



## Neural substrates of child irritability in typically developing and psychiatric populations



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### ABSTRACT

Irritability is an aspect of the negative affectivity domain of temperament, but in severe and dysregulated forms is a symptom of a range of psychopathologies. Better understanding of the neural underpinnings of irritability, outside the context of specific disorders, can help to understand normative variation but also characterize its clinical salience in psychopathology diagnosis. This study assessed brain activation during reward and frustration, domains of behavioral deficits in childhood irritability. Children (age 6–9) presenting in mental health clinics for extreme and impairing irritability ( $n = 26$ ) were compared to healthy children ( $n = 28$ ). Using developmentally sensitive methods, neural activation was measured via a negative mood induction paradigm during fMRI scanning. The clinical group displayed more activation of the anterior cingulate and middle frontal gyrus during reward, but less activation during frustration, than healthy comparison children. The opposite pattern was found in the posterior cingulate. Further, in clinical subjects, parent report of irritability was dimensionally related to decreased activation of the anterior cingulate and striatum during frustration. The results of this study indicate neural dysfunction within brain regions related to reward processing, error monitoring, and emotion regulation underlying clinically impairing irritability. Results are discussed in the context of a growing field of neuroimaging research investigating irritable children.

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### 1. Introduction

Irritability is an aspect of the negative affectivity domain of temperament, which captures variation in the intensity, duration and regulation of children's angry mood and behavior (Rothbart et al., 2000; Snaith and Taylor, 1985). While anger is a normative response to frustration, intense, pervasive and/or dysregulated irritability is maladaptive. In particular, it is a hindrance to early school success and peer relationships (Blair, 2002; Blair et al., 2004; Denham et al., 2011) and is noted as a marker for psychiatric illness, bridging the gap between internalizing and externalizing child psychopathology (Stringaris, 2011). Thus, irritability is a prime construct for investigation within the National Institute of Health's Research Domain Criteria Project (RDoC) which emphasizes

symptoms rather than categorical disorders and highlights the strong, mostly unexplored, neurodevelopmental origins of psychiatric illness (Morris and Cuthbert, 2012; Sanislow et al., 2010).

Although irritability is a growing focus for psychiatric research and therapeutic interest (Leibenluft et al., 2003; Stringaris, 2011), we know little about its neural mechanisms. Critical questions concern the neural deficits associated with excessive irritability and the nature of those defects that might underlie the poor mental health outcomes associated with high irritability. Detecting neural markers could be helpful in differentiating when high irritability in children is an indicator of abnormality (e.g. marking a prodromal phase of psychopathology) from when children are displaying high levels of normative irritable temperament. In already clinically diagnosed children, the nature of ongoing variation and/or deterioration in this circuitry might be linked to increasing impairment and could possibly aid clinicians in therapeutic decisions or predict treatment response.

Several adult neuroimaging studies have investigated the neural correlates of negative mood by inducing it through

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autobiographical scripts (Cerqueira et al., 2010), emotional images or music (Dyck et al., 2011), or direct instruction (Habel et al., 2005). The literature investigating the neurodevelopment of irritability has specifically focused on the negative mood of frustration, defined as the affective response to the prevention of goal attainment or absence of expected reward. Frustration is widely noted in the individual differences literature (Abler et al., 2005; Campbell, 1995; Rich et al., 2011) and clinical community (Fergus et al., 2003; Leibenluft et al., 2003) as the most commonly observed precipitant for temper outbursts in highly irritable children. Frustration is often induced while collecting neural data through paradigms that increase in difficulty (Lewis et al., 2006; Moadab et al., 2010; Perlman and Pelphrey, 2010) or involve an unsolvable task (Pawliczek et al., 2013), which blocks a desired goal, or deceives participants into believing that failing performance will decrease the likelihood of an expected reward (Deveney et al., 2013; Rich et al., 2007).

The fMRI studies cited above have found neural activation changes in the context of frustration induction within three main regions: the anterior cingulate cortex (ACC), amygdala, and striatum, all of which are relevant to cognitive and emotional dysfunction in irritability. The ACC has been linked to error monitoring (Carter et al., 1998), deviation from a potential reward (Amiez et al., 2005), and emotion regulation (Bush et al., 2000). The amygdala is involved in the evaluation of the salience of a potential negative stimulus and the coordination of cortical networks during that evaluation (Pessoa and Adolphs, 2010). Finally, the dorsal and ventral striatum has been linked to general reward response in both humans (Delgado, 2007) and animals (Apicella et al., 1991). Studies focused on mood induction in children have noted the modulation of these regions during frustration. In typically developing children (ages 5–11), Perlman and Pelphrey (2010) induced negative mood through fluctuating difficulty levels of a game, leading children to believe that they would lose a desired prize. Activation related to frustration was noted in the dorsal and ventral ACC with increased connectivity between the ACC and amygdala as difficulty increased (Perlman and Pelphrey, 2011). Deveney and colleagues (2013) investigated children with high levels of irritability who were presenting for clinical care. They found that when negative mood was induced by providing participants with rigged feedback on a cued attention task, leading them to believe that they would lose money, subjects demonstrated amygdala and striatum deactivation relative to healthy subjects. The authors reasoned that their findings might imply overall neural dysregulation occurring when an outcome is worse than expected, which might underlie the exaggerated and inappropriate reaction to frustration exhibited in clinically impaired children. Taken together, these findings provide early evidence for brain circuitry underlying varying aspects of irritability (i.e. evaluation of negative stimuli, reward, emotion regulation).

