

Exploring Longitudinal Mechanisms of Irritability in Children: Implications for Cognitive-Behavioral Intervention

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Severe irritability is a common and clinically important problem longitudinally associated with internalizing and externalizing problems in children. To better understand these mechanisms and to inform treatment research, we tested cognitive-behavioral processes as candidate mediators in the paths from irritability to later problems. **Methods:** A school sample ($N = 238$, 48% female, ages 8–10) was assessed at ~6-month intervals in fall (T1) and spring (T2) of third to fourth grade, and again the following fall (T3). Measures assessed irritability (T1/predictor); anger and sadness coping, intolerance of uncertainty, and rumination; (T1–T2/mediators); and anxiety, depressive symptoms, reactive aggression, and oppositionality (T1–T3/outcomes). Focused cross-lagged panel models, controlling for gender and grade, were specified to examine full ($X_{T1} \rightarrow M_{T2} \rightarrow Y_{T3}$) and half ($X_{T1} \rightarrow M_{T2}$; $M_{T1} \rightarrow Y_{T2}$) longitudinal mediation. Across one or more intervals, irritability predicted higher

depressive symptoms, anxiety, reactive aggression, oppositionality, intolerance of uncertainty, and poor emotion coping. From T1 irritability to T2/T3 outcomes, mediation was found for poor sadness coping leading to reactive aggression and oppositionality; poor anger coping to anxiety, depressive symptoms, and oppositionality; and intolerance of uncertainty to anxiety. Results offer further evidence for internalizing and externalizing outcomes of youth irritability and new evidence suggesting underlying mechanisms. Irritability may confer risk for externalizing problems via poor sadness/anger coping, and for internalizing problems via poor anger coping and intolerance of uncertainty. Theoretical models and psychosocial treatment should consider addressing regulation of various unpleasant emotions as well as psychological flexibility and tolerating uncertainty.

Keywords: irritability; dysregulation; treatment mechanisms; transdiagnostic; emotion regulation

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BROADLY DEFINED AS A PROPENSITY for experiencing anger, irritability is a universal human experience with interindividual, intraindividual, and developmental variability (Stringaris & Taylor, 2015). While normative irritability is transient and mild, severe irritability can include aggression and is associated with depression, anxiety, and social and behavioral problems in children and adolescents (e.g., Burke, Hipwell, & Loeber, 2010; Evans, Pederson, Fite, Blossom, & Cooley, 2016; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016). Recent literature reviews (Brotman, Kircanski, & Leibenluft,

2017; Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Evans et al., 2017; Stringaris, Vidal-Ribas, Brotman, & Leibenluft, 2018) demonstrate the clinical and developmental significance of severe irritability. Further, irritability is a transdiagnostic feature of over a dozen disorders (e.g., oppositional defiant disorder [ODD], disruptive mood dysregulation disorder [DMDD], anxiety disorders, depression) and an associated feature of many more (e.g., autism spectrum disorder [ASD], attention-deficit/hyperactivity disorder [ADHD]). Clearly, irritability is a clinically important problem.

Unfortunately, extant research provides limited guidance to inform the treatment and conceptualization of severe irritability in youth. Severe irritability longitudinally predicts multiple internalizing and externalizing problems (Vidal-Ribas et al., 2016), but little is known about how these developmental pathways unfold or how treatments might address them (Evans et al., 2017). In particular, there is a need for research to help identify specific emotion-regulatory skills and deficits that may offer tractable targets for psychotherapeutic intervention, before irritability leads to subsequent problems with mood, anxiety, and behavioral disorders.

To this end, the present study explores the roles of three candidate mediators—emotion coping, intolerance of uncertainty, and rumination—in the progression from irritability to anxiety, depressive symptoms, reactive aggression, and oppositional behavior. In doing so, we adopt a dimensional, transdiagnostic, experimental therapeutics framework. Below we provide further rationale for this approach, for the selected mediators, and for how they may relate to irritability as well as anxiety, depression, and externalizing behaviors.

Exploring Candidate Mediators

The logic of the present study is consistent with several recent recommendations, including those for advancing evidence-based practice in youth mental health (e.g., Ng & Weisz, 2016; Roberts, Blossom, Evans, Amaro, & Kanine, 2017) and for advancing the clinical science of irritability from a transdiagnostic perspective (Meyers, DeSerisy, & Roy, 2017; Zachary & Jones, 2019). In particular, we adopt an experimental therapeutics framework (Insel & Gogtay, 2014) from a youth psychotherapy perspective. Experimental therapeutics involves identifying putative mechanisms of psychopathology, developing interventions to target those mechanisms, testing whether the treatment exerts the hypothesized effect, and evaluating whether this, in turn, leads to clinical improvement. Adopting such a paradigm entails several challenges for behavioral interventions insofar as the “target” of a behavioral manifestation

may be complex and multifaceted, with multilevel underpinnings (Lewandowski, Ongur, & Keshavan, 2018). Indeed, severe irritability is quite complex and multifaceted, with great diversity in its clinical manifestations (e.g., irritable mood, verbal aggression, physical aggression) and developmental outcomes (e.g., depression, anxiety, ODD; Brotman, Kircanski, & Leibenluft, 2017; Stringaris & Taylor, 2015; Stringaris et al., 2018). Accordingly, it would be useful to better understand the pathways from irritability to its more severe internalizing and externalizing outcomes (Vidal-Ribas et al., 2016).

Brotman, Kircanski, Stringaris, et al.’s (2017) translational model of irritability provides a useful framework through which to develop this kind of research to improve understanding, assessment, and treatment. This model suggests that threat bias (defined as maladaptive attention to threat) and aberrant frustrative nonreward (defined as one’s response to blocked goal attainment) are key processes underlying irritability (Brotman, Kircanski, Stringaris, et al., 2017). In this way, irritability is not only a precursor to but also shares common underpinnings with anxiety (e.g., threat bias, common neural circuitry), depression (e.g., mood disturbance, negative affect), and aggression (e.g., threat bias, and lowered threshold for annoyance and behavioral response).

Still, relatively little is known about the nature of irritability’s associations with anxiety, aggression, and depression. There is a considerable amount of research on the psychological vulnerabilities underlying these internalizing and externalizing problems, many of which are transdiagnostic in character and may help account for the linkages to irritability. Some of these processes may be especially relevant to irritability and may shed light on how and why it confers risk for future psychopathology. From an experimental therapeutics perspective, a better understanding of these developmental pathways could help advance the treatment of irritability and the prevention of internalizing and externalizing disorders. Accordingly, we explore poor emotion coping, intolerance of uncertainty, and rumination as possible mediators in the progression from irritability to subsequent internalizing and externalizing problems.

