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An Exposure-Based Cognitive–Behavioral Therapy for Youth with Severe Irritability: Feasibility and Preliminary Efficacy

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ABSTRACT

Objective: Clinically impairing irritability and temper outbursts are among the most common psychiatric problems in youth and present transdiagnostically; however, few mechanistically informed treatments have been developed. Here, we test the acceptability, feasibility, and preliminary efficacy of a novel exposure-based treatment with integrated parent management skills for youth with severe irritability using a randomized between-subjects multiple baseline design.

Method: $N = 41$ patients (Age, Mean (SD) = 11.23 years (1.85), 62.5% male, 77.5% white) characterized by severe and impairing temper outbursts and irritability were randomized to different baseline observation durations (2, 4, or 6 weeks) prior to active treatment; 40 participants completed the 12 session treatment of exposure-based cognitive–behavioral therapy for irritability with integrated parent management skills. Masked clinician ratings were acquired throughout baseline and treatment phases, as well as 3- and 6-months post-treatment. To examine acceptability and feasibility, drop-out rates and adverse events were examined. Primary clinical outcome measures included clinician-administered measures of irritability severity and improvement. Secondary clinical outcome measures included multi-informant measures of irritability, depression, anxiety, and attention-deficit/hyperactivity disorder symptoms.

Results: No patients dropped out once treatment began, and no adverse events were reported. Irritability symptoms improved during the active phase of treatment across all measurements (all $\beta s > -0.04$, $ps < .011$, Cohen's d range: −0.33 to −0.98). Treatment gains were maintained at follow-up (all $\beta s_{(39)} < -0.001$, $ps > .400$). Sixty-five percent of patients were considered significantly improved or recovered post-treatment based on the primary clinician-rated outcome measure.

Conclusions: Results support acceptability, feasibility, and preliminary efficacy of this novel treatment for youth with severe irritability. Limitations and future directions are also discussed.

Introduction

Irritability is one of the most common presenting problems in pediatric mental health care (Collishaw et al., 2010; Peterson et al., 1996; Vidal-Ribas et al., 2016) and is associated with significant impairment (Laporte et al., 2021) and negative psychiatric outcomes in adulthood (Althoff et al., 2016; Brotman et al., 2006; Copeland et al., 2013; Jha et al., 2020; Orri et al., 2018, 2019; Pickles et al., 2010; Stringaris et al., 2009; Vidal-Ribas et al., 2016). However, targeted treatments are limited. Defined as an increased proneness to anger relative to peers, irritability manifests across mood, anxiety, disruptive behavior, and neurodevelopmental disorders (Brotman et al., 2017; Leibenluft & Stoddard, 2013). Irritability has been found to be independently associated with impairment, above and beyond co-occurring clinical conditions (Dougherty et al., 2018; Laporte et al., 2021). Since the introduction of disruptive mood dysregulation disorder (DMDD; American Psychiatric Association, 2013) to the DSM-5, incorporating tonic (chronically grumpy mood) and phasic (acute temper outbursts) irritability into one diagnosis, research increased (Brotman et al., 2017; Knackfuss et al., 2020; Leibenluft & Stoddard, 2013; Vidal-Ribas et al., 2016). Indeed, psychotherapeutic studies targeting irritability are emerging (Miller et al., 2018; Perepletchikova et al., 2017; Waxmonsky et al., 2016). Here, we present the rationale, acceptability, feasibility, and initial clinical findings for a novel intervention that focuses on exposure to anger-inducing triggers to treat severe irritability and DMDD, while integrating established principles from

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parent management training (PMT) (Barkley, 2013; Brotman et al., 2017; Kazdin et al., 1992; Kircanski et al., 2019).

Extant Cognitive–Behavioral Treatment (CBT) Interventions

Several existing CBT protocols for related constructs of irritability, including disruptive behavior, anger, and aggression, typically target hostile attribution biases and other cognitive processes (Dodge et al., 1997; Lochman & Dodge, 1994; Lochman et al., 1984; Scahill et al., 2012; Sukhodolsky & Scahill, 2012). Such protocols generally have been weighted toward cognitive strategies (e.g., generation of multiple solutions and consideration of consequences for different courses of action in conflicts), relative to behavioral interventions (e.g., in-session exposure, role play) (Kazdin, 2010; Lochman et al., 1984; Scahill et al., 2012; Sukhodolsky & Scahill, 2012). These treatments suggest efficacy of CBT for youth, with meta-analyses revealing effect sizes in the medium range for disruptive behavior (Lochman et al., 2011; Lösel & Beelmann, 2003) and anger-related problems (Sukhodolsky et al., 2004).

Building on this work, transdiagnostic, modular CBT interventions have been applied to treat emotion dysregulation and emotional disorders. Feasibility, acceptability, and preliminary efficacy have been demonstrated for both the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children (UP-C) (Ehrenreich-May et al., 2017) and Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH-ADTC; Evans et al., 2020). Specifically, two recent reports showed preliminary evidence of positive outcomes using the UP-C for anger and irritability (Grossman & Ehrenreich-May, 2020; Hawks et al., 2020). In another report, MATCH reduced irritability significantly across multiple measurements (Evans et al., 2020). While promising, these modular treatments were not designed to directly address irritability. Thus, it is unclear how results may compare to mechanism-informed treatments specifically developed to target severe irritability as seen in DMDD. Though related clinical constructs such as aggressive or disruptive behaviors can arise out of escalated irritability, research has shown irritability to be a distinguishable dimension and to have differential predictions compared to other symptoms of oppositional defiant disorder (ODD), such as defiance or vindictiveness (Burke et al., 2014; Herzhoff & Tackett, 2016; Kuny et al., 2013; Stringaris & Goodman, 2009). Of note, there has been one randomized controlled trial (RCT) of dialectical behavioral therapy for children with DMDD (DBT-C; Perepletchikova et al., 2017), which showed preliminary efficacy in improving outbursts and irritable mood.

Exposure-Based Approach

Our work emphasizes a behavioral approach and evolved from a pathophysiological model of pediatric irritability suggesting two putative core mechanisms of impairing irritability: exaggerated responses to frustrative nonreward and threatening stimuli, and aberrant reward processing (Brotman et al., 2017). To target exaggerated emotional responses to anger-inducing stimuli, we focus on in vivo exposure to stimuli that trigger patients' symptoms of irritability. During in vivo exposures, we teach patients to increase their toleration of negative affect while withholding the typical behavioral response of a temper outburst. Several lines of research suggest that exposure techniques may be helpful in the treatment of irritability (for a review, see Kircanski et al., 2019). Exposure is a behavioral technique extensively used in the treatment of anxiety disorders (Craske et al., 2008, 2014); patients confront and tolerate subjectively threatening stimuli while learning that expected adverse outcomes do not occur. Like fear, anger is an acute, high-arousal emotional state that is typically stimulus-driven (Carver & Harmon-Jones, 2009; Tarpley et al., 2010). We hypothesized that behavioral interventions targeting the threat system that are effective for child anxiety disorders (Ginsburg et al., 2014) may be adapted to benefit the treatment of irritability. The therapist works with the child through the hierarchy in a controlled, graduated manner. Based upon the guiding principles of exposure-based treatments for anxiety, we hypothesize that increasing the child's toleration of anger-provoking stimuli through repeated exposure will reduce the occurrence of temper outbursts and irritability. This study is the first to test an anger/frustration hierarchy for exposure in youth who are being referred to a treatment study to primarily target clinically-impairing irritability.

