, $r=0.43$ for SPHERE-34, 0.48 for PSYCH-14, 0.64 for SOMA-10).

Neuroticism was obtained from either 20 items (scored as yes $=1$, no $=0$) from the Junior Eysenck Personality Questionnaire (JEPQ; Eysenck, 1972; Eysenck & Eysenck, 1975) and/or 12 items (using a 5-point Likert scale and scored 0–4) from the NEO Five-Factor Inventory (NEO-FFI) of the NEO-PI-R (Costa & McCrae, 1992), with more recent assessments using revised versions (NEO-FFI-R, NEO-FFI-3: McCrae & Costa, 2004, 2010). Participants with missing items were excluded and neuroticism was included only when SPHERE had been collected on the same occasion (i.e. 2065 individuals, 84% of the SPHERE sample).

Statistical analyses

Distributions for each of the SPHERE measures were normalized by converting to a proportional scale before transformation into arcsin values (Freeman & Tukey, 1950) (e.g. Birley *et al*. 2006; Wray *et al*. 2007), with outliers (four to eight individuals) winsorized to S.D. ±3.3. Neuroticism was normally distributed with no outliers. In addition, a single family was found to be outlying for the three SPHERE measures, using the %P option in Mx (Neale *et al*. 2003), which provides a likelihood statistic for each family conditional on the genetic model, and this family was excluded from further analyses.

Modelling, which uses all data points regardless of missingness, was performed in Mx using a full

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

information maximum likelihood estimator. The fit of constrained models was compared with the full model by examining the difference in the −2 log likelihood, which is distributed as a χ^2 for given degrees of freedom. We first assessed homogeneity of sampling by examining the means and variances for birth order and zygosity effects as described in McGregor *et al*. (1999), as well as the effects of sex, age and sex × age. Those with significant effects were retained as covariates. We also tested whether the twin correlations for both MZ and dizygotic (DZ) boys and girls could be set equal. If not, this is suggestive of magnitude differences in genetic and/or environmental estimates for boys and girls. Similarly, if correlations for opposite-sex DZ pairs are significantly lower than those of same-sex DZ pairs, this indicates different sources of influence between boys and girls.

At the univariate level and using the five zygosity groups (i.e. MZ females, MZ males, DZ females, DZ males and opposite-sex pairs), we decomposed the variance of each variable into additive genetic (A), common environmental (C) and unique environmental (E) sources of variance. We tested for sex limitation effects relating to the source of genetic influence by setting the correlation between additive genetic sources of influence on opposite-sex pairs to 0.5 and comparing the fit of this model with that of the fully saturated model in which the correlation was free to vary. Magnitude effects were examined by setting A, C, and E influences to be equal for boys and girls and comparing model fit with the fully saturated model, which allowed these estimates to vary.

Finally, we examined the covariation between neuroticism, PSYCH-14 and SOMA-10 in a multivariate sex-limitation model and in a model collapsed over sex. Cholesky decomposition and independent and common pathway modelling approaches (Neale & Cardon, 1992) were examined, which provide A, C, and E variance/covariance matrices from which genetic, common environmental and unshared environmental correlations can be calculated. As Cholesky decomposition is the standard general approach to decomposing variance into genetic and environmental sources, we used this model to test the significance of A and C influences. Akaike's Information Criterion (AIC) was examined to compare model fit between Cholesky, independent and common pathway models.

Results

Means, standard deviations and ranges, as well as sex and age effects for all measures, are shown in Table 1. We found no evidence of birth order [$\Delta\chi^2$ ranged 0.5–7.1, df = 4 (i.e. $\Delta\chi^2_4$)] or zygosity effects ($\Delta\chi^2_8$ ranged 2.8–4.9), but significant sex and sex × age effects were found. Differences were subtle. Girls scored higher for SPHERE-34 (8.6 *v*. 8.2), PSYCH-14 (3.8 *v*. 3.4) and neuroticism (NEO: 23.2 *v*. 21.0; JEPQ: 10.1 *v*. 9.3). *Post-hoc* analyses showed that, for SPHERE-34 and SOMA-10, scores increased with age for girls ($\Delta\chi^2_1$ = 17.1 and 24.7 respectively), but decreased for boys ($\Delta\chi^2_1$ = 5.1 and 4.5 respectively). For PSYCH-14, scores increased with age for girls ($\Delta\chi^2_1$ = 19.0), but did not change significantly for boys ($\Delta\chi^2_1$ = 2.9). These subtle effects of sex and age are shown in a cross-sectional format in Fig. 2, with the sample divided into four age categories (based on the mean age, and mean score, for individuals with multiple measures).

Neuroticism was strongly correlated with PSYCH-14 (Table 2) and to a lesser, but still substantial extent, with SOMA-10 (r = 0.58 with SPHERE-34). While there was no overlap in items for the SPHERE subscales, they nevertheless showed a strong phenotypic correlation.

Genetic modelling

The MZ and DZ twin correlations (Table 1) indicate additive genetic (A), common environmental (C) and unique environmental (E) influences on both SPHERE-34 and PSYCH-14 (i.e. the DZr > 0.5 × MZr) (Martin *et al*. 1988), whereas for SOMA-10 and neuroticism, A and E influences are indicated (i.e. the DZr ≈ 0.5 × MZr). There was some suggestion of magnitude differences in the heritability for boys and girls for PSYCH-14 (i.e. reduced A and increased C suggested for girls compared to boys, as indicated by DZ correlations being similar to MZs for girls, but less than MZs for boys) and preliminary univariate sex limitation modelling showed that PSYCH-14 was significantly less heritable for girls compared to boys (p = 0.03). In addition, there was also some indication that different genetic or environmental factors may influence individual differences in boys and girls for both SPHERE-34 and PSYCH-14 (i.e. opposite-sex correlations significantly lower than same-sex DZ correlations), but this finding was not supported by sex limitation modelling, which showed that genetic sources of influence did not differ significantly for boys and girls.

