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Future Directions in Youth Irritability Research

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ABSTRACT

Research on irritability in children and adolescents has proliferated over the last 20 years. The evidence shows the clinical and developmental significance of irritable mood and behavior in youth, and it has led to significant changes in mental health classification, diagnosis, and services. At the same time, this research (including our own) has led to relatively little new in terms of practical, empirically based guidance to improve interventions and outcomes. In this article, we briefly summarize some of these developments and current evidence-based practices. We then put forth two key substantive challenges (the “whats”) for future research to address: (a) the need for more effective treatments, especially evaluating and adapting evidence-based treatments that are already well-established for problems related to irritability (e.g., cognitive-behavioral therapies for internalizing and externalizing problems); and (b) the need for a better mechanistic understanding of irritability’s phenomenology (e.g., phasic vs. tonic irritability, how frustration unfolds) and putative underlying mechanisms (e.g., cognitive control, threat and reward dysfunction). Lastly, we suggest three methodological approaches (the “hows”) that may expedite progress in such areas: (a) ecological momentary assessment, (b) digital health applications, and (c) leveraging existing datasets. We hope this article will be useful for students and early-career researchers interested in tackling some of these important questions to better meet the needs of severely irritable youth.

Youth mental health research is replete with challenges. As a field, the clinical problems we face are heterogeneous, co-occurring, and shifting. There tends to be little agreement across informants, not to mention across different models and conceptualizations. Complicating matters further, researchers must wrestle with the space between opposite extremes, such as typical to atypical, inhibited to disinhibited, transient to enduring, and infancy to adulthood.

Against this backdrop, youth irritability has recently emerged as a nexus point with great explanatory and clinical potential. Irritability accounts for a portion of the symptom heterogeneity seen in problems like ODD, ADHD, ASD, and PTSD¹ – where some patients experience severe irritability and others do not. Many youth mental health problems, including ones that often co-occur, include irritability as a common associated feature if not as a central part of their diagnostic criteria. This problem, as it manifests in the DSM, is illustrated in Table 2. Chronic irritability in childhood predicts risk for a range of heterotypic and homotypic outcomes in adolescence and adulthood, including ODD, ADHD, depressive, anxiety, and personality disorders, and suicidal thoughts and behaviors (Vidal-Ribas et al., 2016).

Irritability occurs across the lifespan, with presentations that span from typical to atypical, internalizing to externalizing, and from momentary to chronic. Finally, irritability is a common, impairing, and clinically important problem in its own right, identified by youths and caregivers as one of the main reasons for referral in as many as 58% of outpatient therapy cases (Evans et al., 2022).

Not surprisingly, research on youth irritability has exploded. As shown in Figure 1, the number of peer-reviewed articles published each year with titles referring to youth irritability has doubled roughly every 5 years over the last 2+ decades. These developments have attracted new generations of students and early-career researchers (including ourselves) with interests related to youth irritability. At this juncture, it is useful to reflect on the past 20 years of irritability research in order to inform the next.

Background and Significance of Youth Irritability

How did we get here? Beginning in response to significant increases in the rates of pediatric bipolar disorder diagnoses (Blader & Carlson, 2007; Moreno et al., 2007), Leibenluft and colleagues (Leibenluft, 2011; Leibenluft

Table 1. Abbreviations used in this article.

Abbreviation	Meaning
ACT	Acceptance and Commitment Therapy
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BPT	Behavioral Parent Training
CBT	Cognitive Behavioral Therapy
DBT	Dialectical Behavior Therapy
DMDD	Disruptive Mood Dysregulation Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBT	Evidence-Based Treatment
EBP	Evidence-Based Practice
EMA	Ecological Momentary Assessment
HiTOP	Hierarchical Taxonomy of Psychopathology
ICD	International Classification of Diseases
IPT	Interpersonal Psychotherapy
MATCH	Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems
NIMH	National Institute of Mental Health
ODD	Oppositional Defiant Disorder
PCIT	Parent Child Interaction Therapy
PTSD	Posttraumatic Stress Disorder
RCT	Randomized Controlled Trial
RDoC	Research Domain Criteria
SMD	Severe Mood Dysregulation Disorder
UP-C/A	Unified Protocols for Transdiagnostic Treatment of Emotional Disorders in Children and Adolescents

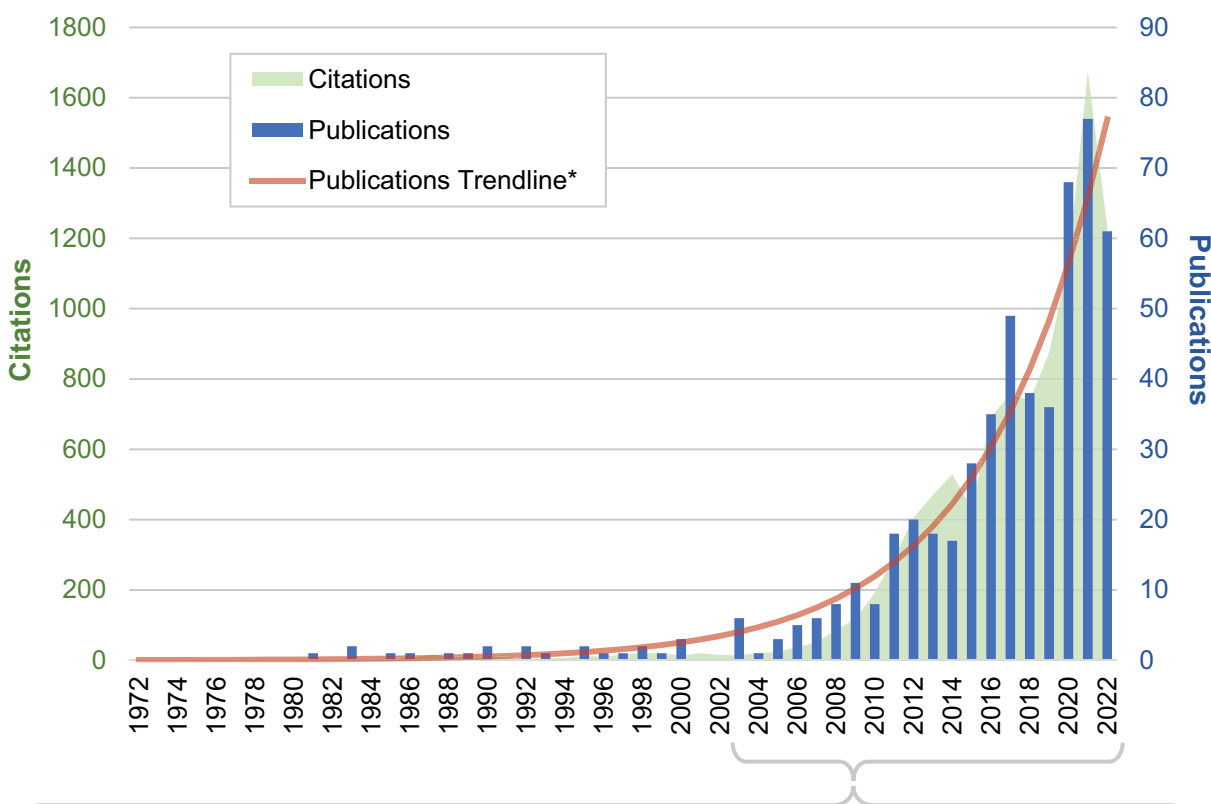
Table 2. Irritable features in the criteria for 15 selected DSM-5 categories affecting youth.

