

Adolescent Irritability: Phenotypic Associations and Genetic Links With Depressed Mood

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Objective: Irritability has been proposed to underlie the developmental link between oppositional problems and depression. Little is known, however, about the genetic and environmental influences on irritability and its overlap with depression. Drawing on the notion of “generalist genes” (genes of general effect that underlie phenotypic overlap between disorders), the authors test the hypothesis that the association between irritability and depression is accounted for by genetic factors.

Method: Data from the G1219 study, a U.K. twin/sibling sample (N=2,651), were used in a cross-sectional and longitudinal design. The irritable and headstrong/hurtful dimensions of oppositional behavior were derived using factor analysis. Regression was used to estimate the association between depression and delinquency. Multivariate genetic analyses were used to estimate the genetic overlaps between the two components of oppositionality (irritability and headstrong/hurtful behaviors) and depression and delinquency.

Results: Irritability showed a significantly stronger phenotypic relationship with depression than with delinquency, whereas headstrong/hurtful behaviors were more strongly related to delinquency than to depression. In multivariate genetic analyses, the genetic correlation between irritability and depression ($r_A=0.70$, 95% CI=0.59–0.82) was significantly higher than that between irritability and delinquency ($r_A=0.57$, 95% CI=0.45–0.69); conversely, the genetic correlation between headstrong/hurtful behaviors and delinquency ($r_A=0.80$, 95% CI=0.72–0.86) was significantly higher than that between headstrong/hurtful behaviors and depression ($r_A=0.46$, 95% CI=0.36–0.57). In longitudinal models, the phenotypic association between irritability at wave 2 and depression at wave 3 was accounted for by the genetic association between irritability and depression at wave 2.

Conclusions: These findings are consistent with the theory that genes with general effects underlie the relationship between irritability and depression.

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Irritable mood, a common and impairing symptom in psychopathology (1–3), has been proposed to underlie the developmental link between oppositional problems in youth and depression in adulthood (4, 5). However, little is known about the genetic and environmental influences on irritability and its overlap with psychiatric disorders.

An unexplained aspect of developmental psychopathology concerns the transition from disruptive behavior problems to mood and anxiety problems (6). A striking example is the recent finding that oppositionality in youth is a potent predictor of depression in young adult life, over and above depression in early life (7). It has recently been proposed that irritable mood may explain this transition from oppositionality to later depression (5, 7, 8). Data suggest that oppositionality in youth comprises at least two dimensions with differential predictions (9–12): an irritable dimension, more strongly associated with depressive disorders than with antisocial behaviors; and a headstrong/hurtful dimension (capturing argumentativeness and rule breaking alongside spiteful behaviors), more

strongly associated with antisocial behaviors than with depressive disorders (5, 11, 12). These differential associations have been demonstrated in a series of longitudinal studies spanning childhood into adulthood (5, 11).

It remains unknown whether such differential phenotypic links are accounted for by genetic or environmental factors. For example, is the overlap between irritability and depression accounted for by one set of shared genes, while a different set of genes explains the link between headstrong/hurtful behaviors and antisociality? Previous genetic studies have found that genetic factors may have broader influences than initially thought; indeed, the “generalist genes” (13) are thought to explain the association between closely linked phenotypes (13, 14). An alternative explanation for such phenotypic overlap lies in the realm of overlapping environmental factors. Family- or person-specific environmental influences may be associated with both irritability and depression and thus underlie their relationship, while a different set of such overlapping environmental risks may underlie the relationship of

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headstrong/hurtful behaviors with antisociality. Answering these questions would help us understand the mechanisms underlying these key developmental pathways.

In this study, we used a twin sample and a genetically informative design to address these questions. We began by examining phenotypic links between the two components of oppositionality (irritability and headstrong/hurtful behaviors) and depressive problems and antisocial behaviors. Based on previous findings, we predicted a double dissociation, such that adolescent irritability would show differential concurrent and longitudinal relationships with depressive problems, while headstrong/hurtful behaviors would be specifically related to antisocial outcomes. We used young people's self-reports, thus complementing previous work based on parent and teacher reports (5, 11, 12) and reexamining previous negative findings (5) on the relationship between self-reported irritability and psychopathology. Focusing on adolescence offers the additional advantage that the differential relationships of irritability can be tested at a time when adult mood problems are emerging (15) and antisocial behaviors reach a peak (16).

