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Attention shifting in the context of emotional faces: Disentangling neural mechanisms of irritability from anxiety

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Abstract

Background: Irritability predicts concurrent and prospective psychiatric disorders across the lifespan. Anxiety commonly co-occurs with irritability, and such comorbidity complicates care. Understanding the mechanisms of comorbid traits is necessary to inform treatment decisions. This study aimed to disentangle neural mechanisms of irritability from anxiety in the context of attentional shifting toward and away from emotional faces in youths from treatment-seeking families.

Methods: Youths ($N = 45$), mean age = 14.01 years (standard deviation = 1.89) completed a dot-probe task during functional magnetic resonance imaging acquisition. Whole-brain activation analyses evaluated the effect of irritability on neural reactivity in the context of varying attentional shifting toward and away from emotional faces, both depending on and above and beyond anxiety (i.e., with anxiety as [a] a moderator and [b] a covariate, respectively).

Results: Higher irritability levels related to distinct task-related patterns of cuneus activation, depending on comorbid anxiety levels. Increased irritability also related to distinct task-related patterns of parietal, temporal, occipital, and cerebellar activation, controlling for anxiety. Overall, youths with higher levels of irritability evinced more pronounced fluctuations in neural reactivity across task conditions.

Conclusion: The present study contributes to a literature delineating the unique and shared neural mechanisms of overlapping symptom dimensions, which will be necessary to ultimately build a brain- and behavior-based nosology that forms the basis for more targeted and effective treatments.

KEYWORDS

adolescents, anxiety, attention, children, dot-probe task, fMRI, irritability

1 | INTRODUCTION

Irritability, characterized by angry mood and outbursts, is one of the most common reasons parents seek care for their children (Peterson, Zhang, Santa Lucia, King, & Lewis, 1996) and predicts concurrent and prospective psychiatric disorders across the lifespan (Brotman et al., 2006; Dougherty et al., 2013; Dougherty et al., 2016; Stringaris, Cohen, Pine, & Leibenluft, 2009). Irritability symptoms are prevalent in typical development (Hameed & Dellasega, 2016) and across externalizing and internalizing disorders, including anxiety

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(Cornacchio, Crum, Coxe, Pincus, & Comer, 2016; Stringaris, 2011). In particular, irritability, and anxiety are strongly related even after controlling for depression, oppositional defiant disorder, and other related disorders (Cornacchio et al., 2016). Such comorbidity between irritability and anxiety complicates care; thus, disentangling distinct and overlapping mechanisms of comorbid traits is necessary to inform treatment. For example, the recent steep increase in antipsychotic prescriptions for anxiety disorders may actually represent providers targeting irritability symptoms, which is concerning given the side effects associated with antipsychotic use (Comer, Mojtabai, & Olfson, 2011). Moreover, there are no established treatments that directly target irritability overlapping with anxiety; the evidence is mixed on whether selective serotonin reuptake inhibitors (often prescribed for anxiety) alleviate pediatric irritability, and although cognitive behavioral therapy (CBT) can be effective for irritability, current anxiety-focused pediatric CBT does not directly address irritability (Duggal, Pathak, & Coleman, 2003; Leibenluft, 2011; Strawn et al., 2014). Furthermore, the presentation of irritability symptoms differs by anxiety level (Stoddard et al., 2014), and a true understanding of transdiagnostic symptoms should thus take into account whether it is impacted by the presence of co-occurring symptoms. Given the complications of overlapping symptom dimensions, the research domain criteria (RDoC) framework emphasizes the need for research on the neural circuitry of dimensional, transdiagnostic symptoms of psychopathology, such as irritability and anxiety (Insel et al., 2010; Morris & Cuthbert, 2012). This approach may help identify how these symptoms influence each other and differentiate shared and unique neural substrates of irritability and anxiety. Here, our overall goal was to characterize the extent to which anxiety moderates neural mechanisms of irritability (i.e., the extent to which neural mechanisms of irritability depend on levels of anxiety) and the unique contributions of irritability beyond anxiety (i.e., neural mechanisms of irritability controlling for anxiety). We examined these mechanisms specifically in the context of attention orienting to faces, which is altered in both irritability and anxiety.

Irritability mechanisms indeed overlap with anxiety as both are associated with altered attention to faces and altered neural patterns during face processing (Abend et al., 2019; Abend, Pine, & Bar-Haim, 2014; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Bradley, Mogg, Falla, & Hamilton, 1998; Hommer et al., 2014; Rich et al., 2008; Salum et al., 2016; Waters, Henry, Mogg, Bradley, & Pine, 2010). For example, aberrant attentional orienting in the context of threat is well-established in pediatric anxiety research (Abend et al., 2014; Abend et al., 2019; Bar-Haim et al., 2007; Bradley et al., 1998; Waters et al., 2010) and has also been observed in irritability (Hommer et al., 2014; Salum et al., 2016). In irritability, processing of other emotional faces, specifically happy and sad faces, has also been implicated (Guyer et al., 2007; Rich et al., 2008; Stoddard et al., 2017; Wiggins et al., 2016). However, the specific neural patterns in the context of attention to emotional faces may differ for irritability and anxiety (Kircanski, White et al., 2018; Stoddard et al., 2017). Face emotion processing (Stoddard et al., 2017) and attentional shifting in the context of emotionally salient faces (Abend et al., 2019; Kircanski, White et al., 2018; Price et al., 2014) may thus be a way to parse irritability and anxiety neural mechanisms (Kircanski, White et al., 2018).

