Do the Genetic or Environmental Determinants of Anxiety and Depression Change with Age? A Longitudinal Study of Australian Twins

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Because the determinants of anxiety and depression in late adolescence and early adulthood may differ from those in later life, we investigated the temporal stability and magnitude of genetic and environmental correlates of symptoms of anxiety and depression across the life span. Data were collected from a population-based Australian sample of 4364 complete twin pairs and 777 singletons aged 20 to 96 years who were followed-up over three studies between 1980 and 1996. Each study contained the 14-item self-report DSSI/sAD scale which was used to measure recently experienced symptoms of anxiety and depression. Symptom scores were then divided and assigned to age intervals according to each subject's age at time of participation. We fitted genetic simplex models to take into account the longitudinal nature of the data. For male anxiety and depression, the best fitting simplex models comprised a single genetic innovation at age 20 which was transmitted, and explained genetic variation in anxiety and depression at ages 30, 40, 50 and 60. Most of the lifetime genetic variation in female anxiety and depression could also be explained by innovations at age 20 which were transmitted to all other ages; however, there were also smaller age-dependent genetic innovations at 30 for anxiety and at 40 and 70 for depression. Although the genetic determinants of anxiety and depression appear relatively stable across the lifespan for males and females, there is some evidence to support additional mid-life and late age gene action in females for depression. The fact that mid-life onset for anxiety occurs one decade before depression is also consistent with a causal relationship (anxiety leading to depression) between these conditions. These findings have significance for large scale depression prevention projects.

Are the determinants of anxiety and depression in early adulthood different from those in later life? Most depressive and anxiety disorders have their onset in adolescence or early adult life and appear to have both strong genetic and unique environmental determinants (Kendler et al., 1986; Kendler et al., 1987; Kendler et al., 1992). But now there is moderately strong evidence from epidemiological, clinical, treatment, longitudinal and neuroimaging studies to suggest that depression that arises after 50 years of age may have at least some unique etiological factors (Brodaty et al., 1997; Henderson, 1994; Krishnan, 2002; Krishnan, 2003; Tupler et al., 2002).

Patients diagnosed with early onset depressive illnesses tend to have longer and more recurrent episodes, increased frequency of comorbid personality and substance abuse disorders, family histories of psychiatric or affective disorders and longer times to remission (Baldwin & Tomenson, 1995; Brodaty et al., 2001; Brodaty et al., 1993; Cole, 1983; Conwell et al., 1989; Hickie et al., 2001; Klein et al., 1988; Klein et al., 1999; Mendlewicz, 1976; Reynolds et al., 1998; Van den Berg et al., 2001).

Older persons with depression tend preferentially to endorse somatic complaints, sleep difficulties and fatigue (Christensen et al., 1999; Gallo et al., 1994; Gottfries, 1998; Jorm, 2000). It is unclear whether this represents a genuine change in illness phenotype with ageing, the consequence of different underlying etiological factors, or a cohort effect (with older people simply being less likely to report the overt psychological symptoms of depression or anxiety). While patients with late-onset disorders do not necessarily

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have more severe or treatment resistant disorders (Brodaty et al., 1991; Brodaty et al., 1997; Conwell et al., 1989; Greenwald & Kramer-Ginsberg, 1988; Heyman et al., 1991; Klein et al., 1999; Reynolds et al., 1998), they do tend to have higher rates of medical comorbidity, notably of concurrent vascular disease, more extensive cerebral changes on magnetic resonance imaging (notably deep white matter and basal ganglia lesions) and a differing pattern of neuropsychological impairment (Hickie et al., 1995, 1997; Naismith et al., 2002, p. 3).

Structural changes on MRI in patients with late-life depression are themselves associated with psychomotor change, neuropsychological impairment, vascular risk factors, impaired treatment response and poorer prognosis (Hickie et al., 1995; Hickie et al., 1997; Naismith et al., 2002; Alexopoulos et al., 2002). Hence, a new illness entity of "vascular depression" has been proposed (Alexopoulos et al., 1997a; Alexopoulos et al., 1997b; Krishnan et al., 1997; Krishnan, 2002) and is thought to be particularly prevalent among persons who develop depression for the first time after 50 years of age. Not only does such a concept have important treatment and prognostic implications, but also raises the prospect of novel methods for prevention based on this more basic understanding of its pathophysiology (Hickie & Scott, 1998).

Differences between early and late onset anxiety and depression might reflect qualitative genetic or environmental differences. For example, recent studies suggest associations between homocysteine and depression in persons residing in the community (den Heijer et al., 2003; Tiemeier et al., 2002). Circulating homocysteine levels are subject to both genetic (e.g., variations in the activity of the methylenetetrahydrofolate reductase [MTHFR] enzyme) and environmental determinants (e.g., dietary folate). Our group has recently demonstrated associations between a higher prevalence of the homozygous or heterozygous forms of the C677T mutation of the MTHFR genotype, late onset depression and structural brain changes in persons with depression (Hickie et al., 2001; Naismith et al., 2002). Interest in the association between ApoE ε4 and late onset depression has been strong, but the results are equivocal. Several studies have demonstrated a significant increase in the ε4 allele frequency (Corder et al., 1993; Schmechel et al., 1993; Holmes et al., 1998; Rigaud et al., 2001) while others have failed to verify the association (Hickie et al., 2001; Holmes et al., 1998; Jackson et al., 2001; Rigaud et al., 2001; Zubenko et al., 1996).