We conducted an fMRI investigation in children who were undergoing clinical treatment for severe irritability and a comparison group of healthy children. We took an RDoC approach to our questions of irritability by recruiting a sample of clinical children who were high in the symptom of irritability, but allowed disorder diagnosis to vary. Based upon previous research, we expected to find (1) decreased anterior cingulate activation in clinically irritable subjects due to difficulties in effective error monitoring and/or emotion regulation during frustration, (2) amygdala deactivation in irritable subjects due to their likely deficits in evaluation of the emotional salience of stimuli during frustration, and (3) potential striatum deactivation during rewarding and punishing episodes due to dysfunctional reward processing in irritable subjects. We further expected greater deficits in our regions of interest in clinical subjects who had greater parent report of irritability.

## 2. Materials and methods

This study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh.

### 2.1. Participants

Thirty-five children (ages 6–9) were recruited from local child psychiatric clinics (Clinical). Parents of potential participants were asked by a clinic receptionist if they were interested in talking to a member of the research team about participation when arriving for a scheduled clinic visit. Parents who expressed interest were introduced to a member of the research staff who explained procedures of the study, but did not specify that irritability was the primary research topic. Parents completed a short screening interview in which they were questioned on primary inclusion criteria: (1) irritability present for at least half the day on most days, (2) irritability is noticeable in more than one setting (e.g. home, peers, school), (3) at least three anger/frustration outbursts per week, (4) these symptoms have negatively and severely affected the child's academics and/or family/social life, (5) irritability has been present for a minimum of 6 months, and (6) their initial reason for seeking care was their child's high irritability.<sup>1</sup> Children were not invited to participate in the study if all of these criteria were not met.

Exclusion criteria included severe systemic medical illnesses, neurological disorders, history of head trauma with loss of consciousness, use of non-psychotropic medications that may produce CNS effects (e.g. steroids), IQ < 70 (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), being unable to complete tasks in English, and autism spectrum disorders or developmental delays. Additional exclusion criteria for scanning purposes included claustrophobia or metal objects in the body. Clinical subjects were permitted to use prescribed medication(s) before scanning, given ethical problems with stopping medication for research purposes.

Thirty-seven physically healthy participants with no personal history of psychiatric diagnosis were recruited from the community (Comparison). There was no history of schizophrenia, autism spectrum disorders, mental retardation or bipolar disorder in first degree relatives or depression, anxiety disorders, ADHD, disruptive behavior disorders, or eating disorders during the lifetime of the child. Recruited participants were matched as closely as possible on age, race, sex, family income, parent education, and IQ (Table 1). Parents/guardians provided written informed consent, and youth provided assent prior to study participation. Participants received monetary compensation, a small prize, and a framed picture of their structural neuroimaging scan (Perlman, 2012).

### 2.2. Symptom assessment<sup>2</sup>

During an initial study visit, taking place in the laboratory, diagnostic assessments of all participants were performed by interviewing the caregiver and child using the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-PL-W; Birmaher et al., 2009), including the Severe Mood Dysregulation Module (SMD; Leibenluft, 2011). K-SADS interviews were completed by a single research assistant who was trained by the

<sup>1</sup> Although recruitment for this study predated the addition of Disruptive Mood Dysregulation Disorder (DMDD) to DSM-5, all subjects in this study would have met DMDD/SMD. We note that, although high levels of irritability might be present, DMDD/SMD is not, currently, dually diagnosed with bipolar disorder. Because this study predated regulations for DMDD diagnosis, and those regulations are still a topic of controversy, all potential subjects who met our high irritability criteria were included in the study regardless of bipolar disorder diagnosis.

<sup>2</sup> Exploratory analyses related to diagnostic category are presented in the supplemental materials.

**Table 1**  
Demographics, clinical variables, and behavior performance.

Demographics	Clinical (n = 26)		Comparison (n = 28)		t/ $\chi^2$	
Age (mean/SD)	8.4	1.2	7.7	1.3	1.9 <sup>§</sup>	
Race (number/percent)	White	8	30.8%	6	21.4%	3.95 <sup>b</sup>
	Black	18	69.2%	18	64.3%	
	Other	0	0%	4	14.3%	
Sex (number/percent)	Male	17	65.4%	14	50%	1.3
Family income (mean/SD)	\$31,900	\$22,800	\$34,700	\$31,700	0.37	
Parent education (mean/SD) <sup>a</sup>	5.0	1.6	5.3	1.1	0.8	
IQ (mean/SD)	97.7	13.8	104.1	13.82	1.7	
Irritability						
MAP-DB Temper Loss (mean/SD)	46.15	18.15	6.52	7.50	10.62 <sup>*</sup>	
Diagnosis						
Bipolar (number/percent)	10	38.5%	–	–	–	
Major depression (number/percent)	7	26.9%	–	–	–	
Anxiety disorders (number/percent)	10	38.5%	–	–	–	
Attention deficit hyperactivity disorder (number/percent)	20	76.9%	–	–	–	
Oppositional defiant disorder (number/percent)	12	46.2%	–	–	–	
Conduct disorder (number/percent)	14	53.8%	–	–	–	
Medication use	18	69.2%	–	–	–	
Antidepressants (number/percent)	3	11.5%	–	–	–	
Antipsychotics (number/percent)	4	15.4%	–	–	–	
Stimulants (number/percent)	14	53.8%	–	–	–	
Benzodiazepines (number/percent)	1	3.8%	–	–	–	
Behavioral performance						
Winning trials reaction time (mean/SD)	394.0 ms	104.4 ms	376.4 ms	108.4 ms	0.6	
Losing trials reaction time (mean/SD)		436.9 ms	165.4 ms	414.1 ms	121.9 ms	0.6
Mood rating winning blocks (mean/SD) <sup>c</sup>		6.4	0.6	6.0	1.1	1.9 <sup>§</sup>
Mood rating losing blocks (mean/SD) <sup>c</sup>		3.5	2.1	3.1	2.0	0.8