Next, we used multivariate twin modeling to test our main hypothesis that the genetic findings would show a double dissociation consistent with the phenotypic findings. We expected that genetic factors shared between irritability and depression would underlie their phenotypic association and, similarly, that genetic factors shared between headstrong/hurtful and antisocial behaviors would explain their phenotypic association. This prediction was based on the notion of generalist genes, which are hypothesized not to be disorder specific but rather to exert wider effects, giving rise to closely linked behavioral (17) or cognitive phenotypes (13, 14). Indeed, we recently provided further empirical evidence in support of this theory by showing substantial genetic links among cognitive bias, depression, and anxiety problems (18).

Method

Sample

Data from the G1219 sample were used as previously described (18–20). The G1219 study is a longitudinal study of 3,640 adolescent twins and siblings (ages 12–19 years at initial contact). The present analyses focus on waves 2 and 3 of the data collection (time 1 and time 2, respectively), which took place, on average, 8 months (range, 0–24 months) and 33 months (range, 24–60 months), respectively, after initial contact. Data were available for 2,651 individuals at time 1 (73% of the original sample) and for 1,597 at time 2 (44% of the original sample). Zygosity was established through a questionnaire measure completed by mothers. The sample consists of 168 monozygotic male, 199 monozygotic female, 138 dizygotic male, 190 dizygotic female, and 463 opposite-sex dizygotic twin pairs and 109 male sibling pairs, 132 female sibling pairs, and 186 opposite-sex sibling pairs. Zygosity was not available for 235 pairs at initial contact. At times 1 and 2, the proportions of boys were 43.9% and 41.3%, respectively. The mean ages at times 1 and 2 were 15 years (range, 12–21) and 17 years (range, 14–23), respectively. To handle the effects of initial response and attrition bias, a single weighting variable was

included in all genetic analyses, as previously described (18). Informed consent was obtained from all adolescents age 16 or older and from parents or guardians of those under age 16. Ethical approval was provided by the Research Ethics Committees of the Institute of Psychiatry, King's College London; the South London and Maudsley NHS Trust; and Goldsmiths, University of London.

Measures

Depression ratings. Depressive symptoms were rated by self-report using the Short Mood and Feelings Questionnaire (21–23). At time 1, a 4-point response format (ranging from “never” to “always”) was used to allow for discrimination at the lower end of the spectrum. The standard 3-point scale was used at time 2.

Delinquent behavior. Using the ASEBA family of instruments (24, 25), we formed a delinquency scale with 11 items, as previously described (26), that captures the elements of lacking guilt, having deviant peers, lying, preferring older peers, running away from home, setting fires, stealing, swearing, truanting, and using alcohol or drugs.

Dimensions of oppositionality. Items used to define dimensions of oppositionality were drawn from the Youth Self-Report (24) (for ages 11–18) and the Adult Self-Report (25) (for ages 18–59) of the ASEBA family of instruments. At time 1, we used the following items from the Youth Self-Report: “argue a lot,” “mean to others,” “destroy others' things,” “disobey parents,” “disobey at school,” “have a hot temper,” “tease others a lot,” “stubborn,” and “mood/feelings change suddenly.” The last item was included because mood lability is a commonly used term to describe chronic irritability (27). At time 2, we used comparable items except that they did not include the item “disobey parents” and the item “stubborn” was rephrased as “stubborn, sullen, or irritable.”

Statistical Analysis

Derivation of the irritable and headstrong/hurtful dimensions. At each wave, we conducted exploratory factor analyses using the oppositionality items with weighted least squares estimation (given the categorical nature of the items) on a random half of the data set. These analyses yielded two factors with eigenvalues ≥ 1 , corresponding to previously described dimensions of oppositionality (10–12, 28). As shown in Table 1, with the exception of the cross-loading “argue a lot” item, all items loaded clearly on either the irritable (“have a hot temper”; “stubborn” [time 1] or “stubborn, sullen or irritable” [time 2]; and “mood/feelings change suddenly”) or the headstrong/hurtful (“disobey parents” [available only at time 1], “mean to others,” “destroy others' things,” “disobey at school,” and “tease others a lot”) factors. An irritability scale was generated from the standardized sum score of the items loading on the “irritable” factor, and a headstrong/hurtful behaviors scale was created from the standardized sum score of the items loading on the “headstrong/hurtful” factor at each of the study's time points.

