Full Title: Dysfunctional Attention Processing in Children with Clinical Irritability

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Ethical Statement: All study procedures were approved by the Institutional Review Board at the University of Pittsburgh. Written parental consent and child assent were obtained from all participants.

Conflict of Interest Statement: The authors have no competing interests to declare.

Abstract

Irritability is a transdiagnostic psychiatric symptom that spans the internalizing-externalizing divide and places children at greater risk for common mental health problems. There is evidence for disrupted affect-biased attention processing in children with high levels of irritability, but the underlying mechanisms supporting this dysfunction are not well understood. 24 children with clinical irritability (IRR) and 25 typically-developing comparison children (TD) ages 6-10 years old completed a modified visual Oddball task, which is optimized for probing the attention system, during functional magnetic resonance imaging (fMRI). Influence of happy, angry, or neutral distractor stimuli were analyzed using two methods. One analysis compared the two groups within each condition using voxel-wise whole brain t-tests. A second analysis examines dimensional irritability (assessed using the Multidimensional Assessment Profile of Disruptive Behavior or MAP-DB) predicting neural functioning across the sample within each condition. Both analytical approaches revealed increased activity in sensorimotor cortex with increased irritability in the affective conditions. In the Neutral condition, there were negative associations between primary sensory and parietal cortex activation and MAP-DB irritability scores. Our findings suggest maladaptive integration of visual-spatial information during sustained attention in clinically irritable children that may underlie disruptions in emotion processing.

Keywords: attention, irritability, development, affect-biased attention, pediatric psychiatry

1. Introduction

Irritability is psychiatric symptom characterized by dysregulated mood (e.g., persistent negative affect) and extreme frustration-related responses (e.g., temper tantrums or anger outbursts). It is trans-diagnostic, noted as a common complaint in nearly every psychiatric disorder (Stringaris, 2011) and is longitudinally predictive of developing depression, anxiety, and other disorders later in life (Stringaris, Maughan, Copeland, Costello, & Angold, 2013; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016). There is evidence for age-specific influence of dimensional irritability on cognitive performance (Tseng et al., 2018) highlighting the value of studying irritability in children as both a dimensional symptom capturing severity (Wakschlag et al., 2018) and as a categorical disorder, Severe Mood Dysregulation (SMD; Leibenluft, 2011) or the more recently established Disruptive Mood Dysregulation Disorder (DMDD; American Psychiatric Association, 2013). Both approaches are critically important to mapping the neurodevelopmental pathophysiology underlying this impairing symptom.

Youth with clinical irritability demonstrate deficits in emotion processing (Thomas et al., 2014, 2012, 2013; Tseng et al., 2016). Specifically, recent evidence suggests that irritability is associated with attentional bias towards angry faces (Hommer et al., 2014; Salum et al., 2017), and that adolescents diagnosed with SMD are equally influenced by emotional and neutral distractors during a task while healthy control adolescents are unaffected by neutral distractors (Rich et al., 2010). These findings suggest that deficits in emotional attentional control may contribute to the observed deficits in emotion processing. However, few studies have examined affect-biased attentional neural system integrity—the efficiency or distribution of processing across the neural network—in children with clinical irritability, and none in young children. One recent study of 8-18-year-olds with a primary diagnosis of DMDD, an anxiety disorder, or

ADHD found that dimensional irritability was associated with increased activity across a number of regions during orienting to angry faces (Kircanski et al., 2018). It is unclear however how children with irritability process task-irrelevant emotional stimuli, a process governed by affect-biased attentional processing. Affect-biased attention, or attentional bias to particular affective content, is hypothesized to shape socio-emotional development across early childhood and can therefore sustain adaptive or maladaptive behaviors (Cole, Luby, & Sullivan, 2008; Morales, Fu, & Pérez-Edgar, 2016). It is therefore possible based on the limited work finding attentional biases in children with irritability that there is a low-level disruption in attentional neural system functioning that impairs the adaptive development of the system.