EMOTION COPING

The capacity to experience and manage different emotions has important implications for psychological well-being. An inability to cope with negative emotions can increase risk for both internalizing and externalizing psychopathology (Compas et al., 2017). Irritability has been defined as a propensity toward anger, which may lead to

aggression (Toohey & DiGiuseppe, 2017; Vidal-Ribas et al., 2016)—in other words, irritability involves a limited ability to cope with unpleasant emotions. Given the association between irritability and various emotional and behavioral problems, it is possible that irritability obstructs youths' ability to adaptively cope with a host of unpleasant emotions, especially sadness or anger, which in turn, increases risk for internalizing and externalizing problems. Some evidence supports these hypotheses. Malhi, Byrow, Outhred, Das, and Fritz (2017) found that, among adolescent females, dysfunctional emotion regulation may play a mediating role in the path from irritability to internalizing problems—however, this study was only cross-sectional. In a longitudinal mediation study, Derella, Johnston, Loeber, and Burke (2019) found that, among school-age boys with conduct problems, a cognitive-behavioral intervention effectively reduced irritability via an indirect pathway involving improvement in emotion regulation skills. Thus, psychosocial treatments targeting emotion regulation may be useful in reducing irritability and related problems. However, further focused, longitudinal research is needed. Here, we investigate coping with *anger* and *sadness* specifically, as these may help elucidate the aggressive and mood components of irritability (Carlson & Klein, 2018).

INTOLERANCE OF UNCERTAINTY

Intolerance of uncertainty, or the tendency for an individual to perceive uncertainty as dangerous, contributes to the development and maintenance of anxiety in youth (Dugas, Buhr, and Ladouceur, 2004). Irritability and intolerance of uncertainty share a common framework, as both represent dysfunctional threat processing predisposing individuals to perceive stimuli as more threatening than they actually are. Similarly, intolerance of uncertainty is a transdiagnostic approach to potential threat in the negative valence system of Research Domain Criteria (RDoC; Fernandez, Jazaieri, & Gross, 2016). It is likely that chronic irritability negatively alters an individual's processing of threat-related information resulting in downstream effects on cognitions and behavior. Traditionally, theoretical models have treated threat bias differently for aggression (Crick & Dodge, 1994) compared to anxiety (Grube & Nitschke, 2013). However, more recent research has suggested common neural and physiological underpinnings in threat processing for irritability as for anxiety (Brotman, Kircanski, Stringaris, et al., 2017; Kircanski et al., 2018)—that is, in both reactive aggression and anxiety, aberrant threat processing increases the likelihood of perceiving a threat; the

distinction arises in the behavioral response activated (aggression involves approach/fight, anxiety involves withdrawal/flight). The same psychological processes implicated in anxiety and reactive aggression also warrant investigation in irritability. Intolerance of uncertainty fits within the aberrant threat processing implicated in Brotman, Kircanski, Stringaris, et al.'s (2017) translational model. It is possible that over time, this limited flexibility associated with irritability could predict subsequent internalizing and externalizing problems.

RUMINATION

Broadly considered a maladaptive emotion regulation strategy, rumination refers to a process of repetitive negative thinking. A wealth of research indicates that rumination maintains and exacerbates internalizing symptoms (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Distinct from worry, rumination involves a process of reviewing past events (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). A growing body of research suggests that rumination may contribute to symptoms of both anxiety and depression (Aldao et al., 2010). The response styles theory of depression (Nolen-Hoeksema, 1991), which suggests that an individual's propensity to engage in a ruminative thought process following experience of negative mood may lead to depression, provides a framework by which irritability may contribute to depression in youth by increasing risk for rumination. Indeed, previous research suggests that early temperament characterized by excessive emotionality assessed at age 3, in conjunction with poor inhibitory control, longitudinally predicts rumination at age 9 (Schweizer, Olino, Dyson, Lappook, & Klein, 2017). Functionally, irritability may capture a similar process, such that an individual with limited frustration tolerance and a tendency to display anger may face increased risk to ruminate, and consequently increase risk for depression. Preliminary support for this model is illustrated in a recent study by Hamilton et al. (2017), showing that trait-like negative affect predicts maladaptive rumination. Similarly, irritability is conceptualized as negatively valenced mood, sometimes described as angry "stewing inside" (Vidal-Ribas et al., 2016). Longitudinally, then, irritability could lead to higher levels of rumination, which in turn might lead to greater depressive symptoms.

The Present Study

Based on this literature, and to advance the clinical science of severe irritability, the present study investigates three putative mechanisms (emotion [anger, sadness] coping, intolerance of uncertainty, and rumination) as possible mediators in the path

from irritability to subsequent emotional and behavioral outcomes (anxiety, depressive symptoms, reactive aggression, and oppositionality) among school-age children. We focus on this developmental period for several reasons: (a) to *inform intervention* at an age when chronic irritable mood and disruptive temper outbursts are common and impairing but non-normative, suggesting clinical significance; (b) to *inform prevention* of future problems (including depression, ODD/conduct disorder [CD], and many anxiety disorders) during or before their likely onset; and (c) to do so at an age when *cognitive-behavioral strategies may be tractable*, given the development of self-regulatory skills in middle childhood, the availability of elementary socio-emotional curricula, and the effectiveness of child- and family-focused interventions at this age.

Because the research reviewed above supports the inclusion of these variables in this way, we put forth the general hypothesis that all three candidate mediators may play a role in the progression from irritability to subsequent emotional and behavioral problems—however, specific paths within these models were viewed as exploratory, intended to help guide future research and intervention development. Finally, we explored gender as a moderator of the direct and indirect paths among irritability, its outcomes, and the proposed mediating variables.

Methods

PARTICIPANTS AND PROCEDURES

Participants were a school-based sample of 238 children (51.7% male; $M_{\text{age}} = 8.9$ years, range 8–10), who at baseline were enrolled in third grade ($n = 106$) or fourth grade ($n = 132$). Children were recruited and assessed on three occasions separated by ~6-month intervals in consecutive fall (T1), spring (T2), and fall (T3) semesters. Self- and teacher-report rating scale measures were collected during the last month of each semester. Self-report measures were collected in approximately 30-minute group administrations. Three trained research assistants read measures aloud while participating students followed along with paper and pencil (teachers and nonparticipating students were not present during administration). Teacher-report data collection occurred separately but roughly concurrently, using de-identified online surveys that teachers completed on all students in their classroom. Teachers were compensated with gift cards, and students were compensated with prizes (e.g., colorful pencils). Parent consent, youth assent, and teacher consent were collected. Of the total sample (defined as the 238 for whom *any* T1 data were collected), the availability of measures at

each occasion was as follows: T1 = 93.7–99.6%, T2 = 92.0–99.2%, and T3 = 71.0–86.6% (see [Table 1](#) for exact figures). This study was approved by the researchers' institutional review board and conducted in partnership with the school's administration.