Although the Adult Self-Report item “stubborn, sullen, or irritable” would be expected to load on the irritability dimension, the Youth Self-Report version of that item (“stubborn”) might be more ambiguous and reflect headstrong as well as irritable tendencies. Although both versions of the item loaded clearly and consistently on the irritable dimension in the factor analyses, we reran all the main analyses with this item excluded to ensure that any potential ambiguity did not bias the study's results.

The results of the exploratory factor analyses were further tested in confirmatory factor analyses in the other half of the sample. A single-factor model in which all the items would load was compared with the two-factor (irritable and headstrong/hurtful) model derived by exploratory factor analysis. All indices of fit from maximum likelihood estimation and the chi-square difference score in weighted least squares estimation indicated a better

TABLE 1. Loadings for the Irritability and Headstrong/Hurtful Factors in an Exploratory Factor Analysis of Oppositionality Items at Times 1 and 2 in a Longitudinal Study of Twins and Siblings

Item	Time 1		Time 2	
	Irritability	Headstrong/Hurtful	Irritability	Headstrong/Hurtful
Argue a lot	0.473 ^a	0.514 ^a	0.509 ^a	0.402 ^a
Mean to others	0.313	0.648 ^a	0.296	0.651 ^a
Destroy things belonging to others	0.163	0.688 ^a	0.266	0.689 ^a
Tease others a lot	0.262	0.558 ^a	0.212	0.580 ^a
Have a hot temper	0.709 ^a	0.320	0.674 ^a	0.330
Mood or feelings change suddenly	0.636 ^a	0.133	0.695 ^a	0.151
Disobey at school	0.159	0.712 ^a	0.229	0.618 ^a
Disobey parents ^b	0.283	0.640 ^a		
Stubborn, sullen, or irritable ^c	0.573 ^a	0.217	0.604 ^a	0.313

^a Factor loadings ≥ 0.40 .

^b This item was available only at time 1.

^c This item included only “stubborn” at time 1 and “stubborn, sullen, or irritable” at time 2.

fit for the two-factor than the single-factor model (see Table S1 in the data supplement that accompanies the online edition of this article). The Cronbach alpha coefficients were 0.67 and 0.55 for the headstrong/hurtful dimension at times 1 and 2, respectively, and 0.61 and 0.66 for the irritable dimension at times 1 and 2, respectively.

Phenotypic analyses. Cross-sectional associations between variables were explored using correlation and robust regression with either depression or delinquency as the outcome and both dimensions of oppositionality entered simultaneously as predictors. Longitudinal associations between the dimensions of oppositionality at time 1 and psychopathology at time 2 were examined using regression models adjusting for the dimensional psychopathology score measured at baseline. For example, where depression scores at time 2 were the outcome, the predictors were the two dimensions—irritable and headstrong/hurtful behavior—at time 1 and the depression scores at time 1. Robust standard error (sandwich) estimators were used in Stata (StataCorp, College Station, Tex.) to account for dependence of twin observations.

Genetic analyses. The twin design compares the degree of similarity among monozygotic (sharing 100% of their genes) and dizygotic twins (sharing on average 50% of their genes). Relative differences in within-pair correlations are used to estimate additive genetic (A), shared environmental (C), and nonshared environmental (E) effects on measures.

Variables were regressed for age and sex, as is standard practice for quantitative genetic model fitting. Variables were transformed to ensure that all skew statistics were between -1 and 1 .

Models were fitted in the Mx program (www.vcu.edu/mx) using raw data maximum likelihood, with weighting corrections to account for selective attrition. The fit statistic provided for raw data modeling (-2 log-likelihood) of the observations to compare the fit of the genetic model to that of a saturated model. Following the principle of parsimony, the fit of submodels was assessed by chi-square difference tests and Akaike's information criterion (χ^2-2df), with lower chi-square values and more negative Akaike values indicating a better fit.

Multivariate genetic models. We used multivariate genetic models to test our hypotheses, using both cross-sectional and longitudinal approaches. In the first (cross-sectional) step, we interpreted a Cholesky decomposition as a correlated-factors solution to examine whether the genetic findings mirrored the phenotypic associations. We tested whether genetic overlap between irritability and depression is stronger than that between headstrong/hurtful behaviors and depression, and whether genetic overlap between headstrong/hurtful behaviors and delinquency is stronger than that between irritability and delinquency.

