A Genetically Informed Study of the Longitudinal Relation Between Irritability and Anxious/Depressed Symptoms

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Objective: Little is known about the longitudinal genetic and environmental association between juvenile irritability and symptoms of anxiety and depression. This study's goal was to assess the relationship between these constructs across a critical developmental period spanning childhood to young adulthood.

Method: Parents (n = 1,348 twin pairs) from the Swedish Twin Study of Child and Adolescent Development completed the Child/Adult Behavior Checklist (CBCL/ABCL) about their twin children. Data were collected during a prospective, 4-wave study starting in childhood (ages 8–9 years) and ending in young adulthood (ages 19–20 years). An irritability score and an anxious/depressed score were computed from CBCL/ABCL item endorsements. Genetically informative cross-lagged models were used to estimate the genetic and environmental relationship between these 2 constructs across time.

Results: Our models suggested that irritability more strongly predicted anxious/depressed symptoms than vice versa, consistent with a causal role of irritability on anxiety/depression at older ages. This relationship was significant only in late childhood/early adolescence. Additive genetic and unique environmental factors were significant contributors to both irritability and anxious/depressed symptoms and were both specific to and shared between these 2 constructs. The same common environmental factors influenced both constructs, although these factors accounted for a smaller amount of variance than genetic or unique environmental factors.

Conclusion: This study adds to our understanding of the developmental relationship between irritability and anxious/depressed symptoms and the contribution of genes and environmental factors to their association across development. Findings suggest the need to monitor for emergence of internalizing symptoms in irritable children and their potential need for therapeutic intervention.

Key Words: irritability, anxiety, depression, genetic, twins

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It is common for youth to experience transient irritability related to specific environmental events. There is a subset of youth (~3% of the general population), however, who expresses stable, clinically significant levels of irritable mood.[1-3] It was previously thought that chronic irritable mood in youth was a risk factor for the development of bipolar disorder later in life,[4,5] but subsequent research has not borne out this developmental psychopathological relationship; rather, longitudinal studies of children exhibiting chronic irritability indicate that this clinical phenotype increases risk of developing internalizing conditions such as generalized anxiety disorder and unipolar depression.[6-11] Related, recent findings suggest that self-reported irritability in youth with anxiety disorders is comparable to that observed in youth with severe mood disorders[12] and have demonstrated that the irritable dimension of oppositional defiant disorder is related to later depressive and anxiety disorders.[13,14] Available longitudinal studies suggest that irritability is heterogeneous and consists of multiple trajectories that are differentially associated with parental psychopathology, particularly maternal depression, as well as development of mood and anxiety conditions later in life.[10,15] Collectively, this implies that chronic irritable mood is modestly prevalent, heterogeneous, associated with parental psychopathology, and predicts development of anxiety and mood-related (internalizing) psychopathology.

Although cross-sectional and longitudinal studies implicate early irritability as a risk factor for multiple internalizing disorders, it is unclear whether these constructs are phenotypically related to each other (e.g. whether early irritability causes or contributes to the development of anxiety/depression later in life) or whether they have shared underlying etiologies (e.g., shared genetic liabilities that cause both irritability and anxiety/depression). Thus far, existing studies have not empirically compared these 2 competing hypotheses.

Individually, irritability, anxiety, and depression are each moderately heritable traits that are influenced by both genetic and environmental factors.[16-18] Pediatric anxiety disorders are associated with higher heritability estimates compared to adults and their genetic effects exhibit a dynamic course throughout development.[17] Genetically informed studies also indicate that anxiety and mood disorders are interrelated facets of a broader internalizing construct, as the anxiety disorders share genetic and environmental risk factors with each other and with related phenotypes such as major depression.[15,18] In addition, there is evidence that irritability shares genetic variation with depression symptoms.[16] Previous studies have primarily investigated the association between irritability and specific disorders such as depression or generalized anxiety disorder; however, the overlap between these internalizing

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constructs, and between internalizing psychopathology and irritability, suggests a need for a comprehensive evaluation of the associations between these constructs and of the genetic and environmental factors that may underlie their comorbidity and developmental co-evolution.

The current study sought to elucidate the nature of the relationship between irritability and anxious/depressed symptoms from childhood through the young adult years. Our purpose was to compare the evidence for a shared liability (genetic or environmental etiology shared between irritability and internalizing psychopathology) versus a direct phenotypic association underlying the relationship between these 2 traits. In this study, we examined the contributions of genetic and environmental factors to the temporal relation between irritability and internalizing symptoms in a population-based cohort of Swedish twins assessed 4 times between the ages of 8 and 20 years. We used a longitudinal cross-lagged model to explore the simultaneous development of these 2 traits over time to provide insight into the possible mechanisms underlying their relationship. Determining the longitudinal relationship between irritability and anxious/depressed symptoms may inform clinical prevention efforts. For example, if early irritability predicts the emergence of anxious/depressed symptoms, then targeting irritability via therapeutics may decrease the likelihood of the manifestation of anxious/depressed symptoms. Alternatively, a shared liability model would indicate risk factors that could be tailored to prevent the development of both irritability and internalizing symptoms.