Only two studies to date have attempted to disentangle the distinct and shared neural mechanisms across the irritability and anxiety symptom dimensions (Kircanski, White et al., 2018; Stoddard et al., 2017). One study examining emotional face processing in youths with varying levels of irritability and anxiety found that while viewing intensely angry faces, youths with concurrent high anxiety and irritability symptoms exhibited decreased connectivity between the left amygdala and left medial prefrontal cortex, whereas youths with higher anxiety and lower irritability levels exhibited increased connectivity, suggesting an interaction between irritability and anxiety in relation to brain function (Stoddard et al., 2017). The same study showed that irritability, above and beyond anxiety, was associated with increased activation in ventral visual and occipital regions to angry or happy faces compared with fearful faces (Stoddard et al., 2017). Another study demonstrated that attentional shifting toward and away from face emotions may inform the investigation of the neural mechanisms of face emotion processing (Kircanski, White et al., 2018). This study examined the neural correlates for orthogonalized measures of irritability and anxiety in the context of attention orienting to angry relative to neutral faces and found different neural patterns for irritability and anxiety when the task probed for attention towards or away from angry faces (Kircanski, White et al., 2018). Irritability was related to increased neural activation in parietal, limbic, and prefrontal regions, whereas anxiety was related to decreased amygdala connectivity to the thalamus, cingulate, and precentral gyrus (Kircanski, White et al., 2018). This study thus established an important new lead by showing that investigating neural correlates of attentional orienting in the context of angry versus neutral faces can inform differentiation of irritability from anxiety. Overall, these studies suggest that altered neural responding to emotional faces among irritable youths may be especially pronounced if a child also has higher levels of anxiety.

The present study expands prior work on face emotion processing in irritability and anxiety (Abend et al., 2019; Kircanski, White et al., 2018; Price et al., 2014; Stoddard et al., 2017) and investigates neural mechanisms of irritability in the context of attentional shifting to multiple emotionally salient faces (i.e., angry, sad, happy), given that difficulty in labeling multiple emotional faces has been associated with irritability both behaviorally and in functional magnetic resonance imaging (fMRI) studies (Guyer et al., 2007; Wiggins et al., 2016). Specifically, we investigated how such neural responses among youths with varying levels of irritability may be moderated by the presence of anxiety (i.e., irritability "depending on" anxiety) or may be above and beyond anxiety levels (i.e., irritability "controlling for" anxiety). By elucidating underlying brain circuits associated with different levels of co-occurring symptoms, this work may inform targets for prevention and treatment (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). Based on previous findings (Kircanski, White et al., 2018; Stoddard et al., 2017), we

hypothesized that (a) neural correlates of irritability would be moderated by anxiety, and that (b) those correlates, both moderated by anxiety and above and beyond anxiety, would be predominantly in parietal, frontal, limbic (i.e., amygdala), ventral visual stream, and occipital regions.

2 | MATERIALS AND METHODS

2.1 | Participants

Data were acquired from 45 youths, between 9.97 and 19.44 years of age ($M = 14.01$; standard deviation [SD] = 1.89; see Table 1). To ensure adequate coverage of irritability and anxiety dimensions, youths from treatment-seeking families were recruited from the community ($n = 30$) as well as a local research clinic ($n = 15$) which had been conducting a randomized controlled trial for a brief behavioral intervention for anxiety and depression (which often presents as irritability in youths; Weersing et al., 2017). Both recruitment sources had significant overlap in ranges of irritability and anxiety (see Supplement 1 for details on recruitment procedures, sample comparisons [Table S1], and psychotropic medication use). Data collection procedures for the current study were identical across recruitment sources. Exclusion criteria for all participants consisted of magnetic resonance imaging (MRI) contraindications (e.g., orthodontic braces) and presence of a major co-occurring neurological disorder. Parental permission and child assent were obtained for participants under 18, and participants aged 18 and above provided written informed consent. The University of California San Diego Institutional Review Board, in joint agreement with the San Diego State University Institutional Review Board, approved all study procedures.

TABLE 1 Demographic and clinical characteristics

Characteristic ($N = 45$)	
Sex, % female	53.30%
Age (years)	
Mean (*SD*)	14.01 (1.89)
Range	9.97–19.43
Race, *N* (%)	
White	25 (55.6%)
African American	4 (8.9%)
Multiracial	8 (17.8%)
Other	5 (11.1%)
Asian or Pacific Islander	1 (2.2%)
Native American or Alaskan Native	2 (4.4%)
Hispanic ethnicity	17 (37.8%)
Irritability	
Mean (*SD*)	1.89 (2.29)
Range	0–10
Anxiety	
Mean (*SD*)	14.98 (11.38)
Range	0–44
Task accuracy, mean % (*SD*)	92.94 (6.95)

Note: Anxiety = total sum of parent-rated screen for child anxiety related disorders (possible range: 0–82; skew = 1.10); irritability = sum of parent-rated affective reactivity index (possible range: 0–12; skew = 1.77).
Abbreviations: *SD*, standard deviation.

