Registered Report

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Neural Correlates of Irritability and Potential Moderating Effects of Inhibitory Control

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ABSTRACT

BACKGROUND: Irritability affects up to 20% of youth and is a primary reason for referral to pediatric mental health clinics. Irritability is thought to be associated with disruptions in processing of reward, threat, and cognitive control; however, empirical study of these associations at both the behavioral and neural level have yielded equivocal findings that may be driven by small sample sizes and differences in study design. Associations between irritability and brain connectivity between cognitive control and reward- or threat-processing circuits remain understudied. Furthermore, better inhibitory control has been linked to lower irritability and differential neural functioning among irritable youth, suggesting that good inhibitory control may serve as a protective factor.

METHODS: We hypothesized that higher irritability scores would be associated with less positive (or negative) connectivity between cognitive control and threat-processing circuits and between cognitive control and reward-processing circuits in the Healthy Brain Network dataset (release 10.0; N = 4135). We also hypothesized that these associations would be moderated by inhibitory control such that weaker associations between irritability and connectivity would be detected in youths with better than with worse inhibitory control. Regression models were used to test whether associations between irritability and between-network connectivity were moderated by inhibitory control.

RESULTS: Counter to our hypothesis, we detected higher irritability associated with reduced connectivity between threat- and reward-processing and cognitive control networks only in 5- to 9-year-old boys. Inhibitory control did not moderate associations of irritability with between-network connectivity.

CONCLUSIONS: Exploratory findings indicate that reduced between-network connectivity may underlie difficulty regulating negative emotions, leading to greater irritability.

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Persistent childhood irritability is characterized by proneness to anger and poor self-regulation in the face of negative emotions and manifests as chronically negative mood and/or a tendency toward anger and temper outbursts (1–3). Affecting as many as 20% of youth (4,5), irritability is a common reason for referral among children and families seeking mental health treatment (6,7) and may also be a marker of future risk, particularly for anxiety and depressive disorders (8). Irritability may also signal severity of risk; for example, compared with children referred for treatment who do not have irritability, children with irritability have higher rates of comorbid disorders (e.g., anxiety, depression, disruptive behavior), more psychosocial impairment, more frequent psychiatric inpatient hospitalizations, and greater deficits in behavioral and emotional control (9). Critically, even in nonclinical samples, youth with higher irritability are more likely to have increased functional impairment (4), which points to the importance of understanding the etiology of persistent irritability. In particular, understanding the behavioral and neural correlates of irritability may have a notable impact on the current public health crisis in youth mental health (10) by providing novel targets for intervention.

Altered reward processing is one proposed affective mechanism underlying irritability that can be studied using frustrative nonreward or unsolvable task paradigms [e.g., (11,12)]. Supporting this, some case-control studies have shown that, relative to typically developing (TD) peers, in response to frustration, youths (8–17 years old) with higher irritability reported higher negative emotion and arousal (13–15), and younger youths (5–12 years old) demonstrated stronger physiological reactivity (16,17). However, one study did not report differences in emotional response to frustration between irritable youths and their TD peers (6–9 years old) (18). Meta-analytic evidence also has not found associations between physiological reactivity and emotional dysregulation, a behavioral construct similar to irritability (19). During frustration-inducing tasks, irritable adolescents (10–15 years old) (13,14) performed slower than their TD peers (e.g., reaction

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time during loss trials), but such differences were not reported in a younger sample of children (6–9 years old) (18). These equivocal reports suggest that more research is needed to understand the role of altered reward processing in irritability.

The neural correlates of reward processing in irritable youth have also been studied, although these studies have also yielded equivocal findings. Findings from task functional magnetic resonance imaging (fMRI) studies suggest increased reward-related activation in reward-circuitry regions. Relative to TD children, irritable children (6–9 years old) demonstrated increased reward-related activation in the anterior cingulate and middle frontal gyrus; however, studies of older youths (8–20 years old) did not detect differences in reward-related activity in other reward-related regions, including the striatum and amygdala (12,20). Some studies have also pointed to decreased frustration-related activation in reward-circuitry regions. For example, relative to TD peers, irritable children (6–9 years old) demonstrated decreased frustration-related activation in the anterior cingulate and middle frontal gyrus (18), and irritable adolescents (8–17 years old) showed decreased frustration-related activation in bilateral striatum and the left amygdala (12). However, another study reported that irritable youths (9–20 years old) showed positive striatal frustration-related activation (20). In sum, irritability appears to be associated with increased reward-related activity and decreased frustration-related activity in reward circuit regions.