In the second (longitudinal) step, we used trivariate and then quadrivariate Cholesky decomposition models. The purpose of the trivariate model was to investigate whether any genetic or environmental relationships remained between irritability at time 1 and delinquency at time 2 on the one hand, and headstrong/hurtful behaviors at time 1 and depression at time 2 on the other, after accounting for headstrong/hurtful behaviors and irritability (both at time 1), respectively. The quadrivariate Cholesky models additionally adjust for depression at time 1 when examining depression at time 2 as an outcome and for delinquency at time 1 when examining delinquency at time 2 as an outcome.

Results

Phenotypic Findings

Scores on the irritability scale were significantly higher in girls than in boys (mean=2.27 [SD=1.57] and mean=1.86 [SD=1.54], respectively; $t=6.6$, $p<0.001$), and scores on the headstrong/hurtful behavior scale were significantly higher in boys than in girls (mean=1.84 [SD=1.85] and mean=1.38 [SD=1.53], respectively; $t=6.9$, $p<0.001$).

The correlations between the study's main variables are listed in Table 2. Irritability showed a stronger association with depression ratings than did headstrong/hurtful behaviors, and headstrong/hurtful behaviors showed a stronger association with delinquency than did irritability. Figure 1 (top panel) shows the findings of cross-sectional robust regression models, with either depression or delinquency as the outcome and with the two dimensions of oppositionality entered simultaneously as predictors. The figure illustrates a double dissociation, in which irritability is significantly more strongly associated with depression than with delinquency, whereas, in contrast, headstrong/hurtful behaviors are significantly more strongly associated with delinquency than with depression. Controlling for gender and age did not alter the pattern of the results.

Longitudinal robust regression models showed the same pattern. Irritability, but not headstrong/hurtful behaviors, at time 1 was a significant predictor of self-report depressive symptom scores at time 2, after controlling for self-report depressive symptom scores at time 1 ($\beta=0.14$

TABLE 2. Cross-Sectional Phenotypic Correlations in a Longitudinal Study of Twins and Siblings^a

Variable	N	Headstrong/Hurtful		Depression Ratings at Time 1		Delinquency at Time 1		Depression Ratings at Time 2		Delinquency at Time 2	
		r _{Ph}	95% CI	r _{Ph}	95% CI	r _{Ph}	95% CI	r _{Ph}	95% CI	r _{Ph}	95% CI
Irritability	2,417	0.46	0.42–0.49	0.45	0.42–0.48	0.40	0.37–0.44	0.33	0.28–0.37	0.27	0.22–0.31
Headstrong/hurtful behavior	2,400	—		0.36	0.32–0.40	0.61	0.59–0.64	0.20	0.15–0.25	0.44	0.40–0.48
Depression ratings at time 1	2,445			—		0.36	0.32–0.40	0.49	0.45–0.53	0.26	0.21–0.31
Delinquency at time 1	2,427					—		0.21	0.16–0.26	0.53	0.49–0.56
Depression ratings at time 2								—		0.33	0.28–0.37

^a r_{Ph} denotes phenotypic correlation coefficients.

TABLE 3. Cross-Sectional Multivariate Genetic Model Results at Time 1, Indicating Genetic and Environmental Influences on Each Variable in a Longitudinal Study of Twins and Siblings^a

Cholesky Model	Irritability		Headstrong/Hurtful		Depression Ratings		Delinquency	
Genetic influences	A or r _A	95% CI	A or r _A	95% CI	A or r _A	95% CI	A or r _A	95% CI
Irritability	0.31	0.23–0.39	0.66	0.53–0.77	0.70	0.59–0.82	0.57	0.45–0.69
Headstrong/hurtful			0.45	0.38–0.52	0.46	0.36–0.57	0.80	0.72–0.86
Depression ratings					0.51	0.45–0.57	0.54	0.45–0.63
Delinquency							0.56	0.49–0.62
Nonshared environmental influences	E or r _E	95% CI	E or r _E	95% CI	E or r _E	95% CI	E or r _E	95% CI
Irritability	0.69	0.61–0.77	0.34	0.26–0.41	0.29	0.21–0.37	0.29	0.21–0.37
Headstrong/hurtful			0.55	0.48–0.62	0.25	0.17–0.33	0.44	0.36–0.51
Depression ratings					0.49	0.43–0.55	0.15	0.06–0.23
Delinquency							0.44	0.38–0.51

^a In this model, genetic and nonshared environmental influences add up to 1 on each variable. The numbers in boldface along the diagonals are heritability coefficients (A) or nonshared environmental influence coefficients (E); the off-diagonal numbers are genetic correlations (r_A) or environmental correlations (r_E).