Parent Management Training (PMT)

The treatment also incorporates parent management skills derived from classic Parent Management Training (PMT; Barkley, 2013; Kazdin et al., 1992). Building from our mechanistic model (Brotman et al., 2017), here we aimed to modify the reinforcing cycle between irritability symptoms and their consequences. PMT is a category of interventions in which the therapist works with the parent/caregiver to target the child's reward processing through operant conditioning (e.g.,

Barkley, 2013; Kazdin, 2005; Kazdin et al., 1992). This is partly rooted in theoretical models of coercive processes between child and parent, in which the parent reacts to the child's misbehavior in a way that further provokes the child's disruptive behavior and escalates the parent's anger response (e.g., Awada & Shelleby, 2021; Patterson, 1982; Zachary et al., 2019). For example, Burke et al. (2008) demonstrated a distinct association between parental hesitancy with discipline and child ODD. In PMT, parents/caregivers are taught to positively reinforce/reward adaptive child behavior, while providing mild negative consequences or not reinforcing/rewarding (e.g., actively ignoring) maladaptive behavior. Here, we taught parents instrumental learning-based skills derived from PMT to target anger-proneness and temper outbursts observed in irritable youth.

PMT has a central role in treating externalizing problems in children (e.g., Chorpita & Daleiden, 2009; Kaminski & Claussen, 2017; McMahon et al., 2006) and several evidence-based protocols have been developed (Barkley, 2013; Kazdin, 2005, 2010), including programs that emphasize behavioral components of parent intervention (BPT; Ward et al., 2016; Zisser et al., 2018). Specifically, meta-analyses have documented medium-to-large effect sizes for decreases in anger and disruptive (e.g., oppositional, antisocial) behaviors (Boldrini et al., 2023; Comer et al., 2013; Dretzke et al., 2009; Furlong et al., 2012; Michelson et al., 2013; Pilling et al., 2013; Scott et al., 2014). These benefits are often maintained through long-term follow-up (Dretzke et al., 2009; Stringaris et al., 2018; Sukhodolsky et al., 2016; Weisz et al., 2017). Although less research has focused on the role of parenting behaviors in internalizing symptoms, parental factors have also been shown to play a mechanistic role in depression and anxiety in youth (e.g., Lebowitz et al., 2021; Webster-Stratton & Herman, 2008). Overall, research indicates significant links between parental factors (e.g., warmth versus hostility) and both externalizing (Kjøbli et al., 2023; Rothenberg et al., 2020; Zachary et al., 2019) and internalizing (Carpenter et al., 2014; Gonzalez & Jones, 2016) symptoms. Consistent with the conceptualization of pediatric irritability at the intersection of internalizing (e.g., irritable, angry, grumpy, cranky, negative mood) and externalizing (e.g., temper outbursts, disruptive behavior, aggression) disorders (Burke et al., 2014; Herzhoff & Tackett, 2016; Kuny et al., 2013; Stringaris & Goodman, 2009), the efficacy of PMT for irritability should be tested.

The Current Study

Our goal was to examine the acceptability, feasibility, and preliminary efficacy of a manualized exposure-based CBT and PMT skills for severe irritability. The novel component of our intervention is not the PMT per se, but the inclusion of exposure, which aims to increase patients' toleration of anger and frustration and development of inhibitory control over maladaptive behavioral responses. To examine acceptability and feasibility, drop-out rates and adverse events were examined. To examine preliminary efficacy, we utilized an across-subjects multiple-baseline design and randomized treatment onset across individuals between three baseline periods (2, 4, and 6 weeks) (Barlow et al., 2009; Ferron & Sentovich, 2002). Multiple baseline designs are standard experimental designs that can be used to test efficacy in a systematic manner (Barlow & Hersen, 1984; Kazdin, 1998; Ollendick, 1995) prior to a gold-standard randomized-control trial (RCT; see Chambless & Ollendick, 2001). Building on the results of our open trial (Kircanski et al., 2018), this design allowed us to compare trajectories of symptom change between baseline and treatment phases, with the expectation that symptoms would change only after the intervention is introduced (Kazdin, 2003). We hypothesized that irritability symptoms would decrease throughout the course of the treatment relative to the baseline period, during which we expected stability in symptom levels. As detailed below, the primary outcome measures were clinician-administered measures of irritability severity and improvement. Secondary outcomes included parent- and child-report measures of irritability and, as irritability commonly co-occurs with other symptoms, multi-informant measures of depression, anxiety, and ADHD symptoms. In an exploratory manner, we examined treatment specificity for irritability and hypothesized that applying exposure to anger-inducing triggers would lead to larger decreases in irritability symptoms compared to other clinical symptoms.

Methods

Participants

Recruitment occurred between January 2018 and July 2021. Participants were recruited within a 50-mile radius of the National Institutes of Health (NIH) campus in Bethesda, Maryland. See Supplements for details regarding recruitment, incentives, and consenting procedures. See Figure 1 for the Consolidated Standards of Reporting Trials (CONSORT) diagram that details participant progress from recruitment to study completion. A total of 143 families completed an onsite evaluation; during the COVID-19 pandemic evaluations were completed virtually via Health Insurance Portability and Accountability Act (HIPAA)-compliant and IRB-

