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BRIEF REPORT

Genetic and Environmental Influences on Internalizing Psychopathology Across Age and Pubertal Development

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Symptoms of anxiety and depression are commonly comorbid and partially share a genetic etiology. Mean levels of anxiety and depression increase over the transition to adolescence, particularly in girls, suggesting a possible role of pubertal development in the activation of underlying genetic risks. The current study examined how genetic and environmental influences on anxiety and depression differed by chronological age and pubertal status. We analyzed composite scores from child self-reports and parent informant-reports of internalizing symptomology in a racially and socioeconomically diverse sample of 1,913 individual twins from 1,006 pairs (ages 8–20 years) from the Texas Twin Project. Biometric models tested age and pubertal status as moderators of genetic and environmental influences shared between and specific to anxiety and depression to determine whether etiology of internalizing symptomology differs across development as a function of age or puberty. Genetic influences did not increase as a function of age or puberty, but instead shared environmental effects decreased with age. In an exploratory model that considered the moderators simultaneously, developmental differences in etiology were reflected in genetic and environmental effects unique to depression. Results suggest that genetic variance in internalizing problems is relatively constant during adolescence, with environmental influences more varied across development.

Keywords: internalizing, anxiety, depression, puberty, behavioral genetics

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Internalizing problems are a broad class of psychopathology symptoms characterized by emotion dysregulation, depressed mood, fear, and worry (Zahn-Waxler, Klimes-Dougan, & Slattery, 2000). Individual differences in internalizing symptoms early in life forecast the eventual emergence of anxiety and depressive disorders throughout the life span (Bittner et al., 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998). Furthermore, average levels of internalizing symptomology increase during childhood and adolescence (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Hankin et al., 1998; Merikangas et al., 2010). Anxiety and depressive disorders show individual developmental trends, with average age of onset occurring earlier in childhood for anxiety relative to depressive disorders (Merikangas et al., 2010). However, the cumulative prevalence rates of mood disorders increase steeply in adolescence, from approximately 4% around age 8 to 17% at age 18, with prevalence increases in anxiety disorders increasing from approximately 23% to 32% during the same time frame (Merikangas et al., 2010). The current article uses a behavioral genetic design to test one hypothesis regarding why internalizing symptoms increase from childhood to adolescence—that advancing pubertal development activates genetic risks for internalizing symptoms.

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Previous Behavioral Genetic Research on Internalizing

Overall, behavioral genetic research provides evidence for heritable influence on anxiety and depressive disorders across the life span (Gregory & Eley, 2007; Hettema, Neale, & Kendler, 2001; Rice, Harold, & Thapar, 2002a; Sullivan, Neale, & Kendler, 2000). Genetic influences on internalizing symptoms possibly change with development, although the research on this hypothesis has been somewhat mixed. On average, the empirical literature supports moderate genetic influences across internalizing symptomology, with large variability in cross-sectional estimates (ranging from approximately 15–80% for depression symptoms and 0–70% for anxiety symptoms; Eaves et al., 1997; Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Lamb et al., 2010; Thapar & McGuffin, 1997; Topolski et al., 1997). Largely, the variability in these heritability estimates reflects methodological heterogeneity across samples, such as reporter, and measured construct (Eley, 1999; Gregory & Eley, 2007; Rice et al., 2002a). For instance, across internalizing symptomology, heritability derived from parent-reported measures tends to reflect stronger genetic influences than child-reports, particularly for anxiety disorders (reviewed in Goldsmith & Lemery, 2000; Gregory & Eley, 2007; Rice et al., 2002a). Some studies using child-reported symptoms found negligible genetic influences, with shared environmental influences predominating (Ehringer et al., 2006; Eley & Stevenson, 1999a). There is also considerable overlap between genetic influences on depression and anxiety, with shared genetic variants estimated to account for 30–80% of their comorbidity (Eley & Stevenson, 1999a; Mosing et al., 2009; Thapar & McGuffin, 1997; reviewed in Franić, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Gregory & Eley, 2007; Rice et al., 2002a).

Additionally, studies using age-heterogeneous samples tend to show higher heritability estimates in older samples, with shared environmental influences present for younger samples (Franić et al., 2010; Lamb et al., 2010; Rice, Harold, & Thapar, 2002b; Scourfield et al., 2003), although there are some conflicting reports (Eley & Stevenson, 1999b; Gjone, Stevenson, Sundet, & Eilertsen, 1996). In studies that have specifically evaluated developmental changes in the etiology of anxiety and depression, a meta-analysis indicates increases in the heritability of anxiety and depression from childhood to adulthood (Bergen, Gardner, & Kendler, 2007; Scourfield et al., 2003). Furthermore, a meta-analysis of longitudinal behavioral genetic studies of psychopathology indicates that genetic factors primarily account for the stability of internalizing symptomology over time, while environmental factors account for change across development (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2017). In addition to stable genetic influences, modest genetic innovation was also noted for internalizing symptoms, indicating emergence of new heritable variation due to genes not previously relevant for internalizing symptoms at earlier ages (Franić et al., 2010; Hannigan et al., 2017; Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008). Furthermore, both stable and innovative genetic influences have been found to contribute to the genetic liability shared across anxiety and depression symptoms, whereas nonshared environmental influences reflect more symptom- and time-specific influences (Waszczuk, Zavos, Gregory, & Eley, 2014, 2016). Taken together, the behavioral genetic literature supports a picture of dynamic developmental changes in the etiology of internalizing symptoms, but like the cross-sectional literature, there is some variability across extant results.

