Journal of Clinical Child & Adolescent Psychology, 00(00), 1–9, 2018

ISSN: 1537-4416 print/1537-4424 online
DOI: https://doi.org/10.1080/15374416.2018.1460847

Irritability, Externalizing, and Internalizing Psychopathology in Adolescence: Cross-Sectional and Longitudinal Associations and Moderation by Sex

Kathryn L. Humphreys and Sophie N. F. Schouboe
Department of Psychology, Stanford University

Katharina Kircanski, Ellen Leibenluft, and Argyris Stringaris
Emotion and Development Branch, National Institute of Mental Health

Ian H. Gotlib
Department of Psychology, Stanford University

Irritability is a common feature of many psychiatric disorders, including both externalizing and internalizing disorders. There is little research, however, examining associations between irritability and these symptom domains, particularly during the important developmental period of adolescence, characterized by sex differences in the prevalence of disorders. We examined the cross-sectional associations between irritability, measured with the Affective Reactivity Index, and symptoms of externalizing and internalizing domains of psychopathology, measured with the Youth Self Report, in a volunteer community sample (N = 183) of 9- to 13-year-old (M = 11.39, SD = 1.07) boys and girls (37% White/Caucasian, 8% Asian, 11% Hispanic, 8% African American, 2% Native American, 2% Pacific Islander, 28% Other, and 3% not reported). A subset of the sample (n = 112) provided data at a 2-year follow-up, used to extend these associations. There were no sex differences in levels of irritability; however, the associations between irritability and symptom domains were moderated by sex. Specifically, in girls, irritability was associated equally with externalizing and internalizing symptoms. In contrast, in boys, irritability was associated more strongly with externalizing symptoms than with internalizing symptoms. Thus, across both sexes, irritability was moderately associated with externalizing symptoms, but the association between irritability and internalizing symptoms was stronger in girls than in boys. At follow-up, sex moderated the association between baseline irritability and later externalizing and internalizing symptoms. These findings indicate that irritability is associated with both externalizing and internalizing symptoms in early adolescence and that irritability is associated with internalizing symptoms more strongly in girls than in boys.

Irritability is a proneness to anger that varies across individuals and may reach pathological levels (Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016). In youth, high levels of irritability have been linked to the subsequent development of multiple psychiatric disorders and to greater overall functional impairment (Brotman et al., 2006; Copeland, Brotman, & Costello, 2015; Dougherty et al., 2013; Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; Stringaris, Maughan, Copeland, Costello, & Angold, 2013). Although frequent and severe irritable mood and temper outbursts are core symptoms of the recent *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) diagnosis of disruptive mood dysregulation disorder (DMDD; American Psychiatric Association [APA], 2013), irritability is also an associated symptom of several other disorders, including oppositional defiant

Correspondence should be addressed to Kathryn Humphreys, Department of Psychology, Bldg. 420 Jordan Hall, Stanford University, Stanford, CA 94305. E-mail: humphrkl@gmail.com

disorder (ODD; Dougherty et al., 2013), conduct disorder (CD; Copeland et al., 2015), generalized anxiety disorder, and major depressive disorder (Stringaris, Cohen, Pine, & Leibenluft, 2009; Stringaris et al., 2013). Thus, irritability as a symptom spans across traditional domains of psychopathology, including both externalizing (i.e., behaviors directed outward) and internalizing (i.e., behaviors focused inward) difficulties. Boys and girls differ in their prevalence rates for many of these disorders that involve irritability; sex differences typically emerge during specific developmental periods, with a higher rate of emotional disorders first appearing in girls in adolescence (Hayward & Sanborn, 2002; Rutter, Caspi, & Moffitt, 2003). Documenting sex differences in the presentation of irritability and its relations with associated psychopathology has important clinical implications, including prioritizing screening for relevant disorders, considering potential functional impairment related to comorbidity (Oland & Shaw, 2005), and developing prevention and treatment strategies based on risk for internalizing (e.g., decreasing rumination) versus externalizing (e.g., positive refocusing) symptoms (Garnefski, Kraaij, & Van Etten, 2005).

In a longitudinal study of adolescents, girls were found to exhibit higher levels of both chronic and episodic irritability than were boys, a sex difference that emerged in later adolescence (Leibenluft et al., 2006). In another study that examined sex differences and irritability, 9- to 16-year-old children who were diagnosed with depression were subgrouped based on depressed mood and irritability: children with depressed mood only, children with irritable mood only, and children with both depressed and irritable mood (Stringaris et al., 2013). Stringaris et al. found that girls made up the clear majority of the group with depressed mood only (78%), boys made up the clear majority of the group with irritable mood only (73%), and boys and girls were roughly evenly distributed in the group with combined depressed and irritable mood (54%). Further, girls with both depressed *and* irritable mood had a significantly higher rate of comorbid CD than did girls with depressed mood only. Thus, boys with depression may be more likely to present with irritability, whereas girls with both irritability and depression may be at heightened risk for externalizing disorders, compared to girls with depression only. These findings highlight both the complexity of potential sex differences in irritability and comorbidity and the need for further study of irritability during early adolescence.