MEASURES

Predictor Variable

Irritability at T1 was assessed using the self-report version of the Affective Reactivity Index (ARI). This instrument was developed by [Stringaris et al. \(2012\)](#) to serve as a brief unidimensional rating scale for assessing youth irritability in clinical and research contexts. It includes six items (e.g., easily annoyed by others, get angry frequently) assessing different facets of irritability, rated on a 3-point scale including 0 (*not true*), 1 (*somewhat true*), and 2 (*certainly true*). The original ARI has a seventh item about impairment that is not part of the total score, and therefore was not used here. Responses to these items were averaged for analyses. Internal consistency was good ($\alpha = .85$).

Candidate Mediator Variables

Emotion coping was assessed using the Children's Emotion Management Scales for Anger and Sadness Coping (CEMS; [Zeman, Cassano, Suveg, & Shipman, 2010](#); [Zeman, Shipman, & Penza-Clyde, 2001](#); [Zeman, Shipman, & Suveg, 2002](#)). The complete CEMS suite includes three different measures targeting anger, sadness, and worry, each with three subscales assessing inhibition, dysregulation, and coping with respect to the emotion of interest. In the present study, only the coping subscales were administered because these provide an index of a child's perceived ability to effectively manage unpleasant emotions—a potentially modifiable target for treatment. At T1 and T2, respectively, internal consistency was acceptable for anger coping (α s: .74, .79) and sadness coping (α s: .73, .69). The worry coping scales were also administered, but because their reliability coefficients were below acceptable (α s: .56, .55), they were not considered for analyses. All items were rated on a 3-point scale from 1 (*hardly ever*) to 3 (*often*), using mean scores for analyses. Anger coping includes four items (e.g., "When I am feeling mad, I control my temper") and sadness coping includes five items (e.g., "I try to calmly deal with what is making me sad").

Intolerance of uncertainty was assessed with the Intolerance of Uncertainty Scale Short Form for Children (IUS-C; [Boulter, Freeston, South, & Rodgers, 2014](#)). Designed and validated for use in child and adolescent populations, the IUS-C was adapted from the adult-oriented Intolerance of

Table 1
Descriptive Statistics and Correlations of Study Variables

	Univariate characteristics			Autocorrelations		Bivariate correlations									
	<i>N</i>	<i>M</i>	<i>SD</i>	T1	T2	1	2	3	4	5	6	7	8	Female	Grade
Time 1															
1. Irritability	224	0.43	0.50	1	–	1	–	–	–	–	–	–	–	–.10	–.10
2. Anger coping	225	2.18	0.58	1	–	–.55**	1	–	–	–	–	–	–	.08	.13*
3. Sadness coping	225	2.12	0.56	1	–	–.26**	.49**	1	–	–	–	–	–	–.12	.05
4. Intolerance of uncertainty	224	2.06	0.82	1	–	.56**	–.16*	–.19**	1	–	–	–	–	.10	–.08
5. Rumination	224	1.70	0.70	1	–	.55**	–.13*	–.28**	.69**	1	–	–	–	.08	–.05
6. Anxiety	223	2.12	0.98	1	–	.43**	–.23**	–.24**	.68**	.60**	1	–	–	.18**	–.01
7. Depressive symptoms	225	0.40	0.42	1	–	.59**	–.26**	–.33**	.55**	.63**	.58**	1	–	.03	.05
8. Reactive aggression	224	1.59	0.91	1	–	.65**	–.10	–.40**	.53**	.47**	.54**	.34**	1	–.07	–.05
9. Oppositional behavior	237	1.30	0.56	1	–	.37**	–.22**	–.30**	.08	.02	.18**	–.04	.17*	–.29**	–.17**
Time 2															
2. Anger coping	221	2.24	0.59	.39**	1	–.38**	1	–	–	–	–	–	–	–.01	.13
3. Sadness coping	221	2.2	0.51	.38**	1	–.25**	.63**	1	–	–	–	–	–	–.17*	.09
4. Intolerance of uncertainty	219	1.74	0.67	.47**	1	.39**	–.23**	–.29**	1	–	–	–	–	.09	–.15*
5. Rumination	220	2.03	0.79	.50**	1	.43**	–.15*	–.21**	.72**	1	–	–	–	.09	–.08
6. Anxiety	221	2.08	0.80	.48**	1	.33**	–.16*	–.24**	.63**	.61**	–	–	–	.21**	–.12
7. Depressive symptoms	221	0.45	0.42	.59**	1	.52**	–.32**	–.36**	.60**	.56**	.60**	1	–	.04	–.17*
8. Reactive aggression	220	1.57	0.80	.63**	1	.57**	–.16*	–.34**	.35**	.49**	.43**	.32**	1	–.24**	–.07
9. Oppositional behavior	236	1.38	0.65	.80**	1	.41**	–.24**	–.32**	.08	.09	.22**	–.04	.35**	–.30**	–.15*
Time 3															
6. Anxiety	169	2.03	0.90	.43**	.53**	.26**	–	–	–	–	1	–	–	.23**	–.00
7. Depressive symptoms	170	0.40	0.42	.55**	.69**	.50**	–	–	–	–	.56**	1	–	.08	–.07
8. Reactive aggression	167	1.45	0.74	.58**	.59**	.54**	–	–	–	–	.57**	.33**	1	–.11	–.02
9. Oppositional behavior	206	1.26	0.52	.62**	.64**	.25**	–	–	–	–	.26**	.00	.30**	–.27**	–.00

* $p < .05$, ** $p < .01$.

Uncertainty Scale–12 (IUS-12; Carleton, Norton, & Asmundson, 2007), which, in turn, was adapted from the original 27-item Intolerance of Uncertainty Scale (Freeston, Rheaume, Letarte, Dugas, & Ladouceur, 1994) for adults. The IUS-C can be used with children at least as young as 8 years old. It includes 12 items assessing children's responses to and beliefs about uncertainty (e.g., "It bothers me when there are things I don't know"; "I always want to know what will happen to me in the future"). Individual items were rated on a 5-point Likert-type scale, from 1 (*not like me*) to 5 (*entirely like me*), with mean scores used in analyses. In the current sample, the IUS-C demonstrated strong internal consistency at T1 ($\alpha = .86$) and T2 ($\alpha = .88$).

Rumination was assessed via the Children's Response Styles Questionnaire—Rumination Subscale (RSQ-R; Abela, Aydin, & Auerbach, 2007), which includes 13 items rated on 4-point scale from 1 (*almost none of the time*) to 4 (*almost all of the time*). Items assess the child's tendency to engage in maladaptive, repetitive negative thinking during periods of sadness (e.g., "When I am sad, I think about how alone I feel"; "When I am sad, I think about my failures, faults, or mistakes"). Mean scores were used for analysis. The RSQ-R has demonstrated reliability and convergent validity (Abela et al., 2007) and in the current study evidenced strong internal consistency across T1 ($\alpha = .86$) and T2 ($\alpha = .88$).