Puberty as a Developmentally Sensitive Period for the Development of Internalizing

The prevalence of internalizing symptoms increases overall from childhood into adolescence. However, females are particularly vulnerable to this developmental increase: After age 15, women are twice as likely to present with depression than men (Moffitt et al., 2007). In depression, midpuberty marks the period when prevalence in girls begins to surpass boys, above and beyond age (Angold, Costello, & Worthman, 1998). Pubertal status is additionally related to increased anxiety symptoms, particularly in girls (Reardon, Leen-Feldner, & Hayward, 2009).

This emerging sex difference has been hypothesized to be driven by sex-differentiated changes in biological and social processes during puberty (Angold et al., 1998; Brooks-Gunn, 1984). Puberty encompasses a diverse array of changes, which are centered on the activation of gonadal hormones resulting in reproductive maturity but also encompass emotional, cognitive, and social transitions (Mendle, 2014). The biopsychosocial transitions of puberty coincide not only with increases in mean levels of internalizing symptoms, particularly in girls, but also with potential increases in the heritability of internalizing symptoms, as suggested by previous meta-analyses (Bergen et al., 2007; Scourfield et al., 2003). Considered together, these lines of research suggest the hypothesis that genetic risks for internalizing symptoms are *activated* by the biological and/or social changes of puberty. By "activation," we mean simply that the overall heritability of internalizing symptoms is greater in postpubertal versus prepubertal/peripubertal children. Such activation effects could be due to (a) genetic amplification, in which the same genetic variants that were relevant to internalizing in prepubertal children continue to influence internalizing symptoms in postpubertal adolescents, but with larger effects, and/or (b) genetic innovation, in which new genetic variants not previously relevant to internalizing symptoms are "turned on" by the biological or social changes of puberty (Briley & Tucker-Drob, 2013). Discriminating between genetic amplification versus innovation requires longitudinal data; therefore, in the current cross-sectional study, we group both processes together under the umbrella of genetic activation.

Both the biological and social changes associated with the pubertal transition might lead to activations in genetic risks for internalizing symptomology. Gonadal hormones that increase at puberty, such as testosterone and estradiol, have been directly associated with internalizing symptoms, in studies of humans across the reproductive life span and in studies of nonhuman animals (Sisk & Zehr, 2005; Young, Midgley, Carlson, & Brown, 2000). Additionally, puberty-related hormones can affect gene expression through binding to DNA transcription factors present in the nervous system in the form of androgen and estrogen receptors (Nilsson & Gustafsson, 2000; Witt, 2007). Hormonal activation of genetic influence would potentially manifest as genetic innovation during puberty, as has been found in previous studies examining symptoms of anxiety and depression in adolescence (Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008).

Adolescents also experience new social demands and stressors as they transition through puberty, which may lead to increased

genetic influence through gene–environment interactions. For instance, school transitions during this period are associated with larger classrooms and more time spent away from the family unit (Anderson, Jacobs, Schramm, & Splittgerber, 2000). Increased autonomy may result in adolescents' greater freedom to select into environments consistent with their genes, thereby exacerbating genetic predispositions. Environmental risk factors for internalizing psychopathology also increase during puberty, with higher depression prevalence in girls being attributed to both increased exposure to stressors and greater stress reactivity (Hankin, Mermelstein, & Roesch, 2007). For instance, early maturing girls appear to be more vulnerable to social stressors, and this at least partially accounts for associations between earlier pubertal onset and internalizing symptoms (Natsuaki et al., 2009).

Goals of the Current Article

Taken together, the literature suggests that adolescents experience complex biological and social changes during the pubertal transition that might confer risk for internalizing problems. Importantly, environmental and hormonal puberty-related processes may interact with genetic influences, resulting in activation of genetic risks. This activation of genetic influence may appear as increasing heritability over the course of development as new puberty-related genetic factors emerge and/or as the relative importance of stable genetic factors increases, such has been noted in previous studies of developmental changes in internalizing etiology (Bergen et al., 2007; Hannigan et al., 2017). In the current study, we tested this using a structural equation modeling framework in which genetic and environmental variance was moderated by age and puberty. Increases in additive genetic variance as a function of developmental moderators would be evidence for genetic activation. Although previous studies suggest etiological changes over time, they have not distinguished between changes resulting from pubertal maturation versus changes due to chronological age. The goals of the current study, therefore, were to test (a) whether the magnitude of genetic and environmental influences on internalizing symptoms differed between childhood and adolescence and (b) whether these potential developmental differences in etiology occur as a function of chronological age or pubertal maturation.

Method

Participants

Twin pairs participated in the Texas Twin Project, a study of school-aged twins in the central Texas area (Harden, Tucker-Drob, & Tackett, 2013). Twins in Grades 3 (when children are typically 8–9 years old) through 12 (when children are typically 17–18 years old) were identified from public school rosters and invited to participate in an in-lab study. Grade 12 is the final year of secondary schooling in the United States. Twins' parents were asked to complete a survey in which they rated the twins on several phenotypes using a battery of validated psychometric instruments. All previous and ongoing aspects of this study received approval from the University of Texas Institutional Review Board under study titles "Genetic & Hormonal Influences on Adolescent Decision-Making" (2016-01–004) and "Cortisol, Socioeconomic Status, and Genetic Influence on Cognitive Development" (2014-11–0021). The current sample included 1,913 individuals from 1,006 pairs (356 monozygotic [MZ], 346 dizygotic [DZ] same sex, 304 dizygotic opposite sex; 50.5% female) ages 7.8–20.1 years ($M = 13.7$, $SD = 3.0$; $< 4\%$ of the sample was over age 18). This includes 31 triplet sets contributing three pairs each, one quadruplet set contributing six pairs, and four families with two sets of twins. This sample is racially and socioeconomically diverse and representative of the surrounding area. Fifty-five percent of the sample reported being non-Hispanic White, 16% reported being Hispanic/Latino, 9% reported being African American, 15% reported being another race or ethnicity, and 4% reported being multiracial/multiethnic (1% did not self-report race/ethnicity). Approximately one third of families reported having received at least one form of means-tested public assistance, such as food stamps, at some point since the twins were born.

