# Disentangling gene-environment correlations and interactions on adolescent depressive symptoms

# Jennifer Y.F. Lau,<sup>1,2</sup> and Thalia C. Eley<sup>1</sup>

<sup>1</sup>Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK; <sup>2</sup>Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institute of Health, Bethesda, USA

Background: Genetic risks for depression may be expressed through greater exposure towards environmental stressors (gene-environment correlation, rGE) and increased susceptibility to these stressors (gene-environment interaction,  $G \times E$ ). While these effects are often studied independently, evidence supports their co-occurrence on depression. Methods: Adolescent twin and sibling data was used to assess correlations and interactions between genetic risks for depressive symptoms and two putative environmental stressors: dependent negative life events and maternal punitive discipline. Results: Moderate genetic effects influenced each environmental risk factor, consistent with rGE. Genetic effects on environmental risks also contributed to depressive outcomes, implying genetic correlations between measures. Genetic effects on depressive symptoms changed across levels of negative life events and maternal punitive discipline, consistent with  $G \times E$ . Finally,  $G \times E$  cooccurred with rGE on depressive outcomes. Conclusions: Adolescents at genetic risk for depressive phenotypes may be exposed to increased social adversity (rGE) and more susceptible to developing symptoms in response to these risks ( $G \times E$ ). **Keywords:** Gene-environment interaction, gene-environment correlation, adolescence, depressive symptoms. Abbreviations: AIC: Akaike's Information Criterion; DZ: Dizygotic; rGE: gene-environment correlation;  $G \times E$ : gene-environment interaction; FS: full sibling; MZ: monozygotic; RMSEA: root mean square error approximation; SMFQ: short Mood and Feelings Questionnaire.

Depressive conditions increase dramatically in adolescence (Hankin et al., 1998), often continuing into adulthood (Pine, Cohen, Cohen, & Brook, 1999). Studying risk mechanisms in adolescence may inform preventative interventions to attenuate later negative outcomes. Explanations for adolescent depression span nature and nurture, with moderate genetic and substantial non-shared (individual-specific) environmental contributions (Rice, Harold, & Thapar, 2002). Putative environmental factors include provoking and chronic stressors, such as life events and negative family relationships (Goodyer, 1990). Recent approaches in psychopathology emphasise the interplay between genetic and environmental influences as important risk mechanisms (Rutter & Silberg, 2002). Gene-environment correlations (rGE) occur when genetic factors influence exposure to certain environmental risks, arising through three processes. Passive rGE occurs when the parental genotype shapes aspects of the family environment (e.g., marital problems). Evocative rGE arises when individuals' genetic dispositions (e.g., negative temperament) evoke certain reactions from others (e.g., maladaptive parenting). Finally, active rGE occurs when individuals select, create and modify their environmental experiences based on genetic dispositions. Gene-environment interactions

 $(G \times E)$  arise when one variable's effects (on a phenotype) vary across levels of another, such as when environmental effects differ across genetic risk levels or when genetic effects change according to environmental exposure.

rGE in adolescence is supported by findings that aspects of the social environment, including life events and negative parent-child relationships, are heritable. Importantly, genetic contributions to these social factors also contribute to depressive symptoms (Lau, Rijsdijk, & Eley, 2006; Pike, McGuire, Hetherington, Reiss, & Plomin, 1996; Rice, Harold, & Thapar, 2003; Silberg et al., 1999; Thapar, Harold, & McGuffin, 1998), implying that genetic risks for depression also increase exposure to high-risk environments. Quantitative and molecular studies attest to  $G \times E$  in adolescence, converging on findings that social factors modify genetic risks on depression (Eley et al., 2004; Silberg, Rutter, Neale, & Eaves, 2001; Eaves et al., 2003).

Although gene-environment correlations and interactions are typically studied independently, several statistical and conceptual reasons warrant joint assessment. First, the presence of rGE may lead to false conclusions of  $G \times E$ . Greater genetic effects for depression at higher environmental risk levels could imply  $G \times E$ . Yet this pattern could also reflect greater frequencies of individuals with a particular genotype in those environments, arising from

© 2008 The Authors

Conflict of interest statement: No conflicts declared.

Journal compilation © 2008 Association for Child and Adolescent Mental Health.

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

rGE (Rutter & Silberg, 2002). Second, multicollinearity arising from correlations between genetic effects on the 'environment' and those influencing depression may reduce the power of detecting interactions between the environmental factor and the remaining genetic component on the phenotype (Purcell, 2002). Thus in the presence of positive findings, one cannot discriminate between 'true' interactions from spurious gene–environment correlations, whilst the absence of positive findings may arise from genetic correlations between the environment and the phenotype.