We measured the irritability and anxiety/depression phenotypes using the Achenbach System of Empirically Based Assessment (ASEBA).[19-21] Our primary goals were as follows: to estimate the temporal relationship between irritability and anxious/depressed symptoms to identify direct associations between these constructs; to clarify whether the genetic and environmental architecture is shared between irritability and anxious/depressed symptoms; and to assess the stability of genetic and environmental contributions to the 2 phenotypes from childhood to young adulthood.

METHOD

Study Participants

Data analyzed in this study are from the Swedish Twin Study of Child and Adolescent Development (TCHAD).[22] All twin pairs residing in Sweden in 1994 and born between May 1985 and December 1986 were contacted for study participation. Data from 2,719 twin individuals were available, although zygosity was not known for some twin pairs or only 1 member of the pair participated, resulting in 1,348 twin pairs for the current analyses. Zygosity groupings included 267 female–female monozygotic (MZ) pairs, 199 female–female dizygotic (DZ) pairs, 254 male monozygotic pairs, 182 male dizygotic pairs, and 408 opposite-sex (OS) dizygotic pairs.

Twins were contacted for study participation at 4 waves via a mailed questionnaire. Of the twins returning study questionnaires, twin ages at the time of the assessments included 8 to 9 years (wave 1, n = 1,090 pairs, 81% response rate), 13 to 14 years (wave 2, n = 1,060, 79% response rate), 16 to 17 years (wave 3, n = 1,065, 79%), and 19 to 20 years (wave 4, n = 576, 43%). The ethics committee of the Karolinska Institute, Stockholm, Sweden, approved the study questionnaires. Zygosity was determined by DNA testing. Twins' DNA was extracted from saliva samples using OraGene (DNA Genotek Inc., Ottawa, ON, Canada) DNA self-collection kit. For twins with no DNA sample, zygosity was determined based on an algorithm derived from discriminant analyses of twins' and parents' responses to validated zygosity questionnaires. For cases with inconclusive zygosity assignments (n = 100, 3.4%), zygosity was coded as unknown; these twins were excluded from analyses.

Derivation of the Irritability and Anxiety/Depression Phenotypes

Parent reports of twin irritability and anxious/depressed symptoms were obtained using items from the Child Behavior Checklist (CBCL) and, when twins were ages 19 to 20 years, the Adult Behavior Checklist (ABCL).[18-20] All items on the CBCL and ABCL were scored on a 3-point scale, where 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true.

The irritability dimension was previously identified using the CBCL oppositionality items and included the following: stubborn, sullen, or irritable; sudden changes in mood; temper tantrums or hot temper; and argues a lot. Examination of the factor structure of the irritability dimension in our sample of twins indicated that the "argues a lot" item did not load highly (factor loading range = −0.05 to 0.30) on the irritability dimension.[23] For this reason, this item was not included as part of the irritability dimension. Thus, the CBCL items defining the irritability dimension across development in this study included the following: stubborn, sullen, or irritable mood; sudden changes in mood; and temper tantrums or hot temper, with all items loading strongly on the irritability factor (range 0.61–0.91).[23] An irritability score was created for each wave by summing the 3 irritability items. The Anxious/Depressed subscale is a factor-derived scale from the standard CBCL/ABCL profile, and includes 13 items tapping anxiety and depressed mood, which do not overlap with the irritability items. The repeated measures of the Irritability score and the Anxious/Depressed subscale of the CBCL/ABCL served as the primary variables in the autoregressive cross-lagged twin models (see Analytic Model section below). Irritability scores and anxious/depressed scores were treated as continuous traits. To evaluate the fit of our entire model, we used the Akaike Information Criterion (AIC)[24] and χ^2 likelihood-ratio test for nested models. The lower the AIC value, the better the balance of explanatory power and parsimony, whereas a nonsignificant likelihood-ratio test statistic indicates that the fit of the model has not significantly decreased after constraining parameters. EFA analyses were performed in Mplus 6,[25] using the weighted least squares mean variance estimator (WLSMV),

TABLE 1 Descriptive Statistics for Irritability and Anxiety/Depression Scores Across 4 Waves of Measurement

Measure	Mean	SD	Range
Irritability			
Wave 1	1.06	1.31	0–6
Wave 2	0.99	1.30	0–6
Wave 3	0.94	1.28	0–6
Wave 4	0.75	1.04	0–6
Anxiety/depression			
Wave 1	1.74	2.46	0–21
Wave 2	1.60	2.43	0–21
Wave 3	1.55	2.46	0–20
Wave 4	2.36	2.69	0–17

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while the autoregressive cross-lagged twin model was conducted with the OpenMx 2.0 package for R statistical software to account for the nonindependence of the items for twin in the same family.[26-28] In OpenMx, we used a full-information maximum likelihood procedure to estimate model parameters and likelihood-based CIs that is robust to nonnormal variable distributions.

