



HHS Public Access

Author manuscript

Dev Psychopathol. Author manuscript; available in PMC 2015 June 22.

Published in final edited form as:

Dev Psychopathol. 2013 November ; 25(4 0 2): 1473–1487. doi:10.1017/S0954579413000722.

The developmental psychopathology of irritability

ELLEN LEIBENLUFT and JOEL STODDARD

National Institute of Mental Health

Abstract

Chronic, severe irritability is common in childhood and is very impairing. Furthermore, childhood irritability predicts suicidality, social impairment, and depressive and anxiety disorders in adulthood. Focusing on both normative and pathologic development, we review the construct of irritability from its origins in aggression and disruptive behavior research to its contemporary relevance for affective psychopathology. We then describe two broad neurocognitive systems that show promise in differentiating irritable from nonirritable youths: aberrant processing of emotional stimuli and impaired context-sensitive regulation. We suggest behavioral, neurocognitive, and physiologic measures that may aid in studying severe irritability and assessing its therapeutics. Finally, we argue for therapeutic trials targeting severe irritability that address emotional aspects of irritability in addition to the associated disruptive behavior.

Clinically significant irritability occurs commonly in children and adolescents (~3% of the general population; Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010; Brotman et al., 2006). Despite its prevalence, the literature on clinically impairing irritability is relatively limited. This insufficient evidence base has adverse clinical consequences, illustrated by the controversy about whether children with chronic, severe irritability and hyperarousal are exhibiting a developmental presentation of bipolar disorder and should be treated as such (American Academy of Child & Adolescent Psychiatry, 2007). Specifically, some investigators claim that youths with severe irritability, without distinct manic episodes, are exhibiting a developmental presentation of bipolar disorder, although data suggest that severe, nonepisodic irritability differs from classic bipolar disorder in longitudinal course, as well as pathophysiology and family history (Leibenluft, 2011). In any case, the controversy regarding pediatric bipolar disorder shines a bright light on the fact that there are many gaps in our knowledge about the presentation, course, and pathophysiology of severe irritability in youth.

Here we present a selective review of irritability throughout childhood, with a specific focus on its severe manifestations and, hence, its relationship to psychopathology. We focus specifically on important gaps in the literature, including the relative dearth of knowledge about the neurobiological mechanisms mediating severe irritability in youth. To lay a conceptual framework for our review, we begin by describing how irritability has been

© Cambridge University Press 2013.

Address correspondence and reprint requests to: Joel Stoddard, Section on Bipolar Spectrum Disorders, Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Building 15K, Room 208, 15K North Drive, MSC-2670, Bethesda, MD 20892-2670; joel.stoddard@nih.gov..

defined for systematic study, including its relationship to anger and aggression. Then we review recent studies describing the course of irritability through childhood and its longitudinal associations with psychopathology. Irritability is a diagnostic criterion for many mental disorders according to DSM-IV. However, it is most central to the diagnosis of oppositional defiant disorder (ODD). Therefore, we focus on studies describing the outcome of youths with ODD. As described below, a major, relatively recent, advance in the understanding of irritability has been the recognition that it predicts depressive and anxious psychopathology, apart from its association with disruptive behaviors. In the final section, we discuss relevant findings in affective neuroscience that may help us understand these associations at the level of neural systems that mediate emotional processing and behavioral control. This review reveals significant gaps in our knowledge, so we conclude with a series of recommendations for future research on irritability that integrates neurobiological, clinical, and longitudinal strategies.

Definitions

As detailed below, most definitions of irritability characterize it as excessive reactivity to negative emotional stimuli and describe it as having an affective component, anger, and a behavioral component, aggression (Berkowitz, 1993; Buss & Durkee, 1957; Caprara et al., 1985). That is, irritable people are overly angry or aggressive in response to provocations (Caprara et al., 1985). We will introduce these concepts before turning to irritability itself.

Spielberger, the developer of influential anger measures, suggested that anger can be defined “as a psychobiological state or condition consisting of subjective feelings that vary in intensity, from mild irritation or annoyance to intense fury and rage, with concomitant activation or arousal of the autonomic nervous system” (Spielberger, Reheiser, & Sydeman, 1995). Two properties of anger are particularly relevant to irritability. First, anger is an emotion with a negative valence; that is, most people find it unpleasant (Watson & Tellegen, 1985). Second, anger can be distinguished from other negative emotions (i.e., from sadness and fear) by its relationship to motivation (reviewed by Carver & Harmon-Jones 2009; see also Panksepp, 2006, for a review of converging ethological evidence). From a motivational perspective, emotions are often divided according to whether they are associated with “approach” or “avoid” behavior. Simply put, if one cannot get what she wants, she may become angry and try harder to achieve her goal (approach), or she may become sad and give up (failure to approach). In contrast, fear is a negative-valence emotion that is associated with threats that are to be avoided. In this formulation, the adaptive function of anger is that its presence is associated with increased effort toward goals that are difficult to achieve (Lewis, Alessandri, & Sullivan, 1990; Weiner, Graham, Stern, & Lawson, 1982).

Aggressive behavior frequently occurs in the context of anger. Aggression is behavior intended to harm another (Berkowitz, 1993). There are many aggression typologies, but the classification of aggression most relevant to developmental psychopathology is the empirical distinction between reactive and proactive aggression (Dodge & Coie, 1987; Vitiello & Stoff, 1997). Reactive aggression, which is nearly synonymous with “emotional aggression” or “hostile aggression,” is accompanied by visible signs of anger and occurs in response to a frustrating event or a perceived threat (Berkowitz, 1983; Dodge, 1980).

Typical manifestations include anger expressions, temper tantrums, and vengeful hostility (Price & Dodge, 1989). Proactive aggression, also known as instrumental aggression (Hartup, 1974), is designed to attain a goal, such as social dominance; typical manifestations include bullying, domination, name-calling, and coercive acts. These sorts of aggressive displays are more typical of boys, whereas girls tend toward more covert forms of aggression, such as relational aggression (i.e., damaging another's relationships or reputation; Côté, Vaillancourt, Barker, Nagin, & Tremblay, 2007; Crick, 1995).

Although the correlation between reactive and proactive aggression within individuals is high ($r = .70 \pm .15$; Vitaro & Brendgen, 2005), the two appear to have differential longitudinal predictions, analogous to those seen in the irritable versus headstrong dimensions of ODD. For example, proactive, but not reactive, aggression at age 10 predicts delinquency 3 years later (Vitaro, Brendgen, & Tremblay, 2002). At age 10, it predicts antisocial behavior at age 26 (Fite, Raine, Stouthamer-Loeber, Loeber, & Pardini, 2010). Reactive, but not proactive, aggression in adolescence predicts anxiety in adulthood (Fite et al., 2010).

Anger and reactive aggression can occur in response to a number of provocations, including threat, noxious stimuli, verbal insults, and frustration (Berkowitz, 1993). In particular, frustration occurs when an individual performs an act in the expectation of a reward and does not receive it or attempts to avoid a punishment yet still receives it (Berkowitz, 1989; Berkowitz & Harmon-Jones, 2004). In healthy individuals, the degree of frustration is proportional to the degree of reward anticipation (Berkowitz, 1993). For this reason, investigators studying the neuroscience of irritability often elicit frustration by manipulating the disparity between expected and received rewards (e.g., Abler, Walter, & Erk, 2005; Siegrist et al., 2005).

Irritability is often described as a trait. Specifically, it is a personality dimension characterized by a tendency to be angry and reactive to slight provocations and disagreements (Caprara et al., 1985). This differs from anger, which is an affective state, and reactive aggression, which is a behavior. The concept of irritability was operationalized in 1957 in a series of studies validating an omnibus assessment of aggression, the Buss–Durkee Hostility Inventory (Buss & Durkee, 1957). The validation of the irritable trait and the construction of an irritability inventory resulted from a factor analysis of over 1,000 participants' responses to the Buss–Durkee Hostility Inventory (Caprara et al., 1985). Since then, “irritable mood” was included in *Index Medicus* to clarify the meaning of irritability for clinical research (Snaith & Taylor, 1985), and several irritability scales were created and validated (Table 1). These scales emphasize angry affect, rapid anger induction, inability to control anger, and increased reactive aggression.

Two basic properties of any trait are heritability and stability. The heritability of irritability has been estimated at approximately 0.3–0.4 in adolescents and adults (Coccaro, Bergerman, Kavoussi, & Seroczynski, 1997; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012), suggesting that environmental and genetic factors play nearly equal roles in its etiology. Irritability has been found to be relatively stable, with some attenuation from school age to adulthood (attention corrected $r = .4$; Olweus, 1979).

Irritability as a Predictor of Psychopathology in Nonclinical Childhood Samples

Here, we summarize longitudinal studies of irritability-related traits in nonclinical populations through childhood, focusing on these constructs as predictors of psychopathology. We emphasize studies that include relatively lengthy follow-up, because long study durations maximize one's ability to predict future psychopathology.

Emotional reactivity and reactive aggression are common from infancy to toddlerhood. Angry expressions appear soon after birth, and interindividual differences in angry or sad facial expressions in response to frustration can be observed by 2 months of age (Lewis et al., 1990). However, longitudinal studies of angry expressions, anger regulation, and reactive aggression beginning in infancy demonstrate limited stability of these constructs, poor interobserver reliability, and poor predictive power for conduct problems in toddlerhood (e.g., Gagne & Goldsmith, 2011; He et al., 2010). Daily, angry outbursts are typical in toddlerhood, especially between 1 and 3 years of age (Potegal & Davidson, 2003; Potegal, Kosorok, & Davidson, 2003), and reactive aggressive interactions between peers are common (Hay, 2005).

From toddlerhood to school age, most children show a decline in aggression (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Côté et al., 2007; Shaw, Gilliom, Ingoldsby, & Nagin, 2003; Vaillancourt, Miller, Fagbemi, Côté, & Tremblay, 2007). This decline is broadly attributed to increasing social competencies (e.g., Dunn & Brown, 1991) and maturation of self-regulation (i.e., the ability to control inner states and behavioral responses; Bell & Deater-Deckard, 2007; Gross, 1998). Studies of preschoolers at temperamental extremes that include irritability (e.g., "difficult" children: Guerin, Gottfried, & Thomas, 1997; high behavioral disinhibition: Hirshfeld-Becker et al., 2003; for a review, see Egger & Angold 2006) suggest that such a temperamental profile predicts a wide range of psychopathology, especially disruptive behavioral disorders. Of course, the effects of innate temperament on irritable behavior cannot be easily disentangled from their interaction with the caregiving environment, (e.g., maternal depression, low responsiveness to the child's distress, and/or hostile parenting; Davidov & Grusec, 2006; Shaw et al., 2003; Vaillancourt et al., 2007).

