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Systematic Review and Meta-analysis: Task-based fMRI Studies in Youths With Irritability

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Abstract

Objective: Childhood irritability, operationalized as disproportionate and frequent temper tantrums and low frustration tolerance relative to peers, is a transdiagnostic symptom across many pediatric disorders. Studies using task-dependent functional magnetic resonance imaging (fMRI) to probe neural dysfunction in irritability have increased. However, an integrated review summarizing the published methods and synthesized fMRI results remains lacking.

Method: We conducted a systematic search using irritability terms and task functional neuroimaging in key databases in March 2021, and identified 30 studies for our systematic review. Sample characteristics and fMRI methods were summarized. A subset of 28 studies met the criteria for extracting coordinate-based data for quantitative meta-analysis. Ten activation-likelihood estimations were performed to examine neural convergence across irritability measures and fMRI task domains.

Results: Systematic review revealed small sample sizes (median = 58, mean age range = 8–16 years) with heterogeneous sample characteristics, irritability measures, tasks, and analytical procedures. Meta-analyses found no evidence for neural activation convergence of irritability across neurocognitive functions related to emotional reactivity, cognitive control, and reward processing, or within each domain. Sensitivity analyses partialing out variances driven by heterogeneous tasks, irritability measures, stimulus types, and developmental ages all yielded null findings. Results were compared with a review on irritability-related structural anomalies from 11 studies.

Conclusion: The lack of neural convergence suggests a need for common, standardized irritability assessments and more homogeneous fMRI tasks. Thoughtfully designed fMRI studies probing commonly defined neurocognitive functions may be more fruitful to elucidate the neural mechanisms of irritability. Open science practices, data mining in large neuroscience databases, and standardized analytical methods promote meaningful collaboration in irritability research.

Keywords

dysregulation; fMRI; irritability; meta-analysis; systematic review

Childhood irritability (hereafter, irritability), an elevated proneness to anger relative to peers,[1,2] has received increased attention in child psychiatry in the last decade. Irritability is characterized by frequent, developmentally inappropriate temper outbursts, low frustration tolerance, and/or irritable and negative mood.[3,4] With an estimated community prevalence of 0.12% to 5%,[5] epidemiological studies have shown that the negative mental health and life outcomes of irritability extend into adulthood,[3] predicting risks of major affective symptoms and disorders (eg, anxious and depressed symptoms)[6–8] and suicidal ideation/attempts.[9] Although irritability is a hallmark feature of disruptive mood dysregulation disorder (DMDD), it is a transdiagnostic symptom commonly co-occurring with major

psychiatric conditions in youths, including attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, major depressive disorder, and autism spectrum disorder (ASD). This highlights the need to study the neural mechanisms of irritability, which may have treatment implications for many pediatric disorders in which irritability occurs.

Over the past decade, many attempts have been made at progress probing the neural mechanisms of irritability using functional magnetic resonance imaging (fMRI). Most of these fMRI studies investigated the brain–behavior association between irritability symptoms and task-related blood-oxygenation–dependent signals.[1,2,10] The current integrated review focused on 3 neurocognitive domains in irritability, namely emotional reactivity, reward processing, and cognitive control. Brotman *et al.*[1] proposed a translational neuroscience model of irritability that outlined 2 neural and/or behavioral pathways of irritability—threat processing and reward processing. Evidence for the threat processing pathway showed that when presented with potentially threatening emotional stimuli (eg, angry and fearful facial expressions), youths with high irritability symptoms and those diagnosed with marked irritability (eg, DMDD) showed aberrant reactivity in subcortical regions, such as the amygdala, insula, and thalamus, relative to typically developing peers.[11–13] These aberrant neural responses are thought to reflect heightened threat responding in youths with high irritability.[1,13] Here, the term “emotion reactivity” was used, given that task fMRI studies in the field commonly compare neural responses to threat or negatively valenced stimuli vs positive and/or neutral stimuli.

Most evidence for the reward processing pathway was grounded in frustrative nonreward, a negative valence construct in the Research Domain Criteria (RDoC)[14] matrix. When the omission of expected reward elicits frustration, youths with high irritability showed aberrant neural responses in fronto-striatal regions, such as the prefrontal cortex, cingulate gyri, and caudate, compared to typically developing youths.[15,16] Other studies also tested reward processing without the use of a rigged reward schedule to evoke frustration, and reported less consistent results in the frontal[17] and temporal[18] gyri. Together, aberrant fronto-striatal responses, notably those elicited by frustrative nonreward, are conceptualized as deficits in reward-related processing underlying irritability.[1]

A smaller body of task fMRI studies investigated cognitive control–related functions, probing the top-down regulation and coordination of cognitive processes. These studies have found that youths with high irritability symptoms showed inhibitory deficits, and that irritability symptom severity was associated with aberrant activation in the superior frontal and temporal gyri, inferior frontal gyri, and anterior cingulate cortices during inhibitory control tasks.[19,20] According to the exposure-targeted model of irritability,[21] cognitive control functions facilitate top-down regulation of frustration and outburst behaviors, which are promising targets for intervention.

Although these results are promising, there are overlapping as well as distinct regions across these individual fMRI studies targeting different neurocognitive domains. It remains largely unknown whether there are convergent neural responses in specific regions that reflect shared neural mechanisms of irritability across threat-responding, frustrative nonreward processing and cognitive control. Also, many past studies had small sample sizes, and

variations in research designs (eg, diagnostic groups, irritability measures, dimensional vs categorical conceptualization of irritability, experimental paradigms) may limit the generalizability of results and contribute to heterogeneous findings across individual studies. Therefore, we conducted a systematic review and meta-analysis to synthesize the irritability fMRI studies published to date, to consolidate the current state of knowledge and to identify neural correlates of irritability that are robust to variations in task validity and study designs.

Methodological issues aside, age and sex differences are relatively neglected in the irritability fMRI literature. There is increasing advocacy for attending to developmental differences in pediatric neuroimaging, as developmental stage may moderate socio-affective brain functions.[22] Fronto-striatal dysfunction following frustrative nonreward was found to be more pronounced in youths with irritability in mid-childhood and early adolescence, compared to late adolescence.[16] However, it remains largely unclear whether the neural correlates of irritability differ as youths transition from one developmental stage to another (eg, from late childhood to early adolescence when prefrontal circuitries important for mood regulation develop markedly).[23] Similarly, although research attending to sex differences in irritability symptoms and classification is emerging,[24] irritability studies investigating sex differences in task-dependent neural responses are scarce.

The current integrated review has 3 major aims. First, we present a systematic review of task fMRI studies focusing on neural activation associated with irritability and related constructs (eg, reactive aggression, anger) in children and adolescents aged 6 to 18 years, the most common age range sampled in the literature of fMRI research in irritability. By summarizing the sample characteristics and methodological aspects of the studies, we provide an overview of the task fMRI study designs. We also summarize the past studies on age and sex differences in the neural correlates of irritability. Second, we conduct a quantitative meta-analysis based on a subset of qualified task fMRI studies to identify the most robust neural correlates of irritability across neurocognitive domains, that is, those with high convergence across all individual studies. To provide a more nuanced understanding of the neural mechanisms of irritability, we also examine the extent to which these neural correlates converge specifically within each of the neurocognitive domains examined, namely, emotion reactivity, reward processing, and cognitive control. Third, we conduct sensitivity analyses to identify potential sources of nonconvergence by systematically removing variances due to study heterogeneity (eg, irritability measurements, dimensional vs categorical conceptualization of irritability, age differences). We discuss the synthesized results in the context of existing neuroscience-informed models of irritability,[1,21] and provide recommendations for future neuroimaging studies on irritability.