Other environmental factors may also change significantly with age, including participation in employment and other social activities, use of concurrent alcohol and other substances and exposure to major loss events (e.g., death of a spouse). The onset of major medical disorders (e.g., heart disease, cancer and stroke) as well as other chronically painful or disabling muscular-skeletal disorders (e.g., osteoarthritis) may also increase the likelihood of experiencing depressive symptoms with age. While one might expect that the accumulation of life stressors and physical ailments would increase the rate of depression in older people, epidemiological evidence suggests that the rate of major depression actually falls with age. Furthermore, there is some suggestion that true depression rates, and associated suicide rates, are falling progressively in older people as a consequence of a mix of physical health (improved vascular health), social (reduced barriers to participation in employment) and health service (improved treatment of depression in primary care) factors (Hall et al., 2003).

It is possible that stress plays a greater role relative to a diathesis in late onset depression (Zuckerman, 1999). For instance, Brodaty and colleagues found that late onset depressives are less likely to have personality disorders or a family history of affective disorder (Brodaty et al., 1991). Another possibility is that elderly people are more resilient, perhaps as consequence of lifelong psychological immunization (Henderson et al., 1998). Another important consideration is that the saliency of environmental stressors underpinning anxiety and depression are likely to change over time, with relationship difficulties being more prominent at younger ages, whereas the impact of loss though death being greater among the elderly (Henderson et al., 1998; Turvey et al., 1999).

Jorm (2000) reviewed 49 studies which investigated the association between anxiety, depression and distress with age. These studies included subjects ranging in age from 18 to 89 years and employed a variety of assessment methods: clinical and nonclinical, categorical and continuous, self-report and clinician-rated scales. Taken as a whole, results were equivocal with no clear pattern emerging. Only 10 studies (all of which used continuous measures of anxiety and depression) controlled for covariates such as sex, marital status, education, employment status, income and so forth. One study reported an increase between the ages of 25 to 44 years followed by a decrease, while the remaining nine studies reported a steady decrease in the levels of anxiety, depression and distress with age. Moreover, the decrease could not be explained by the exclusion of institutionalized elderly subjects from the surveys or by selective mortality of depressives and people suffering anxiety.

In summary, there are both clinical and community studies which suggest differing genetic or environmental determinants of anxiety and depression across the life cycle. Although there is very strong empirical evidence showing that persons who experience anxiety or depression share a common biological substrate, and that their manifestation is dependent upon different aspects of the non-shared environment (Jardine et al., 1984; Kendler et al., 1987; Kendler et al., 1992; Kendler, 1996), the extent to which age-dependent genetic or environmental factors influence incidence-rates remains unclear.

To date, most longitudinal studies of the relevant genetic and environmental determinants of anxiety and depression have been limited to periods of 2 to 6 years (Kendler et al., 1993b, 1993c; Kendler et al., 1998). The available evidence does suggest temporal stability of symptom sets, clinical diagnoses and related personality factors such as neuroticism (Hickie et al., 1999; Wessely & Powell, 1989). The aim of this paper is therefore to determine the extent to which the genetic effects underpinning anxiety and depression vary across the entire life span.

Methods

Subjects

Twins were drawn from the Australian Twin Register (ATR) which is a volunteer register founded in 1978 with almost 28,000 twins of all types and all ages enrolled and in various stages of active contact. The current project was based primarily on an older cohort (Cohort 1) of twin pairs born before 1964 (Jardine et al., 1984). Analyses have shown that this cohort is typical of the Australian population in many respects, including the prevalence of psychiatric symptoms (Kendler et al., 1986), although it is slightly more middle class and educated than average, particularly for males (Baker et al., 1996).

These twins were initially surveyed in 1980–1982 when a Health and Lifestyle Questionnaire (HLQ) was mailed to 5,867 twin pairs over the age of 18 registered with the ATR. In addition to psychiatric symptoms, the HLQ assessment included sociodemographic variables, measures of tobacco use, alcohol consumption, personality and numerous other behavioural measures. Completed questionnaires were received from 3,808 twin pairs and 576 single twins, with a response rate (excluding deaths and non-contacts) of 70%, and a complete pair response rate of 65%.

From 1988 to 1990, the 3,808 complete twin pair respondents from the 1980–1982 study were followed up with another HLQ which incorporated many of the questions sent out to the same twins 8 years previously. Mailed questionnaire or telephone interview data were obtained from 2,997 complete twin pairs and 334 singles, with an individual response rate of 83%, and a complete pair response rate of 79%. At the same time, the 576 incomplete twin pair respondents (singletons) and their co-twins from the 1980–1982 study were also followed-up with an identical questionnaire.

Approximately 2 years after completing the 1988 follow-up questionnaire, a sample of 500 females and 500 males were re-sent the same questionnaire in order to obtain medium term test–retest correlations. Completed questionnaires were returned by 466 female and 421 male respondents. Since these twins were re-surveyed before all of the 1988 survey responses had been returned, uncooperative twins were therefore under-sampled.

Between November 1993 and July 1995, 4,186 twins who had participated in the earlier waves and who were aged 50 years or above at the time, were approached and asked to participate in a study of older Australian twins which also covered a wide range of behavioural and personality measures. Questionnaire responses were received from 3,116 individuals (1,279 complete pairs and 558 singles), with an individual response rate (excluding deaths and non-contacts) of 71%, and a complete pairs response rate of 61%.

Measures

Each HLQ included the 14 anxiety and depression items from the Delusion Symptoms States Inventory /Anxiety and Depression (DSSI/sAD) (see Bedford & Deary, 1997; Foulds & Bedford, 1975). Items were identically phrased in the DDSI/sAD format of inquiry, "*Recently I have had …*" and measured on a 4-point distress scale: (1) *not-at-all,* (2) *a-little,* (3) *a-lot,* and (4) *unbearably*.