[95% CI=0.08 to 0.20] and β=0.01 [95% CI=-0.05 to 0.07], respectively). Conversely, headstrong/hurtful behaviors, but not irritability, were significant predictors of self-reported delinquency scores at time 2, even after adjusting for self-reported delinquency scores at time 1 (β=0.19 [95% CI=0.12 to 0.27] and β=0.05 [95% CI=0.00 to 0.10], respectively). The pattern of results was unchanged when the reduced irritability scale (omitting the “stubborn” item) was used instead (see Table S2 in the online data supplement).

Genetic Analyses

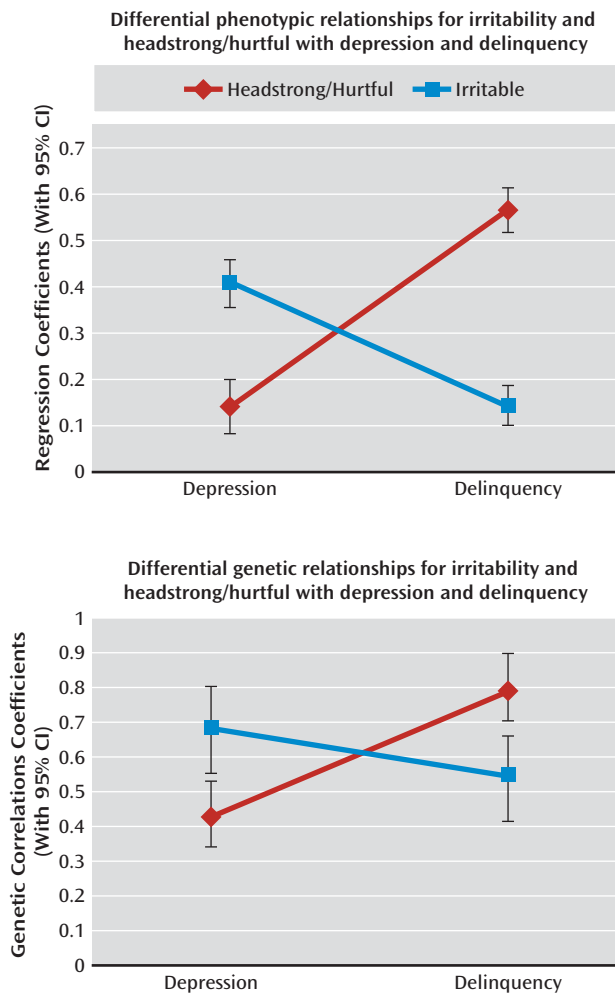
Genetic overlap between irritability and both depression and delinquency was first assessed cross-sectionally. A saturated model was fitted to estimate variances, covariances, and means for the raw data to get a baseline index of fit (χ²=22733.580, df=9337). Subsequent models were compared with the saturated model to determine the best-fitting model. We found that a model without sex differences in A, C, and E parameters but allowing for variance difference across the sexes fit the data best (χ²=22848.251, df=9648, p<0.01; Akaike information criterion=-155.481). The shared environment effect was small and nonsignificant, however, so we present results from an AE model.

Heritability (A) ranged from 0.31 for irritability to 0.56 for delinquency, as shown along the diagonal of Table 3. Genetic correlations (shown in the off diagonals of Table 3 and in Figure 1, lower panel) ranged from 0.46 (between headstrong/hurtful behaviors and depression) to 0.80 (between headstrong/hurtful behaviors and delinquency).

Genetic correlations between headstrong/hurtful behaviors and depression (r_A=0.46) were significantly lower than between headstrong/hurtful behaviors and delinquency (r_A=0.80). Genetic correlations between irritability and delinquency were significantly lower (r_A=0.57) than between irritability and depression (r_A=0.70). These results did not change when using the time 2 data, except that the genetic correlations between irritability and delinquency did not differ significantly from those between irritability and depression (see Table S3 in the online data supplement).