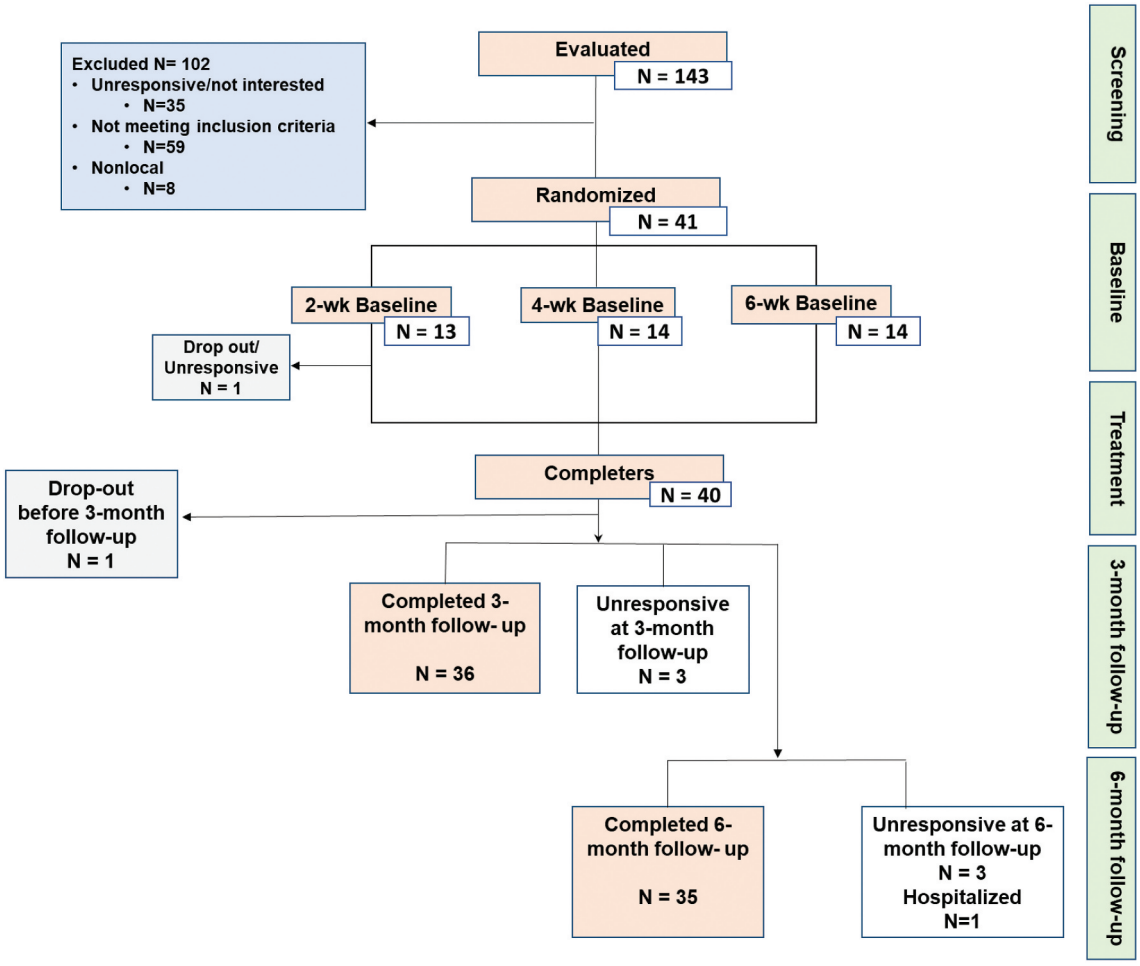

Figure 1. CONSORT diagram.

approved telehealth appointments. A total of 40 youth enrolled in the study; 41 youth received randomized baseline assignments, but one family dropped out from the study before the start of treatment. All 40 youth enrolled in the study (M_{age} = 11.23 years, SD = 1.85 years; 62.5% male; 77.5% white) completed treatment. Demographics and clinical characteristics are provided in Tables 1–4.

Participants were between ages 8–17, fluent in English, and had an IQ above 70. Prior to COVID-19, IQ was assessed by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). During the pandemic, estimation of IQ was based on educational attainment and school placement. Participants presented with at least one of the two core DMDD symptoms, i.e., chronically irritable mood or temper outbursts, with severe impairment in at least one domain (home, school, and peers) and moderate in another, or moderate impairment in two or more domains. Clinical diagnoses were established by licensed clinicians using a semi-structured clinical interview with child and parent [Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version; K-SADS-PL (Kaufman et al. 1997); including a DMDD supplement (Wiggins et al., 2016)].

Youth were excluded from participating if irritability symptoms were attributable to the physiological effects of a drug or another medical condition, were actively suicidal, displayed cardinal symptoms of bipolar disorder such as mania or hypomania, or presented with a current diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive disorder, post-traumatic stress disorder, or autism spectrum disorder (ASD). Other comorbidities such as ADHD, anxiety, or past depressive episodes did not impact participant eligibility.

Procedures

This trial was registered under NCT02531893 on clinicaltrials.gov. All procedures were approved by the National Institute of Mental Health (NIMH) Institutional Review Board (IRB). If the child met initial eligibility criteria, both parent and child completed the

Table 1. Participant demographic information.

Age (Mean, SD)	11.23 (1.85)
Sex (*n*, %)	Male (25, 62.5)
	Female (15, 37.5%)
Any Medication (*n*, %)[a]	**30, 75**
Stimulant (*n*, %)	20, 50
Non-stimulant ADHD medication (*n*, %)	12, 30
Antidepressant (*n*, %)	14, 35
Antipsychotic (*n*, %)	3, 7.5
Anticonvulsant (*n*, %)	1, 2.5
Telehealth completers (*n*, %)	21, 52.5
Race (*n*, %)	White (31, 77.5)
	Black or African American (4, 10)
	Asian (1, 2.5)
	Multiple Races (3, 7.5)
	Unknown (1, 2.5)
Ethnicity (*n*, %)	Not Latino or Hispanic (36, 90%)
	Hispanic or Latino (2, 5)
	Unknown (2, 5)
Primary Diagnosis[b] (*n*, %)	DMDD (25, 62.5)
	ODD (10, 25)
	ADHD (5, 12.5)
IQ (Mean, SD)	113.43 (13.70)
Parent Income	Over $180,000 (13, 32.5%)
	$90,000–$179,999 (9, 22.5%)
	$60,000–$89,999 (1, 2.5%)
	Unknown (17, 42.5%)
Child Opportunity Index (COI)[c]	
Education (Mean, SD, Level)	84.31 (10.07), Very High
Health & Environment (Mean, SD, Level)	71.63 (22.88), High
Social & Economic (Mean, SD, Level)	88.40 (12.97), Very High
Overall COI (Mean, SD, Level)	87.31 (13.01), Very High

Note: DMDD = disruptive mood dysregulation disorder; ADHD = attention deficit hyperactivity disorder; ODD = oppositional defiant disorder. IQ was not assessed for $n = 12$ telehealth completers.

[a]Participants may be prescribed more than one medication type ($n = 14$ prescribed one type; $n = 12$ prescribed two types; $n = 4$ prescribed three types).

[b]Based on DSM-5 guidelines, the DMDD diagnosis supersedes an ODD diagnosis. Therefore, children with both DMDD and ODD were given a primary diagnosis of DMDD.

[c]The Child Opportunity Index (Noelke et al., 2020) is a composite metric of the neighborhood conditions/environment of children that accounts for education, health, social, and economic factors of specific neighborhoods as compared to national averages. The COI reflects U.S. nationally normed scores on a scale of 0–100; COI data were available for $n = 35$ participants.

K-SADS-PL clinical interview to assess the child's diagnostic status and stability on any current medications. Diagnoses were determined by a clinician based on a combination of both parent and child reports. Unless an acute clinical need arose, there were no changes to the patient's outpatient psychiatric treatment regimen during the active treatment trial, including psychotherapy and/or psychotropic medication.