Measures

Zygosity. Opposite-sex twin pairs were all classified as DZ. Zygosity for same-sex twin pairs was classified using a latent-class analysis (LCA) of survey items regarding twins' similarity. Using a five-item scale, parents and two trained research assistants rated the twins' physical similarity (e.g., "facial appearance") and the difficulty of telling them apart. For twin pairs over age 14, each twin also reported on these items. For a subsample of twin pairs ($n = 153$ pairs), zygosity was determined by genotyping (see online supplemental material for additional details), and LCA zygosity classification agreed with genotyped zygosity at $> 95\%$, consistent with previous studies (Heath et al., 2003). In cases of disagreement ($n = 7$ pairs), genotyped zygosity was used rather than LCA zygosity.

Internalizing. Measures of anxiety and depression were obtained via youth self-report and parent-report on an abbreviated version of the Achenbach Child Behavior Checklist (Achenbach, 1991; Lizotte, Chard-Wierschem, Loeber, & Stern, 1992). Parents and twins rated their agreement with each item on a 3-point scale from 0 = *not true* to 2 = *very true or often true.* Construction of combined-reporter composite scores was informed by a series of exploratory and confirmatory factor analyses of twin- and parent-report internalizing symptoms, which are detailed in the online supplemental materials. To create the combined-reporter composite scores, mean scores were calculated separately for anxiety and depression that included both twin- and parent-reported items, with items in which there was direct content overlap first averaged. Items are presented by reporter and construct in Table 1. Reporter-specific anxiety and depression mean scores were significantly correlated with each other ($r_{ANX} = .29$, $p < .001$; $r_{DEP} = .33$, $p < .001$) and were highly correlated with the combined-reporter composites (r between .67 and .91). Mean levels of anxiety and depression by age and sex are shown in Figure 1. Univariate anxiety and depression twin correlations are reported in Table 2.

Puberty. Pubertal status was measured using the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988), a self-report scale indexing physical changes that accompany puberty. Male-only items assessed facial hair growth and deepening of voice. Female-only items rated breast growth and onset of menarche. Both sexes responded to three items on height, skin, and body changes. Twins rated their development on a 4-point scale from 1 = *not yet begun to change* to 4 = *finished*

Table 1
Twin- and Parent-Reported Items by Factor

YSR item (twin-report)	CBCL item (parent-report)	Factor
23. "I am nervous or tense."		Anxiety
24. "I am too fearful or anxious."	25. "Too fearful or anxious."	Anxiety
25. "I am too guilty."	26. "Feels too guilty."	Anxiety
30. "I am self-conscious and easily embarrassed."	36. "Self-conscious or easily embarrassed."	Anxiety
45. "I worry a lot."	49. "Worries."	Anxiety
3. "There is very little that I enjoy."		Depression
7. "I feel lonely."		Depression
9. "I cry a lot."	5. "Cries a lot."	Depression
26. "I feel overtired without good reason."		Depression
43. "I don't have much energy."		Depression
44. "I am unhappy, sad, or depressed."	45. "Unhappy, sad, or depressed."	Depression
	15. "Fears going to school."	Depression
	19. "Feels worthless or inferior."	Depression
	48. "Withdrawn, doesn't get involved with others."	Depression

Anxiety combined reporter composite		Depression combined reporter composite	
Mean (*SD*)	α	Mean (*SD*)	α
.55 (.39)	.77	.29 (.29)	.71

Note. Raw means prior to log-transformation are reported. Five twin-report items and four parent-report items were included in the anxiety composite score, with all four parent-report items directly overlapping twin-report items in content. Six twin-report items and five-parent report items were included in the depression composite score, with two parent-report items overlapping with twin-report items in content. YSR = Youth Self-Report; CBCL = Child Behavior Checklist.

changing (menarche was recoded as 1 = *not reached* to 4 = *reached*). Mean scores were calculated by sex, with girls (M = 2.70, SD = .97) rated as slightly more developed than boys (M = 2.33, SD = .82), as expected given that girls on average reach puberty earlier than boys. The PDS has been established as a reliable measure of pubertal development in comparison to many other established measures of puberty (Bond et al., 2006; Harden, Kretsch, Moore, & Mendle, 2014; Shirtcliff, Dahl, & Pollak, 2009). In the current sample, age and pubertal status were correlated at r = .77. Twin-pair correlations for pubertal status were high in both MZ (r = .76) and DZ (r = .69) twin pairs.

Analyses

All structural equation modeling (SEM) was completed in *Mplus* Version 7.4 (Muthén & Muthén, 2010). The complex survey option was used to correct for nonindependence of data from families contributing more than one pair of twins. Additionally, triplet and quadruplet sets were weighted by .5 and .33, respectively, in order to correct for each individual appearing in multiple pairs. A standard twin model uses known genetic relatedness to decompose the variance in a phenotype into components attributable to additive genetics (*A;* correlated at 1 in MZ and .5 in DZ twins), shared environment (*C;* correlated at 1 for all twins), and nonshared environment (*E;* uncorrelated), which includes measurement error (Neale & Maes, 2004).

Specifically, as depicted in Figure 2, we fit a common and specific factor model parameterized by three sets of *ACE* factors specified to capture variance unique to anxiety, variance unique to depression, and variance common to both phenotypes (Loehlin, 1996). We fit three sets of models (one each for twin-report, parent-report, and combined report). The online supplemental materials report results for reporter-specific models, as well as models testing sex moderation on the etiology in internalizing symptoms. We note that our sample has low power to comprehensively assess sex differences (Verhulst, 2017). We focus here on results of models using the combined-report composite.