Next, we explored the extent to which longitudinal genetic associations showed a pattern similar to the phenotypic associations. We first assessed whether there was shared genetic variance between headstrong/hurtful behaviors at time 1 and depression at time 2, over and above the genetic association already identified between each of these variables and irritability at time 1. This is akin to testing whether there is a partial genetic correlation between headstrong/hurtful behaviors and depression that accounts for their longitudinal association independent of associations with irritability. Similarly, we tested whether there was any shared genetic variance between irritability at time 1 and delinquency at time 2 independent of headstrong/hurtful behaviors at time 1. To do so, we used two separate trivariate Cholesky models. The results are shown in Figure 2. Headstrong/hurtful behaviors at time 1 and depression at time 2 shared no genetic variance after accounting for irritability at time 1. Similarly, irritability at time 1 and delinquency at time 2 shared no genetic vari-

FIGURE 1. Cross-Sectional Phenotypic and Genetic Associations for Irritability and Headstrong/Hurtful Behaviors With Depression and Delinquency in a Longitudinal Study of Twins and Siblings



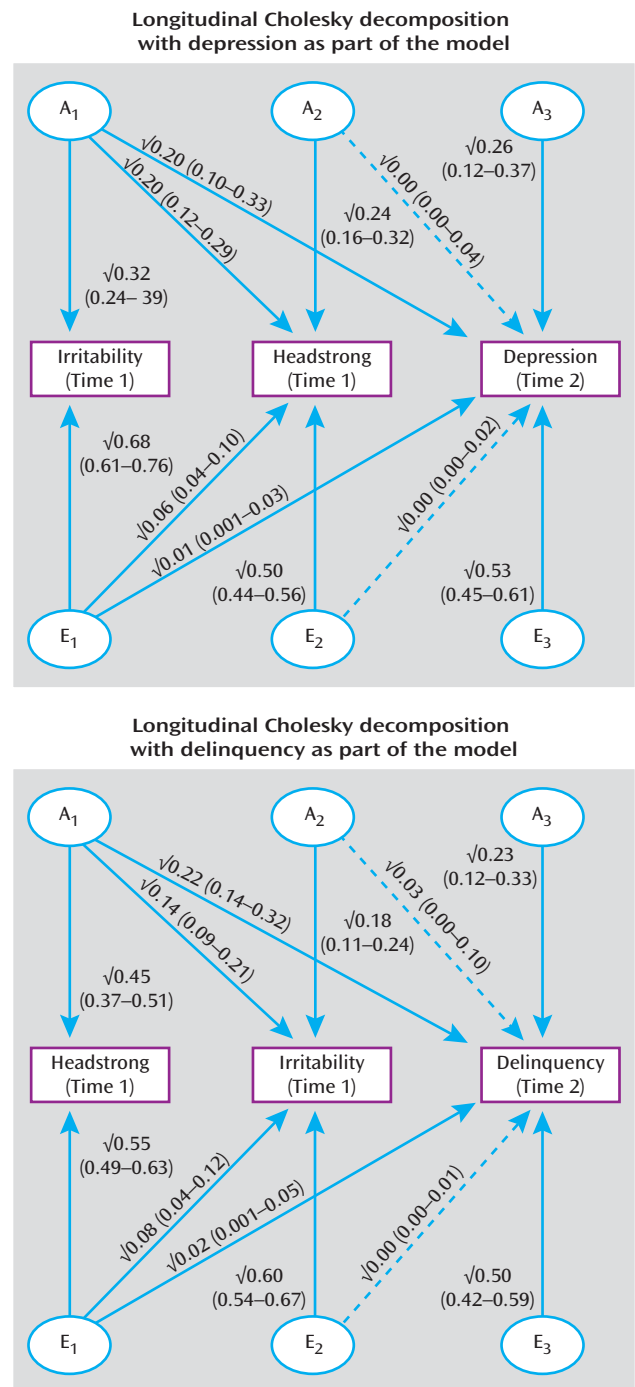
ance after accounting for headstrong/hurtful behaviors at time 1. Again these results remained unchanged when the “stubborn” item was omitted from the irritability scale (see Figure S1 in the online data supplement).

We then asked whether the genetic relationship between irritability at time 1 and depression at time 2 was explained through shared genetic effects between irritability and depression at time 1. As shown in Figure 3, the genetic association between irritability and depression at time 1 fully accounted for the longitudinal association between irritability at time 1 and depression at time 2. Similarly, the relationship between headstrong/hurtful behaviors at time 1 and delinquency at time 2 was explained through the genetic association of headstrong/hurtful behaviors and delinquency at time 1.