2.2 | Symptoms measures

Irritability and anxiety were measured dimensionally via parent-report. Irritability symptoms were measured with the affective reactivity index (6-month version), a reliable 7-item measure of irritability (possible ranged 0–12) with very good psychometric properties ($\alpha = 0.92$; Stringaris et al., 2012). The 41-item screen for child anxiety related emotional disorders total anxiety score was used to measure anxiety symptoms (possible ranged 0–82); it has shown excellent internal consistency ($\alpha = 0.90$; Birmaher et al., 1997).

2.3 | Face emotion attentional demand task

Children performed a jittered, event-related attentional demand (dot-probe) task adapted from the Tel Aviv University/National Institute of Mental Health paradigm during fMRI data acquisition (Figure S1; Abend et al., 2014). This task was modified to include happy and sad faces in addition to neutral and angry. Emotional/neutral or neutral/neutral face pairs were displayed, followed by a probe (< or >) positioned either in place of the emotional face (congruent; attentional demand to emotional face) or the neutral face (incongruent; attentional demand away from emotional face). Participants were instructed to respond quickly and accurately by pressing the button that corresponded to the probe's direction (left or right). Task conditions consisted of angry-neutral, happy-neutral, sad-neutral, and neutral-neutral incongruent face pairs, split into "congruent" and "incongruent" trials (48 trials per condition, total 384 trials). Runs during which overall accuracy rate fell below 65% were excluded. Behavioral attention bias toward the emotional versus neutral face was calculated by subtracting reaction time between congruent and incongruent trials.

2.4 | Neuroimaging acquisition, preprocessing, and analysis

Multiband functional images were acquired allowing for excellent spatial ($2 \times 2 \times 2$ mm) and temporal (TR = 800 ms) resolution and thus better inference to irritability and anxiety mechanisms. Individual-level brain activation during task trials was modeled with the eight task conditions as regressors. Brain activation across each task trial, which included both face and target presentation, was estimated by convolving AFNI's GAM basis function across 500 ms of face stimulus presentation (the most emotionally

salient aspect) for each trial, similar to prior studies using this task (Kircanski, White et al., 2018).

Whole-brain group-level analyses, via AFNI's 3dMVM, included two factors, emotion (i.e., face emotion pair: angry-neutral, happy-neutral, sad-neutral, neutral-neutral) and congruence (congruent, incongruent), as within-subject variables and parent-reported irritability and anxiety as dimensional, between-subject variables. We focused on two contrasts of interest for the present study, that is, the relationship between irritability and brain activation during the dot-probe task, (a) depending on anxiety (Irritability× Anxiety × Emotion × Congruence), that is, testing anxiety as a moderator, and (b) controlling for anxiety (Irritability × Emotion × Congruence + Anxiety), that is, testing anxiety as a covariate. See Supplement 1 for additional details.

3 | RESULTS

3.1 | Participant characteristics

Table 1 summarizes participant characteristics. There was a moderate positive correlation between irritability and anxiety ($r = 0.34$, $p = .02$). Additional information on participant characteristics, including psychotropic medication use, is provided in Supplement 1.

3.2 | Behavior

Overall mean accuracy ($M = 92.94\%$ [$SD = 6.95$]) was well above chance (50%). There were no significant associations of task accuracy with irritability ($r = -0.20$, $p = .18$) or with anxiety ($r = -0.17$, $p = .27$). One-sample t-tests revealed no significant attention bias to happy ($t[44] = 0.48$, $p = .63$), sad ($t[44] = 0.49$, $p = .63$), or angry ($t[44] = -1.91$, $p = .06$) faces, and no significant associations with irritability or anxiety symptoms ($rs < |.22|$, $ps > .14$).

3.3 | Whole-brain analyses

3.3.1 | Irritability × Anxiety × Emotion × Congruence

Whole-brain analyses revealed a significant Irritability × Anxiety × Emotion × Congruence interaction in the right cuneus (Table 2; Figure 1). Specifically, higher irritability related to distinct task-related patterns of cuneus activation, depending on comorbid anxiety levels, but lower levels of irritability, regardless of co-occurring anxiety severity, were not related to differences in cuneus activation across task conditions. That is, during happy-congruent trials, higher levels of irritability in combination with lower anxiety related to greater cuneus activation, but higher irritability with higher anxiety related to decreased cuneus activation. For angry faces, the pattern was the opposite: during angry-congruent trials, higher irritability in combination with lower anxiety was associated with less cuneus activation, but higher irritability with higher anxiety related to greater cuneus activation (Figure 1).