Zygosity

Zygosity was determined based on twins' responses to standard questions about similarity and the degree to which others confused them. Such procedures have previously demonstrated at least 95% agreement with diagnoses based on extensive blood sampling (Martin, 1975; Ooki et al., 1990). Any inconsistencies in responses by individual twins or between co-twins were followed-up by telephone queries, and if doubt still remained, twins were asked to send in photographs. Where blood or buccal swabs were available, zygosity in the same sex twin pairs was also diagnosed by typing nine highly polymorphic DNA microsatellite markers consisting of eight short tandem repeat (STR) loci and the Amelogenin locus (ABI Profiler Kit) in a single PCR amplification as well as three blood groups (ABO, MNS, Rh). The probability of dizygosity given concordance for all markers in our panel was $<10^{-4}$.

Time Series Data

Each subject's age at participation in each study was calculated. Anxiety and depression scores based on completed DSSI/sAD data were calculated and assigned to one of six recoded age intervals: 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and 70+. When generating the longitudinal data set we pooled the imputed observations from all studies and in order to circumvent cases where subjects were ascertained twice in the same 10-year age interval, only the first observation was included. For example, a subject aged 21 in 1980 would also fall within the same age interval during the 1988 follow-up. Additional DSSI/sAD anxiety and depression scores for each subject were only included provided that the subject fell into a higher age interval at the time of the next study. After imputation, the number of subjects with complete DSSI/sAD scores at one, two and three age intervals was 4,910, 4,093 and 502 respectively. No subjects had complete data from 4

or more age intervals. For males, the number of complete twin pairs aged 70 or above was 42 and 23 for MZ and DZ twins respectively. We therefore combined this age cohort with the 60–69-year-old male respondents. The number of complete and incomplete twin pair respondents by age interval, zygosity and sex after imputation is shown in Table 1.

Analysis of Raw Continuous Data

The application of raw data methods to continuous data, based on multivariate normal theory, enables the preliminary testing of basic assumptions concerning the equality of means and variances within twin pairs, across sex and zygosity, as well as tests of hypotheses about the covariance structure. Since this approach uses both complete and incomplete twin pair data it therefore avoids listwise deletion. It has the added advantage of increasing the accuracy of the estimation of the means and variances, thereby improving the covariance estimates.

Genetic Analysis

Standard biometrical genetic model-fitting methods were used (Neale & Cardon, 1992) which decompose the total variance in an observed trait into additive (A) and non-additive (D; dominance or epistasis) genetic variance as well as shared (C) and unique (E) environmental variance. Since MZ twins are genetically identical, the correlations for additive and non-additive genetic effects between MZ twins are both 1.0. For DZ twins, the correlations for additive and non-additive genetic effects are .5 and .25 respectively. An important assumption of the biometrical model is that shared environmental effects correlate to an equal extent in MZ and DZ twin pairs (Kendler et al., 1994; Xian et al., 2000). Non-shared environmental effects are by definition uncorrelated and also reflect measurement error including short-term fluctuations.

Multivariate and Longitudinal Analyses

Multivariate analysis makes use of the additional information in the cross-correlations between relatives for different traits (or same traits measured at different times) and permits us to determine the extent to which genetic and environmental influences are shared in common by several traits or are trait specific (Heath et al., 1994). We initially fit Cholesky triangular decompositions (Neale & Cardon, 1992) to the time series anxiety and depression data. The expected variance-covariance matrix in the Cholesky decomposition is parameterized in terms of n latent factors (where n is the number of variables, or in the present longitudinal case, the same variable measured on three occasions), where all variables load on the first latent factor, $n - 1$ variables load on the second factor and so on, until the final variable loads on the nth factor only. Each source of phenotypic variation (i.e., A, C or D, and E) is parameterized in the same way. In this way, the full factor Cholesky does not distinguish between common factor and specific factor variance and does not estimate a specific factor effect for any variable except the last (Heath et al., 1994); hence the model is more closely related to a principal components analysis than to factor analysis (Morrison, 1976).

Although the Cholesky decomposition allows us to determine the extent to which genetic and environmental influences are shared in common by a trait measured at different time points, it is limited in so far as it does not take full advantage of the time series nature of the data (i.e., that causation is unidirectional through time; Boomsma et al., 1989). Our solution was to fit a simplex model (see Figure 1) which explicitly takes into account the longitudinal nature of the data. Simplex models are autoregressive whereby the latent variable at time i is causally related to the immediately preceding latent variable (η_{i-1}) which can be expressed in the form of the following structural equation:

$$\eta_i = \beta_i \eta_{i-1} + \zeta_i$$

where η_i is the latent variable at time i, β_i is the regression of the latent factor on the immediately preceding latent factor η_{i-1}, and ζ_i is the new input or

Table 1

Number of Complete and Incomplete Twin Pairs by Age Interval and Zygosity

	20–29		30–39		40–49		50–59		60–69		*70+	
	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○
1. MZFF	520	43	553	79	346	60	441	70	267	40	140	24
2. MZMM	234	29	278	50	144	46	148	50	120	36	—	—
3. DZFF	306	54	344	76	202	54	250	80	152	56	65	20
4. DZMM	175	55	166	61	69	37	71	38	65	25	—	—
5. DZFM	430	115	368	150	198	91	212	127	149	118	—	92
Total	1665	296	1709	416	959	288	1122	365	753	275	205	136