Table 2. Participant comorbidities by primary diagnosis.

	Diagnostic Group		
Diagnoses	DMDD ($N = 25$)	ODD ($N = 10$)	ADHD ($N = 5$)
ADHD	20 (80%)	5 (50%)	–
Separation anxiety	4 (16%)	3 (30%)	1 (20%)
Generalized anxiety	13 (52%)	2 (20%)	1 (20%)
Specific phobia	4 (16%)	0	0
Social phobia	1 (4%)	0	1 (20%)
Tic disorder	1 (4%)	0	0
Enuresis	1 (4%)	0	2 (40%)
Chronic motor disorder	2 (8%)	0	0
Excoriation disorder	1 (4%)	0	0

Note: DMDD = disruptive mood dysregulation disorder; ADHD = attention deficit hyperactivity disorder; ODD = oppositional defiant disorder.

We utilized an across-subjects multiple baseline design to assess symptom improvement across baseline and treatment phases (Gliner et al., 2000; Morgan & Morgan, 2001; Onghena & Edgington, 2005). Eligible participants were randomized to different baseline observation periods of either 2, 4, or 6 weeks prior to starting treatment (Ferron & Sentovich, 2002), which were followed by 12 weekly sessions of active treatment. To assess symptoms during the trial, independent, masked clinical evaluators rated participants' symptoms at prescribed intervals during the baseline period, treatment, and at 3- and 6-month post-treatment follow-up. Clinical raters were masked in terms of baseline assignment group and treatment progress. See Supplements for detailed description of clinical ratings procedures.

Our research also utilized in vivo measures of symptoms via ecological-momentary assessment (EMA; Naim, Smith, et al., 2021), which is outside the scope of the present report. However, preliminary analyses of

Table 3. Clinical outcomes: clinician- and self-reported irritability, anxiety, depression, ADHD, and global functioning across treatment and follow-up timepoints.

Outcome measure Mean (SD)	Pretreatment[a] $N = 40$	Mid-Treatment $N = 40$	Post-Treatment $N = 40$	3-month follow-up $N = 36$	6-month follow-up $N = 35$
Clinician ARI Total Score	43.63 (17.43)	39.31 (16.08)	36.11 (19.94)	33.58 (20.59)	31.59 (20.96)
CGI-S Temper Outbursts	4.18 (.81)	3.65 (.864)	3.33 (1.05)	3.17 (1.28)	3.09 (1.36)
CGI-S Mood	3.28 (1.28)	3.08 (1.12)	2.77 (1.25)	2.61 (1.25)	2.60 (1.24)
CGI-S DMDD Severity	4.05 (.85)	3.65 (.80)	3.35 (1.05)	3.08 (1.25)	2.97 (1.29)
Parent ARI	7.12 (2.73)	5.88 (2.55)	4.82 (3.03)	–	–
Child ARI	4.72 (3.70)	4.53 (3.28)	3.9 (3.36)	–	–
Clinician-rated anxiety (PARS)	5.78 (4.93)	5.12 (4.53)	5.20 (4.80)	3.82 (3.57)	5.20 (4.07)
Clinician-rated depression (CDRS)	25.70 (5.32)	24.65 (4.60)	25.13 (8.11)	23.15 (4.76)	24.69 (7.34)
Clinician-rated ADHD (ADHD-RS)	21.30 (14.16)	22.13 (12.70)	21.90 (13.99)	23.12 (12.97)	21.51 (14.50)
Children's Global Assessment Scale (CGAS)	49.38 (8.21)	50.87 (6.77)	53.85 (9.52)	56.53 (12.28)	57.26 (13.36)
Parent SCARED	19.58 (11.55)	18.53 (13.25)	16.97 (12.21)	–	–
Child SCARED	19.45 (18.80)	18.11 (16.47)	17.56 (18.04)	–	–
Parent SMFQ	6.23 (3.70)	5.80 (3.52)	5.03 (3.89)	–	–
Child SMFQ	5.70 (5.92)	4.28 (4.79)	5.33 (5.53)	–	–
Parent CPRS-R (DSM IV *t*-score)	70.21 (12.32)	67.67 (11.40)	67.72 (11.94)	–	–

Note: ARI = Affective Reactivity Scale; CGI-S = Clinical Global Impressions-Severity, PARS = Pediatric Anxiety Rating Scale; CDRS = Children's Depression Rating Scale; ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; SCARED = Screen for Child Anxiety-Related Disorders; SMFQ = Short Mood and Feelings Questionnaire; CPRS-R = Conners' Parent Rating Scale-Revised.
3-month follow-up assessment completed by $n = 36$ participants; 6-month follow-up assessment completed by $n = 35$ participants.
[a]Pretreatment assessment was the last clinical assessment of the baseline phase occurred before the start of treatment.

changes in parental behaviors during the treatment based on EMA parent-ratings are described in the Supplements.

Treatment

We developed a treatment manual, "Exposure-based cognitive behavioral therapy for irritability and disruptive mood dysregulation disorder" (Brotman et al., 2021, available upon request). Treatment included 12 sessions; each consists of a child portion focused on exposure, and a parent portion including PMT skills. Further details regarding treatment modules and adjustments due to COVID-19 are described in the Supplements; information is also documented in the published study protocol (Naim, Kircanski, et al., 2021).

Table 4. Clinical outcomes: improvement in temper outbursts, irritable mood, and DMDD severity as measured by CGI-I.

CGI-I Temper Outbursts ($N = 40$) Mean (SD)	
Pre vs. Mid	4.18 (1.01)
Pre vs. Post	3.82 (1.15)
Pre vs. 3-month follow-up	3.69 (1.37)
Pre vs. 6-month follow-up	3.69 (1.64)
Mid vs. Post	4.28 (1.11)
CGI-I Mood	
Pre vs. Mid	4.56 (1.17)
Pre vs. Post	4.08 (1.16)
Pre vs. 3-month follow-up	3.97 (1.59)
Pre vs. 6-month follow-up	3.89 (1.66)
Mid vs. Post	4.34 (1.26)
CGI-I DMDD Severity	
Pre vs. Mid	4.36 (.93)
Pre vs. Post	3.98 (1.31)
Pre vs. 3-month follow-up	3.86 (1.55)
Pre vs. 6-month follow-up	3.71 (1.55)
Mid vs. Post	4.34 (1.66)

Note: CGI-I = Clinical Global Impressions-Improvement. 3-month follow-up assessment completed by $n = 36$ participants; 6-month follow-up assessment completed by $n = 35$ participants. Pretreatment assessment was the last clinical assessment of the baseline phase occurred before the start of treatment.