Analytic Model

A genetically informed, autoregressive, cross-lagged structural equation model was used to estimate the longitudinal covariance structure of the data. This model examines the stability and change in 2 or more constructs across time and tests the extent to which each trait influences the other at later time points. More specifically, as examined here, this model can be used to explore the simultaneous development of 2 traits and provides some insight into the mechanisms underlying the relationship between them. In autoregressive cross-lagged models, there are 4 central components[29]: the autoregressive parameters that test the stability of each trait across time; the synchronous correlations that measure the within-time covariance between traits at each time point; the cross-lagged components that estimate the extent to which trait A at time 1 influences trait B at time 2, and vice versa; and the innovations or residuals that represent time-specific factors influencing each trait, beyond the influences carried over from earlier time points.

Of these 4 components, the cross-lagged components provide a robust test for spuriousness and allow inferences about the likely causal predominance of 1 variable or the other by ruling out noncausal alternative models.[29,30] Specifically, if the standardized cross-lagged pathway from the first trait at time *t* on the second trait at time *t+1* is significantly larger than the corresponding standardized cross-lagged pathway from the second trait at time *t* on the first trait at time *t+1*, then it is unlikely that the longitudinal relationship between the 2 variables is spurious (due to a third, unmeasured factor that causes both). Although a correlation, and therefore far from definitive proof of causation, such a relationship would provide stronger evidence that trait 1 causes trait 2 rather than vice versa. Alternatively, if there is no difference between the standardized cross-lagged parameters, there is no evidence for a causal relationship, and therefore the correlation between the 2 traits is most likely due to an unmeasured variable underlying both traits. Although not as conclusive an argument for causality as an experimental design with random assignment, this quasi-experimental method controls for the primary noncausal alternative explanation for a correlation between 2 variables—that is, spuriousness.[29] Kenny recommends the use of the cross-lagged model as an intermediate step between testing bivariate cross-sectional/longitudinal relationships and conducting experimental manipulations of the independent variable in establishing a causal relationship.[29] Many variables of interest to social scientists cannot practically or ethically be assessed with true random experimental designs. For such constructs, the cross-lagged model provides a test for spuriousness and allows investigators to augment the body of evidence in support of 1 direction of phenotypic relationship versus another. However, It should be noted that a nonspurious relationship is suggestive, but certainly not definitive, evidence of causality.

In addition to the autoregressive cross-lagged model, we disaggregated measured phenotypic variance into additive genetic (A), common (shared) environmental (C), and unique (nonshared) environmental (E) components. Measured trait variation of twins can estimate genetic and environmental influences because MZ twins are genetically identical, whereas DZ twins share approximately half of their segregating alleles (allowing us to estimate the genetic component), and both twin types are raised together, thus sharing a variety of environmental influences (allowing us to estimate the shared environmental component). Because MZ twins are 100% genetically identical and share 100% of their common environment (C), the amount of disassociation for a given trait is due to unique (nonshared) environmental influences (E). Thus, estimates of E capture unique, individual experiences that influence twins, and also include measurement error. Detailed descriptions of twin models are available.[30] Within the longitudinal model, the initial cross-trait correlation as well as all of the genetic and environmental innovations (residuals) can be decomposed into genetic and environmental sources of variance.

RESULTS

Descriptive statistics for parent-rated irritability and anxious/depressed symptoms in our sample across time are shown in Table 1. Mean irritability levels decreased modestly across time, whereas mean levels of anxiety/depression were relatively consistent across early to mid-adolescence but increased markedly at age 19 to 20 years.

Univariate biometric models indicated that the assumptions of equal means and variances between twins held for

TABLE 2 Model Fit Statistics for a Four-Wave Cross-Lagged Model of Irritability and Anxiety/Depression

Base Model	Comparison Model	−2LL	df	AIC	−2LL Diff.	df Diff.	*p*
Full model	—	52476.9	14746	22984.9	—	—	—
Full model	Nonsignificant C paths fixed to zero	52480.2	14756	22968.2	3.33	10	.97
Nonsignificant C paths fixed to 0	Same autoregressive and cross-lagged structure across time	52540.5	14764	23012.5	60.3	8	4.11E-10
Nonsignificant C paths fixed to 0	Equal cross-lagged paths (within time, across all measurement intervals)	52488.0	14759	22970.0	7.8	3	.05
Nonsignificant C paths fixed to 0	Equal cross-lagged paths (interval between wave 1 and wave 2)	52485.5	14757	22971.5	5.3	1	.02
Nonsignificant C paths fixed to 0	Equal cross-lagged paths (interval between wave 2 and wave 3)	52481.4	14757	22967.4	1.2	1	.28
Nonsignificant C paths fixed to 0	Equal cross-lagged paths (interval between wave 3 and wave 4)	52481.5	14757	22967.5	1.3	1	.26

Note: −2LL = minus twice the loglikelihood; AIC = Akaike's Information Criteria; C path = common environmental path; df = degrees of freedom; Diff. = difference.