Resting-state and psychophysiological studies of connectivity during reward anticipation and performance feedback also suggest that altered reward circuit function is associated with irritability. Specifically, relative to less irritable youths, those with more irritability (9–20 years old) showed negative, as opposed to positive, connectivity between the right amygdala and left superior frontal gyrus during performance feedback (20). Furthermore, during rewarded correct trials, more irritable youths (6–20 years old) demonstrated positive, as opposed to negative, reward-related connectivity between the left amygdala and right middle frontal gyrus, as well as between the bilateral amygdala and superior frontal gyrus (20,21). They also showed negative, as opposed to positive, connectivity between these regions during miss trials (20,21). The opposite pattern was observed across studies during frustration (no reward) blocks: more irritable youths showed negative as opposed to positive connectivity in these regions during hit trials and positive as opposed to negative connectivity during miss trials (21). In sum, studies suggest that irritable youth show negative (vs. positive) connectivity between affective and control regions during frustration trials and positive (vs. negative) connectivity during reward trials, although this pattern of connectivity may be trial dependent (i.e., hit vs. miss). Such evidence suggests that, compared with TD youth, irritable youth may demonstrate differences in the neural function that underlies aberrant reward processing, particularly under emotionally salient conditions; however, research that has examined these processes has leveraged relatively small samples of youth across a wide range of development, using multiple tasks, and leveraging clinical and nonclinical samples. Examining larger samples of youth with a consistent neuroimaging approach that is not reliant on a specific task will clarify the neural correlates of irritability in reward-processing networks.

It has also been proposed that aberrant threat response, referred to as reactive aggression (3), underlies irritability. In irritable youth, threat processing has typically been studied using face-emotion paradigms, operationalizing reactivity to social threat. Compared with TD peers, youths with clinically significant irritability (8–17 years old) reported greater fear of neutral faces (22) as well as a bias toward angry faces (23,24) but not toward or away from happy faces (23). Similar bias in orienting toward threat was observed in irritable youths (6–14 years old) in a large (N = 1872) community-based sample (25). Such biases may be related to face-emotion labeling difficulties, which have been documented in youths with severe irritability (7–18 years old) using both dynamic (26) and static (27,28) face tasks. Notably, however, other studies have not reported difficulties with face-emotion labeling in irritable youths (8–18 years old) using dynamic morphs or masked facial expressions (29–31), again indicating potential task-related differences in performance. These reports provide preliminary support for the hypothesis that threat processing is disrupted in irritability; however, more research is needed to clarify variability across studies and developmental periods.

Threat processing in the brain has primarily been localized in limbic regions, including the amygdala (32), and differential activation and functional connectivity of the amygdala have been implicated in irritability. For example, some studies of irritable youths (8–18 years old) have found abnormalities in amygdala activation during face-emotion processing tasks compared with TD youths, with 2 studies reporting reduced activation in the left amygdala in response to neutral (22) and angry (29) faces and 2 other studies reporting elevated activation in right amygdala in response to fearful faces (33) or in the left amygdala in response to angry faces (24). However, other work has not reported differences in amygdala activation between TD and irritable youths (8–18 years old) in response to viewing emotional faces (24,30,31,34). Instead, these studies reported differences in activation in other regions including the thalamus, cingulate gyrus, middle occipital gyrus, and superior temporal gyrus, although the direction and strength of these associations have been inconsistent across studies (24,30,31,34). In sum, preliminary evidence suggests that irritable youth demonstrate differences in threat processing that may be maintained by differences in connectivity or activation in threat networks. Again, differences between tasks, small samples, and wide age ranges within samples make cross-study comparison challenging. Examining these processes in a large sample of youth across the irritability spectrum with a single neuroimaging modality will improve understanding of the neural correlates of threat-processing dysfunction among irritable youth.

In addition to altered affective processing, irritability may be related to individual differences in executive functions broadly and cognitive control specifically. Cognitive control allows youth to select behavioral responses that are consistent with goal-directed actions in “hot” (i.e., emotionally laden) and “cold” (i.e., nonemotional) contexts (35). In hot contexts, e.g., contexts that involve reward and threat (3,36), irritable youth are theorized to struggle with cognitive control, for example choosing to complete homework before starting a video game. Specifically, irritable adolescents (10–15 years

old) (13,14) performed more slowly on loss trials during frustration-inducing tasks, but these results have not been consistent across development (6–9 years old) (18). Similarly, irritable youth have demonstrated slower, less accurate performance on cold cognition tasks: slower stop signal response latency (10–13 years old) (37), less accurate and slower performance on change trials of a cognitive flexibility task (10–14 years old) (38), longer time to complete a Go/NoGo task (3–5 years old) (39), and poorer accuracy on cued-attention tasks (10–15 years old) (13). Notably, however, these findings have not been reported in other work (12,14,20,40,41). Taken together, this evidence indicates that cognitive control may contribute to deficits in emotion regulation among irritable youth; however, equivocal findings require clarification, particularly related to the contexts and conditions in which irritable youth struggle.