Early adolescence is a developmental period in which psychopathology typically emerges. In particular, the average age of onset for common disorders associated with irritability falls during adolescence, including major depressive disorder, generalized anxiety disorder, and CD (Lee et al., 2014; Paus, Keshavan, & Giedd, 2008). Sex differences in the prevalence of psychiatric disorders also emerge in adolescence, with girls having higher rates of internalizing disorders compared to boys (Hayward & Sanborn, 2002). Because epidemiological studies have spanned large age ranges, it is challenging to examine mechanisms of comorbidity across varying levels of development for boys and girls. Consequently, we know little about the association between irritability and psychopathology at the crucial developmental period of adolescence during which psychiatric disorders typically emerge (Lee et al., 2014). Therefore, to gain a better understanding of sex-specific associations between irritability and both externalizing and internalizing symptom domains, irritability should be examined during early adolescence. Although there is evidence of rank-order consistency in irritability from early to late childhood (see Caspi, Henry, McGee, Moffitt, & Silva, 1995), these developmental precursors may portend psychopathology that reaches the threshold for clinical significance only later in childhood, in adolescence, or in adulthood (Muris & Ollendick, 2005; Rende, 1993).

The symptom of irritability and its relation to broader categories of psychopathology have been studied longitudinally using epidemiological data. The Great Smoky Mountains Study included 1,420 rural and urban youth ages 9–19 years (Brotman et al., 2006; Copeland et al., 2015; Stringaris et al., 2013). In this sample, the lifetime prevalence of severe irritability (operationalized as severe mood dysregulation) was 3.3% (Brotman et al., 2006). Youth who met criteria for severe mood dysregulation had high rates of comorbid externalizing disorders (CD = 26%, ODD = 25%) and internalizing disorders (anxiety = 15%, depressive disorders = 13%). This work was followed by a meta-analysis in which estimates of the association between irritability and prospective psychopathology were obtained (Vidal-Ribas et al., 2016). Irritability was significantly associated with internalizing disorders, for example, depression (odds ratio [*OR*] = 1.80), 95% confidence interval (CI) [1.42, 2.27], and anxiety (*OR* = 1.72), 95% CI [1.31, 2.26]. Somewhat larger estimates were found in the predictive association between irritability and ODD (*OR* = 2.62), 95% CI [1.41, 4.85], which may be due in part to item overlap between irritability and ODD symptoms. The association between irritability and CD was not statistically significant (*OR* = 1.04), 95% CI [0.83, 1.30].

A final issue concerns the dimensional nature of irritability in relation to other forms of psychopathology. In the meta-analysis just noted, irritability was found to be more reliable over time when it was assessed as a dimensional construct than when it was measured as a categorical diagnosis (Vidal-Ribas et al., 2016). Although categorical diagnoses may sometimes be necessary in clinical practice, continuous variation within a disorder or within a set of symptoms is better studied using a dimensional approach (Kraemer, 2007; Kraemer, Noda, & O'Hara, 2004). Adopting a dimensional approach would take advantage of the naturally occurring variation in irritability and psychopathology (i.e., beyond categorical accounts), which would be particularly valuable for children who present prior to meeting full criteria for psychiatric disorders.

The goal of the present study was to examine the associations between irritability and symptoms of both externalizing and internalizing domains of psychopathology in early adolescence and to investigate how these associations differ by sex. In addition to examining cross-sectional associations at a single assessment, we conducted longitudinal analyses with irritability predicting subsequent symptoms at a follow-up assessment conducted approximately two years after the baseline assessment in a subset of the sample for whom we had longitudinal data. We used a well-established dimensional measure of irritability, identified as a priority for research on irritability (Vidal-Ribas et al., 2016), as well as dimensional assessments of externalizing and internalizing symptoms. Given potential sex differences in irritability and its relation to different domains of psychopathology (Stringaris et al., 2013), we examined the role of sex as a moderator of the associations between symptoms of irritability and externalizing and internalizing symptoms. For both cross-sectional and longitudinal approaches, we hypothesized that irritability would be positively associated with both internalizing and externalizing symptoms given prior research (Brotman et al., 2006; Copeland, Angold, Costello, & Egger, 2013; Leibenluft et al., 2006; Stringaris et al., 2013) but that irritability would be more strongly related to externalizing than to internalizing symptoms (e.g., Copeland et al., 2013). Given sex differences in levels of both irritability (e.g., Leibenluft et al., 2006) and psychopathology (Hayward & Sanborn, 2002), we hypothesized that girls would exhibit a stronger association between irritability and internalizing symptoms than would boys. In addition, we predicted that, among boys, the irritability would be more strongly associated with externalizing symptoms than with internalizing symptoms (Caspi et al., 1995; Hawes et al., 2016). Finally, we examined the stability of irritability from the baseline assessment to the 2-year follow-up in the full sample and as a function of sex.

METHODS

Participants

At Wave 1, participants were 183 children (84 boys, 99 girls) ages 9–13 years (*M* age = 11.39 years, *SD* = 1.07) from largely urban and suburban settings who were recruited to take part in a longitudinal study examining psychopathology across the transition through puberty. Participants were volunteers from the community and were not selected to be representative of the population. Children self-identified race: 37% reported White/Caucasian, 8% Asian, 11% Hispanic, 8% African American, 2% Native American, 2% Pacific Islander, 28% Other (e.g., more than one racial identity), and 3% not reported. One hundred seventy participants provided income information; of these, 58% reported an annual household income of over $100,000. Given that the cost of living in Santa Clara County is among the highest in the nation (median household income: $101,173; U.S. Census Bureau, n.d.), an income-to-needs ratio (i.e., household income/Santa Clara County low-income limit for the number of people in household) may better reflect socioeconomic status. Based on having an income-to-needs ratio less than 1, 28% of families in the sample were low income. Participants were selected using a combination of flyers and local media and were recruited on the basis of ranging experiences of early life adversity. We recruited only participants who were eligible to complete a neuroimaging scan because of the inclusion of a functional magnetic resonance imaging session in the larger study protocol, not included here. The study was approved by the Stanford University Institutional Review Board; participants and their parents gave assent and informed consent, respectively. Participants were screened for initial inclusion/exclusion criteria through a telephone interview; potentially eligible individuals were then invited to the laboratory for in-person interviews and assessments. Inclusion criteria were that children be between 9 and 13 years of age and be proficient in English. Exclusion criteria were factors that would preclude a functional magnetic resonance imaging scan (e.g., metal implants; for another component of this project); a history of major neurological or medical illness; severe learning disabilities that would make it difficult for participants to understand the study procedures; and, for female participants, the onset of menses.