The present study was designed to examine affect-biased attention processing in children 6-10 years old with clinical irritability in order to elucidate neural features of the early, disordered foundation of cognition-emotion interactions. To accomplish this, children with clinical irritability and a psychiatrically healthy comparison group completed a modified version of the emotional visual Oddball Task designed for children (Perlman, Hein, Stepp, & The LAMS Consortium, 2014). The Oddball Task (Squires, Squires, & Hillyard, 1975) is the most widely used assessment of attentional system function and has been modified to examine affect-biased attention processing (Hayes, Labar, Petty, McCarthy, & Morey, 2009; Krebs, Park, Bombeke, & Boehler, 2017; Perlman et al., 2014; Siciliano et al., 2017) through the addition of emotional targets, off-targets, or distractors. To successfully complete the task, participants must remain alert for the sparsely presented Oddball stimulus, correctly orient themselves to it when detected, and finally use executive systems to respond and disengage to prepare for the next stimulus. Because there is previous evidence that irritability is associated with attentional bias toward angry faces (Hommer et al., 2014; Salum et al., 2017), we used angry faces in this version of the

task rather than the fearful faces previously used. We hypothesized that the presence of a threatening, angry face would necessitate increased prefrontal activation in order to perform the task and override the distraction, a process that IRR children would be less adept at carrying out than the comparison children (i.e., have decreased activation). Additionally, based upon previous dimensional irritability work in attentional bias (Kircanski et al., 2018), we also predict that increased irritability across the sample will be associated with increased activation of motor and parietal cortex activation during emotional distraction.

2. Method

2.1 Participants

This study was approved by the University of Pittsburgh Institutional Review Board and informed consent was obtained from all participants. Participants were 56 children ages 6-10 years old (7.6 ± 1.09 years) recruited from the Pittsburgh region. For the clinical group (IRR), twenty-eight children were recruited from local child psychiatric clinics and selected based on parental reports of impairing irritable behavior (see supplement for specifics). Twenty-eight children were recruited from the general public as a typically-developing comparison group (TD) matched as closely as possible on age, sex, race, household income, parental education, and IQ to the IRR participants. TD children had no personal history of any psychiatric disorder or history of schizophrenia or bipolar disorder in first-degree relatives. Exclusion criteria for both groups included severe systemic medical illnesses, history of neurological disorders, head trauma with loss of consciousness, or use of non-psychotropic medication that may affect the CNS, an IQ < 70 (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), and autism spectrum disorder or developmental delays. All children were required to be able to complete tasks in English and

be safe to scan in a magnetic resonance imaging (MRI) scanner (no claustrophobia, metal in the body, or other MRI contraindications). Prescription medication in the IRR group was permitted and medication status was controlled for in subsequent analyses. Written consent was obtained from each parent or guardian, assent was obtained from each participant, and participants received monetary compensation for their time, a framed picture of his or her brain, and a small prize for participation (see Perlman, 2012).

The final sample for analysis were 24 IRR and 25 TD children: 6 children (3 TD, 3 IRR) were removed due to excessive motion during fMRI scanning (see *MRI data processing* in the supplement) and 1 child (IRR) was removed for not responding behaviorally to stimuli for the duration of the task (see *Oddball behavioral data analysis*). Group sizes are similar to those in other studies that also balanced the need for a larger sample size and the difficulty in recruiting pediatric psychiatric populations (e.g. Hafeman et al., 2017; Perlman et al., 2015).

2.2 Clinical assessment

Before MR scanning, in-laboratory clinical assessments were conducted with both the caregiver and the child. Final inclusion in the IRR and TD groups were determined based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (KSADS-PL-W; Birmaher et al., 2009) interview which included the Severe Mood Dysregulation Module (SMD; Leibenluft, 2011). Children who met criteria for SMD were included in the IRR group. Comorbidity information for the IRR participants obtained from the KSADS-PL-W is provided in Table 1. Recruitment for this study pre-dated the inclusion of Dysregulated Mood Disruption Disorder (DMDD) into the DSM-5, thus participants were not recruited based on DMDD criteria and bipolar disorder was not an exclusion criterion for the

clinical children. We emphasize the transdiagnostic nature of irritability as a symptom as well as two recent studies that find that transdiagnostic dimensionally-assessed irritability is a better predictor of brain function than categorical diagnoses (Kircanski et al., 2018; Tseng et al., 2018).

Parents also completed the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB; Wakschlag et al., 2014) Temper Loss Scale. The MAP-DB is sensitive to distinctions between normative and dysregulated irritability at early childhood and school age (Wakschlag et al., 2014, 2018) and includes a range of irritable behaviors from mild and commonly occurring to severe and dysregulated forms. Each item of the MAP-DB items is scored on a 6-point objective frequency scale (never in past month to many times each day) with higher scores indicating greater frequency for the behavior in question during the month.