Diagnostic Category	Group	Irritable Features in Diagnostic Criteria (DSM-5-TR; American Psychiatric Association [APA], 2022)
Acute Stress Disorder	Trauma- & Stressor-Related	"Irritable behavior or angry outbursts, typically expressed as verbal or physical aggression toward people or objects" (p. 314)
Antisocial PD	Personality	"Irritability and aggressiveness, as indicated by repeated physical fights or assaults" (p. 748)
Borderline PD	Personality	"Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days" (p. 753)
DMDD	Depressive	"The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observed by others" (p. 178)
GAD	Anxiety	"Irritability" (p. 250)
Hypomanic & Manic Episodes	Bipolar & Related	"Abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy" (pp. 140 & 150)
Major Depressive Episode	Depressive; Bipolar & Related	"In children and adolescents, can be irritable mood" (pp. 141 & 151)
ODD	Disruptive, Impulse-Control, & Conduct	"Angry/irritable mood, which can include losing temper, being touchy or easily annoyed, and angry and resentful" (p. 522)
Pathological Gambling	Substance-Related & Addictive	"Restless or irritable when attempting to cut down or stop gambling" (p. 661)
Persistent Depressive Disorder	Depressive	"In children and adolescents, mood can be irritable" (p. 193)
Premenstrual Dysphoric Disorder	Depressive	"Irritability or anger or increased interpersonal conflicts" (p. 197)
PTSD	Trauma- & Stressor-Related	"Irritable behavior and angry outbursts typically expressed as verbal or physical aggression toward people or objects" (p. 302)
Reactive Attachment Disorder	Trauma- & Stressor-Related	"Episodes of unexplained irritability, sadness, or fearfulness that are evident even during nonthreatening interactions with adult caregivers" (p. 296)
Tobacco Withdrawal Disorder	Substance-Related & Addictive	"Irritability, frustration, or anger" (p. 649)

Table content focuses solely on the diagnostic criteria for each condition. Disorders for which irritability is a common associated feature but not part of the diagnosis (e.g., ADHD, ASD) are not included here. The table also omits instances of aggressive behavior where the aggression is not clearly specified as irritable, reactive, or angry in nature (e.g., Conduct Disorder). PD = Personality Disorder. Permission to use quoted material from APA (2022) was requested from APA Publishing.

et al., 2003) established the syndrome of severe mood dysregulation (SMD) and launched a program of work differentiating chronic irritability from bipolar disorder. As shown in Figure 1, 2003 serves as a rough entry point into research on youth irritability. About 96% of publications on youth irritability emerged since 2003; 80% since 2013. In 2003–2012, researchers established an

evidence base showing that chronic irritability was unique and associated with externalizing and internalizing outcomes but not with bipolar disorder. Around the same time, a growing number of studies showed that irritability was an affective dimension of ODD symptoms (Burke et al., 2014, 2021, 2005; Evans et al., 2016; Rowe et al., 2010; Stringaris & Goodman, 2009a, 2009b).



An incomplete history of events in youth irritability research over the last 20 years:

- 2003 – Criteria established for broad phenotype of severe mood dysregulation (SMD) (Leibenluft et al., 2003)
- 2006 – Early papers on prevalence, correlates, and course of chronic irritability (Brotman et al., 2006; Leibenluft et al., 2006)
- 2007 – Mechanistic studies dissociating SMD from other groups (e.g., Dickstein et al., 2007; Guyer et al., 2007; Rich et al., 2007)
- 2007 – Consensus meeting on impulsive aggression in child psychiatry (Jensen et al., 2007)
- 2008 – Clinical trial of pharmacological and psychosocial therapy (Waxmonsky et al., 2008)
- 2009 – Irritability as a dimension of ODD, longitudinal outcomes (Stringaris et al., 2009; Stringaris & Goodman, 2009a, 2009b)
- 2009 – Randomized controlled trial of a pharmacological therapy, lithium (Dickstein et al., 2009)
- 2010 – Research Domain Criteria (RDoC) efforts launched (Insel et al., 2010)
- 2011 – Review paper on SMD and boundaries of BD (Leibenluft, 2011)
- 2012 – New measures of irritability (ARI, MAPD-DB), *JCPP* special issue (Stringaris et al., 2012, 2012a; Wakschlag et al., 2012)
- 2013 – DSM-5 published with Disruptive Mood Dysregulation Disorder (DMDD) (American Psychiatric Association, 2013)
- 2014 – Irritable dimension and bifactor model of ODD identified (Burke et al., 2014)
- 2014 – NIMH meeting on childhood chronic irritability and pathophysiology of mental illness
- 2015 – Book: *Disruptive mood: Irritability in children and adolescents* (Stringaris & Taylor, 2015)
- 2015 – First Vermont Congress on Pediatric Irritability and Dysregulation
- 2016 – Randomized trial of a psychosocial therapy, joint parent-child behavioral intervention (Waxmonsky et al., 2016)
- 2016 – Special issue of *Journal of Child and Adolescent Psychopharmacology* on DMDD (Carlson, 2016)
- 2016 – First meta-analysis (Vidal-Ribas et al., 2016) and psychosocial treatment review (Sukhodolsky et al., 2016)
- 2017 – *Annual Review* and theoretical papers (Brotman, Kircanski, & Leibenluft, 2017, 2017; Leibenluft, 2017)
- 2017 – Integrative review paper on irritability for ICD-11 (Evans et al., 2017)
- 2019 – Edited Book: *Irritability in pediatric psychopathology* (Roy et al., 2019)
- 2019 – ICD-11 approved with ODD with Chronic Irritability/Anger (World Health Organization, 2019)
- 2020 – Special issue of *Behavior Therapy* on pediatric irritability (Roy & Comer, 2020)
- 2020 – Initial paper on empirically based “AIR” phenotype of Impulsive/Reactive Aggression
- 2021 – Two-part special issue of *Child and Adolescent Psychiatric Clinics* (Carlson & Singh, 2021; Singh & Carlson, 2021)
- 2021 – Transdiagnostic perspectives paper (Klein et al., 2021)
- 2021 – First EMA study of DMDD (Naim, Smith, et al., 2021)
- 2022 – AACAP Presidential Term on outbursts/dysregulation, *JAACAP* review and section (Carlson, Singh, et al., 2022)
- 2022 – Cross-cultural consortium on irritability established (Tseng et al., 2023)
- 2023 – Meta-analysis on irritability in early childhood (Finlay-Jones et al., 2023)