Discussion

Several new findings emerge from this study of the phenotypic and genetic correlates of irritability. The heritability

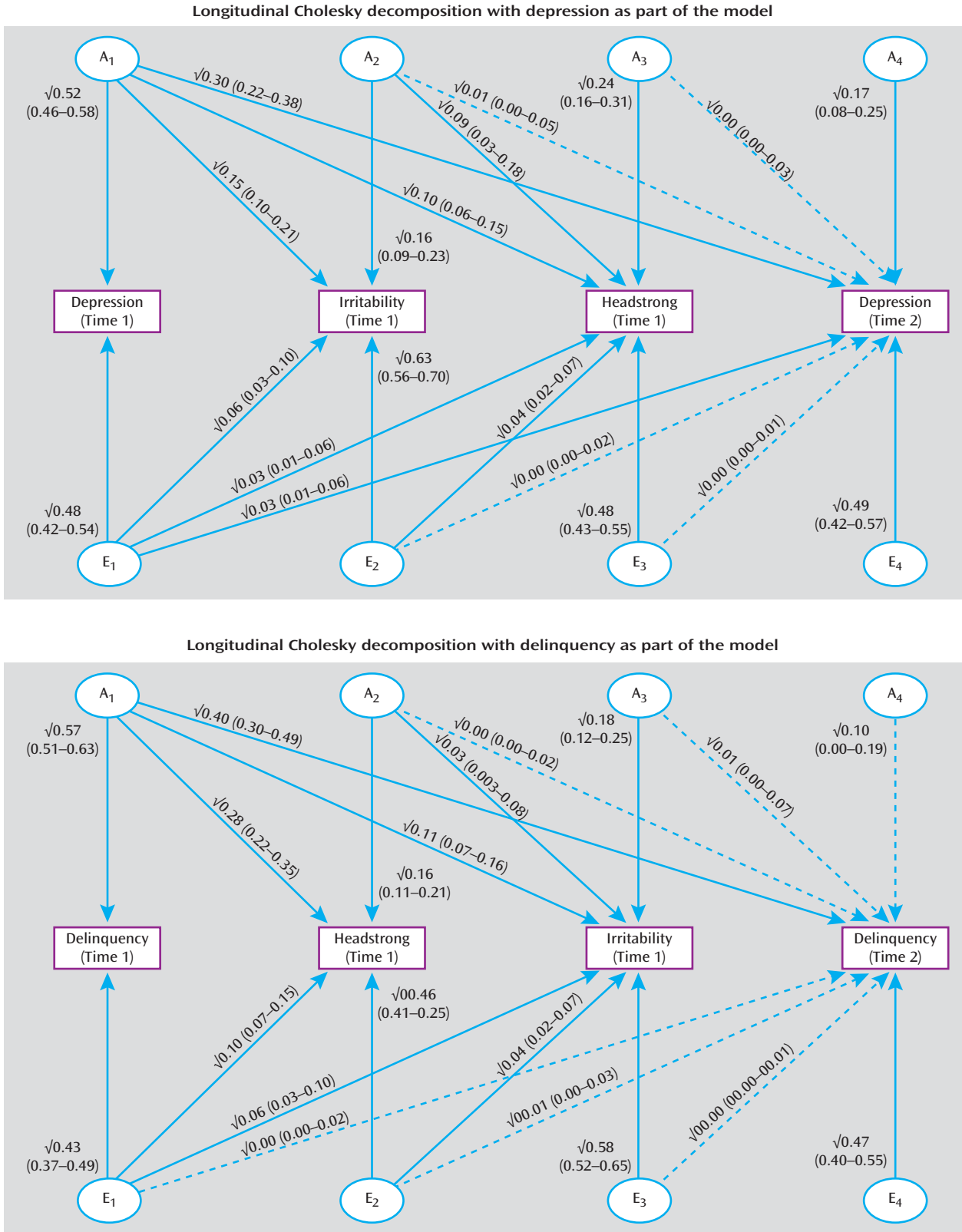
FIGURE 2. Longitudinal Cholesky Decomposition With Depression and With Delinquency as Part of the Model in a Longitudinal Study of Twins and Siblings^a



^a Path coefficients and confidence intervals are shown. “A” denotes genetic effects, and “E” denotes nonshared environmental effects.

of irritability by adolescent self-report is relatively low, consistent with previous data from adults (29). Phenotypically, irritability was specifically related to subsequent depressive symptoms, whereas the headstrong/hurtful dimension was associated with delinquency. Our main hypothesis was that the same pattern of double dissociation would be observed