At Wave 2, approximately two years after the initial session (*M* = 1.94 years, *SD* = 0.25), three fourths of the sample (112 participants: 53 boys, 59 girls) returned for a second visit in which the same assessments were conducted. There were no differences between those participants who did and did not participate in Wave 2 in terms of mean age, pubertal stage, irritability, externalizing, or internalizing measured at Wave 1 (all *p*s > .16). Further, boys and girls did not vary in the length of the interval between Wave 1 and Wave 2 assessments: 1.93 years (*SD* = 0.26) versus 1.74 years (*SD* = 0.26), respectively, $t(110) = 0.27$, $p = .79$.

Procedure

At Wave 1, participants attended two laboratory sessions with a caregiver; both the child and caregiver in each dyad completed measures about the child and family, including assessments of symptoms of psychopathology reported in this article. Because these analyses were not part of the original grant proposal, power analyses were not conducted prior to study initiation; the irritability assessment was introduced after the initiation of data collection. As just noted, 112 of the 183 children with Wave 1 data (73%) returned to complete these measures approximately two years later, as data collection is ongoing for the baseline sample. Participants were compensated for their time.

Measures

Affective Reactivity Index (ARI)

Youth self-reported irritability symptoms using the ARI (Stringaris, Goodman et al., 2012), a seven-item scale that assesses irritability during the preceding 6 months. Responses were scored on a 3-point scale from 0 (*not true*) to 2 (*certainly true*); we summed the first six items to compose the total score. In this sample, the internal consistency of the ARI was good both at baseline (α = .80; girls only α = .81, boys only α = .79) and the 2-year follow-up (α = .79; girls only α = .80, boys only α = .76).

Youth Report Form 4–18 (YSR)

The YSR (Achenbach, 1991) is a youth-reported 113-item rating scale that yields measures of externalizing and internalizing symptoms based on the child's behaviors during the preceding 6 months. Responses were scored on a 3-point scale from 0 (*not true*) to 2 (*very true or often true*). The YSR was normed on a large sample of children and has excellent reliability and validity (Achenbach, 1991). We used the total score from the Externalizing Problems and Internalizing Problems broadband scales as our measures of externalizing and internalizing symptoms, respectively. In this sample, the internal consistency of the internalizing total scores was good both at baseline (α = .91; girls only α = .92, boys only α = .89) and the 2-year follow-up (α = .90; girls only α = .91, boys only α = .90). Similar internal consistency values were found for externalizing total scores at baseline (α = .87; girls only α = .89, boys only α = .84) and the 2-year follow-up (α = .84; girls only α = .84, boys only α = .84).

Data Analysis

At Wave 1, we examined differences between boys and girls on demographic and clinical variables of interest using independent samples *t* tests and chi-square analyses. Then, we conducted a three-way analysis of covariance (ANCOVA; sex by irritability repeated over externalizing and internalizing) of symptom levels, covarying for age and pubertal stage. Finally, we used the PROCESS macro in SPSS (Hayes, 2013) to conduct follow-up analyses of moderation. All tests were two-tailed using an alpha of .05. These same analyses were also conducted on Wave 2 externalizing and internalizing symptoms predicted from Wave 1 irritability, controlling for Wave 2 age and pubertal stage. In addition, we examined irritability level change from Wave 1 to Wave 2 using repeated measures ANCOVA, covarying for age and pubertal stage, as well as partial correlations between Wave 1 and Wave 2 irritability scores after controlling for age and pubertal stage. Sex was included as a covariate or moderator in these overall analyses, and partial correlations were examined within each sex separately. Irritability scores and externalizing and internalizing symptoms were assessed for normality prior to inclusion, and a visual inspection and tests of skewness and kurtosis indicated that the data did not violate assumptions for normality.

RESULTS

Table 1 presents the demographic and clinical variables by sex. Boys and girls differed significantly in age; this finding was expected given that we recruited boys and girls to be matched on pubertal stage rather than on age (on average, boys tend to be older than girls at the same pubertal stage; Tanner & Whitehouse, 1976). There were no significant sex differences for race/ethnicity, household income, or for levels of irritability, externalizing, or internalizing symptoms. When age and pubertal stage were included as covariates using ANCOVA, the association between sex and irritability

TABLE 1
Demographic and Clinical Variables by Participant Sex

	Girls[a]	*Boys*[b]	t *or* χ^2
Age Wave 1	11.00 (1.03)	11.85 (0.93)	−5.81***
Pubertal Stage Wave 1	2.06 (0.73)	1.95 (0.67)	0.98
Race/Ethnicity			
White/Caucasian	33%	42%	5.50
African American	9%	7%	
Hispanic	9%	13%	
Asian	10%	14%	
Native American	2%	1%	
Pacific Islander	2%	0%	
Other	31%	19%	
No Response Given	3%	2%	
Family Income[c]			
Less than $25,000	8%	4%	1.94
$25,001–-$75,000	15%	17%	
$75,001–$150,000	34%	35%	
More than $150,000	36%	37%	
No Response Given	6%	8%	
Income-to-Needs Ratio[c]	1.29 (0.56)	1.34 (0.51)	−0.60
Irritability Wave 1	3.39 (2.70)	3.31 (2.77)	0.19
Externalizing Symptoms Wave 1	9.05 (7.22)	10.57 (6.39)	−1.48
Internalizing Symptoms Wave 1	13.53 (10.26)	11.29 (8.06)	1.63
Age Wave 2	12.91 (0.98)	13.82 (0.96)	−4.93***
Pubertal Stage Wave 2	3.40 (0.79)	3.49 (0.95)	−0.56
Irritability Wave 2[d]	3.02 (2.55)	2.55 (2.19)	1.04
Externalizing Symptoms Wave 2	7.90 (5.86)	9.45 (6.14)	−1.37
Internalizing Symptoms Wave 2	10.41 (8.67)	9.04 (8.30)	0.85