METHOD

Identification of Task fMRI Studies

A systematic search was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25] to identify potential task fMRI studies for the purpose of this review and meta-analysis. Importantly, we conceptualized irritability using a transdiagnostic approach, imposing no restrictions on the diagnostic categories of the samples recruited and irritability measures used in the task fMRI studies. Yet, to

capture the irritability phenotype as conceptualized, we focused on constructs with marked or highly associated features of irritability, which included anger, reactive aggression, and mood dysregulation.[1,3,4] Such conceptualization hence gave rise to the following search terms and their derivatives: (((irritability) OR (anger) OR (reactive aggression) OR (dysregulation)) AND ((child*) OR (adolescent*)) AND ((fMRI) OR (functional magnetic resonance imaging))), which were used to search for peer-reviewed task-fMRI journal articles published in English, from January 2000 to March 2021. The systematic search was run in PubMed, PsycINFO, Medline, and Web of Science. To ensure that the search included all the key fMRI studies of interest, the identified list of articles was cross-checked with a recent narrative review on the neural dysfunctions of irritability.[1] Details of the screening procedures and information regarding the exclusion of articles were outlined in the PRISMA flow chart (Figure 1[26,27]). After independent screening, in-depth reading of full articles, and consensus meetings with senior authors, a final collection of 30 articles were included in the systematic review (Table 1[28–46]), 28 of which included whole-brain analyses and thus qualified for the quantitative meta-analysis. The identified studies were published between 2009 and 2021, 20 of which were published after 2015. Upon independent data extraction, 3 of the 28 studies were further excluded from the main quantitative meta-analysis because significant clusters were found in the ROI analysis only,[19] no significant clusters were reported for any task interaction effects with irritability independent of age,[34] and only significant main effects of irritability were found.[42] This resulted in a final collection of 25 task fMRI studies for the main coordinate-based meta-analysis. A detailed summary of the relevant findings and coordinates extracted from the task fMRI studies can be found in Supplement 1 and Table S1, available online. Coordinates were converted to and reported in the Montreal Neurological Institute space using the Yale BioImage Suite. The current review and meta-analysis was registered with the PROSPERO ID: CRD42021253757.

Systematic Review

To provide an overview of the task fMRI studies, we first summarized the sample characteristics and key fMRI methodologies reported in the studies. For sample characteristics, we extracted the full and subsample sizes, diagnosis, percentage of male participants, recruitment site, average age and age range, and irritability measure used. For fMRI methodologies, we coded whether the studies conducted whole-brain or region-of-interest (ROI) analysis, specific regions of interest (if applicable), fMRI tasks and their neurocognitive domains probed (emotion reactivity, cognitive control, reward processing), and statistical thresholds for conducting those analyses. For emotion reactivity, we categorized studies that used experimental paradigms that involve the perception of and/or engagement with emotional stimuli. Examples are fMRI tasks that invite participants to view emotional facial expressions or to perform a computer game designed to elicit anger and frustration. For cognitive control, we grouped studies with paradigms that demand top-down executive functions, such as tasks requiring participants to inhibit one’s behavior and orient one’s attention with respect to task demands. For reward processing, we identified fMRI tasks that require participants to engage in reward-driven behaviors, often implemented in a game-like setting along with a reward scheme. We acknowledged that these neurocognitive domains are not completely independent of each other, and it is common that some fMRI tasks might be classified into more than one neurocognitive domain, such as the Affective

Posner Task.[15,16] Nonetheless, organizing studies by neurocognitive domains allowed for imposing a systematic framework and increasing study availability for the subgroup quantitative meta-analyses, which are insightful for guiding future research. Moreover, we coded whether sex differences were examined. It should be noted that 2 of the 30 studies included in the systematic review did not qualify for subsequent data extraction for the quantitative meta-analysis because whole-brain analyses were not conducted.[26,27] Still, a qualitative summary of the sample characteristics and fMRI methodologies of these studies was deemed informative for future recruitment and study design.

Quantitative Meta-Analysis

Random effects activation likelihood estimation (ALE) was conducted in GingerALE version 3.0.2.[47] Peak coordinates of the relevant contrasts were extracted from the task fMRI studies and entered to the software, deriving activation likelihood estimates for each voxel. Analyses were conducted where there were adequate numbers of experiments (k = 17) as recommended by Eickhoff *et al.*[48] However, ad justments were made to allow for subgroup analyses of the various neurocognitive dimensions due to study availability.[49] For these subgroup analyses, a minimum of 8 to 10 studies were required to produce valid results while balancing the need for synthesized fMRI findings with statistical rigor.[49–51]

For our main analysis, a within-group analysis was first conducted using all available task fMRI studies (k = 25, 167 foci). Following published guidelines and previous meta-analyses,[48,49,52] statistical significance of the *p*-value maps was set at a cluster-level inference corrected threshold of $p < .05$, with 1,000 thresholding permutations and an uncorrected $p < .001$. Because including all available contrasts from the identified studies would introduce within-group effects from those that reported alternative analyses of similar contrasts, which could affect the Modeled Activation (MA) values in the software algorithm,[48,52] we carefully selected the more interpretable and relevant contrast(s) with respect to the study's key research interest (eg, angry vs neutral faces for facial emotion processing studies[43]; reward vs nonreward conditions during reward anticipation, and performance feedback conditions wherever possible for reward-processing studies).[37] For studies that reported more than one relevant contrast with the same control condition (eg, negative faces vs shapes and positive faces vs shapes[29]), the respective coordinates were pooled as one experiment as recommended.[48,49,52] Given that more studies reported significant task-related neural responses when analyzing parent-reported (k = 4) than child-reported (k = 1) irritability symptoms alone, we prioritized contrasts based on parent report to reduce informant-related variances across individual studies. To gain deeper insight into the functional significance of the neural aberrations associated with irritability, 3 subgroup analyses were conducted separately for each neurocognitive domain defined previously. These included emotion reactivity (k = 19, 138 foci), cognitive control (k = 9, 73 foci), and reward processing (k = 7, 52 foci).

Seven sensitivity analyses were conducted. First, to supplement the main analysis, we increased the study pool by adding the study by Chaarani *et al.*,[19] who conducted a whole-brain structural analysis but only found significant clusters associated with irritability symptoms in the follow-up functional ROI analysis (resulting in a total k = 26, 170 foci).

Second, we conducted an analysis restricting to only emotional reactivity studies that used facial emotional processing tasks or involved facial emotion stimuli (k = 12, 92 foci), given the relatively large number of such tasks, to reduce task heterogeneity in the emotional reactivity domain. Third, 2 measurement sensitivity analyses were performed, restricting analyses to studies assessing irritability using the Affective Reactivity Index (ARI)[53] (k = 10, 90 foci) and diagnostic modules focused on irritability (ie, severe mood dysregulation [SMD] and DMDD modules) from the Kiddie Schedule for Affective Disorder and Schizophrenia (K-SADS)[54,55] (k = 8, 59 foci), respectively. These measurement analyses would provide important insights into the potential divergence of neural correlates regarding a dimensional vs categorical conceptualization of irritability. Relatedly, a phenotype sensitivity analysis was performed by combining the ARI studies with the K-SADS studies (k = 17, 137 foci). A developmental sensitivity analysis was conducted in studies with a mean sample age of less than 15 years (k = 22, 167 foci). We increased the study pool of this sensitivity analysis by adding the work of Karim *et al.*,[34] who found significant clusters for an irritability by age interaction in a mid-childhood sample (mean age = 7.6 years). Study availability precluded us from conducting an ALE-based subtraction analysis with studies that sampled mid- to late-adolescents (k = 4). Finally, to evaluate the impact of sample size, we ran a sensitivity analysis that included only studies with sample sizes greater than the overall median sample size (N > 58; k = 12, 90 foci). Of note, although these sensitivity analyses helped to reduce heterogeneity, some of these analyses and the subgroup analyses for cognitive control and reward processing had small numbers of studies and might not capture subtle effects because of limited power. These results should be interpreted with caution.

RESULTS

Systematic Review

Sample Characteristics.

- Sample size and age. Across all studies included in the systematic review (k = 30), the average sample size was 87 participants (median = 58, SD = 66.89, range = 19–320). The number was comparable (mean = 82, median = 55, SD = 68.51, range = 19–320) when selecting the most relevant clinical groups with marked irritability symptoms (eg, DMDD and SMD) for studies that focused on diagnostic group comparisons without dimensional measures. In terms of age, 26 studies recruited pre- and mid-adolescents with mean ages below 15 years (mean = 13.12, median = 13.8, SD = 1.89, range = 7.6–14.9), whereas only 4 studies recruited late-adolescents aged >15 years (mean = 15.45, median = 15.5, SD = 0.3, range = 15.1–15.7).
- Sex proportion. The average proportion of male participants was 61.1% (median = 54.9%, SD = 18.62), ranging from 33.9% to 100% (4 studies had male participants only).[17,18,41,46]
- Recruitment. Most study samples were recruited from research facilities with clinical services, such as the National Institute of Mental Health (NIMH) (k = 14), Yale Child Study Center (k = 2), and local psychiatric units (k

= 5). Four studies sampled youths who were seeking treatment and at risk for developing significant irritability symptoms in the local community.[11,32,37] Two studies assessed irritability symptoms more broadly in healthy community samples.[20,34] Three studies constituted part of a large-scale research project (EU-Aggressotype and EU-MATRICS project,[29] Bipolar Offspring Study,[30] and IMAGEN[19]). Based on this summary, it is plausible that several studies might have recruited their samples from the same source (eg, NIMH) and that there might be overlapping subjects across these studies.