Figure 1. Peer-reviewed articles with titles related to youth irritability and their citations alongside an incomplete history of youth irritability research. Note. *Trendline estimated from Poisson regression model for year predicting publication count, $R^2 = 0.942$. Historical overview is admittedly incomplete, with apologies for our oversights and to everyone whose important contributions are not acknowledged above. Events included were selected with consideration to “firsts,” citation impact, and general diversity and scope. Publication and citation counts are based on Web of Science search conducted in May 2023 with the following string: ((TI = (“irritability” OR “irritable” OR “disruptive mood dysregulation” OR “severe mood dysregulation” OR “dmdd” OR “smd”) AND TI = (“child” OR “children” OR “childhood” OR “juvenile” OR “juveniles” OR “adolescence” OR “adolescent” OR “adolescents” OR “pediatric” OR “youth” OR “youths”)) NOT TI = (“bowel”)). Timespan: 01-Jan-1971 to 31-Dec-2022.

The accumulating evidence led to the inclusion of DMDD in DSM-5, and later, ODD with chronic irritability/anger in the ICD-11 Mental, Behavioral, and Neurodevelopmental Disorders (Evans et al., 2017; Roy et al., 2014).

The next 10 years (2013–2022) saw a continued acceleration of irritability research. A full review is beyond the scope of the present paper. Much of this work has been reviewed elsewhere (Brotman, Kircanski, Leibenluft et al., 2017a; Brotman, Kircanski, Stringaris et al., 2017b; Burke et al., 2021; Evans et al., 2017; Leibenluft & Kircanski, 2021; Stringaris et al., 2018; Vidal-Ribas et al., 2016). Broadly, evidence on chronic irritability as a syndrome and dimension of ODD converged with and fueled further research on such related topics as tantrums (Wakschlag et al., 2012), rages (Carlson et al., 2009), frustration (Deveney et al., 2013), and reactive aggression (Fite et al., 2018). Today, in addition to being a burgeoning research area, irritability seems far more widely recognized as a primary youth mental health concern, with real-world clinical implications (Evans & Santucci, 2021; Findling et al., 2022).

There is much promise in this research. A better understanding of heterogeneity and comorbidity could increase the scope, effectiveness, and personalization of interventions. A better understanding of developmental pathways from irritability to heterotypic and homotypic outcomes could lead to more effective prevention and screening efforts. A better understanding of neural, physiological, and psychological mechanisms underlying irritability could pave the way toward novel and personalized intervention. Finally, there is great scientific value in investigating this phenomenon that impacts everyone, ranging from the most normative everyday annoyances to severe and impairing outbursts, from categorical to continuous, and moderated by development across the lifespan.

Despite the promise, there is also a risk of following fads and spinning wheels. First, it would be naïve to think that a recent convergence of attention on an apparently novel topic translates to a discovery of a new clinical problem. Severely irritable youth have always been in our homes, schools, and clinics, and irritability itself is a universal human experience. Why should we expect that taking a new look at an “old” phenomenon – long familiar to caregivers, teachers, and clinicians – would lead to scientific or clinical advances? Second, the criticism could be made that this work only amounts to looking at new rearrangements of items and symptoms that were previously arranged differently. For example, much of the research on chronic irritability has operationalized this construct using items taken from measures of ODD (e.g.,

touchy, annoyed, angry), and then analyzed the data in relation to other measures and diagnostic domains (e.g., anxiety, depression). Although these strategies have been useful for bootstrapping progress in an area where there were few existing tools, they are not good measurement or research practices. Third, perhaps the construct of irritability could be better explained as part of broader, superordinate constructs as vulnerabilities contributing to psychopathology, such as negative emotionality or emotion dysregulation (e.g., Cole et al., 2017; Lahey et al., 2017). If this were the case, then it could be more appropriate to measure and model irritability as subsumed in a broader latent space – to better “carve nature at its joints.” Finally, despite a proliferation of strong research, the past 20 years have thus far yielded relatively mixed neuroimaging conclusions (Lee et al., 2022), limited treatment guidance (Brotman & Kircanski, 2022), and relatively modest associations with longitudinal heterotypic outcomes (Vidal-Ribas et al., 2016) – which was already known in different forms (Burke et al., 2005; Knappe et al., 2022; Loth et al., 2014). These signs point to the underwhelming possibility that irritability is perhaps nothing more than a nonspecific symptom.

Although these concerns are real, the evidence reviewed here and elsewhere (e.g., Evans et al., 2017; Vidal-Ribas et al., 2016) do not substantiate them and rather support the developmental and clinical significance of youth irritability. We raise these potential criticisms not to set up a straw man or to respond to them one by one, but rather to provide a skeptical and forward-looking context in which to ground this paper. These criticisms apply to our own research and the broader literature, all of which is embedded in a historical context of the last 20 years. As we enter the next 20 years, this paper offers some thoughts on this topic of future directions for irritability research. It is intended to be selective rather than exhaustive.² We organize this discussion around the “whats” – i.e., topics and questions to focus on in particular – and the “hows” – i.e., methodology and design aspects of how to approach the work.

