Commentary

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Many Roads to Irritability: How Developmental Change and Multiple Risk Pathways Can Impact Negative Findings in Resting-State Connectivity

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Irritability, operationalized as both a chronic disposition to negative emotions as well as outbursts of anger, is one of the most common disabling psychiatric symptoms in childhood (1,2). Parallels have been drawn between irritability and fevers because both are common presenting complaints during childhood; can be due to multiple, disparate causes; and can be markers of illness severity. Just as fevers can be linked to multiple types of infections, autoimmune disorders, and cancers (3), irritability has been linked to autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, depression, and bipolar disorder and is one of the primary symptoms of oppositional defiant disorder and disruptive mood dysregulation disorder (2). While there is evidence that a combination of peripheral and central inflammatory markers interact with the neurons in the ventromedial preoptic nucleus of the hypothalamus to form a fever (4), the interactive neural mechanisms behind irritability are still unclear. DeSerisy *et al.* (1) have attempted to elucidate those brain mechanisms in their registered report just published in *Biological Psychiatry: Global Open Science*, which assessed the resting-state functional connectivity (RSFC) correlates of irritability across childhood and adolescence in a large study population.

Irritability has previously been linked to increased response to reward and decreased response to frustration in reward-related brain regions (5), although as the authors (1) described well, these findings can be difficult to parse due to age differences and small sample sizes. This aberrant reward and frustration processing may underly both a chronic predisposition to negativity as well as a potential for frustrative outbursts when not receiving an anticipated or hoped for reward. In addition, other behavioral and functional neuroimaging studies have indicated that children with higher irritability also have increased response to threat (1,5). Again, this may predispose children to chronic negativity if they are in a physiologically elevated and on-guard state and also predispose children to outbursts of reactive aggression. Moreover, irritability can be seen as one expression of disturbed emotion regulation, and as such, irritability has also been tied to difficulties with cognitive control (6).

Previous research has typically utilized functional neuroimaging or behavioral measures, focusing on reward/frustration, threat, or cognitive control separately, without assessing interactive effects between neural systems. Now, DeSerisy *et al.* (1) have used a large-scale dataset to better understand the interrelated effects of these systems using RSFC, which corresponds to how often neural systems are coactivated together. The authors conducted this project via a registered report, which is particularly commendable, with well-supported hypotheses. Specifically, DeSerisy *et al.* (1) hypothesized that higher irritability in children ages 5 to 17 years would correspond to lower RSFC values between cognitive control and reward-processing regions as well as lower RSFC between cognitive control and threat-processing regions. Stated otherwise, the authors postulated that children with irritability would have less top-down regulation of bottom-up emotion-processing regions in both reward and threat pathways. The authors also hypothesized that this association would be stronger in children lower in behavioral inhibitory control, given that these are the children most likely to exhibit poorer self-regulation skills.

Interestingly, despite using a large, heterogeneous sample enriched for developmental psychopathology and rigorous and strong methodology, DeSerisy *et al.* (1) found no relationship between irritability and RSFC between cognitive control and either threat or reward processing. These negative findings were robust to the inclusion of multiple covariates and to multiple sensitivity analyses. However, there were positive findings when the group was age stratified, as 5- to 9-year-old children showed a significant negative association between irritability and cognitive control and threat-processing RSFC, which secondary analyses showed to be specific to boys. Boys (ages 5 to 9 years) also showed an association between irritability and cognitive control and reward-processing RSFC, although this relationship was not present in any other age- or sex-stratified group. Together, these findings indicate a possible deficit in top-down regulation over threat and possibly in reward processing, deficits associated with increased irritability in younger children, particularly in boys. These findings emphasize that the age-discrepant results in the existing literature may be due to true developmental changes in the underlying causes of irritability. Thus, clinicians should be attuned to developmental changes in irritability, and researchers should strongly consider age or developmental stage when studying mechanisms of and treatments for irritability.