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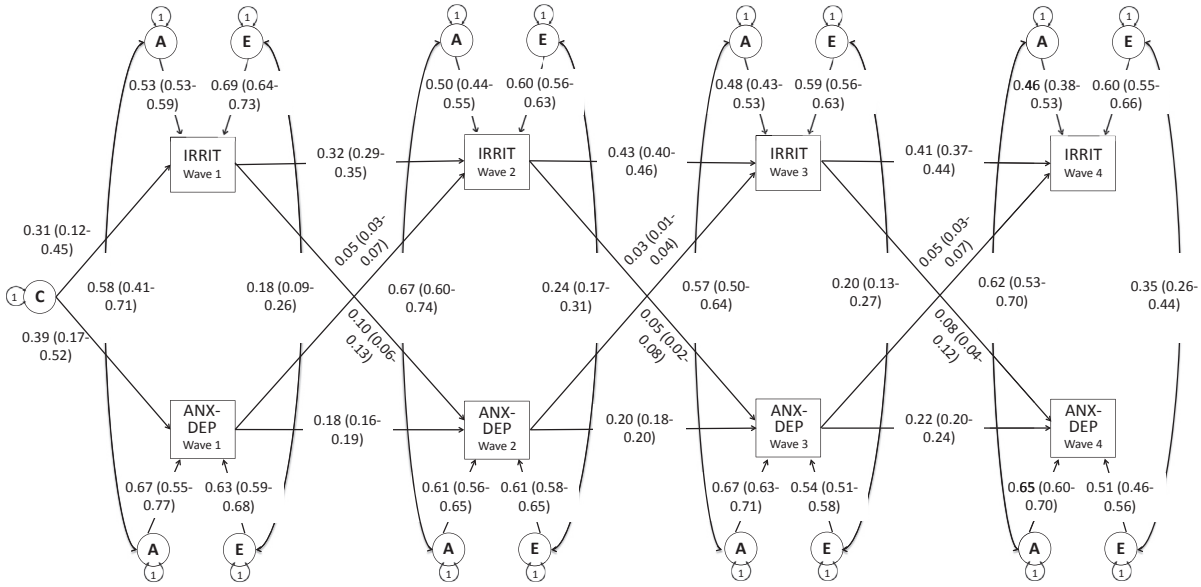
each phenotype at each age, and therefore our data were suitable for multivariate modeling. After fitting a full cross-lagged model with all parameters estimated, we tested several submodels to assess the significance of the parameters (model fit statistics shown in Table 2) to determine which genetic/environmental sources of variance were important to these traits at each age and the relationship between irritability and anxiety/depression across time.

We first tested the significance of the latent genetic and environmental effects on the phenotypes at each time point. In the full model, all of the estimates of additive genetic (A) and unique environmental (E) effects were significant, as evidenced by 95% CIs that did not overlap zero. These results indicate that there are genetic and unique environmental factors influencing both phenotypes, at the first wave and with innovations (novel influences) at each later age. In contrast, a single set of common environmental factors (C) had an impact on both irritability and anxious/depressed symptoms at the first wave, but there were no novel factors having a significant impact on these traits at older ages. We were able to drop all of the C parameters except for a single factor affecting both phenotypes at the first wave without a significant decrease in model fit (likelihood-ratio test $p > .05$ in row 2 of Table 2). It should be noted, however, that genetic/environmental effects at the first wave continue to have effects on traits at later ages through the phenotypic relationship between traits across time. An illustration of this model is shown in Figure 1.

All of the parameters in the model depicted in Figure 1 (standardized estimates are presented) were statistically significant ($p < .05$), including all of the autoregressive and cross-lagged paths. The autoregressive parameters were much larger than the cross-lagged parameters, indicating a substantial continuity of the traits over time. Although the structure of the autoregressive and cross-lagged paths looked similar across time (e.g. the irritability autoregressive path estimates were 0.32–0.43, the anxiety/depression autoregressive path estimates were 0.18–0.22, and the cross-lagged path estimates ranged from 0.05–0.10 for irritability's effect on anxiety/depression and 0.03–0.05 for anxiety/depression's effect on subsequent irritability), equating this structure across time led to a highly significant decrease in model fit (Table 2, row 3).

