Irritability in Children and Adolescents*

Melissa A. Brotman, Katharina Kircanski, and Ellen Leibenluft

Emotion and Development Branch, National Institute of Mental Health, Bethesda, Maryland 20892; email: brotmanm@mail.nih.gov, kircanskik@mail.nih.gov, leibs@mail.nih.gov

Abstract

Irritability is a common and impairing clinical presentation in children and adolescents. Despite its significant public health impact, irritability remains an elusive construct. Chronic and severe irritability is the primary symptom of the new DSM-5 diagnosis, disruptive mood dysregulation disorder (DMDD). However, empirical and clinical approaches to irritability are in their relative infancy, and questions regarding the validity of the DMDD diagnosis have been raised. Moreover, irritability is a trait distributed continuously in youth, thereby fitting within the National Institute of Mental Health Research Domain Criteria initiative. Thus, there are opportunities for scientific review and integration. Accordingly, the goals of this review include (a) clarifying the definitions of irritability; incorporating clinical and translational animal work; (b) reviewing the historical context surrounding the study of irritability; (c) reviewing the prevalence, clinical correlates, and longitudinal course of irritability; (d) presenting behavioral and neurobiological findings associated with irritability; and (e) exploring treatment options and proposing future directions for research.

Keywords

anger, disruptive mood dysregulation disorder, frustration, frustrative nonreward, irritability, threat, neuroimaging
Irritability: low threshold for experiencing anger in response to frustration

Disruptive mood dysregulation disorder (DMDD): a disorder characterized by two core symptoms—severe, recurrent outbursts and irritable or angry mood between outbursts

OVERVIEW, SCOPE, AND GOALS
Over the past decade, there has been an upsurge in research on irritability in children and adolescents (Brotman et al. 2017). Chronic and severe irritability is the primary symptom of disruptive mood dysregulation disorder (DMDD) (Am. Psychiatr. Assoc. 2013), a new diagnosis appearing in the 5th edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Irritability is also an associated symptom of numerous other pediatric disorders (Ambrosini et al. 2013, Burke et al. 2014, Jensen et al. 2007, Shaw et al. 2014, Stoddard et al. 2014). In fact, irritability is a trait distributed continuously in youth (Stringaris & Taylor 2015), thereby fitting well within the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative (Insel et al. 2010). The RDoC approach is designed to elucidate dimensions of brain and behavioral functioning in a translational manner; indeed, the neurobiological and behavioral bases of irritability exhibit parallels across animal species. However, despite its significant public health impact (Conner et al. 2004, Nock et al. 2007, Peterson et al. 1996, Pickles et al. 2010) and increased scientific attention, irritability remains an elusive construct that requires further investigation (Avenevoli et al. 2015). Empirical and clinical approaches to irritability are in their relative infancy, and questions regarding the validity of the DMDD diagnosis have been raised.

This article has several goals. First, we clarify the definitions of irritability and related constructs (frustration, anger, and aggression), drawing upon both clinical and translational animal work. Second, we review the historical context and debate surrounding the diagnosis of severe,
chronic irritability in youth and the consequent emergence of DMDD in the DSM-5. Third, we describe the prevalence, clinical correlates, and longitudinal course of irritability. Fourth, we present behavioral and neurobiological differences between youth with severe irritability and typically developing children. Finally, we review extant treatment options and propose future directions for irritability research, highlighting the need for strong phenotypic measurement and the development of novel clinical interventions based on demonstrated pathophysiological mechanisms.

DEFINITIONS AND PHENOTYPIC REFINEMENT

Clinical Definition of Irritability

Irritability is conceptualized as a low threshold for experiencing anger in response to frustration (Buss & Durkee 1957, Caprara et al. 1985, Deveney et al. 2013, Leibenluft 2011, Leibenluft & Stoddard 2013, Snaith & Taylor 1985). At a recent NIMH expert workshop on childhood irritability (Avenevoli et al. 2015), the construct was framed as having two components: tonic and phasic. The tonic component refers to persistently angry, grumpy, or grouchy mood, whereas the phasic component refers to behavioral outbursts of intense anger (Copeland et al. 2015). Thus, the tonic component of irritability is a mood state that is more enduring than temper outbursts of intense anger (Vidal-Ribas et al. 2016). These two components of irritability form the two core symptoms of DMDD: severe recurrent temper outbursts (i.e., phasic irritability) and irritable or angry mood between outbursts (i.e., tonic irritability) (Am. Psychiatr. Assoc. 2013). However, preliminary evidence suggests that tonic and phasic irritability are highly correlated and difficult to differentiate (Copeland et al. 2015). Therefore, notwithstanding the need to meet both symptom criteria for a diagnosis of DMDD, the extent to which these are independent constructs is unclear; additional work to address this question is needed.

Frustration, Anger, and Aggression

Irritability, frustration, anger, and aggression are interrelated constructs (Buss & Durkee 1957, Caprara et al. 1985, Dollard et al. 1939, Leibenluft & Stoddard 2013). Frustration refers to the initial, normative, affective reaction to a blocked goal (Amsel 1958). Anger is an emotion (Spielberger et al. 1995) that is often elicited by frustration (and, as we describe below, sometimes by threat) (Brotman et al. 2017, Dollard et al. 1939). Anger can serve an adaptive function because it is associated with increased effort toward goal attainment (Carver & Harmon-Jones 2009, Leibenluft & Stoddard 2013). Aggression refers to verbal or motor behavior motivated by anger or frustration (Berkowitz 1989, Dollard et al. 1939). Thus, anger is an emotion, often precipitated by frustration, and aggression is a behavioral output of anger. As described above, irritability is conceptualized as a low threshold for experiencing anger in response to frustration, and it is frequently associated with heightened verbal and/or physical aggression.

Frustrative Nonreward and Threat

The concepts described above relate to two key constructs in translational research on irritability: frustrative nonreward (Amsel 1958) and threat (Brotman et al. 2017). Translational research examines these constructs behaviorally and neurobiologically across multiple species, including rodents, primates, and humans.

Frustrative nonreward refers to the behavior that occurs when an organism expects to receive a reward (e.g., food) but does not (Papini & Dudley 1997). Frustrative nonreward is one construct
in the RDoC matrix, thus supporting translational research on irritability within that framework. Frustrative nonreward was first described in rodent work (Amsel 1958) as an adaptive, normative response to blocked goal attainment. It is characterized by increased motor activity and aggression in rodents (Amsel 1958, Burokas et al. 2012), nonhuman primates (Davenport & Thompson 1965), children (Ryan & Watson 1968), and adults (Dollard et al. 1939). Such behaviors resemble the features of temper outbursts in children and adolescents. Affectively, frustrative nonreward is linked with anger (Berkowitz 1989).

Like rewards, threats are intrinsic motivators of behavior conserved across species (Fanselow 1994, LeDoux & Pine 2016). Specifically, threats are stimuli that endanger safety. Characteristics of a threatening stimulus in a given situation, such as its imminence, drive neural and behavioral responses. Whereas a distal threat produces fear responding, an imminent threat produces rage responding, or active behavioral engagement with the threat stimulus in an attempt to neutralize it (Blair 2010, Carver & Harmon-Jones 2009, Fanselow 1994). In humans, irritability can involve an aberrant expression of this normative response to threat, referred to as reactive aggression. As described below, compared with healthy children, irritable youth tend to orient to threatening stimuli in the environment and are more likely to interpret ambiguous stimuli as threatening (Brotman et al. 2017); this interpretation may elevate risk for anger and aggression (Dodge 1980).