The neural circuits that support cognitive control circuitry, i.e., the dual-control network (frontoparietal and cingulo-opercular circuits) (42,43), act in a top-down regulatory capacity to downregulate, or suppress, affective circuitry in TD youth (43–45) and so facilitate appropriate emotion regulation and use of adaptive coping techniques (46). In typical development, frontoparietal circuitry initiates and adjusts control (e.g., suppressing affective circuitry to shift attention away from emotionally salient stimuli), and cingulo-opercular circuitry maintains control (e.g., preventing affective circuitry from overriding control in the face of emotionally salient stimuli) (42,43). However, there is limited evidence examining network-based associations between cognitive control networks and affective circuitry in irritable youth. Using a whole-brain network approach in 8- to 22-year-old youths, one study reported distinct patterns of connectivity within and between frontoparietal, sensorimotor, salience, and subcortical networks associated with irritability during induced frustration (47). Such work provides preliminary evidence that connectivity between frontoparietal, cingulo-opercular, reward, and threat-processing networks may be disrupted in irritable youth.

Inhibitory control, or a person's ability to inhibit automatic responses in favor of task-specific goal-directed ones, may moderate network integration between cognitive control and affective circuits in irritable youth. Inhibitory control (measured outside the scanner) moderated the neural mechanisms of irritability during reward processing (performed inside the scanner) in youths (9–19 years old). During reward anticipation, among youths with high irritability, those with lower inhibitory control demonstrated greater connectivity between the ventral striatum and bilateral cuneus than those with higher inhibitory control (48). During performance feedback, youths with high irritability and lower inhibitory control demonstrated greater connectivity between the right ventral striatum and right middle frontal gyrus during hit conditions and reduced connectivity between these regions during miss conditions; the opposite pattern was observed among youths with high irritability and higher inhibitory control (48). Furthermore, youths with high irritability and lower inhibitory control demonstrated greater left amygdala connectivity with the right inferior temporal gyrus whereas youths with high irritability and higher inhibitory control demonstrated less connectivity between these regions during performance feedback, regardless of condition (48). Together, these findings suggest that better inhibitory control may buffer the effects of aberrant neural processing of reward, resulting in less irritability. However, larger studies should examine whether inhibitory control moderates associations between circuits that govern cognitive control and reward processing as well as threat processing, which to our knowledge has not yet been examined. If inhibitory control is a moderator of irritability, then targeting inhibitory control or cognitive control circuitry in treatment has the potential to improve outcomes among irritable youth.

In sum, many previous studies of irritable youth have been characterized by small sample sizes, wide age ranges covering many developmental periods, and variability in clinical and nonclinical definitions of irritability and have used a wide array of behavioral and neural tasks to tap reward, threat, and cognitive control processes. In the current study, we aimed to address gaps in the literature in a registered report examining resting-state network connectivity in the Healthy Brain Network (HBN) dataset, a large, publicly available sample of youths ages 5 to 21 years with a wide range of irritability severity. Registered reports offer an important opportunity to avoid publication biases, p-hacking, and hypothesizing after results are known or harking (49–52), which are practices that contribute to a lack of replicability in many fields (53). We used resting-state fMRI data to investigate how connectivity between the neural circuits that underlie cognitive control, reward, and threat processes may underpin irritability and how inhibitory control may moderate these associations. Resting-state fMRI provides important information about underlying circuit function in relation to stable psychological constructs (54,55), such as irritability. Additionally, relative to task fMRI, resting-state fMRI can be more directly compared and replicated across studies because it is not specific to varying task design features, which may help resolve equivocal findings that derive from different tasks in previous studies (56). Resting-state fMRI can also reduce participant burden from difficult task demands and allow for inclusion of youth with psychiatric symptoms associated with irritability who may be unable to complete fMRI tasks (57,58).

Herein, we examined associations of irritability with between-network connectivity (cognitive control–reward processing, cognitive control–threat processing) measured using resting-state fMRI and whether these associations are moderated by behavioral performance on an inhibitory control task. Given previous findings that cognitive behavioral therapy increased connectivity between amygdala and cognitive control networks (59), we hypothesized that higher irritability scores would be associated with less positive (or negative) connectivity between cognitive control and threat-processing networks and between cognitive control and reward-processing networks (Figure S1 and Supplemental Introduction). We also hypothesized stronger (vs. weaker) associations between irritability symptoms and between-network connectivity in youths with worse (vs. better) inhibitory control. Finally, given that irritability in TD youth decreases from early childhood until age 10 followed by increases until age 13 before declining across late adolescence (4,60–62), we tested these hypotheses in samples stratified by age and by using age as a continuous variable.