Next, we focus on the temporal relationship between irritability and anxiety/depression. The magnitude of the standardized cross-lagged paths indicated that irritability had a stronger effect on anxiety/depression at subsequent measurement occasions ($\beta = 0.05$–0.10) than anxiety/depression had on irritability ($\beta = 0.03$–0.05), although both effects were small. To formally test for spuriousness, we constrained these cross-lagged paths to equality between phenotypes but within time, and tested the change in model fit (Table 2, rows 4–7). For example, we constrained the effect of irritability at wave 1 on anxiety/depression at wave 2 to be equal to the effect of anxiety/depression at wave 1 on irritability at wave 2, and so on for each pair of measurement occasions. We found that including these constraints across all waves led to a significant decrease in model fit ($p = .05$). Testing each pair of waves individually (Table 2, rows 5–7) indicated that this was primarily driven by a lack of equivalence of the cross-lagged paths during the first time interval, from wave 1 to wave 2 ($p = .02$). Specifically, the effect of irritability at age 8 to 9 years on anxiety/depression at ages 13 to 14 was larger than the effect of anxiety/depression on irritability, providing support for irritability having a direct phenotypic effect on later anxiety/depression rather than vice versa, as well as evidence against a spurious relationship induced by a third factor. This effect appears to be

FIGURE 1 Path diagram presenting results from the cross-lagged model of the associations between irritability (IRRIT) and anxious/depressed (ANX-DEP) symptoms at ages 8 to 9 (wave 1), 12 to 13 (wave 2), 16 to 17 (wave 3), and 19 to 20 (wave 4) years. Note: A = additive genetic factors; C = common environmental factors; E = unique environmental.



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developmentally specific, as constraining the cross-lagged paths to equality between the later waves did not lead to a statistically significant decrease in model fit. Accordingly, this model suggests that the relationship between irritability and depression in this age group is not spurious, but rather that irritability in late childhood may directly influence anxiety/depression symptoms in adolescence.

Of note, the autoregressive and cross-lagged path coefficients are similar to regression β coefficients. So, for example, the autoregressive coefficients represent the direct relationship between a 1-SD increase in irritability or anxious/depressed symptoms at time t and the corresponding increase in the trait at time $t + 1$. Following path tracing rules, we can identify the variance/covariance within and between these 2 traits across time. Table 3 presents the proportions of these variance/covariance components that are due, respectively, to additive genetic (A), common environmental (C), and unique environmental (E) factors. The cells in this table each represent the proportion of variance in irritability or anxiety/depression (on the diagonals) or the proportion of covariance that each trait shares with itself and with the other trait at each time point (off-diagonals) that can be accounted for by A (upper third), C (middle third), and E (lower third). As an example, the variance in anxiety/depression at wave 1/age 8 to 9 years is accounted for by 45% genetic factors, 15% common environment, and 40% unique environment, whereas the covariance between anxiety/depression at wave 1 and irritability at wave 4 is 50% A, 20% C, and 30% E. These numbers take into account both the time-specific genetic and environmental effects, and those effects that are carried over from earlier ages through the autoregressive and cross-lagged paths.

The majority of the variance in irritability and anxiety/depression, as well as their covariance within and across time, was attributable to genetic factors (41%–74%), with smaller effects attributable to unique environmental (17%–53%) and common environmental (2%–27%) factors (Table 3). Within each wave, the correlation between genetic factors influencing, respectively, irritability and anxiety/depression was high (0.57–0.67) but was lower for unique environmental factors (0.18–0.35).

TABLE 3 Proportions of Variance and Covariance Accounted for by Additive Genetic, Common Environmental, and Unique Environmental (ACE) Factors Associated With Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL) Irritability (Irrit) and Anxious/Depressed (Anx/Dep) Symptom Scores Across Waves

	Anx/Dep T1	Irrit T1	Anx/Dep T2	Irrit T2	Anx/Dep T3	Irrit T3	Anx/Dep T4	Irrit T4
Proportions Due to Additive Genetic (A) Factors								
Anx/Dep T1	0.45							
Irrit T1	0.56	0.42						
Anx/Dep T2	0.46	0.50	0.49					
Irrit T2	0.52	0.43	0.65	0.51				
Anx/Dep T3	0.47	0.49	0.52	0.65	0.58			
Irrit T3	0.51	0.44	0.61	0.52	0.74	0.48		
Anx/Dep T4	0.47	0.48	0.52	0.61	0.59	0.66	0.62	
Irrit T4	0.50	0.45	0.61	0.53	0.68	0.51	0.67	0.46
Proportions Due to Common (Shared) Environmental (C) Factors								
Anx/Dep T1	0.15							
Irrit T1	0.27	0.10						
Anx/Dep T2	0.16	0.20	0.04					
Irrit T2	0.22	0.12	0.08	0.03				
Anx/Dep T3	0.17	0.19	0.05	0.07	0.01			
Irrit T3	0.21	0.12	0.07	0.03	0.03	0.01		
Anx/Dep T4	0.17	0.17	0.05	0.06	0.01	0.02	0.00	
Irrit T4	0.20	0.13	0.06	0.04	0.02	0.01	0.01	0.00
Proportions Due to Unique (Nonshared) Environmental (E) Factors								
Anx/Dep T1	0.40							
Irrit T1	0.17	0.49						
Anx/Dep T2	0.37	0.30	0.47					
Irrit T2	0.26	0.45	0.23	0.47				
Anx/Dep T3	0.37	0.32	0.46	0.28	0.41			
Irrit T3	0.28	0.44	0.28	0.45	0.23	0.50		
Anx/Dep T4	0.35	0.35	0.44	0.33	0.40	0.32	0.38	
Irrit T4	0.30	0.42	0.33	0.43	0.29	0.48	0.32	0.53