**HISTORICAL CONTEXT OF IRRITABILITY RESEARCH AND DEVELOPMENT OF DSM-5 DISRUPTIVE MOOD DYSREGULATION DISORDER**

In clinical settings, chronic, severe, and impairing irritability is a common presentation in children and adolescents. Here, we review the historical context and continuing debate surrounding the most appropriate diagnosis for youth with DMDD (Roy et al. 2014).

**The Controversy Regarding the Diagnosis of Bipolar Disorder in Youth**

In the 1990s, there was nosological debate surrounding the clinical conceptualization of youth presenting with severe irritability and hyperarousal symptoms (Biederman et al. 1998, Leibenluft et al. 2003). Although these youth did not exhibit clearly demarcated episodes of hypomania or mania, some researchers and clinicians, largely in the United States, considered these children to have a developmental presentation of bipolar disorder (BD). Thus, in the United States between 1994 and 2003, the rate of youth receiving a diagnosis of BD in outpatient clinics increased 40-fold (Moreno et al. 2007). Moreover, the percentage of youth in the United States receiving a hospital discharge diagnosis of BD surged from approximately 10% in the mid-1990s to over 30% in the mid-2000s (Blader & Carlson 2007), resulting in a 72.1-fold difference between the United States and England in psychiatric hospital discharge rates of pediatric BD (James et al. 2014). It is plausible that pediatric BD was underdiagnosed prior to this period. However, a more likely explanation for such dramatic increases in the diagnosis was a broadening of symptom criteria for pediatric BD in clinical practice, incorporating nonepisodic irritability and hyperarousal, in addition to classically defined episodes of hypomania or mania.

To empirically test the formulation of severe irritability as a developmental presentation of BD, Leibenluft and colleagues (Leibenluft 2011, Leibenluft et al. 2003) operationalized research criteria for severe irritability and hyperarousal symptoms [severe mood dysregulation (SMD)] and compared children meeting these criteria to children with classically defined episodic BD [narrow phenotype BD (NP-BD)]. The hyperarousal symptoms of SMD overlap with both attention deficit hyperactivity disorder (ADHD) and criteria B symptoms present during episodes of
hypomania or mania (e.g., insomnia, distractibility, pressured speech). Specifically, youth with SMD exhibit at least three of the following: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, and intrusiveness. Importantly, in SMD, these symptoms are present chronically, not episodically. A series of studies examined longitudinal course of illness (Stringaris et al. 2010), familial aggregation (Brotman et al. 2007), and pathophysiological correlates of SMD versus NP-BD (see Leibenluft 2011 for a review). Across these studies, the clinical and pathophysiological distinction between SMD and NP-BD was confirmed; evidence did not support the conceptualization of SMD as a pediatric BD phenotype.

Most importantly, longitudinal studies showed that risk for future hypomanic or manic episodes was 50 times higher in youth with NP-BD than in youth with SMD (Stringaris et al. 2010). Instead, youth with high levels of irritability were at increased risk for unipolar depression and anxiety disorders later in life (Brotman et al. 2006; Copeland et al. 2014; Leibenluft et al. 2006; Stringaris et al. 2009, 2010). In addition, youth meeting SMD criteria were significantly less likely than those with NP-BD to have a parent diagnosed with BD (Brotman et al. 2007). Thus, collectively, this line of work supported the conceptualization of chronic irritability and hyperarousal as a unique phenotype, not a developmental presentation of BD.

With results indicating that chronic irritability and pediatric NP-BD are distinct phenotypes (see Leibenluft 2011 for a review), research began to focus on irritability as an important clinical entity in its own right. For instance, it has now been demonstrated that chronically irritable youth have high levels of functional impairment (Stringaris et al. 2010) and are at significant risk for suicidality (Conner et al. 2004, Nock et al. 2007, Pickles et al. 2010) and continued impairment in adulthood (Copeland et al. 2014, Stringaris et al. 2009), even after the effects of other psychiatric symptoms and diagnoses are statistically controlled.

**Development of DSM-5 Disruptive Mood Dysregulation Disorder**

Irritability is present in numerous DSM disorders, including oppositional defiant disorder (ODD), ADHD, anxiety disorders, major depressive disorder, and BD (Ambrosini et al. 2013, Burke et al. 2014, Jensen et al. 2007, Shaw et al. 2014, Stoddard et al. 2014). However, irritability is the primary symptom associated with DMDD. The DSM-5 formulation of DMDD was based on the syndrome of SMD. To meet criteria for DMDD, youth must exhibit severe, recurrent, and functionally impairing temper outbursts at least three times a week, and these outbursts must be out of proportion to the situation and developmentally inappropriate. The youth must also exhibit severe and chronic irritable mood between outbursts. These two core symptoms (temper outbursts and irritable mood) must be present for at least one year, across at least two of three settings (i.e., home, school, peers). Of note, unlike SMD, DMDD does not require hyperarousal symptoms (e.g., insomnia, agitation, and distractibility). If such symptoms are present, then the cooccurring diagnosis of ADHD should be considered.

Over the past few years, controversy surrounding the diagnosis of pediatric BD has shifted to the diagnosis of DMDD in children and adolescents (Althoff et al. 2016; Axelson et al. 2012; Freeman et al. 2016; Fristad et al. 2016; Margulies et al. 2012; Mayes et al. 2015, 2016; Mitchell et al. 2016; Roy et al. 2014; Stringaris 2011, 2013; Tufan et al. 2016). Researchers and clinicians have raised concerns about the validity of the DMDD diagnosis (Axelson et al. 2012, Mayes et al. 2015, Regier et al. 2013), asserting that it cannot be differentiated from disruptive behavior disorders (DBDs) such as ODD (Freeman et al. 2016). Some have suggested that adding an irritability specifier for ODD would be preferable to the new diagnosis of DMDD (Runions et al. 2016) because there is strong phenotypic overlap between ODD and DMDD. Indeed, DMDD lies at the extreme end of the distribution of the most irritable ODD youth. In particular, youth with
DMDD are highly impaired and in need of substantially more services than are most ODD youth. In developing the DSM-5, there was concern that simply adding irritability as an ODD specifier would not adequately address the major public health concern for these youth. Clinicians do not typically utilize DSM specifiers in routine practice. Finally, ODD is listed in the DBD section of the DSM-5, whereas DMDD is placed in the mood disorders section, reflecting the significant irritable mood component of DMDD. As noted, there are longitudinal associations between early irritability and later depression (Brotman et al. 2006; Copeland et al. 2014; Leibenluft et al. 2006; Stringaris et al. 2009, 2010).

There is debate as to whether the addition of DMDD will serve the stated purpose of decreasing the misdiagnosis of pediatric BD. Early evidence suggests that DMDD may decrease the rate of BD diagnosis in youth (Margulies et al. 2012); however, further research is clearly needed. Others have raised concerns that, with the introduction of DMDD, BD will not be diagnosed when such a diagnosis is indeed warranted. Preliminary guidelines to address this concern have been suggested, emphasizing the presence of distinct hypomanic or manic episodes in BD but not in DMDD. Finally, although some investigators contend that DMDD may pathologize normative irritable behavior in children, the diagnosis requires associated severe impairment, potentially mitigating this concern.

Ongoing research integrating dimensional (i.e., RDoC) and categorical (i.e., DSM) approaches will elucidate the validity, clinical utility, and public health impact of the DMDD diagnosis. Further clarifications of clinical terms (e.g., irritable mood, temper outburst), advances in measurement, and translational approaches will facilitate the phenotypic refinement of chronic, severe irritability and ultimately treatment development.