2.3 Oddball task paradigm

Participants completed one run of the classic Oddball paradigm (Squires et al., 1975) modified to include an emotional component (Perlman et al., 2014). Before the task, the child was told the story of a little girl who went grocery shopping with her mother while carrying a bag of marbles. While at the store, the girl drops her bag of marbles and needs the child to help her pick them up. Participants were instructed to press the button whenever they see a marble (the Oddball stimulus) and to not press when they see a block (standard stimulus). Children were also informed that they would see produce as well as other people in the grocery store while they were looking for marbles, but they should ignore these distractors to focus on finding the marbles. Children were asked to keep a mental count of how many marbles they had collected during the game. This added cognitive load requires participants to focus on the shapes rather than the distractor stimuli during each trial and keeps the task from being too easy.

The task (see Figure 1) consisted of a total of 141 trials, 24 Oddball and 117 standard. Each trial contained a 2-second presentation of the regular or Oddball slide followed by a 1-second cross hair centered on a white screen. The standard trials contained squares with either produce (108 trials) or neutral faces (9 trials). The Oddball trials had circles paired with either angry faces (8 trials), happy faces (8 trials), or produce (neutral; 8 trials). All faces were selected from the NimStim stimulus set (Tottenham et al., 2009). Oddball trials were interspersed with 6-8 standard trials creating a slow event-related design. This semi-predicable task design enhances anticipation of the Oddball stimulus, thus engaging the attentional network. In the present design specifically, the Neutral condition thus represents the most purely “Oddball” condition as the oddball stimulus is the only part of the grid that changes significantly in comparison to the preceding standard trials.

2.4 Oddball behavioral data analysis

Overall and within condition accuracy and reaction time was extracted for each participant. Accuracy was calculated as number of correct responses divided by the total number of trials of that type. For Oddball trials, a correct response is a button press while for standard trials no button press was considered a correct response. Children whose accuracy for any one trial type (happy Oddball, angry Oddball, neutral Oddball, or standard) was not higher than 60% were removed from analyses. One child (IRR) was removed who did not respond to more than half the trials. Group differences in accuracy and RT for each Oddball condition (happy, angry, and neutral) were assessed using independent sample t-tests. To inform our understanding of how each child experienced the various stimuli in the task (faces and produce), across the sample paired t-tests compared accuracy between each Oddball condition and each standard condition. Further, across the sample Spearman correlations were used to test if MAP-

DB Temper Loss scores predicted behavior. Spearman correlations were chosen due to the non-normal distribution of the Temper Loss Scores (see Supplementary Figure 1).

2.5 MR Acquisition and Processing

MR neuroimaging data were acquired on a 3-Tesla Siemens Trio MR scanner equipped with a 20-channel head coil. Full MRI acquisition, preprocessing, and within-subject analysis information are included in the Supplement.

2.6 Between Group Differences in Neural Activation

Voxel-wise group level analyses were conducted using FSL's randomise function (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Specifically, because of the relatively small sample, parametric t-tests comparing IRR to TD were conducted for each of the three conditions, Angry, Happy, and Neutral. Resulting t-statistic maps were clustered at voxel $p < 0.001$, cluster FWE corrected $p < 0.05$. Participant age at scan and medication status were included in the group level models as covariates of non-interest. To determine a minimum cluster size that minimizes the likelihood of false positives, we used AFNI's 3dFWHMx and 3dClustSim to estimate appropriate cluster sizes to minimize the false-positive rate (Cox, Chen, Glen, Reynolds, & Taylor, 2017). This method was developed based on recent work showing that BOLD fMRI noise does not fit a Gaussian distribution (Eklund, Nichols, & Knutsson, 2016). Autocorrelation function parameters were used to generate 10,000 Monte Carlo simulations and produced an estimate of cluster size that is conservative, minimizing the false-positive rate. From our simulations, a conservative cluster size for over voxel-wise and cluster-wise threshold is 52.9.

2.7 Neural Activation Associated with Dimensional Irritability

Voxel-wise linear regression was used to assess the linear relationship between subject level parameter estimates for each condition and Temper Loss scores, controlling for age and medication status. Resulting t-statistical maps were clustered and reported using the same thresholds as the between group analysis (voxel $p < 0.001$, cluster FWE corrected $p < 0.05$, and minimum cluster size of 52.9 voxels).