<sup>a</sup> 1, less than 7th grade; 2, middle school; 3, partial high school; 4, completed high school; 5, 4 year-no degree; 6, 4 year degree; 7, post graduate; 8, no information; <sup>b</sup> Fisher's exact test (2 sided); <sup>c</sup> ratings ranged from 1 (most negative) to 7 (most positive); <sup>\*</sup>  $p < 0.001$ , <sup>§</sup>  $p < 0.10$ .

developers of the K-SADS and has several years of experience conducting K-SADS interviews on multiple studies of child psychopathology. All Clinical participants were confirmed to meet criteria for irritability through the SMD module. The rest of the K-SADS interview was used to characterize co-morbid diagnoses. Children were also given a present/absent score for each of 7 diagnostic categories based on K-SADS-PLW criteria: bipolar disorder, major depression, anxiety disorders, ADHD, conduct disorder, and oppositional defiant disorder (Table 1 and supplementary materials). Comparison children were required to be free of meeting any K-SADS diagnostic criteria. A final sample of 28 Clinical (mean age = 8.35, SD = 1.25) and 29 Comparison (mean age = 7.74, SD = 1.25) participants were included in neuroimaging data collection after 7 Clinical and 8 Comparison children were eliminated from the study due to not fully meeting inclusion/exclusion criteria after the K-SADS was administered.

### 2.3. Irritability parent questionnaire

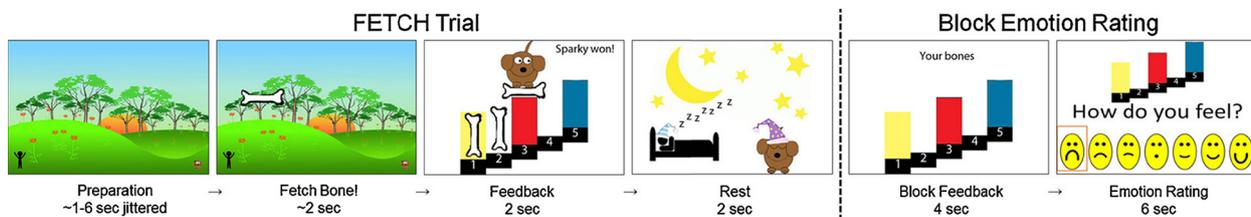
During the initial visit, parents also completed the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB), which is a developmentally sensitive questionnaire aimed at distinguishing normative misbehavior from clinically concerning patterns of disruptive behavior and for characterizing irritability dimensionally (Wakschlag et al., 2012). For the MAP-DB questionnaire, we used the Temper Loss subscale as a dimensional measure of both irritable mood and the behavioral manifestations of irritability. The MAP-DB distinguishes normative variation from clinically problematic irritability via assessment of behavioral quality (e.g. "tantrums till exhausted"), context (e.g. tantrums for no reason), and objective frequency of the behavior (e.g. from never/rarely to many times per day). Cronbach's  $\alpha$  for the current sample was 0.97.

Note that this scale was used to characterize level of irritability, for the purposes of dimensional analysis, and not as a cut-off score for inclusion/exclusion.

### 2.4. Neuroimaging paradigm

fMRI scanning occurred either in the afternoon on the same day as the initial morning laboratory visit or on a separate day according to parent preference. During fMRI scanning, participants completed the Frustrative Emotion Task for Children (FETCH), which has been used previously to induce frustration in preschool and school age children (Perlman et al., 2014). Outside of the scanner participants were told that their performance during the game would determine from which of three boxes they would choose their final prize. The large, blue box contained exciting toys that were attractive to children. The medium, red box contained an assortment of stickers, and the small, yellow box contained a single broken crayon. The selection of the disappointing prize box was modeled after studies using a similar technique to set up the expectation that children would receive their desired prize (Cole, 1986; Saarni, 1984).

In the task, subjects competed with Sparky, "a very sneaky dog", to fetch bones by pressing a button as soon as the bone appeared on the screen (Fig. 1). Each trial began with an empty landscape that appeared for a randomly varied, "jittered" (Miezin et al., 2000), period of 1–6 s during which the subject was told to relax before a new bone appeared (preparation phase). Next, a bone appeared at a random location in that landscape for up to 2 s during which the subject was able to press their button in order to grab the bone (fetch phase). Although the subject was unaware, each trial was fixed so that sometimes the child could fetch the bone before Sparky (win trials), but sometimes the dog would fetch the bone before the child's possible reaction time (lose trials). Win trials were indicated



**Fig. 1.** Left: visual representation of a single losing trial of the FETCH task. Right: visual representation of the end of block online emotion rating. Children were asked to rate their own level of positive/negative feelings after blocks in which they earned nearly enough bones to win their prize or blocks in which they lost all previously earned bones.

by an animated line drawing portraying the child grabbing the bone and placing it within one of the prize boxes during the feedback period, while lose trials showed Sparky grabbing the bone and then taking a bone out of a previously won box. As soon as the button was pressed (on win trials) or as soon as Sparky grabbed the bone (on lose trials), feedback appeared on the screen (feedback phase) so that the fetch and feedback phases combined for 4 s in total. Finally, the subjects were told to rest and clear their mind before the next trial during a 2-s inter-stimulus interval. The task was animated and contained engaging sound effects, which were audible through headphones.