METHODS AND MATERIALS

Participants

Data were analyzed from the HBN (release 10.0; April 13, 2022), an ongoing initiative in the New York City area that aims to examine heterogeneity and impairment in developmental psychopathology (63). Details regarding participant recruitment, consent procedures, and exclusion criteria can be found in Supplemental Methods.

MRI Acquisition

Data release 10.0 contains available brain imaging data from 3451 participants. MRI acquisition occurred at 4 different locations. Scan parameters at the individual sites can be found in Supplemental Methods. Acquisition protocols and parameters can be found in previous reports (63) and at https://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network. Two resting-state scans lasting 5 minutes each were acquired; participants viewed a fixation cross located at the center of the computer screen. Resting-state scans were supplemented by general connectivity resting-state acquisitions, i.e., passive movie viewing, to increase scan length and usability (64) because irritable youth are a population known to be particularly sensitive to motion artifact and data loss. Sensitivity analyses were used to examine the proposed model in the subsample of youths with complete resting-state data only.

Behavioral Assessment

Data release 10.0 contains questionnaire and behavioral data from 4135 participants. Demographic information, psychiatric symptoms, and diagnoses were obtained through parent-report questionnaire and interview (Supplemental Methods).

Parent- and self-reported irritability were assessed using the Affective Reactivity Index (ARI) (6,65). The ARI is a 7-item assessment of irritability symptoms and functional impairment. Functional impairment does not contribute to children's total ARI scores. The ARI is a well-validated instrument for assessing irritability in children and adults ages 5 to 58 (65,66) in numerous settings and across reporters [e.g., parent/caregivers (6,65), self (6,65), teacher (67), clinician (68)]. Caregivers completed the ARI parent-report form, and youths completed the ARI child form. The total score (range 0–6) was used as a continuous variable in all analyses.

Inhibitory control was assessed via the Eriksen flanker task, which consisted of a series of images containing 5 arrows. For each image, participants were asked to focus on the center arrow and indicate whether the arrow was pointing left or right by pushing a button with their left or right index finger. The flanking arrows could be pointing the same way (congruent) or the opposite way (incongruent). Stimuli and timing of presentation are available for download (69). We used age-adjusted standard scores computed by the NIH Toolbox algorithm that took into account both accuracy and reaction time (70). Before analyses were conducted, outliers ($z > |4|$) were removed.

fMRI Data Preprocessing

The fMRIprep and XCP-D pipelines were developed to work together to minimize data loss during preprocessing and preparation for analysis, thereby maximizing robustness and reproducibility in large datasets (Supplemental Methods).

Network Identification

To define the networks of interest, we extracted functional connectivity between a priori–identified regions. For cognitive control networks, we followed Dosenbach's dual-control network (42), which is supported by empirical research [e.g., (71)]. For the reward network, we used regions identified by Neurosynth activation likelihood estimation meta-analysis using the search term "reward." This result included activations in previous work for both reward anticipation and feedback. Threat circuitry was defined as regions belonging to an emotional reactivity network identified by Neurosynth activation likelihood estimation meta-analysis using the search term "threatening." Both network masks are available for download (http://osf.io/ufzw9).

Between-Network Connectivity

To examine connectivity between control and reward or threat networks, we extracted functional connectivity between regions in each network. We calculated connectivity values for each region within each network with every region in the other network and averaged those connectivity values to obtain an average between-network connectivity score for each participant.

Whole-Brain Connectivity

For completeness, we also examined associations between irritability symptoms and whole-brain network connectivity; details are provided in the Supplement.

Statistical Analyses

Preregistration of statistical analyses can be found at: http://osf.io/ufzw9. Multiple linear regression analyses [lm function in R studio version 4.1.1; (72)] were used to examine whether inhibitory control moderated associations between childhood irritability (parent-reported ARI scores) and between-network connectivity (either control/reward or control/threat). Main effects of between-network connectivity (either control/reward or control/threat) on childhood irritability tested our first hypothesis that reduced connectivity (less positive or negative) between control and reward circuits and between control and threat circuits would be associated with higher irritability symptoms. The inhibitory control $\times$ between-network connectivity interaction term tested our second hypothesis that inhibitory control would moderate connectivity-irritability associations. The interaction term was calculated by multiplying the standardized between-network functional connectivity scores (either control/reward or control/threat) and flanker scores for each participant. Finally, to investigate differences across developmental periods, we tested the above models in 1) samples stratified by age (5–10:0, 10:1–13:11, 14:0–17:11, >18.0) and 2) using age as a continuous variable to test linear and nonlinear effects of age. We included the following potential confounding variables or important covariates, which are known to be associated with irritability, inhibitory control, reward processing, threat processing, and/or functional connectivity: socioeconomic status, attention, mood and anxiety

symptoms, diagnostic status, and number of comorbid diagnoses (Supplemental Methods). Sensitivity analyses examined potential additional confounding variables, defined connectivity values using alternate atlases, used only resting-state MRI data, and used self-reported ARI as the dependent variable (Supplemental Methods).