EPIDEMIOLOGY, CLINICAL FEATURES, GENETICS, AND PUBLIC HEALTH IMPACT OF IRRITABILITY

Epidemiology of Irritability

Relatively frequent temper outbursts can be normative (Copeland et al. 2015), especially in preschool-aged youth (Wakschlag et al. 2015, Wiggins et al. 2014). Developmentally, the frequency of temper outbursts is highest during the preschool years and follows a well-defined trajectory (Wakschlag et al. 2012), decreasing into later childhood and further into adulthood. Whereas some studies examining the prevalence of severe irritability have utilized symptom distributions, other investigators have operationalized irritability using specific categorical thresholds. Categorical definitions include SMD (Brotman et al. 2006), DMDD (Althoff et al. 2016; Copeland et al. 2013, 2014; Dougherty et al. 2014, 2016), the irritable component of ODD (Stringaris & Goodman 2009a), and other categorical conceptualizations of chronic irritability (Leibenluft et al. 2006). Because data collection for most of these studies predated the use of irritability-specific measures, one limitation of this body of work is that the criteria operationalizing irritability were generated in a post hoc manner. For example, multiple studies drew items from the Child and Adolescent Psychiatric Assessment, which were not originally designed to ascertain SMD or DMDD (Brotman et al. 2006; Copeland et al. 2013, 2014).

Perhaps due to these ongoing developments in measurement, prevalence estimates for SMD and DMDD have been variable across studies, ranging from 0.1% to 5.3%. Leveraging epidemiological data from the Great Smoky Mountains Study, Brotman and colleagues (2006) found that 3.3% of community youth met criteria for the irritability and hyperarousal symptoms associated with SMD. However, impairment criteria (e.g., impairment at home or at school) were not taken into account; when the impairment criteria were included, the prevalence rate dropped to 1.8%.
With respect to DMDD, Copeland et al. (2013) reported that the three-month prevalence of DMDD across three community samples ranged from 0.8% to 3.3%, with the highest rate in preschoolers. Althoff et al. (2016) found that only 0.1% of adolescents met diagnostic criteria for DMDD with the strictest frequency criteria (i.e., temper outbursts three or more times per week) and exclusion of youth with elevated/expansive mood. However, when the authors removed the frequency cutoff for temper outbursts and also included youth with symptoms of elevated/expansive mood, 5.3% of adolescents met DMDD criteria.

Studies examining the prevalence of irritability generally report rates consistent with the rates reported for SMD or DMDD. In a Dutch population of youth aged 4–16, 3.5% were rated as high on a combination of aggressive behavior, attention problems, anxiety, and depression (Child Behavior Checklist-Dysregulation profile) (Althoff et al. 2010). The highest prevalence (approximately 20% of adolescents) was reported by Pickles et al. (2010), who used a single irritability item encompassing frequency, severity, and duration.

Clinical Correlates and Course

After the preschool period, levels of irritability tend to be relatively stable over time in youth (Caprara et al. 2007), and this level of stability is similar to that documented for anxiety and depression. Stability estimates range from 0.29 to 0.88 (Basten et al. 2016, Leadbeater & Homel 2015, Stringaris et al. 2012a, Vidal-Ribas et al. 2016, Whelan et al. 2013). Whether dimensionally or categorically defined, irritability has been associated cross-sectionally with DBDs, mood disorders, and anxiety disorders (Brotman et al. 2006, Copeland et al. 2013).

Youth who meet criteria for SMD generally meet criteria for three DSM disorders (Leibenluft 2011). The most common cooccurring diagnosis is ADHD, with rates higher than 75% (e.g., Brotman et al. 2010, Leibenluft 2011). Of course, SMD may be enriched for ADHD, as SMD requires hyperarousal symptoms. With respect to DMDD, rates of cooccurring emotional and behavioral disorders, including ADHD, are also high but somewhat more variable across samples (Copeland et al. 2013, Dougherty et al. 2014). As noted above, most studies of DMDD have used interview- or questionnaire-based symptom reports in a post hoc manner to generate the diagnosis. Thus, estimates of comorbidities need further verification following a priori assessment of DMDD (Copeland et al. 2013, Dougherty et al. 2014). Given phenotypic overlap (Stringaris & Goodman 2009b), ODD is also strongly present among youth with SMD (Adleman et al. 2011, Copeland et al. 2014, Dougherty et al. 2014, Leibenluft 2011), but the diagnosis of DMDD supersedes ODD such that ODD is not diagnosed in the context of DMDD (Am. Psychiatr. Assoc. 2013).

Both cross-sectionally and longitudinally, there is an association between irritability and mood and anxiety disorders. Approximately half of youth who meet SMD criteria have a cooccurring anxiety disorder (Dickstein et al. 2005). In reports of preschool- and school-aged community children with DMDD, rates of anxiety are also high (Copeland et al. 2013, Dougherty et al. 2014).

Irritability in youth often predicts anxiety disorders and depression in adulthood (Althoff et al. 2010, Brotman et al. 2006, Copeland et al. 2014, Whelan et al. 2013). In one study, Brotman and colleagues (2006) found that the presence of SMD in childhood predicted depression in adulthood more strongly than did the presence of a depressive disorder itself during childhood. Similarly, several epidemiological studies of preschool- (Dougherty et al. 2013, 2014, 2016) and school-aged youth have reported an association between early irritability and later anxiety and depressive disorders. Chronic irritability (Leibenluft et al. 2006, Stringaris et al. 2009) and the irritable dimension of ODD (Althoff et al. 2014, Stringaris & Goodman 2009a) have been shown to uniquely predict depression and anxiety, above and beyond the influence of baseline diagnoses. Finally, adult studies suggest that depression may present initially with irritability (Judd et al.
2013), and irritability is an important symptom of depression (Fava et al. 2010) that may mark a heightened severity of illness.

**Genetics and Familiality**

The heritability of irritability is approximately 30% to 40% (Coccaro et al. 1997), similar to heritability estimates for anxiety and depression (Eley 1999). Recent work has demonstrated that the genetic influences on irritability change over time and differ between boys and girls (Roberson-Nay et al. 2015). Specifically, males show increasing heritability from early childhood through young adulthood, whereas females show decreasing heritability. Furthermore, evidence suggests that the phenotypic association between early irritability and later depression has a genetic component (Savage et al. 2015, Stringaris et al. 2012b). For example, in a large twin study, Stringaris and colleagues (2012b) demonstrated that the longitudinal association between early irritability and later depression is partially due to common genetic factors. Subsequently, Savage et al. (2015) found that the genetic association between irritability and depression is developmentally dynamic; i.e., irritability during late childhood and early adolescence predicted later anxiety and depression.

Consistent with these genetically informative twin studies, familial associations between irritability and depression has been documented (Whelan et al. 2015, Wiggins et al. 2014). Having a family history of depression is associated with scoring higher on the irritable dimension of ODD (Krieger et al. 2013). Moreover, the relation between maternal depression and offspring depression appears to be mediated by the presence of early irritability in offspring (Whelan et al. 2015). Wiggins et al. (2014) found that maternal depression was associated with offspring irritability, and offspring irritability predicted later maternal depression. The association between maternal depression and child irritability likely has both genetic and environmental components; however, research has yet to elucidate the precise nature of these relations.