3.3.2 | Irritability × Emotion × Congruence, controlling for anxiety

A significant Irritability × Emotion × Congruence interaction, controlling for anxiety, emerged for multiple clusters across parietal, temporal, occipital, and cerebellar regions (see Table 2 for details on all clusters). A set of three clusters emerged in the right inferior parietal lobule: one situated predominantly in the right inferior parietal lobule ($k = 382$; Figure 2a), and two adjacent clusters extending into the right postcentral gyrus ($k = 110$) and the right precuneus ($k = 105$). Additional clusters were in the left lingual gyrus ($k = 150$; Figure 2b), right superior TR gyrus ($k = 101$; Figure 2c), left inferior occipital gyrus ($k = 81$), and right pyramis ($k = 553$). Activation patterns in three representative clusters are displayed in Figure 2. Across all clusters, higher irritability levels were associated with marked differences in neural activation across task conditions, whereas lower irritability levels were associated with little difference in activation among task conditions. That is, higher irritability levels were associated with increased activation during happy-incongruent versus happy-congruent trials. Moreover, in youths with higher levels of irritability, the pattern of activation between congruent and incongruent trials was the opposite for happy versus angry faces, and to a lesser extent, happy versus sad faces: greater activation to the incongruent versus congruent condition in the positive emotion face conditions but less activation to the incongruent versus congruent condition in the negative emotion face conditions.

Table 2 lists whole-brain results for all model contrasts. Post hoc analyses revealed that additional clusters in the contrasts of interest were influenced by outlying values from one single subject. These clusters are therefore not further discussed in the main manuscript (see Table 2 and Supplement 1 for additional details).

3.4 | Additional analyses

To assess the potential impact of age, gender, comorbid depression, psychotropic medication use, and head motion post-censoring on our main results, post hoc analyses were conducted. To summarize, after taking these potential factors into account, our main results remained significant. We furthermore completed additional whole-brain analyses with age entered as a covariate which demonstrated the same activation patterns as the original analyses. See Supplement 1 for additional details.

4 | DISCUSSION

The focus of the present study was to help disentangle the overlap of the irritability versus anxiety symptom dimensions by characterizing

TABLE 2 Significant clusters resulting from whole-brain activation analysis

Irritability × Anxiety × Emotion × Congruence[a]						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
233	6.11	−35	−57	58	7	Left superior parietal lobule
65	**7.10**	**21**	**−91**	**30**	**19**	**Right cuneus**
Irritability × Emotion × Congruence[a]						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
3724[b]	13.28	29	−25	70	4, 5, 6, 7, 40	Bilateral postcentral gyrus, left precentral gyrus, left superior parietal lobule
553	14.92	19	−69	−30	–	Right pyramis
382	**11.66**	**49**	**−43**	**52**	**40**	**Right inferior parietal lobule**
150	**8.58**	**−25**	**−71**	**−18**	**18, 19**	**Left lingual gyrus**
144[b]	12.83	9	−25	36	31	Right cingulate gyrus
110[b]	13.29	23	59	2	10	Right superior frontal gyrus
110	8.27	53	−29	44	2, 40	Right postcentral gyrus, right inferior parietal lobule
105[b]	9.20	51	−27	−14	20, 21	Right middle temporal gyrus
105	12.08	29	−75	42	7, 19	Right precuneus, right inferior parietal lobule
101	**14.32**	**45**	**−39**	**6**	**41**	**Right superior temporal gyrus**
94[b]	7.94	41	−25	38	3	Right postcentral gyrus
92[b]	8.26	41	5	−14	38	Right parahippocampal gyrus
81	8.46	−25	−95	0	18	Left inferior occipital gyrus
78[b]	8.42	19	63	24	9, 10	Right superior frontal gyrus
70[b]	10.16	43	29	10	10, 46	Right inferior frontal gyrus
Irritability × Anxiety × Emotion						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
1883	9.6518	−3	−45	68	7, 40	Bilateral postcentral gyrus, left superior/inferior parietal lobule
Irritability × Anxiety × Congruence						
k	$F_{1,41}$	***x***	***y***	***z***	**BA**	**Region**
723	59.55	23	−69	−32	18	Right pyramis, right declive, right uvula
Irritability × Anxiety						
k	$F_{1,41}$	***x***	***y***	***z***	**BA**	**Region**
321	59.75	−19	−65	54	7	Left precuneus, left superior parietal lobule
214	56.50	15	−61	54	7	Right precuneus, right superior parietal lobule
141	28.94	−17	−61	12	18, 30, 31	Left posterior cingulate
134	37.90	−5	−81	28	18	Left cuneus
117	40.07	61	−23	42	1, 2, 3	Right postcentral gyrus
113	62.37	−15	−87	30	18, 19	Left cuneus
87	34.39	37	−43	64	40	Right inferior parietal lobule
67	17.75	−37	−39	−2	37	Left fusiform gyrus
67	34.72	45	−19	60	3	Right postcentral gyrus
60	25.11	25	−93	−2	18	Right lingual gyrus, right cuneus
Irritability × Emotion						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
8045	20.01	−55	−29	44	6, 7	Left postcentral gyrus, right precuneus
1455	15.45	−9	−89	−10	18, 19	Left middle occipital gyrus, left cuneus

(Continues)

TABLE 2 (Continued)