RESULTS

Participants

Participants included 1430 youths ages 5 to 18 years (mean age = 10.18, SD = 2.67) (Table 1) from the HBN dataset. Inclusion criteria are detailed in the Supplement (Figure S2).

Between-Network Connectivity Is Associated With Parent-Reported Irritability Symptoms in 5- to 9-Year-Old Boys

In the total sample, the connectivity between networks (threat processing and cognitive control, reward processing and cognitive control) was not associated with parent-reported irritability symptoms nor was the interaction between connectivity and inhibitory control (Table 2); inhibitory control was positively associated with irritability.

Linear effects of age were negatively associated with irritability (Table 2); nonlinear effects of age were nonsignificant (Table S2). In age-stratified analyses, connectivity between threat-processing and cognitive control networks was negatively associated with irritability in 5- to 9-year-old children (p = .04, η^2 = 0.0000001) (Table S3); the association of irritability with connectivity between reward-processing and cognitive control networks was nonsignificant (p = .08, η^2 = 0.0002).

In unregistered, exploratory sex-stratified analyses, associations of irritability with connectivity between threat-processing and cognitive control and between reward-processing and cognitive control networks in boys was nonsignificant (ps = .06–.08) (Table S4). Furthermore, in analyses examining stratification by age and sex, connectivity between threat and control networks and between reward and control networks were negatively associated with irritability in 5- to 9-year-old boys (Figure 1 and Table S5).

Sensitivity Analyses

Models that included additional diagnoses as covariates showed similar results (Tables S6–S10), as did analyses with alternate atlases (Tables S11–S21), a model including only resting-state data (i.e., excluding passive movie watching conditions; n = 1388) (Table S22), and a model including only youths without attention-deficit/hyperactivity disorder (ADHD) (n = 561) (Table S23). No significant associations were detected with self-reported irritability (Tables S24 and S25).

Within-Network Connectivity

Within-network connectivity was not associated with irritability in any network (control, reward, or threat) nor was the within-network connectivity × inhibitory control interaction term (Table 3).

Table 1. Participant Demographic and Diagnostic Characteristics (N = 1430)

	Mean (SD) or n (%)
Demographic Characteristics	
Sex, Girls	496 (34.69%)
Age Bands, Years	
5–10:0	776 (54.27%)
10:1–13:11	495 (34.62%)
14:0–17:11	159 (11.12%)
Race/Ethnicity	
Asian	47 (3.29%)
Black	194 (13.57%)
Hispanic	134 (9.37%)
Multiracial	234 (16.36%)
Other[a]	27 (1.89%)
White	736 (51.47%)
Socioeconomic Status, Barratt Total Score	50.42 (13.58)
Full Scale IQ	101.9 (15.51)
Framewise Displacement, mm	0.12 (0.1)
Enrollment Year	
2016	53
2017	380
2018	501
2019	481
2020	15
MRI Scan Site	
Staten Island	689
Midtown Manhattan	534
Rutgers	206
Cornell	1
Diagnostic Characteristics	
Number of Diagnoses	
No diagnosis	119 (8.32%)
Single diagnosis	347 (24.27%)
Two diagnoses	397 (27.76%)
Three diagnoses	256 (17.90%)
Four diagnoses	141 (9.86%)
Five or more diagnoses	170 (11.89%)
Anxiety Disorder Diagnosis	503 (35.17%)
Depressive Disorder Diagnosis	107 (7.48%)
Attention-Deficit/Hyperactivity Disorder Diagnosis, Any Presentation	869 (60.77%)
Disruptive Mood Dysregulation Disorder Diagnosis	16 (1.12%)
Disruptive Behavior Disorder Diagnosis[b]	922 (64.48%)
Parent-Report SCARED	13.96 (11.18)
Self-Report SCARED	22.46 (15.81)
Parent-Report MFQ	8.98 (8.39)
Self-Report MFQ	13.39 (11.11)
Parent-Report SWAN	0.48 (0.96)
YSR Attention Problems T Score	61.33 (10.38)

MFQ, Mood and Feelings Questionnaire; MRI, magnetic resonance imaging; SCARED, Screen for Child Anxiety Related Disorders; SWAN, Strengths and Weaknesses of Attention-Deficit/Hyperactivity Symptoms and Normal Behavior Scale; YSR, Youth Self-Report of the Child Behavior Checklist.