Prior to SEM, anxiety and depression mean scores were log-transformed to correct for positive skew. Age, age^2, sex, Age × Sex, African American race and Hispanic/Latino ethnicity, and puberty were regressed out of the mean scores to reduce the potential for main effects of moderators presenting as potential artifacts in the results (age was centered at 13). African American race and Hispanic/Latino ethnicity have been associated with earlier pubertal development (Wu, Mendola, & Buck, 2002). Consequently, membership in both race/ethnic groups was included as a covariate (with White and other race/ethnicity as the reference group) in order to reduce the potential for interaction effects being the artifact of group differences in pubertal development. Age and sex, including age^2 and an Age × Sex interaction, were included in order to prevent estimates of genetic influence from being

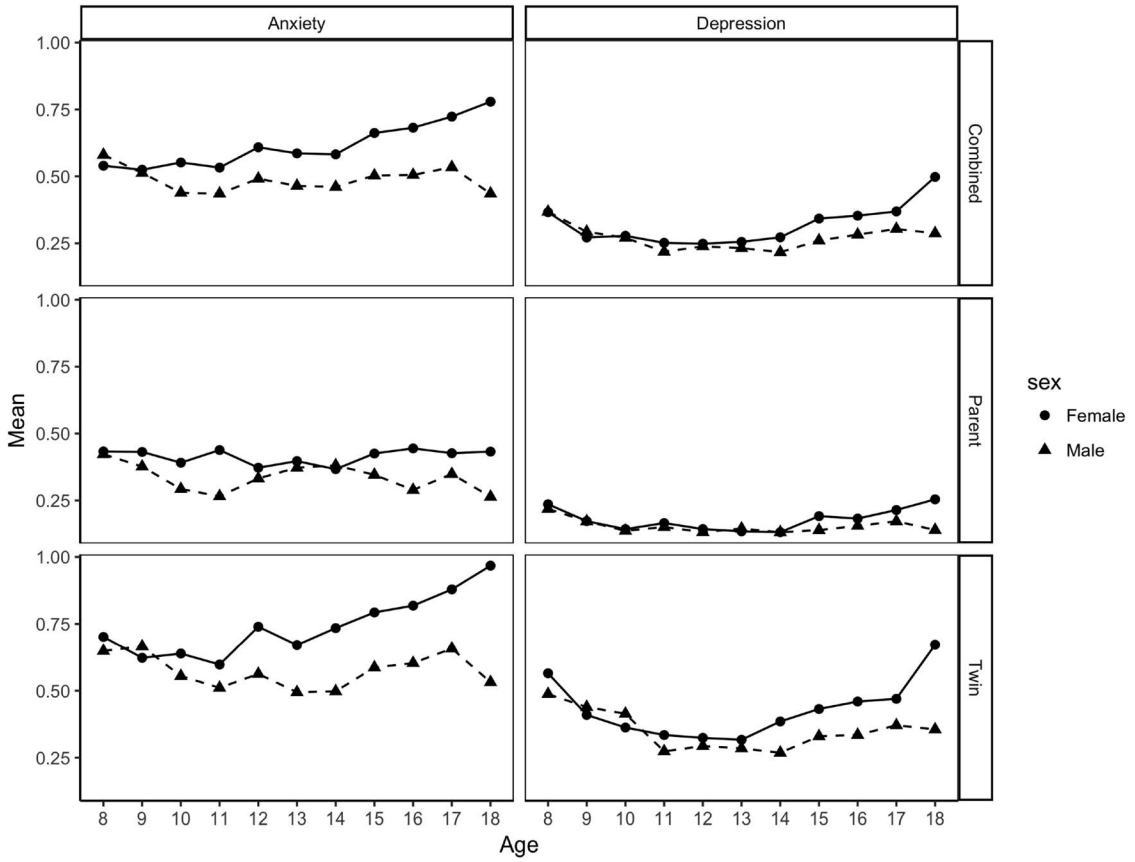

Figure 1. Anxiety and depression means by age and by sex. Ages 8–18 shown due to maximal coverage within the sample (< 4% of the sample over age 18). For the combined-report composite, both anxiety and depression symptoms increased with age (β = 0.09, *SE* = 0.03, $p < .001$; β = 0.06, *SE* = 0.03, $p < .05$, respectively).

overestimated due to the fact that MZ twins are necessarily same sex (McGue & Bouchard, 1984), as well as to maintain consistency with the analytic pipeline used in previous studies investigating other phenotypes in this data set (Harden et al., 2015). Standardized residuals were then specified as observed variables in SEM analyses. By controlling for the effects of age and puberty in the means of the focal variables, we removed the variance associated with age and with puberty from the phenotypic means, thereby accounting for the main effects of age and puberty on the constructs.

Table 2
Five-Group Univariate Twin Correlations by Reporter

Measure	MZF	MZM	DZF	DZM	DZO
Anxiety					
Combined	.48***	.21**	−.002	.154*	.122*
Twin	.43***	.30***	.02	.13	.12*
Parent	.50***	.29***	.10	.23**	.24**
Depression					
Combined	.43***	.31***	.18**	.15*	.21***
Twin	.44***	.31***	.12	.16	.20***
Parent	.30***	.21*	.18*	.05	.28***

Note. Anxiety and depression scores standardized prior to modeling. MZF = monozygotic female; MZM = monozygotic male; DZF = dizygotic female; DZM = dizygotic male; DZO = dizygotic opposite sex.
* $p < .05$. ** $p < .01$. *** $p < .001$.