To minimise biases associated with rGE, studies of G × E have only considered stressors showing negligible genetic influence. However, as rGE is likely to co-occur with  $G \times E$  on depression (Eaves et al., 2003), this restrictive use of environmental risk data is over-simplistic. Indeed studies have found that the same environmental risk (e.g., life events) is involved in both gene-environment correlation and interaction on depression (Silberg et al., 1999; Silberg et al., 2001). Similarly, the same genetic factor contributed towards environmental risk exposure (rGE) and interacted with its occurrence  $(G \times E)$  in another study (Eaves et al., 2003). This co-existence of rGE and  $G \times E$  argues for joint assessment, yet differentiation of these forms of interplay. To our knowledge only one study has modelled and demonstrated the simultaneous effects of both on adolescent depression (Eaves et al., 2003). Genes for depressive symptoms first influenced exposure to negative life events (rGE). While life events had main effects on depression, they also interacted with genetic factors on symptoms ( $G \times E$ ). These interactions occurred between genetic factors previously implicated in life events exposure and genetic factors specific to depression. Thus both the same environmental (life events) and genetic influences were involved in both rGE and  $G \times E$ .

The present study aimed to replicate these seminal findings using another model-fitting approach (Purcell, 2002). We explored interactions and correlations between genetic risk for depressive symptoms and environmental factors in four steps, focusing on two environmental factors: dependent negative life events, which arise in part from an individual's behaviour and are likely to reflect greater genetic effects; and maternal punitive discipline, an aspect of the family environment likely influenced by parental genotype. First, to test rGE, we assessed genetic influences on negative life events and maternal punitive discipline. Next, we investigated genetic overlap between each environmental factor and depressive symptoms to yield support for genetic correlation. Third, we assessed changes in genetic effects across negative life events and maternal punitive discipline, to test  $G \times E$ . As this method estimates main effects of the environmental risk on depressive symptoms, it protects against spurious detection of  $G \times E$ . Yet correlations between the environmental factor and depressive symptoms may also influence failure to detect  $G \times E$ . Thus joint analysis of  $G \times E$  and rGE is implemented in the final analysis. We also addressed whether the same aetiological factors are involved in both rGE and  $G \times E$ .

### Method

#### Sample

Twins and siblings from the G1219 longitudinal study were recruited through a random selection of twins born between 1985 and 1988 and the offspring of adults from a large-scale population-based study (see Lau et al., 2006). Initial invitations to complete a depression rating scale (Wave 1) were returned by 47% and 40% of individuals in each group. Following initial replies, all twins and siblings aged 12 to 19 years were sent further questionnaires (N = 1,820 families), comprising Wave 2 data, used in the current analyses. Questionnaires were returned by 2,651 individuals from 1,372 families (73% of the Wave 1 sample). Informed consent was obtained from parents of adolescents under 16 and from adolescents themselves when over 16. Ethical approval for the study was given by the Research Ethics Committee of the Institute of Psychiatry and South London and Maudsley NHS Trust. Mean age of participants was 15 years (SD = 20 months, range 12-21). Of the sample, 56.1% was female. Zygosity was established using a parent-report questionnaire that discriminates monozygotic (MZ) and dizygotic (DZ) twins with an accuracy of over 90%, from physical similarity (Cohen, Dibble, Grawe, & Pollin, 1975). Zygosity was assigned using full agreement of the same measure at two time-points, yielding more stringent classifications. This gave 68 MZ male twin pairs, 199 MZ female twin pairs, 138 DZ male twin pairs, 190 DZ female pairs and 463 opposite-sex DZ pairs. 235 pairs of unknown zygosity were excluded from analyses. Data from 109 male sibling pairs, 132 female sibling pairs and 186 opposite-sex sibling pairs were also used.

To assess the representativeness of the G1219 sample relative to the general population, we compared the distribution of parental educational qualifications and home ownership status to that of a large national sample of parents of 10,000 5- to 15-year-olds (Meltzer, Gatward, Goodman, & Ford, 2000). G1219 parents had somewhat higher educational levels (39% versus 32% educated to  $\ensuremath{\bar{A}}\xspace$  level  $^1$  or above) and levels of house ownership (82% versus 68%) compared to the national sample. To reduce initial response biases associated with parental education levels, we created a sampling weight to match the distribution of educational qualifications in the national sample. To account for attrition between waves, a response weight from the inverse of the predicted probability of families remaining at Wave 2 was constructed using significant predictors. Girls and individuals whose parents had higher educational qualifications and were owner-occupiers were more likely to respond at Wave 2. The response weight was

<sup>&</sup>lt;sup>1</sup>Internationally recognised pre-university qualifications, typically taken at age 18.

then multiplied by the sampling weight to provide a single weighting variable, used in all analyses to account for biases associated with initial response and attrition rates. Weights compensate for unequal response rates among individuals from different social strata by adjusting parameter estimates to allow population inferences of results.

#### Measures

Self-reported data on depressive symptoms, negative life events and maternal punitive discipline at Wave 2 were used for these analyses. Depressive symptoms were measured by the short Mood and Feelings Questionnaire (Angold et al., 1995) consisting of 13 items assessed over the past two weeks. Molecular genetic analyses of extreme depression in G1219 (Eley et al., 2004) warranted using a four-point response format (never, sometimes, often, always), allowing better discrimination of lower scores. Items were summed to generate total symptom scores. The SMFQ has good internal consistency (Cronbach's alpha = .90); adequate test-retest reliability (.66) (Angold et al., 1995; Costello & Angold, 1988); correlates well with other measures (.67 with Children's Depressive Inventory) (Angold et al., 1995); and is reasonably sensitive (.60-.75) and specific (.61-.74) when discriminating depressed from non-depressed cases (Thapar & McGuffin, 1998). Cronbach's alpha indexing internal consistency in our sample was .90.