Covariation between neuroticism, PSYCH-14, and SOMA-10, was initially examined in a sex-limited ACE Cholesky model. While the genetic correlations suggested neuroticism was more strongly related to anxiety/depression than somatic distress in girls [0.89 (95% confidence intervals (CI) 0.32–1.0) *v*. 0.51 (−0.01 to 1.0)] than boys [0.76 (0.17–1.0) *v*. 0.67 (0.002–1.0)], the CIs were wide and both genetic and environmental pathways could be set equal for boys and girls

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

Table 1. *Sample demographics: mean, S.D., range, sex and age effects and twin correlations (with 95% CI) for SPHERE-34, PSYCH-14, SOMA-10 and neuroticism*

	SPHERE-34	PSYCH-14	SOMA-10	Neuroticism
Mean ± S.D. (range)[a]				
Males	8.2 ± 5.6 (0–34)	3.4 ± 3.1 (0–14)	2.8 ± 2.0 (0–10)	−0.15 ± 0.9 (−2.6 to 2.3)
Females	8.6 ± 6.0 (0–33)	3.8 ± 3.3 (0–14)	2.9 ± 2.0 (0–10)	0.03 ± 0.9 (−2.6 to 2.8)
Sex and age effects[b] [$\Delta\chi^2$ (β)]				
Sex	3.9* (−0.04)	9.0** (−0.06)	3.1 (−0.04)	22.2*** (−0.11)
Age	1.1 (0.02)	2.9 (0.04)	2.8 (0.04)	0.9 (0.02)
Sex × age	25.6*** (−0.11)	21.0*** (−0.10)	31.6*** (−0.12)	2.9 (−0.04)
Twin correlations[c] (95% CI)				
MZ (414 pairs)[d]	0.48 (0.40–0.54)	0.38 (0.30–0.46)	0.43 (0.35–0.50)	0.52 (0.44–0.59)
DZ (752–753 pairs)	0.30 (0.23–0.36)	0.24 (0.17–0.31)	0.23 (0.16–0.29)	0.23 (0.16–0.29)
MZF (226 pairs)	0.46 (0.37–0.55)	0.36 (0.25–0.46)	0.39 (0.28–0.48)	0.48 (0.37–0.57)
MZM (188 pairs)	0.49 (0.38–0.58)	0.41 (0.29–0.51)	0.48 (0.36–0.57)	0.57 (0.46–0.65)
DZF (214 pairs)	0.34 (0.21–0.44)	0.35 (0.23–0.46)	0.25 (0.12–0.36)	0.21 (0.07–0.33)
DZM (193 pairs)	0.38 (0.25–0.48)	0.26 (0.12–0.38)	0.33 (0.19–0.44)	0.28 (0.12–0.41)
DZOS (345–346 pairs)	0.23 (0.12–0.32)	0.17 (0.06–0.27)	0.16 (0.05–0.26)	0.27 (0.15–0.37)

CI, Confidence intervals; SPHERE, Somatic and Psychological Health Report; MZ, monozygotic; DZ, dizygotic; F, female; M, male; OS, opposite sex.

[a] Means for neuroticism are based on the combined NEO/Junior Eysenck Personality Questionnaire (JEPQ) measure. NEO raw scores = 22.4 ± 7.2 (2, 45), JEPQ raw scores = 9.4 ± 4.5 (0, 20).

[b] β weights for sex and age effects are based on standardized covariates and dependent variables. Effects for neuroticism are for a combined NEO/JEPQ measure, which is described in the method.

[c] For all variables, MZM = MZF and DZM = DZF ($\Delta\chi^2_2$ ranged 0.4–2.3), suggesting no magnitude differences in genetic influence based on sex. However, sex limitation modelling suggests that, for PSYCH-14, genetic estimates are larger in boys than girls ($\Delta\chi^2_1 = 4.8$, $p = 0.03$). Also, different genetic and/or environmental sources influencing boys and girls are indicated for SPHERE-34 (i.e. DZO < DZ same-sex, $\Delta\chi^2_1 = 4.0$, $p = 0.04$) and PSYCH-14 ($\Delta\chi^2_1 = 4.0$, $p = 0.05$) and are suggestive for SOMA-10 ($\Delta\chi^2_1 = 3.0$, $p = 0.08$), but not neuroticism ($\Delta\chi^2_1 = 0.2$, $p = 0.67$). Sex limitation modelling further assessed genetic sources, but did not find significant differences between boys and girls ($\Delta\chi^2_1$ ranges 0.0–2.0, p ranges 0.16–0.99).

[d] Neuroticism was available for 84% of the SPHERE sample, for which pair numbers are listed here.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.00001$.

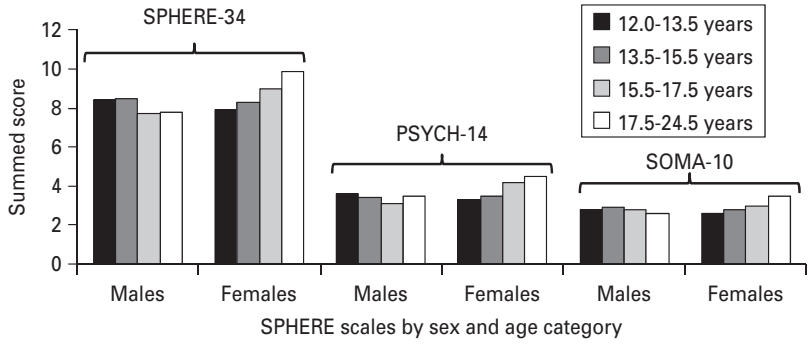

Fig. 2. Summed scores for Somatic and Psychological Health Report (SPHERE-34), PSYCH-14 and SOMA-10, meaned separately for sex and for four age categories.