Trials were grouped together with the intention of inducing a positive/happy or negative/frustrated mood for approximately 1 min. This was done by slowly accumulating bones to make the subject feel like s/he was gaining momentum toward winning or by slowly losing bones to make the subject feel like the desired prize was gradually slipping away. This served to make each win or lose trial more salient because it was generally grouped in an overarching context that was more directly oriented toward a final prize. Five bones had to be accumulated in sequence in order to win a prize from the large (blue) box. Thus, 5 win trials and 1 lose trial were presented in an unpredictable order to induce positive mood (all but one bone necessary to win the final prize), followed by 5 lose trials and 1 win trial, presented in an unpredictable order, in order to induce negative mood. After each 5 trials, children were shown their cumulative bones (either 4 when positive mood was induced or 0 when negative mood was induced). They were asked to complete an online emotion rating by choosing from a spectrum of seven line drawn faces representing how they were feeling, ranging from a negative to a positive mood (see Fig. 1). The full task began with a positive mood induction and alternated between positive and negative mood inductions to include seven total inductions. At the end of the game, the addition of an extra win trial allowed all children to fill the blue box (5 bones) and receive their desired prize. Thus, the task contained more winning trials (23 total) than losing trials (18 total) in order to allow the task to end on a positive mood induction. All children completed a practice version of the task before scanning to ensure comprehension.

## 2.5. Data acquisition

Neuroimaging data were collected using a 3.0 Tesla Siemens Trio MRI scanner. BOLD images covering 33 axial slices (3 mm thick, 0.75 mm gap, TR/TE=2000/20 ms, FOV=220 × 207 mm<sup>2</sup>, matrix=128 × 120 for in-plane resolution of 1.7 × 1.7 mm<sup>2</sup> Flip angle FA=80°) were acquired with a gradient echo EPI sequence for 9:10 min:s (272 successive brain volumes). This sequence was chosen because of its strength in signal recovery from regions prone to susceptibility gradients near air/tissue interfaces through optimization of the imaging slice orientation (Deichmann et al., 2003). Structural 3D MPRAGE images were acquired in the same session in 3:47 min:s (1 mm isotropic voxel, TR/TI/TE=2100/1050/3.43 ms, FA=8°, GRAPPA acceleration factor=2).

## 2.6. Data analysis

Data were preprocessed and analyzed using BrainVoyager QX 2.8 (Brain Innovation: Maastricht, The Netherlands). Preprocessing included slice time correction (cubic spline interpolation), alignment of slice (cubic spline interpolation to the first non-discarded scan time), 3-dimensional motion correction (tri-linear interpolation), spatial smoothing (6 mm Gaussian kernel), linear trend removal, and temporal high-pass filtering (fast-Fourier transform based with a cutoff of 3 cycles/time course). The functional data sets were co-registered to the Talairach-transformed (Talairach and Tournoux, 1988) T1-weighted anatomical image series to create a 4-dimensional data representation.

We employed a modified “scrubbing” technique (Power et al., 2012) to remove excessive participant movement from our analyses. Frame displacement (i.e. shift in position in any of 6 directions/rotations) was calculated for the duration of the time-course. Trials in which the subject moved more than 1.7 mm (the size of a native space voxel; 1.7 × 1.7 × 3 mm) were removed from analysis with the stipulation that subjects could lose up to 4 events per win condition (17%), 4 events per loss condition (21%), and 10 baselines (24%) before being excluded from analysis entirely. Two Clinical subjects and one Comparison subject were deemed to have excessive movement and were, thus, excluded from analysis. This left a final sample of 26 Clinical and 28 Comparison subjects. Of the remaining subjects, groups did not significantly differ in mean frame displacement [ $F(1,52)=0.98, p=0.12$ ], number of trials lost [ $F(1,52)=1.00, p=0.13$ ], or maximum movement [ $F(1,52)=0.06, p=0.39$ ]. Z-transformed participant movement was also entered as a covariate of no interest at the individual participant level.

We analyzed this task using an event-related analytical design with all win trials as part of the win condition and all lose trials as part of the lose condition. Note that this task can also be analyzed as a block design (Perlman et al., 2014). A multi-participant statistical analysis was performed by multiple linear regression of the time course of the BOLD response in each voxel. Regressors were generated to represent the design matrix of the experiment and a general linear model was computed to fit these regressors to each participant’s z-normalized volume time courses. Model predictors were defined for each trial type (win/lose) by convolving an ideal boxcar response with a gamma-function model of the hemodynamic response (Friston et al., 1997). Boxcar values were equal to 1 during the win and lose trials (approximately 2 s during which the bone appeared combined with 2 s of feedback) and 0 during baseline (the 2 s rest inter stimulus interval combined with approximately 1–6 jittered seconds during the preparation phase).

Our initial analysis strategy employed a whole-brain approach. We computed a 2(group: Clinical/Comparison) × 2(condition: win/lose) ANOVA to examine the main effects of condition and group and the group × condition interaction across the whole brain. Activation maps were visualized on a Talairach-transformed template brain, displayed at a resolution of 1 mm<sup>3</sup>, and all p-values set to an uncorrected threshold of  $p < 0.005$ . To correct for multiple comparisons we implemented a randomization technique to

estimate a corrected cluster-level confidence for the entire volume ( $\alpha = 0.05$ , 10,000 iterations; BrainVoyager Cluster-level Statistical Threshold Estimator). This family wise error correction (FWE) method uses a nonparametric Monte Carlo simulation that calculates the likelihood of obtaining a cluster of randomly generated voxels across the entire volume at the given individual voxel probability threshold (Forman et al., 1995). We extracted beta values from 3 mm spheres centered around peak voxels in order to visualize and interpret the direction of interaction effects. Subsequently, we tested the effects of both sex and age on the noted interaction effects using ANCOVA models.