**Public Health Impact**

Irritability is one of the most common reasons that children and adolescents are referred for psychiatric evaluation and care (Peterson et al. 1996). In addition to being linked to other forms of psychopathology (e.g., anxiety and depressive disorders), irritability in youth predicts significant impairment in adulthood, including academic problems, poverty, and suicidality (Conner et al. 2004, Copeland et al. 2014, Cornacchio et al. 2016, Leibenluft et al. 2006, Nock et al. 2007, Pickles et al. 2010, Stringaris et al. 2009). Given this substantial public health impact, further research is needed to elucidate the biological underpinnings of severe irritability.

**PATHOPHYSIOLOGY OF IRRITABILITY**

In this section, we review research conducted to date on the behavioral and neurobiological correlates of irritability in children and adolescents. These pathophysiological correlates are organized into two broad domains: aberrant reward processing and aberrant threat and face emotion processing. In reviewing the literature, we integrate behavioral and neuroimaging findings and highlight cross-species work that reflects a translational perspective. Here, we reiterate that irritability is a promising construct to be studied under the RDoC initiative (Insel et al. 2010).

**Aberrant Reward Processing**

The experience of frustration is central to irritability, and it occurs when an action fails to elicit an expected positive outcome or attainment of a goal (i.e., a reward). Irritable children and adolescents
may be particularly vulnerable to frustration because they have impairments in reward processing. As we review below, numerous studies have demonstrated aberrant reward processing in youth with severe irritability and related clinical problems. Specific areas of dysfunction include reward learning and prediction error deficits, anomalous sensitivity to rewards, and aberrant responses to reward omission. The observed behavioral deficits correspond with dysfunction in the prefrontal cortex, striatum, anterior cingulate, and amygdala.

**Reward learning and prediction error deficits.** Children and adolescents with severe irritability exhibit deficits in learning from reward and punishment contingencies (Adleman et al. 2011, Dickstein et al. 2007). In typical laboratory paradigms that probe reward learning, an individual’s response (e.g., button press) to one stimulus is reinforced with a reward (e.g., monetary gain). Response reversal paradigms can be used to examine youths’ abilities to detect and shift behavior following changes in reinforcement contingencies. Specifically, following initial learning, reversal trials are presented in which a previously rewarded stimulus is no longer rewarded. Participants must learn a new set of contingencies (e.g., respond to a different stimulus) (Costa et al. 2015) in order to continue to receive rewards and adapt their behavior accordingly. Across these paradigms, youth with severe irritability show deficits in learning initial contingencies and in adapting their behavior to switched contingencies. Such impairments may result in a more frequent experience of frustrative nonreward for these children, compared to typically developing, healthy youth (Adleman et al. 2011, Dickstein et al. 2007).

Behavioral deficits in reward learning may be driven by impairments in prediction error signaling in the brain, which involves midbrain dopamine neurons (Schultz 2002, Tobler et al. 2005). Prediction error refers to the neural signaling that encodes the difference between an expected outcome and a received outcome. For example, not receiving a reward when it is expected would produce a large (negatively deflecting) prediction error signal. Prediction error serves to update reward expectations on a trial-by-trial basis, facilitating the learning process and optimal behavioral performance. Aberrant prediction error signaling has been implicated in children with irritability and aggression. Such aberrant prediction error signaling may fail to appropriately modify reward expectations over time (e.g., a reward continues to be expected when it should not be, given previous nonreward outcomes). This might account for these youths’ poorer behavioral performance and, hence, more frequent experience of frustrative nonreward.

The anatomic circuit mediating response reversal learning and prediction error shows significant cross-species preservation involving frontal and striatal brain regions (Blair 2010). In humans, the unexpected omission of reward is normatively associated with prefrontal and striatal activation (O’Doherty et al. 2004). However, neuroimaging studies of reversal learning in youth with SMD show deficient engagement of the inferior frontal gyrus (IFG) and caudate following reward omission (Adleman et al. 2011). Similarly, youth with DBDs exhibit abnormal prefrontal cortex activation during reward learning (Finger et al. 2011). The IFG mediates attentional functions necessary for behavioral response selection and inhibition. Frontal projections also modulate striatal activity, in order to adjust behavior after errors (Cools et al. 2002). The caudate, highly innervated by dopamine neurons (Nakamura & Hikosaka 2006), plays a central role in reward-based and other feedback-dependent learning (Cools et al. 2006). Further supporting the proposition that irritable children may have deficits in prediction error signaling, these youth exhibit aberrant striatal responses on other neuroimaging paradigms that involve reward receipt and omission (Deveney et al. 2013). Consistent with this, anomalous striatal activity during reward paradigms has been found in youth with DBDs (Gatzke-Kopp et al. 2009).

In sum, learning positive and negative contingencies for behavior and appropriately updating changing contingencies to modify behavior are critical for effective reward learning. Demonstrated
behavioral and neurobiological impairments in reward learning may contribute to irritable youths’ greater risk of frustration in the context of nonreward. That is, these deficits may engender a higher probability of being in surprising nonreward situations that cause frustration (e.g., blocked goals) and a decreased tolerance for situations in which youth do not receive an expected positive outcome or reach a desired goal (Blair 2010).

**Cognitive control deficits.** Flexible goal-directed behavior is needed to adapt to changing reward contingencies. Cognitive control refers to the ability to allocate and shift mental resources, such as attention, based on ever-changing contexts and demands in the environment. One component of cognitive control is inhibitory control, the ability to inhibit a prepotent or dominant response (Luna et al. 2004). Responding to behavioral errors is a second component of cognitive control. An error, in this context, refers to the failure to appropriately inhibit a behavior in accordance with task demands. Impairments in inhibitory control are associated with trait anger (Gagne & Goldsmith 2011). These behavioral findings are supported by psychophysiological work examining event-related potentials (ERPs) through electroencephalography (EEG). These studies consistently demonstrate that abnormal attention- and inhibition-relevant processing is associated with irritability (Rich et al. 2007), trait anger (Liu et al. 2015), and trait aggression (Lamm et al. 2011). These ERP-derived impairments in inhibitory control and error monitoring implicate prefrontal (Lamm et al. 2011) and anterior cingulate cortex (ACC) regions (Pawliczek et al. 2013). Cognitive control is a broad construct involving multiple subprocesses (e.g., attention, error monitoring, inhibition), each with distinct neural correlates; future research is needed to specify the relations of these different subprocesses to the etiology and maintenance of irritability.

**Aberrant sensitivity to rewards.** In addition to deficient reward learning and cognitive control, studies suggest that youth with severe irritability display a heightened sensitivity to the receipt of rewards. Normatively, the experience of anger increases individuals’ visual attention toward stimuli signaling reward (Carver & Harmon-Jones 2009). In youth with severe irritability, three studies demonstrate increased activation of frontal brain regions to reward receipt (Bebko et al. 2014, Kessel et al. 2016, Perlman et al. 2015). However, a limitation in these studies is that sensitivity to rewards was inferred from patterns of neural activation during functional magnetic resonance imaging (fMRI) or EEG paradigms, without corresponding behavioral correlates reported. If irritable youth process reward stimuli differently than do typically developing children, this may increase their propensity for frustration following unanticipated reward omission. That is, the withholding of a reward may be both more surprising, as a function of their reward learning deficits, and more aversive, as a function of their heightened sensitivity to rewards.