- Socioeconomic status and race/ethnicity. Only 7 studies provided socioeconomic information of the sample, most of whom were from mid- to high-income households and with parents attaining high school or degree-level education. Eight studies reported race/ethnicity; 6 of those studies recruited primarily White participants (mean = 64.6%, median = 62.8%, SD = 13.55, range = 50% to 80.4%), whereas 2 studies recruited predominantly Hispanic/Latinx[32] and Black[39] participants.
- Diagnosis. The samples included multiple clinical/research diagnoses: ADHD (n = 207, k = 8), DMDD (n = 199, k = 5), BD (n = 183, k = 7), SMD (n = 165, k = 8), anxiety (n = 152, k = 4), and ASD (n = 116, k = 3), and oppositional defiant disorder (ODD) and/or conduct disorder (CD; n = 108, k = 1).
- Irritability measures. Three categories of irritability measures were observed. Ten studies assessed diagnostic categories with marked irritability symptoms using the K-SADS in their main analyses.[15,38,44] For dimensional approaches, 10 studies assessed irritability symptoms using the ARI,[16] whereas 10 other studies used other dimensional measures assessing clinical features associated with irritability symptoms, such as the Child Behavior Checklist (CBCL),[17,33,36] Reactive–Proactive Aggression Questionnaire,[18,29] and Child/Adolescent Symptom Inventory.[17,46]

fMRI Methods

- fMRI tasks. A wide array of experimental tasks were used to probe neural dysfunction pertinent to irritability. Of the 30 studies, 22 studies focused on emotional reactivity, 14 of which involved the perception of and/or engagement with emotional facial stimuli.[12,36] Seven studies probing reward processing included mostly the Monetary Incentive Delay Task,[17,32,37] the Affective Posner Task,[15,16] and other point-based tasks.[18,39] Eleven studies probing cognitive control encompassed various subdomains of cognitive control functions in irritability, such as inhibitory control on the Stop Signal Task[19,27] and Flanker Task,[20] reversal learning,[28] and attention control processes.[38] Some studies involving emotional reactivity[11,35] and reward processing[16] also probed attention processes (eg, attention orienting).
- fMRI analytical thresholds. Heterogeneous analytical thresholds were observed across studies. Most analytical thresholds used in the whole-brain analyses were voxelwise corrected (k = 18). Other correction methods included those based

on familywise error rate (k = 5) and false discovery rate (k = 1). Four studies reported uncorrected alpha levels. For ROI analyses, similar to whole-brain, most thresholds were not clearly stated (k = 10). Other correction methods for ROI included those based on cluster-extent (k = 2), Bonferroni correction (k = 2), familywise error rate (k = 1), false discovery rate (k = 1), and voxelwise correction (k = 1).

- Sex differences. Of the 30 studies, only 5 studies examined sex differences in the task-dependent neural correlates of irritability; almost all yielded no significant findings (Table S1, available online), except for 2 studies that reported a main effect of sex in the left amygdala[42] and increased activation in several regions important for salience detection during frustrative nonreward processing in younger boys (eg, insula and pre-/post-central gyri).[16] Seventeen studies did not report analyzing sex as a covariate or sex by irritability interaction in their analyses. The 8 studies that analyzed sex as a covariate yielded mostly null findings; only one study found sex differences in the salience network during inhibitory control, such as the thalamus and cingulate.[20]

Meta-Analysis: No Evidence for Convergent Neural Correlates of Irritability

Main and Subgroup Analyses.—The main analysis inclusive of 25 task fMRI studies of irritability (167 foci) across all neurocognitive domains revealed no clusters of convergence. Figure 2 visualizes the unthresholded positive *z*-score map. The 3 subsequent subgroup analyses focusing on 19 fMRI tasks (138 foci) probing emotional reactivity, 9 fMRI tasks (73 foci) probing cognitive control, and 7 fMRI tasks (52 foci) probing reward processing, respectively, all revealed no evidence for convergence within domain, suggesting that the null finding in the main analysis was not driven by heterogeneity in tasks across neurocognitive domains.

Sensitivity Analyses.—As outlined earlier, 7 sensitivity analyses were conducted. Given the null findings above, sensitivity analyses may help identify potential sources of nonconvergence by systematically removing variances contributed by study heterogeneity. In the first sensitivity analysis adding ROI coordinates from the work by Chaarani *et al.*[19] to increase the study pool (k = 26, 170 foci) and hence power, no convergent clusters were found. Second, restricting the analysis to the emotional face tasks only (k = 12, 92 foci) revealed no clusters of convergence. Third, the measurement sensitivity analyses also found no evidence for convergence within the 10 studies (90 foci) that dimensionally indexed irritability with the ARI, and within the 8 studies (59 foci) that analyzed diagnostic categories with marked irritability on the K-SADS. The phenotype sensitivity analysis (k = 17, 137 foci) aggregating the ARI studies and the K-SADS studies (which characterized marked irritability using the SMD and DMDD modules) yielded null results. The developmental sensitivity analysis on 22 studies (167 foci) with a mean age of <15 years produced no convergent findings. Finally, the sensitivity analysis on 12 studies (90 foci) with at least a median sample size of 58 participants also yielded null results.

Descriptive ROI Findings.—Of the 25 studies qualified for the meta-analysis, 15 studies also conducted ROI analyses investigating the association of irritability symptom

severity with and/or irritability group differences in task-dependent neural responses in *a priori* defined brain regions. The hypothesized regions comprised regions in the salience network underlying the threat-processing pathway (eg, amygdala, insula, and anterior cingulate cortex) and fronto-striatal regions (eg, inferior frontal gyrus, caudate, nucleus accumbens, and putamen) underlying the reward-processing pathway in irritability.[1] Six of the 15 studies (7 foci) reported significant irritability-related ROI findings. Notably, 2 of 3 studies found youths with high irritability showing increased activation during reward processing[16,17] and decreased activation during a reversal learning task[28] in the caudate; 2 of 3 studies found increased putamen activation in youths with high irritability during reward processing tasks.[16,17] Despite the postulated role of the amygdala in mediating aberrant threat responding in irritability, only 2 of 12 studies found increased amygdala responses in youths with high irritability during emotional face tasks.[29,35] Figure 3 presents a summary of the ROI findings.

Relevant Structural MRI Literature

Given that the main meta-analyses showed no convergent results among the fMRI studies, a comparison with the structural MRI literature may be helpful to clarify whether the null results were partly related to poor fMRI task validity. We conducted a systematic review in the structural MRI literature using the same irritability search terms and identified 11 studies (Figure S1, available online). Sample characteristics and key findings were summarized (Table S2, available online). Of the 11 studies, 8 studies examined gray and white matter volumes, 5 of which found reduced volumes in widely distributed frontal regions, including the inferior frontal gyrus and prefrontal regions, whereas 3 studies reported reduced insular volume. Findings on cortical thickness and surface area were inconclusive. This structural review was not preregistered.

DISCUSSION

To our knowledge, this is the first integrated and meta-analytic synthesis of task fMRI findings in youths with irritability. We followed the latest recommendations on coordinate-based fMRI meta-analysis,[48,52] and found no evidence for convergence in the irritability fMRI literature either in the main analysis across neurocognitive task domains or in the subgroup analyses for emotion reactivity, reward processing, and cognitive control. Further sensitivity analyses restricting studies by stimulus type, dimensional and categorical irritability measures, irritability phenotype, and developmental ages also revealed no significant convergence across studies. The absence of neural convergence might stem from marked heterogeneity in clinical characteristics, small samples, and variations in fMRI task design, irritability measurements, and statistical procedures, such as thresholding, across individual studies. Moreover, a descriptive summary of ROI results suggested altered neural responses during reward tasks in the caudate and putamen associated with high irritability, consistent with the striatal reward processing pathway of irritability.[1]

Heterogeneous Irritability Samples

Although the mean sample size (N = 87) seemed moderate for neuroimaging research, we noticed considerable variability in the sample sizes; indeed, the median sample size (N =

58) was small across studies. Small sample size not only reduces the power to detect subtle effects, which are common for tasks probing socio-affective processing,[56] but also may result in inflated estimates, hampering the generalizability of the neuroimaging findings. All of these could contribute to the lack of convergence in the past fMRI studies in irritability.