Irritability × Emotion						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
1364	12.30	41	27	34	9, 10	Right middle frontal gyrus, right superior frontal gyrus
1080	16.08	41	−9	−24	38	Right superior temporal gyrus
386	11.24	31	−25	−38	–	Right cerebellar tonsil
383	16.82	9	−71	−28	–	Right pyramis
347	11.57	−35	−17	−14	21, 36	Left parahippocampal gyrus, left middle temporal gyrus
286	11.23	−17	−7	28	–	Left cingulate gyrus
271	13.15	25	−93	−18	17, 18	Right lingual gyrus
215	13.33	41	−39	2	–	Right lentiform nucleus
202	14.98	53	−55	−16	37	Right declive, right tuber
155	10.74	−9	−47	24	31	Left cingulate gyrus
139	11.23	−49	−55	−20	37	Left declive
139	10.02	43	31	8	47	Right inferior frontal gyrus
135	11.75	−33	−31	12	41	Left transverse temporal gyrus
108	7.99	−25	19	−22	38, 47	Left uncus, left inferior frontal gyrus
103	9.22	49	−61	−34	–	Right pyramis, right cerebellar tonsil
97	15.05	−7	−83	−30	–	Left pyramis
91	8.40	43	−25	2	13, 22	Right superior temporal gyrus, right insula
78	9.21	−19	41	18	9	Left medial frontal gyrus, left superior frontal gyrus
76	8.24	17	−87	30	19	Right cuneus
74	8.40	51	41	6	46	Right inferior frontal gyrus
72	13.61	−59	−7	38	6	Left precentral gyrus
63	11.77	37	−29	42	40	Right inferior parietal lobule, right postcentral gyrus
Irritability × Congruence						
k	$F_{1,41}$	***x***	***y***	***z***	**BA**	**Region**
1203	23.71	−47	−33	60	4, 6, 7, 40	Left postcentral gyrus, precentral gyrus
99	18.23	−13	−43	24	31	Left precuneus, left cingulate gyrus
Emotion × Congruence						
k	$F_{3,123}$	***x***	***y***	***z***	**BA**	**Region**
106	7.41	23	47	36	9	Right superior frontal gyrus
Irritability						
k	$F_{1,41}$	***x***	***y***	***z***	**BA**	**Region**
955	31.34	11	−81	−30	–	Left cerebellar tonsil
757	20.24	−19	−53	66	7	Left postcentral gyrus
109	19.98	7	−55	38	7	Right precuneus
83	17.61	11	−55	72	7	Right postcentral gyrus
82	18.71	−47	−43	−12	37	Right postcentral gyrus, middle temporal gyrus
Anxiety						
k	$F_{1,41}$	***x***	***y***	***z***	**BA**	**Region**
133	22.99	−53	−17	28	3, 4	Left postcentral gyrus

Emotion						
k	$F_{3,123}$	*x*	*y*	*z*	BA	Region
73	8.09	35	−73	−22	19	Right declive
67	6.93	37	−31	44	40	Right inferior parietal lobule
Congruence						
k	$F_{1,41}$	*x*	*y*	*z*	BA	Region
145	23.95	39	29	40	8	Right middle frontal gyrus

Note: Clusters significant at whole-brain-corrected threshold of $p < .05$ (see Method for details on cluster threshold).
Abbreviation: BA, Brodmann area.
[a]Contrast of interest in this study; extracted values for bolded clusters are presented in Figures 1 and 2; no significant clusters emerged in the analyses for any contrasts that are not listed.
[b](For contrasts of interest only) these clusters were driven by outlying values (defined as 3 standard deviations away from the median for one or more conditions) and are therefore not a focus of the results and discussion (see Supplement 1 for more details).

the extent to which irritability neural mechanisms are moderated by anxiety and characterizing irritability neural mechanisms above and beyond anxiety. To this end, we examined neural activation in the context of attentional shifting toward and away from emotional faces in youths with varying levels of irritability and anxiety. As hypothesized, we found that irritability and anxiety interacted in relation to neural activation and that irritability was associated with neural activation controlling for anxiety, consistent with previous work (Kircanski, White et al., 2018; Stoddard et al., 2017). Overall, the present study contributes to a literature delineating the unique and shared neural mechanisms of overlapping symptom dimensions, which will be necessary to ultimately build a brain- and behavior-based nosology that forms the basis for more targeted and effective treatments (Redish & Gordon, 2016).

To summarize, activation differences associated with irritability (irritability-by-anxiety interactions as well as adjusting for anxiety) were located in occipital, parietal, and ventral visual stream regions, similar to prior studies examining interactions between irritability and anxiety (Kircanski, White et al., 2018; Stoddard et al., 2017) as well as TR regions, consistent with prior work examining irritability alone (Wiggins et al., 2016). Unlike other studies (Kircanski, White et al., 2018; Stoddard et al., 2017), we did not find differences in prefrontal and limbic activation depending on irritability and anxiety. This may be due to the specific task design of the present study, as ours is the first to probe responses to attentional shifting to a range of emotional faces, as opposed to only angry faces (Kircanski, White et al., 2018), or viewing of emotional faces without attentional shifting (Stoddard et al., 2017). Moreover, we did not find behavioral (i.e., attention bias reaction time) differences based on irritability or anxiety. This may be because the task is more reliable for eliciting brain function than reaction time-based attentional biases (White et al., 2016). The neural findings in the absence of behavioral findings also speak to the added value of MRI studies, and brain imaging's potential to be more sensitive to mechanisms of symptom dimensions than behavior alone (Liuzzi et al., 2020).