Note. Values are mean (standard deviation) or percentage.
[a]n = 99.
[b]n = 84.
[c]Available n = 170.
[d]At Wave 2, n = 59 girls and n = 53 boys.
***p < .001.

remained nonsignificant, $F(1, 179) = 0.05$, $p = .82$, partial $\eta^2 < .001$.

Cross-Sectional Associations at Wave 1

We conducted a three-way repeated measures ANCOVA (sex and irritability repeated over externalizing and internalizing) to test the interaction of sex, irritability, and symptom domain, covarying for age and pubertal stage. This analysis yielded a significant three-way interaction of sex, irritability, and symptom domain, $F(1, 172) = 6.16$, $p = .014$, partial $\eta^2 = .04$, indicating that the association between irritability and each symptom domain was moderated by sex. This interaction remained statistically significant after additional covariates (i.e., income-to-needs ratio; race, i.e., White/Caucasian vs. else) were included in the model, $F(1, 156) = 7.19$, $p = .008$, partial $\eta^2 = .04$. However, given the reduced sample size for participants with complete data for these variables, in subsequent analyses only age and pubertal stage were included in the models. We probed the nature of the three-way interaction in two ways. First, we used PROCESS (Model 1) to examine the role of sex as a moderator of the association between irritability and each domain separately, covarying for age and pubertal stage. The regression coefficients indicated that the degree of association between irritability and externalizing symptoms was significant in both girls (coefficient = 1.84, $SE = 0.20$), $t(172) = 9.36$, $p < .001$, and boys (coefficient = 1.42, $SE = 0.21$), $t(172) = 6.93$, $p < .001$; sex did not significantly moderate this association, $F(1, 172) = 2.10$, $p = .15$, indicating that boys and girls did not differ significantly in the strength of the relation between irritability and externalizing symptoms (see Figure 1A).

We repeated this analysis with internalizing symptoms as the outcome in the moderation analysis. Again, there was a significant association between irritability and internalizing symptoms in both girls (coefficient = 2.37, $SE = 0.30$), $t(172) = 7.91$, $p < .001$, and boys (coefficient = 1.00, $SE = 0.31$), $t(172) = 3.18$, $p = .002$. The interaction of sex and irritability in this analysis was statistically significant, $F(1, 172) = 9.92$, $p = .002$ (see Figure 1B). Simple partial correlations (covarying for the effects of age and pubertal stage) conducted within each sex separately indicated that the magnitude of the association

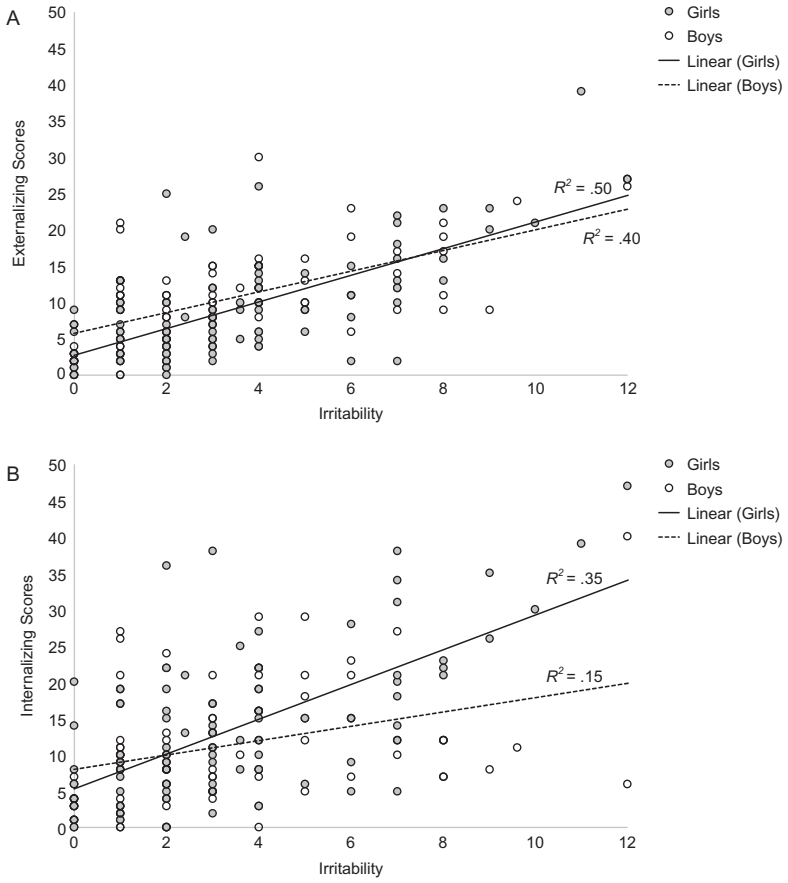

FIGURE 1 The cross-sectional association between irritability in (A) externalizing symptoms and (B) internalizing symptoms by participant sex.

between irritability and internalizing symptoms was nearly twice as strong in girls, $r(92) = .62$, $p < .001$, as it was in boys, $r(78) = .34$, $p = .002$.