Myriad clinical conditions, including DMDD/SMD, ADHD, ASD, ODD, anxiety, and BD, were included in the reviewed studies, which highlights the transdiagnostic feature of irritability. This raises the critical question as to what extent irritability is mediated by similar neural mechanisms across diagnostic categories. We attempted to address this by restricting irritability phenotypes in our sensitivity analysis, yet yielded nonconvergence. Still, as in many other phenotypes in psychiatry, heterogeneity in irritability is a clinical reality and a challenging issue in fMRI research. Heterogeneous clinical features and developmental differences in the irritability phenotype might interact with neurobiological alterations. Even within youths with irritability but without comorbid conditions, there are variances in irritability symptom presentation, which may have different etiological pathways and may be mediated by different brain alterations. For instance, research has started to show that irritable mood (tonic irritability) and temper outbursts (phasic irritability) relate to different genetic and environmental influences in DMDD,[57] as well as psychiatric risks (eg, ADHD,[58] depressive disorders, and anxiety disorders[59]). These intricate dimensions are not well captured in the current irritability measures. Novel methods and measurements indexing these symptom dimensions in a more fine-grained manner needs to be developed (eg, ecological momentary assessment) and tested for their psychometric properties, which will facilitate future studies parsing the neurobiological underpinnings of different aspects of irritability (eg, tonic vs phasic irritability).

Moreover, youths with clinical diagnoses are likely to receive psychotropic medications or psychotherapy and/or to have environmental risk factors, such as socioeconomic disadvantages and adverse childhood experiences,[32] which have been shown to alter socio-affective brain functions mediating affective symptoms and regulation.[60] However, comprehensive reporting of sample socioeconomic status and race/ethnicity information is rare in the field (ie, <30% of the studies reviewed here). Among the studies that reported this sociodemographic information, the majority included predominantly White participants from mid- to high-income households with parents attaining high school or degree-level education, whereas only 2 studies recruited predominantly Hispanic/Latinx[32] and Black[39] participants, and only one study included youths with trauma histories.[32] Thus, the generalizability of the past findings to diverse, representative populations is unclear. Future studies should include more diverse samples, report sociodemographic composition of the study samples, and evaluate and discuss how the sociodemographic sample characteristics affect their findings. Importantly, more research is needed to examine the impact of early life adversity and trauma on the etiology and development of childhood irritability, as youths from marginalized and adverse backgrounds represent one of the most vulnerable groups to develop irritability symptoms and deserve timely intervention.[32,61,62]

Studies differ in irritability measures. The most commonly used dimensional measures is the ARI,[53] whereas the most widely adopted categorical measure is irritability-related modules (ie, DMDD, ODD, SMD) on the K-SADS. Some other measures included selected

items on the CBCL[17,33,36] and Reactive Proactive Questionnaire.[18,29] Although dimensional measures are more sensitive in capturing individual differences in irritability symptoms and are well suited for sensitivity analyses partialing out comorbidity-related variances, categorical approaches allow for identifying the most significant neural correlates in youths with severe forms of irritability warranting clinical attention. Still, there is no gold standard for assessing irritability, and these various measures of irritability differ in measurement validity, reliability, and informant agreement across development.[54,55] None of the existing measures are sensitive to low-to-modest irritability symptoms[54]—an issue highly relevant for typically developing and/or community samples. More justification in the choice of irritability assessments is preferable, as irritability-related subscales or items extracted from larger pools, compared to those specifically designed for assessing irritability, might vary psychometrically and relate subtly to different aspects of neural dysregulation.[63,64] This relates to the previous discussion on characterizing the different aspects of irritability, as increasing studies rely on latent variable techniques[58,59] or individual assessment items[57,65] to index tonic and phasic irritability, but their psychometric properties await critical evaluation.

Low study availability precluded us from examining age- and sex-related differences in neural convergence. However, we conducted a sensitivity analysis focusing on pre- and early-adolescents only (<15 years of age) and found no convergent results. Thus, questions remain as to whether age- and sex-related pubertal and hormonal changes might have contributed to the null results, as recent evidence points to an interplay between pubertal hormones and maturation of fronto-limbic circuitries,[66] overlapping with the threat and reward processing pathways of irritability.[1] Studies that directly examined sex moderation on irritability-related neural responses are scarce, with only one study finding significant sex moderation effects during frustrative nonreward processing.[16] Together with studies that analyzed sex as a covariate or main effect,[20,42] these sex differences emerged primarily in the salience network.

Heterogeneous fMRI Tasks and Analytical Procedures

Our null findings contrast with the few recent coordinate-based fMRI meta-analyses on irritability-related constructs. For instance, 2 meta-analyses found that state anger (k = 39)[67] and anger experience (k = 26)[68] were associated with activations in the anterior insula/inferior frontal gyrus and anterior cingulate cortex,[67,68] and in the ventrolateral prefrontal cortex.[68] In a more relevant meta-analysis (k = 68),[69] frustrative nonreward processing was associated with deactivation in the orbitofrontal cortex, posterior cingulate cortex, and ventral striatum, and heightened activation in the midcingulo-insular regions. It is thought that the deactivation patterns represent frontal neural deficiency, which disinhibits aggressive responding to frustrative events.[69] These meta-analyses, however, were performed in primarily healthy young adults, with a larger collection of studies using more homogeneous tasks. Therefore, such spatial convergence might not generalize to developmental clinical groups (childhood irritability in this case) in which neural convergence is a complex function of developmental changes, symptom variations, and compensatory neural mechanisms.[49,69]

Regarding other relevant phenotypes, a recent meta-analysis in youths with depression or anxiety disorders (k = 48)[70] reported increased activation in the bilateral amygdala (especially for anxiety disorders) across a range of emotion regulation and decision-making tasks, which extended to the anterior cingulate and putamen—regions in the salience network that were also reported in some of the individual irritability studies reviewed here. However, no significant clusters were found when restricting to youths with major depressive disorder (MDD), suggesting that the lack of neural convergence may not be an issue specific to the irritability phenotype.

Diverse fMRI tasks across multiple neurocognitive domains have been used in past studies in irritability. Although a conceptual framework categorizing studies into emotional reactivity, cognitive control, and reward processing was useful to facilitate systematic analyses of neural convergence, within-domain heterogeneity was still present. This is evident in the emotional reactivity studies reviewed. Although most of these studies were fundamentally facial emotion recognition tasks, these paradigms involved varied task demands probing passive and active attentional processes, priming, and control conditions ranging from nose width ratings to gender and shape recognition that potentially involve different psychological processes. Stimulus variations such as the use of morphed vs non-morphed faces, types of emotions, valence and arousal, and presentation duration might address specific research questions concerning emotion processing in irritability; but that likely further contributes to nonconvergence across individual studies, given the corresponding impact on the underlying psychological operations and hence associated neural responses. Similarly, a variety of reward tasks were used. Of note, these reward tasks varied in the reward contexts, as some involved the elicitation of frustration via rigged reward,[15,16] whereas others occurred in more conventional reward settings.[17] A recent study found task-dependent functional connectivity to be predictive of irritability symptom severity only when frustration was evoked during scan,[71] highlighting the importance of emotional contexts. There is also inconsistency in operationalizing the temporal dimensions of reward processing in these reward tasks. We strove to reconstruct the full temporal course by carefully pooling study contrasts that reflect the core phases of reward processing (eg, reward anticipation, reward receipt, and feedback), and yet no significant convergent clusters were found. Studies probing cognitive control are mixed, partly because there is no generally agreed-upon definition of cognitive control dysfunctions in irritability. These subordinate functions range from inhibitory control,[19,20,27] reversal learning,[28] to attention control processes[38]; the latter are shared with emotional reactivity and reward processing studies that have attention-related demands.[16,35] Although we do not rule out the possibility that the neural correlates of irritability are indeed very heterogeneous because of its transdiagnostic nature and the myriad neurocognitive functions that are potentially affected, the heterogeneity in fMRI task designs reflect a lack of consensus in the key neurocognitive constructs of interest and the empirical approaches in probing those neurocognitive processes in irritability research. Study variances related to task heterogeneity are coupled with heterogeneous statistical thresholds in the fMRI analyses. Therefore, the absence of neural convergence is perhaps less surprising.