The Whats

What #1: Evidence-Based Treatments for Irritability

Of all the goals being pursued in youth irritability research, there may be none more important than that of improving treatment, services, and outcomes. This question is usefully approached from an *evidence-based practice* (EBP) perspective (Evans & Santucci, 2021).

²For example, see Evans et al. (2023) for a review of measurement in youth irritability, which is not touched on here but includes several areas for future directions.

Briefly, EBP exists at the intersection of (a) the best available evidence, (b) clinician expertise/judgment, and (c) patient preferences and values (Spring, 2007) – often likened to a three-legged stool or Venn diagram with three circles. We focus here on the “evidence” leg in terms of clinical trials, although there is also a need for attention toward assessment, clinician expertise, and patient factors (Roberts et al., 2016).

Regarding the question of what intervention works best for treating a particular problem, the strongest evidence comes from multiple, independent, well-powered randomized controlled trials (RCTs) testing a specified intervention relative to an active comparison group in reducing a specific problem. This type of evidence is needed for treatments to be considered “well-established” or “probably efficacious” as evidence-based treatments (EBTs; Southam-Gerow & Prinstein, 2014; Tolin et al., 2015). Unfortunately, there is a paucity of this kind of research on treatments for youth irritability specifically (Breux et al., 2022; Evans & Santucci, 2021; Kircanski, Clayton et al., 2018; Singh et al., 2021; Stringaris et al., 2018; Sukhodolsky et al., 2016; Waxmonsky et al., 2021). This has led to “cries for help” for desperately needed irritability RCTs, particularly for non-pharmacological interventions (Brotman & Kircanski, 2022). However, these same reviews conclude that there *are* well-established psychosocial interventions recommended for irritability because they are effective for treating an array of irritability-related problems. For example, ample evidence suggests behavioral parent training (BPT) is effective for treating ODD, ADHD, and externalizing problems – all commonly associated with irritability (Bakker et al., 2017; Beelmann et al., 2023; Coates et al., 2015; Kaminski & Claussen, 2017; Piquero et al., 2016). Similarly, evidence supports the effectiveness of CBT and interpersonal psychotherapy (IPT) for youth depression (Weersing et al., 2017), different forms of CBT with exposure for youth anxiety (Higa-McMillan et al., 2016) and traumatic stress (Dorsey et al., 2017), dialectical behavior therapy (DBT) for self-injurious thoughts and behaviors in adolescents (Glenn et al., 2019), and adjunctive family skill-building plus psychoeducation for pediatric bipolar disorder (Brickman & Fristad, 2022; see also effectivechildtherapy.com). The EBT toolkit contains many tools relevant to youth irritability.

Accordingly, for *clinical practice*, the current and near-future EBP approach involves (a) recognizing that irritability manifests as part of a larger clinical picture, including many different disorders and problems; (b) conducting a comprehensive, multi-source assessment to identify the larger problem(s); (c) selecting the most appropriate EBT,

while considering clinician and client factors; and (d) proceeding with treatment planning and administration, including progress monitoring and outcome evaluation (Evans & Santucci, 2021). Additionally, some evidence (Evans et al., 2021; Evans, Weisz et al., 2020) suggests that a flexible, personalizable EBT framework such as MATCH (Chorpita & Weisz, 2009) or UP-C (Ehrenreich-May et al., 2017) may be particularly effective for irritable youth.

For future directions in *research*, however, there is a long way to go. Even the EBTs noted above as relevant for treating irritability-related problems have limited evidence when it comes to irritability specifically. Evidence to date mostly comes from secondary analyses of existing trials or small initial pilot studies. Accordingly, research is needed to test the efficacy and effectiveness of these EBTs in large-scale RCTs that focus on irritability as a treatment target and clinical outcome.

But where to begin? Given the transdiagnostic nature of irritability and the high degree of symptom heterogeneity and comorbidity (Table 2), a treatment-referred irritable youth could find themselves *en route* to a wide array of possible diagnostic conclusions. These conclusions, in turn, would lead to an even wider array of potential treatment options. We focus on the handful of well-established psychosocial programs that are likely to be helpful in addressing some of the most common irritability-related conditions affecting youth: BPT for ODD, ADHD, Conduct Disorder, and other externalizing problems; CBT for a variety of emotional and behavioral problems; IPT for adolescent depression; and DBT for adolescent self-injurious thoughts and behaviors.

Specific Intervention Approaches

When working directly with youths, programs for anger, irritability, and aggression are likely to be helpful for improving emotion regulation and social problem-solving skills, with support from several RCTs (Sukhodolsky et al., 2016). For instance, CBT approaches have shown initial efficacy in the treatment of youth aggression, conduct problems, and emotion dysregulation, including Stop Now and Plan (SNAP; (Augimeri et al., 2007; Burke & Loeber, 2015; Derella et al., 2019). More recently, an intervention focused on exposure-based CBT and other intervention strategies (e.g., BPT) is being tested, showing initial feasibility for treating youth with DMDD (Kircanski, Clayton et al., 2018; Naim, Kircanski et al., 2021).

Many of these CBT programs for youth are accompanied by BPT for parents or caregivers. As noted above, BPT is well-established for child externalizing problems broadly, and this evidence is accumulating for irritability as well. In fact, BPT is the most commonly studied treatment form in research on

irritability/dysregulation (Waxmonsky et al., 2021); however, much of the existing evidence is from secondary analysis rather than as primary treatment target (Fernández de la Cruz et al., 2015; Waxmonsky et al., 2016). As one example of a new RCT, Fongaro et al. are currently conducting a multi-site, 3-arm, masked, randomized trial comparing the efficacy of BPT as compared to Nonviolent Resistance Training and Treatment As Usual in the treatment of irritability in youth with ADHD, ODD, DMDD, Conduct Disorder, and other mood/anxiety disorders (Fongaro et al., 2022). We look forward to findings from this research and call for more studies like it.