Second, we conducted separate post hoc analyses within each sex to test whether the association between irritability and externalizing symptoms was comparable to the association between irritability and internalizing symptoms, after controlling for the effects of age and pubertal stage. In boys, the partial correlation between irritability and externalizing symptoms was significantly stronger than was the association between irritability and internalizing symptoms ($z = 2.92$, $p = .004$); in contrast, in girls these two correlations did not differ significantly ($z = -1.23$, $p = .22$).

Finally, because four items that assess irritability are included in the YSR Externalizing Total Scale (see Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012), we reran all analyses using the YSR scale with these four irritability items excluded. All results just reported remained statistically significant when the modified scale was used, indicating that the association between irritability and externalizing symptoms was not driven by the shared content of items assessing irritability.

Irritability at Wave 1 Predicting Externalizing and Internalizing Symptoms at Wave 2

We conducted analyses with irritability assessed at Wave 1 as a predictor of externalizing and internalizing symptoms assessed at Wave 2 (M age = 13.34, $SD = 1.07$) in the subset of participants who provided data at both waves. The three-way interaction of irritability, sex, and symptom domain found at Wave 1 was, again, statistically significant for irritability assessed at Wave 1 and symptoms assessed at Wave 2, $F(1, 106) = 4.92$, $p = .029$, partial $\eta^2 = .04$, covarying for age and pubertal stage at Wave 2. Moderation analysis indicated that the association between Wave 1 irritability and Wave 2 externalizing symptoms was significant in girls (coefficient = 0.68, $SE = 0.28$), $t(106) = 2.39$, $p = .019$, and boys (coefficient = 0.74, $SE = 0.28$), $t(106) = 2.60$, $p = .011$; as in the cross-sectional analyses, sex did not significantly moderate this association, $F(1, 106) = 0.02$, $p = .88$.

There was a significant association between Wave 1 irritability and Wave 2 internalizing symptoms in girls (coefficient = 1.21, $SE = 0.41$), $t(106) = 2.93$, $p = .004$, but not in boys (coefficient = 0.35, $SE = 0.41$), $t(106) = 0.85$, $p = .40$. Despite the difference in the magnitude of these effects, the interaction of sex and Wave 1 irritability did not reach statistical significance, $F(1, 106) = 2.16$, $p = .15$, likely due to the limited power in this smaller sample. Simple partial correlations (covarying for age and pubertal stage) conducted within each sex separately revealed that the magnitude of the association between irritability and Wave 2 internalizing symptoms was stronger in girls, $r(55) = .39$, $p = .003$, than in boys, $r(49) = .13$, $p = .38$. As in the cross-sectional analyses, in boys the partial correlation between irritability and externalizing symptoms was significantly stronger than was the association between irritability and internalizing symptoms ($z = 1.97$, $p = .049$); in contrast, in girls these two correlations did not differ significantly ($z = -0.60$, $p = .55$).

We repeated the analysis examining the three-way interaction of irritability, sex, and symptom domain covarying for Wave 1 externalizing and internalizing symptoms and for Wave 2 irritability levels; the interaction was no longer statistically significant, $F(1, 100) = 1.75$, $p = .19$, partial $\eta^2 = .02$. This conservative approach, however, is likely to be underpowered given that variance in Wave 2 symptom levels were predicted by scores at Wave 1 (i.e., correlations were .41 for externalizing and .38 for internalizing across both Waves).

Stability of Irritability

Using a repeated measures ANCOVA, covarying for age and pubertal stage at both assessments, we examined levels of irritability at Wave 1 and Wave 2 in individuals with both data points, with sex included as a potential moderator. The between-subjects analyses again indicated, across both time points, that there were no significant differences between boys and girls in terms of irritability, $F(1, 108) = 0.19$, $p = .662$, partial $\eta^2 = .002$. Further, neither wave, $F(1, 108) = 0.67$, $p = .42$, partial $\eta^2 = .006$, nor the Wave × Sex interaction, $F(1, 108) = 0.76$, $p = .39$, partial $\eta^2 = .007$, were associated with levels of irritability.

Partial correlations indicated that overall there was a positive, moderate association between Wave 1 and Wave 2 irritability, $r(106) = .47$, $p < .001$, after partialling out the effect of sex, age, and pubertal stage. Similar patterns were found when this was repeated within each sex separately, although this was somewhat stronger in girls, $r(53) = .58$, $p < .001$, than in boys, $r(47) = .39$, $p = .006$; this sex difference did not reach statistical significance ($Z = 1.21$, $p = .23$).

DISCUSSION

Researchers have demonstrated that the association of irritability with externalizing and internalizing psychopathology is variable and complex. In the present study we examined cross-sectional associations among irritability, externalizing and internalizing symptoms, and sex in a sample of 183 adolescents. Consistent with previous research and our hypotheses, we found positive associations between irritability and symptoms of both externalizing and internalizing psychopathology. Important to note, the magnitude of these associations was moderated by participant sex. Specifically, only in boys was there a stronger association between irritability and externalizing (compared to internalizing) symptoms; in girls, irritability was comparably associated with

symptoms of both broad domains of psychopathology. At a 2-year follow-up assessment, results were consistent with the patterns obtained in the cross-sectional analyses, indicating that, longitudinally, irritability is a stronger predictor of subsequent externalizing than of internalizing symptoms in boys but was equally predictive of both symptom domains in girls. In addition, we found that levels of irritability were relatively stable across the pubertal transition (i.e., from baseline to follow-up) for both girls and boys, with moderate positive correlations over time.