Irritability has not been characterized systematically through middle childhood, but there are relevant studies. During this developmental phase, anger/frustration correlates modestly with both poor self-regulation and conduct problems ($r_s = \sim .4$) and has a heritability of 0.25 (confidence interval [CI] = 0.02–0.58; Deater-Deckard, Petrill, & Thompson, 2007). Individuals who persist in angry, reactive aggression through middle childhood experience peer rejection, attribute hostile intentions to others, and are less flexible in both interpreting social cues and responding to them (Crick & Dodge, 1994, 1996; Price & Dodge, 1989). In longitudinal, community-based studies, preadolescent youths who exhibit reactive aggression are at risk for affective and anxious psychopathology in adolescence (Vitaro et al., 2002).

In a related and influential series of studies, Frick et al. (1993) described the trait of oppositionality as consisting of overt aggression-related behavior that is not destructive, such as temper outbursts, noncompliance, and argumentativeness. Oppositionality can be measured along a continuum in the general population with the extreme end representing ODD (Frick et al., 1993; Hoffenaar & Hoeksma, 2002). In population-based, longitudinal studies tracing oppositionality throughout childhood, oppositionality was highest at age 4 and then declined for most youths, but it was stable for those whose baseline oppositionality was either extremely high (7%–20%) or extremely low (7%–10%; Bongers, Koot, van der Ende, & Verhulst, 2004; Boylan, Vaillancourt, & Szatmari, 2012; Nagin & Tremblay, 1999). Children who had a high-stable trajectory of oppositional symptoms were at risk for depressive, anxious, and conduct symptoms in adolescence (Boylan et al., 2012).

For most youths, irritability maintains a stable course through adolescence, with higher levels predicting aggression, generalized anxiety, and depression in young adulthood. In 500 youths followed from 12 to 20 years of age, Caprara, Paciello, Gerbino, and Cugini (2007) found that the mean level and rank order of self-reported irritability was stable for most youths. The exception was 23% of participants who had moderate levels of irritability that decreased throughout adolescence. More girls than boys (34.9% vs. 28.1%) had stably high levels of irritability, which was longitudinally associated with self-reported physical aggression, verbal aggression, and violence.

Using data from the Children in the Community Study (Cohen & Cohen, 1996), a longitudinal community-based study of 776 participants followed from 13.8 (± 2.6) to 33.2 (± 2.9) years of age, Leibenluft and colleagues (Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; Stringaris, Cohen, Pine, & Leibenluft, 2009) focused on the stability and diagnostic predictions of episodic versus chronic irritability. The motivation for this comparison was the suggestion by some researchers that bipolar disorder presents in children as chronic irritability, rather than with *distinct manic episodes*, that include irritability and/or euphoria that is more severe than the child's baseline level and is accompanied by manic symptoms such as distractibility and decreased need for sleep (Biederman, 1998; Mick, Spencer, Wozniak, & Biederman, 2005; Papolos & Papolos, 2007). Chronic and episodic irritability were distinct constructs, in that the Pearson correlation between chronic irritability at mean ages 13.8 and 16.2 years was .56, higher than the correlation between episodic and chronic irritability measured simultaneously (i.e., .34 at 13.8 years or .26 at 16.2 years). Episodic and chronic irritability had different trajectories, with episodic irritability increasing linearly through adolescence and chronic irritability tracing a shallow inverted U that peaked in midadolescence. Perhaps of most importance, the irritability subtypes differed in their longitudinal predictions. Specifically, chronic irritability at mean age 13.8 years predicted attention-deficit/hyperactivity disorder (ADHD) at mean age 16.2 years and major depression at mean age 22.1 years, whereas episodic irritability at mean age 13.8 years predicted simple phobia and mania at mean age 16.2 years. When the authors extended the analysis, chronic irritability at mean age 13.8 years predicted major depressive disorders and generalized anxiety disorder at age 33.2 years, but it did not predict bipolar disorder or axis II disorders (Stringaris et al., 2009). Furthermore, after controlling the effects of depression

and anxiety, chronic irritability in adolescence predicted lower income and education attainment (Stringaris et al., 2009).

Two other longitudinal, community-based studies reported associations between chronic irritability in adolescence and subsequent depressive symptoms. In the landmark Isle of Wight study, 14- to 15-year-old adolescents were assessed at baseline and then again 30 years later (Pickles et al., 2010). There were three strong adolescent predictors of adult suicidality: irritability (odds ratio [OR] = 3.2, CI = 1.9–5.3), worry (OR = 3.0, CI = 1.8–5.1), and minor depression (OR 3.4, CI = 1.7–6.7). Note that the relationship between parent-reported irritability in adolescence and adult suicidality was not mediated by either psychopathology or adult self-reported irritability. Finally, a study of 2,615 twins assessed at age 15 (range = 12–21) and again at age 17 (range = 14–23) found that genetic factors accounted for both cross-sectional and longitudinal associations between irritability and depression (Stringaris, Zaros, et al., 2012). The heritability of irritability was 0.31.

In summary, these longitudinal studies in nonclinical samples suggest that normative irritability peaks in toddlerhood. After toddlerhood, one can begin to discern stable developmental trajectories associated with increased risk for future psychopathology. Although studies are limited in middle childhood, data in adolescents suggest a largely stable course through this age and an association between irritability and subsequent unipolar mood and anxiety disorders. Unlike antisocial behavior (Moffitt, 1993), there is little evidence of the emergence in adolescence of a large group of youths with severe irritability or reactive aggression.

Longitudinal Studies of ODD and Its Symptom Dimensions

Here, we examine the longitudinal course of irritability as it manifests as a component of ODD and oppositionality. Irritability is a criterion for many DSM-IV diagnoses, including mood, anxiety, and disruptive behavior disorders; however, in children, the diagnosis in which irritability features most prominently is ODD. Therefore, to examine the longitudinal outcome of severe irritability when it is conceptualized as a nosologic category, we review the course of ODD. However, there are two ways in which this categorical view overlaps with a dimensional perspective on oppositional behavior. First, youths at the extreme end of the oppositionality trait dimension (Frick et al., 1993) meet criteria for ODD. Second, recent studies find differences in longitudinal predictions between the irritable and headstrong dimensions embedded within both ODD and the oppositionality trait. Therefore, in addition to studies of ODD, in this section we describe studies based on the trait of oppositionality.

To meet criteria for ODD, a child must exhibit a chronic pattern of “negativistic, hostile, defiant” behavior, defined by having four of eight symptoms to a clinically impairing degree (DSM-IV) for at least 6 months. These eight symptoms are temper loss, anger/resentment, easily annoyed, argumentative, defiant, deliberately annoys others, blames others, or spiteful/vindictive. In the British Child Mental Health Survey (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004), ODD was present in 3.4% of boys and 1.4% of girls from 5 years old until adolescence, when the rate declined (note the decline in adolescence did not occur if, contrary to DSM-IV, ODD was diagnosed in the presence of conduct disorder).

Although ODD is a precursor to a broad array of adult psychopathology (Kim-Cohen et al., 2003; Nock, Kazdin, Hiripi, & Kessler, 2007), epidemiologic (Copeland, Shanahan, Costello, & Angold, 2009; Rowe, Maughan, Pickles, Costello, & Angold, 2002) and clinical (Burke, Loeber, Lahey, & Rathouz, 2005; Loeber, Burke, & Pardini, 2009) studies indicate that childhood ODD is more strongly predictive of emotional disorders than antisocial behavior in adulthood. Burke et al. (2005) suggested that an affective dimension of ODD may account for these associations. Stringaris and Goodman (2009a, 2009b) tested this hypothesis in a series of studies examining whether an affective dimension of either ODD or oppositionality predicts emotional psychopathology. Specifically, Stringaris and Goodman (2009a, 2009b) suggested that oppositionality encompasses three dimensions: irritable (temper outbursts, anger, and easily annoyed), headstrong (noncompliance, arguing, annoying, and blaming others), and hurtful (spitefulness and vindictiveness). In 7,912 youths from the British Child Mental Health Survey followed over 3 years, these dimensions correlated highly ($r_s = .62-.78$) but had specific longitudinal associations. The irritable domain predicted depression and generalized anxiety disorder, whereas the headstrong dimension predicted ADHD and conduct disorder (Stringaris & Goodman, 2009a).

Subsequent studies yielded similar findings. Using factor analysis, Burke, Hipwell, and Loeber (2010) explored the longitudinal associations of ODD symptoms in girls ($n = 2,451$, ages 5–8 years) followed for 5 years. The symptoms touchy, angry, and spiteful clustered together in a negative affectivity dimension that, like irritability, uniquely predicted depressive outcomes. In the first wave of the epidemiologic Great Smokey Mountain Study ($n = 1,420$, mean age = 9 years), a two-factor solution of ODD symptoms largely mapped onto Stringaris and Goodman's irritable and headstrong dimensions (Rowe, Costello, Angold, Copeland, & Maughan, 2010). Irritability at age 9 years predicted anxiety and substance use disorders at age 16 years. These data indicate that a focus on the disruptive behaviors characteristic of ODD should be complemented by a focus on the emotional predictions carried by the irritability dimension, so that attention can be paid to the possible prevention of emotional disorders.

Thus far we have discussed clinically significant irritability in the context of ODD. In addition, two longitudinal studies isolated and followed extremely irritable children from community-based samples, most of whom would meet criteria for ODD (Althoff et al., 2010; Brotman et al., 2006). In a post hoc analysis of the Great Smokey Mountain Study (see Rowe et al., 2010, above), Brotman et al. (2006) identified youths with severe mood dysregulation (SMD; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003), that is, those with severely impairing chronic irritability and hyperarousal symptoms. SMD had a prevalence of 3.3% throughout childhood and predicted depressive disorders at age 18 years. Althoff et al. (2010) followed 4- to 16-year-old children drawn from Dutch birth registries for 14 years. The Child Behavior Checklist dysregulation phenotype is defined by extreme values on the anxious/depressed, attention problems, and aggressive behavior subscales and may be related to severe irritability (Althoff, 2010). It was present in 3.8% of 2,076 participants at Wave 1 and was associated with anxiety and disruptive behavioral disorders 14 years later.

The Neurobiology of Irritability

Little is known about the neural underpinnings of irritability. Proposed models generally focus on poor frontal inhibition of limbic and autonomic systems (e.g., irritability: Leibenluft, 2011; reactive aggression: Blair, 2010; anger and self-regulation: Bell & Deater-Deckard, 2007). Here we focus on ways in which these broader observations may be better specified in future research programs. Based on available data and current conceptualizations, we discuss two broad constructs that show promise in differentiating irritable from nonirritable youths, that is, processing of emotional stimuli and impaired context-sensitive regulation. Dysfunctional attention–emotion interactions are likely to underlie deficits in both of these domains. The elucidation of neural mechanisms mediating irritability could guide the development of novel interventions.