Given the high rates of irritability and associated comorbidities, a transdiagnostic approach to psychotherapy seems appropriate, although current evidence comes more from open trials and secondary analyses than new RCTs. For example, MATCH (MATCH-ADTC; Chorpita & Weisz, 2009) has been proposed as a transdiagnostic treatment with both CBT and BPT components, where secondary analyses from 2 RCTs suggest it is likely to be helpful for irritable youths (Evans et al., 2021; Evans, Weisz et al., 2020). Similarly, the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children and Adolescents (UP-C/A; Ehrenreich-May et al., 2017) is a transdiagnostic CBT intervention; however, unlike MATCH, UP-C/A has been specifically adapted for treatment of youth irritability while simultaneously targeting other transdiagnostic mechanisms (e.g., emotion regulation) and parenting behaviors (Grossman & Ehrenreich-May, 2020). Initial pilot data on acceptability, feasibility, and effectiveness of UP-C/A for irritability appears promising (Hawks et al., 2020).

Third-wave approaches to psychotherapy have also been effective and efficacious at treating near-neighbor problems to irritability, including DBT for anger, suicidality and non-suicidal self-injury (Ciesinski et al., 2022; DeCou et al., 2019), and IPT for child behavioral dysregulation (Miller et al., 2018). Preliminary efficacy results of a small-scale trial also provide support for the feasibility and preliminary efficacy of DBT for children with DMDD (Perepletchikova et al., 2017), and a recent meta-analysis revealed promising effects of DBT for general externalizing problems (Jakubovic & Drabick, 2023). Less research has considered parent- or youth-directed ACT as an approach for youth with behavioral problems (e.g., Bodden & Matthijssen, 2021; Whittingham et al., 2019); this may be a useful direction for future research, however differences in terminology may need to be reconciled (e.g., cognitive inflexibility vs. irritability). These are all important directions for future research – designing new studies to test existing approaches for youth irritability.

Finally, a handful of more recent intervention developments are worth noting. Collaborative and Proactive Solutions (CPS) has been implemented across settings, including in schools, with families, and in therapy settings, with studies supporting its initial effectiveness for irritability, defiance, and caregiver/family domains comparability to BPT (Greene & Winkler, 2019; Mulraney et al., 2022; Murrihy et al., 2022; Ollendick et al., 2016). More broadly, efficacious interventions for youth emotion dysregulation are worth considering relative to irritability (Eadeh et al., 2021; Waxmonsky et al., 2021). Many of these overlap with diagnostic groups. For example, Regulating Emotions Like An Expert (RELAX; Breaux & Langberg, 2020) and Managing Frustration for Children (MFC; Rosen et al., 2019) appear promising for youth with ADHD, while advances have been made for youth with ASD (Beck et al., 2020; Conner et al., 2019).

Taken together, these interventions have been tested across a variety of modalities. In addition to group vs. individual, and parent vs. child, studies have shown that virtual modalities are acceptable to families, show preliminary efficacy, and may provide a feasible alternative to face-to-face services (e.g., i-PCIT, Comer et al., 2017; BPT for ADHD; Rahali et al., 2022). As with the broader field of youth mental health intervention and implementation science, irritability researchers should attend to the modality for delivering treatment to increase reach, accessibility, and personalization while striving to maintain or improve effectiveness.

Cross-Cutting Intervention Issues

Several key questions remain to be addressed and should be addressed by researchers pursuing RCTs of EBTs for irritability. First, we have reviewed **many treatments above – but which ones to focus on?** All are useful for different individuals and under different circumstances, and we have emphasized some major EBTs, but this should be driven by the researcher's interests and the population/problem. For example, a randomized trial comparing CBT to IPT and usual care may be informative for treatment of adolescents with persistent (tonic) irritable mood, while comparing BPT to CPS and usual care may particularly useful for advancing the treatment of angry and aggressive (phasic) outbursts in children. At this stage in the science, feasibility, efficacy, and effectiveness need to be established specifically for the treatment of youth irritability.

Second, there is the question of **whether to adapt the intervention specifically for irritability or stay close to the original protocol.** Analyses of well-established protocols' effectiveness for irritability can often be accomplished via secondary analyses of earlier RCT data

(Derella et al., 2019; Evans, Weisz et al., 2020; Fernández de la Cruz et al., 2015), particularly if the original trials collected irritability-related variables or ones that could be recoded to examine irritability. Researchers are encouraged to seek out ideal datasets to look at whether well-established programs (BPT/CBT/IPT/DBT) are specifically effective in reducing irritability and related problems. Conversely, a strong case for adaptation can be made when researchers are collecting new data; ideally, irritability and related problems would be the focus of referral, treatment, and measurement. For example, UP-C/A, was originally designed for child anxiety and depression, so there was a compelling rationale to make modifications to apply specifically to anger and irritability (Grossman & Ehrenreich-May, 2020; Hawks et al., 2020). Similarly, PCIT was already one of the most effective BPT programs when Luby et al. (2018) developed an augmented version by adding an “emotion development module” to promote young children’s emotional competence and regulation, in addition to behavioral regulation. The UP-C/A, DBT, and IPT pilot studies described above provide additional examples (Hawks et al., 2020; Miller et al., 2018; Perepletchikova et al., 2017). The goal is to make already-effective EBTs as effective as possible for irritability. This work, though, should be pursued with caution, with deliberate theoretical or practical justification for each change made. Deviating from an established protocol risks weakening the effects of the intervention; and as more changes get made, the consequences of those changes becomes unclear.

A third question has to do with **whether irritability is a symptom of other disorders as opposed to a core problem in its own right**. We have argued above for using EBTs to treat the core problem in which the irritable features are embedded. At present, this is simply an EBP approach following the best *available* evidence over more experimental treatments. Research is needed to determine whether this is really the most effective approach for treating irritable youths (e.g., via different core treatments) or if interventions more targeted toward irritability could be more effective for most irritable youths. These choices have implications for the architecture of the intervention (Sauer-Zavala et al., 2017) including whether it may include elements drawn from other EBTs (e.g., parenting skills), or more of a unified irritability-specific model of how the treatment works (akin to behavioral activation or exposure).

Fourth, apart from being adapted, **little is known about how treatments should be personalized for irritable youths**. This question has received relatively little examination in the youth mental health literature broadly (Ng & Weisz, 2016), and it is especially relevant to youth

irritability (Evans & Santucci, 2021). Although evidence supports transdiagnostic treatments that can be personalized, there is little evidence to guide when and how interventions should be personalized. This is an empirical question worthy of investigation, which may benefit from engaging collaboratively with clinicians.