Structural MRI obviates validity and reliability issues in task fMRI.[72] Our review on structural MRI suggests potential irritability-related volumetric reductions in widely

distributed frontal regions, possibly implicating decreased top-down regulation in irritable mood and outbursts.[61,73,74] A few studies report volumetric reduction in the salience network, possibly implicating neural alterations associated with early stimulus detection and response.[61,73] However, this structural review is based on a small number of studies using different irritability measures. This highlights the need for more research, especially those studies examining other morphometrics such as cortical thickness and surface area. Thus, it remains unclear whether limitations with task fMRI and/or constructs/measures of irritability contributed to the lack of convergence in fMRI findings.

Common to many fields of research, bias for publishing novel and significant findings contributes to the use of individualized task designs, flexible preprocessing pipelines, analytical procedures, and thresholding that are unique to individual studies. These research practices often give rise to study findings that are replicable only in well-powered fMRI analyses with sufficiently large samples and representative ranges of irritability symptoms, both of which are difficult to achieve in individual laboratories. However, this does not necessarily suggest that task fMRI studies on irritability should be replaced with an alternative neuroimaging modality, as task fMRI is critical to understanding the functional significance of altered neural functions and their associations with irritability.[1,2,10] In addition to neural activation, task fMRI enables investigation on functional connectivity. Indeed, emerging evidence shows that individual differences in irritability may be reflected in the disrupted integration between and within brain regions and networks.[71,75] As a limitation, the current meta-analysis inferred functional neural convergence based on peak coordinates; future work with a direct synthesis of full voxelwise statistical maps may bypass some of the issues related to the researcher's degrees of freedom in the preprocessing, analyzing, and thresholding of fMRI data and may uncover neural dysfunctions associated with irritability.

Several recommendations are noted here for moving irritability fMRI research forward. First, an agreed-upon battery of irritability phenotype measurements will facilitate comparisons and data pooling across studies and increase sample sizes, potentially improving the convergence of findings. Likewise, we encourage more detailed assessments of symptom dimensions in irritability, parsing possibly different neurobiological substrates of tonic and phasic irritability. Relatedly, more thorough clinical assessments of comorbidities would provide the necessary information to clarify irritability-related neural responses that are independent of co-occurring symptoms and heterogeneous features within specific diagnostic groups (eg, ADHD and ASD). Second, sample characteristics, including information about psychiatric medication, pubertal development, and other environmental risk factors (eg, socioeconomic disadvantages and chronic stress) are useful to identify exogenous sources of individual variances, enhancing the robustness of fMRI findings. Transparent reporting of potentially overlapping participants and a wider range of recruitment sites, especially in underrepresented populations and/or those at risk for severe irritability, are needed to diversify the study samples. Third, mining population-based neuroimaging datasets, such as the Adolescent Brain Cognitive Development Study (ABCD),[76] provides the opportunity to improve clinical heterogeneity and to overcome small sample sizes in individual studies. As measures specifically designed for assessing irritability symptoms are not common in these large-scale studies (eg, ARI),[53] we advocate

for including such irritability measures that are well-validated and reliable in future study protocols. Fourth, fMRI task heterogeneity implies that a better incentive structure is needed to motivate the use of fMRI tasks that validly and reliably probe neurocognitive functions informing the pathophysiology of irritability. This does not mean imposing a stringent framework on fMRI paradigms, as testing novel task designs in individual laboratories are valuable training opportunities for early-career researchers and benefit new hypothesis generation.[77] Instead, pre-registration of fMRI task designs and analysis plans can promote task homogeneity and standardized processing pipelines across individual studies, while ensuring reasonable between-study variations that address specific research questions. Fifth, open task and data sharing are currently underway in our laboratories to promote collaborative irritability research. Pediatric neuroimaging in youths with irritability can be challenging, especially when frustration tasks and deception are involved. Making mock scan protocols, experimental setups, task instructions, and debriefing procedures openly available may help to overcome this challenge. Sixth, the past fMRI studies on irritability were largely conducted at a regional level. Multivariate approaches examining neural coactivation and connectivity patterns across the whole brain may provide a more comprehensive understanding of the neural circuitries and interactions mediating irritability.[71] Other neuroimaging modalities such as connectivity studies using fractional anisotropy[75] and functional near-infrared spectroscopy measuring real-time cortical neural responses during interactive tasks[78] offer novel angles to study neural dysfunctions in irritability. Studies analyzing both task fMRI and task-free resting state data also allow for clarifying task-related neural noises.[72] Finally, frustration realistically occurs in social and interactive contexts among youths. To enhance ecological validity, future irritability research might investigate neural dysfunctions during frustrative social nonreward, such as social rejection.

This study is the first systematic review and quantitative synthesis of the task fMRI studies on irritability. We observed vast clinical heterogeneity and methodological variations across studies, potentially contributing to the absence of neural convergence in irritability as shown in the quantitative syntheses across neurocognitive domains and sensitivity syntheses restricting stimulus type, irritability measures, and developmental ages. Nonetheless, when implemented thoughtfully, task fMRI studies provide valuable empirical evidence for elucidating the functional neural mechanisms mediating irritability symptoms. The use of large samples, common standardized measurements of irritability, comprehensive assessments of heterogeneous clinical features, and more homogeneous fMRI tasks probing well-defined neurocognitive domains central to the pathophysiology of irritability are key to improving research practice and data quality in the field. Open science and innovative research methods such as multivariate analysis and multimodal neuroimaging provide novel avenues for advancing the current state of knowledge in the neural mechanisms of irritability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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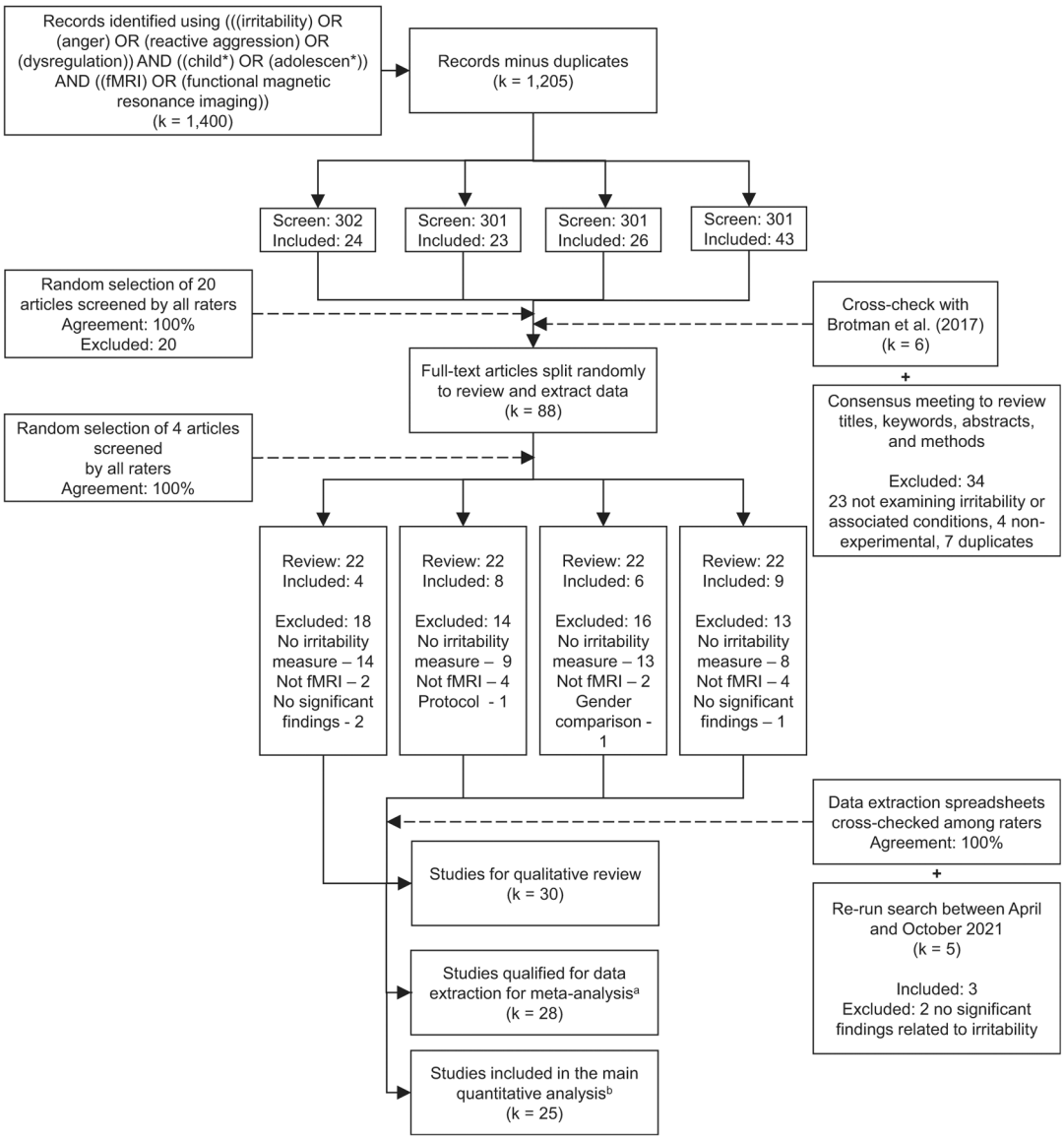