**Aberrant responses to frustration.** Frustrative nonreward involves blocking one’s ability to obtain an expected reward (Amsel 1958). There are interindividual differences in the degree of evoked frustration following blocked goal attainment (Pawliczek et al. 2013). For example, high trait aggression is associated with higher levels of frustration following an unsolvable task (Pawliczek et al. 2013), and trait irritability is associated with higher levels of frustration during unexpected reward omission (Deveney et al. 2013; Rich et al. 2007, 2011). Consistent with the RDoC conceptualization, frustrative nonreward can be studied across species. In rodents, nonhuman primates, and humans (Amsel 1958, Burokas et al. 2012, Davenport & Thompson 1965, Deveney et al. 2013), frustration can be induced through repeated and deliberate reward omission. The Affective Posner task is a modified, frustrative version of the Posner paradigm, which assesses spatial attention and orienting in humans. The original Posner task was adapted to have a motivational component in the form of positive or negative feedback on each trial (i.e., monetary gain or loss based on
behavioral performance). Furthermore, frustration was designed to be induced through repeated inaccurate negative feedback (i.e., monetary loss) even when participants performed correctly on a trial.

During the frustration condition of the Affective Posner task, children with severe irritability report higher levels of arousal than do healthy youth (Rich et al. 2007, 2011). Moreover, irritable youth exhibit anomalies in behavioral performance and neural functioning during the frustration condition (Deveney et al. 2013). Specifically, irritable children exhibit lower response accuracy (Rich et al. 2007) and diminished ability to shift their spatial attention as needed for successful task performance (Deveney et al. 2013). These behavioral deficits are associated with aberrant ERP signals (Rich et al. 2007), as well as ACC and medial frontal gyrus dysfunction assessed using magnetoencephalography (Rich et al. 2011). In fMRI studies utilizing this paradigm, atypical deactivation of the amygdala, striatum, and posterior cortex during frustration is observed in irritable children (Deveney et al. 2013). Consistent with findings from the Affective Posner task, Perlman and colleagues (2015) have employed the Frustrative Emotion Task for Children in which reward attainment is repeatedly blocked. These investigators found similar ACC and middle frontal gyrus dysfunction in children with irritability.

Although there are many advantages of probing frustration in irritable youth, there are also several challenges. First, it is difficult to construct salient, developmentally appropriate paradigms (Perlman et al. 2014, 2015; Rich et al. 2007, 2011). Second, there are inherent effects of time and task order in many paradigms. For example, it is often difficult to disentangle baseline neural deficits from the neural effects of frustration because reward learning and frustration are confounded with time. Third, many of these paradigms require deception in order for participants to expect, and ultimately not receive, rewards. Thus, there are ethical considerations, especially when studying children with psychiatric illnesses.

Summary. In the context of frustrative nonreward, youth with chronic, severe irritability exhibit attentional impairments along with neural dysfunction in frontal regions, the striatum, and the amygdala. Coupled with aberrant reward learning (Adleman et al. 2011) and reward sensitivity (Bebko et al. 2014, Perlman et al. 2015), these anomalies could contribute to the greater vulnerability to frustration observed in youth with severe irritability.

Aberrant Threat Processing

A second, core pathophysiological mechanism of irritability in youth appears to be aberrant threat processing (Brotman et al. 2017). Anger involves approach behavior toward threat (Blair 2010, Fanselow 1994). Although this can be adaptive in the context of objectively threatening stimuli, inappropriately perceiving threat may lower the threshold for an aggressive or angry response. Processing of social stimuli, including facial stimuli, plays a primary role in humans’ aggressive, angry, or hostile responses to perceived threat or provocation (Dodge 1980). Thus, face emotion processing paradigms have been employed to explore deficits in face emotion labeling and aberrant threat processing in irritable youth. In these studies, youth with irritability have been shown to mislabel and misinterpret face emotions, with corresponding pathophysiological abnormalities.

Face emotion processing paradigms. Face emotion processing paradigms are among the most commonly administered fMRI paradigms in the study of severe irritability. The different tasks that have been used vary along several dimensions. First, tasks may probe conscious processing (i.e., supraliminal, unmasked faces) and/or nonconscious or automatic processing (i.e., subliminal or masked faces). Second, unmasked face emotion processing can be explicit and/or implicit within a...
task. During explicit face emotion processing, participants are instructed to direct their attention toward the face emotion (e.g., face emotion labeling, ratings of subjective fear). In contrast, during implicit processing, participants are told to focus on a stimulus feature other than emotion (e.g., gender, nose width). Third, the specific face emotions conveyed by the stimuli may vary; studies in this area have included neutral, angry, fearful, and happy faces (Brotman et al. 2010; Thomas et al. 2012, 2013), affectively ambiguous faces, and/or faces expressing differing emotional intensities (Stoddard et al. 2016, Wiggins et al. 2016).

**Behavioral findings.** Dot-probe paradigms generally utilize supraliminal stimulus durations to probe attentional biases to threatening stimuli (i.e., angry faces). Specifically, participants simultaneously see one emotional facial expression (e.g., angry) and one neutral expression on opposite sides of a computer screen. This face pair is followed by a probe (e.g., asterisk) in one of the two locations, and participants indicate the location of the probe as quickly and accurately as possible. Biased allocation of visual attention is measured using latencies to respond to the probe.

Behavioral work demonstrates that, relative to typically developing children, youth with SMD orient their attention toward threatening, relative to neutral, faces (Hommer et al. 2014). Consistent with this early attentional processing of threat, higher levels of trait anger have been associated with a tendency to direct attention toward threatening, rather than neutral, facial expressions (Van Honk et al. 2001). These findings are similar to the threat-relevant attentional bias that has been documented in pediatric and adult anxiety disorders (Bar-Haim et al. 2007). In addition, compared with healthy children, youth with severe irritability require less intense expression of anger in an ambiguous face in order to label the face as angry (Stoddard et al. 2016). Also compared with healthy children, those with SMD report being more fearful of neutral faces (Brotman et al. 2010), suggesting that irritable youth may perceive neutral faces as threatening. Other behavioral work has repeatedly demonstrated that irritable youth exhibit a generalized behavioral deficit in face emotion labeling (Guyer et al. 2007). Thus, across a number of different behavioral paradigms, investigators have observed an association between aberrant processing of face emotions, including threatening faces, and irritability.

**Neuroimaging findings.** The limbic system and prefrontal cortex are involved in threat processing. Various aberrations in the prefrontal cortex and limbic system have emerged across studies of youth with severe irritability, although the precise nature of these neural deficits is unclear. In two studies, children with SMD, relative to typically developing youth, exhibited amygdala hypoactivity during explicit processing of face emotions (Brotman et al. 2010), but hyperactivity during implicit processing (Brotman et al. 2010, Thomas et al. 2013). Brotman et al. (2010) found amygdala hypoactivation while SMD youth were rating their own subjective fear of neutral faces. These same youth displayed amygdala hyperactivation when they were rating the nose widths of the neutral faces (Brotman et al. 2010). This finding was replicated in irritable youth while they were completing implicit gender ratings of angry, fearful, and neutral faces (Thomas et al. 2013). However, integrating implicit and explicit processing within a single task, Thomas and colleagues (2012) found aberrant amygdala modulation in irritable youth as a function of increasing anger intensity in a face. Specifically, whereas healthy youth showed greater amygdala activation with increasing anger intensity, SMD youth did not parametrically track emotion intensity in the amygdala (Thomas et al. 2012). Given that amygdala activation in SMD was consistent across both implicit and explicit task demands, these results are contrary to those of Brotman et al. (2010). Thus, the extent to which the aberrant amygdala activity associated with irritability is specifically influenced by task demands is currently unclear.
Whereas the aforementioned studies focused on irritability categorically defined, recent work has examined irritability as a symptom dimension. Wiggins et al. (2016) found that amygdala activation was differentially associated with severity of irritability across different disorders. Specifically, higher levels of irritability in youth with DMDD were associated with heightened amygdala activation to ambiguous angry and happy faces, but relative hypoactivation to ambiguous fearful faces. In contrast, higher levels of irritability in BD were associated with relative hyperactivation in the amygdala to ambiguous fearful faces, indicating unique neural correlates of irritability across the two distinct disorders of DMDD and BD. Taken together, these results consistently implicate the amygdala in the pathophysiology of irritability in the context of aberrant face emotion processing.

