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Review

Pediatric Irritability: A Systems Neuroscience Approach

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Irritability, defined as an increased propensity to exhibit increased anger relative to one's peers, is a common clinical problem in youth. Irritability can be conceptualized as aberrant responses to frustration (where frustration is the emotional response to blocked goal attainment) and/or aberrant 'approach' responses to threat. Irritable youth show hyper-reactivity to threat mediated by dysfunction in amygdala, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), insula, striatum, and association cortex. Irritable youth also show abnormalities in reward learning, cognitive control, and responses to frustration. These abnormalities are mediated by circuitry that includes the inferior frontal gyrus (iFG), striatum, ACC, and parietal cortex. Effective treatments for irritability are lacking, but pathophysiological research could lead to more precisely targeted interventions.

Irritability in Children

Irritability (see Glossary) can be defined as an increased propensity to exhibit anger relative to one's peers. Recently, this clinical problem has become the focus of considerable research interest in child psychiatry and clinical neuroscience [1]. This interest stems from recognition the irritability's clinical importance of irritability, given that it is one of the most common reasons children present for mental healthcare [2]. Reflecting this, irritability is the primary feature of a new diagnosis in ***DSM-5***, **Disruptive Mood Dysregulation Disorder** (DMDD) [3]. Moreover, irritability is prominent in other childhood psychiatric illnesses, including oppositional defiant disorder, **anxiety disorders**, **attention deficit hyperactivity disorder** (ADHD), post-traumatic stress disorder, conduct disorder, major depressive disorder, bipolar disorder (BD), and autism spectrum disorders.

Youth with DMDD suffer significant impairment and often require multiple clinical interventions (e.g., medication, school placement, and individual and family psychotherapies) to function adequately at home and school [4,5]. However, the efficacy of commonly used treatments for irritability is limited or, in some instances, unknown. Most such treatments are not designed to target irritability specifically and none are based on an understanding of the relevant neurobiology (for a promising avenue that could be an exception, see [6]). Recent work has yielded much information about the presentation, course, and impact of irritability in youth (Box 1). The next challenge is clear: to elucidate the neural mechanisms of irritability in order to guide the development of novel interventions. Pathophysiological studies targeting irritability specifically remain rare, but there is a considerable foundation of work on related phenotypes, such as **reactive aggression** (Box 2). Within the realm of psychopathology, irritability is a relatively tractable research target because it is an evoked response and, hence, can be modeled in animals and studied in real time during neuroimaging. Since research on the neural mechanisms of irritability is relatively nascent and rapidly evolving, it is important for investigators to specify neuroscientific conceptualizations to guide research, highlight areas where emerging data warrant follow-up, and discuss approaches to developing promising research paradigms.

Trends

Irritability in youth is a common clinical problem that may result from aberrant responses to frustration and/or aberrant approach responses to threat.

Irritability and anxiety are associated cross-sectionally, longitudinally, and genetically. These associations suggest that disequilibrium in threat response circuitry is important in the pathophysiology of irritability.

Studies using simple or complex social stimuli find hyper-reactivity to threat in irritable youth, mediated by dysfunction in the amygdala, mPFC, ACC, insula, striatum, and association cortex.

Studies find reward-learning abnormalities in irritable youth, as well as cognitive control deficits and exaggerated responses during paradigms modeling frustration. Such abnormalities are associated with dysfunction in regions mediating reward learning (e.g., iFG, striatum, and ventromedial PFC) and cognitive control and attention (e.g., ACC and parietal cortex).

Pathophysiological studies of irritability are enabling the development of mechanism-based, well-targeted, effective interventions.

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Box 1. Clinical Presentation, Longitudinal Course, and Genetic Epidemiology

In *DSM-5*, the diagnostic criteria for DMDD require both tonic and phasic irritability. **Phasic irritability**, which is usually the most salient clinical feature, can be operationalized as temper outbursts that are developmentally inappropriate in frequency and severity and that usually occur in response to frustration. Most outbursts are verbal but most irritable children also have some outbursts that involve mild physical involvement or even physical aggression. In addition to outbursts, DMDD requires **tonic irritability** (i.e., between-outburst mood that is angry most days, most of the time). Arguably, the research described in this review is most germane to phasic irritability, which can be evoked using frustration paradigms and whose time course and phenomenology is more akin to the evoked responses of fMRI paradigms than is tonic irritability. Since tonic irritability is a long-lasting mood (rather than a brief emotion linked to a stimulus), it is more challenging to model in the scanner. Importantly, the extent to which phasic and tonic irritability are distinct phenomena in terms of clinical presentation, longitudinal course, or treatment response remains unclear [81,82], and studies have not yet undertaken the complex task of attempting to dissociate their pathophysiology.