The Life Events Scale for Adolescents (Coddington, 1984) is a checklist of 50 events requiring some social readjustment by individuals following their occurrence. Twenty-four sum as a total negative event scale, 12 are 'independent' (e.g., death of a parent) and 12 are 'dependent' (e.g., break-up with boy/girlfriend), classified over their likelihood of arising from an individual's behaviour. As twin designs are illequipped to estimate heritability of measures obligatorily shared among siblings (Purcell & Koenen, 2005), independent events were excluded from the negative events scale, retaining only dependent negative events.<sup>2</sup> This decision was further reinforced by conceptual considerations that greater genetic effects were expected for dependent than independent negative events, as these may occur partially from an individual's behaviour.

Maternal punitive discipline was assessed by the Negative Sanctions sub-scale, adapted from a well-validated parent-child relationship measure (Hetherington & Clingempeel, 1992). Only maternal parenting data was used for the present analyses. Cronbach's alpha for this sub-scale has been calculated at .66 (O'Connor, Dunn, Jenkins, Pickering, & Rasbash, 2001). It correlates well with other related questionnaires. Cronbach's alpha of the scale in our sample was .80.

#### Statistical analyses

Both descriptive and model-fitting analyses were performed with Mx (Neale, 1997). This software controls for non-independence of data from family members and incorporates weighting variables into descriptive and model-fitting analyses.

Descriptive statistics were derived through saturated models that estimate the variance, covariance and means of all variables. Group differences associated with sex and zygosity were tested by comparing models where means were constrained across males and females or zygosity groups with models where means differed across these groups. Significant differences in fit between models ( $\chi^2$ ) index significant group effects.

Four sets of model-fitting analyses were performed separately on negative life events and maternal punitive discipline data. First, univariate models partitioned variance of each measure into genetic and environmental effects. Genetic contributions to putative environmental measures support gene-environment correlation. Genetic  $(a^2)$ , shared environmental  $(c^2)$  and non-shared environmental (e<sup>2</sup>) estimates were derived by comparing within-pair similarity among MZ twins, who share 100% of their genetic makeup, and DZ twins (and full siblings (FS)), who share on average 50% of genes. Higher MZ compared to DZ and FS resemblance is attributed to increased genetic similarity among MZ twins and used to estimate heritability. Within-pair similarity not due to genetic factors is assigned as shared environmental variance. Non-shared environmental influences are estimated from within-pair MZ differences and also include measurement error. Sex differences in the decomposition of variance into different sized or types of genetic and environmental parameters (quantitative and qualitative sex effects respectively), and in the overall variance of each measure are tested through sub-models.

Next, bivariate Cholesky decomposition models parameterised the covariance between depressive symptoms and each environmental measure into 'common factors' ( $A_1$ ,  $C_1$ ,  $E_1$ ) influencing both depressive symptoms and the environmental factor, and 'specific factors' ( $A_2$ ,  $C_2$ ,  $E_2$ ) unique to depressive symptoms (Figure 1). Although any ordering of the variables explains the variance-covariance matrix between variables equally well, the order influences interpretation of results, and is often justified by hypothesised causal or temporal relationships between variables. In these analyses, the order of variables is



**Figure 1** Bivariate genetic analysis of environmental risk and depressive symptom data for one member of a twin/sibling pair

<sup>&</sup>lt;sup>2</sup>A full list of items used is given in Appendix A.

consistent with theories that environmental variables predict subsequent depressive symptoms. Total genetic variance on depression is composed of common genetic ( $a_c$ ) and unique genetic ( $a_u$ ) effects (Figure 1), defined according to whether they are shared or specific to depression. The proportion by which the 'common' (shared) factor explains total genetic variance on depression is calculated as:  $a_c/a_c + a_u$ , and indexes the extent of genetic overlap (or correlation) with the environmental factor. Similarly,  $c_c/c_c + c_u$  and  $e_c/e_c + e_u$  indicate shared and non-shared environmental overlap between the environmental factor and depression.

Third, models of gene-environment interaction incorporated interaction coefficients into univariate models to test environmental moderation of genetic effects on depressive symptoms (Figure 2). Genetic paths to the phenotype were redefined as linear functions of the environmental 'moderator' (M) (Purcell, 2002): a +  $\beta_X$ M where 'a' represents 'main' genetic effects and  $\beta_{\rm X}$  is a regression coefficient marking the extent to which genetic effects change as a function of the moderator. Thus the significance of  $\beta_X$  indicates moderation of genetic effects on depressive symptoms by environmental risk, or linear gene-environment interaction. Interactions between shared and non-shared environmental effects on depressive symptoms with an environmental moderator are similarly re-expressed as  $c + \beta_Y M$  and e +  $\beta_Z$ M and tested by the significance of each beta term. Main effects of the environmental moderation on depression were included in the model by redefining the estimated mean ( $\mu$ ) of depression as:  $\mu + \beta_m M$  where  $\beta_X$  is the standardised regression coefficient when predicting the phenotype from the moderator.