[a]Indian, Native American Indigenous Persons, Native Hawaii/Other Pacific Islander, parent-report other races.

[b]Includes attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder.

Table 2. Multiple Linear Regression Results: Inhibitory Control and Between-Network Connectivity as Predictors of Parent-Reported Irritability

	Threat-Control				Reward-Control			
	β	*t* Value	*p* Value	η^2	β	*t* Value	*p* Value	η^2
Between-Network Connectivity	−1.51	$t_{1362} = -1.69$	.09	0.0003	−1.28	$t_{1362} = -1.46$	.14	0.0001
Inhibitory Control[a]	0.10	$t_{1362} = 2.44$	.01	0.002	0.10	$t_{1362} = 2.35$	.02	0.002
Inhibitory Control × Connectivity Interaction	−0.70	$t_{1362} = -0.94$	.35	0.002	−0.61	$t_{1362} = -0.78$	.43	0.002
Age	−0.06	$t_{1362} = -2.02$	.04	0.0003	−0.06	$t_{1362} = -2.00$	.05	0.0002
Sex	0.01	$t_{1362} = 0.23$	.82	0.001	0.01	$t_{1362} = 0.25$	.80	0.001
Socioeconomic Status	−0.02	$t_{1362} = -0.90$	.37	0.004	−0.02	$t_{1362} = -0.91$	.37	0.004
Study Site	0.01	$t_{1362} = 0.69$	.49	0.00001	0.01	$t_{1362} = 0.66$	.51	0.00001
Number of Diagnoses	0.07	$t_{1362} = 4.67$	<.001	0.10	0.07	$t_{1362} = 4.68$	<.001	0.10
Parent-Report SCARED	0.08	$t_{1362} = 2.93$	.003	0.08	0.08	$t_{1362} = 2.93$	.003	0.08
Parent-Report MFQ	0.36	$t_{1362} = 13.19$	<.001	0.16	0.36	$t_{1362} = 13.19$	<.001	0.16
Parent-Report SWAN	0.21	$t_{1362} = 8.50$	<.001	0.05	0.21	$t_{1362} = 8.47$	<.001	0.05
Full Scale IQ	0.01	$t_{1362} = 3.48$	.001	0.008	0.01	$t_{1362} = 3.46$	<.001	0.01
Enrollment Year	−0.06	$t_{1362} = -2.21$	.03	0.004	−0.06	$t_{1362} = -2.21$	.03	0.004
Framewise Displacement	−1.97	$t_{1362} = -1.06$	.29	0.001	−2.11	$t_{1362} = -1.14$	.25	0.001

MFQ, Mood and Feelings Questionnaire; SCARED, Screen for Child Anxiety Related Disorders; SWAN, Strengths and Weaknesses of Attention-Deficit/Hyperactivity Symptoms and Normal Behavior Scale.

[a]Age-adjusted standard scores from the NIH Toolbox flanker task (70).

Whole-Brain Analyses

Irritability was associated with reduced connectivity between the right insula (salience 4) and right visual cortex (visual 30) (Table 4 and Table S26). Similar results were obtained in analyses that leveraged network-based whole-brain connectivity and network-based statistics (Supplemental Results).

DISCUSSION

Using a large, open dataset of youths from New York City and preregistered analyses, we elucidated a possible neural mechanism underlying irritability in young boys. Reduced connectivity between regions in threat- or reward-processing networks and those in cognitive control networks were associated with higher parent-reported irritability only in 5- to 9-year-old boys. We did not hypothesize this age × sex interaction, and thus our results require replication. Inhibitory control did not moderate associations of irritability with between-network connectivity. Inhibitory control was positively (not negatively) (73,74) associated with irritability. Taken together, connectivity between control and threat- or reward-processing networks may play a larger role in irritability for boys during early childhood, and behavioral overcontrol may play a larger role during middle adolescence. Such findings underscore the importance of preregistering and testing models across developmental periods. Interventions that target brain circuitry in young children and behavior in adolescents may be the most efficacious approach to treating irritability and preventing the development of future psychopathology.