The present findings indicate that sex is an important factor in understanding the association between irritability and broad domains of psychopathology. In girls, there was a moderate positive association between irritability and both externalizing and internalizing symptoms, suggesting that irritability is associated with a wide range of mental health difficulties in adolescent girls. In contrast, in boys, although the association between irritability and both externalizing and internalizing symptoms was statistically significant and positive, the strength of the association between irritability and externalizing symptoms was twice as strong as the correlation between irritability and internalizing symptoms. This may reflect several factors. For example, there may be sex differences in phenotypic expression of the same underlying liability (i.e., external vs. internal manifestations of irritable mood). Sex-specific manifestations have been noted for other disorders (e.g., the genetic liability of Tourette syndrome and types of obsessive-compulsive disorder is similar but is more likely to present as chronic tics in males and obsessive-compulsive behaviors in female individuals; Pauls & Lechman, 1986). It is possible that, for individuals high in genetic liability for irritability, the expression of irritability corresponds to greater externalizing behaviors in boys, whereas in girls the corresponding symptom expressions are as likely to be externalizing as internalizing in nature. Sex differences in the role of genetically and environmentally mediated risk for irritability may be particularly salient in adolescence, such that genetic influences of irritability increase across development in male individuals and decrease in female individuals, whereas environmental influences have attenuating effects on irritability in male individuals but remain stable in female individuals (Roberson-Nay et al., 2015). It is also possible that documented sex differences in socialization pressures affect male individuals' willingness to report specific forms of symptoms (i.e., internalizing symptoms) even when they are experienced (Rutter et al., 2003).

Of interest, despite the finding that sex moderated the association between irritability and internalizing symptoms, there were no sex differences in overall levels of irritability. We should note, however, that large epidemiological samples are better suited to examining rates of sex differences in symptoms and disorders than are smaller, volunteer samples (Rutter et al., 2003). That said, previous findings are mixed with respect to sex differences in the prevalence of severe irritability and/or in levels of irritability measured dimensionally. Whereas some investigators have found higher levels of irritability in girls, particularly later in adolescence at older ages than the participants in our sample (Leibenluft et al., 2006; Leibenluft & Stoddard, 2013), other researchers have not found sex differences in irritability (Sparks et al., 2014; Stoddard et al., 2014; Stringaris, Goodman et al., 2012).

Irritability, as a symptom, is found across various forms of psychiatric disorder. From a nosologic perspective, DMDD is placed in the Depressive Disorders section of the *DSM* rather than in the Disruptive, Impulse-Control, and Conduct Disorders section along with ODD or CD. Of interest, the *DSM-5* scientific review committee preferred to co-list DMDD in both of these sections; however, *DSM* guidelines required selecting only one location. The final placement of DMDD within the Depressive Disorders section is likely due to the findings of shared genetic links between irritability and depression (Stringaris, Zavos et al., 2012) and that individuals who meet criteria for DMDD are at high risk for developing mood disorders later in life (Casteel & Valora, 2010), highlighting the mood component of DMDD (Roy, Lopes, & Klein, 2014). The *DSM-5* does not permit comorbidity of DMDD and ODD; priority is given to DMDD in the presence of co-occurring ODD (APA, 2013), and though it is likely that all children with DMDD would meet criteria for ODD, the reverse is not true. Thus, conceptually placing irritability within traditional separations of externalizing and internalizing psychopathology is difficult given (a) the overlap of irritability with both sets of symptom domains, (b) the high correlation between externalizing and internalizing psychopathology (Angold, Costello, & Erkanli, 1999), and (c) the association of irritability with high rates of comorbidity (Stringaris & Goodman, 2009). Consequently, conceptual divisions among forms of psychopathology, including irritability, may not be clear, particularly in early adolescence.

Despite our growing understanding of irritability as a risk factor in the etiology and course of psychopathology, its functional role is not well understood (Wakschlag et al., 2015). Recent work indicates that cognitive flexibility may be an important correlate of irritability in children who are experiencing psychopathology (Perlman et al., 2015). Providing further support for this possibility, Hawes et al. (2016) recently reported in a sample of 503 boys that cognitive control moderated the association between irritability and externalizing (i.e., antisocial personality features) in adulthood. More specifically, high levels of cognitive control assessed in adolescence appeared to buffer high-irritability boys from developing antisocial features. Thus, irritability in the context of strong self-regulatory abilities may protect against the development of functionally impairing externalizing symptoms, whereas individuals with high levels of irritability but lower flexibility are at greater risk for developing disorder. Future research would benefit from

examining executive functioning as a mediator and/or moderator of the association between irritability and the development of psychopathology.

We should note four limitations of this research. First, we conducted dimensional rather than categorical assessments of both irritability and internalizing and externalizing psychopathology, because the sample was relatively healthy and we did not recruit participants on the basis of clinical diagnosis or treatment seeking. Given that irritability can be conceptualized as a continuous trait that varies within and across the population, including in individuals who do and who do not have clinically diagnosable disorders (Born & Steiner, 1999), we believe that the use of the ARI to assess irritability dimensionally is reasonable in our nonclinical sample. Nevertheless, examining potential unique correlates of irritability in distinct forms of disorder remains an important area of study (Stoddard et al., 2014). It is possible that a group with a higher level of clinical impairment would be characterized by stronger associations between irritability and externalizing, and internalizing symptoms; the low mean severity and reduced range of irritability in this sample is a limitation, particularly considering the role of irritability in a clinical context. Second, the sample is skewed toward higher income. Although our income-to-needs ratio analyses indicated that at least one fourth of participants were identified as low income, the majority of participants had incomes well above the U.S. average, perhaps not surprising given the high cost of living in this area. It is important to consider both the high racial/ethnic diversity and the relatively high household income levels in this sample when generalizing to other samples. Third, although we conducted prospective analyses, a controlled experiment or intervention is needed to make strong causal inferences between irritability and other symptom domains. Finally, we used a single informant in assessing our variables of interest. Given discrepancies between informants in child psychopathology research (De Los Reyes & Kazdin, 2005), the use of multiple informants will likely provide a richer view of the manifestation of irritability, particularly given the importance of both internal mood states and external behaviors in contributing to the phenotype of irritability.