Note: Each cell represents the proportion of the individual variance in each trait (diagonals) or covariance between traits (off-diagonals) that can be accounted for by A (upper third), C (middle third), and E (lower third). These include both the time-specific effects and the ACE effects on the traits at previous waves that are carried over through the autoregressive and cross-lagged paths. Variance components sum to unity across A, C, and E. Wave 1 = ages 8 to 9 years; wave 2 = ages 13 to 14 years; wave 3 = ages 16 to 17 years; wave 4 = ages 19 to 20 years.

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DISCUSSION

The primary aim of the current study was to determine the nature of the relationship between irritability and anxious/depressed symptoms across development and to quantify the genetic and environmental effects on this relationship. The current results are inconsistent with a model where anxiety/depression symptoms cause irritability or where both are caused by an unmeasured third variable, leaving the possibility that irritability potentially plays a causal role in the expression of anxiety/depression symptoms.

This effect appears to be developmentally specific, with irritability measured during childhood (ages 8–9 years) significantly predicting anxious/depressed symptoms during early–middle puberty (ages 13–14). In addition, we found strong and stable effects of additive genetic and unique environmental factors influencing both irritability and anxiety/depression, with evidence that the genetic factors and, to a lesser degree the environmental factors, are shared between these 2 traits. The common environment also bore a significant albeit smaller impact on these traits, and the aspects of the common environment relevant to these traits were established in childhood, with no new common environmental factors influencing these traits at older ages. In addition, these C factors overlapped entirely between irritability and anxiety/depression.

Our findings are consistent with a number of studies finding evidence to suggest that irritability and diagnostic phenotypes with significant irritability expression (i.e., oppositional defiant disorder) predict development of anxiety and depressive problems.[4,7,10,17] Most of the extant studies have linked irritability to adult emotional problems and outcomes, whereas the present study shows a similar effect across the age of normative pubertal transition. Thus, rather than simply viewing irritability as a byproduct or correlate of emotional problems, this study adds to accumulating evidence indicating that irritability is a risk factor for the onset of internalizing problems within childhood and into adulthood, and that genetic factors play a role in this manifestation.

Beyond ruling out potential spuriousness and providing incremental support for a small but significant link between irritability and internalizing psychopathology, results of this study indicate that there are genetic and environmental factors that are specific to each phenotype as well as shared, and that these genetic and environmental contributions are present early in development, with additional novel genetic and unique environmental influences emerging during development. Robust, shared genetic covariation was observed between irritability and symptoms of anxiety and depression at each wave of the study. Smaller but stable contributions emerged for nonshared environment, with the strongest correlation between unique environmental factors influencing both irritability and anxiety/depression occurring in young adulthood, when most youths have moved away from the home environment. Finally, the stability of genetic and environmental influences associated with each of the 2 phenotypes was examined separately (i.e., autoregressive paths). Estimates suggest moderate levels of genetic and nonshared environmental influences on irritability as well as anxious/depressed symptoms, which is again consistent with the literature.[31,32]

In contrast to additive genetic and nonshared environmental effects, a single set of common environmental factors influenced irritability and anxious/depressed symptoms at the first wave, with no new common environmental factors emerging after middle childhood. This finding suggests that components of the early shared environment that cause twins to be similar continue to exert influence on irritability and anxious/depressed symptom expression well after their occurrence, indicating that shared environmental events experienced early in life have an enduring and lasting impact on the expression of these traits throughout development into young adulthood. The fact that there were no common environmental factors unique to either trait suggests a shared environmental (e.g., family, neighborhood, peers) liability to both irritability and internalizing psychopathology, although these factors accounted for less of the variance in these 2 traits than genetic or unique environmental factors, especially at older ages. Overall, our findings provide evidence for a complex relationship between irritability and internalizing (anxiety/depression) symptoms in which these traits exhibit a shared underlying genetic and environmental liability, as well as incremental, potentially causal, effects of childhood irritability on adolescent internalizing problems.

Irritable mood is a transdiagnostic dimensional construct that is predictive of a number of clinically relevant outcomes (internalizing psychopathology, oppositional defiant disorder) and is well suited for exploration with multiple methods (e.g., neuroimaging, behavioral) across numerous levels of analysis in human and model organisms. The study of irritability is consistent with the mission of the Research Domain Criteria (RDoC),[33] and examination of irritable mood is likely to generate important, clinically relevant questions about the developmental origins, pathophysiology, and development of internalizing and externalizing conditions. Because the predictive relationship between irritability and anxiety/depression was specific to the transition between age 8 to 9 years and age 13 to 14, spanning the normative period of pubertal maturation, our findings suggest that pubertal development may play a role in the transition from irritable mood to internalizing symptom development, given that the cross-path from irritability at ages 8 to 9 years to anxious/depressed symptoms at ages 13 to 14 was larger than all other cross-paths. Moreover, shared genetic covariation between irritability and anxious/depressed symptomatology was strongest at ages 13 to 14 years, again suggesting that this point in development is critical to the expression of these 2 traits and their genetic covariation. Research has consistently shown that the transition from middle childhood/preadolescence into early adolescence is marked by a robust increase in the prevalence of anxiety and depressive symptoms,[34,35] supporting longitudinal research that straddles this critical period of development.