Broadly, increased irritability severity was associated with altered neural activation during attentional shifting in the context of emotional faces, both depending on and controlling for anxiety. Overall, higher irritability was associated with more pronounced fluctuations in neural activation across task conditions, that is, greater differences in response to congruent versus incongruent trials, the direction of which differed depending on specific face emotion. This overall pattern is consistent with other face emotion studies on irritability, for example (Wiggins et al., 2016). More pronounced fluctuations in neural activation may represent increased effort required for youths with greater levels of irritability to process and respond to varying task conditions, which may be in turn mediated by attention processes or difficulty disengaging from the emotional face. Alternatively, higher irritability levels may increase cognitive load and manifest as neural differences in the context of attentional shifting. Indeed, in line with both of these possibilities, the parietal, occipital, ventral visual stream, and TR regions that emerged in the present study have been associated with attention (Viviani, 2013) working memory (Braunlich, Gomez-Lavin, & Seger, 2015), emotion regulation (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Viviani, 2013) and social cognition (Van Overwalle, 2009), suggesting that both "hot" emotional processing and "cool" executive functioning aspects may interact in the context of irritability. However, additional work is needed to specify the processes, attentional or otherwise, that may mediate the "pronounced neural fluctuations" profile of irritability.

Interestingly, we found that the patterns of activation associated with increased irritability were the opposite for positive versus negative face emotions, for example, greater activation to congruent versus incongruent happy faces, but greater activation to incongruent versus congruent angry faces in youths with higher levels of irritability. This was evident in analyses that examined irritability moderated by anxiety (happy vs. angry faces) as well as irritability above and beyond anxiety (happy vs. angry faces, and to a lesser extent, happy vs. sad faces). These findings are of particular interest because sad is colloquially conceptualized as the "opposite" of happy, yet our results indicate that anger may be closer to the "opposite" emotion, at least in the context of irritability. Indeed, both happy and angry faces are considered high arousal, approach-related stimuli, though of opposite valence, whereas sad faces are typically considered low arousal, withdrawal-related stimuli (Kensinger, 2004).