Perhaps even more intriguing, however, DeSerisy *et al.* (1) found that inhibitory control, which can be thought of as a proxy for both self-regulation and the ability to inhibit angry outbursts, was not negatively associated with irritability as hypothesized, but instead inhibitory control and irritability demonstrated a positive association in 5- to 14-year-old children. This association is particularly interesting given the very disparate diagnoses associated with irritability, which range from those typically thought of as having deficits related to inhibitory control such as ADHD to those that are characterized by heightened

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inhibitory control (but less cognitive flexibility), such as anxiety (2,7). Although many psychiatric diagnoses are characterized by poor inhibitory control, high inhibitory control has consistently been demonstrated to be a risk factor for child anxiety (7,8). In the current study, both ADHD and anxiety symptoms were positively associated with irritability, demonstrating that both forms of aberrant inhibitory control could be related to increased irritability. However, the significant positive association between inhibitory control and irritability was only present when anxiety symptoms in the same model were also positively associated with irritability. For example, in boys, inhibitory control and irritability were positively associated, as were anxiety symptoms and irritability, while in girls, neither were significant. Similarly, while in both the 5- to 9-year-old and 10- to 13-year-old children, there was a positive association of both inhibitory control and anxiety with irritability, in 14- to 17-year-old participants, neither were significant. Findings hint at two quite different mechanisms being at play that may vary by sex and have different neural correlates, but both result in irritability.

Given the need to move toward understanding what types of neural mechanisms may underlie clinically important behaviors such as irritability, we suggest that it is essential to carefully assess where there may be multiple mechanisms operating differently but producing the same measurable behavior, potentially clouding our ability to find neural correlates even in big datasets. The findings here suggest that anxiety and ADHD symptoms may be differentially related to irritability based on their relationship with inhibitory control. From another vantage point, findings parallel the constructs of overcontrol [as DeSerisy *et al.* (1) allude to in the discussion] and undercontrol. Overcontrol, a phenotype characterized by inflexibility, risk aversion, and detail-focused processing, especially for errors, can be associated with higher inhibitory control and has often been associated (although not synonymous) with childhood anxiety disorders (9). In contrast, undercontrol is a phenotype characterized by impulsivity, emotional dysregulation, and global processing as well as less inhibitory control and is often associated (although not synonymous) with ADHD. To be clear, while less common, an individual can have an anxiety disorder and be undercontrolled or have a diagnosis of ADHD and be overcontrolled, although in our clinical experience, the latter tends to be quite high in irritability (9). In the context of the current study, an overcontrolled child with anxiety may demonstrate heightened threat responding when learning multiplication tables and attempt to use elevated inhibitory control to perfect their skills, which could result in increased irritability when they cannot get a problem right (frustrative reward). Conversely, an undercontrolled child with ADHD may skip problems on their multiplication homework to play video games, and when they receive a poor grade (frustrative reward), they may exhibit poor inhibitory control resulting in increased irritability. As this example illustrates, the constellation of characteristics together is what confers risk, providing an important framework for future research. Specifically, taking a person-centered approach may provide insight into how mechanisms may hang together to predict psychiatric symptoms. The authors have taken a step toward assessing the interactive mechanisms of threat, reward, and inhibitory control in relation to irritability. Findings provide a future direction focusing on how various combinations of these mechanisms are related to irritability or other psychiatric presentations.

In sum, while DeSerisy *et al.*'s (1) methodologically strong registered report showed only limited, age- and sex-specific interactions between cognitive control and reward- and threat-processing region connectivity and irritability and demonstrated results opposite of hypothesized patterns of inhibitory control, it still provides important information for clinicians and researchers who are working to understand a broad, transdiagnostic construct such as irritability or the "fever" of childhood psychopathology. Taking a step back, seeing age- and sex-limited effects emphasizes the importance of considering developmental context. Seeing the opposite of the hypothesized finding of higher inhibitory control being associated with higher irritability may demonstrate how multiple pathways of risk from the same aberrant mechanism can lead to a presentation of irritability. Thus, similar to a fever, examining the constellation of risk factors and related psychiatric presentations that interact and contribute to elevated irritability may continue to provide further understanding of how neural connectivity patterns result in this impairing childhood psychiatric presentation.

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Article Information

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