Relatedly, the presented outcomes of this study carry clinical implications. Given the overlap in genetic and

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environmental factors, as well as indications of a smaller but potentially causal phenotypic relationship between irritability and internalizing psychopathology, our findings suggest the use of transdiagnostic treatments to target both irritability and anxiety/depression symptoms.[36] A growing body of research, including the present study, implicate shared dimensional etiologies underlying the broad domain of internalizing psychopathology and related constructs, including irritability—contradicting traditional boundaries of clinical diagnoses. Treatment approaches that recognize the interrelation between these phenotypes were developed to target the common elements of several disorders using 1 unified treatment model. Our data support the application of transdiagnostic treatments given the observation that irritability serves as a risk factor for internalizing symptom onset and the observation of significant shared genetic and environmental factors between these traits, indicating that irritability and internalizing conditions may respond to similar interventions and therapies.

This study has some limitations, including its reliance on the CBCL/ABCL to generate an index of both irritable mood and anxious/depressed symptoms. Although this study replicated a previously identified factor structure,[16] construct validation of this specific phenotypic measure is lacking, and the irritability dimension has not been considerably studied. Relatedly, examination of the contribution of genes and environment to irritability and anxiety/depression using other established measures, especially those with multiple informants, is needed. Although this study relied on parent report of child irritability, similar outcomes were found for self-report using a cross-sectional model of measured irritability and depression symptoms.[16] In addition, we did not have measures of irritability before age 8 years. Longitudinal designs from early life into young adulthood may be informative, given evidence of associations between preschool irritability and later depression.[11] Moreover, given the complexity of the model, we could not examine sex-specific genetic and environmental effects. It is well documented that rates of depressive and anxiety symptoms increase in adolescence, particularly for females.[34,35] Given that middle childhood irritability is a predictor of pubertal anxiety/depression symptoms, it would be interesting if future research tested whether sex differences were related to this association and whether genetic or environmentally based quantitative or qualitative sex effects were present. Finally, our measure of irritability is a measure of irritable mood and behavior. For this reason, associations between irritability and other phenotypes may be influenced by the aggregation of these differential aspects.

Given the transdiagnostic nature of irritability and its expression across a number of internalizing and externalizing dimensions, a better understanding of the genetic and environmental contributions to its chronic and episodic expression could inform the extant literature and promote development of psychological and pharmacological therapeutics. At this point in time, it is not known whether a unified treatment approach to irritable mood is appropriate or whether differing treatment approaches are needed based on diagnostic contextual features. Unified treatments have been developed for the anxiety disorders, given the many commonalities in etiology, comorbidity, and other relevant factors, which outweigh differences.[36,37] This cannot be said of the many disorders in which irritability manifests, however. For these reasons, aspects of diagnostic context may play an important role in treatment-related differences for chronic irritable mood in juveniles.

In all, genetic factors appear to impart robust and dynamic effects on irritability and anxious/depressed symptoms throughout development. In addition to a shared genetic and environmental liability, our results suggest evidence for the role of irritable mood affecting anxious/depressed symptoms. An important next step is to disaggregate anxiety- and depression-related symptomatology to determine whether their relationships with irritability are stronger for one versus the other phenotype, particularly during the pubertal years. We repeated our statistical analyses using the CBCL *DSM*-oriented Affective Problems scale, which corresponds well with *DSM* major depressive disorder,[38] and result patterns did not differ significantly from those found with the CBCL anxious/depressed symptom scale. Nonetheless, additional attention to these correlated emotional constructs in isolation of each other is warranted. &