Processing of emotional stimuli

A limited literature suggests that severely irritable youths have aberrant neurocognitive responses to emotional stimuli, particularly in social contexts, making them more vulnerable to anger and reactive aggression. We present evidence suggesting that preconscious neural mechanisms draw irritable youths' cognitive resources toward aversive social and affective signals and that irritable youths might tend to perceive ambiguous social signals as hostile. Then, we present data suggesting that youths with clinically significant irritability have impairments in face emotion recognition as well as amygdala dysfunction.

Selective attention paradigms can be used to measure interindividual differences in the extent to which a stimulus is considered salient. The limited available data suggest that negatively valenced social and emotional stimuli may be particularly salient for irritable youths (Table 2). On the visual search and the emotional Stroop tasks, trait anger is associated with greater interference from distracting emotional stimuli (Cohen, Eckhardt, & Schagat, 1998; Smith & Waterman, 2003; van Honk, Tuiten, de Haan, van den Hout, & Stam, 2001). The dot probe paradigm measures attentional biases toward or away from threatening faces or other negative stimuli. Here, the literature on irritable individuals is limited and the data are mixed, with some studies showing a bias toward, and some a bias away from, negative stimuli in angry or aggressive individuals (Kimonis, Frick, Munoz, & Aucoin, 2007; Reid, Salmon, & Lovibond, 2006; Schippell, Vasey, Cravens-Brown, & Bretveld, 2003; Smith & Waterman, 2003). Thus, although considerably more work is needed to identify associations between irritability and impairment in early attentional processes, these data suggest that threatening or other negative stimuli may be particularly salient to irritable individuals and thus more likely to capture and/or hold their attention.

Two hypotheses suggest mechanisms that may mediate increased salience of emotional stimuli in irritable youths. In one account, Blair (2010) argues that reactive aggression is mediated through the threat–response system involving the amygdala, the hypothalamus, and the periaqueductal gray area. Partially overlapping fear and rage circuitry, which mediates both stress and arousal responses, is well documented in animals (Panksepp, 2006). Either a failure of cortical areas to suppress this system or its hypersensitivity may be associated with pathologic reactive aggression (Blair, Mitchell, & Blair, 2005). For example, in 10 individuals with pathologic reactive aggression (i.e., intermittent explosive disorder),

viewing of angry faces was associated with increased amygdala activity and reduced orbitofrontal cortex activity, relative to healthy subjects (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). In subjects high in trait anger, resting state functional magnetic resonance imaging (fMRI) found reduced functional amygdala–orbitofrontal cortex connectivity (Fulwiler, King, & Zhang, 2012). This formulation of overlapping circuitry between fearful and angry responses has clinical relevance in youths, given cross-sectional and longitudinal associations between anxiety and irritability (Leibenluft, 2011).

In the second hypothesis, van Honk et al. (2001) suggested that the distracting effect of angry faces in those with high trait anger reflects a bias toward approach responses. In the classic formulation by Gray (1990), opposing neural systems mediate the motivation to approach an emotional stimulus (behavioral activation system) or avoid it (behavioral inhibition system). An angry face could represent a threat to be avoided or a challenge to be approached and engaged (Öhman, 1986), and a person's disposition toward approach or avoidance might be reflected in his or her behavioral response. According to this account, angry individuals would have high behavioral activation system activity and would be more likely to approach the threatening stimulus (Beaver, Lawrence, Passamonti, & Calder, 2008). Evidence suggests that individuals with reactive aggression or trait anger may demonstrate increased approach responses, in the form of increased attention to positive emotional stimuli (Ford et al., 2010; Kimonis et al., 2007). Thus, van Honk et al. emphasize a hyperactive approach system, whereas Blair emphasizes dysregulation in the threat system that may mediate either an approach to or avoidance of threat.

The evidence discussed thus far focuses on individuals' responses to unambiguously threatening stimuli. However, an influential theory in the cognitive underpinnings of reactive aggression is that of Dodge, who suggested that children prone to reactive aggression exhibit a hostile attribution bias, that is, a bias toward responding to social cues as if they reflected malicious intent (Crick & Dodge, 1994; Dodge, 1980; Dodge & Coie, 1987). Though hostile attribution bias has been documented in youths with reactive aggression and in adults with trait anger/irritability (Epps & Kendall, 1995), its neurobiology is not well understood (e.g., Lee & Hoaken, 2007). Two eye-tracking studies suggest possible attentional mechanisms. When viewing social scenes, aggressive children (Horsley, de Castro, & van der Schoot, 2010) and adults with high trait anger (Wilkowski, Robinson, Gordon, & Troop-Gordon, 2007) did not differ from healthy subjects on initial fixation of clearly hostile social cues. Instead, compared to healthy subjects, angry, aggressive subjects spent more time looking back at ambiguous cues and less time viewing unambiguously hostile cues. The authors suggest that angry subjects have such strong expectations of hostility that they more quickly assess overt hostility and work harder to interpret ambiguous social cues (Horsley et al., 2010; Wilkowski & Robinson, 2008). Given evidence of hostile attribution bias in youths with reactive aggression (de Castro, Veerman, Koops, Bosch, & Monshouwer, 2002), more study of the mediating neural mechanisms is warranted.

Although hostile attribution bias studies focus on the processing of complex social scenarios, other research examines the ability of severely irritable youths, in particular those with the SMD phenotype, to identify facial emotions. Across emotions, youths with SMD

make more errors than do healthy subjects when labeling facial expressions (Guyer et al., 2007) and require more intense emotional expression to label affect accurately (Rich et al., 2008). It is notable that these studies did not detect a relative advantage or disadvantage within the SMD group for identifying angry affect, and in that sense they were not consistent with a hostile attribution bias. However, within the context of fMRI scanning (Brotman et al., 2010), youths with SMD rated themselves as more fearful of neutral faces than did healthy youths or nonirritable youths with ADHD. Youths with SMD have not been tested specifically for hostile attribution bias.

Given these face emotion identification deficits in SMD, two fMRI studies focused on the neural circuitry mediating face emotion processing in SMD. One compared youths with SMD to those with bipolar disorder, ADHD subjects without irritability, and healthy subjects. As noted above, during this scanning procedure, youths with SMD rated themselves as more fearful of neutral faces than did nonirritable youths, with or without ADHD. In addition, compared to other groups, youths with SMD demonstrated amygdala hypoactivation while explicitly processing the emotion on a neutral face but hyperactivation while rating nose width on the face (i.e., during implicit processing of the emotional stimulus; Brotman et al., 2010). Research suggests that such amygdala hypoactivation may be a signature of aberrant processing of social threat (Kret, Denollet, Grèzes, & de Gelder, 2011).

In a second study, SMD youths, as well as those with bipolar disorder and healthy subjects, rated the gender (implicit emotion processing) or hostility (explicit emotion processing) of faces that varied in emotional intensity between neutral and either happy or angry (Thomas et al., 2012). A parametric analysis found that, as the degree of anger on a face increased, healthy subjects showed increasing amygdala activity, whereas subjects with SMD (or bipolar disorder) did not. This suggests amygdala hyposensitivity to subtle changes in face emotion in SMD; such insensitivity might also be associated with the deficit in face emotion labeling described above.

In summary, evidence suggests aberrant attention–emotion interactions in irritable youths. Specifically, in irritable youths, attentional resources may be drawn toward an emotional stimulus, perhaps especially when that stimulus is threatening. Irritable youths may also have a heightened tendency to respond to inherent or perceived stimulus properties that trigger threat and/or motivational neural systems. Finally, data suggest that clinically irritable youths have impairments in face-emotion labeling and aberrant amygdala responses, although the precise nature of the latter remains to be defined clearly. In youths with severe irritability, aberrant early social information processing may compete with potentially corrective regulatory mechanisms for scarce attentional resources. Next, we describe how these regulatory mechanisms may be disrupted in clinical irritability.

Context sensitive regulation and frustration

As noted above, frustration occurs when an individual's progress toward a goal is blocked. Adaptive responses to frustration include modifying one's strategy toward the current goal or directing one's efforts toward an alternative goal. This is one example of the emotion regulatory process that Ochsner (2008) calls “context sensitive regulation,” that is, the

ability to learn from, and adapt constructively to, changing environmental contingencies. For example, Blair (2010) has suggested that individuals who have difficulty adapting their behavior by inhibiting responses that were previously rewarded, and instead executing newly rewarded responses, will be at increased risk to experience frustration. Context sensitive regulation depends upon prefrontal regions associated with goal-directed behavior via cognitive control (Miller & Cohen, 2001).

In laboratory settings, reversal learning paradigms can be used to assess this adaptive ability. In such paradigms, individuals attempt to win points or money by performing a task in which the rewarded object (A vs. B) changes continuously and the individual must detect the change in reward contingencies. Studies suggest that youths with SMD have deficits in reversal learning and other measures of cognitive flexibility (Dickstein et al., 2007). During reversal learning, the difference in caudate and ventrolateral prefrontal cortex (PFC) activation between incorrect and correct trials is less in youths with SMD versus healthy subjects (Adleman et al., 2011). The ventrolateral PFC facilitates the inhibition of prior responses and the execution of an alternative action, whereas the caudate mediates motor learning in response to error signals and other reward-related information. Thus, these data suggest that youths with SMD have deficits in engaging these regions as needed to learn from errors and adapt their behavior.

Frustration can be induced by changing reward contingencies so that subjects are unable to attain a desired reward (Berkowitz, 1989). In this way, frustration paradigms can, like response reversal paradigms, be used to elicit and study deficits in context-dependent regulation. It can be argued that the neurophysiology of irritability is a relatively tractable clinical research problem because it can be induced in the laboratory or during scanning through the use of frustration paradigms.

The literature seeking to define the neural correlates of frustration in healthy subjects is limited, and the corresponding literature in clinical populations is extremely sparse. Studies in healthy adults or children suggest that frustration elicits activation in widely distributed neural circuitry, including regions that mediate reversal learning (Abler et al., 2005). Specifically, it appears that frustration engages circuitry mediating emotional responses and learning (e.g., amygdala and ventromedial PFC [vmPFC]); causing attentional shifts (e.g., ventrolateral PFC and dorsal parietal cortex); and resolving response conflict (e.g., dorsolateral prefrontal and anterior cingulate cortex). Finally, some frustration studies find insula engagement, perhaps reflecting the role of this region in mediating physical distress, such as might be precipitated by the unpleasant experience of being unable to attain a desired goal.

For example, Abler et al. (2005) found that frustration in healthy adults was associated with increased right anterior insula and ventral PFC activity and decreased ventral striatal activity. The latter is consistent with the prediction error signaling that occurs when an expected reward does not occur (Knutson, Adams, Fong, & Hommer, 2001). Other groups report similar neurocorrelates, specifically increased vmPFC activation in response to frustration in nonclinical populations (Alia-Klein et al., 2007; Perlman & Pelphrey, 2011; Siegrist et al., 2005). Moreover, this response may be more intense for those high in trait

anger (Alia-Klein et al., 2007). Amygdala–vmPFC functional connectivity during frustration may vary developmentally (Perlman & Pelphry 2011). The vmPFC involvement across studies may relate to the prominent role this region plays in mediating emotional valence associations.