Frontal regions also have been implicated in aberrant face emotion processing in youth with severe irritability (Thomas et al. 2012, Wiggins et al. 2016), particularly during nonconscious processing (Thomas et al. 2013, Tseng et al. 2016). For example, during masked processing of angry and happy faces, Tseng et al. (2016) found increased ventromedial prefrontal cortex activation in irritable, relative to healthy, children. In this same study, across both masked and unmasked angry faces, SMD youth showed increased activation of the parahippocampal gyrus. Together, these task-based fMRI results indicate prefrontal and limbic dysfunction across a range of different face emotions and processing conditions.

Finally, task-based fMRI work has been expanded to examinations of functional connectivity and resting state. Findings to date implicate aberrant regional coupling in irritable and emotionally dysregulated youth (Bebko et al. 2015, Hulvershorn et al. 2014, Posner et al. 2013), although the precise nature of these anomalies is currently unclear. For example, Hulvershorn et al. (2014) found that emotionally labile youth with ADHD showed greater positive intrinsic functional connectivity between the amygdala and insula/superior temporal gyrus. However, Posner and colleagues (2013) found that emotional lability was associated with reduced connectivity between the prefrontal cortex and striatum. Notably, all of the subjects in these studies were diagnosed with ADHD, and the phenotype of focus was emotional lability rather than irritability per se. The one direct study of youth with severe irritability indicated no resting state connectivity anomalies relative to healthy youth; however, this study involved a small sample size and may be subject to Type II error (Stoddard et al. 2015). Finally, structural differences (reduced gray matter volume) have been found in SMD in the prefrontal cortex (Adleman et al. 2012). Future studies with larger sample sizes are needed to examine both brain structure and connectivity in relation to irritability, both dimensionally and categorically defined.

TREATMENT

As reviewed above, irritability is relatively common, and in severe forms quite impairing, with a substantial public health impact. Pathophysiological research on irritability, despite its relative recency, has already implicated several key behavioral and neurobiological impairments centered on the domains of reward and threat processing. Research on treatment interventions for chronic, severe irritability is in its infancy. Below, we describe the pharmacological and psychosocial research to date relevant to the treatment of irritability. Notably, many of these studies did not primarily target irritability; instead, irritability was often examined in the context of other disorders. This dearth of research highlights the need for novel pharmacological and psychological treatments.

Psychopharmacological Agents

Clinical and pathophysiological work has demonstrated that early irritability should not be considered a developmental presentation of BD. This has significant pharmacological treatment
RCT: randomized controlled trial

implications, as BD is typically treated with mood stabilizers and atypical antipsychotics, whereas selective serotonin reuptake inhibitors (SSRIs) are relatively contraindicated because of concerns about mania induction. There has been only one randomized controlled trial (RCT) of medication for severe irritability in youth (Dickstein et al. 2009). In that small study, Dickstein and colleagues (2009) found no benefit of lithium over placebo in youth with SMD. Whereas lithium has been a first-line agent for BD, its lack of efficacy for the treatment of severe irritability provides additional support for the differentiation of severe irritability versus BD in youth.

Selective serotonin reuptake inhibitors. There is indirect evidence for the use of SSRIs in pediatric irritability from adult studies suggesting that SSRIs may be effective in the treatment of intermittent explosive disorder and in the treatment of irritability and outbursts in the context of depression. Specifically, in a double-blind, randomized, placebo-controlled RCT of adults with intermittent explosive disorder, fluoxetine reduced aggression and irritability (Coccaro et al. 2009). Similarly, anger attacks decreased in a group of depressed patients treated with SSRIs (i.e., fluoxetine or sertraline) or a tricyclic antidepressant (i.e., imipramine) (Fava & Rosenbaum 1999). Finally, a literature review found that SSRIs were effective in treating premenstrual irritability (Dimmock et al. 2000). Despite this preliminary, promising evidence for SSRIs in the treatment of irritability, research is greatly needed in youth (Kim & Boylan 2016). In fact, two SSRI RCTs are currently ongoing (clinicaltrials.gov identifiers NCT00794040 and NCT01714310); one is at the NIMH intramural research program, and the other is at the University of California, Los Angeles. Data have yet to be published.

Stimulants. In addition to SSRIs, stimulants show significant promise in the treatment of irritability and aggression in youth with ADHD (Blader et al. 2010, 2016). Connor and colleagues (2002) conducted a meta-analysis examining the effect of stimulants on aggression. Across 28 studies, the authors found a medium to large effect size (0.69–0.84) of stimulants on the reduction of aggressive behavior in ADHD youth (Connor et al. 2002). This is consistent with reports indicating that emotional instability in ADHD can be effectively treated with stimulants (Shaw et al. 2014). Moreover, post hoc analyses from the Multimodal Treatment Study of Children with ADHD found that stimulants (or stimulants plus behavioral management) were superior to behavioral management alone in the treatment of irritability (Fernández de la Cruz et al. 2015). Stimulant monotherapy (plus behavioral treatment) has been shown to decrease aggressive behavior and outbursts in a large cohort of youth with ADHD and aggression (Blader et al. 2010, 2016; Waxmonsky et al. 2008).

Atypical antipsychotics. Considerable evidence has supported the efficacy of atypical antipsychotics in reducing irritability symptoms in the context of autism spectrum disorders (Ji & Findling 2015). Risperidone and aripiprazole, second-generation antipsychotics, are the only pharmacological agents that have received US Food and Drug Administration indication for the treatment of irritability, but the indication is specific to the presence of autism (Marcus et al. 2009, McCracken et al. 2002). One open trial examined risperidone in the treatment of youth with SMD (without autism) (Krieger et al. 2011), and results indicated significant reductions in irritability. However, given the well-known side-effect burden of atypical agents, especially in youth, additional work is needed to explore relative costs and benefits for use in irritable children.

Psychotherapeutic Interventions

Given the significant side effects and potential neurobiological sequelae of medications, and the impact of environmental context on irritability, effective psychological treatments are needed
for these highly impaired youth. There are several psychotherapeutic interventions that have been developed for irritability-related clinical syndromes (e.g., DBDs), and preliminary studies in SMD have been conducted (Waxmonsky et al. 2016). Below, we review the two broad categories of approaches under which these interventions fall: parent management training (PMT) and cognitive behavioral therapy (CBT).

Parent management training. PMT is a behavioral treatment derived largely from parent-child interaction research by Patterson and colleagues (Patterson 1975). In PMT, parents are taught to reinforce children’s prosocial behavior and not to reinforce youths’ maladaptive behaviors, such as defiance and temper outbursts (Kazdin 2010). In early sessions, parents are instructed to focus on increasing youths’ positive behaviors through positive reinforcement, such as providing praise or a reward after the target positive behavior occurs. In later sessions, parents are taught how to utilize active ignoring, time-outs, or other nonreinforcing consequences for problematic behavior. Throughout the intervention, parents learn to be more consistent in their delivery of consequences for child behaviors. The potential importance of consistency of rewards (and nonrewards) for irritable youth is worth noting, given the behavioral and neural findings reviewed above. That is, irritable youth may be particularly sensitive to inconsistent parental contingencies for their behavior because they have difficulty learning reward contingencies (Adleman et al. 2011, Dickstein et al. 2007), are more sensitive to rewards and blocked goals (Deveney et al. 2013; Perlman et al. 2015; Rich et al. 2007, 2011), and exhibit corresponding striatal, frontal, and limbic dysfunction (Adleman et al. 2011, Deveney et al. 2013).