The final analysis explored *joint models of gene–environment correlation and interaction*. Employing similar principles, the bivariate Cholesky decomposition is extended to include interaction terms representing environmental moderation of paths (Figure 3). Gene– environment correlation and genetic correlations between environmental risk and depressive symptoms are reflected by the common genetic path (a<sub>c</sub>) influencing both the environmental risk and depressive symptoms. Re-defining this common genetic path on depression as a linear function of the environmental moderator (a<sub>c</sub> +  $\beta_{xc}$ M) within the bivariate model allows assessment of gene–environment interaction in the presence of gene– environment correlation. Genetic effects involved in *both* correlation and interaction with the environment are



**Figure 2** Univariate model of gene–environment interaction on depressive symptoms for one member of a twin or siblings pair



**Figure 3** Bivariate model incorporating interactions between environmental measures and latent genetic and environmental effects on depressive symptoms whilst assessing genetic correlation between the environmental measure and depressive symptoms for one member of a twin or sibling pair

distinguished by the significance of the interaction term associated with the common genetic factor ( $a_c + \beta_{xc}M$ ) contributing to both the environmental risk and depression. The significance of the interaction coefficient associated with unique genetic factor ( $a_u + \beta_{xu}M$ ) indicates that a different genetic factor is involved in correlation and interaction with the environment.

Interactions between the environmental risk and shared and non-shared environmental effects were specified using these principles (Figure 2). Any overlap in shared and non-shared environmental variance between the environmental risk measure and depression is explained by the 'common' set of factors ( $C_c$  and  $E_c$ ) contributing to both measures. Expressing these 'common' paths as linear functions of the moderator ( $c_c + \beta_{vc}M$  and  $e_c + \beta_{zc}M$ ) allows similar assessment of an environmentenvironment interaction in the context of sharing a common environmental risk. Estimating interaction between non-shared environmental effects and the environmental measure forms a critical test of geneenvironment interactions, that the results are not explained by increasing error variance in individuals reporting higher levels of environmental risk (heterodasticity) (Wichers et al., 2002). Unlike the univariate model of gene-environment interaction, no single term representing main effects of the environmental moderator on the phenotype is estimated. Instead this model assumes that all main effects are included in the 'common' genetic, shared and non-shared environmental paths shared between the environmental moderator and the phenotype.

Chi-square, Akaike's information criterion (AIC) and root mean squared error approximation (RMSEA) indexed model-fit. Lower  $\chi^2$  values, more negative AIC and values of RMSEA below .10 generally indicate good fit and parsimony. Sex differences in univariate models were determined by selection of the sub-model with the lowest fit statistics. Significant sex effects in the decomposition of variance into different sized or types of genetic and environmental parameters were incorporated in subsequent bivariate and interaction models by allowing separate parameters (A, C and E) for males and females. Significant sex differences in the overall variance of measures were included in subsequent models

#### © 2008 The Authors

|              | MZ twins      |       | DZ twins |      |              |      | Full siblings |       |              |       |
|--------------|---------------|-------|----------|------|--------------|------|---------------|-------|--------------|-------|
|              |               |       |          |      | Opposite-sex |      |               |       | Opposite-sex |       |
|              | М             | F     | М        | F    | М            | F    | М             | F     | М            | F     |
| Depressive   | symptoms      |       |          |      |              |      |               |       |              |       |
| Mean         | 5.84          | 8.03  | 6.92     | 8.77 | 6.99         | 9.05 | 6.73          | 10.98 | 8.03         | 10.27 |
| SD           | 4.71          | 6.99  | 5.58     | 7.22 | 5.84         | 6.73 | 5.16          | 7.73  | 6.17         | 7.84  |
| $N^{a}$      | 313           | 392   | 250      | 374  | 324          | 331  | 104           | 181   | 114          | 133   |
| r            | .30           | .50   | .13      | .39  | .24          |      | .21           | .21   | .32          |       |
| Negative lif | e events      |       |          |      |              |      |               |       |              |       |
| Mean         | 1.70          | 1.70  | 2.01     | 1.94 | 1.92         | 1.80 | 1.80          | 1.91  | 1.88         | 2.01  |
| SD           | 1.82          | 1.75  | 1.89     | 1.82 | 1.81         | 1.78 | 1.67          | 1.86  | 1.60         | 1.81  |
| $N^a$        | 313           | 387   | 248      | 376  | 323          | 335  | 103           | 184   | 114          | 131   |
| R            | .57           | .50   | .42      | .41  | .35          |      | .03           | .35   | .45          |       |
| Maternal p   | unitive disci | pline |          |      |              |      |               |       |              |       |
| Mean         | 7.69          | 7.18  | 7.12     | 7.87 | 7.17         | 6.97 | 6.61          | 6.52  | 6.24         | 6.93  |
| SD           | 4.02          | 3.82  | 3.51     | 3.84 | 3.70         | 3.55 | 3.62          | 3.71  | 3.46         | 3.88  |
| $N^{a}$      | 289           | 365   | 226      | 353  | 301          | 325  | 96            | 174   | 107          | 129   |
| R            | .55           | .53   | .29      | .38  | .30          |      | .47           | .40   | .30          |       |