Outcome Variables

Depressive symptoms were assessed using the Short Mood and Feelings Questionnaire (SMFQ; Angold et al., 1995). The SMFQ includes 13 items that reflect cognitive (e.g., "I thought nobody really loved me") and behavioral (e.g., "I cried a lot") indicators of depression. Items were rated on a 3-point Likert-type scale from 0 (*not true*) to 2 (*true*), and responses were averaged for analysis. The SMFQ has well-established convergent, predictive, and criterion validity (Angold et al., 1995; Kuo, Vander Stoep, & Stewart, 2005; McKenzie et al., 2011). Reliability was strong across all three time points (α s = .88–.89).

Anxiety was assessed using the eight-item PROMIS Pediatric Anxiety Short Form (Irwin et al., 2010). From item banks originally developed by the National Institutes of Health (NIH) for brief and valid assessment of youth anxiety symptoms (Irwin et al., 2010), the short PROMIS measure captures youths' cognitive and behavioral symptoms of anxiety (e.g., "I felt nervous"; "I worried about what could happen next to me"). Items were rated on a 5-point scale from 1 (*never*) to 5 (*always*) and averaged for analysis. Internal consistency was strong across time points (α s = .86–.91).

Reactive and proactive aggression were assessed via self-report using Dodge and Coie's (1987) six-item scale. This measure includes three items each for reactive (e.g., "When teased or threatened, I get angry easily and fight back") and proactive (e.g., "I threaten or bully others to get what I want") aggression, all rated on a 5-point scale from 1 (*never*) to 5 (*almost always*). Mean scale scores were used for analyses. Reactive aggression was modeled as the outcome of interest given that it is centrally implicated in youth irritability (Brotman, Kircanski, Stringaris, et al., 2017). Proactive aggression was modeled as a covariate, a common practice to control for statistical overlap between the two types (Fite, Craig, Colder, Lochman, & Wells, 2016). Internal consistency was adequate for both reactive (α s = .74–.79) and proactive (α s = .82–.91) aggression.

Oppositional behavior was assessed via teacher report using the Disruptive Behavior Disorders Checklist (Pelham, Gnagy, Greenslade, & Milich, 1992). These items ask teachers to rate children's behavior on a scale from 1 (*not at all*) to 4 (*very much*) on all eight DSM criteria items for ODD (touchy, angry, temper, argues, defies, blames, annoys, spiteful). Responses to all eight items were averaged and used for analyses. Internal consistency was strong across all time points (α s = .94–.95).

Demographic Covariates

Gender (0 = male, 1 = female) and *grade level* (third, fourth) were available through a combination of teacher report and school records at T1. These demographic variables were included in analyses as covariates, as well as to explore associations with study variables across time points. Other potential sociodemographic covariates and descriptive characteristics (e.g., socioeconomic status, ethnicity) were not available at the person level.

ANALYTIC STRATEGY

Study aims were investigated through a series of path analyses estimated in Mplus Version 8 (Muthén & Muthén, 2017). Specifically, focused cross-lagged models were estimated (Figure 1, top panel) to examine two types of longitudinal mediation: full (Figure 1, middle panel) and half (Figure 1, bottom panel). Full mediation ($X_{T1} \rightarrow M_{T2} \rightarrow Y_{T3}$) provides the strongest evidence for mechanistic processes (Cole & Maxwell, 2003; Jose, 2016). Half mediation ($X_{T1} \rightarrow M_{T2}$; $M_{T1} \rightarrow Y_{T2}$) provides slightly less compelling evidence, but it is stronger than any models containing one or more cross-sectional paths (Cole & Maxwell, 2003; Kline, 2016). The half-mediation pathways are also