($\Delta\chi^2_1$ ranged 0.0–3.0). Thus, we collapsed over sex to examine the significance of A and C contributions in a Cholesky model (Table 2). Small C components, which accounted for 3% of total variance for neuroticism, 11% for PSYCH-14 and 7% for SOMA-10 could be dropped from the model without worsening fit ($\Delta\chi^2_6 = 2.3$, $p = 0.89$), while A components were essential to maintain fit ($\Delta\chi^2_6 = 41.5$, $p = 2.3 \times 10^{-7}$). In examining models containing only A and E components, both the Cholesky and independent pathway models containing either one or two common A and E factors provided a good fit to the data

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

Table 2. *Model fitting results (best-fitting model shown in **bold**), plus the additive genetic (A) and unshared environmental (E) estimates (shown as percentages of total variance with 95% CI) and phenotypic, genetic and unshared environmental correlations derived from trivariate AE Cholesky analyses of neuroticism, PSYCH-14 and SOMA-10*

Model[a]	−2 log likelihood	df	AIC
1. Cholesky ACE	17140.043	6949	3242.043
2. Cholesky AE	**17142.314**	**6955**	**3232.314**
3. Cholesky CE	17183.808	6955	3273.808
4. Independent Pathway, 2 Factor A, 2 Factor E, plus specifics	17142.314	6953	3236.314
5. Independent Pathway, 1 Factor A, 1 Factor E, plus specifics	17143.279	6955	3233.279
6. Common Pathway, 1 Common Factor, plus specifics	17167.600	6954	3259.600

	% Additive genetic factors (95% CI)			Total	% Unshared environmental factors (95% CI)			
	A1	A2	A3	A (h^2)[b]	E1	E2	E3	Total E
Neuroticism	**52[c] (46–59)** *Ac_1 = 29* *As_1 = 23*	–	–	52	**48[c] (41–54)** *Ec_1 = 15* *Es_1 = 33*	–	–	48
PSYCH-14	**22 (17–29)**	**18[c] (13–23)** *Ac_2 = 11* *As_2 = 7*	–	40	**19 (14–24)**	**41[c] (37–46)** *Ec_2 = 5;* *Es_2 = 36*	–	60
SOMA-10	**16 (10–22)**	**17 (10–24)**	**10 (04–16)**	43	**04 (02–06)**	**06 (04–09)**	**47 (42–53)**	57

	Correlations								
	Phenotypic *r* (r_p)			Genetic *r* (r_g)			Unshared environmental *r* (r_e)		
	1	2	3	1	2	3	1	2	3
1. Neuroticism	1			1			1		
2. PSYCH-14	0.64	1		0.75	1		0.56	1	
3. SOMA-10	0.42	0.60	1	0.61	0.87	1	0.25	0.41	1

CI, Confidence intervals; AIC, Akaike's Information Criterion.

[a] In a Cholesky decomposition, each of the trivariate variance/covariance matrices is decomposed into the product of a lower triangular matrix and its transpose. This decomposition generates a first factor that influences all variables, a second factor independent of the first that influences the second and third variables and a third factor independent of the first and second that influences only the third variable. Independent pathway models allow for one or more genetic or environmental common factors to be specified, with any remaining variance showing as specific influences. Common pathway models specify genetic and environmental influence on a latent variable that loads onto each phenotype, with remaining variance showing as specific influences.

[b] Total A [heritability (h^2)] for Somatic and Psychological Health Report-34, determined from univariate analyses, = 49%.

[c] Additive genetic factor A1 for neuroticism (52%) includes specific genetic variance (As_1 = 23%). Remaining variance for neuroticism (Ac_1 = 29%) represents genetic influences common to all measures. Similarly, the unshared environmental factor E1 for neuroticism (48%) includes specific environmental variance (Es_1 = 33%) and variance due to environmental factors that are common to all measures (Ec_1 = 15%). In the same way, additive genetic factor A2 (18%) includes specific genetic variance (As_2 = 7%) and genetic variance in common with SOMA-10 (Ac_2 = 11%). A similar breakdown can be shown for the unshared environmental factor E2 (41%; Es_2 = 36, Ec_2 = 5). Variance specific to neuroticism and PSYCH-14 was identified by changing the order of the variables and running the model with either neuroticism or PSYCH-14 specified last. This does not change model fit. A3 and E3 in the model above represent variance specific to SOMA-10.

(Table 2) with the AE Cholesky having the lowest AIC and thus designated as the best-fitting model. We then estimated variance specific to neuroticism and PSYCH-14 by changing the order of the variables and re-running the model with each of these variables specified last. Note that this does not change model fit.