**Table 1** Data for depressive symptoms, negative life events and maternal punitive discipline scores at Wave 2 of the G1219 sample in MZ, DZ and FS pairs (SD = deviation; N = number of participants; r = correlation)

<sup>*a*</sup>This refers to the number of individuals.

by estimating sex-specific scalar terms. Significant interactions in the final two models are indicated through a significant change in model-fit ( $\chi^2$ ) following removal of the respective coefficient terms from the model. All models were fit to age-regressed and where appropriate log-transformed scores, minimising mean age effects and correcting for positive skew. Environmental measures were standardised to reflect deviations from the mean rather than absolute values. Separate means for each sex by zygosity group minimised mean sex or zygosity effects. Gene–environment interactions were tested without these modifications with few changes to overall result patterns.

#### Results

#### Descriptive analyses

Table 1 presents descriptive data for depression symptoms, negative life events and maternal punitive discipline across male and female twins and siblings. Girls reported significantly higher depressive scores (mean = 8.92 for females and 6.54 for males) but were similar to boys in negative life events (means = 1.83 for females and 1.85 for males) and maternal punitive discipline (means = 7.09 for females and 6.97 for males). Full siblings showed higher depressive scores and less maternal punitive discipline compared to twins in both sexes, and DZ and full sibling females reported more life events than MZ females. Age correlated modestly with symptom scores (r = .06, p < .01). Older adolescents reported less punitive discipline (r = -.16, p < .001). No relationship between age and negative life events emerged (r = .01, n.s.). Depressive symptoms correlated with more negative life events (.33, p < .001)and maternal punitive discipline (.26, p < .001).

#### Univariate models

A model including male-female differences in overall variance but not in the decomposition of variance into genetic and environmental parameters presented best fit to depressive symptoms:-2LL = 6621.57, df = 2367,  $\chi^2(20) = 34.69$ , p = .02, AIC = -5.31, RMSEA = .07 as reported elsewhere (Lau et al., 2006). Thus parameter estimates apply to the whole sample, revealing moderate genetic effects of 40% (21–55%), minimal shared environmental input of 9% (0-23%) and substantial non-shared environmental influences of 51% (44-59%). A model including no sex effects fit negative life events and maternal punitive discipline data best. Fit statistics were: -2LL = 6140.54, df = 2438,  $\chi^2(21) = 31.66$ , p = .06, AIC = -10.34, RMSEA = .02 for negative life events and -2LL = 5904.73, df = 2352,  $\chi^2(21) =$ 13.77, p = .88, AIC = -28.23 for maternal punitive discipline. RMSEA was incalculable for the latter model but the low  $\chi^2$  suggests good fit. Parameter estimates were similar for negative life events and maternal punitive discipline. Genetic effects were **37%** (16–52%) and **31%** (12–50%) respectively; shared environmental contributions were 7% (0-21%) and **19%** (5-33%); and non-shared environmental influences were 56% (48-65%) and **50%** (43–58%).

#### Bivariate models

Results of bivariate Cholesly decomposition models are displayed in Table 2, divided into effects of common factors (A<sub>1</sub>, C<sub>1</sub>, E<sub>1</sub>) on the environmental measure and depressive symptoms, and effects of unique factors (A<sub>2</sub>, C<sub>2</sub>, E<sub>2</sub>) on depressive symptoms.

|   | Common effects<br>on environmental risk |                                    |                                      | Common effects on depressive symptoms |                        |                  | Specific effects on<br>depressive symptoms |             |             |
|---|---|------------------------------------|--------------------------------------|---------------------------------------|------------------------|------------------|--|-------------|-------------|
|   | $a_{M}^{2}$                             | $c_{\rm M}^2$                      | $e_{\rm M}^2$                        | $a_{C}^{2}$                           | $c_{C}^{2}$            | $e_{\rm C}^2$    | $a_{U}^{2}$                                | $c_{U}^{2}$ | $e_{U}^{2}$ |
| $\begin{array}{l} \text{DEP-NLE} \\ -2\text{LL} = 1259 \end{array}$ | 33 (13–48)<br>91.68, df = 486           | 9 (1–23)<br>60, $\chi^2$ (70) = 1  | 58 (50–67)<br>104.85, p = .01        | 8 (1−19)<br>, AIC = −35.              | 9 (0–23)<br>16, RMSEA  | 2 (1–4)<br>= .02 | 30 (17–42)                                 | 0 (0–13)    | 50 (44–57)  |
| $\begin{array}{l} \text{DEP-MPD} \\ -2\text{LL} = 1258 \end{array}$ | 32 (13–51)<br>83.12, df = 484           | 18 (3–32)<br>40, $\chi^2$ (70) = 8 | 50 (43–58)<br>84.79, <i>p</i> = .11, | 10 (1–34)<br>AIC = -55.2              | 0 (0–10)<br>1, RMSEA = | 1 (0–3)<br>= .01 | 26 (1–45)                                  | 11 (0–24)   | 52 (45–59)  |

**Table 2** Summary model-fitting statistics and parameter estimates with 95% confidence intervals of the bivariate models of depressive symptoms (DEP) and negative life events (NLE), and depressive symptoms (DEP) and maternal punitive discipline (MPD)