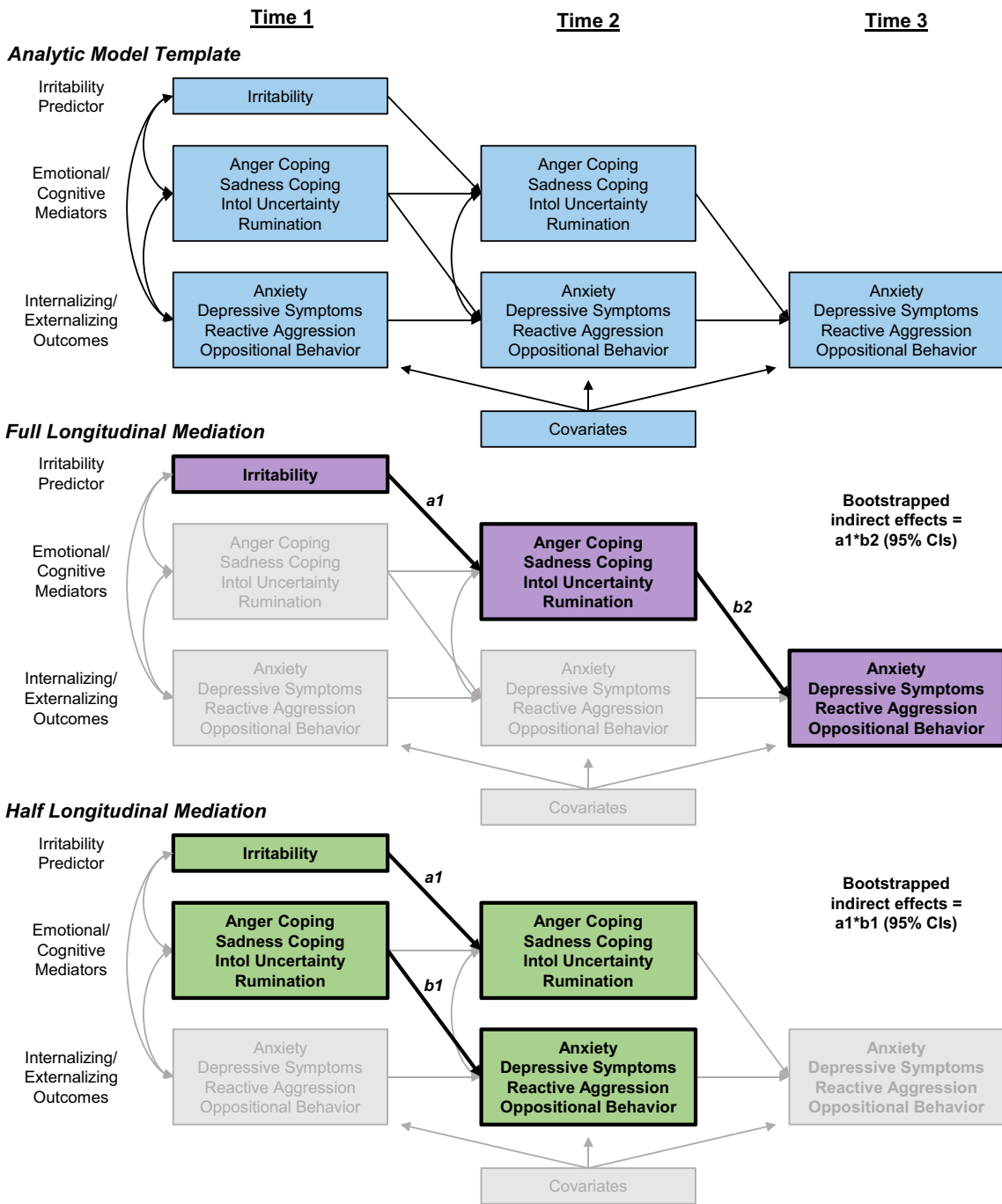


FIGURE 1 Analytic diagram and criteria for full- and half-longitudinal mediation. *Note.* Models were estimated separately for each mediator-outcome combination but are consolidated here for conceptual clarity. Covariates include gender and grade level for all models, plus proactive aggression in the reactive aggression models. All model variables were regressed on all covariates and control for prior levels where applicable. Intol = intolerance of.

useful because they provide a picture of intervals occurring within the same school year and across two different school years.

Significance of indirect effects was assessed through the 95% CIs around the product term of the *a* and *b* path coefficients, with a standardized

effect size calculated as ab/SD_Y (MacKinnon, 2012). It should be noted that thresholds for interpreting standardized indirect effect sizes have not been established, and it is often emphasized that ostensibly small mediation effects can be quite meaningful; they are also naturally smaller due to

the multiplicative term (by way of analogy, consider Cohen's thresholds of 0.01, 0.09, and 0.25 for R^2 as opposed to the corresponding .10, .30, and .50 thresholds for r ; Miočević, O'Rourke, MacKinnon, & Brown, 2018; Preacher & Kelley, 2011). Although the significance of ab is both necessary and sufficient to establish longitudinal mediation (Cole & Maxwell, 2003; Kline, 2016), auxiliary analyses were conducted to explore the implied c paths from irritability at T1 to internalizing and externalizing problems at T2 and T3. These further analyses offered the additional benefit of elucidating the behavioral outcomes of self-reported irritability in this sample. Last, the possibility of gender differences was explored through multiple-group models. The a , b , and c paths were constrained to be equivalent across gender; then we removed these constraints and allowed parameters to be estimated separately for boys and girls. These models were compared using a χ^2 difference test to detect the presence of gender differences.

All models controlled for grade level and gender. Reactive aggression models also controlled for proactive aggression. Models were estimated using maximum likelihood with 1,000 bootstrapped draws, an approach that provides an unbiased test of indirect effects and accommodates non-normality and missingness (Kline, 2016; MacKinnon, 2012; Muthén & Muthén, 2017). Regarding distributional assumptions, endogenous variables showed slight positive departures from normality (skewness: $Mdn = 1.22$, range = -0.41 – 2.56 ; kurtosis: $Mdn = 1.16$, range = -0.95 – 6.60). Because our models were just identified or fully saturated (see Figure 1, top panel), fit statistics are noninformative (e.g., CFI/TLI = 1, RMSEA = 0, $\chi^2 = 0$, $df = 0$) and are therefore not reported. Instead, evaluations of model results focus specifically on the paths and product terms of interest.

Results

Table 1 presents descriptive statistics and correlations for variables of interest. Irritability showed zero-order correlations with all mediator and outcome variables across all time points, and cross-sectional patterns of correlations among study variables were similar at T1, T2, and T3. Regarding hypothesized associations, irritability was cross-sectionally most strongly correlated with anger coping, intolerance of uncertainty, and rumination ($r_s = .55$ – $.56$), with a weaker correlation for sadness coping ($r = .26$). Longitudinally, irritability at T1 showed small to medium correlations with all candidate mediators at T2 ($r_s = .25$ – $.43$). With respect to outcome variables, irritability showed large cross-sectional correlations

with depression ($r = .59$) and reactive aggression ($r = .65$), but slightly lower correlations with anxiety ($r = .43$) and oppositional behavior ($r = .37$). Over time, T1 irritability's correlations with T2/T3 outcomes remained strong for depressive symptoms and reactive aggression ($r_s = .55$ – $.63$), whereas the corresponding associations for anxiety and oppositional behavior were somewhat lower ($r_s = .25$ – $.41$). Repeated measures showed significant but variable stability ($r_s = .38$ – $.80$). Only a few clear but modest covariate correlations were found; anxiety was higher among girls and oppositional behavior among boys. Overall, these preliminary results confirmed the presence of longitudinal associations that would be further investigated via cross-lagged mediation models.

LONGITUDINAL MEDIATION MODELS

Table 2 presents the results of the planned mediation models summarized in Figure 1. Emotion coping models showed that T1 irritability consistently predicted subsequent problems coping with both anger and sadness at T2. From there, results were mixed for mediational paths leading to subsequent problems. Specifically, poor anger coping at T1 predicted higher depressive symptoms, oppositionality, and (marginally) anxiety at T2—however, these paths were not seen from T2 to T3. Conversely, poor sadness coping predicted greater reactive aggression and oppositional behavior from T2 to T3, but these same paths were not observed from T1 to T2. Thus, emotion coping models provide some evidence supporting the following mediational pathways: irritability leading to anxiety, depressive symptoms, and oppositionality via poor anger coping (half mediation) and irritability leading to reactive aggression and oppositionality via poor sadness coping (full mediation). Bootstrapped tests of indirect effects confirmed the statistical significance of all five of these mediational pathways. The magnitudes of these significant indirect effects appeared to be relatively small but consistent; a 1-point increase in irritability mean scores at T1 would predict later internalizing and externalizing problems that were 0.029–0.067 standard deviations higher via the longitudinal indirect effects. No other direct or indirect coefficients of interest were significant.