Our follow-up strategy was to employ a region-of-interest (ROI) approach. Reward related tasks in typically developing children have found increased activation of multiple regions of the striatum (Helfinstein et al., 2013). Previous research also suggests children suffering from extreme irritability experience abnormal activation of the ACC (Fergus et al., 2003; Rich et al., 2007), amygdala (Deveney et al., 2013), and striatum (Adleman et al., 2011) during reward/frustration tasks. Thus, we conducted ROI analyses on the AFNI (National Institutes of Health, Bethesda, MD) defined ACC, bilateral striatum (caudate, putamen, and nucleus accumbens), and bilateral amygdala. Mean beta values were extracted from each whole region for each subject in each condition and submitted to a group-by-condition ANOVA in SPSS version 20 (IBM Software).

### 2.7. Medication effects

A problem for all neuroimaging studies of clinical populations is the potential confounding effect of psychotropic medication, as it is difficult to recruit medication-free participants into such studies (Phillips et al., 2008). Thus, variables representing the taking of each psychotropic medication class (antipsychotic, antidepressant, mood stabilizer, benzodiazepines, and stimulant) were examined (see Table 1). These analyses were completed to ascertain which between group effects, if any, might be driven by medication usage amongst specific Clinical subjects. Due to small numbers of subjects taking various medication categories, we conducted analyses for the taking vs. not taking of both stimulant medication and all types of medication combined. All analyses were computed by *t*-test with extracted BOLD signal from a 3 mm sphere centered on the peak voxel of the whole-brain group  $\times$  condition interaction (lose > win) as the dependent variable and the medication variable of interest as the independent variable for the Clinical group only.

Next, we looked within each, AFNI defined, region of interest (ACC, striatum, and amygdala) in order to examine the dimensional relationship between irritability (parent report on MAP-DB questionnaire) and neural response to frustration for the Clinical group only and both groups together. Here we examined neural response to loss trials and correlated each voxel with irritability. We also correlated activation during both win and lose trials with the respective win and lose average online mood ratings for each region of interest. All *p*-values for these analyses were subjected to an uncorrected threshold of  $p < 0.005$  with the FWE correction described above implemented to control for the voxelwise error rate at  $p < 0.05$ .

## 3. Results

### 3.1. Diagnostic, parent report data, and task performance

As expected, participants in the Clinical and Comparison groups significantly differed from each other on parent reported irritability [ $t(52) = 19.3$ ,  $p < 0.001$ ] (Table 1). There were no sex differences noted in parent reported irritability [ $t(52) = 1.02$ ,  $p = 0.31$ ]. For the

clinical group, there were no sex differences in obtaining ADHD [ $t(24) = 0.89$ ,  $p = 0.39$ ], Conduct Disorder [ $t(24) = 0.68$ ,  $p = 0.50$ ], or ODD diagnoses [ $t(24) = -0.68$ ,  $p = 0.50$ ].

Reaction time on both win [ $t(52) = 0.58$ ,  $p = 0.55$ ] and lose [ $t(52) = 0.61$ ,  $p = 0.56$ ] trials did not significantly differ between groups. For the online mood ratings, a paired samples *T* test revealed an overall significant difference between the winning and losing blocks [ $t(53) = 10.75$ ,  $p < 0.001$ ], which indicated that negative mood was sufficiently induced in both groups during loss. Groups, however, did not significantly differ on self-report of mood during the losing blocks [ $t(52) = 0.75$ ,  $p = 0.46$ ]. The Clinical group rated themselves as marginally significantly more positive than the Comparison group on winning blocks [ $t(52) = 1.86$ ,  $p = 0.07$ ].

### 3.2. Whole-brain ANOVA

The 2(group: Clinical/Comparison)  $\times$  2(condition: win/lose) ANOVA revealed a main effect of group in the postcentral gyrus [ $F(1,52) \geq 8.60$ ,  $p < 0.005$ ] (see Table 2 for specific cluster size, statistical value, and location information for all analyses). A Clinical > Comparison contrast revealed significantly more activation in this region for the Clinical than for Comparison group [ $t(53) \geq 2.93$ , minimum significant cluster size = 19 vox<sup>3</sup>]. We found a main effect of condition in 7 different clusters [ $F(1,52) \geq 8.99$ , minimum significant cluster size = 31 vox]. A lose > win contrast revealed more activation in the superior temporal gyrus, inferior temporal gyrus, right middle frontal gyrus, caudate head, and putamen for the win condition and more activation in the left middle frontal gyrus and inferior frontal gyrus for the lose condition [ $t(53) \geq 2.93$ ].