Note: ●● Complete twin pairs, ●○ Incomplete twin pairs
MZFF = monozygotic female twin pairs, MZMM = monozygotic male twin pairs, DZFF = dizygotic female twin pairs, DZMM = dizygotic male twin pairs, DZFM = opposite sex dizygotic female-male twin pairs
*70+ males combined with males 60–69 yrs

innovation at time *i*. When using data from MZ and DZ twin pairs, structural equations can be specified for additive genetic sources of variation (A), common environmental (C), non-additive genetic sources of variation such as dominance or epistasis (D), and unique environmental sources of variation (E). A measurement model can then be written to describe the relationship between the latent and observed variables:

$$y_i = \lambda_i \eta_i + \varepsilon_i$$

where λ_i is the factor loading of the observed phenotype on the latent variable at time *i*, and ε_i is a measurement error term which affects the phenotype, but is uncorrelated with η_i. In order for the model to be identified, either the factor loadings on the observed variables must be set to unity and the variance of the innovations estimated, or alternatively, the variances of the innovation terms need to be standardized to one and the factor loadings estimated. In the present study, we used the first option.

A final point concerns the distinction between innovations of latent factors (ζ_i) and the measurement errors pertaining to observed variables (ε_i). Although an innovation on a latent factor at time *i* is not caused by the preceding latent factor at time *i*–1, it nevertheless influences every subsequent time point. This is in contrast to measurement errors which are terms that do not influence observed variables at subsequent time points. Simplex designs therefore permit the discrimination of transient factors effecting measurement at one time point from factors that are continuously present or exert a long-term influence throughout the time series (Boomsma et al., 1989; Neale & Cardon, 1992). The variance of the last measurement error parameter must be constrained equal with at least one of the preceding error terms in order for the model to be identified. This is because error variance on these occasions would otherwise be indistinguishable from innovation variance. The error parameters will also include variance attributable to short-term non-shared environmental effects and since these effects are likely to be different across the life-span, it is more appropriate to constrain the last two error parameters.

The full female simplex models in the present study consisted of 44 parameters: six innovations (ζ) and five transmission coefficients (β) for each source of variation (A, C and E), five error terms ($\varepsilon_1 - \varepsilon_6$, where $\varepsilon_5 = \varepsilon_6$), and six means.

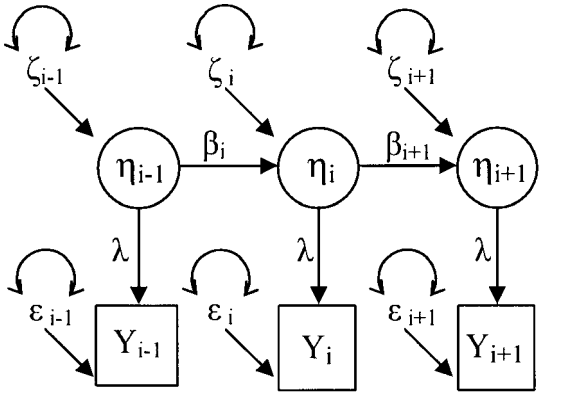

Figure 1

General simplex model.

Note: η = latent variable at time *i*, β = regression of the latent factor on the previous latent factor, ζ = new input or innovation at time *i*, λ = factor loadings, ε = error parameters.

Results

In order to minimize the problems arising from the non-normal distribution of the DSSI anxiety and depression scores, all scores were normal ranked by sex. We then tested for differences in means and variances within twin pairs, between zygosity groups and between study cohorts and found no more than expected by chance.

Multivariate Analysis

We began by fitting multivariate Cholesky models to the longitudinal twin data to identify the most significant sources of covariance. In each case, the AE Cholesky provided a better fit when compared to the full ACE model confirming previous findings that shared environmental effects provide no more than a minor contribution to variation in anxiety and depression (Kendler et al., 1986; Kendler et al., 1987). Because the central aim was to determine the extent to which genetic effects vary across the entire life span, simplex models were then fitted to the data. The AE simplex models provided an improved fit over the AE Cholesky solutions and we therefore began to simplify the genetic and environmental simplex structures. Specifically, our intention was to test the significance of genetic and environmental innovations at each age by dropping them one by one from the model.

Female Anxiety

Compared to the full AE simplex model, there was a significant deterioration in model fit when the genetic innovation at 30 was dropped, but there were no significant changes in model fits when the remaining genetic innovations at 40, 50, 60 and 70 were removed one at a time (Table 2). Simultaneously removing the same genetic innovations from 40 through to 70 also caused no significant deterioration in model fit. Likewise, a model which removed the non-shared environmental innovations from 30 onwards did not cause a significant deterioration in model fit. Apart from the additive genetic and non-shared innovations at 20, the best fitting model (Figure 2) required an additional genetic innovation

Table 2

Multivariate Model Fitting Results for the Longitudinal Measures of Female Anxiety