To address our hypotheses regarding developmental differences in etiology, we fit a series of models in which the path coefficients from the *ACE* components to internalizing symptoms interacted with age, pubertal status, and both simultaneously (Purcell, 2002). Our primary analyses evaluated the interaction effects of age and pubertal status separately. These interaction models test whether the relative similarity of MZ to DZ twins differs as either a function of age or as a function of pubertal differences.

We fit an additional exploratory model that allowed for simultaneous differences across age and puberty in order to distinguish developmental differences specific to one above and beyond the other (e.g., differences across levels of puberty above and beyond what may be explained by differences across age). The simultaneous moderation analysis allows the variance of MZ and DZ twins to differ as a function of both age and puberty, thus accounting for the interaction effects of the other moderator. One noted difficulty is that age and puberty are collinear, and in tests of simultaneous moderators, power demands increase as the moderators are more correlated. Given the increased power demand to disentangle unique moderation effects, this model is considered exploratory. We previously followed this analytic strategy when investigating developmen-

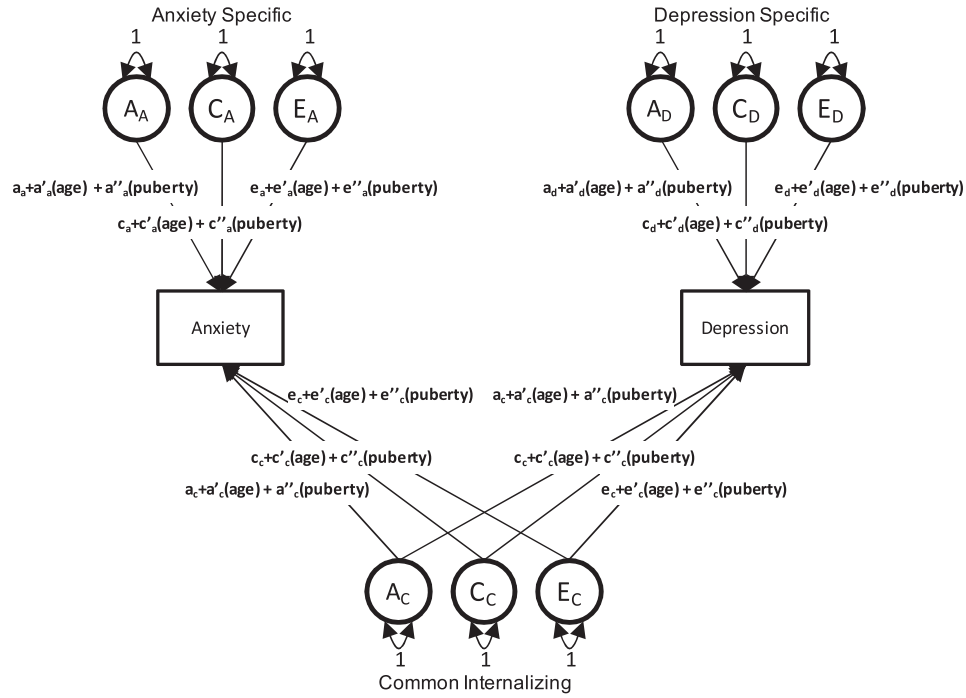

Figure 2. Behavioral genetic model of anxiety and depression. A = additive genetic; C = shared environmental; E = nonshared environmental. Only one twin per pair shown.

tal differences in genetic and environmental influences on externalizing (Harden et al., 2015).

The overall goodness of fit of the main effects–only model was evaluated using chi-square test of model fit, root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis index (TLI). Acceptability of model fit is demonstrated by lower, nonsignificant chi-square values; RMSEA $< .06$; and CFI/TLI values $> .95$ (Hu & Bentler, 1999). These global fits statistics were not available for the models including age and puberty interaction effects, so model comparisons were evaluating using Akaike information criterion (AIC) and Bayesian information criterion (BIC) to determine relative fit to the base model and to the other interaction models, with lower AIC/BIC noting improved fit. Additionally, we evaluated the significance of the interaction parameters to quantify the presence of developmental moderation.

Results

Genetic and Environmental Main Effects on Depression and Anxiety

The common and specific pathways model with no interaction terms (main effects only) fit the data well, $\chi^2 = 17.55$ (17), $p = .42$; RMSEA = .01; CFI/TLI = .999/.999; AIC/BIC = 10,183.55/10,237.54, and parameter estimates are reported in the first column of Table 3. Shared environmental variance was minimal regardless of internalizing domain; however, given previous evidence for shared environmental influence in internalizing, particularly for the younger portion of this age range, we maintained the *C* component in moderation models. Additive genetic and nonshared environmental influences were significant for variance common between anxiety and depression, as well as unique to each domain. Of the variance in anxiety, unique additive genetic effects accounted for 8.6% of the variance, unique nonshared environment 36.7%, common additive genetic effects with depression 21.6%, and common nonshared environment 33.1%. Of the variance in depression, unique additive genetic effects accounted for 16.5% of the variance, unique nonshared environment 28.0%, common additive genetic effects with anxiety 21.9%, and common nonshared environmental effects 33.6%.

Are There Age- or Puberty-Related Differences in Genetic Influences on Internalizing?

Age-only moderation. Estimates from a model that allowed the *ACE* paths to differ as a function of age are presented in the second column of Table 3. The AIC value was slightly lower (10,169.48) and the BIC value slightly higher (10,267.75) than in the no-moderation model, indicating relatively similar goodness of fit. Additive genetic and nonshared environmental influences were significant for all internalizing domains and were not moderated by age. Shared environmental variance was minimal, with significant decreases with age for variance common across internalizing domains. The total, model-implied shared environmental influence on anxiety was estimated at 11.3% at 8 years old and decreased to 0.6% at 18 years old (Figure 3, top panel). For depression, the total, model-implied shared environmental influence was estimated at 18.6% at 8 years old and decreased to 3.4% at 18 years old (Figure 3, bottom panel).