3. Results

3.1 Sample demographic, clinical, and behavioral features

Demographic, clinical, and behavioral sample characteristics and results are summarized in Table 1. IRR children taking medication were prescribed stimulants (N=15), anti-psychotics (N=8), mood stabilizers (N=1), and/or benzodiazepines (N=1). Across the sample, Temper Loss scores were not correlated with any of the behavioral measures from the Oddball task (Spearman's ρ s < 0.20 , p s > 0.06).

3.3 Between Group Differences in Affect-Biased Attention Processing

Clusters resulting from the voxel-wise analysis of the Oddball task are fully listed in Table 2.

3.4 Neural Activation Associated with Dimensional Irritability

The full results are listed in Table 2. In the Neutral condition, decreased left inferior parietal lobule, right angular gyrus, left superior frontal gyrus, and left cuneus activation was associated with increased irritability. Clusters from the Neutral condition results are presented in Figure 2.

4. Discussion

Similar to another study using a dimensional approach to examining attention systems in 8-18 year old children and adolescents with varying levels of clinical irritability (Kircanski et al., 2018), we found that activation in the parietal, motor, and prefrontal cortex was predicted by irritability scores. Unlike the previous study, however, our findings were largely limited to the neutral condition. Contrary to expectations at the outset, our findings point to a minimal influence of affective condition interacting with attentional systems (the happy and angry conditions) in a way that was predicted by clinical group or irritability scores in this age range. Our results may therefore reflect more foundational attentional system dysfunction in younger children with clinical levels of irritability. Our results provide support for need to study the developmentally-specific influence of irritability on brain function.

These results contribute to our understanding of the neural mechanisms underlying the deficits in emotion processing found in youth with clinical irritability—when taken together with previous findings, our results lend support for a neurodevelopmental model of irritability. As mentioned in the introduction, there is evidence that 8-18-year-old youth with clinical irritability have general deficits in processing emotional information (Deveney, Brotman, Decker, Pine, & Leibenluft, 2012; Rich et al., 2010; Thomas et al., 2012, 2013, 2014). Our study of 6-10-year-old children did not find a large influence of emotional distractor during attention orienting. Instead, we largely found differences in primary sensory regions in the group analysis and associations with irritability in secondary, sensory integration regions in the dimensional analysis. There are several possible explanations for the discrepancies in these findings. First, this previous work all included paradigms that expected the youth to process the emotional information as task-relevant stimuli or presented during anticipation of task-relevant stimuli. In our study, children were explicitly told to ignore the distractor images and the distractors were presented at the same time

as the task-relevant stimuli, forcing a choice between allocating attention to the faces (not necessary for task completion) or the oddball (required for task completion). The second possible explanation has to do with the large developmental demand of childhood: the development of cognitive control (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Luna, Garver, Urban, Lazar, & Sweeney, 2004) supported by growth and integration of the prefrontal and parietal cortices which peak in growth during middle childhood (Shaw et al., 2008). Since we largely found group and dimensional irritability associations in the neutral condition, our findings may indicate that more foundational cognitive functional influences of clinical irritability rather than broad dysfunctions in emotion processing are present in children compared to adolescents. It is therefore possible that disruptions in attentional processing in young children with clinically impairing irritability are subtler during the years in which gray matter growth peaks. Since children are developing cognitive control during these years, differences in performance in a purely attention orienting task such as the oddball task may be subtler. This is supported by the lack of differences in reaction time between groups and the modest difference in reaction time during the Neutral trials. These differences may magnify, however, as typically developing children continue to improve in network integration—the developmentally expectant process across adolescence (Marek, Hwang, Foran, Hallquist, & Luna, 2015; Medaglia et al., 2018)—while children high in irritability do not. This theory is supported by our results from the dimensional analysis, as reduced bilateral activation of parietal cortex was associated with increased irritability in these children during the neutral trials. The parietal cortex serves as an information integration hub that is highly interconnected with the prefrontal cortex to support higher cognition (Andersen, Asanuma, Essick, & Siegel, 1990; Scherf, Sweeney, & Luna, 2006; Ullman, Almeida, & Klingberg, 2014), thus the developmental trajectory of the parietal cortex

could influence development of the prefrontal cortex. This interpretation is speculative, of course, as longitudinal work is needed to fully map the neurodevelopmental process unfolding as children high in irritability enter adolescence and adulthood.