FIGURE 3. Longitudinal Cholesky Decomposition With Depression and With Delinquency as Part of the Model, Adjusted for Depression/Delinquency at Time 1 in a Longitudinal Study of Twins and Siblings^a



in the multivariate genetic analyses, and this was found to be the case. The genetic relationship between headstrong/hurtful behaviors and depression was due entirely to the overlap with the irritable dimension. Conversely, the genetic relationship between irritability and delinquency was due entirely to the overlap with headstrong/hurtful behaviors. Also, the concurrent genetic relationship between irritability and depression at time 1 accounted for the genetic relationships between irritability at time 1 and depression at time 2. The same pattern of results was observed for the relationship between headstrong/hurtful behaviors at time 1 and delinquency at time 2. In previous longitudinal analyses (10–12, 28), headstrong items have been shown to be differentially strongly related to ADHD and conduct problems, whereas hurtful items were preferential predictors of more aggressive conduct problems and callous and unemotional traits. However, in this study, headstrong/hurtful behaviors emerged as a common factor, in keeping with another recent epidemiologic study (10), possibly reflecting the limited number of items available.

Irritability has traditionally been studied in the context of antisocial behavior in both early life and adulthood (30, 31). However, it is debated whether disruptive behaviors form a unitary construct. Consistent with our previous findings (5, 11, 12), we show here that the relationship between irritability and antisociality may result from their correlation with headstrong/hurtful behaviors. Our findings support a model whereby irritability is linked with depression, forming part of a nexus of negative mood with common genetic underpinnings. The finding that strong phenotypic links between syndrome constellations or disorders may be explained by genetic, as opposed to environmental, overlap is consistent with prior theory (13, 14) and empirical data (18).

Our findings have several implications. First, they are relevant for understanding developmental transitions. Recent evidence suggests that oppositional behaviors are the most robust early predictor of depression in young adult life (4), even after adjusting for conduct disorder or early depression. Our findings go a step further by showing that the relationship between oppositional problems and depressive symptoms may be due to the irritability component of oppositionality, rather than to disruptive headstrong and hurtful behaviors. The findings of this study are based on adolescent self-report and thus extend previous findings based on parent and teacher report (5, 11, 12). In contrast to the present study, in past work we did not find that self-reported irritability predicted psychiatric disorders (5). These different findings may be due to the considerably smaller size of the previous study, differences in duration of follow-up, and the different instruments used.

Second, our findings may have implications about the etiology of depression. We found that the relationship between irritability and depression is largely explained by common genes. By contrast, we found only a small overlap in nonshared environmental factors between ir-

ritability and depression. It will be important to characterize the shared genetic mechanisms between irritability and depression, which may include affective processing mechanisms.

Third, our findings support the clinical notion that irritability is a presenting symptom of depression and that patients presenting with irritability should be screened carefully for depression (2, 32–34). This thinking is reflected in the youth criteria but not the adult criteria for depression in DSM-IV. Whether interventions targeting irritability would treat and/or prevent depressive symptoms is a topic for future research.

This study has several limitations. First, there was considerable attrition at follow-up. However, while attrition bias poses a problem for estimating prevalences, it is less likely to bias associations between variables (35). Second, the study relied on an existing measure out of which the irritability and headstrong/hurtful items were extracted. However, the modest internal consistencies of the scales would reduce the power of detecting differences. Given the double dissociations we observed in this study, it seems unlikely that internal consistency had differential effects on the study's results. Third, our use of age-appropriate versions of the ASEBA scales at times 1 and 2 meant that one item in the irritability scale was worded differently in the two study waves (“stubborn” at time 1 and “stubborn, sullen, or irritable” at time 2). Although both versions of this item loaded clearly and consistently on the irritability factor, we repeated all the main analyses with this item excluded to ensure that any potential ambiguity in the simpler (time 1) wording had not biased the findings. All of the key findings remained unchanged.

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Clinical Guidance: Association of Irritability, Impulsive Hurtfulness, and Risk Taking With Future Depression, Delinquency, and Substance Abuse in Adolescents

Irritability predicted depression, whereas impulsive and hurtful behaviors were more strongly related to delinquency, over the course of adolescence in this twin study by Stringaris et al. These traits were also linked to their outcomes by common genetic diathesis. In a study by Schneider et al. (p. 39), increased risk-taking behavior in an experimental setting predicted later substance abuse in adolescents. In an editorial, Wamboldt (p. 4) points out that early identification of these traits should guide early treatment interventions.