Table 3
Unstandardized Parameter Estimates: Combined Report Composite

Variable	No moderation	Age moderation	Puberty moderation	Age + puberty moderation
Variance common to anxiety and depression				
Main effect of A (a_c)	.46*** (.04)	.37** (.12)	.30 (.17)	.37** (.13)
Age interaction (ac′)	—	.05 (.05)	—	.05 (.04)
Puberty interaction (ac′′)	—	—	.09 (.08)	–.01 (.10)
Main effect of C (c_c)	.000 (.000)	.15 (.10)	.25 (.25)	.11 (.41)
Age interaction (cc′)	—	–.04** (.01)	—	.06 (.04)
Puberty interaction (cc′′)	—	—	–.09 (.10)	–.14 (.19)
Main effect of E (e_c)	.57*** (.03)	.58*** (.16)	.55*** (.06)	.58*** (.08)
Age interaction (ec′)	—	–.002 (.01)	—	–.02 (.02)
Puberty interaction (ec′′)	—	—	.02 (.03)	.03 (.05)
Variance unique to anxiety				
Main effect of A (a_a)	.29*** (.06)	.29*** (.07)	.37*** (.09)	.24 (.13)
Age interaction (aa′)	—	–.02 (.03)	—	–.01 (.04)
Puberty interaction (aa′′)	—	—	–.05 (.06)	–.03 (.06)
Main effect of C (c_a)	.000 (.000)	.001 (.13)	.000 (.001)	.000 (.000)
Age interaction (ca′)	—	–.001 (.13)	—	.000 (.000)
Puberty interaction (ca′′)	—	—	.000 (.001)	.000 (.000)
Main effect of E (e_a)	.60*** (.03)	.59*** (.03)	.63*** (.05)	.74*** (.05)
Age interaction (ea′)	—	.01 (.01)	—	.01 (.02)
Puberty interaction (ea′′)	—	—	–.02 (.03)	–.06 (.03)
Variance unique to depression				
Main effect of A (a_d)	.40*** (.05)	.34*** (.08)	.20 (.13)	.31*** (.09)
Age interaction (ad′)	—	.03 (.04)	—	–.02 (.02)
Puberty interaction (ad′′)	—	—	.11 (.11)	.13* (.05)
Main effect of C (c_d)	.000 (.001)	.08 (.15)	.08 (.16)	.38** (.14)
Age interaction (cd′)	—	.04 (.03)	—	.06* (.03)
Puberty interaction (cd′′)	—	—	–.11 (.15)	–.25** (.09)
Main effect of E (e_d)	.52*** (.4)	.53*** (.04)	.45*** (.07)	.05 (.15)
Age interaction (ed′)	—	.01 (.02)	—	.11*** (.03)
Puberty interaction (ed′′)	—	—	.05 (.05)	.07 (.09)
Model fit				
AIC	10,183.55	10,169.48	9,876.33	9,920.26
BIC	10,237.54	10,267.75	9,973.44	10,061.07

Note. Age centered at 13 and pubertal status centered at 1. Anxiety and depression composites standardized prior to modeling. Squaring the path coefficient provides the measure of genetic and environmental variance as a function of the interaction term (e.g., squaring the A path indicates heritability as a function of the moderator). *SE* in parentheses. AIC = Akaike information criterion; BIC = Bayesian information criterion.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Puberty-only moderation. Estimates from a model in which the *ACE* paths differed as a function of pubertal development are reported in the third column of Table 3. In comparison to the no-moderation and the age-only interaction models, the puberty moderation model showed lower AIC and BIC values (9,876.33/9,973.44), demonstrating better fit in the model allowing for differences across puberty. Despite improved fit, no significant moderation by puberty was detected. Nonshared environmental influence was significant across all internalizing domains. For variance unique to anxiety, additive genetic influence was significant, with no shared environmental influence estimated. For variance unique to depression and variance common across internalizing domains, the model suggested that both shared environmental influence and genetic influences were moderated by puberty, with slight increases in additive genetic influences and decreases in shared environmental influences. However, these effects were not statistically significant. Overall, familial variance (shared environmental plus genetic influences) remained fairly stable across puberty.

Both age and puberty moderation. Estimates from a model in which the *ACE* paths differed as a function of both age and puberty simultaneously are reported in the fourth column of Table 3. AIC and BIC values were lower for this model in comparison to both the no-moderation and the age-only moderation model, but they were slightly higher than the puberty-only moderation model (9,920.26/10,061.07) suggesting that the puberty-only model was the best-fitting, most parsimonious model, although these differences in model fit were minimal. First, for variance unique to depression, significant additive genetic and shared environmental influences were detected, with minimal nonshared environmental influences. Furthermore, several significant moderation effects were detected: Additive genetic influences increased with pubertal development, shared environmental influences increased with age after accounting for decreases with puberty, and nonshared environmental influences increased with age. None of these moderation effects were detected in previous models, but for the shared environment, this may have been masked by the countervailing influence of the other moderator. Second, for common variance across internalizing, significant additive genetic and nonshared environmental influences were detected, with modest shared environmental influences. The shared environment variance by age effect was no longer apparent, and no moderation effects were detected in the variance common across internalizing domains.