Despite these limitations, the present findings indicate that irritability is positively and moderately associated with both externalizing and internalizing symptoms in a volunteer community sample of early adolescents. Although boys and girls did not differ in their mean levels of irritability, the magnitude of the association between irritability and internalizing symptoms differed by sex. Whereas in girls, irritability was equally likely to be associated with both externalizing and internalizing symptoms, in boys, irritability was more strongly related to externalizing than to internalizing symptoms. We urge clinicians to note that children and adolescents who present with high levels of irritability are also likely to be at risk for or currently experiencing symptoms of externalizing and internalizing symptoms. Specifically, given that presence of high levels of irritability may result in underidentification of anxiety disorders (Stoddard et al., 2014), it will be important to conduct careful assessments of the internalizing domain of psychopathology, particularly in girls. Future research should extend the present findings by examining the consequences of the differential associations between irritability and externalizing and internalizing symptoms through adolescence and into early adulthood.

FUNDING

This research was supported by National Institute of Mental Health Grants F32-MH107129 (K.L.H.), F32-MH096385 (K.K.), and R01-MH101495 (I.H.G.), the Brain & Behavior Research Foundation (formerly NARSAD) Young Investigator Award 23819, and a Klingenstein Third Generation Foundation Fellowship Award to K.L.H. The authors have declared that they have no competing or potential conflicts of interest.

REFERENCES

Achenbach. (1991). *Integrative guide to the 1991 CBCL 4-18, YSR, and TRF profiled*. Burlington, VT: University of Vermont.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. Arlington, Virginia: Author.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *The Journal of Child Psychology and Psychiatry*, *40*(1), 57–87. doi:10.1111/jcpp.1999.40.issue-1

Born, L., & Steiner, M. (1999). Irritability: The forgotten dimension of female-specific mood disorders. *Archives of Women's Mental Health*, *2*(4), 153–167. doi:10.1007/s007370050044

Brotman, M. A., Schmajuk, M., Rich, B. A., Dickstein, D. P., Guyer, A. E., Costello, E. J., … Leibenluft, E. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological Psychiatry*, *60*(9), 991–997. doi:10.1016/j.biopsych.2006.08.042

Caspi, A., Henry, B., McGee, R. O., Moffitt, T. E., & Silva, P. A. (1995). Temperamental origins of child and adolescent behavior problems: From age three to age fifteen. *Child Development*, *66*(1), 55–68. doi:10.2307/1131190

Casteel, B., & Valora, J. (2010, February). *DSM-5 proposed revisions include new diagnostic category of temper dysregulation with dysphoria (TDD) criteria to differentiate children with TDD from those with bipolar disorder or oppositional defiant disorder*. American Psychiatric Association, Arlington, Virginia.

Copeland, W. E., Angold, A., Costello, E. J., & Egger, H. (2013). Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *American Journal of Psychiatry*, *170*(2), 173–179. doi:10.1176/appi.ajp.2012.12010132

Copeland, W. E., Brotman, M. A., & Costello, E. J. (2015). Normative irritability in youth: Developmental findings from the Great Smoky Mountains Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(8), 635–642. doi:10.1016/j.jaac.2015.05.008

De Los Reyes, A., & Kazdin, A. E. (2005). Informant discrepancies in the assessment of childhood psychopathology: A critical review, theoretical

framework, and recommendations for further study. *Psychological Bulletin*, *131*, 483–509. doi:10.1037/0033-2909.131.4.483

Dougherty, L. R., Smith, V. C., Bufferd, S. J., Stringaris, A., Leibenluft, E., Carlson, G. A., & Klein, D. N. (2013). Preschool irritability: Longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(12), 1304–1313. doi:10.1016/j.jaac.2013.09.007

Garnefski, N., Kraaij, V., & van Etten, M. (2005). Specificity of relations between adolescents' cognitive emotion regulation strategies and internalizing and externalizing psychopathology. *Journal of Adolescence*, *28* (5), 619–631. doi:10.1016/J.ADOLESCENCE.2004.12.009

Hawes, S. W., Perlman, S. B., Byrd, A. L., Raine, A., Loeber, R., & Pardini, D. A. (2016). Chronic anger as a precursor to adult antisocial personality features: The moderating influence of cognitive control. *Journal of Abnormal Psychology*, *125*(1), 64–74. doi:10.1037/abn0000129

Hayes, A. (2013). *Introduction to mediation, moderation, and conditional process analysis. New York, NY: Guilford*. New York, NY: Guilford Press.