There are many remaining questions relating to the aims, stages, and methods of the research. Some of these (e.g., experimental therapeutics, digital health) are discussed in more depth below, while others (e.g., principles of design for efficacy vs. effectiveness, and all of the above, such as masked evaluations) are relevant to treatment more generally and beyond the scope of this paper, but readers are referred elsewhere (Chan et al., 2013; La Greca et al., 2009; Weisz et al., 2015). In short, it is important that youth irritability intervention research be carried out with high standards of methodological rigor.

What #2: A Better Understanding of the Problem

The current and near-future state of EBP for irritability, as summarized above, is less than ideal. In contrast to irritability treatments, well-established treatments noted above for depression, anxiety, disruptive behavior, and PTSD all have at least two things in common: (a) they clearly identify and measure the problem they are intended to treat; and (b) they are based in a theoretical understanding of how the treatment could engage with at least one target mechanism or process thought to underlie the disorder, which in turn may lead to symptom reduction. To date, irritability-*specific* intervention research remains very limited in both these respects. A better understanding of the mechanistic processes contributing to and maintaining different types of youth irritability is essential to develop more effective interventions. Thus, the following sections describe some promising approaches that could be ideal for facilitating transformative advances in youth irritability intervention research.

Translational Framework

Although definitions vary, the basic idea of translational research is that work progresses from basic science to clinical application (bench to bedside) in an efficient, cumulative manner involving multiple disciplines and different goals at each stage (Fort et al., 2017). But this description does not characterize youth irritability research to date, which can perhaps better be described as “working backwards” translationally. That is, much of the progress in this area (as reviewed above) has involved assessing irritability by drawing items from measures originally designed to measure something

else, or treating irritability with EBTs that were originally developed for other problems. Much has been learned this way, but there are inherent constraints when a body of work sets its roots and evolves in reverse from the products of other, more advanced bodies of work.

For instance, consider measures of youth depression, which delineate core dimensions such as negative mood or physical symptoms – which represent different facets relating to depression in youth (Kovacs, 2015). This model was developed by drawing from decades of data and theory pertaining to depression across development. In contrast, little is known about the heterogeneity and potential multidimensionality of irritability, and this problem is compounded when irritability is measured through miscellaneous items (ranging from feeling moody to aggressive outbursts) selected from different instruments and diagnostic categories. Thus, what is needed are more deliberate and forward-looking approaches to studying irritability within a translational framework.

Experimental Therapeutics

Although not a new approach, there has been increasing momentum toward an experimental therapeutics in clinical child and adolescent psychology (White, 2022) and in the clinical and health sciences more generally (Gordon, 2017; Lewandowski et al., 2018; Waldman et al., 2009). This idea behind this approach is that researchers first identify a putative mechanism underlying the disorder, and then test different intervention strategies to see if they engage that mechanism. Finally, intervention research would test whether the mechanism serves as a mediator between a specific intervention and its effects on clinical outcomes. In this way, experimental therapeutics can test not only *whether* the intervention works, but also *how* it works. This model carries important implications for basic and translational research as well as intervention research. For example, Glenn et al. (2022) tested models of suicidal thoughts in adolescents using intensive longitudinal methods and found that interpersonal negative life events predicted suicidal thoughts, and that this association was mediated by feelings of thwarted belongingness related to family but not friends. Such findings are especially useful because they test potential risk factors and mediators (thwarted belongingness) for a clinical outcome of interest (suicidal thoughts) and provide insight on where to target clinical interventions to disrupt the chain and lead to better outcomes (perceived family belongingness). At the same time, they can yield information about what is less likely to work (in this case, possibly thwarted friend belongingness), so even “null” results can serve as useful findings.

Such approaches could be valuable for irritability as well. However, the field of irritability research lacks a strong phenomenological and mechanistic understanding of processes related to irritability that would yield testable pathways such as those tested by Glenn et al. for suicidal thoughts. To be sure, there have been notable advances in developing and testing translational models of irritability (Brotman, Kircanski, Stringaris et al., 2017b). There is a need for precise models that will yield empirical results with specific implications for intervention development and testing. In other words, more effective interventions are most likely to stem from a better understanding of the problem. In the following sections we highlight a few of these mechanisms, and how they may relate to the heterogeneous phenomenology of irritability.

Phasic and Tonic Dimensions

Irritability is sometimes separated into two different types – phasic (i.e., temper outbursts) and tonic (i.e., irritable mood) – which are distinct but highly correlated dimensions (Brotman, Kircanski, Stringaris et al., 2017b; Leibenluft, 2017). They differ in stability, heritability (Moore et al., 2019), and in their associations with other forms of psychopathology such as ADHD and ODD (Cardinale et al., 2021; Hawes et al., 2020; Silver et al., 2021). Most research on phasic and tonic irritability has been conducted in youth ages 8–18, although these distinct dimensions have been identified in children as young as 3 (Silver et al., 2022). The limited research in other age groups leaves outstanding questions particularly for early childhood and adulthood.

Yet there are also outstanding concerns about measurement. There are few very measures that neatly disentangle both phasic and tonic irritability, and a paucity of measures for phasic irritability specifically (Carlson, Silver et al., 2022; Klein et al., 2021). Accurate measurements of both dimensions are needed to further our understanding of their unique and shared variance, while also informing both research and clinical advancements. Given that phasic and tonic irritability are inherently temporal and context-related (e.g., phasic occurring in relatively short bursts related to some trigger, while tonic occurs as a more persistent, pervasive mood), these constructs may be especially well-suited for real-time measurement via EMA, as discussed below. At the same time, there is a need for measures that incorporate multiple informants, such as parents or teachers, as they would provide a context-sensitive understanding of the presentation of these symptoms (De Los Reyes et al., 2023). Yet more work is also needed on measuring and identifying the neurobiological

mechanisms underlying both dimensions through neuroimaging and behavioral paradigms. Examining the underpinnings of phasic and tonic irritability is a relatively new and promising area of research. To the extent that these irritability dimensions have different underlying mechanisms, this may lead to different treatment approaches.

Reward and Threat Dysfunction

Brotman et al.'s (2017b) translational model posits that severe irritability could be mediated by (a) *reward-system dysfunction*, where irritability is linked to aberrant emotional and behavioral responses to reward processes, especially frustrative nonreward; and (b) *threat-system dysfunction*, where irritability is linked to aberrant approach (rather than withdrawal) responses in relation to threat. This model was built by synthesizing research findings largely pertaining to youths with severe mood dysregulation or chronic irritability to healthy volunteers or other diagnostic groups available at that time (Brotman et al., 2017). Notably, it has advantages including relations to RDoC (Meyers et al., 2017) as well as to genetics and animal models.