Measures

Primary Outcome Measures

***Clinician-rated affective reactivity index (CL-ARI;* Haller et al., 2020).** The CL-ARI is a 12-item measure of the patient's temper outbursts and irritable mood over the past week, based on a semi-structured clinical interview with parent and child. Items assess frequency, duration, and severity of irritability and related impairment. All items (but one) are ranked on a 5-point Likert-style scale. The total CL-ARI score is the total weighted sum of the three subscale scores: temper outbursts, irritable mood between outbursts, and impairment. Possible scores range from 0 to 100. The CL-ARI total score has demonstrated good internal consistency (Cronbach's $\alpha = .89$), high inter-rater reliability (ICC = .90), and moderate test–retest reliability (ICC = .67, 95% CI range [.28–.85]) (Haller et al., 2020).

***Clinical global impressions-severity and improvement (CGI-S, CGI-I;* Busner & Targum, 2007; Guy, 1976).** The CGI-S measures symptom severity, and the CGI-I measures patient improvement since the last assessment. In the current study, the CGI-S reflects the clinician's impression of the severity of the child's clinical symptoms across three sub-scales: temper outbursts,

irritable mood, and overall DMDD symptom severity over the past 7 days (Haller et al., 2022; Towbin et al., 2020). Assessments were rated on a scale of 1–7 (1 = normal functioning, 3 = mildly ill, 4 = moderately ill, and 7 = among the most extremely ill patients). The CGI-I assesses the same three sub-scales but is rated within patient relative to a comparison week. In the current study, CGI scores at mid- and post-treatment were compared to prior assessment timepoints, i.e., pre- and mid-treatment assessments, where applicable; follow-up assessments scores were compared to pre- and post-treatment scores. CGI-I score ranges between 1 and 8; lower scores (1–4) indicate improvement and higher scores (6–8) indicate worsening symptoms, a rating of 5 indicates no change. The CGI-S has demonstrated moderate-to-high test–retest reliability across clinical samples, for example, in a depressed inpatient sample (ICC range = .64 – .88, 95% CI range [.38–.94]) (Kadouri et al., 2007).

The CL-ARI and CGI-S were collected at each rating timepoint. The CGI-I was collected at mid-treatment, post-treatment, and follow-up timepoints. See Table 2 in Naim, Kircanski et al. (2021) for a detailed assessment timeline. Prior to administration with patients, all ratings clinicians achieved inter-rater reliability of ICC > .80.

Secondary Outcome Measures: Clinician-Report

Clinician-rated measures of anxiety, depression, ADHD, and global functioning were collected at pre-, mid-, and post-treatment, and follow-up assessment timepoints. See Supplements for detailed descriptions of measures.

Secondary Outcome Measures: Parent- and Child-Report

Parent- and child-rated measures of irritability (Affective Reactivity Index; Stringaris et al., 2012) were collected prior to the start of each session. Parent- and child-rated measures of anxiety and depression, and parent-rated ADHD symptoms, were collected at pre-, mid-, and post-treatment timepoints. See Supplements for detailed descriptions of measures.

Analytic Procedure

Primary Outcome Measures

CL-ARI and CGI-S. For CL-ARI and CGI-S subscales, multilevel mixed-effects regression models with robust standard errors were used to analyze nested within-subject data using Hierarchical Linear Modeling (HLM software, version 8.0, Raudenbush & Congdon, 2021). Specifically, a three-phase piecewise linear mixed model was applied, where the break point between phases corresponded to individual-specific timing of pre- and post-treatment assessments (Brilleman et al., 2017). This allowed for comparison of slopes of change across each trial phase in the same model, particularly between baseline versus treatment phases. See Supplements for more information on the dataset structure and an illustration of coding procedure.

The slope and intercept for each phase were included together in a single model. Level-1 outcome measures included within-subject repeated data, specifically CL-ARI total score and CGI-S subscales. Time since pre-treatment assessment (in weeks) was entered in all models as the predictor at level-1. Thus, the model generated a beta coefficient and intercept for each phase of the treatment based on the same scale such that these could be directly compared. To examine potential moderating effect of age on treatment efficacy and symptoms change over time, models were re-run with age entered at level-2. Similarly, models were replicated accounting for baseline ODD diagnosis to test whether ODD at baseline is a moderator of the slope of irritability and if changes in irritability are held while covarying for this variable. Baseline ODD diagnosis was entered at level-2. Notably, as based on DSM-5 guidelines DMDD diagnosis supersedes an ODD diagnosis, only a subset of $N = 10$ had an ODD diagnosis.

See below for an example of the model used to predict CL-ARI total score based on time (in weeks) since pretreatment assessment for each phase:

Level-1 Model:

$$CL - ARI_{ij} = \beta_{0j} + \beta_{1j} * \left(Time\_BL_j\right) + \beta_{2j} * \left(Time\_TX_{ij}\right) + \beta_{3j} * \left(Time\_FU_{ij}\right) + r_{ij}$$

Level-2 Model:

$$\beta_{0j} = \gamma_{00} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + u_{2j}$$

$$\beta_{3j} = \gamma_{30} + u_{3j}$$

If significant changes occurred during treatment and not during baseline, this would indicate that decreases are due to treatment rather than other effects of time or expectancy.

To ensure that each baseline group (2, 4 or 6 weeks) did not differ in their rate of symptom change across the different phases, multilevel models were conducted as

previously described, with the addition of baseline assignment entered at level-2 as a between-subjects categorical predictor. Baseline group was entered in the model uncentered. Dummy coding was used to label each of the baseline groups (0 = *participant not in that group*; 1 = *participant in that group*) in the level-2 file. See Supplements for an example of the models used to compare symptom change between baseline groups.

CGI-I. The CGI-I is an ordinal rating of relative improvement in symptoms between the current time point and a specified comparison week. Two-sided one-sample *t*-tests were used to evaluate whether significant change occurred between the following pairs of time points: pre- to mid-treatment, mid- to post-treatment, and pre- to post-treatment. Additional *t*-tests assessed significant change from pre- and post-treatment to 3- and 6-month follow-up timepoints. The test value for all *t*-tests was 5, which indicates no clinical change. Lastly, to assess any differences in improvement between pre- to mid-treatment versus mid- to post-treatment intervals, a two-sided paired samples *t*-test was performed.

Secondary Outcome Measures

Multilevel mixed-effects regression models with robust standard errors were conducted to analyze nested within-subject data for secondary outcome measures of anxiety, depression, ADHD, and clinical-rated global functioning (see Supplements for model descriptions). False discovery rate (FDR) correction (Benjamini & Hochberg, 1995) with $q = .05$ was used within both sets of analyses for primary and secondary outcome measures to account for multiple comparisons. All reported results reflect FDR-corrected *p*-values.

