

Irritability moderates amygdala-prefrontal connectivity while attending to angry faces: A computational modeling approach

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KEY POINTS

Question: What is the neural circuitry mediating attention orienting to angry faces in youth with irritability?

Findings: During attention orienting to angry faces, amygdala connectivity with the bilateral inferior frontal gyrus, insula, caudate, and thalamus/pulvinar was differentiated by irritability level and attention bias. While elevated attention bias was associated with weaker amygdala connectivity to those regions in youth with high irritability, in youth with low irritability it was associated with stronger amygdala connectivity.

Meaning: Enhanced neural regulation may be adaptive during disengagement from anger-related cues and serve as a protective factor against irritability in the context of aberrant attentional processing.

ABSTRACT

Importance: Irritability, defined as proneness to anger, is among the most common reasons youth are brought in for psychiatric care. Youth with irritability demonstrate aberrant processing of anger-related stimuli; however, the neural mechanisms remain unknown. Neurobiological studies are needed to improve therapeutics for youth with irritability.

Objectives: Using computational tools to probe neural circuitry, we applied a drift-diffusion model (DDM) to derive a latent behavioral metric of attentional bias to angry faces in youth with varying levels of irritability during functional magnetic resonance imaging (fMRI).

Design, setting, and participants: We examined associations among irritability, task behavior using a DDM-based index for preferential allocation of attention to angry faces (i.e., extra-decisional time bias; Δt_0), and amygdala connectivity during attention orienting task. Our transdiagnostic sample was enriched for irritability and included 351 youth (ages 8 to 18; $M=12.92$ years, 51% male) with primary diagnosis of either attention deficit/hyperactivity disorder [ADHD], disruptive mood dysregulation disorder [DMDD], anxiety disorders, or healthy controls). Models accounted for age, sex, in-scanner motion, and co-occurring symptoms of anxiety.

Main outcomes measures: Youth and parents rated youth's irritability using the Affective Reactivity Index. A functional magnetic resonance imaging dot-probe task was used to assess attention orienting to angry faces.

Results: During attention orienting to angry faces, amygdala connectivity with the bilateral inferior frontal gyrus (IFG), insula, caudate, and thalamus/pulvinar was differentiated by

irritability level and behavioral attention bias, Δt_0 . Connectivity was weaker in youth with high irritability who also demonstrated greater attention bias to angry faces, Δt_0 , all $t_{S350} > 4.46$, $p < .001$. In contrast, in youth with low irritability, elevated Δt_0 was associated with stronger connectivity in those regions. No main effects were found for irritability.

Conclusions and relevance: While in youth with low irritability, anger-related attention bias was associated with stronger amygdala-frontal connectivity, youth with both high irritability and attention bias exhibited decreased top-down regulation of the amygdala during attentional orienting to angry faces. As irritability is associated with reactive aggression, these results suggest improving top-down regulation of the amygdala during attentional processing of anger-related stimuli may decrease clinical manifestations of anger and aggression in irritable youth.

Trial registration: ClinicalTrials.gov identifier: NCT00025935 NCT00018057