Table 2 shows estimates for the best fitting model with 95% CI (Fig. 3 shows the pathway model). A

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

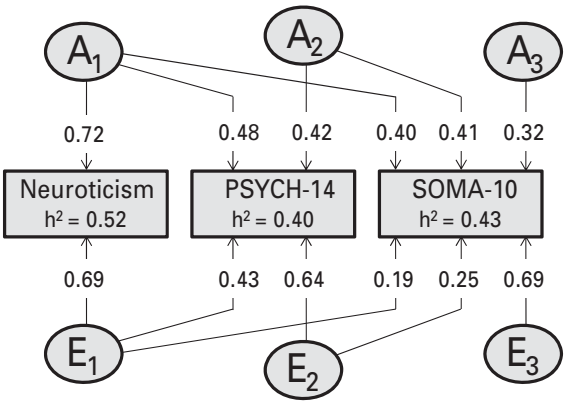

Fig. 3. Parameter estimates for the trivariate AE Cholesky model showing covariation between neuroticism, PSYCH-14 and SOMA-10. The model includes additive genetic (A1, A2, A3) and unshared environmental (E1, E2, E3) sources. Estimates are standardized such that when squared they indicate the percentage of variance accounted for. The factors A1 and E1 account for all of the variance for neuroticism [i.e. they include specific genetic (23%) and environmental (33%) variance for neuroticism], while the factors A2 and E2 are independent of neuroticism [Note: A2 and E2 include specific genetic (7%) and environmental (36%) variance for PSYCH-14]. Heritability (h^2) is shown for each variable.

genetic factor (A1) accounts for all of the genetic variance in neuroticism, which includes 23% specific variance for neuroticism and 29% that is in common with the variance for PSYCH-14 and SOMA-10, plus 22% of the variance in PSYCH-14 and 16% in SOMA-10. A second genetic factor (A2), independent of A1, accounts for a further common source of genetic variance between PSYCH-14 (i.e. 11% of the variance: 18% minus 7% specific genetic variance) and SOMA-10 (17%). The genetic factor (A3) accounts for specific genetic variance for SOMA-10 (10%). These common sources of genetic influence are reflected in the genetic correlations (as the smaller environmental overlap is reflected in the unshared environmental correlations; see Table 2).

In contrast to the strong genetic association among the three measures, common environmental effects (i.e. the common influence subsumed in factors E1 and E2) are generally much less, with specific environmental effects accounting for a substantial amount of the variance (i.e. 33% for neuroticism, 36% for PSYCH-14, 47% for SOMA-10). As can be seen in Table 2, E1, after adjusting for the specific environmental variation for neuroticism, accounted for only 15% of the variance for neuroticism and 4% for SOMA-10, but 19% for PSYCH-14 (i.e. variance accounted by A1 and E1 are approximately the same for PSYCH-14). A second independent factor (E2) accounts for further common environmental influences for PSYCH-14 (5%) and SOMA-10 (6%), which again is approximately half that accounted for by A2.

Discussion

In the current study we sought to identify the role of neuroticism, a known risk factor for common mental disorders (Kotov *et al*. 2010), as the major shared risk that may best explain the co-morbidity between anxiety/depression and somatic distress. We targeted adolescents and young adults as they pass through this key stage of onset of both of these syndrome sets (Merikangas *et al*. 2010). All measures from the SPHERE questionnaire were moderately heritable (40–49%), consistent with similar measures (Lamb *et al*. 2010; Bartels *et al*. 2011; Vassend *et al*. 2011) and similar to neuroticism (52%). Genetic sources accounted for most of the covariation between neuroticism, anxiety/depression and somatic symptoms. However, genetic overlap between anxiety/depression and somatic symptoms was not solely due to their relationship with neuroticism. This represents the first genetic study to examine the role of neuroticism in the covariation between anxiety/depressive and somatic symptoms in adolescence.

A strongly influential common factor was identified, accounting for just over half of the genetic variance in anxiety/depression and neuroticism and approximately one-third of the genetic variance in somatic distress. This factor may reflect a susceptibility to psychological distress (i.e. an increased likelihood of responding to situations with fear, sadness, embarrassment, anger, guilt and disgust), which is core to the neuroticism domain, and neuroticism-related characteristics, such as a proneness to irrational ideas, poor impulse control and poor stress management (McCrae & Costa, 2010). Further, neuroticism is related to a self- or body-focused disposition (Pennebaker & Watson, 1991), which is known to correlate with level of somatic symptom reporting (Robbins & Kirmayer, 1991) and to be an associated feature of mood and anxiety disorders (APA, 2000). Cognitive processes may also contribute as difficulty in discriminating emotional feelings and bodily sensations or in expressing emotions have been related to neuroticism and depressed mood (Parker *et al*. 1989) and may also influence self-report of somatic symptoms (Kirmayer *et al*. 1994).

At a neurobiological level, there are likely to be a variety of paths that are relevant to the expression of both depression and somatic symptoms. For example, serotonergic activity appears to influence both depression and somatization, although with differing relevance to each (Rief *et al*. 2004) and has also been

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

linked to neuroticism (Frokjaer *et al*. 2010). Disturbed circadian function (Hickie & Rogers, 2011) appears to be a major risk factor to onset of both mood disorders and related somatic syndromes (particularly prolonged fatigue) and treatments targeting melatonin secretion may well provide novel treatment strategies. We have investigated extensively the relationships between exposure to infective agents and onset of both somatic and affective syndromes (Hickie *et al*. 2006). Disturbed immune function may also be a factor and one that we have previously investigated in adult twin samples (Hickie *et al*. 1999*a*). For example, cytokine activity can influence pain perception and induce symptoms such as fatigue, depressed mood and altered cognition (Vollmer-Conna *et al*. 2004; Dimsdale & Dantzer, 2011), although concentrations of immune parameters can differ between patients with depression and those with somatization (Rief *et al*. 2010). Further, levels of pro-inflammatory cytokines have been associated with neuroticism (Sutin *et al*. 2010).