Finally, the group  $\times$  condition interaction, revealed three clusters of activation located in the ACC/medial prefrontal cortex and a fourth cluster located in the posterior cingulate (PCC) [ $F(1,52) \geq 8.60$ , minimum significant cluster size = 17 vox; see Fig. 2]. Extraction and comparison of beta values centered around the peak activation voxels were conducted for post hoc interaction interpretation purposes only. The results of independent samples *t*-tests revealed a significant group difference for the winning condition [ $t(52) = -2.56$ ,  $p = 0.01$ ] and a near significant difference for the losing condition [ $t(52) = 1.73$ ,  $p = 0.09$ ] in the ACC region. Here, the Clinical group increased activation during the winning condition, while the Control group increased activation during the losing condition (see Fig. 2). In the PCC, we observed a significant group difference for the losing condition [ $t(52) = -2.01$ ,  $p = 0.05$ ], but not for the winning condition [ $t(52) = 1.12$ ,  $p = 0.27$ ]. The Clinical group displayed increased activation during the losing condition relative to the Control group. Finally, we tested the effects of both child age and sex on this interaction effect using ANCOVA models. There was no significant relationship between either age [ $F(1,51) = 1.81$ ,  $p = 0.19$ ] or sex [ $F(1,51) = 0.26$ ,  $p = 0.61$ ] and ACC activation, nor was there a significant relationship between either age [ $F(1,51) = 0.05$ ,  $p = 0.83$ ] or sex [ $F(1,51) = 1.20$ ,  $p = 0.28$ ] and PCC activation.

### 3.3. Region of interest analysis

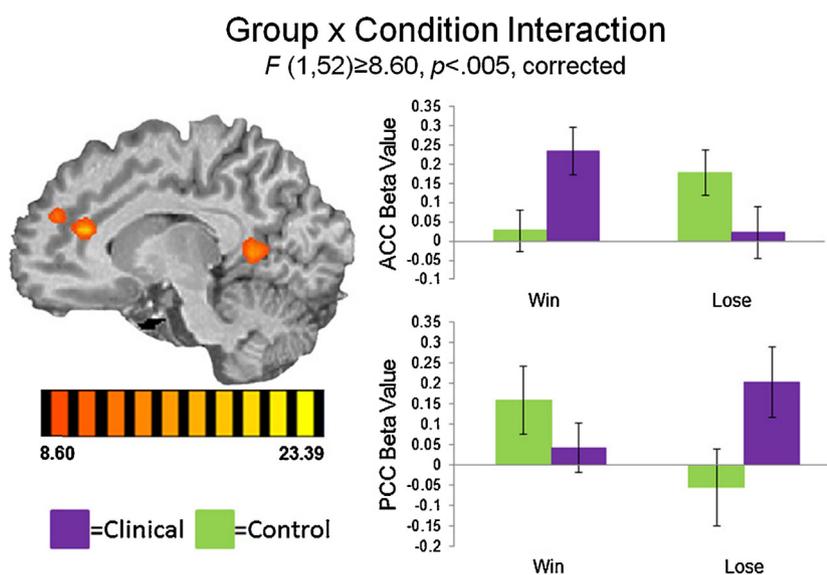
For the striatum region, we found a significant main effect of condition [ $F(1,52) = 3.34$ ,  $p = 0.05$ ], where win was greater than lose, but no main effect of group or a group  $\times$  condition interaction. Finally, for the amygdala region, we did not find any significant effects.

<sup>3</sup> FWE correction minimum cluster sizes are reported in  $1.7 \times 1.7 \times 3$  mm native space.

**Table 2**  
Neural activity clusters; whole brain ANOVA\*.

	Region	Hemisphere	BA	Peak voxel (x, y, z)	Size (1 mm <sup>3</sup> )	Average stat value (F, p)
Main effect group	PCG	R	3	56, -20, 39	1750	10.76, 0.002
Main effect condition	STG	R	38	53, 19, -19	6323	13.04, 0.002
	MFG	R	10	29, 55, 6	1877	11.43, 0.002
	MFG	L	10	-47, 46, 9	1406	11.28, 0.002
	ITG	L	19	-49, -71, -3	5574	13.73, 0.001
	IFG	L	47	-55, 22, -12	3525	13.45, 0.001
	Caudate Head	R	-	11, 7, 0	5551	14.09, 0.001
	Putamen	L	-	-16, 7, 0	8847	16.12, 0.001
Group × Condition interaction	SFG	R	9	11, 49, 24	578	10.12, 0.003
	PHG/PCC	R	30	11, -47, 6	907	11.04, 0.002
	ACC	R	32	11, 34, 18	901	11.60, 0.002
	MFG	L	10	-1, 55, 21	643	11.04, 0.002

\*Whole brain statistical threshold  $p < 0.005$ ; FWE corrected  $p < 0.05$ . BA, Brodmann area; PCG, postcentral gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus; ITG, inferior temporal gyrus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; PHG/PCC, parahippocampal gyrus/posterior cingulate cortex; ACC, anterior cingulate cortex.



**Fig. 2.** Whole-brain ANOVA revealed a group × condition interaction in the anterior cingulate (ACC)/medial prefrontal cortex and posterior cingulate (ACC).

#### 3.4. Medication effects (clinical subjects only)

For the ACC cluster (see Table 2), the use of any psychotropic medication [ $t(24) = 0.57, p = 0.57$ ] and the use of stimulants in particular [ $t(24) = -0.21, p = 0.84$ ] did not affect the lose > win contrast. For the posterior cingulate cluster, the use of psychotropic medication [ $t(24) = 1.09, p = 0.29$ ] did not contribute to the lose > win contrast. However, activation in the posterior cingulate was significantly higher for those clinical subjects taking stimulant medications as compared to those not taking stimulants [ $t(24) = 2.32, p = 0.03$ ].