Since the emergence of this model, more work has been conducted examining the exact underpinnings of these deficits. For example, irritable youth demonstrate increased attention bias toward threat (Elvin et al., 2022; Salum et al., 2017) and aberrant reward processing (Dougherty et al., 2018; Kryza-Lacombe et al., 2021, 2022; Perlman et al., 2015) including increased reward sensitivity. Some have examined threat and reward processing with irritability and other diagnostic groups, including youth with anxiety (Kircanski, White et al., 2018; Stoddard et al., 2017). Studies using group comparisons are interesting and useful but often have small samples and unstandardized methods (Lee et al., 2022). And of course, group-based studies only focus on the groups that they choose to study, making it unclear how specific these findings are to irritable youths as compared to other or overlapping groups, such as DMDD vs. ODD, or irritability in depression vs. ADHD. Thus, more transdiagnostic and dimensional work is needed to elucidate irritability's potential unique contribution to threat and reward dysfunction.

Cognitive Mechanisms

One particular area of focus is on the cognitive mechanisms that underlie and maintain irritability. Some studies have identified broad cognitive control deficits (Cerqueira et al., 2010; Seymour et al., 2020) while other studies have parsed apart the exact mechanisms that may be driving irritability-related phenomena, including inhibitory

control (Deveney et al., 2019; Liuzzi et al., 2020; Nili et al., 2022), cognitive flexibility (Li et al., 2017), and executive functioning (Colonna et al., 2022). For example, some of this evidence suggests that irritable youths have greater difficulty ignoring irrelevant stimuli and inhibiting their impulses toward goal-directed behavior in cognitive tasks (i.e., inhibitory or cognitive control). Such deficits may be at play when severely irritable youths are unable to inhibit a temper outburst in response to a minor provocation. However, this evidence is somewhat more mixed for irritability than it is for ADHD (Uran & Kılıç, 2015) and with respect "hot" vs. "cool" situations involving cognitive control (Colonna et al., 2022), underscoring the need for more research.

At the same time, there is a serious need for more longitudinal work examining mechanisms among irritability, cognitive/neural mechanisms, and psychopathology across multiple timepoints (Cardinale et al., 2022; Evans, Blossom et al., 2020). This could help identify the stability of these deficits across development, elucidate potential early risk factors, and inform therapeutic development, particularly as it relates to cognition. There is also a need for more frustration-induction paradigms in conjunction with cognitive tasks to parse apart the relationship between cognition, frustrative nonreward, and irritability in laboratory settings (Cerqueira et al., 2010; Seymour et al., 2020). Work in this area has elucidated broader deficits, but questions remain about how these deficits could be driving irritable children's aberrant responses to frustrative nonreward (Brotman, Kircanski, Stringaris et al., 2017b). Such paradigms also provide the opportunity to collect physiological measures, such as heart rate variability, to provide another measurement of both frustration and irritability related symptoms.

Taken together, these areas (phasic/tonic, threat/reward, cognitive mechanisms) highlight several potentially important avenues of mechanistic work moving forward. In particular, it would be valuable to test specific hypotheses about phasic and tonic irritability (clinical phenotypes) in relation to reward, threat, and cognitive processes thought to underlie them – which could potentially serve as targets for intervention within an experimental therapeutics framework. It is important to develop specific models and testable hypotheses that render useful findings, whether significant or null. We also emphasize the importance of maintaining the real-world, real-time experiences for youths and families affected by irritability, as this is both the focus and the end goal of the research at hand. Below we conclude with a few methodological suggestions in line with these goals.

The Hows

How #1: Real-Time and Real-World Context

Ecological momentary assessment (EMA) has been identified as a key future direction for youth irritability research for several years (e.g., Brotman et al., 2017); but this work is still in its infancy. Broadly, EMA refers to repeated measurement of individuals' behaviors or experiences in real time and in their natural environment.³ These methods provide the unique opportunity to understand the presentation of psychopathology in vivo, mitigating the biases of retrospective recall measures (Russell & Gajos, 2020). Researchers have frequently used EMA increasingly to study depression, anxiety, suicidal thoughts and behaviors, and substance use. Only a few teams have applied it to youth anger (Whalen et al., 2009), and emotional variability in ADHD (Rosen et al., 2015), but EMA is increasingly common in youth mental health studies generally (Heron et al., 2017; Russell & Gajos, 2020).

To date, few studies have leveraged EMA to assess irritability (Flynn et al., 2021; Naim et al., 2021; Naim et al., 2022; Tseng et al., 2023), although preliminary efficacy of this methodology has been established in this population (Naim, Smith et al., 2021). A recent study used EMA to examine positive and negative affective fluctuations across youth with DMDD, ADHD, an anxiety disorder, and healthy controls, and found that DMDD youth demonstrated the highest level of aberrant labile mood when compared to other clinical groups (Naim et al., 2022). Future work should continue to incorporate EMA to elucidate the real-time experiences of youth with irritability. This is particularly necessary for distinguishing phasic and tonic irritability, as EMA may provide a unique opportunity to assess the triggers of temper outbursts throughout daily life. EMA also provides the chance to examine the stability of frustrated mood throughout a period of time. A transdiagnostic approach is recommended to study real-time irritability across different forms of psychopathology (Naim, Smith et al., 2021; Naim et al., 2022). With few exceptions (e.g., Rosen et al., 2015, the use of multiple and proxy informants is largely neglected in the EMA literature (Trull & Ebner-Priemer, 2020). Incorporating parent-report and youth-report in EMA studies is a key future direction. This could lead to understanding multiple perspectives on youth irritability as well as the dyadic parent-child interactions that may maintain irritable mood and behavior.