Hayward, C., & Sanborn, K. (2002). Puberty and the Emergence of Gender Differences in Psychopathology. *Journal of Adolescent Health*, *30* (4SUPPL. 1), 49–58. doi:10.1016/S1054-139X(02)00336-1

Kraemer, H. C. (2007). DSM categories and dimensions in clinical and research contexts. *International Journal of Methods in Psychiatric Research*, *16*(Suppl 1), S8–S15. doi:10.1002/mpr.211

Kraemer, H. C., Noda, A., & O'Hara, R. (2004). Categorical versus dimensional approaches to diagnosis: Methodological challenges. *Journal of Psychiatric Research*, *38*(1), 17–25. doi:10.1016/S0022-3956(03)00097-9

Lee, B. F. S., Heimer, H., Giedd, N., Lein, E. S., Šestan, N., Weinberger, D. R., & Casey, B. J. (2014). Adolescent mental health— Opportunity and obligation. *Science*, *346*(6209), 547–549. doi:10.1126/science.1260497

Leibenluft, E., Cohen, P., Gorrindo, T., Brook, J. S., & Pine, D. S. (2006). Chronic versus episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. *Journal of Child and Adolescent Psychopharmacology*, *16*(4), 456–466. doi:10.1089/cap.2006.16.456

Leibenluft, E., & Stoddard, J. (2013). The developmental psychopathology of irritability. *Development and Psychopathology*, *25*(4pt2), 1473–1487. doi:10.1017/S0954579413000722

Muris, P., & Ollendick, T. H. (2005). The role of temperament in the etiology of child psychopathology. *Clinical Child and Family Psychology Review*, *8*(4), 271–289. doi:10.1007/s10567-005-8809-y

Oland, A. A., & Shaw, D. S. (2005). Pure versus co-occurring externalizing and internalizing symptoms in children: The potential role of socio-developmental milestones. *Clinical Child and Family Psychology Review*, *8*(4), 247–270. doi:10.1007/s10567-005-8808-z

Pauls, D. L., & Lechman, J. F. (1986). The inheritance of Gilles de la Tourette's syndrome and associated behaviors. *The New Englad Journal of Medicine*, *315*(16), 993–997. doi:10.1056/NEJM198610163151604

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9* (12), 947–957. doi:10.1038/nrn2513

Perlman, S. B., Jones, B. M., Wakschlag, L. S., Axelson, D., Birmaher, B., & Phillips, M. L. (2015). Neural substrates of child irritability in typically developing and psychiatric populations. *Developmental Cognitive Neuroscience*, *14*, 71–80. doi:10.1016/j.dcn.2015.07.003

Rende, R. D. (1993). Longitudinal relations between temperament traits and behavioral syndromes in middle childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *32*(2), 287–290. doi:10.1097/00004583-199303000-00008

Roberson-Nay, R., Leibenluft, E., Brotman, M. A., Myers, J., Larsson, H., Lichtenstein, P., & Kendler, K. S. (2015). Longitudinal stability of genetic and environmental influences on irritability: From childhood to young adulthood. *American Journal of Psychiatry*, *172*(7), 657–664. doi:10.1176/appi.ajp.2015.14040509

Roy, A. K., Lopes, V., & Klein, R. G. (2014). Disruptive mood dysregulation disorder: A new diagnostic approach to chronic irritability in youth. *American Journal of Psychiatry*, *171*(9), 918–924. doi:10.1176/appi.ajp.2014.13101301

Rutter, M., Caspi, A., & Moffitt, T. E. (2003). Using sex differences in psychopathology to study causal mechanisms: Unifying issues and research strategies. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *44*(8), 1092–1115. doi:10.1111/1469-7610.00194

Sparks, G. M., Axelson, D. A., Yu, H., Ha, W., Ballester, J., Diler, R. S., … Birmaher, B. (2014). Disruptive mood dysregulation disorder and chronic irritability in youth at familial risk for bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(4), 408–416. doi:10.1016/j.jaac.2013.12.026

Stoddard, J., Stringaris, A., Brotman, M. A., Montville, D., Pine, D. S., & Leibenluft, E. (2014). Irritability in child and adolescent anxiety disorders. *Depression and Anxiety*, *31*(7), 566–573. doi:10.1002/da.22151

Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. *The American Journal of Psychiatry*, *166*(9), 1048–1054. doi:10.1176/appi.ajp.2009.08121849

Stringaris, A., & Goodman, R. (2009). Mood lability and psychopathology in youth. *Psychological Medicine*, *39*(8), 1237–1245. doi:10.1017/S0033291708004662

Stringaris, A., Goodman, R., Ferdinando, S., Razdan, V., Muhrer, E., Leibenluft, E., & Brotman, M. A. (2012). The Affective Reactivity Index: A concise irritability scale for clinical and research settings. *Journal of Child Psychology and Psychiatry*, *53*(11), 1109–1117. doi:10.1111/j.1469-7610.2012.02561.x

Stringaris, A., Maughan, B., Copeland, W. S., Costello, E. J., & Angold, A. (2013). Irritable mood as a symptom of depression in youth: Prevalence, developmental, and clinical correlates in the great smoky mountains study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(8), 831–840. doi:10.1016/j.jaac.2013.05.017

Stringaris, A., Zavos, H., Leibenluft, E., Maughan, B., & Eley, T. C. (2012). Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *The American Journal of Psychiatry*, *169*, 47–54. doi:10.1176/appi.ajp.2011.10101549

Tanner, J. M., & Whitehouse, R. H. (1976). Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Archives of Disease in Childhood*, *51*(3), 170–179. doi:10.1136/adc.51.3.170

U.S. Census Bureau. (n.d.). *QuickFacts Santa Clara County, California; UNITED STATES*. Retrieved from https://www.census.gov/quickfacts/fact/table/santaclaracountycalifornia,US/PST045216

Vidal-Ribas, P., Brotman, M. A., Valdivieso, I., Leibenluft, E., & Stringaris, A. (2016). The status of irritability in psychiatry: A conceptual and quantitative review. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 556–570. doi:10.1016/j.jaac.2016.04.014

Wakschlag, L. S., Estabrook, R., Petitclerc, A., Henry, D., Burns, J. L., Perlman, S. B., … Briggs-Gowan, M. L. (2015). Clinical implications of a dimensional approach: The normal: Abnormalspectrum of early irritability. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(8), 626–634. doi:10.1016/j.jaac.2015.05.016