This study has several notable strengths. It is the first study to examine affect-biased attention processing in young children (6-10-year-olds) with clinical irritability, lending important insight to the early influences of irritability on the attentional neural system. Additionally, we used an age-appropriate paradigm by incorporating a story and bright, colorful stimuli in order to maximize child engagement and included task-irrelevant emotional stimuli presented at the same time as the target stimulus in order to specifically probe affect-biased attention processing. There were several limitations, however, that are important to consider. First, due to the time constraints of working with younger children, we were unable to test a wide variety of stimuli, vary the difficulty from trial to trial, or collect multiple runs of the task. These variables could influence the extent that the emotional distractor affects attention processing and further inform our understanding of affect-biased attention processing in irritability (Siciliano et al., 2017). Second, this study was cross-sectional, and the age range was relatively limited. In order to effectively examine changes in emotion-cognition aspects of the attention network as these children mature, longitudinal work is needed to examine the relationship between aberrations in affect-biased detection during childhood and psychiatric outcomes in these children. Lastly, a large proportion of IRR children were taking medication at the time of the scan (67%). It should be noted however that we controlled for medication status in these analyses and we did not find differences in symptomology on the basis of medication status.

Conclusions

Our study contributes to increasing evidence for a neurodevelopmental model of psychopathology, particularly for mood and anxiety disorders (Camacho, Wakschlag, & Perlman, in press; Cole et al., 2008; Wakschlag et al., 2018). We provide evidence for dysfunctions in low-level processing of salient stimuli in children with irritability rather than the broad emotion dysfunction that is found at older ages. Foundational dysfunctions in attentional control could confer additional risk for psychopathology in children. Future work must probe a deeper neurodevelopmental understanding of the relationship between child psychopathology and dysfunctional affect-biased attentional systems.

Acknowledgements

This work was supported by National Institutes of Health [K01 MH094467 to SBP, R01 MH107540 to SBP, T32 MH019986 to HTK, R01 MH107652 to LSW] and the National Science Foundation [GRFP No. 174745 to MCC]. The authors thank the many families that have contributed their time to this study. We thank Lisa Bemis and Tyler Hein for their help with participant recruitment and data collection. MCC, HTK, and SBP contributed to the design of the analysis, MCC and FF carried out the analysis, MCC, LSW, and SBP contributed to the interpretation of results, MCC wrote the initial draft, and all authors contributed to revisions and share responsibility for the final work. The authors have declared that they have no competing or potential conflicts of interest.

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Tables

Table 1: Sample demographics, clinical information, and task performance summary for the typically developing comparison (TD) and clinical (IRR) groups of children. MAP-DB refers to the Multidimensional Assessment Profile of Disruptive Behavior; SD denotes standard deviation.

	TD N=25	IRR N=24	Statistic <i>p-value</i>
Demographic Information			
Age			$t(47)=-1.62$
<i>Mean (SD) years</i>	7.87 (1.25)	8.40 (1.00)	$p=0.112$
Number of Males	13	14	$\chi^2(1)=0.20$
<i>Percent of total</i>	52.0%	58.3%	$p=0.656$
Annual Family Income			$t(47)=0.06$
<i>Mean (SD) thousands of dollars</i>	34.84 (32.49)	34.33 (25.33)	$p=0.952$
Race			$\chi^2(3)=2.30$
White or Caucasian	6	8	$p=0.513$
Black or African American	17	16	
Asian	1	0	
Native Hawaiian or Pacific Islander	1	0	
Ethnicity			$\chi^2(1)=4.18$
Hispanic or Latino	4	0	$p=0.041^*$
Not Hispanic or Latino	21	25	
Clinical Information			
MAP-DB Temper Loss	7.16 (7.77)	47.63 (17.44)	$t(47)=-10.57$
<i>Mean (SD) [range]</i>	[0-32]	[20-81]	$p<0.001^{**}$
Number taking psychotropic medication	0	16	$\chi^2(1)=24.75$
<i>Percent of total</i>	0.0%	66.7%	$p<0.001^{**}$
Lifetime Diagnoses			
<i>Number of children (% of total)</i>			
Attention Deficit Hyperactive Disorder	0 (0%)	18 (75.0%)	
Oppositional Defiant Disorder	0 (0%)	11 (45.8%)	
Anxiety Disorder	0 (0%)	9 (37.5%)	
Bipolar Disorder	0 (0%)	9 (37.5%)	
Major Depressive Disorder	0 (0%)	7 (29.2%)	
Conduct Disorder	0 (0%)	13 (54.2%)	
Severe Mood Dysregulation	0 (0%)	24 (100%)	
Task Behavioral Performance			
Angry RT (<i>Mean±SD milliseconds</i>)	781.54±159.22	777.35±157.18	$t(47)=0.09$; $p=0.927$
Happy RT	805.03±223.00	715.40±135.76	$t(47)=1.69$; $p=0.098$
Neutral RT	964.97±238.19	848.79±152.13	$t(47)=2.03$; $p=0.049^*$