Few studies focus on the brain circuitry mediating frustration in clinical populations. Lewis, Granic, and Lamm (2006) found differences in the N2 potential during frustration among three groups of children: anxiety and aggression, aggression only, and healthy. Focusing on signal sources corresponding to the vmPFC, they found high N2 potential in the anxious–aggressive group, low and late N2 potential in the aggressive-only group, and low tonic N2 potential for healthy children (Lamm, Granic, Zelazo, & Lewis, 2011). Moreover, evidence suggested that successful psychotherapeutic treatment normalized vmPFC activity in children with externalizing symptoms (Lewis et al., 2008; Woltering, Granic, Lamm, & Lewis, 2011). These results suggest increased vmPFC engagement during frustration in clinically irritable youths.

In studies using first event-related potential (ERP) and then magnetoencephalography, Rich et al. (2011) used the affective Posner task, an attentional task with rigged feedback, to induce frustration. These studies provide further evidence for prefrontal abnormalities in youths with severe irritability during frustration. Using ERP, the authors found that SMD youths, compared to both healthy subjects and those with bipolar disorder, had deficits in early attentional processes (i.e., N1) in frontal, as well as temporal and central, sites (Rich et al., 2007). Using magnetoencephalography, the authors found that SMD youths responded to negative feedback with significantly greater anterior cingulate cortex and medial frontal gyrus activation than did healthy subjects (Rich et al., 2011). This suggests that negative feedback may have a disproportionate impact on the ability of irritable youths to monitor their own emotional state and to choose appropriately among competing behavioral options.

In summary, evidence suggests that context-sensitive regulation is disturbed in clinically irritable youths, consistent with their excessive responses and vulnerability to frustration. As discussed below, studies of frustration in clinical populations hold promise for further defining the pathophysiology of irritability and suggesting novel treatment approaches.

Future Directions

Measurement and phenotyping

An important maxim in research is that the ability to measure a variable is a prerequisite for studying it. Given this, the relative lack of scales to measure the presence of, and change in, clinically impairing irritability is both notable and an impediment to progress in the field (Table 1). Put simply, there is a need for better instrumentation to facilitate better phenotyping. First, the development of more refined scales would clarify whether there is a clinically meaningful typology of irritability that could guide diagnosis and treatment. Second, scales that are sensitive to change are needed for treatment trials. Third, pathophysiological studies require symptom measures that can be correlated with brain-based measures and other putative biomarkers.

The intense emotional nature of temper outbursts might compromise both a parent's and a child's ability to report these phenomena accurately. For example, the “peak-end” rule, or the tendency for recent, or severe, events to have a particularly marked impact on responses (Kahneman, Fredrickson, Schreiber, & Redelmeier, 1993), may diminish the probability of acquiring valid data. New approaches, both technological (e.g., ecological momentary assessment; Ebner-Priemer & Trull, 2009) and psychometric (e.g., item response theory; Wakschlag et al., 2012) should be applied to the development of additional measurement techniques for measuring irritability, especially at the clinically meaningful end of the severity spectrum.

In discussing phenotyping irritability, it is also important to note that irritability is a symptom that is present across a number of DSM-IV disorders. This complicates the study of irritability as a distinct psychopathologic entity, because irritability occurring in the context of different mental disorders might have different underlying mechanisms and therefore require different treatment approaches. In contrast, irritability fits well within the framework of the recent National Institute of Mental Health Research Domain Criteria (RDoC; Insel et al., 2010) initiative. Under RDoC, research is organized around dimensional constructs that cut across multiple diagnoses, have translational value (e.g., can be elicited in model animals), and can be examined at multiple levels (e.g., molecular, brain circuitry, and environmental). Irritability lends itself to an RDoC approach, in that it can be measured dimensionally across diagnoses, modeled in animals using reward paradigms, and studied at different levels of analysis. The current RDoC draft includes the construct of frustrative nonre-ward within the negative emotionality domain; this construct could be said to encompass irritability (National Institute of Mental Health Research Domain Criteria Project, 2011).

The developmental trajectory of irritability in healthy youths

Idioms such as “the terrible twos” are evidence that, in healthy children, the degree and expression of irritability varies developmentally, which is well known. It is important to define this developmental trajectory to inform future research as well as parents and clinicians, thus facilitating assessment and potential intervention. The research described earlier demonstrates that investigators have made progress in this regard, but many important questions remain. For example, it is both challenging and particularly important to define the boundary between normative and nonnormative behavior in preschoolers, because the normative peak of irritability occurs then and stable patterns of behavior begin to emerge (Wakschlag et al., 2012). In addition, there has been relatively little research about irritability in middle childhood, in part because measurement presents some significant challenges. That is, children in this age group spend significant periods of time away from their parents, meaning that parental report is necessary but not sufficient. The development of self-report scales for this age group presents a number of challenges, whereas the acquisition of data from teachers can pose ethical and logistical issues. However, middle childhood is an important time for research on irritability: irritability typically decreases during this time, so it is clinically important to understand why it does not do so in some children.

Predicting the longitudinal course of irritability

Multiple studies now show longitudinal associations between affective symptoms of ODD/irritability and mood/anxiety disorders. The longitudinal course of irritability presents an example of the developmental psychopathology principle of multi-finality (Cicchetti & Rogosch, 1996). That is, severe irritability in childhood is associated with different potential outcomes in later life, including depression, anxiety, or no psychopathology. A major goal of developmental research is identifying which at-risk individuals will go on to develop psychopathology, so that preventive measures can be targeted appropriately. The research describing associations between irritability and psychopathology is relatively recent, so it is not surprising that little is known about mediators and moderators of subsequent psychopathology. Given preliminary data suggesting a genetic link between irritability and depressive disorders (Stringaris, Zavos, et al., 2012), the impact of family history is an important area for future research. A plausible hypothesis is that family history of depression confers risk for irritability and that, among those with such a family history, the presence of nonnormative irritability is associated with an increased risk for subsequent depression. If this hypothesis is supported, preventive psychotherapeutic interventions could be tested in this population (e.g., Garber et al., 2009). It is also unknown whether the severity of irritability has predictive value in terms of subsequent psychopathology, and this can be tested in existing data sets. Finally, family environment is likely to play an important role in determining the course of irritability, including the development of subsequent psychopathology.

Genetic and environmental contributions to irritability

Current heritability estimates suggest that both genetic and environmental factors play a significant role in determining a person's trait level of irritability. Numerous factors have been associated with both state and trait changes in reactive aggression and anger, from specific genotypes to hot weather (Berkowitz 1993). Clearly, no one single factor will determine a person's tendency toward irritability. Therefore, future research needs not only to identify a range of etiologic factors, but also to understand the developmental timing of their influence and effects, cofactors required for the promotion or suppression of their effects, and the resulting neural changes.

Candidate gene approaches have implicated some alleles in the pathogenesis of negative affectivity and aggression. In an early suggestion of a genetic by environmental interaction, an allele coding for higher levels of monoamine oxidase A (MAOA) protects against the development of antisocial behavior in children, particularly males, exposed to early maltreatment (Caspi et al., 2002). In addition, higher levels of MAOA are weakly associated with a tendency to experience negative affects in males (Eley et al., 2003). Both associations may be due to the effects of the polymorphism on neural systems influencing emotional processing and impulsive aggression, especially in males (Meyer-Lindeberg et al., 2006).

Similarly, the low activity, short allele of the serotonin transporter linked polymorphic region gene (*5-HTTLPR*) influences a person's tendency toward negative affect (Sen, Burmeister, & Ghosh, 2004) and impulsivity (Lin & Tsai, 2004; Retz, Retz-Junginger, Supprian, Thome, & Rösler, 2004). Like MAOA, there may be a genetic by environmental

interaction between *5-HTTLPR* and stressful life experiences in predicting psychopathology (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi et al., 2003; Karg, Burmeister, Shedden, & Sen, 2011). In addition, data suggest that *5-HTTLPR* may be associated with amygdala hyperresponsiveness ($d = 0.54$ in 13 studies; Munafò, Brown, & Hariri, 2008). Several other candidate genes may also influence irritability, including brain-derived neurotrophic factor (Terracciano et al., 2011), catechol-*O*-methyltransferase (Rujescu, Giegling, Gietl, Hartmann, & Moller, 2003), and dopamine receptor D4 (Kang, Namkoong, & Kim, 2008). Future research on the genetic susceptibility to irritability will likely focus not only on identifying genetic factors, but also on genetic and environmental factors with which candidate genes interact to both produce and protect against irritability and related psychopathology (e.g., Belsky et al., 2009).

We briefly considered some environmental factors above that influence trait anger and reactive aggression. Parental, peer, and socioeconomic factors have all been associated prospectively with increased reactive aggression or trait anger (Cole & Deater-Deckard, 2009; Lahey, Waldman, & McBurnett, 1999). One prominent case in point is child maltreatment, specifically physical abuse. Not only is it a risk factor for reactive aggression (Dodge, Bates, & Petit, 1990; Shields & Cicchetti, 1998) and trait anger (Springer, Sheridan, Kuo, & Carnes, 2007), but like severe irritability, it has also been associated with increased attentional bias toward angry faces (Pollak, Klorman, Thatcher, & Cicchetti, 2001; Pollak & Tolley-Schell, 2003) and deficits in social information processing (Dodge et al., 1990; Teisl & Cicchetti 2008). Nevertheless, though the literature on affective processing in physical abuse and irritability converges in these findings, it diverges in others. For example, unlike our findings in SMD, Pollak and colleagues (Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak et al., 2001; Pollak & Sinha, 2002) found that those with a history of physical abuse recognize angry affect more quickly and accurately than those without a history of maltreatment do. Clearly, there is a need for further studies that include large samples and measures of both irritability and physical abuse.

Differences in such social and affective processing have recently been shown to be influenced by multiple protective and deleterious factors across development (e.g., Teisl & Cicchetti, 2008; Leist & Dadds, 2009). Therefore, a challenge for future research will be to elucidate the mechanisms by which these diverse experiences bring about lasting behavioral changes in susceptible individuals. A prominent example from rodent stress research demonstrates that caregiving behavior during developmentally sensitive periods impacts on offspring behavior and causes neural alterations that are transmitted epigenetically to future generations (Meany, 2001). Intense interest in this area has led to the extension of these findings to humans, where data suggest that adversity may be related to amygdala hypertrophy and prefrontal and hippo-campal atrophy (Davidson & McEwen, 2012). Despite these deleterious effects of stress, the brain remains plastic and may normalize in response to other, potentially corrective experiences, such as meditation, exercise, and psychotherapy (Davidson & McEwen, 2012). Future research will continue to identify active ingredients of behavioral interventions associated with both positive affective and cognitive responses, and normalization of brain measures (e.g., electrophysiologic normalization of PFC signal in psychotherapy responders).