Bivariate models included a sex-specific scalar to account for male-female variance differences, but lack of sex differences in the size or type of genetic and environmental influences warranted equating parameter estimates across males and females. Both models fit well. Total genetic and environmental effects on each environmental measure mirror univariate findings. Similar results pertaining to genetic and environmental overlap with depressive symptoms characterised negative life events and maternal punitive discipline. Most of the genetic variation on depressive symptoms is specific, but significant genetic overlap with both negative life events and maternal punitive discipline was found. For negative life events, shared genetic effects explained 21% of the total genetic variance (8/8 + 30) on depressive symptoms whilst for maternal punitive discipline this proportion was 28% (10/10 + 26). Shared environmental effects on depression were non-significant with no significant overlap with either environmental measure. Non-shared environmental factors were largely specific to each measure.

#### Models of gene-environment interaction

Genetic paths ( $\beta_X$ ) to depressive symptoms were moderated by both environmental measures, evident by significant worsening in model-fit following removal of respective beta coefficients from the model:  $\Delta\chi^2(1) = 3.85$ , p = .05 and ( $\Delta\chi^2(1) = 8.61$ , p < .01). Non-shared environmental effects ( $\beta_Z$ ) varied across levels of maternal punitive discipline too ( $\Delta\chi^2(1) = 6.32$ , p = .05). Main effects of negative life events and maternal punitive discipline were significant ( $\Delta\chi^2(1) = 236.39$ , p < .001 and  $\Delta\chi^2(1) = 49.80$ , p < .001).

# Combined models of gene-environment correlation and interaction

Interactions between variance components and each environmental moderator were explored in the presence of genetic correlations between measures. Negative life events significantly moderated common genetic effects ( $\beta_{\rm xc}$ ) on depression:  $\Delta \chi^2(1) = 3.86$ , p < .05. Thus the best-fitting solution included one interaction term, yielding excellent fit: -2LL =

12113.12, df = 4698,  $\chi^2(69) = 69.96$ , AIC = -68.04, RMSEA = .03. Maternal punitive discipline moderated unique genetic ( $\beta_{xu}$ ,  $\Delta \chi^2(1) = 7.73$ , p < .01) and unique ( $\beta_{zu}$ ,  $\Delta \chi^2(1) = 5.62$ , p < .05) and common ( $\beta_{zc}$ ,  $\Delta \chi^2(1) = 5.12$ , p < .05) non-shared environmental effects on depression. Retaining significant interaction terms in the model gave excellent fit: -2LL =11273.58, df = 4316,  $\chi^2(67) = 70.91$ , AIC = -63.09, RMSEA = .03. Of note, as the 'common' genetic factor  $(\beta_{xc})$  was moderated by exposure to negative life events, this suggests that the same genetic influences were implicated in both correlation and interaction with negative life events. As the 'unique' genetic factor ( $\beta_{xu}$ ) was moderated by exposure to maternal punitive discipline, this suggests that distinct genetic effects contribute to correlation as those moderated by this parenting factor.

Figure. 4a and b plot changes in the total variance components (both common and unique variance) across raw environmental scores. These indicate that total phenotypic variance increases with greater negative life events and maternal punitive discipline. This may be driven by larger genetic variance at environmental extremes. For maternal discipline, larger non-shared environmental variance may also explain increased phenotypic variability.

### Discussion

The novelty of the current study lies in its integrated analysis of rGE and  $G \times E$  on depression across two putative environmental risk factors. Moderate genetic influences were found on negative life events and maternal punitive discipline that also contributed to depressive symptoms. Genetic risks for depressive symptoms changed significantly across levels of negative life events and punitive parenting, even after controlling for gene-environment correlations. Results showed increased phenotypic variance at higher levels of each environmental factor, tentatively attributing these to increased genetic effects. For maternal punitive discipline, increased variance may also be explained by larger non-shared environmental influences at higher risk levels. Whilst negative life events and maternal punitive discipline were involved in rGE and  $G \times E$ , distinct genetic



**Figure 4** (a) Plot of genetic variance of depressive symptom scores across negative life events, (b) Plot of genetic and non-shared environmental variance of depressive symptom scores across maternal punitive discipline.

factors contributed to each process with maternal discipline. However, the same genetic factor influenced life events and interacted with this stressor.

Previous findings demonstrating co-dependence of these forms of interplay on adolescent depressive outcomes (Eaves et al., 2003) were replicated, despite different analytic strategies (Markov Chain Monte Carlo versus Maximum Likelihood). Moreover these results applied to maternal discipline, another well-documented stressor on depression. These findings highlight the complexity of interplay between risk factors on depressive outcomes, beyond that typically explored in genetic designs. Whilst exciting implications follow, several limitations affect interpretation. First, although a large sample required for detecting interactions was used, fewer individuals reported extreme environmental risk levels, particularly life events. This means that power to detect genetic effects decreases at higher ends of the environmental spectrum. Confirming these results in samples selected for social adversity will prove valuable. Second, our cross-sectional design precluded inferences of temporality between rGE and  $G \times E$  on symptoms.