Effect Sizes

While standardizing variables in our statistical models enables a more direct interpretation of coefficients (Snijders & Bosker, 2012), we also examined within-subjects Cohen's *d* for repeated measures as an estimate of effect size (e.g., Lenhard & Lenhard, 2016), considering pre- and post-assessments. In addition, for all multilevel models, semi-partial R^2 was calculated (see Supplements for details on the statistical software used to calculate R^2).

Reliable Change Index

In addition to analyses examining symptom change over time, Jacobson and Truax's (1991) Reliable Change method (RC) was used to assess the clinically significant changes in CL-ARI and CGI-S from pre- to post-treatment. Because no established clinical or diagnostic cutoff exists for CL-ARI, RC was calculated based on the standard error of the mean pre- and post-treatment difference scores within the current treatment sample. The RC generates outcome categories for each participant, such that a score of $0 < RC < 1.96$ indicates improvement, and $RC \geq 1.96$ indicates recovery.

Results

No patient dropped out from treatment once started. No adverse events (AEs) or reportable events occurred during the trial. Only one child's medication was changed during the study; it was changed to a different medication of the same category (stimulant). This change was due to reported reduced appetite, not changes in psychiatric symptoms (e.g., irritability, mood, or inattention).

Primary Outcome Measures

Clinician-Rated Irritability (CL-ARI)

Baseline groups (2, 4, 6 weeks) did not differ in pretreatment CL-ARI scores (all $\beta s_{(39)} < 4.08$, $ps > .396$). Across all participants, CL-ARI scores did not change during the baseline period ($\beta_{(37)} = -1.11$, SE = 0.89, $p = .220$). CL-ARI scores decreased significantly during treatment ($\beta_{(39)} = -0.63$, SE = 0.23, $p\ adj. = .009$) with a moderate effect size (ES) as measured by Cohen's *d* ($d = -0.33$), and a weak ES as measured by semi-partial R^2 ($R^2 = 0.04$, 95% CI [0.01,0.09]). Baseline groups did not differ in the slope of change during treatment (all $\beta s_{(37)} < .76$, $ps > .081$). Treatment gains were maintained across both the 3- and 6-month follow-up assessments ($\beta_{(39)} = -0.08$, SE = 0.16, $p = .614$). See Figure 2.

Clinician-Rated Symptom Severity (CGI-S)

Baseline groups did not differ in pretreatment for CGI-S Irritable Mood and DMDD Severity subscales (all $\beta s_{(37)} < .40$, $ps > .269$). The 2-week baseline group had higher CGI-S Temper Outburst scores at pretreatment relative to the 6-week baseline group ($\beta_{(37)} = .49$, SE = .23, $p = .038$). CGI-S scores decreased significantly during treatment across all subscales ($\beta_{(39)temper} = -0.07$, SE = .01, $p\ adj. = .004$; $\beta_{(39)mood} = -0.04$, SE = .01, $p\ adj. = .011$; $\beta_{(39)DMDD} = -0.06$, SE = .01, $p\ adj. = .002$) with moderate to large ES as measured by Cohen's *d* ($d_{\text{temper}} = -0.98$; $d_{\text{mood}} = -0.36$; $d_{\text{DMDD}} = -0.74$) and weak ES as measured by semi-partial R^2 ($R^2_{\text{temper}} = 0.12$, 95% CI [0.07, 0.19]; $R^2_{\text{mood}} = 0.04$, 95% CI [0.01, 0.09]; $R^2_{\text{DMDD}} = 0.10$, 95% CI [0.05, 0.16]). Slopes of change during treatment for all CGI-S subscales were similar across baseline groups (all $\beta s_{(37)} < .04$, $ps > .082$). Treatment gains were maintained across 3- and 6-month follow-up assessments (all $\beta s_{(39)} < -0.001$, $ps > .400$). See Figure 2.

Clinician-Rated Symptom Improvement (CGI-I)

Analyses examined if the magnitude of improvement was different from no-change (score of 5) between all pairs of time points (between pre- to mid-treatment, pre- to post-treatment, mid- to post-treatment, and from post-treatment to 3- and 6-month follow-ups). *t*-Tests yielded significant results for all comparisons across the three subscales, except for post-treatment to 3-month follow-up comparisons. Specifically, CGI-I Temper Outburst subscale showed improvement at all other timepoints (all $M_{diff} < -.72$, 95% CI range [−1.88, −.14], $ts_{(39)} < -1.48$, $ps < .009$), with large ES as measured by Cohen's *d* (all $d_{temper} > 1.10$); CGI-I Irritable Mood subscale showed improvement at all other timepoints (all $M_{diff} < -.44$, 95% CI range [−1.68,−.06], $ts_{(39)} < -2.34$, $ps < .025$); with large Cohen's *d* ES (all $d_{mood} > 1.17$); CGI-I DMDD Severity subscale also showed improvement at all other timepoints (all $M_{diff} < -.64$, 95% CI range [−1.82,−.22], $ts_{(39)} < -2.74$, $ps < .010$); with large Cohen's *d* ES (all $d_{DMDD} > .93$). Change from post-treatment to 3-month follow-up was not statistically significant for any of the CGI-I subscales (all $ps > .053$), indicating that no significant additional improvement occurred from the end of the treatment to 3-month follow-up, albeit improvement was maintained, and symptoms did not worsen.

Comparing magnitude of improvement during the first six sessions (pre- to mid-treatment) versus improvement during the last six sessions (mid- to post-treatment) revealed no significant differences in any CGI-I subscale (all $M_{diff} < .34$, $SDs > 1.54$, 95% CI range [−.61,.93], $ts_{(39)} < -1.19$, $ps > .244$).

All original findings for primary outcome measures held when adding age to the models. Age was not significantly associated with symptom change (all $ps > 0.090$). As secondary analyses, we replicated these models including baseline ODD diagnosis (binary coded as present/absent) as a covariate to test if patterns remain when