We also identified a second common genetic factor, independent of neuroticism and specific to anxiety/depression and somatic distress. It is unclear what this genetic factor may represent, but given the complex psychological and biological processes involved as we discuss above, it is plausible that there may be some genetic effects in common with anxiety/depression and somatic distress that are independent of neuroticism. Interestingly, while this second genetic factor has a strong influence on somatic distress, accounting for more than one-third of the genetic variance, it has less influence on anxiety/depression, where it accounts for approximately one-quarter of the genetic variance. As the complex physiology underlying somatic symptoms is increasingly recognized as immune related (Dimsdale & Dantzer, 2011), this factor may reflect cytokine activity specific to these traits.

Our results extend those found in adult samples and are consistent with reported relationships between neuroticism and generalized anxiety disorder (Hettema *et al*. 2006; Kendler *et al*. 2007), major depression (Hettema *et al*. 2006; Kendler *et al*. 2007) and somatic health (Vassend *et al*. 2011). The identification of a second genetic factor is in contrast with Boomsma *et al*. (2000), where a single common factor was found to account for all genetic covariation between measures of depression, anxiety, somatic anxiety and neuroticism. Notably, we found an independent pathway model allowing only a single common genetic source to have only a slightly worse fit than our best-fitting Cholsky model; thus, both models are worthy of consideration. However, in contrast to the independent pathway model, all elements of the Cholesky model were significant, adding to confidence in this model, which had the best AIC fit.

In contrast to the genetic influences, unshared environmental influences were largely specific to each variable, (r_g ranges 0.61–0.87 while r_e ranges 0.25–0.56). These reflect environmental risk factors unique to the individual and to the trait and at least a moderate degree of trait-specific measurement error [based on reliability reports for similar symptom scales (e.g. Vallejo *et al*. 2007) and our own estimates of stability over 2–6 months]. Even so, the finding of small overlapping unshared environmental factors suggests that some environmental risk factors are relevant to all measures or are independent of neuroticism and common to anxiety/depression and somatic distress. For example, exposure to stressors can promote pro-inflammatory processes (Raison *et al*. 2006), which could potentially influence multiple related traits. However, common unshared environmental factors may also include correlated measurement error, including state effects.

In addition to the finding of a major role of genetic factors on the relationship between neuroticism and anxiety/depressive and somatic symptoms in adolescence, the subtle differences for girls and boys across this period of adolescence are worth noting. In girls, we found that, for each of the SPHERE measures, the number of symptoms increased slightly over time (from 12 to 25 years), whereas in boys the symptom scores either decreased or showed no significant change. Although not all studies are in agreement (Bartels *et al*. 2011), similar patterns have been reported previously for depression in adolescents (Sund *et al*. 2001; Angold *et al*. 2002; Lamb *et al*. 2010). For neuroticism, while girls had higher scores than boys, as has been found previously (McCrae *et al*. 2002), we detected no change in scores across adolescence in either girls or boys. This is consistent with what has been shown in adulthood (Terracciano *et al*. 2006), while varying age effects have been reported for adolescents. McCrae *et al*. (2002) found no age affects in American high school students, but found small increases for girls with age in a replication sample of Flemish adolescents and, interestingly, in a sample of gifted students, perhaps suggesting a cognitive component to the increases found. It is possible that increases over age in girls compared to boys, as found for our anxiety/depressive and somatic symptoms, may also reflect differing cognitive styles.

Limitations

A limitation of this study, despite the large sample ($n = 2459$), was the lack of power to explore sex differences underlying covariation between the traits.

https://doi.org/10.1017/S0033291711002431 Published online by Cambridge University Press

Although not significant, our results suggested neuroticism had a stronger genetic relationship with anxiety/depression than somatic distress and this was more prominent in girls than boys. Fanous *et al*. (2002) hypothesized that neuroticism and depression may be more genetically correlated in females, but, in an adult sample, they found correlations to be higher, although not significantly, in males. At a univariate level, we did find significantly higher heritability in boys compared to girls for anxiety/depression (PSYCH-14). A recent review of childhood and adolescent anxiety and depression reports small to negligible sex differences in genetic aetiology (Franic *et al*. 2010), but, interestingly, a higher heritability for boys has been found for self-rated depression in children and adolescents, although no difference was found for parental ratings of depression in the same individuals (Rice *et al*. 2002). Most recently, a higher heritability for adolescent girls for self-reported anxiety/depression and somatic complaints was found (Bartels *et al*. 2011), a finding also reported for teacher ratings of depressive symptoms in young adolescents (Happonen *et al*. 2002) and for mother-rated separation anxiety in children and adolescents (Feigon *et al*. 2001). Clearly, further research using large samples is required to clarify the role of sex in the genetic aetiology of childhood and adolescent anxiety and depression and the role of factors such as phenotype definition and participant age.

The use of dimensional (continuous) rather than categorical measures of anxiety/depression and somatic distress is also a potential limitation. Categorical classification is optimal when no meaningful clinical variation exists among those diagnosed positive or among those negative (Kraemer, 2007). However, the range in symptom count found for anxiety/depression (0–14) and somatic distress (0–10) suggests that the full range of variability would not be captured in a select number of categories. Supporting the use of a dimensional measure, at least for depression, are studies showing a linear relationship between symptom count and impairment or disability (Ustun and Sartorius, 1995; Sakashita *et al*. 2007) and others indicating depression is best conceptualized as one latent continuous dimension (Ruscio & Ruscio, 2000; Slade & Andrews, 2005).