Physiologic markers of irritability

Biologic measures may be used to predict risk or evaluate therapeutic interventions (Cicchetti & Gunnar, 2008). For example, during the development of psychopathology and over the course of effective treatment, one would expect alterations in brain function to be associated with changes in peripheral measures of stress and arousal. Arousal physiology is altered in children prone to react aggressively and angrily (e.g., Hubbard, McAuliffe, Morrow, & Romano, 2002). The identification of physiologic response patterns that detect or predict pathologic irritability has obvious research and clinical applications. An imbalance between sympathetic arousal and adrenocortical stress response may be associated with disruptive problems in children (Bauer, Quas, & Boyce, 2002). Lewis, Ramsay, and Sullivan (2006) found that, in response to frustration, a greater increase in heart rate predicted anger, whereas low cortisol response predicted sadness. Moreover, they found that a group defined by high heart rate and low cortisol displayed the most anger. Whether this interaction goes on to predict pathologic irritability in an individual awaits longitudinal study.

Psychological and neural mechanisms mediating frustration

The psychological and neural mechanisms mediating frustration are likely to be both tractable and clinically important research foci. As noted above, frustration is an emotional response evoked by blocked goal attainment. As such, frustration can be induced in a number of experimental contexts, for example, during ERP measurement or fMRI scanning. In that sense, studies of frustration are similar to those of anxiety syndromes, where pathophysiologically relevant responses are induced while neural measurements are obtained (Davis, Walker, Miles, & Grillon, 2010). The clinical importance of frustration studies stems from the fact that irritability, which is one of the most common presenting complaints in child psychiatry clinics, reflects a low threshold for, or aberrant responses to, frustration.

However, the design of tasks that can be used to induce frustration poses a number of methodological challenges. First, if a paradigm is to be frustrating, the withheld reward must be emotionally salient to subjects, who are likely to vary by gender, developmental age, temperament, and interests. Paradigms that attempt to model frustration in a social context (e.g., modeling frustrating encounters with peers or parents) may be particularly challenging to design, but they are of obvious clinical importance. Second, although the time course of frustrative responses, that is, the affective chronometry of frustration (Davidson, 1998), has not been well studied, clinical observation suggests that the offset of frustration is not immediate and that this offset differs between irritable and nonirritable subjects. How and why frustration's offset differs between individuals with and without psychopathology is an important focus for research. These considerations indicate that order effects may occur in studies of frustration and must be considered in the experimental design. Third, an "effective" and ecologically valid frustration task will evoke different responses in irritable versus nonirritable youths, and such differences may complicate the acquisition or interpretation of data. For example, irritable youths may be more likely than nonirritable youths to discontinue the testing or to move so much that fMRI data are not usable.

The most important point is that frustration paradigms pose a number of ethical issues. Although investigators use such paradigms to induce frustration, a paramount consideration is to not cause the child undue discomfort or to elicit destructive behavior. One important standard is that the degree of frustration must not exceed that which the child often encounters in daily life (e.g., while doing homework or playing a game with peers; Miller, Wendler, & Swartzman, 2005). Clinical staff familiar with the child should be involved in the decision as to whether, and when, he or she should participate, and such staff should be available to monitor the research procedure. In addition, frustration paradigms often involve some degree of deception, for example, asking participants to play a rigged game or telling participants that they are receiving feedback from peers when the feedback is determined by an experimental algorithm. It is important for investigators to work collaboratively with their institutional review board to design assent, consent, and debriefing procedures that are appropriate for use in such circumstances.

Attentional dysfunction in irritable youths

Several lines of reasoning suggest that attentional dysfunction plays an important role in mediating clinically significant irritability in youths; one prominent goal of frustration studies is to elucidate such dysfunction. Considerable research documents reciprocal interactions between emotional and attentional processes at both neural and behavioral levels (Oliveira, Pessoa, Izhikevich, Pereira, & Bronner, 2010), and a particularly relevant line of research indicates associations between effective attention regulation and effective emotion regulation (Bell & Calkins, 2012). Further suggestive evidence for associations between attentional dysfunction and irritability is provided by the high comorbidity between ODD and ADHD (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). The problem of irritability in youths with ADHD is an important topic that is now receiving increased research attention (Sobanski et al., 2010).

Of course, there are multiple attentional subtypes, mediated by distinct but overlapping circuitry, so dysfunctional attention–emotion interactions in irritable youths are likely to be complex. As described earlier, current hypotheses link the neural systems mediating fear and anger. Therefore, it would be important to test for the presence in irritable youths of early, preconscious attentional biases toward threatening stimuli, such as have been well documented in anxiety. Furthermore, the landmark work associating hostile attribution bias with reactive aggression could be extended through the use of imaging techniques in order to identify the mediating neural circuitry. The specification of dysfunctional attentional mechanisms in irritability could provide important clues as to novel interventions, such as has occurred with attention bias modification training in anxiety disorders.

Treatment and prevention

The ultimate goal of research is to facilitate the development of both pharmacologic and psychotherapeutic treatment and preventive strategies. Given the extent to which irritability figures in the clinical presentation of many children, it has been a relatively neglected target for pharmacologic treatment trials. One reason may be that pharmacologic treatment trials are typically designed for a specific DSM-defined mental disorder and irritability cuts across a number of psychiatric diagnoses. Irritability has been reported as a secondary outcome in

ADHD stimulant trials, with data suggesting that stimulant treatment may decrease aggression in youths with ADHD (Connor, Glatt, Lopez, Jackson, & Melloni, 2002). In a more limited number of trials, irritability was the specific target. For example, one trial resulted in an FDA indication for risperidone in the treatment of irritability in youths with autism (McCracken et al., 2002).

The use of risperidone and other second-generation anti-psychotic medications (SGAs) is increasing in the treatment of youths with ADHD (Alessi-Severini, Biscontri, Collins, Sareen, & Enns, 2012; Fullerton et al., 2012). Although the reasons driving this increase are unknown, one possibility is that clinicians are using SGAs to treat aggressive behavior and irritability in youths with ADHD. In addition, to the extent that youths with chronic irritability and ADHD symptoms are viewed as having bipolar disorder, that would tend to increase the use of SGAs in irritable youths. Such treatment is first line for bipolar disorder, and stimulants or antidepressants (for anxiety-related irritability) are contraindicated (Leibenluft, 2011). More attention has focused recently on the pharmacologic treatment of irritability (Hulvershorn, Fosselman, Dickstein & Janicak, 2012a, 2012b; Jairam, Prabhuswamy, & Dullur, 2012), as well as on the development of rating scales for irritability that can be used in treatment trials and other research (Stringaris, Goodman, et al., 2012). Such trials are of the utmost importance, given the significant metabolic side effects of the SGAs and the need for more benign and well-targeted treatments (Correll et al., 2009).

Psychotherapeutic treatments are likely to be at least as important if not more important than psychopharmacologic approaches in the treatment of irritability, because irritability is not linked to one clear psychiatric syndrome and is often context dependent. A rich body of literature demonstrates effective psychotherapeutic approaches to the treatment of conduct problems, antisocial behavior, and aggression (Weisz, Jensen-Doss, & Hawley, 2006). Given the contribution of environmental factors to aggressive behavior, many of these include parent training in addition to child-centered approaches (Kazdin, 2010). However, many of these therapies are targeted toward aggressive behavior, with a particular focus on proactive aggression rather than on irritability and reactive aggression. Pathophysiological research can further psychotherapeutic treatment development by identifying both environmental and cognitive (e.g., attentional) factors that contribute to irritability.

Summary

This review of the psychological, psychiatric, and epidemiologic disciplines indicates that significant advancements have been made in clarifying the construct of irritability, creating measures to facilitate research, establishing the importance of irritability in developmental affective psychopathology, and suggesting possible neurocognitive and affective mechanisms. Much of this work has been accomplished only in the past quarter century, since the construct of irritability was validated and irritable mood was introduced into *Indexus Medicus*, thus facilitating clinical research. Future research should be designed to replicate current findings while including larger samples as well as measures in multiple domains. Such research will facilitate the identification of individuals at risk for severe irritability and of novel treatment targets throughout development. The development and

testing of novel treatments will help to address the urgent need for evidence-based guidance for clinicians treating youths with severe irritability and their families.

References

- Abler B, Walter H, Erk S. Neural correlates of frustration. *NeuroReport*. 2005; 16:669–672. [PubMed: 15858403]
- Adleman NE, Kayser R, Dickstein D, Blair RJR, Pine D, Leibenluft E. Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2011; 50:1173–1185. [PubMed: 22024005]
- Alessi-Severini S, Biscontri RG, Collins DM, Sareen J, Enns MW. Ten years of antipsychotic prescribing to children: A Canadian population-based study. *Canadian Journal of Psychiatry*. 2012; 57:52–58.
- Alia-Klein N, Goldstein RZ, Tomasi D, Zhang L, Fagin-Jones S, Wang G, et al. What is in a word? No versus yes differentially engage the lateral orbitalfrontal cortex. *Emotion*. 2007; 7:649–659. [PubMed: 17683220]
- Althoff RR. Dysregulated children reconsidered. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2010; 49:302–305. [PubMed: 20410722]
- Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. Adult outcomes of childhood dysregulation: A 14-year follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2010; 49:1105–1116. [PubMed: 20970698]
- American Academy of Child & Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007; 46:107–125. [PubMed: 17195735]
- Bauer AM, Quas JA, Boyce WT. Associations between physiological reactivity and children's behavior: Advantages of a multi-system approach. *Journal of Developmental and Behavioral Pediatrics*. 2002; 23:102–113. [PubMed: 11943973]
- Beaver JD, Lawrence AD, Passamonti L, Calder AJ. Appetitive motivation predicts the neural response to facial signals of aggression. *Journal of Neuroscience*. 2008; 28:2719–2725. [PubMed: 18337401]
- Bell, MA.; Calkins, SD. Attentional control and emotion regulation in early development.. In: Posner, MI., editor. *Cognitive neuroscience of attention*. 2nd ed.. Guilford Press; New York: 2012. p. 322-330.
- Bell MA, Deater-Deckard K. Biological systems and the development of self-regulation: Integrating behavior, genetics, and psychophysiology. *Journal of Developmental & Behavioral Pediatrics*. 2007; 28:409–420. [PubMed: 18049327]
- Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Molecular Psychiatry*. 2009; 14:746–754. [PubMed: 19455150]
- Berkowitz L. Aversively stimulated aggression: Some parallels and differences in research with animals and humans. *American Psychologist*. 1983; 38:1135–1144. [PubMed: 6359985]
- Berkowitz L. Frustration–aggression hypothesis: Examination and reformulation. *Psychological Bulletin*. 1989; 106:59–73. [PubMed: 2667009]
- Berkowitz, L. *Aggression: Its causes, consequences, and control*. McGraw–Hill; New York: 1993.
- Berkowitz L, Harmon-Jones E. Toward an understanding of the determinants of anger. *Emotion*. 2004; 4:107–130. [PubMed: 15222847]
- Biederman J. Resolved: Mania is mistaken for ADHD in prepubertal children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1998; 37:1091–1093. [PubMed: 9785721]
- Blair, JR.; Mitchell, DG.; Blair, K. *The psychopath*. Blackwell; Malden, MA: 2005. A neurocognitive account of reactive aggression.; p. 96-109.
- Blair RJR. Psychopathy, frustration, and reactive aggression: The role of ventromedial prefrontal cortex. *British Journal of Psychology*. 2010; 101:383–399. [PubMed: 19321035]