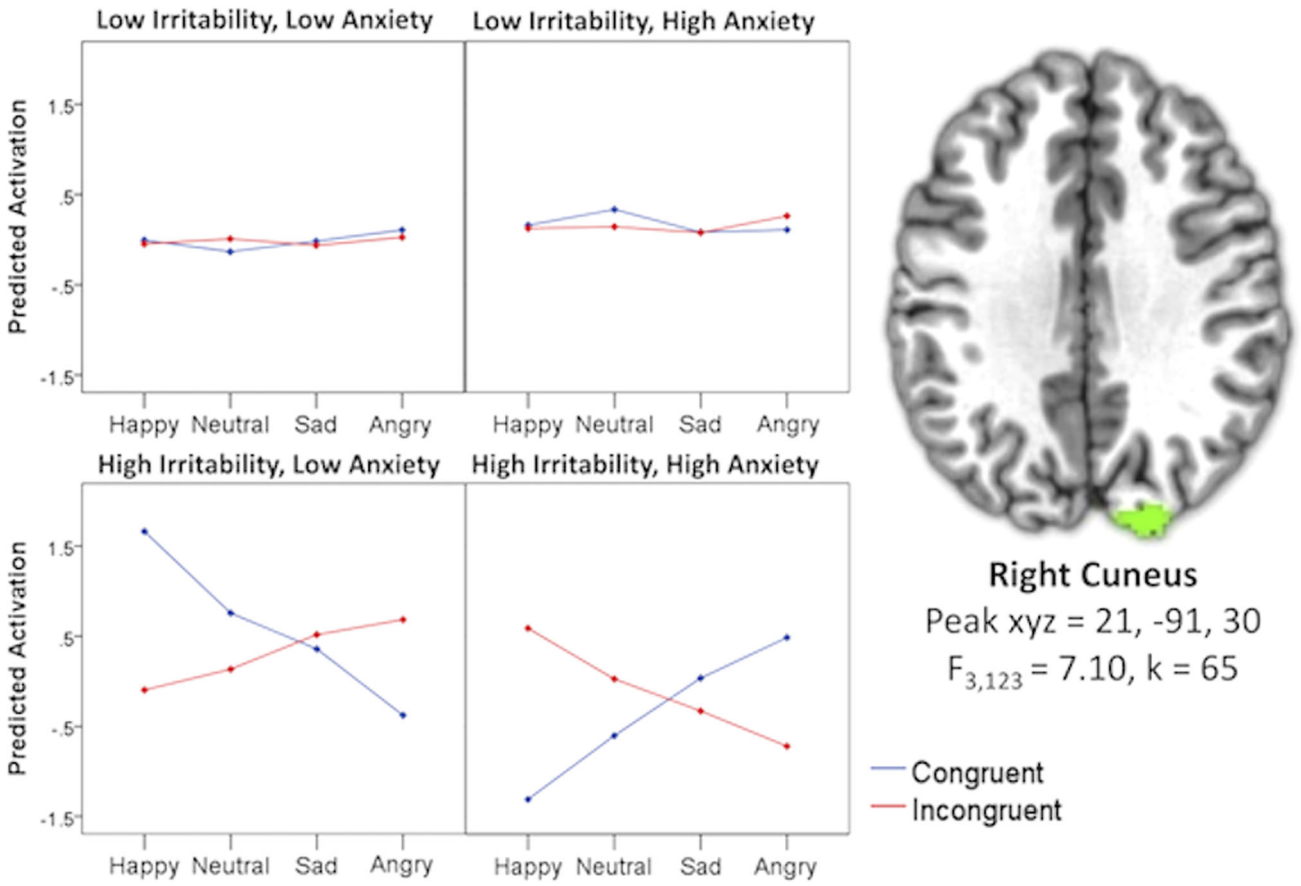

FIGURE 1 Irritability × Anxiety × Emotion × Congruence interaction predicts activation in the right cuneus. Irritability and anxiety were used as continuous variables in the analyses. For illustrative purposes, predicted activation was plotted at minimum and maximum values of irritability (low = 0, high = 10) and anxiety (low = 0, high = 44), resulting in four patterns of predicted cuneus activation: low-low, low-high, high-low, and high-high. For this and all figures, brain images represent axial sections (left = left) with threshold set at whole-brain-corrected $p < .05$, and the *x*-axis represents face emotion categories

The similarities (other than valence) between happy and angry faces may be particularly relevant for comparing irritability and anxiety neural mechanisms, as irritability is associated with negative affect, approach responses (anger), whereas in anxiety the response is more commonly withdrawal (Brotman et al., 2017; Hu, Gendron, Liu, Zhao, & Li, 2017). In this study, by including happy and sad in addition to angry faces, we were able to parse effects related to arousal/approach as well as valence.

Another possibility that may explain our findings with divergent patterns to congruent and incongruent negative versus positive face emotions is that neutral faces (when paired with happy faces) may be perceived as threatening (i.e., negative, approach emotion) by youths with greater levels of irritability. The face pairs presented in our dot-probe task always had a neutral face paired with an emotional face (happy, angry, or sad). For youths with increased irritability, the angry face may be perceived as more threatening relative to the neutral face in angry-neutral pairings, whereas for happy-neutral pairs, the neutral face may be perceived as more threatening relative to the happy face. Indeed, prior work has suggested that neutral faces may not be truly "neutral," especially to children with psychopathology and may thus be interpreted differently depending on context (e.g., the emotional face it is paired with in the dot-probe task; Lange, Allart, Keijsers, Rinck, & Becker, 2012). Thus, congruent versus incongruent activation patterns that appear similar between the neutral (vs. happy) face and the angry (vs. neutral) face may reflect difficulty disengaging from the more threatening face, respectively. Indeed, as prior work has shown that irritability is related to more pronounced fluctuations in neural responses to ambiguous faces (Wiggins et al., 2016), future research is needed to characterize the subjective experience of faces that appear neutral but may be interpreted as ambiguous and/or threatening by those with greater levels of irritability.

5 | LIMITATIONS

We note several limitations of the present study. First, our sample consisted of a predominantly nonclinical sample. However, we achieved variability across the irritability/anxiety spectrum by enriching our sample with youths with prior clinical diagnoses.