Altered Between-Network Connectivity Underlies Irritability

We detected associations between more negative connectivity between network pairs (threat-control, reward-control) and higher parent-reported irritability only in 5- to 9-year-old boys. Reduced connectivity between the amygdala, a primary hub in the threat network, and the ventromedial and dorsolateral prefrontal cortices, in the cognitive control network, are associated with emotion dysregulation in adolescent depression (75,76) and maintenance of negative affect in healthy adults (77). Stronger connectivity between the amygdala and these same prefrontal cortex regions has been associated with successful cognitive reappraisal and the reduction of negative affect (77–79). In contrast, among youths with ADHD, positive connectivity between the amygdala and anterior cingulate cortex has been associated with emotional lability, indicating that reduced amygdala–control network connectivity may uniquely underlie mood-related irritability (80) [for review, see (81)]. Together, young boys with reduced connectivity between threat-processing and control networks may have greater difficulty engaging adaptive emotion regulation strategies in the face of negative emotions, leading to greater parent-reported irritability. We also observed a nonsignificant, negative association of irritability with connectivity between reward-processing and control networks (Supplemental Discussion). Finally, we detected sex- and age-specific differences in between-network connectivity associated with irritability that were not part of our preregistered hypotheses. Sex-specific maturation of within- and between-network connectivity may contribute to emotion dysregulation differently in boys and girls (82–87) (Supplemental Discussion).

Inhibitory Control Was Positively Associated With Irritability

Contrary to our hypothesis and the existing literature (73,74), inhibitory control was positively associated with irritability in 5- to 14-year-olds. This potentially paradoxical finding may be associated with the high prevalence of ADHD and/or anxiety symptoms in the HBN sample (88) (Supplemental Discussion).

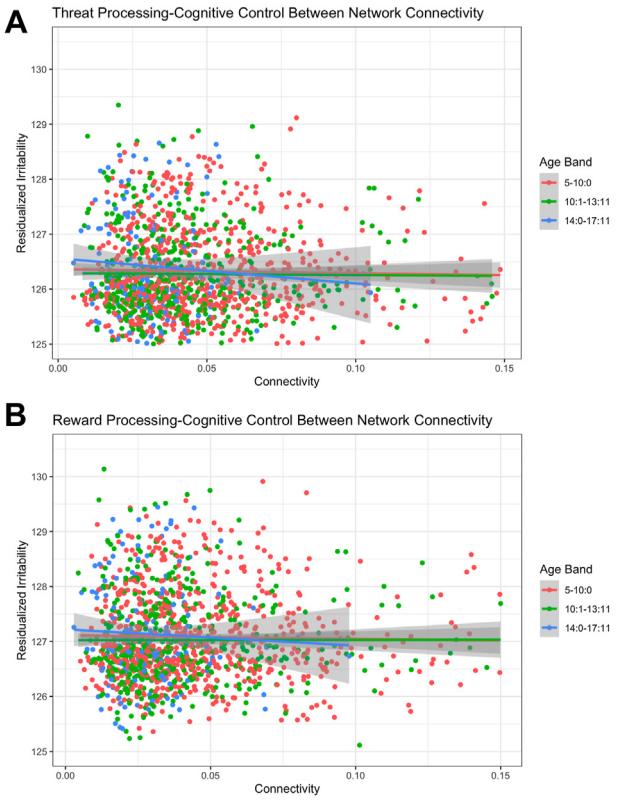

Figure 1. **(A)** Age-stratified associations between parent-reported irritability and between-network connectivity (threat processing–cognitive control). **(B)** Age-stratified associations between parent-reported irritability and between-network connectivity (reward processing–cognitive control). Associations between connectivity and irritability are split by age group for visualization. Pink lines represent children 5:0 to 10:0 years old. Green lines represent children 10:1 to 13:11 years old. Blue lines represent children 14:0 to 17:11 years old. Irritability scores for all youths were residualized for other variables included in the analyses prior to graphing: inhibitory control, age, sex, socioeconomic status, site of magnetic resonance imaging scan, number of diagnoses, parent-reported anxiety symptoms, parent-reported depression symptoms, parent-reported attention-deficit/hyperactivity disorder symptoms, intelligence, enrollment year, and average in-scanner motion.

Whole-Brain Connectivity

In whole-brain analyses, we detected reduced connectivity between the salience network, the medial parietal network, the visual network, and the dorsal attention network. This replicated previous findings in a small sample (N = 69) (Supplemental Discussion).

Limitations

Although HBN is weighted for psychopathology, which allows investigation into the neural mechanisms of childhood psychopathology, findings in this dataset may not generalize to TD populations. Our findings also may not generalize to girls, older adolescents, youths of lower socioeconomic status, or youths of color because these youths are underrepresented in HBN. Our cross-sectional work is unable to test directional effects of between-network connectivity, inhibitory control, or their

Table 3. Multiple Linear Regression Results: Inhibitory Control and Within-Network Connectivity as Predictors of Parent-Reported Irritability