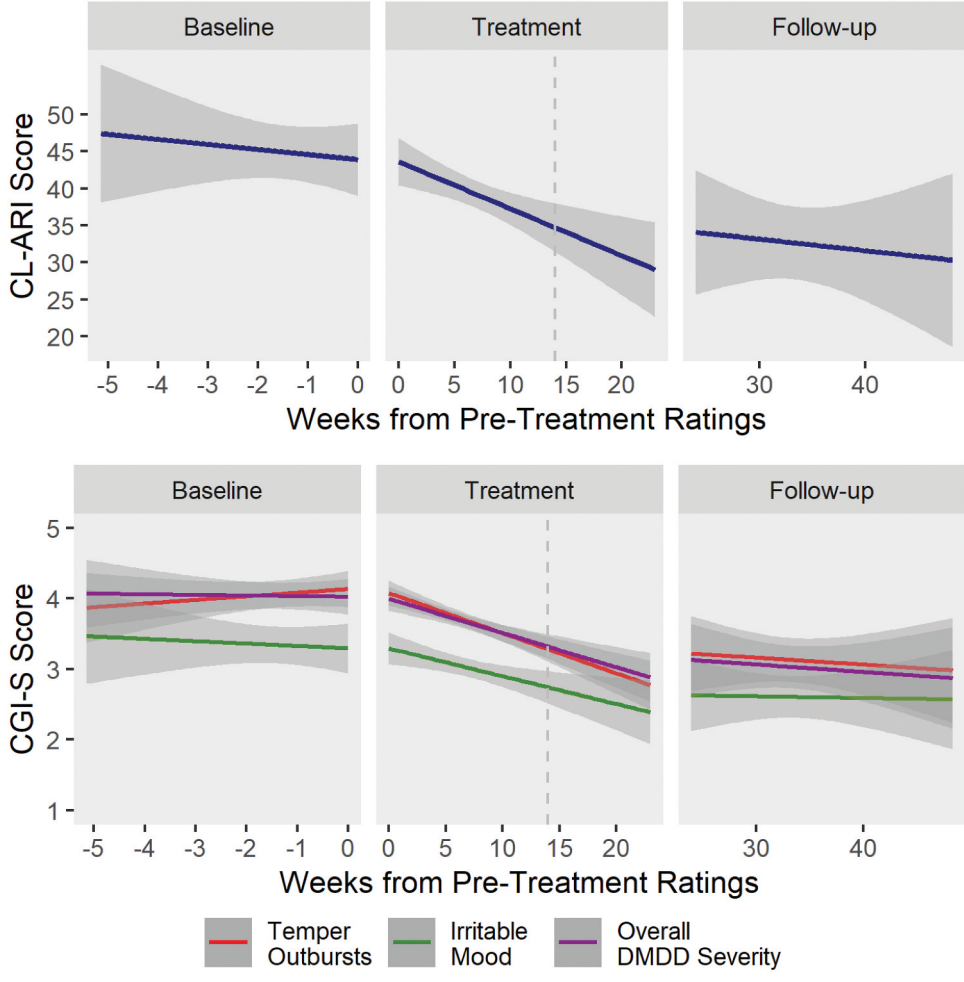

Figure 2. Clinician-rated irritability change across study phases as measured by CL-ARI and CGI-S. Abbreviations: CGI-S = Clinical Global Impressions-Severity; CL-ARI = Clinician Affective Reactivity Scale. x = 0 represents pretreatment assessment. Dashed gray line represents mean participant length in treatment = 14.1 weeks (SD = 1.9 weeks); one participant took 23 weeks to complete all treatment sessions. Shaded gray regions represent standard error (SE).

adjusting for baseline ODD symptoms. All original findings held covarying for baseline ODD, demonstrating similar patterns of symptoms stability at baseline ($ps > 0.481$), a significant decrease during treatment (all $ps < 0.042$), and maintained improvement at follow-up assessments ($ps > 0.074$). ODD at baseline did not significantly moderate the slope of irritability over time ($ps > 0.144$).

Secondary Outcome Measures

See Supplements for detailed results of secondary outcomes. Broadly, clinician-reported global functioning increased from pre- to post-treatment ($p = .035$). Parent- and child-reported irritability decreased from pre- to post-treatment ($p_{parent}\ adj. = .002$, $p_{child}\ adj. = .044$). No changes were observed in clinician, parent, or child reports of anxiety, depression, or ADHD from pre- to post-treatment (all $ps > .179$).

Reliable Change Index

Clinician-Rated Irritability (CL-ARI)

Reliable Change Index (RCI), based on the equation suggested by Jacobson and Truax (1991), indicated a significant positive clinical change in the majority of the sample, with 35% ($n = 14$) of the participants were considered recovered at post-treatment, and 23% ($n = 9$) were considered improved.

Clinician-Rated Symptom Severity (CGI-S)

For the CGI-S Temper Outburst subscale, 60% ($n = 24$) of the participants were considered recovered at post-treatment, while for the CGI-S Irritable Mood subscale, 25% ($n = 10$) of participants were considered recovered at post-treatment, and 25% ($n = 10$) were improved. For the CGI-S DMDD Severity subscale, 47% ($n = 19$) of participants were considered recovered at post-treatment.

See Supplements for additional analyses conducted to compare changes across measures between the sub-groups of patients who were treated before the outbreak of COVID-19 pandemic and patients who were treated via telehealth. Overall, these sub-groups did not differ in slopes of symptom change (all $ps > 0.310$).

Discussion

Building on a mechanistic translational model identifying core deficits in reward and threat processing in irritability (Brotman et al., 2017), our study supports the acceptability, feasibility, and preliminary efficacy of a novel 12-week, manualized exposure-based CBT with parent management skills for youth with severe and impairing irritability. This is one of only a few psychosocial interventions (Miller et al., 2018; Perepletchikova et al., 2017; Sukhodolsky et al., 2016; Waxmonsky et al., 2016) designed to specifically target pediatric irritability, and it is the first to use in vivo exposure to anger-inducing stimuli in youth (Grodnitzky & Tafrate, 2000).

All participants attended and completed all treatment sessions once starting, and no patient dropped out of treatment, demonstrating acceptability and feasibility of the current protocol. After the emergence of the COVID-19 pandemic, weekly sessions pivoted to a telehealth format; all enrolled participants remained in the protocol. While some have questioned the rationale of exposure for anger (Abramowitz, 2013), this preliminary treatment protocol is promising. Moreover, there were no adverse events or reportable events occurring in the current study. This points to the safety of using exposure to treat anger for youth with severe impairing irritability.

Preliminary efficacy of the treatment was supported. Irritability improved during the active phase of treatment across several clinician-, parent-, and child-rated irritability metrics. This consistency suggests robustness of the results. Overall functioning also improved. By the end of the treatment, 65% of the patients were considered significantly improved or recovered based on the primary clinician-rated outcome measure. Effect size measures based on Cohen's *d* for primary and secondary outcomes ranged from medium to large; however, effect sizes were smaller when operationalized as semi-partial R^2. As R^2 estimate includes all repeated assessments in the current study, these observed weak R^2 could be partially explained by high intra- and between-subjects variability across outcome measures. When the active treatment was completed, symptoms did not regress to baseline levels; in fact, gains were maintained at 3- and 6- month follow-up. Our treatment also demonstrated specificity, as irritability but not anxiety, depression, or ADHD symptoms improved over treatment.

Relative to other studies of similar phenotypes in the literature (e.g., Dretzke et al., 2009; Michelson et al., 2013; Scott et al., 2014) and to DMDD, subthreshold DMDD (see Naim, Kircanski et al., 2021 for operationalization), and severe mood dysregulation disorder (SMD) samples from our group (Dickstein et al., 2009; Haller et al., 2022; Towbin et al., 2020), patients in the present study exhibited comparable levels of baseline symptoms severity and impairment. When we compare the efficacy of our treatment protocol with other treatment studies in our lab with positive outcomes (Stoddard et al., 2016; Towbin et al., 2020), improvement ratios were similar as measured by CGI-S and CGAS. However, these studies applied pharmacological

or computer-based interventions and not a psychological intervention.