In healthy youth, the frequency of temper outbursts peaks during the preschool years and then gradually declines, in tandem with PFC development [81,83]. While temper loss is common in preschoolers, normative and non-normative tantrums can be distinguished using a parent-completed developmentally sensitive questionnaire [84]. Furthermore, non-normative temper loss predicts the onset of mood and behavioral symptoms and disorders 16 months later [85]. In infants, it is possible to identify individual differences in responses to frustration; maternal, rather than lab-based, measures of infant irritability, are better predictors of irritability in toddlerhood [86,87]. A new wave of lab-based and observational studies in infants using novel techniques may have more predictive power. Finally, normal adolescence is typically associated with a small upsurge in both tonic and phasic anger proneness [81,88].

Irritable youth (i.e., those with increased tonic and phasic anger, relative to their peers) are at elevated risk of developing anxiety, unipolar depressive disorders, and/or suicidality during adolescence and early adulthood, and to have decreased educational and income attainment [89]. Twin studies suggest that the heritability of irritability is approximately 0.4–0.6 [90–92]. Longitudinal associations between irritability and depression and/or anxiety are partially genetically mediated, and the proportion of the variance in irritability accounted for by genetic factors differs with gender and age [90–92]. Environmental factors also have a significant role in the etiology of irritability, as evidenced by the efficacy of parenting interventions in decreasing child irritability, especially in young children [93].

These are the goals of this review, with an emphasis on studies that include clinically impaired youth.

The Neuroscience of Irritability

Translational models of irritability focus on two closely related but separable processes: dysfunctional **threat** and **reward** processing [1] (Figure 1, Key Figure). Thus, one hypothesis suggests that irritability reflects dysfunction in the amygdala-hypothalamic-periaqueductal gray (PAG) threat response circuitry, such that approach responses occur in contexts where the normative response would be freezing or flight [7]. Thus, the common co-occurrence of anxiety and irritability, as well as the genetic and longitudinal links between them (Boxes 1 and 2), may represent vacillation between abnormal avoid and approach responses to threat, reflecting disequilibrium in the mediating circuitry that is, in part, genetically mediated. As discussed below, data in irritable youth and related phenotypes demonstrate abnormalities in threat processing specifically, and in social information processing more broadly. Also as discussed below, this theory has been probed using threat stimuli that are relatively simple, such as angry faces, or that involve more complex social interaction paradigms.

The second hypothesis suggests associations between irritability and abnormal reward processing, specifically in the form of aberrant responses to **frustrative nonreward** (FNR). In a landmark study, Amsel defined FNR as the psychological state induced by the failure to receive a reward that a rodent has been conditioned to expect. Amsel showed that FNR is associated with increased motor activity and aggression [8]. Research has documented FNR responses in nonhuman primates and humans [9–11] (Figure 1). This work is also clinically relevant, since temper outbursts in irritable children often occur in response to **frustration**. Taken together, these basic and clinical data suggest that pathological temper outbursts in children reflect FNR responses that are abnormal in their intensity, duration, and/or the strength of the provocation

Glossary

Anxiety disorders: a group of related psychiatric diagnoses characterized by an abnormally heightened tendency to avoid threatening stimuli, and by impairment related to this tendency.
Attention deficit hyperactivity disorder (ADHD): *DSM-5* diagnosis characterized by persistent inattention and/or impulsivity-hyperactivity that interferes with function or development.
Cognitive control: psychological processes that facilitate flexible behavior and attention deployment in response to changing goals and environmental circumstances.
Disruptive mood dysregulation disorder (DMDD): childhood diagnosis, new in *DSM-5*, characterized by severe, impairing, chronic irritability (both phasic and tonic).
***Diagnostic and Statistical Manual Fifth Edition* (*DSM-5*)[3]:** the compilation of standardized criteria for psychiatric diagnoses in the USA, published by the American Psychiatric Association.
Ecological validity: the degree to which research findings are likely to generalize to real-world situations.
Explicit face emotion processing paradigm: cognitive task in which the subject is asked to label the emotion on a face.
Frustration: emotional response to blocked goal attainment.
Frustrative non-reward (FNR)[8]: as per Amsel (see main text), the psychological state induced by the failure to receive a reward that an organism has been conditioned to expect.
Hostile interpretation bias: the tendency to interpret ambiguous social stimuli as hostile. The stimuli can be either simple (e.g., faces) or complex (e.g., vignettes, or behavior; in this case the commonly used term is 'hostile attribution bias').
Implicit face emotion-processing paradigm: cognitive task in which the subject is asked to attend to a facial feature other than the emotional display (e.g., gender of the face).
Irritability: an increased propensity to experience anger, relative to one's peers.
Oppositional defiant disorder (ODD): childhood diagnosis in *DSM-5* characterized by impairment due