	Coefficient	t Value	p Value	η^2
Within Control Network				
Within-Network Connectivity	−1.03	−1.41	.16	0.00003
Inhibitory Control[a]	0.09	2.30	.02	0.002
Inhibitory Control × Connectivity Interaction	−0.33	−0.62	.54	0.001
Age	−0.06	−2.05	.04	0.0002
Sex	0.01	0.25	.81	0.001
SES	−0.02	−0.90	.37	0.004
Study Site	0.01	0.64	.52	0.000003
Number of Diagnoses	0.07	4.68	<.001	0.10
Parent-Report SCARED	0.08	2.93	.003	0.08
Parent-Report MFQ	0.36	13.20	<.001	0.16
Parent-Report SWAN	0.21	8.47	<.001	0.05
Full Scale IQ	0.01	3.46	.001	0.008
Enrollment Year	−0.06	−2.22	.03	0.004
Framewise Displacement	−2.11	−1.14	.25	0.001
Within Threat Network				
Within-Network Connectivity	−0.83	−0.76	.44	0.00003
Inhibitory Control[a]	0.09	2.25	.02	0.002
Inhibitory Control × Connectivity Interaction	−0.60	−0.59	.55	0.001
Age	−0.06	−1.99	.05	0.0002
Sex	0.02	0.35	.72	0.001
SES	−0.02	−0.89	.37	0.004
Study Site	0.01	0.64	.53	0.00001
Number of Diagnoses	0.07	4.67	<.001	0.10
Parent-Report SCARED	0.08	2.94	.003	0.08
Parent-Report MFQ	0.36	13.18	<.001	0.16
Parent-Report SWAN	0.21	8.42	<.001	0.05
Full Scale IQ	0.01	3.47	.001	0.008
Enrollment Year	−0.06	−2.18	.03	0.004
Framewise Displacement	−2.59	−1.42	.16	0.001
Within Reward Network				
Within-Network Connectivity	−1.53	−1.47	.14	0.001
Inhibitory Control[a]	0.10	2.34	.02	0.002
Inhibitory Control × Connectivity Interaction	−0.88	−0.86	.39	0.002
Age	−0.06	−2.00	.05	0.0003
Sex	0.02	0.31	.76	0.001
SES	−0.02	−0.90	.37	0.004
Study Site	0.01	0.69	.49	0.00001
Number of Diagnoses	0.07	4.65	<.001	0.10
Parent-Report SCARED	0.08	2.94	.003	0.08
Parent-Report MFQ	0.36	13.17	<.001	0.16
Parent-Report SWAN	0.21	8.47	<.001	0.05
Full Scale IQ	0.01	3.40	.001	0.008
Enrollment Year	−0.06	−2.17	.03	0.004
Framewise Displacement	−2.20	−1.20	.23	0.001

MFQ, Mood and Feelings Questionnaire; SCARED, Screen for Child Anxiety Related Disorders; SES, socioeconomic status; SWAN, Strengths and Weaknesses of Attention-Deficit/Hyperactivity Symptoms and Normal Behavior Scale.

[a]Age-adjusted standard scores from the NIH Toolbox flanker task (70).

Table 4. FWE-Corrected Whole-Brain Connectivity

Whole-Brain Connectivity					
Whole-Brain Connectivity	Region/Network	Region/Network	*t* Score	*p* Value	Adjusted *p* Value[a]
Regionwise WBC	Right salience 4	Right visual 30	−3.5136763	.00045426	.01907875
Networkwise WBC	Right salience	Right visual	−3.1178118	.001854477	.04450746
	Right salience	Left dorsal attention	−2.8226017	.004822611	.05787134
NBS Threshold[b]	Region	Region	Component Edges Adjusted *p* Value[a]	Strength	Strength Adjusted *p* Value[a]
NBS Threshold 3	No components survived FWE correction at this threshold.				
NBS Threshold 4	Right cingulo-opercular 35	Left visual 1	.95	1.23	.05
NBS Threshold 5	Right cingulo-opercular 35	Left visual 1	.05	0.23	.02

FWE, familywise error; NBS, network-based statistic; WBC, whole-brain connectivity.

[a]FWE-corrected *p* value.

[b]Components filtered for significance after FWE correction.

interaction on irritability. Finally, 60% of our sample qualified for an ADHD diagnosis, making it difficult to separate ADHD-specific neural mechanisms and irritability-specific mechanisms.

Conclusions

Although this work requires replication, our exploratory findings highlight the potential differential contribution of between-network connectivity to irritability across child development in a large, cross-sectional, open dataset. Our findings indicate sex-specific differences in neural mechanisms of irritability. Aberrations in between-network connectivity explain irritability in young boys whereas behavioral overcontrol explains irritability during middle adolescence. Neither between-network connectivity nor inhibitory control contributed to irritability in girls, older adolescents, or young adults. Identifying developmentally sensitive, sex-specific neural markers of irritability has the potential to contribute to the development of novel, noninvasive, personalized, and brain-dependent treatments for irritable youths and may reduce the downstream incidence of irritability-related disorders in adolescence.

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