- Bongers IL, Koot HM, van der Ende J, Verhulst FC. Developmental trajectories of externalizing behaviors in childhood and adolescence. *Child Development*. 2004; 75:1523–1537. [PubMed: 15369529]
- Boylan K, Vaillancourt T, Szatmari P. Linking oppositional behaviour trajectories to the development of depressive symptoms in childhood. *Child Psychiatry & Human Development*. 2012; 43:484–497. [PubMed: 22228549]
- Brotman MA, Rich BA, Guyer AE, Lunsford JR, Horsey SE, Reising MM, et al. Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *American Journal of Psychiatry*. 2010; 167:61–69. [PubMed: 19917597]
- Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological Psychiatry*. 2006; 60:991–997. [PubMed: 17056393]
- Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2010; 49:484–492. [PubMed: 20431468]
- Burke JD, Loeber R, Lahey BB, Rathouz PJ. Developmental transitions among affective and behavioral disorders in adolescent boys. *Journal of Child Psychology and Psychiatry*. 2005; 46:1200–1210. [PubMed: 16238667]
- Buss AH, Durkee A. An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology*. 1957; 21:343–349. [PubMed: 13463189]
- Caprara GV, Cinanni V, D'Imperio G, Passerini S, Renzi P, Travaglia G. Indicators of impulsive aggression: Present status of research on irritability and emotional susceptibility scales. *Personality and Individual Differences*. 1985; 6:665–674.
- Caprara GV, Paciello M, Gerbino M, Cugini C. Individual differences conducive to aggression and violence: Trajectories and correlates of irritability and hostile rumination through adolescence. *Aggressive Behavior*. 2007; 33:359–374. [PubMed: 17593560]
- Carver CS, Harmon-Jones E. Anger is an approach-related affect: Evidence and implications. *Psychological Bulletin*. 2009; 135:183–204. [PubMed: 19254075]
- Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*. 2010; 167:509–527. [PubMed: 20231323]
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. *Science*. 2002; 297:851–854. [PubMed: 12161658]
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*. 2003; 301:386–389. [PubMed: 12869766]
- Cicchetti D, Gunnar MR. Integrating biological measures into the design and evaluation of preventive interventions. *Development and Psychopathology*. 2008; 20:737–743. [PubMed: 18606029]
- Cicchetti D, Rogosch FA. Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*. 1996; 8:597–600.
- Coccaro EF, Bergerman CS, Kavoussi RJ, Seroczynski AD. Heritability of aggression and irritability: A twin study of the Buss–Durkee aggression scales in adult male subjects. *Biological Psychiatry*. 1997; 41:273–284. [PubMed: 9024950]
- Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological Psychiatry*. 2007; 62:168–178. [PubMed: 17210136]
- Cohen DJ, Eckhardt CI, Schagat KD. Attention allocation and habituation to anger-related stimuli during a visual search task. *Aggressive Behavior*. 1998; 24:399–409.
- Cohen, P.; Cohen, J. *Life values and adolescent mental health*. Erlbaum; Mahwah, NJ: 1996.
- Cole PM, Deater-Deckard K. Emotion regulation, risk, and psychopathology. *Journal of Child Psychology and Psychiatry*. 2009; 50:1327–1330. [PubMed: 19843190]
- Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni RH. Psychopharmacology and aggression: I. A meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. *Journal*

- of the American Academy of Child & Adolescent Psychiatry. 2002; 41:253–261. [PubMed: 11886019]
- Copeland WE, Shanahan L, Costello E, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Archives of General Psychiatry*. 2009; 66:764–772. [PubMed: 19581568]
- Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *Journal of the American Medical Association*. 2009; 302:1765–1773. [PubMed: 19861668]
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*. 2003; 60:837–844. [PubMed: 12912767]
- Côté SM, Vaillancourt T, Barker ED, Nagin D, Tremblay RE. The joint development of physical and indirect aggression: Predictors of continuity and change during childhood. *Development and Psychopathology*. 2007; 19:37–55. [PubMed: 17241483]
- Côté SM, Vaillancourt T, LeBlanc J, Nagin D, Tremblay RE. The development of physical aggression from toddlerhood to pre-adolescence: A nation wide longitudinal study of Canadian children. *Journal of Abnormal Child Psychology*. 2006; 34:68–82.
- Crick NR. Relational aggression: The role of intent attributions, feelings of distress, and provocation type. *Development and Psychopathology*. 1995; 7:313–322.
- Crick NR, Dodge KA. A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin*. 1994; 115:74–101.
- Crick NR, Dodge KA. Social information-processing mechanisms in reactive and proactive aggression. *Child Development*. 1996; 67:993–1002. [PubMed: 8706540]
- Davidov M, Grusec JE. Untangling the links of parental responsiveness to distress and warmth to child outcomes. *Child Development*. 2006; 77:44–58. [PubMed: 16460524]
- Davidson RJ. Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition & Emotion*. 1998; 12:307–330.
- Davidson RJ, McEwen BS. Social influences on neuroplasticity: Stress and interventions to promote well-being. *Nature Neuroscience*. 2012; 15:689–695.
- Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology*. 2010; 35:105–135. [PubMed: 19693004]
- Deater-Deckard K, Petrill SA, Thompson LA. Anger/frustration, task persistence, and conduct problems in childhood: A behavioral genetic analysis. *Journal of Child Psychology and Psychiatry*. 2007; 48:80–87. [PubMed: 17244273]
- de Castro BO, Veerman JW, Koops WM, Bosch JD, Monshouwer HJ. Hostile attribution of intent and aggressive behavior: A meta-analysis. *Child Development*. 2002; 73:916–934. [PubMed: 12038560]
- Dickstein DP, Nelson EE, McClure EB, Grimley ME, Knopf L, Brotman MA, et al. Cognitive flexibility in phenotypes of pediatric bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007; 46:341–355. [PubMed: 17314720]
- Dodge KA. Social cognition and children's aggressive behavior. *Child Development*. 1980; 51:162–170. [PubMed: 7363732]
- Dodge KA, Bates JE, Pettit GS. Mechanisms in the cycle of violence. *Science*. 1990; 250:1678–1683. [PubMed: 2270481]
- Dodge KA, Coie JD. Social information processing factors in reactive and proactive aggression: Aggression in children's peer groups. *Journal of Personality and Social Psychology*. 1987; 53:1146–1158. [PubMed: 3694454]
- Dunn, J.; Brown, J. Relationships, talk about feelings, and the development of affect regulation in early childhood.. In: Garber, J.; Dodge, KA., editors. *The development of emotion regulation and dysregulation*. Cambridge University Press; New York: 1991. p. 89-108.
- Ebner-Priemer UW, Trull TJ. Ecological momentary assessment of mood disorders and mood dysregulation. *Psychological Assessment*. 2009; 21:463–475. [PubMed: 19947781]

- Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: Presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry*. 2006; 47:313–337. [PubMed: 16492262]
- Eley TC, Tahir E, Angleitner A, Harriss K, McClay J, Plomin R, et al. Association analysis of MAOA and COMT with neuroticism assessed by peers. *American Journal of Medical Genetics*. 2003; 120B:90–96. [PubMed: 12815746]
- Epps J, Kendall P. Hostile attributional bias in adults. *Cognitive Therapy and Research*. 1995; 19:159–178.
- Fite PJ, Raine A, Stouthamer-Loeber M, Loeber R, Pardini DA. Reactive and proactive aggression in adolescent males. *Criminal Justice and Behavior*. 2010; 37:141–157. [PubMed: 20589225]
- Ford BQ, Tamir M, Brunye TT, Shirer WR, Mahoney CR, Taylor HA. Keeping your eyes on the prize: Anger and visual attention to threats and rewards. *Psychological Science*. 2010; 21:1098–1105. [PubMed: 20581342]
- Frick PJ, Lahey BB, Loeber R, Tannenbaum L, van Horn Y, Christ MAG, et al. Oppositional defiant disorder and conduct disorder: A meta-analytic review of factor analyses and cross-validation in a clinic sample. *Clinical Psychology Review*. 1993; 13:319–340.
- Fullerton CA, Epstein AM, Frank RG, Normand S-LT, Fu CX, McGuire TG. Medication use and spending trends among children with ADHD in Florida's Medicaid program, 1996–2005. *Psychiatric Services*. 2012; 63:115–121. [PubMed: 22302327]
- Fulwiler CE, King JA, Zhang N. Amygdala–orbitofrontal resting-state functional connectivity is associated with trait anger. *NeuroReport*. 2012; 23:606–610. [PubMed: 22617448]
- Gagne JR, Goldsmith H. A longitudinal analysis of anger and inhibitory control in twins from 12 to 36 months of age. *Developmental Science*. 2011; 14:112–124. [PubMed: 21159093]
- Garber JG, Clarke GN, Weersing VR, Beardslee WR, Brent DA, Gladstone TRG, et al. Prevention of depression in at-risk adolescents: A randomized controlled trial. *Journal of the American Medical Association*. 2009; 301:2215–2224. [PubMed: 19491183]
- Gray JA. Brain systems that mediate both emotion and cognition. *Cognition & Emotion*. 1990; 4:269–288.
- Gross JJ. The emerging field of emotion regulation: An integrative review. *Review of General Psychology*. 1998; 2:271–299.
- Guerin DW, Gottfried AW, Thomas CW. Difficult temperament and behaviour problems: A longitudinal study from 1.5 to 12 years. *International Journal of Behavioral Development*. 1997; 21:71–90.
- Guyer AE, McClure EB, Adler AD, Brotman MA, Rich BA, Kimes AS, et al. Specificity of facial expression labeling deficits in childhood psychopathology. *Journal of Child Psychology and Psychiatry*. 2007; 48:863–871. [PubMed: 17714371]
- Hartup WW. Aggression in childhood: Developmental perspectives. *American Psychologist*. 1974; 29:336–341. [PubMed: 4847493]
- Hay, DF. The beginnings of aggression in infancy.. In: Tremblay, RE.; Hartup, WW.; Archer, J., editors. *Developmental origins of aggression*. Guilford Press; New York: 2005. p. 107-132.
- He J, Degnan KA, McDermott JM, Henderson HA, Hane AA, Xu Q, et al. Anger and approach motivation in infancy: Relations to early childhood inhibitory control and behavior problems. *Infancy*. 2010; 15:246–269. [PubMed: 25705134]
- Hirshfeld-Becker DR, Biederman J, Calltharp S, Rosenbaum ED, Faraone SV, Rosenbaum JF. Behavioral inhibition and disinhibition as hypothesized precursors to psychopathology: Implications for pediatric bipolar disorder. *Biological Psychiatry*. 2003; 53:985–999. [PubMed: 12788244]
- Hoffenaar PJ, Hoeksma JB. The structure of oppositionality: Response dispositions and situational aspects. *Journal of Child Psychology and Psychiatry*. 2002; 43:375–385. [PubMed: 11944879]
- Horsley T, de Castro B, Van der Schoot M. In the eye of the beholder: Eye-tracking assessment of social information processing in aggressive behavior. *Journal of Abnormal Child Psychology*. 2010; 38:587–599. [PubMed: 19823928]