Model	–2LL	*df*	Δ–2LL	Δ*df*	*p*
Cholesky					
ACE	24497.12	9577			
AE	24503.69	9598	6.57	21	1.00
CE	24546.14	9598	49.01	21	< .001
E	24858.48	9619	361.35	42	< .001
Simplex					
ACE	24498.07	9602			
AE	24511.46	9613	13.40	11	.27
CE	24554.05	9613	55.98	11	< .001
E	24859.63	9624	361.57	22	< .001
AE simplex sub-models					
Drop ζg_2	24516.39	9614	4.93	1	.03
Drop ζg_3	24514.01	9614	2.55	1	.11
Drop ζg_4	24513.14	9614	1.68	1	.20
Drop ζg_5	24513.20	9614	1.74	1	.19
Drop ζg_6	24511.95	9614	0.49	1	.49
Drop $\zeta g_3 - \zeta g_6$	24517.61	9617	6.15	4	.19
Drop ζe_2	24511.46	9614	0.00	1	1.00
Drop ζe_3	24512.10	9614	0.63	1	.43
Drop ζe_4	24512.81	9614	1.35	1	.25
Drop ζe_5	24511.46	9614	0.00	1	1.00
Drop ζe_6	24511.53	9614	0.07	1	.79
Drop $\zeta e_2 - \zeta e_6$	24513.49	9618	2.02	5	.85
Drop $\zeta g_3 - \zeta g_6$ & $\zeta e_2 - \zeta e_6$	24521.28	9622	9.82	9	.37

Note: –2LL = –2 × Log Likelihood
Significant innovations are in bold
$\zeta g_1 - \zeta g_6$ = Additive genetic effects for age intervals 20–29 through 70+ yrs
$\zeta e_1 - \zeta e_6$ = Additive genetic effects for age intervals 20–29 through 70+ yrs

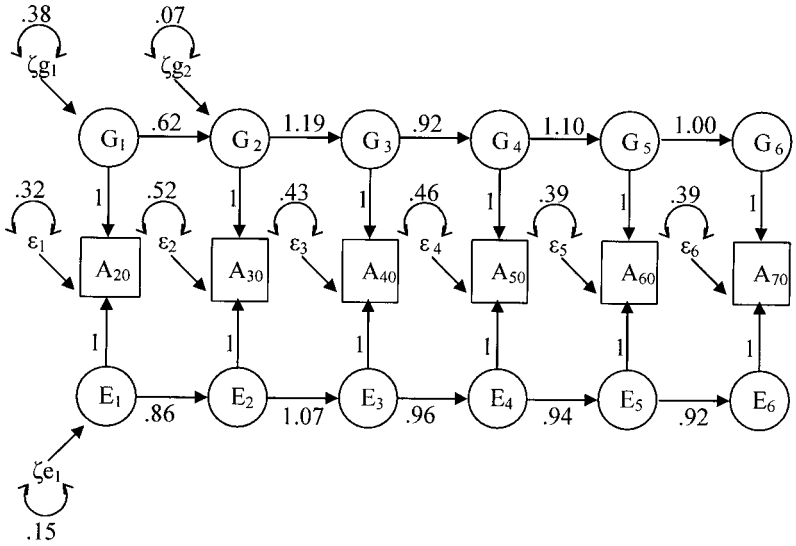

Figure 2

Best fitting simplex model for female anxiety with unstandardized variance components and path coefficients.

Note: $G_1 - G_6$ = additive genetic effects, $E_1 - E_6$ = non-shared environmental effects, ζ_g = additive genetic innovations, ζ_e = non-shared environmental innovations, ε = error terms, where ε_5 is constrained equal to ε_6

at 30 in order to explain the variation in female anxiety across the life span.

Female Depression

The additive genetic innovation at 40 was significant and the innovation at 70 approached significance (Table 3). For non-shared environmental effects, the innovation at 50 was significant but innovations at 30, 40, 60 and 70 could each be removed from the model. The best fitting model (Figure 3) for female depression included an additive genetic innovation at 20, as well as smaller genetic innovations at 40 and 70. This model also included non-shared environmental innovations at 20 and 50.

Male Anxiety

Model fitting results for male anxiety are shown in Table 4. Unlike their female counterparts, none of the additive genetic or non-shared environmental innovations from 30 onwards were significant and the best fitting model (Figure 4) required one genetic and one non-shared environmental innovation at 20 in order to explain the variation in male anxiety across the life span.

Male Depression

As with male anxiety, simultaneously dropping the genetic innovations at 30, 40, 50 and 60 resulted in no significant deterioration in the model fit. The non-shared environmental innovations from 30 onwards could also be dropped from the final model shown in Figure 5.

Discussion

In this longitudinal study of Australian twins, familial aggregation for anxiety and depression was evident at each age interval for both males and females and was best explained by additive gene action. These conclusions are supported by previous research which has found no evidence of shared environmental factors in the etiology of symptoms of anxiety and depression in twins (Kendler et al., 1986; Kendler et al., 1987; Kendler, 1998).

The best fitting simplex models for male anxiety and depression revealed that genetic variation at all age intervals could be entirely explained by genetic innovations at age 20. By contrast, for females, there was evidence of differences in the genetic determinants of anxiety and depression between young and elderly subjects. The most likely explanation is that with considerably fewer males than females in our sample, we simply did not have the power to detect later genetic innovations. An alternative interpretation is that there are significant sex differences in the etiology of depression. Genetic correlations for major depression in men and women are only in the range from .50 to .65 (Kendler et al., 2001a), and it is likely that the genetic risk factors for major depression are not entirely the same in males and females (Kendler & Prescott, 1999). Although men may be more prone to forgetting depressive episodes which had not previously reached formal diagnostic criteria (Wilhelm & Parker, 1994) there is stronger empirical evidence which suggests that the increased risk for major depression in women is caused by a greater role of genetic factors (Kendler et al., 2001a; Kendler et al., 2001c).

Genetic variance across the life span in female anxiety and depression was mostly attributable to innovations at age 20. This suggests a strong degree of genetic continuity over time. Since the contribution made by the non-shared environment was relatively small this meant that additive gene action at age 20 was accounting for nearly all of the observed longitudinal stability in women's symptom scores. Our results also support the inclusion of age-specific genetic effects underpinning female anxiety and depression: at 30 for female anxiety and at 40 and 70 for female depression. Although smaller, these additional genetic innovations warrant further investigation.