When examining our treatment effects in the context of previous studies from other research groups studying similar phenotypes, comparisons are complicated by different inclusion criteria, assessment tools, and sample sizes. Despite this, current effect sizes are generally comparable to overall medium effect sizes reported in both meta-analyses on CBT efficacy for anger (Sukhodolsky et al., 2004) and on PMT efficacy for disruptive behavior (Comer et al., 2013; Furlong et al., 2012; Pilling et al., 2013; Stringaris et al., 2018). Specifically, findings were comparable between the current study and four prior clinical studies focusing on severe irritability, all of which included reports on pre- to post-treatment change and effect sizes (Grossman & Ehrenreich-May, 2020; Miller et al., 2018; Perepletchikova et al., 2017; Waxmonsky et al., 2016). First, the effect sizes of clinical improvement for CL-ARI and CGI-S during treatment in the current study (ranging between 0.33 and 0.98) were similar or larger than those reported for pre- to post-treatment change in an RCT of an integrative group therapy for children with ADHD and SMD (Waxmonsky et al., 2016), for both mood and behavioral components of irritability (ranging between 0.27 and 0.73).

Second, CGI-I levels were consistent with those reported in a pilot randomized trial of interpersonal psychotherapy (IPT) for 10 youth with DMDD/SMD (Miller et al., 2018), indicating values within the improvement category for both studies. Pre- to post-score changes for youth- and parent-reported ARI were similar between Miller et al. (2018) and our study, although CGI-S change was slightly lower in our study. Third, findings were consistent with reliable change in anger symptoms reported in a case study applying the UP-C protocol for a child with anger and irritability (Grossman & Ehrenreich-May, 2020). Finally, relative to DBT for DMDD, changes in CGI-S scores from pre-to post-treatment were similar; however, the mean remission rate based on RCI recovered category found in our study across primary outcome measures was slightly lower (41.75% compared to 52.4%; Perepletchikova et al., 2017).

Youth in this study presented at least one of two core DMDD symptoms: phasic temper outbursts or chronically irritable mood. Twenty-five participants met full DMDD criteria. When these two core symptoms are examined separately, current results suggest a potentially stronger effect of the treatment in decreasing temper outbursts (ES = −0.98) versus irritable mood (ES = −0.36). Speculatively, since exposure focuses on acute responses to triggering stimuli, exposure may be more effective in the treatment of temper outbursts relative to a chronically irritable mood. The PMT component of our study, focusing on modifying parental contingent behaviors to reduce unintentional reinforcement for temper outbursts, may also have a greater influence on temper outburst versus irritable mood. An alternative explanation is that the severity of the mood component at baseline was lower than the severity of the irritable mood, based on the CGI-S. From this perspective, the more moderate decrease from pre- to post-treatment could be due to a floor effect. Nevertheless, both components significantly decreased throughout treatment.

Treatment was not associated with any significant changes in anxiety, depressive, or ADHD symptoms, measured via clinician-, parent-, or youth-report. Though irritability often co-occurs with other clinical symptoms (Stoddard et al., 2014; Stringaris et al., 2009; Vidal-Ribas et al., 2016), including in the current sample, treatment did not worsen these comorbid symptoms. Moreover, the observed treatment effects held when covarying for oppositional behavioral symptoms measured by an ODD diagnosis at baseline. These findings suggest specificity of the treatment in targeting irritability. Treatment specificity is rarely studied, particularly in pediatric populations. A recent study by Silverman and colleagues (Silverman et al., 2019) illustrates such specificity in a treatment efficacy study of youth with anxiety disorders; findings demonstrate that both group-based CBT and CBT with parent involvement produces symptom reduction but through different mechanisms. In the current study, the observed specificity of the treatment on irritability symptom reduction may be due to the focus on increasing affective tolerance and inhibitory control in the context of anger-inducing stimuli, versus, for example, anxiety-provoking stimuli. However, more work is needed to further explore these ideas.

The results of this preliminary study should be considered in light of several limitations. First, the relatively small sample size and homogeneous ethnic and narrow socioeconomic composition limits the generalizability of our results. We believe that some of the barriers to participation in our research among minoritized and disadvantaged populations are associated with factors such as limited ability to reach those communities to inform them of studies, the times at which treatment sessions were usually provided (weekdays between 8am-5pm) and needing to commute. We are actively working on increasing the diversity of our recruitment strategies to offer treatment opportunities to more individuals in need. For example, we currently target specific zip codes and neighborhoods categorized with inequitable

opportunity based on the Childhood Opportunity Index (COI; Noelke et al., 2020), with an effort to reach out and provide resources to schools and organizations of diverse backgrounds. Overall, our treatment is personalized by protocol and could be adapted to the cultural context and needs of families. Further work with more diverse and/or disadvantaged samples is needed and would increase the utility of our treatment across individuals. Second, the current study was not a randomized controlled trial (RCT); hence, no control group was included. Although multiple baseline randomization reduces several potential confounds and alternative explanations, an RCT contrasting the current intervention with another approach will be needed as a further step toward testing efficacy. Moreover, given the integration of parent management skills and CBT in this protocol, the relative effect of each component could not be disentangled and the mechanistic question of coercive processes versus habituation or inhibitory learning could not be addressed. This study was a first step, and future studies might use a dismantling approach to examine the unique contribution of each technique to clinical outcomes. Larger, multisite studies are needed to expand on the present findings and address this mechanistic question.

Notably, as presented in our protocol (Naim, Kircanski, et al., 2021), our study initially incorporated neuroimaging tasks to target and examine putative mechanisms. However, due to COVID-19 and transitioning to telehealth (see more details in the Methods section) and relatively low compliance pre-COVID for these tasks, we were not able to test questions regarding brain-related mechanisms of change. Additional measures in the current study included assessments of in vivo mood and behavior using ecological momentary assessment (EMA, Naim, Smith, et al., 2021) and treatment process (i.e., therapist adherence, therapeutic alliance) as described in Naim, Kircanski, et al. (2021). Reports on these measures will be forthcoming as the current report focuses on traditional clinician and self-reported symptom outcome measures.

Critically, results of the present study provide preliminary support for the acceptability, feasibility, and potential efficacy of exposure-based CBT with parent management skills for youth with severe irritability, an understudied population with a need for evidence-based treatment development. Patients tolerated and benefited from in vivo exposures to frustration and anger. This study sets the foundation to further explore exposure-based treatments for pediatric irritability. Future work should examine the unique contribution of exposure versus parent management skills, center on testing efficacy using rigorous experimental designs, including RCTs, and integrate assessment of potential psychobiological mechanisms to better understand putative mechanistic targets.

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Disclosure Statement

No potential conflict of interest was reported by the author(s).

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