A further limitation may be the conceptualization of anxiety/depression and somatic distress as distinct syndromes, given the relative lack of empirical data to support a clear separation. Somatic syndromes, together with anxiety and depression, may be considered part of a broader spectrum of internalizing disorders (Krueger *et al*. 2003). Nevertheless, factor analytic studies show a clear separation (Gillespie *et al*. 1999; Kirk *et al*. 1999), consistent with studies showing, for example, that not all patients with somatic disorders meet criteria for other psychological disorders (Hickie *et al*. 1990) and that patients with fatigue do not show specific response to antidepressant pharmacotherapy (Vercoulen *et al*. 1996).

We must also acknowledge that we are not yet sufficiently powered to detect common environmental influences. Based on our current sample size and twin correlations, we have >75% power to detect additive genetic influences in a univariate model, but only 5–37% power to identify common environmental influences (i.e. 37% for SPHERE-34, 25% for PSYCH-14, 5% for SOMA-10). Therefore, our genetic estimates from the AE model may be slightly inflated. However, negligible C estimates are consistent with the literature for self-rated depression and somatic complaints (Happonen *et al*. 2002; Rice *et al*. 2002; Bartels *et al*. 2011).

Although our study design precluded examination of longitudinal relationships, data collection is ongoing and future analyses will address age-related changes in genetic and environmental influence. Here, we show that, in adolescents, the genetic risk factors indexed by neuroticism do not fully account for the genetic overlap found between measures of psychological and somatic health.

Acknowledgements

This work was supported by grants from the Australian Research Council (ARC), the National Health & Medical Research Council (NHMRC) and Beyond Blue, Australia.

Declaration of Interest

None.

References

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association: Washington, DC.

Angold A, Erkanli A, Silberg J, Eaves L, Costello EJ (2002). Depression scale scores in 8–17-year-olds: effects of age and gender. *Journal of Child Psychology and Psychiatry* **43**, 1052–1063.

Bartels M, van de Aa N, van Beijsterveldt CE, Middeldorp CM, Boomsma DI (2011). Adolescent self-report of emotional and behavioral problems: interactions of genetic factors with sex and age. *Journal of the Canadian Academy of Child and Adolescent Psychiatry* **20**, 35–52.

Birley AJ, Gillespie NA, Heath AC, Sullivan PF, Boomsma DI, Martin NG (2006). Heritability and nineteen-year stability of long and short EPQ-R

Neuroticism scales. *Personality and Individual Differences* **40**, 737–747.

Boomsma DI, Beem AL, van den Berg M, Dolan CV, Koopmans JR, Vink JM, de Geus EJ, Slagboom PE (2000). Netherlands twin family study of anxious depression (NETSAD). *Twin Research* **3**, 323–334.

Costa PT, McCrae RR (1992). *Revised NEO Personality Inventory* (*NEO PI-R*) *and NEO Five-Factor Inventory* (*NEO-FFI*): *Professional Manual*. PAR: Lutz.

Dimsdale JE, Dantzer R (2011). A biological substrate for somatoform disorders: importance of pathophysiology. *Psychosomatic Medicine* **69**, 850–854.

Eysenck HJ, Eysenck SBG (1975). *Manual for the Eysenck Personality Questionnaire* (*Adult and Junior*). Digits: San Diego, CA.

Eysenck SBG (1972). *Junior Eysenck Personality Inventory*. EdITS/Educational and Industrial Testing Service: San Diego, CA.

Fanous A, Gardner CO, Prescott CA, Cancro R, Kendler KS (2002). Neuroticism, major depression and gender: a population-based twin study. *Psychological Medicine* **32**, 719–728.

Feigon SA, Waldman ID, Levy F, Hay DA (2001). Genetic and environmental influences on separation anxiety disorder symptoms and their moderation by age and sex. *Behavior Genetics* **31**, 403–411.

Franic S, Middeldorp CM, Dolan CV, Ligthart L, Boomsma DI (2010). Childhood and adolescent anxiety and depression: beyond heritability. *Journal of the American Academy of Child & Adolescent Psychiatry* **49**, 820–829.

Freeman MF, Tukey JW (1950). Transformations related to the angular scale and the square root. *Annals of Mathematical Statistics* **21**, 607–611.

Frokjaer VG, Vinberg M, Erritzoe D, Baare W, Holst KK, Mortensen EL, Arfan H, Madsen J, Jernigan TL, Kessing LV, Knudsen GM (2010). Familial risk for mood disorder and the personality risk factor, neuroticism, interact in their association with frontolimbic serotonin 2A receptor binding. *Neuropsychopharmacology* **35**, 1129–1137.

Gillespie N, Kirk KM, Heath AC, Martin NG, Hickie I (1999). Somatic distress as a distinct psychological dimension. *Social Psychiatry and Psychiatric Epidemiology* **34**, 451–458.

Gillespie NA, Evans DE, Wright MM, Martin NG (2004). Genetic simplex modeling of Eysenck's dimensions of personality in a sample of young Australian twins. *Twin Research* **7**, 637–648.

Gillespie NA, Zhu G, Heath AC, Hickie IB, Martin NG (2000). The genetic aetiology of somatic distress. *Psychological Medicine* **30**, 1051–1061.

Goldberg DA (1996). A dimensional model for common mental disorders. *British Journal of Psychiatry* **168**, 44–49.

Hamilton BA, Naismith SL, Scott EM, Purcell S, Hickie IB (2011). Disability is already pronounced in young people with early stages of affective disorders: data from an early intervention service. *Journal of Affective Disorders* **131**, 84–91.

Happonen M, Pulkkinen L, Kaprio J, van der Meere J, Viken RJ, Rose RJ (2002). The heritability of depressive symptoms: multiple informants and multiple measures. *Journal of Child Psychology and Psychiatry* **43**, 471–479.

Hetrick SE, Parker AG, Hickie IB, Purcell R, Yung AR, McGorry PD (2008). Early identification and intervention in depressive disorders: towards a clinical staging model. *Psychotherapy and Psychosomatics* **77**, 263–270.

Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS (2006). A population-based twin study of the relationship between neuroticism and internalizing disorders. *American Journal of Psychiatry* **163**, 857–864.

Hettema JM, Prescott CA, Kendler KS (2004). Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. *American Journal of Psychiatry* **161**, 1581–1587.

Hickie I, Bennett B, Lloyd A, Heath A, Martin N (1999*a*). Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: a twin study. *Psychological Medicine* **29**, 269–277.

Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A (2006). Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *British Medical Journal* **333**, 575.

Hickie I, Hadzi-Pavlovic D, Ricci C (1997). Reviving the diagnosis of neurasthenia. *Psychological Medicine* **27**, 989–994.

Hickie I, Kirk K, Martin N (1999*b*). Unique genetic and environmental determinants of prolonged fatigue: a twin study. *Psychological Medicine* **29**, 259–268.

Hickie I, Koschera A, Hadzi-Pavlovic D, Bennett B, Lloyd A (1999*c*). The temporal stability and co-morbidity of prolonged fatigue: a longitudinal study in primary care. *Psychological Medicine* **29**, 855–861.

Hickie I, Lloyd A, Wakefield D, Parker G (1990). The psychiatric status of patients with the chronic fatigue syndrome. *British Journal of Psychiatry* **156**, 534–540.

Hickie IB, Davenport TA, Hadzi-Pavlovic D, Koschera A, Naismith SL, Scott EM, Wilhelm KA (2001*a*). Development of a simple screening tool for common mental disorders in general practice. *Medical Journal of Australia* **175**, S10–S24.

Hickie IB, Davenport TA, Scott EM, Hadzi-Pavlovic D, Naismith SL, Koschera A (2001*b*). Unmet need for recognition of common mental disorders in Australian general practice. *Medical Journal of Australia* **175** (Suppl.) S18–S24.

Hickie IB, Rogers NL (2011). Novel melatonin-based therapies: potential advances in the treatment of major depression. *Lancet* **378**, 621–631.

Kato K, Sullivan PF, Evengard B, Pedersen NL (2009). A population-based twin study of functional somatic syndromes. *Psychological Medicine* **39**, 497–505.

Kendler KS, Gardner CO, Gatz M, Pederson NL (2007). The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychological Medicine* **37**, 453–462.

Kendler KS, Gardner CO, Lichtenstein P (2008). A developmental twin study of symptoms of anxiety and

depression: evidence for genetic innovation and attenuation. *Psychological Medicine* **38**, 1567–1575.

Kirk KM, Hickie IB, Martin NG (1999). Fatigue as related to anxiety and depression in a community-based sample of twins aged over 50. *Social Psychiatry and Psychiatric Epidemiology* **34**, 85–90.

Kirmayer LJ, Robbins JM, Paris J (1994). Somatoform disorders: personality and the social matrix of somatic distress. *Journal of Abnormal Psychology* **103**, 125–136.

Kotov R, Gamez W, Schmidt F, Watson D (2010). Linking 'big' personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychological Bulletin* **136**, 768–821.

Kraemer HC (2007). DSM categories and dimensions in clinical and research contexts. *International Journal of Methods in Psychiatric Research* **16**, S8–S15.

Krueger RF, Chentsova-Dutton YE, Markon KE, Goldberg D, Ormel J (2003). A cross-cultural study of the structure of comorbidity among common psychopathological syndromes in the general health care setting. *Journal of Abnormal Psychology* **112**, 437–447.

Lamb DJ, Middeldorp CM, van Beijsterveldt CEM, Bartels M, van der Aa N, Polderman TJC, Boomsma DI (2010). Heritability of anxious-depressive and withdrawn behavior: age-related changes during adolescence. *Journal of American Academy of Child & Adolescent Psychiatry* **49**, 248–255.

McCrae RR, Costa PT (2004). A contemplated revision of the NEO Five-Factor Inventory. *Personality and Individual Differences* **36**, 587–596.

McCrae RR, Costa PT (2010). *NEO Inventories for the NEO Personality Inventory-3* (*NEO-PI-3*), *NEO Five-Factor Inventory-3* (*NEO-FFI-3*), *NEO Personality Inventory-Revised* (*NEO PI-R*): *Professional Manual*. PAR: Lutz, FL.

McCrae RR, Costa Jr. PT, Terracciano A, Parker WD, Mills CJ, de Fruyt F, Mervielde I (2002). Personality trait development from age 12 to age 18: longitudinal, cross-sectional, and cross-cultural analyses. *Journal of Personality and Social Psychology* **83**, 1456–1468.

McGorry P (2011). Transition to adulthood: the critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. *Schizophrenia Bulletin* **37**, 524–530.

McGorry PD, Purcell R, Goldstone S, Amminger GP (2011). Age of onset and timing of treatment for mental and substance use disorders: implications for preventive intervention strategies and models of care. *Current Opinion in Psychiatry* **24**, 301–306.

McGregor B, Pfitzner J, Zhu G, Grace M, Eldridge A, Pearson J, Mayne C, Aitken JF, Green AC, Martin NG (1999). Genetic and environmental contributions to size, color, shape, and other characteristics of melanocytic naevi in a sample of adolescent twins. *Genetic Epidemiology* **16**, 40–53.

Martin NG, Jardine R, Andrews G, Heath AC (1988). Anxiety disorders and neuroticism: are there genetic factors specific to panic. *Acta Psychiatrica Scandinavica* **77**, 698–706.