The genetic innovation which approaches significance at 70 for female depression supports the notion of a small but significant difference between older and younger female subjects. It is consistent with the notion that new pathophysiologies that increase in prevalence with age may be relevant. Such factors could include genetic risks to neurodegenerative disease (e.g., APO ε4) or vascular disease (e.g., MTHFR genotype).

The genetic innovation for female depression at age 40 also suggests small differences in etiology. One possible explanation is the approach or onset of menopause. There is empirical evidence showing that a decrease in ovarian estrogen production is a risk factor for depressive symptomatology (Maartens et al., 2002) and that genetic factors also play a role in menopausal age while shared environmental factors do not (Do et al., 2000), but the extent to which variation in age at menopause and depressive symptoms covary remains speculative. More compelling is the ordering of the innovations for female anxiety at 30 and depression at 40. Kendler and colleagues in a factor analysis of DSSI items have shown that while anxiety items consistently loaded positively on a primary "depression-distress" factor, the majority of depression items did not load highly on their anxiety factor (Kendler et al., 1987). This implies a temporal precedence of anxiety over depression and indeed, numerous studies have demonstrated that a history of anxiety disorders significantly increases the risk of developing major depression (Breslau et al., 1995; Ulusahin & Ulug, 1997; Parker et al., 1997; Breslau et al., 1998; Pine et al., 1998; Parker et al., 1999; Wittchen et al., 2000; Fava et al., 2000; Stein et al., 2001).

Limitations

It was not possible to have information from each subject at every 10-year age interval because each

Table 3

Multivariate Model Fitting Results for the Longitudinal Measures of Female Depression

Model	–2LL	*df*	Δ–2LL	Δ*df*	*p*
Cholesky					
ACE	22683.89	9577			
AE	22696.15	9598	12.25	21	.93
CE	22724.98	9598	41.09	21	< .01
E	22974.83	9619	290.93	42	< .001
Simplex					
ACE	22687.00	9602			
AE	22704.27	9613	17.27	11	.10
CE	22734.40	9613	47.40	11	< .001
E	22979.17	9624	292.18	22	< .001
AE Simplex sub-models					
Drop ζg_2	22704.29	9614	0.02	1	.89
Drop ζg_3	22714.58	9614	10.31	1	< .01
Drop ζg_4	22704.53	9614	0.26	1	.61
Drop ζg_5	22706.76	9614	2.49	1	.12
Drop ζg_6	22707.72	9614	3.45	1	.06
Drop ζg_2, $\zeta g_4 - \zeta g_5$	22706.99	9616	2.72	3	
Drop ζe_2	22704.27	9614	0.00	1	1.00
Drop ζe_3	22704.47	9614	0.20	1	.65
Drop ζe_4	22713.39	9614	9.12	1	< .01
Drop ζe_5	22704.91	9614	0.64	1	.42
Drop ζe_6	22704.27	9614	0.00	1	1.00
Drop $\zeta e_2 - \zeta e_3, \zeta e_5 - \zeta e_6$	22705.12	9617	0.85	4	.93
Drop ζg_2, $\zeta g_4 - \zeta g_5$ & $\zeta e_2 - \zeta e_3, \zeta e_5 - \zeta e_6$	22710.01	9620	5.74	7	.57

Note: –2LL = –2 × Log Likelihood
Significant innovations are in bold
$\zeta g_1 - \zeta g_6$ = Additive genetic effects for age intervals 20–29 through 70+ yrs
$\zeta e_1 - \zeta e_6$ = Additive genetic effects for age intervals 20–29 through 70+ yrs

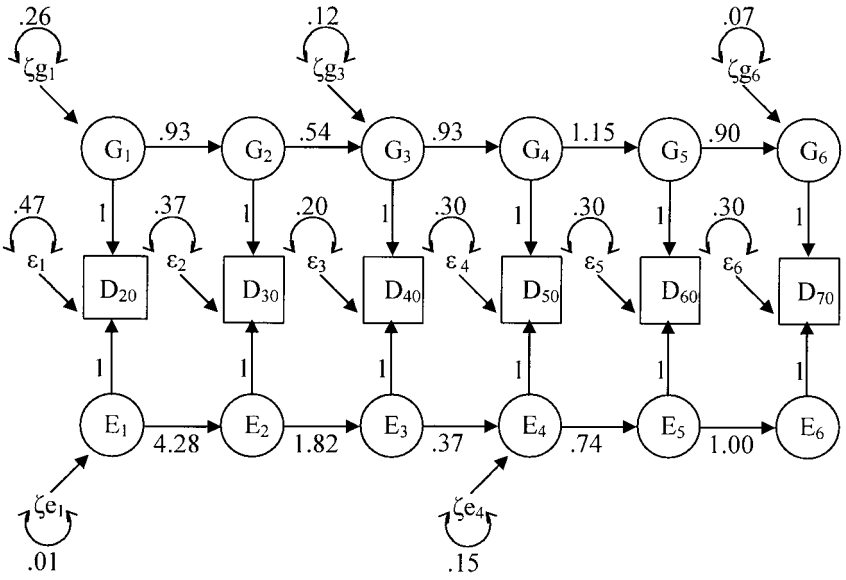

Figure 3

Best fitting simplex model for female depression with unstandardized variance components and path coefficients.