FIGURE 1.

PRISMA Flowchart Outlining Literature Search History

Note: Because of the COVID-19 pandemic's impact on research, the same systematic search was re-run from April 2021 to October 2021 to ensure comprehensive coverage of studies, and identified 3 articles that were eligible for the systematic review and meta-analysis.

[a]Two studies[26,27] were excluded from data extraction because no whole-brain analyses/findings were reported.

[b]Studies reported significant task-dependent neural responses associated with irritability symptoms or irritability-related group differences in the whole-brain analyses across neurocognitive domains (further detailed in Methods).

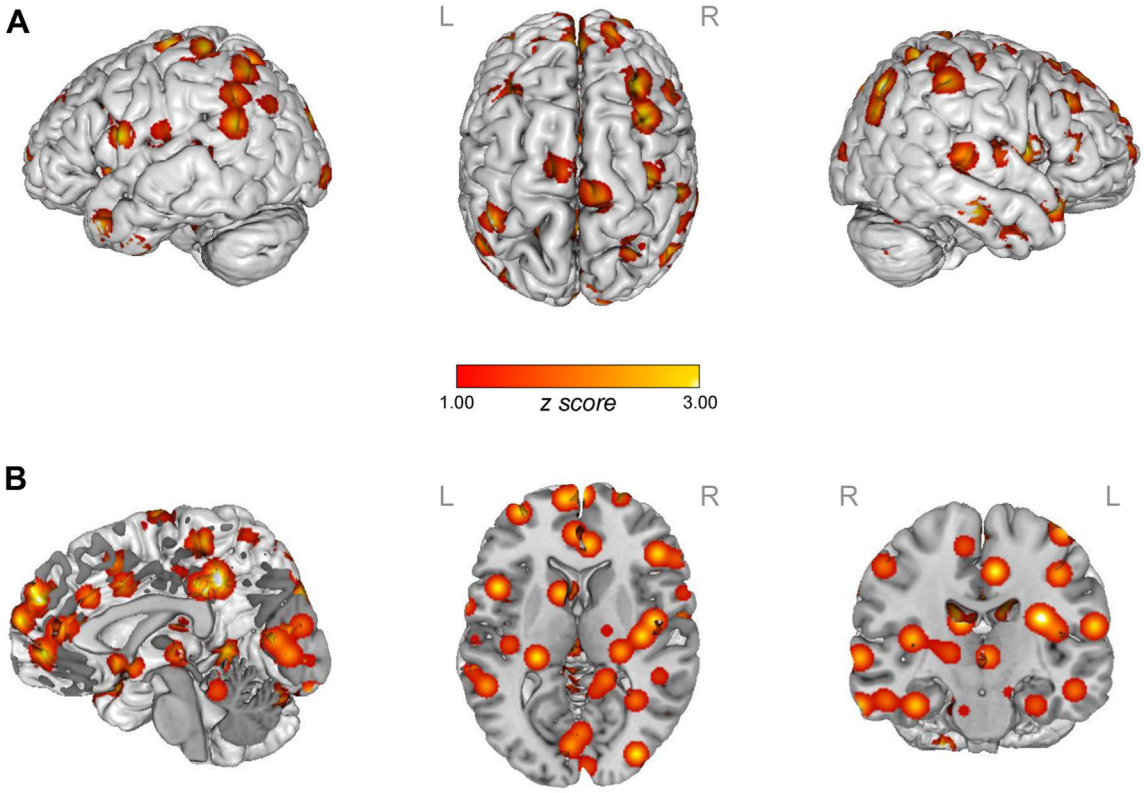

FIGURE 2.

Unthresholded Positive *z*-Score Map Derived From Task Functional Magnetic Resonance Imaging (fMRI) Studies on Irritability (k = 25)

Note: Task fMRI studies included in the main quantitative meta-analysis across neurocognitive domains. (A) Cortical regions and (B) subcortical regions in sagittal, axial, and coronal views (left to right) are presented. No convergent neural correlates of irritability were found across individual studies. L/R = left/right hemisphere.

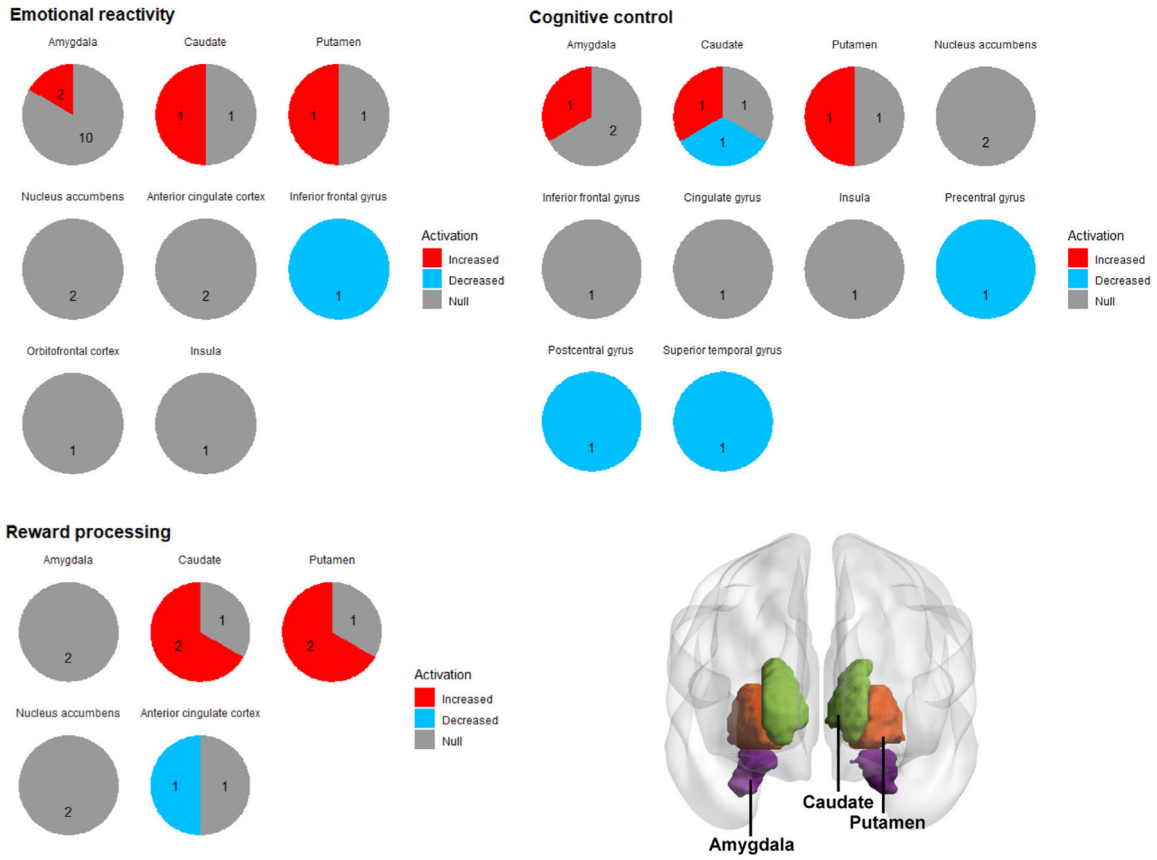

FIGURE 3.