Across the intolerance of uncertainty and rumination models, we found evidence only for irritability predicting one outcome: intolerance of uncertainty. In turn, from T1 to T2, intolerance of uncertainty predicted greater levels of anxiety; the corresponding T1–T3 path was not significant. Bootstrapped indirect effects confirmed the significance of this half-mediation path, with an indirect effect size of

Table 2
Results of Half- and Full-Longitudinal Mediation Models

Model ($X \rightarrow M \rightarrow Y$)	Path coefficients						Indirect effects						Gender
	a1		b1		b2		Half mediation ($a1 * b1$) ^a			Full mediation ($a1 * b2$) ^b			χ^2 diff
	Est	(SE)	Est	(SE)	Est	(SE)	Est	[95% CI]	ES ^c	Est	[95% CI]	ES ^c	df = 3
Anger coping													
Irr → ACop → Anx	-.28	(.10)**	-.16	(.08) ⁺	.05	(.10)	.046	[.001, .13]*	.057	-.014	[-.094, .04]	-.016	1.76
Irr → ACop → Dep	-.28	(.10)**	-.10	(.05)*	-.02	(.05)	.028	[.003, .07]*	.067	.004	[-.020, .04]	.010	0.34
Irr → ACop → Rea	-.25	(.09)**	-.07	(.08)	-.03	(.08)	.017	[-.015, .08]	.021	.008	[-.024, .06]	.011	0.84
Irr → ACop → Opp	-.26	(.09)**	-.13	(.06)*	-.03	(.04)	.032	[.003, .08]*	.049	.006	[-.014, .03]	.012	4.74
Sadness coping													
Irr → SCop → Anx	-.18	(.07)*	-.08	(.10)	.03	(.12)	.015	[-.013, .07]	.019	-.005	[-.065, .04]	-.006	4.36
Irr → SCop → Dep	-.15	(.08)*	-.05	(.05)	.01	(.06)	.007	[-.004, .03]	.017	-.001	[-.022, .02]	-.002	3.03
Irr → SCop → Rea	-.17	(.07)*	-.08	(.09)	-.24	(.10)*	.014	[-.010, .06]	.018	.041	[.006, .12]*	.056	2.74
Irr → SCop → Opp	-.14	(.07)*	.00	(.05)	-.11	(.05)*	.000	[-.019, .02]	.000	.015	[.001, .05]*	.029	2.89
Intol uncertainty													
Irr → IOU → Anx	.22	(.11)*	.25	(.09)**	-.03	(.12)	.054	[.007, .17]*	.067	-.007	[-.081, .04]	-.008	1.71
Irr → IOU → Dep	.18	(.13)	.05	(.04)	.07	(.05)	.010	[-.003, .04]	.024	.014	[-.004, .06]	.033	3.27
Irr → IOU → Rea	.17	(.13)	.11	(.06) ⁺	.16	(.12)	.018	[-.004, .07]	.023	.027	[-.007, .16]	.037	8.29*
Irr → IOU → Opp	.27	(.12)*	.02	(.03)	.04	(.04)	.006	[-.007, .03]	.009	.010	[-.005, .05]	.019	3.45
Rumination													
Irr → Rum → Anx	.02	(.09)	.24	(.08)**	.03	(.14)	.005	[-.040, .06]	.006	.001	[-.022, .04]	.001	4.07
Irr → Rum → Dep	-.02	(.10)	.04	(.05)	.07	(.06)	-.001	[-.023, .01]	-.002	-.002	[-.025, .01]	-.005	3.53
Irr → Rum → Rea	.04	(.11)	.10	(.08)	.21	(.13) ⁺	.004	[-.013, .06]	.005	.009	[-.021, .11]	.012	6.32 ⁺
Irr → Rum → Opp	.09	(.10)	.07	(.04) ⁺	.05	(.05)	.006	[-.005, .03]	.009	.004	[-.003, .03]	.008	3.78

Note. See Figure 1 for a visual depiction of key model paths and estimates. Bold indicates significance. Irr = irritability, ACop = anger coping, Anx = anxiety, Dep = depressive symptoms, Rea = reactive aggression, Opp = oppositional behavior, SCop = sadness coping, IOU = intolerance of uncertainty, Rum = rumination.

^a Half-longitudinal mediation: irritability at T1, mediators at T2, outcomes at T2.

^b Full-longitudinal mediation: irritability at T1, mediators at T2, outcomes at T3.

^c ES = effect size, calculated as the ratio of the indirect effect ($a*b$) to the standard deviation (SD) of Y (MacKinnon, 2012). This ES allows for consistent interpretation of indirect effects in terms of SD units of Y . For example, in the half-mediation models for anger coping, a 1-point increase in Affective Reactivity Index (ARI) mean scores at T1 corresponds to a .057 SD higher level of anxiety, a .067 SD higher level of depressive symptoms, and a .049 SD higher level of oppositional behavior at T2, all through the indirect effects of poor anger coping.

⁺ $p < .10$, * $p < .05$, ** $p < .01$.

0.067, consistent with the higher indirect effects identified above for anger coping. Although none of the irritability mediation pathways were significant for rumination, the path from rumination at T1 to greater anxiety at T2 was found to be significant, and other *b* paths for rumination showed marginal statistical significance for both reactive aggression and oppositional behaviors. These results suggest that perhaps rumination is relevant for these emotional and behavioral problems in a way that does not stem directly from irritability over the longitudinal interval assessed here.

SUPPLEMENTARY ANALYSES

Additional models were estimated to explore direct effects and gender moderation. First, models were specified to explore direct effects from T1 irritability leading to internalizing and externalizing problems at T2 and T3 (i.e., the *c* paths). As above, these models controlled for grade level, gender, and stability, while reactive aggression models additionally controlled for proactive aggression. From T1 to T2, irritability predicted significantly higher levels of anxiety ($B = 0.233, SE = 0.115, p = .043$), depressive symptoms ($B = 0.193, SE = 0.080, p = .015$), reactive aggression ($B = 0.405, SE = 0.143, p = .005$), and oppositional behavior ($B = 0.165, SE = 0.069, p = .017$). Similar results were obtained from T1 to T3 for depressive symptoms ($B = 0.245, SE = 0.073, p = .001$) and reactive aggression ($B = 0.444, SE = 0.144, p = .002$)—however, prediction to T3 anxiety was marginal ($B = 0.281, SE = 0.168, p = .095$) and oppositional behavior nonsignificant ($B = 0.035, SE = 0.064, p = .585$). Overall, these results confirm that irritability predicts significantly greater internalizing and externalizing problems across longitudinal intervals of approximately 6 and 12 months, further underscoring the importance of the mediational pathways explored above.

Finally, all of the foregoing models were reestimated as multiple-group models comparing boys versus girls. As shown in the rightmost column of Table 2, these comparison tests were largely nonsignificant ($ps > .09$) with the one exception of the intolerance of uncertainty and reactive aggression model ($p = .040$), which showed no significant paths in the combined sample model. When inspected by gender, boys showed a trend toward significant paths from intolerance of uncertainty toward reactive aggression at both T1 \rightarrow T2 ($B = 0.199, SE = 0.108, p = .065$) and T2 \rightarrow T3 ($B = 0.338, SE = 0.199, p = .089$), whereas girls did not ($ps > .47$). Thus, these differences did not appear to be meaningful. Similar to the primary mediation models, there was no evidence of gender moderation in any of the direct paths leading from

irritability at T1 to internalizing or externalizing problems at T2 or T3, χ^2 diff ($df = 1$) = 0.029 to 1.947, $ps > .16$.