Note: $G_1 - G_6$ = additive genetic effects, $E_1 - E_6$ = non-shared environmental effects, ζg = additive genetic innovations, ζe = non-shared environmental innovations, ε = error terms (where $\varepsilon_5 = \varepsilon_6$)

Table 4

Multivariate Model Fitting Results for the Longitudinal Measures of Male Anxiety

Model	–2LL	*df*	Δ–2LL	Δ*df*	*p*
Cholesky					
ACE	12442.37	4906			
AE	12443.07	4921	0.70	15	1.00
CE	12461.09	4921	18.72	15	.23
E	12559.97	4936	117.60	30	<.001
Simplex					
ACE	12447.82	4920			
AE	12448.77	4929	0.95	9	1.00
CE	12465.63	4929	17.71	9	<.05
E	12561.06	4938	113.24	18	<.001
AE Simplex sub-model					
Drop ζg_2	12448.90	4930	0.14	1	.71
Drop ζg_3	12448.77	4930	0.00	1	1.00
Drop ζg_4	12448.77	7930	0.00	1	1.00
Drop ζg_5	12449.58	4930	0.82	1	.37
Drop $\zeta g_2 - \zeta g_5$	12449.71	4933	0.95	4	.92
Drop ζe_2	12448.77	4930	0.00	1	1.00
Drop ζe_3	12448.93	4930	0.17	1	.68
Drop ζe_4	12448.77	4930	0.00	1	1.00
Drop ζe_5	12448.77	4930	0.00	1	1.00
Drop $\zeta e_2 - \zeta e_5$	12448.93	4933	0.17	4	1.00
Drop $\zeta g_2 - \zeta g_5$ & $\zeta e_2 - \zeta e_5$	12449.86	4937	1.10	8	1.00

Note: –2LL = –2 × Log Likelihood
$\zeta g_1 - \zeta g_5$ = Additive genetic effects for age intervals 20–29 through to 60+ yrs
$\zeta e_1 - \zeta e_5$ = Additive genetic effects for age intervals 20–29 through to 60+ yrs

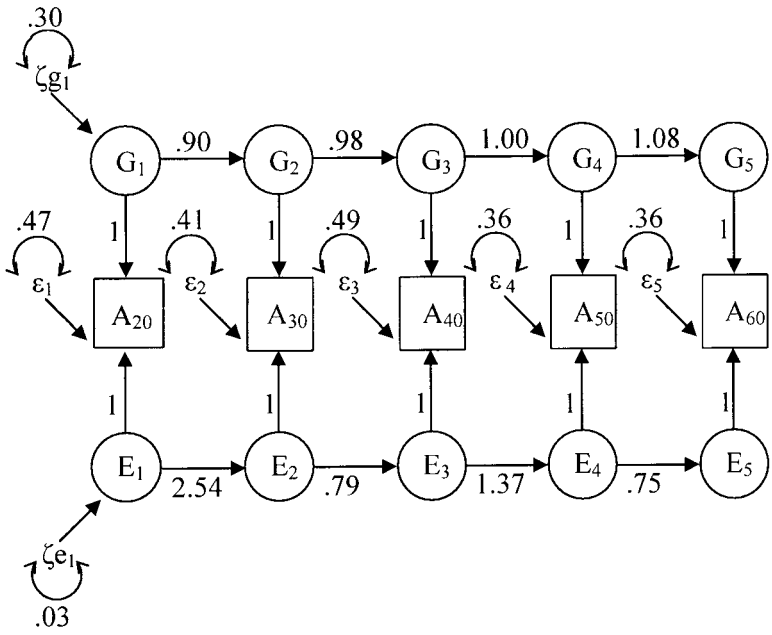

Figure 4

Best fitting simplex model for male anxiety with unstandardized variance components and path coefficients.

Note: $G_1 - G_5$ = additive genetic effects, $E_1 - E_5$ = non-shared environmental effects, ζg = additive genetic innovations, ζe = non-shared environmental innovations, ε = error terms (where $\varepsilon_5 = \varepsilon_6$)

Table 5

Multivariate Model Fitting Results for the Longitudinal Measures of Male Depression

Model	–2LL	*df*	Δ–2LL	Δ*df*	*p*
Cholesky					
ACE	11429.89	4906			
AE	11430.82	4921	0.93	15	1.00
CE	11443.80	4921	13.91	15	.53
E	11534.65	4936	104.75	30	< .001
Simplex					
ACE	11438.28	4920			
AE	11439.62	4929	1.34	9	1.00
CE	11451.14	4929	12.86	9	.17
E	11537.99	4938	99.71	18	< .001
AE Simplex sub-model					
Drop ζg_2	11439.73	4930	0.12	1	.73
Drop ζg_3	11439.62	4930	0.00	1	1.00
Drop ζg_4	11439.62	4930	0.00	1	1.00
Drop ζg_5	11441.41	4930	1.80	1	.18
Drop $\zeta g_2 - \zeta g_5$	11441.54	4933	1.92	4	.75
Drop ζe_2	11439.62	4930	0.00	1	1.00
Drop ζe_3	11439.62	4930	0.00	1	1.00
Drop ζe_4	11439.62	4930	0.00	1	1.00
Drop ζe_5	11439.62	4930	0.00	1	1.00
Drop $\zeta e_2 - \zeta e_5$	11439.62	4933	0.00	4	1.00
Drop $\zeta g_2 - \zeta g_5$ & $\zeta e_2 - \zeta e_5$	11441.54	4937	1.92	8	.98