Indeed, PMT has been shown to be efficacious for improving oppositional behaviors, aggression, emotional dysregulation, and antisocial and conduct problems in youth. Utilizing data from the SPOKES trial (ISRCTN 77566446; Scott et al. 2010), an RCT of 112 children aged 5 to 6 years with elevated levels of oppositionality, Scott & O’Connor (2012) found that oppositional youth with high levels of emotional dysregulation were effectively treated (effect size of 0.84) in a PMT condition relative to a control condition. Efficacy for parenting interventions has also been demonstrated in group formats (Pilling et al. 2013, Waxmonsky et al. 2016). Group-based PMT for parents of children aged 3 to 11 years with ODD and conduct disorder was included in the United Kingdom’s National Institute for Health and Clinical Excellence official guidelines (Pilling et al. 2013). Initial work has begun to explore PMT for SMD. In a recent study, Waxmonsky and colleagues (2016) reported feasibility of a group-based parenting intervention for SMD, although the preliminary results were only suggestive of its efficacy on primary outcome measures. Future parenting intervention work focused specifically on addressing the pathophysiology of chronic, severe irritability is needed.

Cognitive behavioral therapy. As opposed to PMT that is conducted with parents, CBT involves the therapist working directly with the child. CBT has been shown to be effective for youth with anger and aggression problems. During treatment, the child learns skills to reduce maladaptive cognitions and behavioral responses in anger-inducing situations (Kazdin 2010). Many of the cognitive skills that are developed in CBT for disruptive behavior are based on the social information processing model of Dodge and colleagues (Crick & Dodge 1994, Dodge 1980). In this model, children’s processing of others’ social cues follows a series of steps: encoding the cues, interpreting the cues, searching for responses to the cues, selecting one of these responses, and enacting the selected response. Dysfunction in one or more of these processes is theorized to elevate risk for anger and aggressive behavioral responses. As indicated above, the pathophysiological work in SMD and DMDD is consistent with aspects of this model. That is, irritable youth are more likely than healthy children to misinterpret face emotions and to perceive ambiguous
and neutral facial expressions as more threatening (Brotman et al. 2010, Stoddard et al. 2016), with corresponding neural dysfunction in the amygdala and prefrontal cortex during face emotion processing (Brotman et al. 2010, Thomas et al. 2012, Tseng et al. 2016, Wiggins et al. 2016). CBT teaches irritable and aggressive youth more adaptive ways to interpret and respond to social situations that lead to anger and aggression.

Several CBT protocols have been developed, including Problem-Solving Training developed by Kazdin (2010), group-based Anger Control Training developed by Lochman et al. (2010), and most recently, an individual child CBT protocol for anger and aggression by Sukhodolsky & Scahill (2012). The Sukhodolsky & Scahill manual includes three foci: managing emotional arousal, addressing hostile interpretations of social stimuli, and developing social skills (Sukhodolsky et al. 2016a). Consistent with these foci, a meta-analysis of CBT for DBDs indicated that the most effective interventions were improving social skills, providing direct feedback to the child, and modeling appropriate behaviors. Integrating an RDoC perspective, Sukhodolsky et al. (2016a,b) recently presented the rationale and design of an RCT of CBT for anger and aggression in youth, targeted to the construct of frustrative nonreward. In addition to assessing clinical improvement, the investigators will measure the behavioral and neural correlates of symptom improvement, illustrating a mechanism-based treatment approach (Sukhodolsky et al. 2016b).

**Novel psychological treatments.** Also building on the social information processing work by Dodge and colleagues (Crick & Dodge 1994, Dodge 1980), preliminary studies have used computer-based training approaches to attempt to modify irritable youths’ interpretation of social stimuli. Termed interpretation bias training (IBT), this intervention involves providing computerized feedback such that youth are trained to perceive ambiguous faces in a more benign and less hostile manner (Penton-Voak et al. 2013). One RCT of IBT in aggressive youth showed that training over the course of four or five days was associated with reductions in blinded ratings of aggressive behavior. In an open trial, Stoddard et al. (2016) utilized the same task in youth with DMDD. Consistent with the findings by Penton-Voak et al. (2013), training DMDD youth to perceive ambiguous faces in a more benign manner was associated with decreased irritability. In a small subsample, this training was associated with neurobiological changes as well (Stoddard et al. 2016). These two studies of IBT suggest promise; however, due to the open training in DMDD and small sample sizes, larger-scale RCTs of IBT for DMDD are clearly needed.

**FUTURE DIRECTIONS**

The past decade has witnessed significant advancements in the clinical conceptualization, pathophysiological understanding, and treatment of chronic, severe irritability in youth. Although great strides have been made, numerous gaps remain. First, further refinement of the construct of irritability, its measurement, and its differentiation from related concepts is warranted. This work will need to integrate traditional categorical taxonomies (e.g., DSM) and dimensional approaches (e.g., RDoC). In particular, reliability and validity studies, as well as gold-standard clinician inventories, are needed for accurate phenotypic measurement in pathophysiological and treatment research. For example, the SMD and DMDD modules developed by Leibenluft and colleagues (e.g., Wiggins et al. 2016) for the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children have been designed to assess for those respective disorders. The Affective Reactivity Index (Stringaris et al. 2012a) has been developed as a dimensional measure of irritability and preliminarily shows strong psychometric properties. More consistent use of irritability measures across studies will likely enhance reliability in findings and also will foster big data aggregation. In addition, developmentally sensitive, multimodal (e.g., observational,
ecological momentary assessment), longitudinal characterization studies should elucidate both normative and pathological developmental trajectories of irritability (Wakschlag et al. 2015).

Second, recent innovations in bioinformatics have led to significant developments in understanding brain and behavioral functioning (Costa et al. 2015, Pereira et al. 2009). For example, using multivoxel pattern analysis and Bayesian models, researchers are beginning to classify patients on the basis of neural activation. Given the heterogeneity of irritable youth, such an approach may be fruitful in identifying subgroups that may respond differentially to treatment interventions; this approach is consistent with the field’s movement toward personalized medicine (Insel 2009).

Third, we need to continue to develop pathophysiologically informed treatment interventions. In particular, interventions should work to integrate the neural and behavioral deficits in reward and threat processing found in irritable youth. Irritability continues to be a common and costly presenting problem in youth, providing significant research opportunities. The field of irritability research is primed for further developments in measurement, pathophysiology, and treatment, which will be essential for addressing this pressing public health need.

SUMMARY POINTS

1. Irritability is one of the most common reasons that youth are referred for psychiatric evaluation and care.
2. Irritability in childhood and adolescence often predicts anxiety disorders and depression in adulthood.
3. There are two translational research constructs on irritability: frustrative nonreward and threat.
4. In the context of frustrative nonreward, youth with chronic, severe irritability exhibit attentional impairments and neural dysfunction in frontal regions, the striatum, and the amygdala.
5. Irritable youth are more likely than healthy youth to misinterpret face emotions and to perceive ambiguous and neutral facial expressions as threatening, with corresponding neural dysfunction in the amygdala and prefrontal cortex during face emotion processing.
6. Research on the treatment of irritability is in its infancy; ongoing studies are examining several different pharmacological and psychotherapeutic interventions in this population.