Discussion

Previous work has shown that youth irritability predicts internalizing and externalizing problems—but little is known about how this risk is conferred or how psychosocial treatments might intervene. The present study sought to address this gap by exploring candidate psychological mediators (emotion coping, intolerance of uncertainty, rumination) in the paths from irritability to internalizing (anxiety, depressive symptoms) and externalizing (reactive aggression, oppositionality) problems in school-age children. Despite variation across intervals (6 vs. 12 months) and mediation frameworks (half vs. full longitudinal), results revealed three interesting mediational patterns. First, irritability conferred risk for externalizing problems—both reactive aggression and oppositional behavior—via poor sadness coping (full mediation). Second, irritability may confer risk for oppositionality and internalizing problems—both anxiety and depression—via poor anger coping (half mediation). Third, irritability may confer risk for anxiety via intolerance of uncertainty (half mediation). Additionally, rumination did not play a mediating role for irritability, and auxiliary analyses generally supported the direct pathways from irritability to subsequent internalizing and externalizing problems.

In interpreting these results, it bears reiterating that irritability—especially when measured dimensionally in community samples, as was the case here—does not necessarily represent a clinical problem (Stringaris et al., 2018). Instead, irritability is a basic human mood state that becomes clinically relevant to the extent that it implicates myriad other problems that likely do warrant clinical attention—namely, internalizing and externalizing problems. In other words, irritability here was conceptualized as an “upstream” predictor of greater “downstream” problems, and mediation analyses were designed to elucidate the intervening, dimensional, transdiagnostic processes by which these problems develop and might be addressed, consistent with prevailing frameworks (e.g., experimental therapeutics, RDoC; Lewandowski et al., 2018; Meyers et al., 2017). Indeed, the present results accord with what has been documented by longitudinal meta-analyses (Vidal-Ribas et al., 2016), showing that irritability predicted subsequent anxiety, depressed mood, reactive aggression, and oppositional behaviors over the course of a single school year (T1 \rightarrow T2), and even into the following school year (T1 \rightarrow T3) as was the case for depressed mood and reactive aggression. The nonsignificant T1

→ T3 result for oppositional behaviors might be accounted for by students having different classrooms/teachers at T3, which could lead to an attenuation due to either real behavior changes or methodological effects. Some level of attenuation over time is to be expected in longitudinal research, and the overall pattern of results supports the paths from irritability to internalizing and externalizing problems per most variables and occasions. Overall, these direct effects (a) align with extant literature, (b) inform our interpretation of primary results (below), and (c) confirm the importance of exploring the longitudinal mechanisms stemming from irritability.

Three specific cognitive-behavioral deficits were found to stem from elevated baseline irritability: poor anger coping, poor sadness coping, and intolerance of uncertainty. These processes have shown relevance for multiple branches of developmental psychopathology, and they offer implications for transdiagnostic conceptualization and treatment of irritability. In the present sample, higher levels of irritability were associated with greater difficulties in coping with both anger and sadness. These associations were robust, persisting longitudinally even after controlling for grade level, gender, and stability. Thus, children with severe irritability not only have a greater propensity for experiencing intense anger; they also have greater difficulty—and increasing difficulties over time—with effectively managing these unpleasant emotions. Moreover, the present findings enrich our understanding of the emotional valence and dysregulation associated with irritability. For example, as part of a working definition, it has been stated “irritability is a mood, and anger is its defining emotion” (Vidal-Ribas et al., 2016, p. 557). While this is a useful theoretical and practical operationalization, the present findings caution against clinicians focusing too narrowly on anger as *the* major discrete emotion that irritable children have difficulty regulating. We did find that irritability had relatively stronger relations with anger coping than with sadness coping, but both effects were significant, robust, and persistent. Thus, intervention strategies targeting general difficulties coping with various negatively valenced mood states (e.g., Southam-Gerow, 2013) may be especially helpful for youth with severe irritability. In support of this hypothesis, recent evidence has shown promise for transdiagnostic psychotherapies that cut across multiple domains of psychopathology as being especially helpful for youth with severe irritability and mood dysregulation (Evans et al., 2019; Miller et al., 2018; Perepletchikova et al., 2017).

The present findings also highlight robust cross-sectional and longitudinal associations of irritabil-

ity with intolerance of uncertainty. Severe irritability is associated with deficits in cognitive, emotional, and behavioral flexibility (Evans et al., 2017). Thus, irritable children may have a stronger preference for consistency and assuredness compared to their less irritable peers. Relatedly, severe irritability involves aberrant responses to frustrative nonreward or blocked goal attainment, as well as a heightened sensitivity for perceiving threat (Brotman, Kircanski, & Leibenluft, 2017). In everyday life, this could be interpreted simply as a child having (perhaps distorted) expectations for a desired outcome and then experiencing disproportionately intense anger when those expectations are not met. The threat component could manifest as a tendency to perceive ambiguous circumstances as threatening. The present results highlight the role that intolerance of uncertainty may play in irritability—that is, for children with severe irritability, the experience of uncertainty may represent a violation of a child’s preference for consistency, a blocked goal in that their expected outcome is not delivered, as well as an ambiguous stimulus that may be perceived as threatening. Our findings that irritability is cross-sectionally and longitudinally associated with intolerance of uncertainty, and that this plays a role in the development of anxiety, represent a useful step forward in advancing theory and practice.

The findings for rumination were more mixed. Irritability did not predict rumination over time in the longitudinal mediation models that included covariates and controlled for baseline—however, irritability showed zero-order correlations with rumination both cross-sectionally and longitudinally. Thus, although our exploratory mediation tests were not supported for rumination, it should not be concluded that rumination is irrelevant to irritability in youth. Rather, perhaps rumination is a central part of irritability, but it manifests concurrently rather than longitudinally. For example, the angry “stewing inside” described by Vidal-Ribas et al. (2016) may only occur as a part of the irritable mood and not increase over time as a sequela of irritability. Additionally, our findings converge with previous results supporting the relevance of rumination to anxiety and depressed mood, which also intersect with irritability. Further research may be helpful in better understanding how rumination relates to irritability. It is possible that rumination may be relevant to some types of irritability but not others. For example, Riglin et al. (2018) recently differentiated an *early-onset* irritability trajectory, associated with male gender and childhood ADHD, from an *adolescent-onset* irritability trajectory, associated with female gender and adolescent depression.