#### 3.5. Correlational analyses<sup>4</sup>

##### 3.5.1. Clinical subjects only

In the ACC region, we found one cluster in which irritability correlated negatively with the loss trials [ $r(24) \geq -0.53, p < 0.005$ ; minimum significant cluster size = 4 vox (see Fig. 3 and Table 3 for

specific cluster size, statistical value, and location information)]. In the striatum region, we found a single cluster, within the right putamen, in which irritability correlated negatively with the loss trials [ $r(24) \geq -0.53, p < 0.005$ ; minimum significant cluster size = 7 vox]. For the amygdala region, we did not find any significant effects.

##### 3.5.2. All subjects

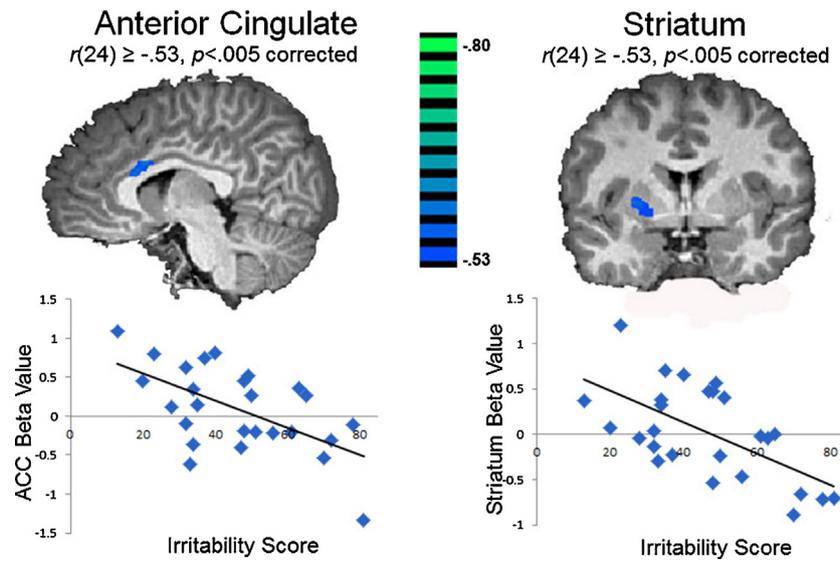
In the striatum region, we found a single cluster, within the left caudate body, in which positive mood rating correlated negatively with activation during win trials for all subjects [ $r(52) \geq -0.38, p < 0.005$ ; minimum significant cluster size = 4 vox]. This indicates that more positive mood during winning (higher rating score) was related to decreased striatum activation. No significant correlations were found for the lose trials in the striatum region or for win or lose trials within the ACC or amygdala regions.

## 4. Discussion

We found evidence for differences in frustration related neural activation between clinically irritable children and their typically developing counterparts. Specifically, our observed

<sup>4</sup> Note that in whole-brain analyses, there were no significant correlations with irritability after controlling for multiple comparisons.

## Neural Activation During Loss: Relationship to Irritability



**Fig. 3.** Region of interest correlations revealed negative correlations with irritability and activation in the anterior cingulate (ACC) and striatum in the clinical group.

group  $\times$  condition interaction found that Clinical subjects displayed moderately less activation of the ACC and middle frontal gyrus during the losing condition, in contrast to the Comparison group, and that this activation correlated negatively with parent report of irritability. The ACC has been linked to error monitoring (Carter et al., 1998), deviation from a potential reward (Amiez et al., 2005), and emotion regulation (Bush et al., 2000), all of which are germane to the current study. Clinically irritable subjects, who are known to suffer from anger/frustration outbursts (Leibenluft et al., 2006), may find it particularly challenging to exert cortical control over subcortical regions while encountering a blocked goal. Our own work has found that increased frustration and deviation from reward is coupled with increased bottom down control of the amygdala by the ACC in a similar frustration task (Perlman and Pelphrey, 2011). Further, Stadler and colleagues (2007) found reduced activation of the ACC in children and adolescents suffering from conduct disorder while viewing negative affective images. Temperament (novelty seeking in this case) was also a significant predictor of ACC responsiveness, echoing the dimensional nature of reactivity of the ACC found in our study. Taken together our findings and those from previous literature indicate that the ACC might be a region particularly sensitive to the experience of blocked goals, the reactivity to which may possibly distinguish normative from

abnormal emotional processing. It must be noted, however, that in a magnetoencephalography study, Rich and colleagues (Rich et al., 2011) found that adolescent clinically irritable subjects *increased* activation of the ACC and reported increased arousal during negative feedback. Thus, modulation of the ACC during frustration may differ based measurement technique, sample characteristics (such as age in this case), or type of frustration (e.g. social, monetary) induced.

We also found a significant group  $\times$  condition interaction in the ventral PCC. The PCC is a region commonly associated with the default mode network (Buckner et al., 2008; Leech et al., 2012), which has not previously been linked to irritability, but has been noted to be dysfunctional in psychopathology in general (Whitfield-Gabrieli and Ford, 2012). We found that clinical subjects differed from control subjects by failing to show task-dependent deactivation in this region during frustration. Failure to suppress PCC activity in the clinical group may be associated with the intrusion of internal mentation during task performance and might suggest dysregulation in controlling the balance between an internal and external attentional focus. Alterations in default mode network function in clinically irritable children may also underlie the chronic and persistent aspect of irritability (Leibenluft et al., 2006) that accompanies the anger/frustration

**Table 3**  
Neural activity clusters; irritability and online mood rating correlational analysis\*.

	Hemisphere	BA	Peak voxel (x, y, z)	Size (1mm <sup>3</sup> )	Average stat value (r, p)
Irritability					
ACC	R	24	6, 11, 26	161	-0.56, 0.003
Striatum	R	-	27, -1, 4	405	-0.55, 0.004
Amygdala	-	-	-	-	-
Online mood rating					
ACC	-	-	-	-	-
Striatum (all subjects)	L	-	-12, -1, 8	226	-0.42, 0.002
Striatum (Control only)	L	-	-9, -1, 10	471	-0.57, 0.002
Amygdala	-	-	-	-	-