Note: –2LL = –2 × Log Likelihood
$\zeta g_1 - \zeta g_5$ = Additive genetic effects for age intervals 20–29 through to 60+ yrs
$\zeta e_1 - \zeta e_5$ = Additive genetic effects for age intervals 20–29 through to 60+ yrs

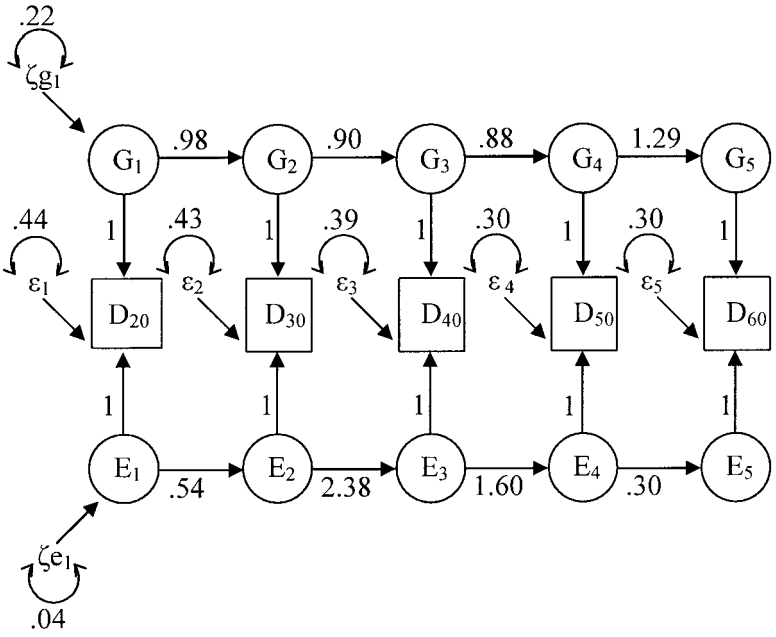

Figure 5

Best fitting simplex model for male depression with unstandardized variance components and path coefficients.

Note: $G_1 - G_5$ = additive genetic effects, $E_1 - E_5$ = non-shared environmental effects, ζg = additive genetic innovations, ζe = non-shared environmental innovations, ε = error terms (where $\varepsilon_5 = \varepsilon_6$)

subject was followed up for a maximum of 15 years. The current analyses were also based on a population-based sample using a short continuous measure of mood and affect. The scale's immediate advantage was the cost of administration and even though the items were worded to capture "recently experienced" symptoms of anxiety and depression, the factor scores were stable over time.

Despite the benefits of economy and reliability, a common criticism of continuous measures is that they do not constitute formal clinical diagnoses. In addition, the environmental risk factors contributing to depression as measured by continuous indices versus formal categorical diagnoses may not be the same. Foley and colleagues examined the degree to which self-report continuous measures of depression provided a reliable index of lifetime history of major depression (Foley et al., 2001). The authors found that after adjusting for diagnostic unreliability and temporal fluctuations, the genetic correlation between lifetime history of major depression and the self-report measures was .70 (Foley et al., 2001) whereas the non-shared environmental correlation between the same indices was only .24 (Foley et al., 2001). This suggests that while self-report measures do in fact provide a very good index of the genetic risk for lifetime history of major depression, the non-shared environmental effects underpinning continuous measures do not.

Foley and colleagues have also argued that the size of their cross-time environmental factor correlation meant that self-report measures of recently experienced psychological distress were more likely capturing risk factors "proximal" to the time of measurement, and hence represented only a subset of risk factors for lifetime history of major depression which accrue over the lifetime such as persistent interpersonal problems and stressful life events (SLEs; Foley et al., 2001). Since the DSSI items were reworded to capture only recently experienced distress, the variance attributable to error cannot therefore preclude the presence of non-shared environmental or "state" effects, whereas the non-shared environmental innovations and transmission coefficients measure enduring environmental risks. Since state effects are likely to include transitory environmental and psychological effects which can alter symptom levels (Duncan-Jones et al., 1990) within the 10-year age intervals, this explains why the error terms were much larger than the non-shared environmental innovation parameters.

Although evidence suggests that there are no overall gender differences in terms of the liability to report or experience stressful life events, significant gender differences do exist in relation to specific SLEs (Kendler et al., 2001c). For instance, males report significantly higher rates of job loss, legal problems, robbery and work-related problems whereas females report a greater frequency of housing problems, loss of confidant, problems getting along with, and crises involving, individuals in close social networks (Kendler et al., 2001c), most of which are also likely to have different onset times. It is also worth considering that contrary to the expectation of being entirely random, there is empirical evidence which suggests that the frequency and occurrence of SLEs is also partly under genetic control (Plomin et al., 1990; McGue & Lykken, 1992; Kendler et al., 1993a; Jockin et al., 1996; Kendler et al., 2001b).

The above analyses remain exploratory since the models which we fitted were not exhaustive. Other possible modeling strategies include biometric growth models (Neale & McArdle, 2000) which we intend to investigate in the future. Nevertheless, our simplex model-fitting approach provides a significant advance in terms of our understanding of the stability of genetic and environmental effects causing variation in the symptoms of anxiety and depression throughout life.

Conclusions

In both males and females, most genetic and environmental determinants of depression and anxiety are evident by age 20. This has important implications for planning of large scale universal or indicated prevention programs (see Hickie, 2002). If we are to have major effects on incidence then we need to target environmental interventions that modify genetic risk by the adolescent years. Our finding of a small but near significant genetic innovation for female depression at later ages lends support to the notion of attempting to reduce anxiety in early or mid-life to prevent later depression, as well as reducing other possible risk factors (e.g., vascular disease) in older persons.

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