Medland SE, Nyholt DR, Painter JN, McEvoy BP, McRae AF, Zhu G, Gordon SD, Ferreira MA, Wright MJ, Henders AK, Campbell MJ, Duffy DL, Hansell NK, Macgregor S, Slutske WS, Heath AC, Montgomery GW, Martin NG (2009). Common variants in the trichohyalin gene are associated with straight hair in Europeans. *American Journal of Human Genetics* **85**, 750–755.

Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J (2010). Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication – Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 980–989.

Neale MC, Boker SM, Xie G, Maes HH (2003). *Mx: Statistical Modeling*. Department of Psychiatry: Richmond, VA.

Neale MC, Cardon LR (1992). *Methodology for Genetic Studies of Twins and Families*. Kluwer Academic Publishers: Dordrecht.

Neale MC, Eaves LJ, Kendler KS (1994). The power of the classical twin study to resolve variation in threshold traits. *Behavior Genetics* **24**, 239–258.

Parker JD, Taylor GJ, Bagby RM (1989). The alexithymia construct: relationship with sociodemographic variables and intelligence. *Comprehensive Psychiatry* **30**, 434–441.

Pennebaker JW, Watson D (1991). The psychology of somatic symptoms. In *Current Concepts of Somatization* (ed. L. J. Kirmayer and J. M. Robbins). American Psychiatric Press: Washington DC.

Raison CL, Capuron L, Miller AH (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology* **27**, 24–31.

Rettew DC, Vink JM, Willemsen G, Doyle A, Hudziak JJ, Boomsma DI (2006). The genetic architecture of neuroticism in 3301 Dutch adolescent twins as a function of age and sex: a study from the Dutch Twin Register. *Twin Research and Human Genetics* **9**, 24–29.

Rice F, Harold GT, Thapar A (2002). Assessing the effects of age, sex, and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psycholgy & Psychiatry* **43**, 1039–1051.

Rief W, Hennings A, Riemer S, Euteneuer F (2010). Psychobiological differences between depression and somatization. *Journal of Psychosomatic Research* **68**, 496–502.

Rief W, Pilger F, Ihle D, Verlerk R, Scharpe S, Maes M (2004). Psychobiological aspects of somatoform disorders: contributions of monoaminergic transmitter systems. *Neuropsychobiology* **49**, 24–29.

Robbins JM, Kirmayer LJ (1991). Cognitive and social factors in somatization. In *Current Concepts of Somatization: Research and Clinical Perspectives* (ed. L. J. Kirmayer and J. M. Robbins), pp. 107–141. American Psychiatric Press: Washington DC.

Ruscio J, Ruscio AM (2000). Informing the continuity controversy: a taxometric analysis of depression. *Journal of Abnormal Psychology* **109**, 473–487.

Sakashita C, Slade T, Andrews G (2007). Empirical investigation of two assumptions in the diagnosis of DSM-IV major depressive episode. *Australian and New Zealand Journal of Psychiatry* **41**, 17–23.

Slade T, Andrews G (2005). Latent structure of depression in a community sample: a taxometric analysis. *Psychological Medicine* **35**, 489–497.

Sund AM, Larsson B, Wichstrom L (2001). Depressive symptoms among young Norwegian adolescents as measured by The Mood and Feelings Questionnaire (MFQ). *European Child & Adolescent Psychiatry* **10**, 222–229.

Sutin AR, Terracciano A, Deiana B, Naitza S, Ferrucci L, Uda M, Schlessinger D, Costa Jr. PT (2010). High neuroticism and low conscientiousness are associated with interleukin-6. *Psychological Medicine* **40**, 1485–1493.

Terracciano A, Costa Jr. PT, McCrae RR (2006). Personality plasticity after age 30. *Personality and Social Psychology Bulletin* **32**, 999–1009.

Ustun TB, Sartorius N (eds.) (1995). *Mental Illness in General Health Care: An International Study*. John Wiley & Sons: London.

Vaccarino AL, Sills TL, Evans KR, Kalali AH (2009). Multiple pain complaints in patients with major depressive disorder. *Psychosomatic Medicine* **71**, 159–162.

Vallejo MA, Jordan CM, Diaz MI, Comeche MI, Ortega J (2007). Psychological assessment via the internet: a reliability and validity study of online (vs paper-and-pencil) versions of the General Health Questionnaire-28 (GHQ-28) and the Symptoms Check-List-90-Revised (SCL-90-R). *Journal of Medical Internet Research* **9**, e2.

van der Linden G, Chalder T, Hickie I, Koschera A, Sham P, Wessely S (1999). Fatigue and psychiatric disorder: different or the same? *Psychological Medicine* **29**, 863–868.

Vassend O, Roysamb E, Nielsen CS (2011). Neuroticism and self-reported somatic health: a twin study. *Psychology & Health*. Published online: 14 June 2011. doi:10.1080/08870446.2010.540665.

Vercoulen JH, Swanink CM, Zitman FG, Vreden SG, Hoofs MP, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G (1996). Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* **347**, 858–861.

Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, Davenport T, Wakefield D, Hickie I, Lloyd A (2004). Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. *Psychological Medicine* **34**, 1289–1297.

Wijeratne C, Hickie I, Davenport T (2006). Is there an independent somatic symptom dimension in older people? *Journal of Psychosomatic Research* **61**, 197–204.

Wray NR, Birley AJ, Sullivan PF, Visscher PM, Martin NG (2007). Genetic and phenotypic stability of measures of neuroticism over 22 years. *Twin Research and Human Genetics* **10**, 695–702.

Wright MJ, Martin NG (2004). The Brisbane Adolescent Twin Study: outline of study methods and research projects. *Australian Journal of Psychology* **56**, 65–78.