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REFERENCES

1. Caprara GV, Paciello M, Gerbino M, Cugini C. Individual differences conducive to aggression and violence: trajectories and correlates of irritability and hostile rumination through adolescence. Aggress Behav. 2007;33:359-374.
2. Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. Adult outcomes of childhood dysregulation: a 14-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2010;49:1105-1116.
3. Brotman MA, Schmajuk M, Rich BA, *et al*. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry. 2006;60:991-997.
4. Biederman J, Petty CR, Monuteaux MC, *et al*. The Child Behavior Checklist-Pediatric Bipolar Disorder profile predicts a subsequent diagnosis of bipolar disorder and associated impairments in ADHD youth growing up: a longitudinal analysis. J Clin Psychiatry. 2009;70:732-740.
5. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011;168:129-142.
6. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry. 2009;166:1048-1054.
7. Copeland WE, Shanahan L, Costello J, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009;66:764-772.
8. Stringaris A, Goodman R. Mood lability and psychopathology in youth. Psychol Med. 2009;39:1237-1245.
9. Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J Child Adolesc Psychopharmacol. 2006;16:456-466.
10. Leibenluft E, Stoddard J. The developmental psychopathology of irritability. Dev Psychopathol. 2013;23:1473-1487.
11. Dougherty LR, Smith VC, Bufferd SJ, *et al*. Preschool irritability: longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. J Am Acad Child Adolesc Psychiatry. 2013;52:1304-1313.
12. Stoddard J, Stringaris A, Brotman M, Montville D, Pine DS, Leibenluft E. Irritability in child and adolescent anxiety disorders. Depress Anxiety. 2014;31:566-573.
13. Kuny AV, Althoff RR, Copeland W, *et al*. Separating the domains of oppositional behavior: comparing latent models of the Conners' Oppositional Subscale. J Am Acad Child Adolesc Psychiatry. 2013;52:172-183.
14. Eley TC, Lichtenstein P, Stevenson J. Sex differences in the etiology of aggressive and nonaggressive antisocial behavior: results from two twin studies. Child Dev. 1999;70:155-168.
15. Wiggins JL, Mitchell C, Stringaris A, Leibenluft E. Developmental trajectories of irritability and bidirectional associations with maternal depression. J Am Acad Child Adolesc Psychiatry. 2014;53:1191-1205.
16. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley T. Adolescent irritability: phenotypic associations and genetic links with depressed mood. Am J Psychiatry. 2012;169:47-54.
17. Perez JA, Otowa T, Roberson-Nay R, Hettema JM. The genetics of anxiety disorders. In: Charney DS, Buxbaum JD, Sklar P, Nestler EJ, eds. Neurobiology of Mental Illness. 4th ed. New York: Oxford University Press; 2013.
18. Eley TC, Bolton D, O'Connor TG, Perrin S, Smith P, Plomin R. A twin study of anxiety-related behaviours in pre-school children. J Child Psychol Psychiatry. 2003;44:945-960.
19. Achenbach TM. Manual of the Teacher's Report Form and 1991 Profile. Burlington, VT: University of Vermont Department of Psychiatry; 1991.
20. Achenbach YM. Integrative Guide for the 1991 CBCL/4-18, YSR, and TRF Profiles. Burlington, VT: University of Vermont Department of Psychiatry; 1991.
21. Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2003.
22. Lichtenstein P, Tuvblad C, Larsson H, Carlström E. The Swedish Twin Study of Child and Adolescent Development: the TCHAD-study. Twin Res Hum Genet. 2007;10:67-73.
23. Roberson-Nay R, Leibenluft E, Brotman MA. Longitudinal stability of genetic and environmental influences on irritability: from childhood to young adulthood. Am J Psychiatry. (In press).
24. Akaike H. Factor analysis and AIC. Psychometrika. 1987;52:317-332.
25. Muthén LK, Muthén BO. Mplus user's guide. Los Angeles: Muthén and Muthén; 2007.
26. Boker S, Neale M, Maes H, *et al*. OpenMx: an open source extended structural equation modeling framework. Psychometrika. 2011;76:306-317.
27. Boker S, Neale M, Maes H, *et al*. OpenMx: Multipurpose Software for Statistical Modeling. (Version R package version 1.0.4). 2011.
28. R Core Team: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2013. Available at: http://www.R-project.org/.
29. Kenny DA. Cross-lagged panel correlation: A test for spuriousness. Psychol Bull. 1975;82:887-903.
30. Kenny DA, Harackiewicz JM. Cross-lagged panel correlation: practice and promise. J Applied Psychol. 1979;64:372-379.
31. Neale MC, Cardon LR. Methodology for genetic studies of twins and families. Dordrecht, Netherlands: Klüver; 1992.
32. Nivard MG, Dolan CV, Kendler KS, *et al*. Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. Psychol Med. 2014;4:1-11.
33. Insel T, Cuthbert B, Garvey M, *et al*. Research Domain Criteria (RDoC): developing a valid diagnostic framework for research on mental disorders. Am J Psychiatry. 2010;167:748-751.
34. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. Arch Gen Psychiatry. 2003;60:837-844.
35. Merikangas KR, He J, Burstein M, *et al*. Lifetime prevalence of mental disorders in U.S. adolescents: results from the national comorbidity survey replication-adolescent supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49:980-989.
36. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. Behav Ther. 2004;35:205-230.
37. Wilamowska ZA, Thompson-Hollands J, Fairholme CP, Ellard KK, Farchione TJ, Barlow DH. Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. Depress Anxiety. 2010;27:882-890.
38. Ferdinand RF. Validity of the CBCL/YSR DSM-IV anxiety problems and affective problems. J Anx Disord. 2008;22:126-734.

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