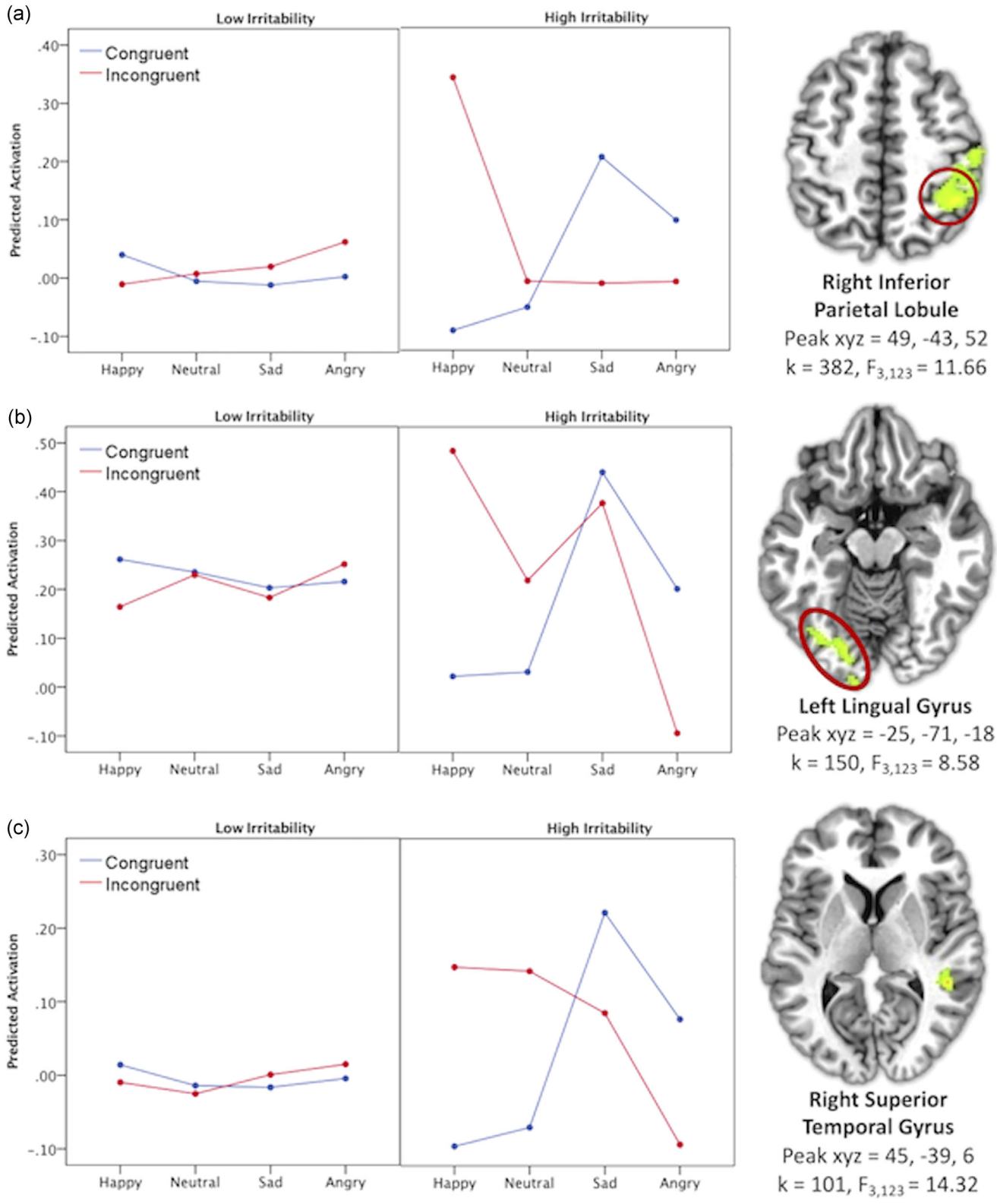

FIGURE 2 Irritability x emotion x congruence, above and beyond anxiety, predicts neural activation controlling for anxiety. In (a) right inferior parietal lobule, (b) left lingual gyrus, and (c) right superior temporal gyrus. Irritability was used as a continuous variable in the analyses. For illustrative purposes, predicted activation was plotted at minimum and maximum irritability values (i.e., low = 0, high = 10)

Furthermore, despite the lack of formal clinical diagnosis, our non-clinical sample consisted of youths with considerable variability in irritability/anxiety, as these families were treatment-seeking. Second, we had a modest sample size ($N = 45$), although our sample size is comparable to (Thomas et al., 2013, $N = 53$) or greater than (Tseng et al., 2015, $N = 38$; Weathers et al., 2013, $N = 42$) other studies examining the neural mechanisms of irritability. Sample size, however, is only one aspect that influences power to detect effects; the number of runs and length of task also influence power (Nee, 2019). As we collected multiple runs in a relatively long task, this somewhat mitigates a modest sample size. Nevertheless, it will be necessary to replicate our findings in a larger clinical sample. Third, it cannot be ruled out that neural modulation for congruent versus incongruent trials across happy, sad, and angry conditions was due to chance differences, especially in light of apparent modulation for neutral-congruent versus incongruent trials, which would be expected to be approximately equal. However, the consistency of the modulation differences between youths with lower versus higher levels of irritability suggests that these results may indeed reflect a pattern of irritability.

6 | CONCLUSIONS

Our findings indicate that alterations in neural reactivity in the context of attention shifting toward and away from emotional faces may contribute to irritability, above and beyond anxiety symptoms, and that anxiety itself impacts irritability neural mechanisms. These findings, along with previous work, suggest that considering concurrent anxiety levels is important for understanding the heterogeneity in irritability neural mechanisms (Cornacchio et al., 2016; Stoddard et al., 2017). Characterizing the neural mechanisms associated with symptom dimensions such as irritability and the overlap with comorbid anxiety may help lay the groundwork for informing treatment. Effective interventions are needed to mitigate the negative outcomes associated with pediatric irritability into adulthood (Copeland, Shanahan, Egger, Angold, & Costello, 2014; Fichter, Kohlboeck, Quadflieg, Wyschkon, & Esser, 2009). A recent randomized controlled study found improvements in anxiety and associated neural risk markers following a computerized attention training protocol (Liu, Taber-Thomas, Fu, & Perez-Edgar, 2018). Promising treatments for irritability are also beginning to emerge. This includes similar computerized (Stoddard et al., 2016) and exposure-based (Kircanski, Clayton, Leibenluft, & Brotman, 2018) interventions, which will benefit from studies that disentangle the unique and common mechanisms of these related symptom dimensions.

7 | FUTURE DIRECTIONS

Our work examining differences in neural activation in response to attentional shifting in the context of emotional faces, a nexus between irritability and anxiety, lays the groundwork for future work to examine these symptom dimensions. Longitudinal studies are needed to characterize changes in neural circuitry associated with dimensional irritability and other comorbid symptoms across development and will be necessary to characterize whether the brain profiles precede or are a consequence of symptoms. Additionally, larger samples powered to examine a variety of irritability-related symptom dimensions beyond anxiety, including depression, attention deficit, and autism symptoms, will be necessary to further disentangle irritability. Overall, the current study supports "RDoC-ian" perspectives that examining symptom profiles, not isolated symptom dimensions or diagnostic categories, will be necessary to gain a better understanding of psychopathology and lay the groundwork for a brain- and behavior-based nosology that leads to targeted and effective treatments (Redish & Gordon, 2016).

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The deidentified data used in the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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