Descriptive Summary of Region of Interest (ROI) Findings (k = 15)

Note: Pie charts summarize the respective proportions of task functional magnetic resonance imaging (fMRI) studies that reported an association with irritability symptoms or a related group difference between high vs low irritability groups in each region of interest (ROI). The brain image depicts the anatomical locations of amygdala, caudate, and putamen, which revealed the greatest number of significant findings across individual studies.

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TABLE 1

Overview of Task fMRI Studies in Child Irritability (k = 30)

	Sample characteristics									fMRI task domain				Whole brain		Region of interest	
Study	**N**	**Diagnostic group(s)**	**n**	**% Male participants**	**Recruitment**	**Age range (mean age), y**	**SES**	**% White participants**	**Irritability measure**	**Task**	**ER**	**CC**	**RP**	**Other**	**Threshold**	**Region**	**Threshold**
Adleman *et al.* (2011)28	82	BD	26	58.5	NIMH	8–17 (13.9)	—	—	K-SADS (SMD)	Probabilistic response reversal task		✓		Reversal learning	Yes Voxelwise $p < .005$, uncorrected (k > 20)	Yes Bilateral caudate	$\alpha = .05$, cluster-extent corrected in each ROI
		SMD	22													Bilateral cingulate gyri	
		HV	34													Bilateral inferior frontal gyri	
Aggensteiner *et al.* (2020)29	177	ODD and/or CD	108	77.3	EU-Aggressotype and EU-MATRICS project	8–18 (13.2)	—	—	Reactive-Proactive Aggression Questionnaire (child)	Emotional facial perception task	✓				Yes Voxelwise $p < .001$, uncorrected (k>10)	Yes Bilateral amygdala	$\alpha = .05$, FWE corrected
		HV	69						K-SADS (ODD/CD)							Insula	
																Orbitofrontal cortex	
																Anterior cingulate cortex	
Bertocci *et al.* (2019)30	96	Offspring of parent with bipolar disorder	20	53.7	Bipolar Offspring Study (BIOS)	— (14.1)	—	—	Child Affective Lability Scale (Irritability factor; child)	Emotional facial perception task	✓				Yes Voxelwise $p < .001$, corrected $\alpha = .05$	No	
		Offspring with a parent with a non-BD Axis-I disorder	21														
		Validation sample of youths with a variety of psychiatric disorders and behavioral and emotional dysregulation	55	54.5	Longitudinal Assessment of Manic Symptoms study (LAMS)	— (13.7)	—	—	Child Affective Lability Scale (Irritability factor; child)								
Brotman *et al.*[a] (2010)26	127	SMD	29	53.5	NIMH	8–17 (13.8)	—	—	K-SADS (SMD)	Emotional facial perception task	✓				No	Yes Bilateral amygdala	$\alpha = .05$
		ADHD	18														
		BD	43														
		HV	37														
Bubenzer-Busch *et al.* (2016)18	34	ADHD with comorbid DBD	27	100	Outpatient services at Aachen University Hospital	9–14 (11)	—	—	Reactive-Proactive Aggression Questionnaire (child)	Point subtraction aggression game	✓		✓		Yes Voxelwise $p < .001$, FWE-corrected $\alpha = .05$	No	
		HV	27														
Chaarani *et al.*[b] (2020)19	320	Irritable - moderate, high	160	51	IMAGEN study	14–15 (14.5)	—	—	Development and Well-Being Assessment (DAWBA) - Irritability	Stop signal task		✓		Inhibitory control	Yes Voxelwise $p < .005$, corrected $\alpha = .05$	Yes Bilateral superior temporal gyri	$\alpha = .05$

	Sample characteristics									fMRI task domain				Whole brain			Region of interest	
Study	N	Diagnostic group(s)	n	% Male participants	Recruitment	Age range (mean age), y	SES	% White participants	Irritability measure	Task	ER	CC	RP	Other	Threshold		Region	Threshold
									items closely resembling ARI (parent)									
		HV	160														Bilateral insula	
																	Bilateral inferior frontal gyri	
																	R ventral pre- and postcentral gyri	
Crum *et al.* (2020)31	155	Internalizing and externalizing conditions	98	59.4	Boys Town National Research Hospital, Center for Neurobehavioral Research	10–18 (15.3)	—	—	ARI (parent, child)	Affective Stroop task	✓	✓			Yes	Voxelwise $p < .001$, FDR corrected $\alpha = .05$	No	
		HV	57		Community													
[a]Deveney *et al.* (2012)27	96	BD	32	62.2	NIMH	8–18 (13.8)	—	—	K-SADS (SMD)	Stop signal task		✓		Inhibitory control	No		Yes	Bilateral putamen	$\alpha = .05$, voxelwise corrected
		SMD	26															Bilateral caudate	
		ADHD	17															Bilateral nucleus accumbens	
		HV	21															Bilateral anterior cingulate cortices	
																		Bilateral ventrolateral orbitofrontal cortices	
Deveney *et al.* (2013)15	42	SMD	19	61.9	NIMH	8–17 (14)	—	—	K-SADS (SMD)	Affective Posner task	✓	✓	✓	Frustrative nonreward	Yes	Voxelwise $p < .001$, corrected $\alpha = .05$	Yes	Bilateral amygdala	—
		HV	23															Bilateral caudate	
																		Bilateral putamen	
																		Bilateral nucleus accumbens	
Gatzke-Kopp *et al.* (2009)17	30	ADHD and/or CD	19	100	Community	12–16 (13.3)	Mean annual income = USD70, 500	78.8	Adolescent Symptom Inventory (ODD, CD, ADHD, Dysthymia, MDD)	Monetary incentive delay task			✓		Yes	Voxelwise $p < .01$, corrected $\alpha = .05$	Yes	Bilateral anterior cingulate cortices	$\alpha = .05$, cluster-level corrected
		HV	11						CBCL (aggression, attention problems, anxious/depressed)									Bilateral caudate	
																		Bilateral putamen	
Hodgdon *et al.* (2021)32	31	Treatment-seeking patients with varied levels of irritability and complex trauma, mostly	31	41.9	Local middle/high schools in San Diego	11–18 (14.5)	Maternal education less than high school = 64.5%; mean	0 (83.9% Hispanic/ Latinx; 6.5% Asian/Pacific Islander; 9.7%	ARI (parent, child)	Frustrative monetary incentive delay task	✓	✓	✓	Attention orienting following frustration	Yes	Voxelwise $p < .005$, corrected $\alpha = .05$	No		