\*Map threshold  $p < 0.005$ ; FWE corrected  $p < 0.05$ . BA, Brodmann area; ACC, anterior cingulate cortex.

outbursts noted above. Additionally, we found that activation of the PCC was significantly higher for those clinical subjects taking versus not taking stimulant medications. Thus, an alternative explanation may be that increased PCC activation was driven by subjects who were prescribed stimulant medication. Peterson and colleagues (2009) found that taking stimulant medication improved suppression of default mode activity (i.e. less mind wandering) in child ADHD subjects. This indicates that the PCC may be particularly sensitive to stimulant medication, however the directionality of this effect may differ depending on specific symptomatology.

Our study was initially designed to examine neural response to frustration in irritable children, but also served to assess reward related brain function, which is less frequently addressed in the literature. Our finding of increased activation in the ACC during win trials for the Clinical group may reflect alterations in reward expectancy (Shidara and Richmond, 2002) that persist after a particularly frustrating incident or that clinically irritable children find it particularly rewarding when advances are made toward a desired goal. We also found that self-report of emotion during winning episodes was negatively correlated with caudate activation, but only for the Comparison group. While these results are difficult to interpret further, given interactions with emotion, temperament, and clinical status, they hint at the possibility of differential reward function in irritable clinical children, which is a research area ripe for future investigation.

To our knowledge, this was the first neuroimaging study to examine brain alterations as a correlate of parent reported irritability in clinical children. We found a region of the ACC and a region of the striatum that correlated negatively with irritability score on a scale designed to quantify irritable impairment dimensionally. Children who are highly irritable suffer from emotion regulation difficulties, which may impede the cognitive resources necessary to monitor errors or process divergence in goal advancement. Our behavioral analyses indicated that clinically irritable children may have been particularly sensitive to reward. This may be related to the correlation in the putamen, in which Clinical children rated by their parents as suffering from the most extreme clinical variations in irritability displayed deactivation for loss trials. Extreme positive emotion during happy events coupled with emotion dysregulation during negative events is often noted as “mood swings” in clinically irritable youth (Carlson, 2007).

Contrary to other investigations of highly irritable subjects (Brotman et al., 2010; Deveney et al., 2013), our study found no amygdala effects of frustration in irritable children who were younger than those samples in which amygdala effects were found. It seems likely that this specific task design, which contains repeated win and lose trials for the purposes of frustration induction, may be poorly oriented to examine the rapid activation of the amygdala often seen with slow event-related designs. Our study also did not include photographic images (e.g. facial expressions, emotional scenes), which are often used to probe amygdala functioning. Additionally, we note that in Deveney and colleagues' (2013) study, the interstimulus interval between stimulus presentation and induced frustration was not jittered and neural responses to feedback were not isolated. Thus, it is possible that observed effects in the amygdala were due to differences in attention rather than response to frustration. It may also be the case that similar online mood ratings between both groups during frustration might reflect the lack of amygdala findings. Future studies will be needed to focus specifically on the subcortical basis of frustration in irritable children and examine differences across age.

Although we found substantial evidence for specific neural circuitry related to irritability, our study has limitations worth noting.

First, because we defined irritability from an RDoC perspective, diagnoses of psychopathology were variable. Approximately half of clinical subjects were medicated with varying types and dosages. Given the small sample size of fMRI studies, it is difficult to explore the role of any individual medication or diagnosis beyond the exploratory analyses presented in the supplementary materials. Future large-scale studies aimed at irritability as a primary research question may be able to disentangle the roles of clinical diagnosis and medication more directly. Second, win and lose trials were always compared against a baseline condition, which occurred partly during anticipation of the next trial. While this is the norm for reward related tasks, and most tasks in general, it is possible that anticipation during baseline may have engaged specific circuitry related to frustration and, thus, contributed to null amygdala results. Clinical children may also have a longer carry-over of negative affect from previous trials. Third, the task goal was to accrue five bones in a sequence. Thus, the fourth win trial in a sequence might feel differently from a win trial which was immediately preceded by a loss trial. Our analyses did not model the discrepancy between trials within blocks due to the small number of trials required for scanning young children. We note that this task has been analyzed as a block design in the past (Perlman et al., 2014), however, block analysis of this task is more susceptible to the baseline issues noted above. Finally, no group differences were observed in behavior or self-reported mood during frustration blocks. It is possible that this task elicited the same level of negative mood in both groups of subjects, but that differences in the observed neural circuitry underlying emotion regulation would yield differences in frustration reactions in real-world settings or that this neural circuitry would further decline with development, leading to differential self-report at later ages. It is also possible that our relatively simple emotion scale, which probed only valence and not arousal, was not sensitive to slight differences in affect or that our design suffered from demand characteristics. It is also possible that, although practice with the experimenter was designed to ensure understanding, Clinical children might not have understood the scale on the same level that Comparison children might have.

Our findings point to neural circuitry distinguishing clinical irritability from normative functioning, which is important to guide neuroscientifically oriented research on irritability as a cross-cutting substrate of developmental psychopathology. Future longitudinal studies will be necessary to examine the neurodevelopment of psychopathology onset in irritable children.

#### Conflict of interest statement

The authors of this work declare no conflicts of interest.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dcn.2015.07.003>

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