FUTURE ISSUES

1. Further refinement of the construct of irritability, its measurement, and its differentiation from related concepts is needed.
2. Reliability and validity studies, in addition to gold-standard clinician inventories, will facilitate accurate phenotypic measurement.
3. The development of pathophysiologically informed treatment interventions for severe irritability in youth is an essential next step.
4. Interventions should work to integrate and target neural and behavioral deficits in reward and threat processing found in irritable youth.
5. Innovations in bioinformatics have led to significant developments in understanding brain and behavioral functioning. Given the heterogeneity of irritable youth, such an approach may be effective in identifying subgroups that may respond differentially to treatment interventions, in a manner consistent with the field’s movement towards precision medicine.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Work was supported by the NIMH Intramural Research Program (ZIAMH002786-15, ZIAMH002778-17), conducted under NIH Clinical Study Protocols 15-M-0182 (ClinicalTrials.gov identifier: NCT02531893), 02-M-0021 (ClinicalTrials.gov identifier: NCT00025935), and 00-M-0198 (ClinicalTrials.gov identifier: NCT00006177).

LITERATURE CITED


Blader JC, Pliszka SR, Jensen PS, Schooler NR, Kafantaris V. 2010. Stimulant-responsive and stimulant-refractory aggressive behavior among children with ADHD. *Pediatrics* 126:e796–806


The Annual Review of Cancer Biology reviews a range of subjects representing important and emerging areas in the field of cancer research. The Annual Review of Cancer Biology includes three broad themes: Cancer Cell Biology, Tumorigenesis and Cancer Progression, and Translational Cancer Science.

TABLE OF CONTENTS FOR VOLUME 1:

- How Tumor Virology Evolved into Cancer Biology and Transformed Oncology, Harold Varmus
- The Role of Autophagy in Cancer, Naiara Santana-Codina, Joseph D. Mancias, Alec C. Kimmelman
- Cell Cycle–Targeted Cancer Therapies, Charles J. Sherr, Jiri Bartek
- Ubiquitin in Cell-Cycle Regulation and Dysregulation in Cancer, Natalie A. Borg, Vishva M. Dixit
- The Two Faces of Reactive Oxygen Species in Cancer, Colleen R. Reczek, Navdeep S. Chandel
- Analyzing Tumor Metabolism In Vivo, Brandon Faubert, Ralph J. DeBerardinis
- Stress-Induced Mutagenesis: Implications in Cancer and Drug Resistance, Devon M. Fitzgerald, P.J. Hastings, Susan M. Rosenberg
- Synthetic Lethality in Cancer Therapeutics, Roderick L. Beijersbergen, Lodewyck F.A. Wessels, René Bernards
- Noncoding RNAs in Cancer Development, Chao-Po Lin, Lin He
- p53: Multiple Facets of a Rubik’s Cube, Yun Zhang, Guillermima Lozano
- Resisting Resistance, Ivana Bozic, Martin A. Nowak
- Deciphering Genetic Intratumor Heterogeneity and Its Impact on Cancer Evolution, Rachel Rosenthal, Nicholas McGranahan, Javier Herrero, Charles Swanton
- Immune-Suppressing Cellular Elements of the Tumor Microenvironment, Douglas T. Fearon
- Overcoming On-Target Resistance to Tyrosine Kinase Inhibitors in Lung Cancer, Ibiayi Dagogo-Jack, Jeffrey A. Engelman, Alice T. Shaw
- Apoptosis and Cancer, Anthony Letai
- Chemical Carcinogenesis Models of Cancer: Back to the Future, Melissa Q. McCreery, Allan Balmain
- Extracellular Matrix Remodeling and Stiffening Modulate Tumor Phenotype and Treatment Response, Jennifer L. Leight, Allison P. Drain, Valerie M. Weaver
- Aneuploidy in Cancer: Seq-ing Answers to Old Questions, Kristin A. Knouse, Teresa Davoli, Stephen J. Elledge, Angelika Amon
- The Role of Chromatin-Associated Proteins in Cancer, Kristian Helin, Saverio Minucci
- Targeted Differentiation Therapy with Mutant IDH Inhibitors: Early Experiences and Parallels with Other Differentiation Agents, Eytan Stein, Katharine Yen
- Determinants of Organotropic Metastasis, Heath A. Smith, Yibin Kang
- Multiple Roles for the MLL/COMPASS Family in the Epigenetic Regulation of Gene Expression and in Cancer, Joshua J. Meeks, Ali Shilatifard
- Chimeric Antigen Receptors: A Paradigm Shift in Immunotherapy, Michel Sadelain
Contents

Clinical Psychology Training: Accreditation and Beyond
Robert W. Levenson ................................................................. 1

Personal Sensing: Understanding Mental Health Using Ubiquitous Sensors and Machine Learning
David C. Mohr, Mi Zhang, and Stephen M. Schueller ......................................... 23

The Philosophy of Nosology
Peter Zachar and Kenneth S. Kendler ......................................................... 49

Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account

Memory Reconsolidation Interference as an Emerging Treatment for Emotional Disorders: Strengths, Limitations, Challenges, and Opportunities
Tom Beckers and Merel Kindt ..................................................................... 99

Schooling and Children’s Mental Health: Realigning Resources to Reduce Disparities and Advance Public Health
Marc S. Atkins, Elise Cappella, Elisa S. Shernoff, Tara G. Mehta, and Erika L. Gustafson ................................................................. 123

Psychological Treatments for the World: Lessons from Low- and Middle-Income Countries
Daisy R. Singla, Brandon A. Kohrt, Laura K. Murray, Arpita Anand, Bruce F. Chorpita, and Vikram Patel ................................................................. 149

Sex Differences in Binge Eating: Gonadal Hormone Effects Across Development
Kelly L. Klump, Kristen M. Culbert, and Cheryl L. Sisk ........................................... 183

Panic Disorder Comorbidity with Medical Conditions and Treatment Implications
Alicia E. Meuret, Juliet Kroll, and Thomas Ritz .................................................. 209

Emotions in Depression: What Do We Really Know?
Jonathan Rottenberg .............................................................................. 241
Predictive Processing, Source Monitoring, and Psychosis
Juliet D. Griffin and Paul C. Fletcher ................................................................. 265

Controversies in Narcissism
Joshua D. Miller, Donald R. Lynam, Courtland S. Hyatt, and W. Keith Campbell .... 291

Irritability in Children and Adolescents
Melissa A. Brotman, Katharina Kircanski, and Ellen Leibenluft ......................... 317

Trait Impulsivity and the Externalizing Spectrum
Theodore P. Beauchaine, Aimee R. Zisner, and Colin L. Sauder .......................... 343

Subjective Cognitive Decline in Preclinical Alzheimer’s Disease
Laura A. Rabin, Colette M. Smart, and Rebecca E. Amariglio ............................ 369

Medical Marijuana and Marijuana Legalization
Rosalie Liccardo Pacula and Rosanna Smart .................................................. 397

Lovesick: How Couples’ Relationships Influence Health
Janice K. Kiecolt-Glaser and Stephanie J. Wilson ............................................. 421

The Link Between Mental Illness and Firearm Violence: Implications for Social Policy and Clinical Practice
John S. Rozel and Edward P. Mulvey ................................................................. 445

Reward Processing, Neuroeconomics, and Psychopathology
David H. Zald and Michael T. Treadway .......................................................... 471

Self-Regulation and Psychopathology: Toward an Integrative Translational Research Paradigm
Timothy J. Strauman ......................................................................................... 497

Child Maltreatment and Risk for Psychopathology in Childhood and Adulthood
Sara R. Jaffee ...................................................................................................... 525