Additional limitations concern measurement. Depression was assessed using questionnaire measures of mood fluctuation in non-clinical subjects, cautioning against generalising findings to patients. Measurement of negative life events by a 'count' of recent dependent events may further reflect oversimplistic depictions of social adversity. Because these checklists rely on the presence (or absence) of an event, they minimise recall biases, comprising more 'objective' measures of life events. Yet more subjective elements such as personal appraisals of severity are omitted, leading to under- or over-estimations of the impact of events on outcome. Finally, self-reported measures of all three constructs may lead to a 'halo' effect where associations among measures are inflated by mood-dependent response biases. While it is possible that any shared genetic effects between environmental measures and depressive symptoms may reflect genetic influences on 'response style', reassuringly our pattern of findings is consistent with those of other studies using different reporters (Pike et al., 1996; Silberg et al., 2001).

Despite these caveats, our results also hold several theoretical implications on how genetic and environmental risks operate on adolescent depression. First, genetic risks for adolescent depression may be expressed through exposure towards dependent negative events and punitive parenting. Second, not only are individual differences on psychopathology accentuated during stress (Caspi & Moffitt, 1991) but genetic dispositions may have greater opportunity to show their effects. Thus social adversity may 'trigger' genetic risks, increasing the probability of developing symptoms. Intriguingly, Figure 1 suggests that levels of social adversity falling approximately one standard deviation away from the mean are adequate in evoking genetic risks. For maternal punitive discipline, genetic variance begins to increase approximately at a score of 4 (mean: 7.03, SD: 3.71), while for negative life events, genetic effects also rise after 4 events (mean: 1.84, SD: 1.81). Such patterns are suggestive of what levels of social adversity can be considered 'maladaptive'. Finally, our findings suggest that adolescents with greater genetic liability are exposed to environmental adversity and may be more susceptible towards risky environments. While provocative, these findings are only the first step in elucidating risk mechanisms.

rGE may emerge through three processes (Scarr & McCartney, 1983). First, they could be mediated *passively* through the parental genotype contributing to the offspring's genetic propensity for depression, through occurrence of familial stressors (e.g., parental divorce). Shared genetic effects between environmental factors and depressive symptoms could reflect *evocative* processes, where genetic risks for adolescent depression elicit negative reactions from others resulting in interpersonal stressors. Finally, genetic risks for depressive symptoms may be expressed through *active* life choices that alter exposure to negative stressors (e.g., failing exams). Differentiating between these different processes empirically has yet to be instantiated.

Processes mediating gene-environment interactions could include diathesis-stress factors identified at the level of candidate genes and associated neurobiological systems (Caspi et al., 2003; Eley et al., 2004); brain function and structure (Hariri et al., 2002); and personality factors or cognitive vulnerability. Thus greater genetic sensitivity to stress could be mediated through enhanced amygdala function. Additionally they may influence cognitive stress reactivity, e.g., negative attributions that then precipitate depressive symptoms (Lau et al., 2006). While pathways encompassing 'stress reactivity' should be depicted from DNA to the phenotype, links between levels also require study.

Finally, although replication for these results is essential, tentative analytical implications for molecular genetic studies examining associations between DNA polymorphisms and depression can be made. The presence of gene-environment interaction implies that unless studies control for environmental history, heterogeneity in samples could lead to false results. For example, 'control' individuals could possess genetic susceptibility but not manifest the phenotype due to lack of exposure to the relevant environment. Such a scenario may lead to no casecontrol differences in genotypic frequencies. Including measured environments such as dependent negative events, as well as maternal punitive discipline, in molecular genetic analyses may pre-empt avoiding false negative results.

In summary, we examined correlations and interactions between genetic risks on adolescent depressive symptoms and two environmental factors. Joint analyses ensure that the effects of one do not bias estimates of the other, whilst recognising their cooccurrence. Our findings pave the way for understanding intermediate processes through which interactions and correlations are expressed. Addressing these issues inevitably requires multidisciplinary approaches.

#### Acknowledgements

The G1219 study was supported by the W T Grant Foundation and by a Medical Research Council training fellowship to the second author. The first author was supported by a Medical Research Council doctoral studentship. We would like to thank the families who took part, and Robert Plomin, Abram Sterne, Richard Williamson, Pak Sham, Maria Napolitano and Alessandra Iervolino for support and help with the project, and Shaun Purcell and Fruhling Rijsdijk for support with the statistical procedures.