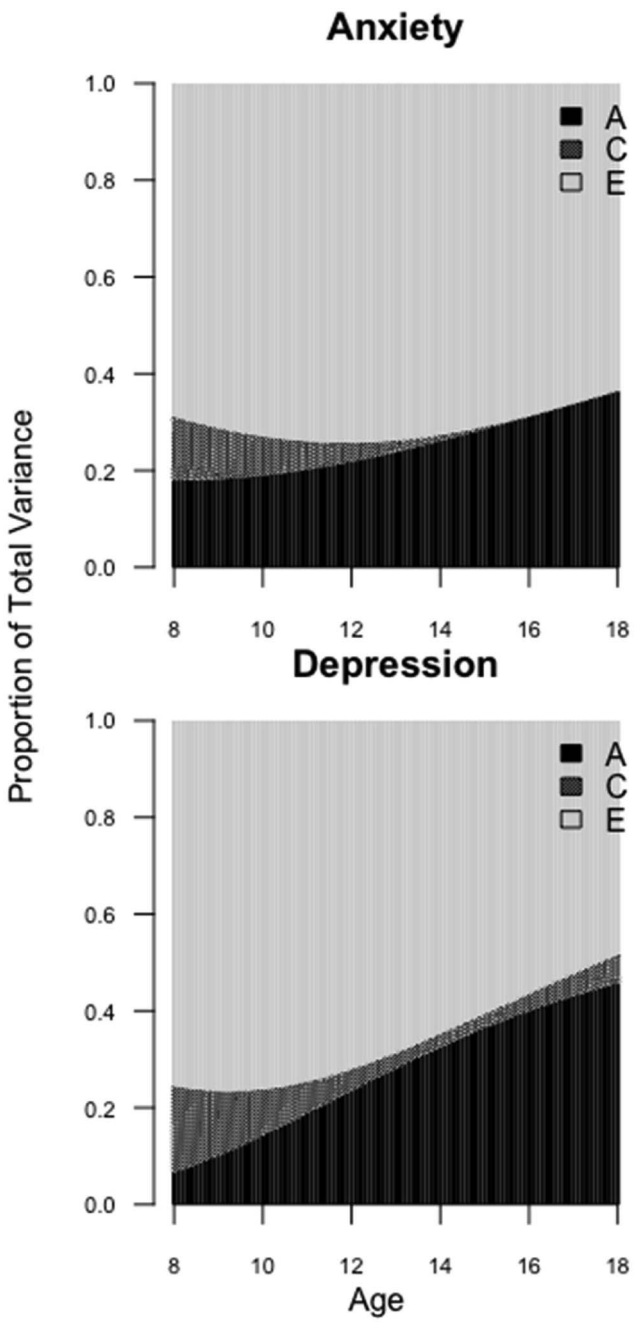

Figure 3. Age-related differences in the total variance of anxiety and depression. Figure based on parameters from age moderation model summarized in Table 3. Areas represent the proportion of total variance in anxiety (top panel) and depression (bottom panel) both shared with and unique from each other due to additive genetic (A), shared environmental (C), and nonshared environmental (E) influences.

Last, for variance unique to anxiety only, significant nonshared environmental influences were detected, with modest genetic influences and negligible shared environmental influences and moderation effects. It should be noted that this model was exploratory given the power demands of simultaneous age and puberty moderation due to their high phenotypic correlation. These effects are visually depicted in Figure 4.

Results of the age, puberty, and simultaneous moderation models specific to reporter are reported in the online supplemental materials, as well as tests of sex differences. There was no evidence of sex differences in etiology in the models using the combined-reporter composite. Reporter-specific models were largely in line with the combined results, indicating few significant developmental differences in etiology, with small interaction effects occurring on environmental influences in some but not all models.

Discussion

The current study aimed to detect whether the genetic and environmental etiology of internalizing symptoms differed across age or pubertal status in a sample of middle childhood to late adolescent twins. We combined self- and parent-reports of anxiety and depression symptoms and estimated influences that were common across the internalizing spectrum versus specific to anxiety or depression. Contrary to our hypothesis, there were no significant developmental differences as a function of age or pubertal status on the genetic variance common across internalizing or unique to anxiety or depression in our primary analyses considering age and puberty moderation individually. Moderation by age was detected for the variance common to internalizing symptoms, such that shared environmental influences decreased with age. The lack of significant interaction effects in these single developmental moderator models suggests that developmental differences in additive genetic variance in internalizing symptoms are relatively small. In our exploratory model considering simultaneous moderation as a function of age and as a function of puberty, several differences in the etiology unique to depression were noted. These included genetic increases with puberty, nonshared environmental increases with age, and countervailing effects of age and puberty on the shared environment. However, given the exploratory nature of this model, these results must be considered preliminary and interpreted with caution.

Epidemiological studies find increases in the prevalence of internalizing psychopathology, particularly in girls, following the onset of puberty, while some behavioral genetic studies have found evidence for developmental changes in the heritability of internalizing symptoms. Integrating these lines of research, we hypothesized that there would be puberty-related activation of genetic influences on internalizing, as evidenced by higher heritability of internalizing symptoms with greater pubertal development. However, we failed to find evidence for our hypothesis; genetic activation was detected only in an exploratory model considering differences across puberty after accounting for differences across chronological age. Overall, developmental differences in genetic influence across internalizing domains were minimal when the moderators were considered separately. Differences in the environmental influences on internalizing were associated largely with age rather than puberty.