How #2: Digital Health Applications

The smartphones and other digital technologies that make EMA viable as a research tool also open up a world of possibilities for digital health for irritability. While the previous section discusses EMA mainly as a research tool, we focus here on digital health as a mechanism for better meeting mental health needs in the population. Indeed, NIMH has highlighted this digital health as a priority, defining it broadly to include mHealth, health information technology (e.g., smartphones, wearables, internet resources), and other types of data and science (e.g., genetic, biological, social, behavioral) in a way that helps consumers, clinicians, and researchers measure, manage, and improve health. The explosion of telehealth and mHealth during the COVID-19 pandemic illustrates how digital health could better reach the needs of youths and families (Peek et al., 2020). It has vast potential for enhancing efficiencies in health care delivery by increasing patient access to health information, extending the reach of health care experts into communities with noted access barriers (e.g., rural and low-income populations), and potentially reducing the overall cost of health care through the automation of services.

Despite irritability being common, impairing, and in need of more effective and available treatments, little work has been done in the realm of digital health and dissemination (Evans et al., 2022; Kircanski, Clayton et al., 2018). Digital health studies of irritability that have been conducted demonstrate preliminary efficacy in decreasing symptoms in adults (Economides et al., 2018) and children (Diaz-Stransky et al., 2020). Yet more work in this area is needed, particularly in the development of care that could be quickly administered in times of salient need (e.g., during an aggressive outburst). Digital health tools would also allow a wider dissemination of irritability treatment to diverse populations, making it an incredibly necessary area for future research. Intervention scientists working on addressing the irritability gaps highlighted above are especially encouraged to consider digital health dissemination and application, such as through telehealth (Venturo-Conerly et al., 2022) and single-session digital interventions (Schleider et al., 2020).

How #3: Leveraging Existing Datasets

Finally, some of the most important and cutting-edge work in youth irritability research involves data that

³For the purposes of this paper, we use the term EMA to include experience sampling methods, daily diary studies, intensive longitudinal methods, and ambulatory assessment – all of which are closely related and overlapping terms.

have already been collected. As argued elsewhere (Evans & Karlovich, 2022), large-scale longitudinal datasets provide incredibly valuable opportunities for analysts to explore trajectories of change across development (Yu et al., 2023). With cross-sectional datasets on common measures, and collaborative generosity and open science practices, it is quite feasible to generate aggregate datasets that reach total sample sizes in the thousands by pooling together datasets with sample sizes in the hundreds (e.g., Evans, Bonadio et al., 2020). Alternatively, researchers can also bolster their work by conducting parallel analyses to replicate or extend their results across multiple samples (e.g., Cardinale et al., 2019; Dougherty et al., 2021). These cited examples are relatively straightforward insofar as they only required obtaining and then analyzing existing datasets using the variables they already contained, but this only scratches the surface. A robust methodological literature has developed around integrative data analysis and harmonization methods (Hussong et al., 2013), which can allow researchers to combine different measures of the same construct across different datasets, even different informants and developmental periods. The youth irritability literature would benefit from creative and methodologically sound application of these techniques to existing datasets. Some such efforts are just getting started, such as the Cross-Cultural Consortium on Irritability led by Wan-Ling Tseng and colleagues.

Particular quantitative and computational methods, including network analysis, latent class/profile models, growth mixture modeling, and various machine learning techniques have only begun to scratch the surface in the youth irritability literature. While all statistical approaches produce more precise estimates with larger samples, these approaches in particular tend to require larger samples; and with large samples, they hold more promise for validation, generalizability, and even predictive utility of results (e.g., see Wakschlag et al., 2023 for an irritability risk calculator proof of concept). With large samples from existing datasets, there is potential to capture a clearer picture of irritability within the broader context of psychopathology, across development, and from typical to atypical. Although analyzing existing datasets may not sound like the most exciting or innovative approach, such studies can be transformative. For example, Burke et al.'s (2014) analysis of pooled data from 5 large community samples with parent-reported ODD measures (total $N = 16,280$) provided a definitive answer regarding the bifactor structure and symptoms of the irritable dimension of ODD (touchy;

angry; temper). Large-scale analysis of existing data can answer important questions more quickly and clearly than new data collection efforts.

A final note for early-career and student researchers interested in analyzing existing data: It may not be obvious, but these datasets are often freely available – especially for large studies. Sometimes all it takes is an internet search, a brief application process, scouring the online supplemental materials associated with an article, or a courteous e-mail to an author (and a potential collaborator) – and the dataset of your dreams could be yours to analyze for a stated purpose. As a starting point, a few repositories of potentially relevant child/adolescent and longitudinal datasets are listed here.⁴ However, finding the study that is best suited to your needs may not be a matter of browsing what is on the shelf. Instead, we recommend articulating the research question of interest, and then searching to locate datasets that could meet your needs. From there, the only remaining steps are determining whether and how the data could be accessed for your analysis. Happy searching!

Concluding Comments

With any paper like this, the ideas put forth above cannot help but reflect our own interests, views, and inclinations. But making prescriptions about the future research directions is not a task to be taken lightly. Accordingly, we have attempted to clearly identify, describe, and provide useful guidance around the specific areas that we think are most likely to move the needle most quickly for a large number of youth with irritability and related problems. In addition, this paper is selective and non-exhaustive. At the risk of continuing to omit important aspects, we also wish to underscore the importance of continued work in a few other areas that we have not discussed here, including assessment, measurement, standardization, and informants generally; cultural and sociodemographic differences; integration of irritability into broader frameworks including DSM, ICD, RDoC, and HITOP; novel technologies such as wearable devices, passive monitoring, and digital phenotyping; the need for research across the lifespan including infancy through all of adulthood (not just children/adolescents); and more!

After two remarkably productive decades, research on youth irritability faces unique challenges and opportunities. Two major challenges – the “whats” – confronting the research community involve moving

⁴<https://www.icpsr.umich.edu/web/pages/ICPSR/index.html>; <https://dash.nichd.nih.gov/>; <https://nda.nih.gov/>; <https://nces.ed.gov/ecls/>; <https://nda.nih.gov/abcd/request-access.html>; <https://nyu.databrary.org/>; <https://www.landscaping-longitudinal-research.com/>.

toward more effective treatments and understanding exactly how irritability operates from a mechanistic perspective. While there are many different ways these challenges could be pursued, we have emphasized three opportunities – the “hows” – that seem particularly accessible and impactful: EMA, digital health, and analysis of existing data. Hopefully our estimations and prognostications will be of some use for those working on tackling important problems in this area. In particular, this paper was written with an eye toward current and future students and early-career researchers interested in youth irritability. They will be the ones not only to prognosticate, but to actually chart the course.

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