## **Correspondence to**

Jennifer Lau, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institute of Health, 15K North Drive, Bethesda, MD 20892-2670, USA; Tel: +1 301 435 5050; Email: lau j@mail.nih.gov

## References

- Angold, A., Costello, E.J., Messer, S.C., Pickles, A., Winder, F., & Silver, D. (1995). The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, 5, 1–12.
- Caspi, A., & Moffitt, T.E. (1991). Individual differences are accentuated during periods of social change: The sample case of girls at puberty. *Journal of Personality and Social Psychology*, *61*, 157–168.
- Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386–389.
- Coddington, R.D. (1984). Measuring the stressfulness of a child's environment. In J.H. Humphrey (Ed.), *Stress in childhood* (pp. 97–126). New York: AMS Press Inc.
- Cohen, D.J., Dibble, E., Grawe, J.M., & Pollin, W. (1975). Reliably separating identical from fraternal twins. *Archives of General Psychiatry*, *32*, 1371–1375.
- Costello, E.J., & Angold, A. (1988). Scales to assess child and adolescent depression: Checklists, screens, and nets. *Journal of the American Academy of Child and Adolescent Psychiatry*, 27, 726–737.
- Eaves, L., Silberg, J., & Erkanli, A. (2003). Resolving multiple epigenetic pathways to adolescent depression. *Journal of Child Psychology and Psychiatry*, 44, 1006–1014.
- Eley, T.C., Sugden, K., Gregory, A.M., Sterne, A., Plomin, R., & Craig, I.W. (2004). Gene–environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*, *9*, 908–915.
- Goodyer, I.M. (1990). Family relationships, life events and childhood psychopathology. *Journal of Child Psychology and Psychiatry*, *31*, 161–192.
- Hankin, B.L., Abramson, L.Y., Moffitt, T.E., Silva, A., McGee, R., & Angell, K.E. (1998). Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology*, 107, 128–140.
- Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M. F., & Weinberger, D.R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, 297, 400–403.
- Hetherington, E.M., & Clingempeel, W.G. (1992). Coping with marital transitions: A family systems perspective. *Monographs of the Society for Research in Child Development, 2–3* (Serial No. 227).
- Lau, J.Y.F., Rijsdijk, F.V., & Eley, T.C. (2006). I think, therefore I am: A twin study of attributional style in adolescents. *Journal of Child Psychology and Psychiatry*, 47, 696–703.
- Meltzer, H., Gatward, R., Goodman, R., & Ford, T. (2000). *Mental health of children and adolescents in Great Britain*. London: The Stationery Office.

- Neale, M.C. (1997). *Mx: Statistical modelling* (4th edn). Box 126 MCV, Richmond, VA 23298: Department of Psychiatry.
- O'Connor, T.G., Dunn, J.F., Jenkins, J.M., Pickering, K., & Rasbash, J. (2001). Family settings and children's adjustment: Differential adjustment within and across families. *British Journal of Psychiatry*, *179*, 110–115.
- Pike, A., McGuire, S., Hetherington, E.M., Reiss, D., & Plomin, R. (1996). Family environment and adolescent depressive symptoms and antisocial behaviour: A multivariate genetic analysis. *Developmental Psychology*, *32*, 590–603.
- Pine, D.S., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent depressive symptoms as predictors of adult depression: Moodiness or mood disorder? *American Journal of Psychiatry*, 156, 133–135.
- Purcell, S. (2002). Variance components models for gene–environment interaction in twin analysis. *Twin Research*, 5, 554–571.
- Purcell, S., & Koenen, K.C. (2005). Environmental mediation and the twin design. *Behavior Genetics*, 35, 491–498.
- Rice, F., Harold, G., & Thapar, A. (2002). The genetic aetiology of childhood depression: A review. *Journal of Child Psychology and Psychiatry*, 43, 65–79.
- Rice, F., Harold, G.T., & Thapar, A. (2003). Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psychology and Psychiatry*, 44, 977–987.
- Rutter, M., & Silberg, J. (2002). Gene–environment interplay in relation to emotional and behavioral disturbance. *Annual Review of Psychology*, 53, 463–490.
- Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype  $\rightarrow$  environmental effects. *Child Development*, 54, 424–435.
- Silberg, J., Pickles, A., Rutter, M., Hewitt, J., Simonoff,E., Maes, H., Carbonneau, R., Murrelle, L., Foley, D.,& Eaves, L.J. (1999). The influence of genetic factors

and life stress on depression among adolescent girls. *Archives of General Psychiatry*, *56*, 225–232.

- Silberg, J., Rutter, M., Neale, M., & Eaves, L. (2001). Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *British Journal of Psychiatry*, 179, 116–121.
- Thapar, A., Harold, G., & McGuffin, P. (1998). Life events and depressive symptoms in childhood–shared genes or shared adversity? A research note. *Journal of Child Psychology and Psychiatry*, *39*, 1153–1158.
- Thapar, A., & McGuffin, P. (1998). Validity of the shortened Mood and Feelings Questionnaire in a community sample of children and adolescents: A preliminary research note. *Psychiatry Research*, *81*, 259–268.
- Wichers, M.C., Purcell, S., Danckaerts, M., Derom, C., Derom, R., Vlietinck, R., & Van Os, J. (2002). Prenatal life and post-natal psychopathology: Evidence for negative gene-birth weight interaction. *Psychological Medicine*, 32, 1165–1174.

Manuscript accepted 5 June 2007

# Appendix A: Dependent negative life events scale

Becoming involved with drugs Being sent away from home Failing to achieve something you want Appearance in juvenile court Start of problem between you and parents Suspension from school Failing end of year exams Getting pregnant or fathering pregnancy Being responsible for a car accident Breaking up with boy/girlfriend Being told to break up with boy/girlfriend Being invited by a friend to break the law Copyright of Journal of Child Psychology & Psychiatry is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.