	Sample characteristics								fMRI task domain				Whole brain		Region of interest	
Study	**N**	**Diagnostic group(s)**	**n**	**% Male participants**	**Recruitment**	**Age range (mean age), y**	**SES**	**% White participants**	**Irritability measure**	**Task**	**ER**	**CC**	**RP**	**Other**	**Threshold**	**Region**	**Threshold**
		Hispanic/Latinx and of low SES					monthly household income = USD2,772	African American/ Black)									
Ibrahim *et al.* (2019)33	57	ASD	20	80.2	Yale Child Study Center Autism Program	8–16 (12.7)	—	80.4	CBCL (externalizing, aggression)	Emotional facial perception task	✓				Yes — Voxelwise $p < .01$, corrected $\alpha = .05$	Yes — Bilateral amygdala	$\alpha = .05$
		ASD with disruptive behavior	18														
		HV	19														
[b] Karim *et al.* (2017)34	51	Child HV	30	52.4	Community	4–12 (7.6)	—	70.0	Child Behavior Questionnaire Long Form (anger and frustration; parent)	KidVid task	✓				Yes — Voxelwise $p < .005$, FWE corrected $\alpha = .05$	No	
		Adult HV	21			20–44 (26.7)											
Kircanski *et al.* (2018)35	197	DMDD	54	53.8	NIMH	8–18 (13.1)	Mean = 35.2, Holling-shead 2-Factor Index	—	ARI (parent, child)	Dot-probe task with emotional faces	✓	✓			Yes — Voxelwise $p < .005$, corrected $\alpha = .05$	Yes — Bilateral amygdala	$\alpha = .05$, Bonferroni correction
		ADHD	37														
		Anxiety	50														
		HV	56														
Kryza-Lacombe *et al.* (2020a)11	45	Treatment-seeking children with varied levels of irritability and anxiety	45	47.7	Community	9–19 (14)	—	55.6	ARI (parent)	Dot-probe task with emotional faces	✓	✓			Yes — Voxelwise $p < .005$, corrected $\alpha = .05$	Yes — Bilateral amygdala	$\alpha = .05$
					Local research clinic												
Kryza-Lacombe *et al.* (2020b)36	120	High-functioning ASD	47	76.7	Autism and Communication Disorders Center, University of Michigan	8–19 (14.2)	—	—	CBCL (irritability; parent)	Gender identification with emotional faces	✓				Yes — Voxelwise $p < .005$, corrected $\alpha = .05$	Yes — Bilateral amygdala	$\alpha = .05$, FDR corrected
		Non-ASD	73		Community												
Kryza-Lacombe *et al.* (2021)37	52	Intervention seeking	34	46.1	Community	10–20 (13.8)	Mean monthly household income = USD7,069	50.0	ARI (parent, child)	Monetary incentive delay task			✓		Yes — Voxelwise $p < .005$, corrected $\alpha = .05$	No	
		HV	18		Research clinic												
Liuzzi *et al.* (2020)20	19	HV	19	36.8	Community	11–15 (13.2)	—	52.6	ARI (parent, child)	Flanker task		✓		Inhibitory control	Yes — Voxelwise $p < .005$, corrected $\alpha = .05$	No	
Pagliaccio *et al.* (2017)38	83	DMDD	31	51.8	NIMH	8–18 (15.1)	—	—	K-SADS (DMDD)	Global-local affective attention task		✓		Cognitive flexibility	Yes — Voxelwise $p < .001$, FWE corrected $\alpha = .025$	No	
		ADHD	25						ARI (parent, child)								
		HV	27														

	Sample characteristics									fMRI task domain				Whole brain		Region of interest	
Study	**N**	**Diagnostic group(s)**	**n**	**% Male participants**	**Recruitment**	**Age range (mean age), y**	**SES**	**% White participants**	**Irritability measure**	**Task**	**ER**	**CC**	**RP**	**Other**	**Threshold**	**Region**	**Threshold**
Perlman *et al.* (2015)39	54	Irritability - high	26	57.7	Local child psychiatric unit	6–9y (8.1)	Mean parental education = 5.15 (4-year no degree); mean household income = USD33,300	26.1 (66.8% Black)	K-SADS (SMD)	FETCH task	✓		✓		Yes Voxelwise $p < .005$, FWE corrected $\alpha = .05$	Yes Bilateral striatum	$\alpha = .05$
		HV	28		Community				Multidimensional Assessment Profile of Disruptive Behavior (temper loss; parent)							Bilateral amygdala Anterior cingulate cortex	
Stoddard *et al.* (2017)40	115	DMDD	37	55.7	Youths undergoing treatment for clinically significant disorders	8–17 (13.2)	Mean = 35.5, Holling-shead 2-Factor Index	—	ARI (parent, child)	Emotional facial perception task	✓				Yes Voxelwise $p < .001$, corrected $\alpha = .05$	No	
		ADHD	24						K-SADS (DMDD)								
		Anxiety	32														
		HV	22														
Strenziok *et al.* (2011)41	20	HV	20	100	NIMH	14–17 (15.7)	—	—	State Trait Anger Expression Inventory (STAXI)	Social mental imagery task	✓			Mental imagery of aggressive and non-aggressive interactions with a peer	Yes Voxelwise $p < .005$, corrected $\alpha = .05$	No	
$C_{\text{Thomas } et\ al.}$ (2012)42	57	BD	19	52.6	NIMH	8–18 (14.9)	—	—	K-SADS (SMD)	Emotional facial perception task	✓				Yes Voxelwise $p < .005$, corrected $\alpha = .05$	Yes Bilateral amygdala	$\alpha = .05$
		SMD	15														
		HV	23														
Thomas *et al.* (2013)43	53	BD	19	47.2	NIMH	— (14.2)	—	—	K-SADS (SMD)	Emotional facial perception task	✓				Yes Voxelwise $p < .001$, corrected $\alpha = .05$	Yes R amygdala	$\alpha = .05$
		SMD	19														
		HV	15														
Thomas *et al.* (2014)44	60	BD	20	48.3	NIMH	8–18 (14.8)	—	—	K-SADS (SMD)	Affective priming task with emotional faces	✓				Yes Voxelwise $p < .005$, uncorrected ($k \geq 20$)	Yes Bilateral amygdala	$\alpha = .05$
		SMD	18														
		HV	22														
Tseng *et al.* (2016)12	37	SMD	17	62.2	NIMH	8–18 (14.5)	—	—	K-SADS (SMD)	Modified affective priming task with emotional faces	✓				Yes Voxelwise $p \leq .005$, uncorrected ($k > 20$)	Yes Bilateral amygdala	$\alpha = .05$
		HV	20						ARI (parent, child)								
Tseng *et al.* (2019)16	195	DMDD	52	50.3	NIMH clinics	8–18 (12.9)	Mean = 32.0, Holling-shead 2-Factor Index	—	ARI (parent, child)	Affective Posner 2 task	✓	✓	✓	Attention orienting following frustrative nonreward	Yes Voxelwise $p < .0001$, corrected $\alpha = .05$	Yes Bilateral amygdala	$\alpha = .05$, Bonferroni correction

	Sample characteristics								fMRI task domain					Whole brain		Region of interest	
Study	N	Diagnostic group(s)	n	% Male participants	Recruitment	Age range (mean age), y	SES	% White participants	Irritability measure	Task	ER	CC	RP	Other	Threshold	Region	Threshold
		Anxiety	42													Bilateral striatum (caudate, putamen, nucleus accumbens)	
		ADHD	40														
		HV	61														
Tseng *et al.* (2021)45	59	Anxiety	28	33.9	NIMH	— (13.2)	—	—	ARI (parent, child)	Threat extinction recall task with emotional faces	✓			Threat–safety discrimination	Yes	Voxelwise $p < .0001$, clusterwise FWE corrected $\alpha = .05$	No		
		HV	31														
Wiggins *et al.* (2016)13	71	BD	24	60.6	NIMH clinics	9–21 (15.7)	—	—	ARI (parent, child)	Emotional facial perception task	✓				Yes	Voxelwise $p < .005$, corrected $\alpha = .05$	No		
		DMDD	25														
		HV	22														
Yang *et al.* (2017)46	48	ASD	31	100	Yale Child Study Center	4–18 (10.9)	—	—	5–12 y: Child Symptom Inventory–4 (ODD)	Biological motion perception task				Social perception	Yes	Voxelwise $p < .05$, corrected $\alpha = .05$	No		
		HV	17						12–18 y: Adolescent Symptom Inventory–4 (ODD)								

Note: ADHD = attention-deficit/hyperactivity disorder; ARI = Affective Reactivity Index; ASD = autism spectrum disorder; BD = bipolar disorder; CBCL = Child Behavior Checklist; CC = cognitive control; CD = conduct disorder; DBD = disruptive behavior disorder; DMDD = disruptive mood dysregulation disorder; ER = emotion reactivity; FDR = false discovery rate; fMRI = functional magnetic resonance imaging; FWE = familywise error rate; HV = healthy volunteers; K-SADS = Kiddie Schedule for Affective Disorder and Schizophrenia; MDD = major depressive disorder; NIMH = National Institute of Mental Health; ODD = oppositional defiant disorder; ROI = region of interest; RP = reward processing; SES = socioeconomic status; SMD = severe mood dysregulation; L/R = left/right hemisphere; — = not applicable or not reported.

[a]Studies included ROI analyses only and thus were excluded from the quantitative meta-analysis.

[b]Studies were qualified for the quantitative analysis but were excluded from the main analysis because significant results were found only in the ROI analysis informed by a whole-brain structural analysis,[19] and no significant clusters were reported for any task interaction effects with irritability (without age interaction).[34]

[c]Reference 42 was excluded from any GingerALE analyses, as only significant main effects of irritability were found upon data extraction.