Similarly, our overall absence of gender differences suggests that these findings pertaining to irritability apply similarly to boys and girls, at least during middle childhood. If gender does play a moderating role in the course, correlates, or outcomes of irritability, this may become more apparent in adolescence than in childhood (Humphreys et al., 2018; Riglin et al., 2018).

When the present results pertaining to irritability, outcomes, and candidate mediators are considered collectively, the implications for clinical conceptualization, intervention development, and treatment become especially intriguing. To the extent that irritability could be an early warning sign on the pathway to more severe internalizing and externalizing problems, intolerance of uncertainty and emotion coping may represent useful targets for intervention. In particular, coping with anger, sadness, and uncertainty may play key roles in the development of aggression and mood problems among irritable youth. The specific pattern of results reveals an ostensible incongruence between mechanisms and outcomes (i.e., externalizing with sadness coping, but internalizing with anger coping). It may be the case that children are better at identifying *that* they are upset than *how* they are upset, and that this is especially the case among youth with elevated behavioral problems. Indeed, a meta-analysis from the emotional development literature confirms that deficits in emotional knowledge are linked to internalizing, externalizing, and social problems (Trentacosta & Fine, 2010). This too suggests that, rather than focusing on any one discrete emotion, interventions should focus on building skills in regulating or learning to tolerate unpleasant emotions and uncertainty broadly conceptualized. A related implication is that clinical child practitioners should employ terminology used by the child and family rather than that of the research literature (e.g., “upset” instead of “irritable”).

Last, it is intriguing to consider the present findings in relation to traditional conceptualizations of “internalizing” versus “externalizing.” Coping with sadness (internalizing) mediated the path from irritability to aggression/oppositionality (externalizing), whereas coping with anger (externalizing) half mediated the path from irritability to anxiety/depression (internalizing). These findings resonate with the conceptualization of irritability as a phenomenon that cuts across traditional boundaries of psychopathology (Brotman, Kircanski, & Leibenluft, 2017; Evans et al., 2017; Stringaris & Taylor, 2015). In this transdiagnostic conceptualization, irritability shares commonalities with depression (e.g., negative mood) and anxiety (e.g.,

threat-bias association), but unlike these affective states, irritability is linked to an approach/aggressive response rather than withdrawal (Brotman, Kircanski, Stringaris, et al., 2017; Vidal-Ribas et al., 2016). Similarly, findings such as these could help elucidate other aspects of the intersection between internalizing and externalizing psychopathology, such as the common or *p* factor (Caspi et al., 2014; Lahey et al., 2012), as well as the heterotypic pathways from childhood to adulthood (Loth, Drabick, Leibenluft, & Hulvershorn, 2014). Future research is needed to examine interesting hypotheses such as these.

LIMITATIONS AND IMPLICATIONS

Despite this study’s strengths (e.g., longitudinal mediation; multiple outcomes, mediators, and informants), some limitations should be noted. First, the sample was school based with limited diversity in terms of ethnic background, socioeconomic status, age range, and severity. Future research should pursue these directions to determine the replicability and generalizability of these findings, particularly their applicability to diverse samples of clinically referred youth. Here it is important to reiterate that results were not *uniformly* significant across all intervals tested—thus, replication across different intervals and contexts would be helpful. Indeed, a second limitation is that our semester intervals may not be the ideal length for detecting extant associations among irritability, its outcomes, and relevant mediators. It is possible, for example, that the development of rumination takes longer than three semesters, or that the mechanisms leading from irritability to oppositional behavior could unfold with a single semester—these are important questions for developmental-clinical research to explore. Third, due to practical considerations, constructs were assessed using brief self-/teacher-report measures. Because many of these constructs (e.g., irritability, emotion regulation) may also be conceptualized as *processes*, future research might involve paradigms designed to elicit and measure such processes in real time (e.g., lab-based frustration paradigms, ecological momentary assessment).

Fourth, all measures were not collected across both informants or at all measurement occasions, limiting the possibilities for modeling and inference. Future research will benefit from fully cross-lagged panel models with all variables repeatedly assessed over at least three occasions to confirm directionality, stability, and consistency of effects. Here, we employed a focused longitudinal model and tested full- and half-longitudinal mediation models, both of which extend upon and expand prior cross-

sectional work (e.g., Malhi et al., 2017), but nevertheless could still be strengthened. In addition to fully cross-lagged multiwave designs, future research may benefit from exploring outcomes and mediation via growth and latent difference score models, which test different underlying theories of change (Selig & Preacher, 2009). Finally, the present analysis conceptualized irritability as a precursor, potential treatment targets as mediators, and internalizing and externalizing problems as outcomes. While this framework was consistent with our theoretical model, treatment focus, and data availability, it is by no means the only possible model through which these variables may be relevant to irritability. For example, future work might consider the role of intolerance of uncertainty, rumination, and coping in the development and maintenance of irritability.

If it is indeed the case that identifying and treating the mechanisms underlying irritability-related problems may improve outcomes, then the present findings offer clinical scientists and practitioners considerable food for thought. Specifically, candidate targets for psychosocial interventions include identifying and coping with various unpleasant emotions like anger and sadness (not focusing on any one discrete emotion). Further, irritability interventions might seek to increase flexibility, reduce rigidity, and challenge expectations that may set up irritable youth for frustrative nonreward difficulties. These implications could be realized in multiple ways, including adaptations of established interventions, such as behavior therapy, cognitive-behavioral therapy, dialectical behavior therapy, and interpersonal therapy (Evans et al., under review; Miller et al., 2018; Perepletchikova et al., 2017; Waxmonsky et al., 2016), as well as the development of mechanism-focused techniques, such as exposure and bias modification (Kircanski et al., 2018; Stoddard et al., 2016). In addition, considering the school-based nature of the present sample, these findings raise interesting questions about whether irritability and the other transdiagnostic variables could be potentially useful for early assessment and intervention to help forestall internalizing and externalizing problems in school settings. All of these implications remain preliminary at this juncture, but they highlight the potential of further research in assessment, prevention, and intervention related to the psychosocial mechanisms of irritability in children.

Conclusions

The present study provides further evidence for multiple internalizing and externalizing outcomes of youth irritability, and new evidence regarding the

mechanisms that may mediate these outcomes. Specifically, irritability may confer risk for (a) externalizing problems via poor sadness and anger coping, (b) internalizing problems via poor anger coping, and (c) anxiety symptoms via intolerance of uncertainty. Emotion coping, intolerance of uncertainty, and rumination may all be relevant to the clinical conceptualization and treatment of severe irritability, though perhaps in different ways. Cognitive-behavioral treatments targeting these processes may be helpful for addressing severe irritability in children, but further research is needed to advance this evidence base for direct clinical relevance.

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