Mood disorders more than quadruple in prevalence between the ages of 8 and 18, yet we find minimal age- or puberty-related differences in the magnitude of genetic variance in internalizing symptoms in a cross-sectional sample spanning this age range. Our prediction, which seemed theoretically plausible, that genetic in-

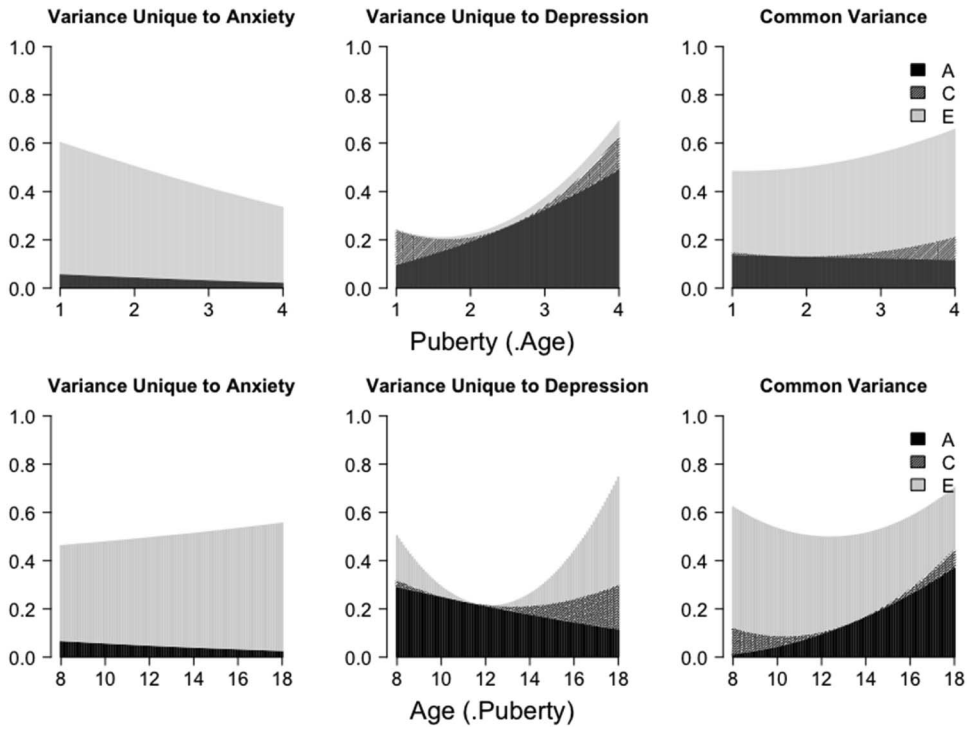

Figure 4. Developmental differences in genetic and environmental etiology on anxiety and depression. Figure based on parameter estimates from the simultaneous age and puberty moderation model (fourth column, Table 3). The top row of Puberty (.Age) depicts the moderating effects of age controlling for differences across puberty. The bottom row of Age (.Puberty) depicts the moderating effects of puberty controlling for differences across age. A = additive genetic; C = shared environmental; E = nonshared environmental. Unstandardized variance components are represented.

fluences on internalizing are activated with advancing age or pubertal development, was not supported, in contrast to our previous research on externalizing (Harden et al., 2015). With this understanding, future work should consider more complex hypotheses regarding the mechanisms underlying changes in internalizing that occur during this transitional period in development.

Results do not accord with our initial hypotheses, but they do align with some previous studies that have also failed to find evidence for developmental changes in genetic and environmental influences on internalizing symptomology. Specifically, some previous research reported threshold differences across age groups and across sex without concomitant differences in the etiology for those groups (Topolski et al., 1997). That is, the threshold of vulnerability to developing internalizing symptoms may change with development, even as the relative importance of genetic and environmental contribution to underlying risk remains the same. Similarly, longitudinal work has found evidence for relative stability in genetic influences, with only modest new genetic effects emerging over time (Bergen et al., 2007; Hannigan et al., 2017; Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008). In addition to modest genetic innovation, previous work also suggests the presence of genetic attenuation over age (Kendler, Gardner, & Lichtenstein, 2008). In the presence of both innovation and attenuation, the overall genetic variance may change relatively little, consistent with our results.

Several limitations and opportunities for future research warrant discussion. First, as noted above, despite a large sample size, due to the low prevalence of internalizing symptoms in our sample, there may be insufficient power to differentiate between interactions effects resulting from age and puberty simultaneously given their collinearity. As such, the results of our exploratory model are considered tentative prior to replication. However, it is important to note that this limit to power is specific to the simultaneous moderation models, as our sample is adequately powered to detect single moderation effects (Harden et al., 2015). Second, reporter differences have been identified as a source of variability in genetic and environmental estimates on internalizing symptoms in the previous literature (Gregory & Eley, 2007; Rice et al., 2002a). As such, we used anxiety and depression composite scores derived from a combination of both child- and parent-report in order to reduce effects of reporter differences in the models. (Results of reporter-specific measures are presented in the online supplemental materials.) When comparing informant and self-reports of child and adolescent internalizing symptoms, agreement between informants (e.g., parents and teachers) is higher than agreement between informant and self-reports (Phares, Compas, & Howell, 1989). Both informant and self-reports may be valuable in accurately depicting behavior, as they capitalize on differentially available information (Vazire & Carlson, 2011). However, it must be

considered that differences between child- and parent-report contribute to discrepancies between our findings and the literature.

The current study measured internalizing symptoms in a diverse population-based sample capturing normative as opposed to clinical ranges of psychopathology. Across the entire continuum, internalizing problems contribute to negative life outcomes, and normal-range variation in internalizing symptomology in adolescence forecasts the development of anxious and affective disorders later in life (Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000). Nevertheless, the extent to which genetic influences on normative variation in symptoms capture the same variants that are relevant for clinical-level pathology is unclear, and results might differ if using a high-risk or clinical sample selected for greater numbers of symptoms. Additionally, the current study used a cross-sectional sample to examine developmental moderation of internalizing etiology. Future studies using longitudinal assessment of internalizing symptoms, along with multimodel measurement of developmental changes (e.g., hormones, social contexts) in a genetically informative sample, will shed further light on the source of etiological changes across development. Identifying the mechanisms for sex-specific developmental changes in internalizing symptomology remains an important goal for future research.

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