- Hubbard JA, McAuliffe MD, Morrow MT, Romano LJ. Reactive and proactive aggression in childhood and adolescence: Precursors, outcomes, processes, experiences, and measurement. *Journal of Personality*. 2010; 78:95–118. [PubMed: 20433614]
- Hulvershorn LA, Fosselman DD, Dickstein DP, Janicak PG. Psychopharmacology of nonepisodic irritability, aggression, and mood swings in children and adolescents: Part I. Stimulants and antidepressants. *Psychopharmacology Review*. 2012a; 47:1.
- Hulvershorn LA, Fosselman DD, Dickstein DP, Janicak PG. Psychopharmacology of nonepisodic irritability, aggression, and mood swings in children and adolescents: Part II. Antipsychotics, antimanic agents, and alpha agonists. *Psychopharmacology Review*. 2012b; 47:9.
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010; 167:748–751. [PubMed: 20595427]
- Jairam R, Prabhuswamy M, Dullur P. Do we really know how to treat a child with bipolar disorder or one with severe mood dysregulation? Is there a magic bullet? *Depression Research and Treatment*. 2012; 2012:967302. [PubMed: 22203894]
- Kahneman D, Fredrickson DL, Schreiber CA, Redelmeier DA. When more pain is preferred to less: Adding a better end. *Psychological Science*. 1993; 4:401–405.
- Kang JI, Namkoong K, Kim SJ. Association of DRD4 and COMT polymorphisms with anger and forgiveness traits in healthy volunteers. *Neuroscience Letters*. 2008; 430:252–257. [PubMed: 18063308]
- Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry*. 2011; 68:444–454. [PubMed: 21199959]
- Kazdin, AE. Problem-solving skills training and parent management training for oppositional defiant disorder and conduct disorder.. In: Weisz, JR.; Kazdin, AE., editors. *Evidence-based psychotherapies for children and adolescents*. 2nd ed.. Guilford Press; New York: 2010. p. 211-226.
- Kazdin AE, Rodgers A, Colbus D, Siegel T. Children's Hostility Inventory: Measurement of aggression and hostility in psychiatric inpatient children. *Journal of Clinical Child Psychology*. 1987; 16:320–328.
- Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry*. 2003; 60:709–717. [PubMed: 12860775]
- Kimonis E, Frick P, Munoz L, Aucoin K. Can a laboratory measure of emotional processing enhance the statistical prediction of aggression and delinquency in detained adolescents with callous–unemotional traits? *Journal of Abnormal Child Psychology*. 2007; 35:773–785. [PubMed: 17510788]
- Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary rewards selectively recruits nucleus accumbens. *Journal of Neuroscience*. 2001; 21:1–5.
- Kret ME, Denollet J, Grèzes J, de Gelder B. The role of negative affectivity and social inhibition in perceiving social threat: An fMRI study. *Neuropsychologia*. 2011; 49:1187–1193. [PubMed: 21315749]
- Lahey BB, Waldman ID, McBurnett K. Annotation: The development of antisocial behavior: An integrative causal model. *Journal of Child Psychology and Psychiatry*. 1999; 40:669–682. [PubMed: 10433402]
- Lamm C, Granic I, Zelazo PD, Lewis MD. Magnitude and chronometry of neural mechanisms of emotion regulation in subtypes of aggressive children. *Brain and Cognition*. 2011; 77:159–169. [PubMed: 21940093]
- Lee V, Hoaken PNS. Cognition, emotion, and neurobiological development: Mediating the relation between maltreatment and aggression. *Child Maltreatment*. 2007; 12:281–298. [PubMed: 17631627]
- Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *American Journal of Psychiatry*. 2011; 168:129–142. [PubMed: 21123313]

- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining the clinical phenotypes of juvenile mania. *American Journal of Psychiatry*. 2003; 160:430–437. [PubMed: 12611821]
- Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. *Journal of Child and Adolescent Psychopharmacology*. 2006; 16:456–466. [PubMed: 16958570]
- Leist T, Dadds MR. Adolescents' ability to read different emotional faces relates to their history of maltreatment and type of psychopathology. *Clinical Child Psychology and Psychiatry*. 2009; 14:237–250. [PubMed: 19293321]
- Lewis M, Alessandri SM, Sullivan MW. Violation of expectancy, loss of control, and anger expressions in young infants. *Developmental Psychology*. 1990; 26:745–751.
- Lewis M, Ramsay DS, Sullivan MW. The relation of ANS and HPA activation to infant anger and sadness response to goal blockage. *Developmental Psychobiology*. 2006; 48:397–405. [PubMed: 16770761]
- Lewis MD, Granic I, Lamm C. Behavioral differences in aggressive children linked with neural mechanisms of emotion regulation. *Annals of the New York Academy of Sciences*. 2006; 1094:164–177. [PubMed: 17347349]
- Lewis MD, Granic I, Lamm C, Zelazo PD, Stieben J, Todd RM, et al. Changes in the neural bases of emotion regulation associated with clinical improvement in children with behavior problems. *Development and Psychopathology*. 2008; 20:913–939. [PubMed: 18606038]
- Lin PY, Tsai G. Association between serotonin transporter gene promoter polymorphism and suicide: Results of a meta-analysis. *Biological Psychiatry*. 2004; 55:1023–1030. [PubMed: 15121487]
- Loeber R, Burke J, Pardini DA. Perspectives on oppositional defiant disorder, conduct disorder, and psychopathic features. *Journal of Child Psychology and Psychiatry*. 2009; 50:133–142. [PubMed: 19220596]
- Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct disorder and oppositional defiant disorder in a national sample: Developmental epidemiology. *Journal of Child Psychology and Psychiatry*. 2004; 45:609–621. [PubMed: 15055379]
- McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. *New England Journal of Medicine*. 2002; 347:314–321. [PubMed: 12151468]
- Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Reviews Neuroscience*. 2001; 24:1161–1192.
- Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Ahmad RH, Pezawas L, Blasi G, et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences*. 2006; 103:6269–6274.
- Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. *Biological Psychiatry*. 2005; 58:576–582. [PubMed: 16084859]
- Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. 2001; 24:167–202.
- Miller FG, Wendler D, Swartzman LC. Deception in research on the placebo effect. *PLoS Medicine*. 2005; 2:e262. doi:10.1371/journal.pmed.0020262. [PubMed: 16173830]
- Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychological Review*. 1993; 100:674–701. [PubMed: 8255953]
- Munafò MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: A meta-analysis. *Biological Psychiatry*. 2008; 63:852–857. [PubMed: 17949693]
- Nagin D, Tremblay RE. Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. *Child Development*. 1999; 70:1181–1196. [PubMed: 10546339]
- National Institute of Mental Health Research Domain Criteria Project. Negative valence systems: Workshop proceedings.. Paper presented at the RDoC Workshops; 2011. from <http://www.nimh.nih.gov/research-funding/rdoc/negative-valence-systems-workshop.pdf>

- Nock MK, Kazdin AE, Hiripi E, Kessler RC. Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: Results from the National Comorbidity Survey Replication. *Journal of Child Psychology and Psychiatry*. 2007; 48:703–713. [PubMed: 17593151]
- Ochsner KN. The social–emotional processing stream: Five core constructs and their translational potential for schizophrenia. *Biological Psychiatry*. 2008; 64:48–61. [PubMed: 18549876]
- Öhman A. Face the beast and fear the face: Animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology*. 1986; 23:123–145. [PubMed: 3704069]
- Oliveira L, Pessoa L, Izhikevich EM, Pereira MG, Bronner B. Attention and emotion. *Scholarpedia*. 2010; 5:6314. doi:10.4249/scholarpedia.6314.
- Olweus D. Stability of aggressive reaction patterns in males: A review. *Psychological Bulletin*. 1979; 86:852–875. [PubMed: 482487]
- Panksepp J. Emotional endophenotypes in evolutionary psychiatry. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2006; 30:774–784. [PubMed: 16554114]
- Papoulos, D.; Papoulos, J. *The bipolar child: The definitive and reassuring guide to childhood's most misunderstood disorder*. Broadway Books; New York: 2007.
- Perlman SB, Pelphrey KA. Developing connections for affective regulation: Age-related changes in emotional brain connectivity. *Journal of Experimental Child Psychology*. 2011; 108:607–620. [PubMed: 20971474]
- Pickles A, Aglan A, Collishaw S, Messer J, Rutter M, Maughan B. Predictors of suicidality across the life span: The Isle of Wight study. *Psychological Medicine*. 2010; 40:1453–1466. [PubMed: 19939326]
- Pollak SD, Cicchetti D, Klorman R, Brumaghim JT. Cognitive brain event-related potentials and emotion processing in maltreated children. *Child Development*. 1997; 68:773–787.
- Pollak SD, Klorman R, Thatcher JE, Cicchetti D. P3b reflects maltreated children's reactions to facial displays of emotion. *Psychophysiology*. 2001; 38:267–274. [PubMed: 11347872]
- Pollak SD, Sinha P. Effects of early experience on children's recognition of facial displays of emotion. *Developmental Psychology*. 2002; 38:784–791. [PubMed: 12220055]
- Pollak SD, Tolley-Schell SA. Selective attention to facial emotion in physically abused children. *Journal of Abnormal Psychology*. 2003; 112:323–338. [PubMed: 12943012]
- Potegal M, Davidson RJ. Temper tantrums in young children: 1. Behavioral composition. *Journal of Developmental & Behavioral Pediatrics*. 2003; 24:140–147. [PubMed: 12806225]
- Potegal M, Kosorok MR, Davidson RJ. Temper tantrums in young children: 2. Tantrum duration and temporal organization. *Journal of Developmental and Behavioral Pediatrics*. 2003; 24:148–154. [PubMed: 12806226]
- Price JM, Dodge KA. Reactive and proactive aggression in childhood: Relations to peer status and social context dimensions. *Journal of Abnormal Child Psychology*. 1989; 17:455–471. [PubMed: 2794257]
- Reid S, Salmon K, Lovibond P. Cognitive biases in childhood anxiety, depression, and aggression: Are they pervasive or specific? *Cognitive Therapy and Research*. 2006; 30:531–549.
- Retz W, Retz-Junginger P, Supprian T, Thome J, Rösler M. Association of serotonin transporter promoter gene polymorphism with violence: Relation with personality disorders, impulsivity, and childhood ADHD psychopathology. *Behavioral Sciences & the Law*. 2004; 22:415–425. [PubMed: 15211560]
- Rich BA, Carver FW, Holroyd T, Rosen HR, Mendoza JK, Cornwell BR, et al. Different neural pathways to negative affect in youth with pediatric bipolar disorder and severe mood dysregulation. *Journal of Psychiatric Research*. 2011; 45:1283–1294. [PubMed: 21561628]
- Rich BA, Grimley ME, Schmajuk M, Blair KS, Blair RJR, Leibenluft E. Face emotion labeling deficits in children with bipolar disorder and severe mood dysregulation. *Development and Psychopathology*. 2008; 20:529–546. [PubMed: 18423093]
- Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Differential psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *American Journal of Psychiatry*. 2007; 164:309–317. [PubMed: 17267795]

- Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. *Journal of Abnormal Psychology*. 2010; 119:726–738. [PubMed: 21090876]
- Rowe R, Maughan B, Pickles A, Costello EJ, Angold A. The relationship between DSM-IV oppositional defiant disorder and conduct disorder: Findings from the Great Smoky Mountains Study. *Journal of Child Psychology and Psychiatry*. 2002; 43:365–373. [PubMed: 11944878]
- Rujescu D, Giegling I, Gietl A, Hartmann AM, Moller HJ. A functional single nucleotide polymorphism (V158M) in the COMT gene is associated with aggressive personality traits. *Biological Psychiatry*. 2003; 54:34–39. [PubMed: 12842306]
- Schippell PL, Vasey MW, Cravens-Brown LM, Bretveld RA. Suppressed attention to rejection, ridicule, and failure cues: A unique correlate of reactive but not proactive aggression in youth. *Journal of Clinical Child and Adolescent Psychology*. 2003; 32:40–55. [PubMed: 12573931]
- Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics*. 2004; 127B:85–89. [PubMed: 15108187]
- Shaw DS, Gilliom M, Ingoldsby EM, Nagin DS. Trajectories leading to school-age conduct problems. *Developmental Psychology*. 2003; 39:189–200. [PubMed: 12661881]
- Shields A, Cicchetti D. Reactive aggression among maltreated children: The contributions of attention and emotion dysregulation. *Journal of Clinical Child Psychology*. 1998; 27:381–395. [PubMed: 9866075]
- Siegrist J, Menrath I, Stocker T, Klein M, Kellerman T, Shah NJ, et al. Differential brain activation according to chronic social reward frustration. *NeuroReport*. 2005; 16:1899–1903. [PubMed: 16272875]
- Smith P, Waterman M. Processing bias for aggression words in forensic and nonforensic samples. *Cognition & Emotion*. 2003; 17:681–701.
- Snaith RP, Taylor CM. Irritability: Definition, assessment and associated factors. *British Journal of Psychiatry*. 1985; 147:127–136. [PubMed: 3840045]
- Sobanski E, Banaschewski T, Asherson P, Buitelaar J, Chen W, Franke B, et al. Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): Clinical correlates and familial prevalence. *Journal of Child Psychology and Psychiatry*. 2010; 51:915–923. [PubMed: 20132417]
- Spielberger CD, Reheiser EC, Sydeman SJ. Measuring the experience, expression, and control of anger. *Issues in Comprehensive Pediatric Nursing*. 1995; 18:207–232. [PubMed: 8707652]
- Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: Results from a large population-based sample of men and women. *Child Abuse & Neglect*. 2007; 31:517–530. [PubMed: 17532465]
- Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: A 20-year prospective community-based study. *American Journal of Psychiatry*. 2009; 166:1048–1054. [PubMed: 19570932]
- Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009a; 48:404–412. [PubMed: 19318881]
- Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *Journal of Child Psychology and Psychiatry*. 2009b; 50:216–223. [PubMed: 19166573]
- Stringaris A, Goodman R, Ferdinanso S, Razdun V, Muhrer E, Leibenluft E, et al. The Affective Reactivity Index: A concise irritability scale for clinical and research settings. *Journal of Child Psychology and Psychiatry*. 2012; 53:1109–1117. [PubMed: 22574736]
- Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *American Journal of Psychiatry*. 2012; 169:47–54. [PubMed: 22193524]
- Teisl M, Cicchetti D. Physical abuse, cognitive and emotional processes, and aggressive/disruptive behavior problems. *Social Development*. 2008; 17:1–23.
- Terracciano A, Lobina M, Piras MG, Mulas A, Cannas A, Meirelles O, et al. Neuroticism, depressive symptoms, and serum BDNF. *Psychosomatic Medicine*. 2011; 73:638–642. [PubMed: 21949427]

- Thomas LA, Brotman MA, Muhrer EM, Rosen BR, Bones BL, Reynolds RC, et al. Parametric modulation of neural activity by emotion in youth with bipolar disorder, youth with severe mood dysregulation, and healthy volunteers. *Archives of General Psychiatry*. 2012 Advance online publication. doi:10.1001/archgenpsychiatry.2012.913.
- Vaillancourt T, Miller JL, Fagbemi J, Côté S, Tremblay RE. Trajectories and predictors of indirect aggression: Results from a nationally representative longitudinal study of Canadian children aged 2–10. *Aggressive Behavior*. 2007; 33:314–326. [PubMed: 17593562]
- van Honk J, Tuiten A, de Haan E, van den Hout M, Stam H. Attentional biases for angry faces: Relationships to trait anger and anxiety. *Cognition & Emotion*. 2001; 15:279–297.
- Vitaro, F.; Brendgen, M. Proactive and reactive aggression: A developmental perspective.. In: Tremblay, RE.; Hartup, WW.; Archer, J., editors. *Developmental origins of aggression*. Guilford Press; New York: 2005. p. 178-201.
- Vitaro F, Brendgen M, Tremblay RE. Reactively and proactively aggressive children: Antecedent and subsequent characteristics. *Journal of Child Psychology and Psychiatry*. 2002; 43:495–505. [PubMed: 12030595]
- Vitiello B, Stoff DM. Subtypes of aggression and their relevance to child psychiatry. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997; 36:307–315. [PubMed: 9055510]
- Wakschlag LS, Choi SW, Carter AS, Hullsiek H, Burns J, McCarthy K, et al. Defining the developmental parameters of temper loss in early childhood: Implications for developmental psychopathology. *Journal of Child Psychology and Psychiatry*. 2012; 53:1099–1108. [PubMed: 22928674]
- Watson D, Tellegen A. Toward a consensual structure of mood. *Psychological Bulletin*. 1985; 98:219–235. [PubMed: 3901060]
- Weiner B, Graham S, Stern P, Lawson ME. Using affective cues to infer causal thoughts. *Developmental Psychology*. 1982; 18:278–286.
- Weisz JR, Jensen-Doss A, Hawley KM. Evidence-based youth psychotherapies versus usual clinical care: A meta-analysis of direct comparisons. *American Psychologist*. 2006; 61:671–689. [PubMed: 17032068]
- Wilkowski BM, Robinson MD. The cognitive basis of trait anger and reactive aggression: An integrative analysis. *Personality and Social Psychology Review*. 2008; 12:3–21. [PubMed: 18453470]
- Wilkowski BM, Robinson MD, Gordon RD, Troop-Gordon W. Tracking the evil eye: Trait anger and selective attention within ambiguously hostile scenes. *Journal of Research in Personality*. 2007; 41:650–666. [PubMed: 24920865]
- Woltering S, Granic I, Lamm C, Lewis MD. Neural changes associated with treatment outcome in children with externalizing problems. *Biological Psychiatry*. 2011; 70:873–879. [PubMed: 21741030]

Table 1

Measures of irritability

Scale	Notes
BDHI irritability subscale (Buss & Durkee, 1957)	A priori scale of irritability as part of an omnibus metric of aggression-related personality traits
Irritability Scale—Youth Version (Capara et al., 1985)	BDHI-based scale for adolescents in the general population
Irritability, Depression, and Anxiety Scale (Snaith & Taylor, 1985)	Irritability scale designed for use in adults with psychopathology, has two subscales to assess overt and covert irritability
Children's Hostility Inventory irritability subscale (Kazdin, Rodgers, Colbus, & Siegel, 1987)	BDHI-based scale for use in pediatric populations with psychopathology, especially conduct problems
Affective Reactivity Index (Stringaris et al., 2012)	Brief scale designed to focus on irritable mood in children for both clinical and research purposes, assesses mood rather than hostility or aggressive behaviors

Note: BDHI, Buss–Durkee Hostility Inventory.

Table 2

Studies of selective attention in trait anger and reactive aggression

Attentional Phenomenon	Task	Reference	Participants	Findings
Bias to the location of an emotional stimulus	Dot probe	Schippell et al., 2003	90 typical youths, ages 11–16 years	Reactive aggression related to bias away from words signifying social threat, for example, rejection or ridicule
		Smith & Waterman, 2003	50 incarcerated adolescents and 30 undergrads	Trait anxiety and anger associated with bias toward aggressive words, regardless of study group
		Reid et al., 2006	133 typical youths, ages 8–14 years	Specific bias toward threatening words related to high RCMAS anxiety, but not CBCL aggression or CDI depressive symptoms
		Kimonis et al., 2007	68 incarcerated male adolescents	Reactive aggression associated with a bias toward positive but not distressing IAPS pictures
Interference by distracting emotional stimuli	Visual search	Cohen et al., 1998	130 undergrads	During insult but not at baseline, trait anger associated with slower search times when distractors are anger-related words versus positive or neutral words
	Emotional Stroop	van Honk et al., 2001	42 undergrads, selected for high/low trait anger	Trait anger associated with a latency naming a color film over angry versus neutral Ekman faces
		Smith & Waterman, 2003	50 incarcerated youths and 30 undergrads	Trait anger across groups associated with a latency for naming the color ink of aggressive words

Note: RCMAS, Revised Children's Manifest Anxiety Scale; CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; IAPS, International Affective Picture System.