Angry Accuracy (<i>Mean±SD percent</i>)	91.02±12.24	94.27±8.23	$t(47)=-1.09$; $p=0.283$
Happy Accuracy	90.00±14.88	92.71±12.72	$t(47)=-0.68$; $p=0.498$
Neutral Accuracy	89.50±14.73	87.00±13.53	$t(47)=0.62$; $p=0.536$
Standard Accuracy (produce)	99.22±0.95	97.61±4.69	$t(47)=1.42$; $p=0.165$
Standard Accuracy (neutral faces)	98.22±4.16	95.83±7.19	$t(47)=1.65$; $p=0.111$

* $p<0.05$, ** $p<0.005$

Table 2: Clusters and parameter estimates for the main effect of condition during the oddball task (voxel $p < 0.001$, cluster FWE corrected $p < 0.05$, extent > 52.9 voxels). These clusters were extracted controlling for current medication status and age at scan. There were no surviving clusters for the Angry condition dimensional analysis.

Region		Peak <i>t</i> -statistic	Extent Voxels	MNI Coordinates			Parameter Estimate <i>Mean</i> ± <i>SD</i>	
				X	Y	Z		
Between Group Analysis								
<i>Angry</i>							<i>TD</i>	<i>IRR</i>
IRR>TD	Left postcentral gyrus	5.251	393	-40	-24	46	0.49±2.74	4.19±3.29
<i>Happy</i>								
IRR>TD	Left lateral occipital cortex	4.646	141	-26	-88	4	-0.03±2.69	2.26±1.97
	Left lateral occipital cortex	3.788	53	-22	-80	20	-0.33±2.72	1.80±3.06
<i>Neutral</i>								
IRR>TD	Left postcentral gyrus	5.563	343	-30	-32	52	0.07±2.10	2.98±3.91
	Cerebellar vermis	4.849	104	4	-58	-6	-0.42±3.11	2.94±5.33
Dimensional Analysis with MAP-DB Temper Loss								
							<i>Full Sample</i>	
<i>Happy</i>								
	Right postcentral gyrus	-5.397	53	14	-46	76	-1.06±3.97	
<i>Neutral</i>								
	Left inferior parietal lobule	-5.230	68	-38	-74	52	-0.53±4.90	
	Right angular gyrus	-5.048	78	56	-68	32	-0.43±4.09	
	Left superior frontal gyrus	-4.356	59	-6	56	4	-0.50±4.88	
	Left cuneus	-4.343	61	-16	-62	20	-1.08±4.12	

Figures

Figure 1: Design for the modified affective Oddball task. Oddball trials were presented in random condition order (angry, happy, neutral) interspersed with 6-8 regular trials, thus an oddball stimulus was on the screen every 18-24 seconds in a slow event-related design. The design for the first 130 seconds of the task is depicted here.

Figure 2: Activation associated with dimensionally assessed irritability in the Neutral condition using the MAP-DB Temper Loss scale. Clusters presented are FWE-corrected $p < 0.05$, voxel $p < 0.001$ and at least 52.9 voxels. Scatter plots below illustrate the negative linear relationship with MAP-DB Temper Loss scores.

Supplement

SMD criteria used for recruitment of IRR subjects

Interested parents were interviewed over the phone to assess if their child: (1) was irritable for at least half the day on most days, (2) presented noticeable irritability in more than one setting (e.g. home, peers, school), (3) had at least three anger/frustration outbursts per week, (4) had irritability which negatively and severely affected the child's academics and/or family/social life, (5) this irritability has been present for a minimum of 6 months, and (6) their initial reason for seeking care was their child's high irritability.

MR Acquisition

Participants were instructed to lie still with a button box in their right hand in order to play the task. A whole brain T1-weighted structural MRI were collected using a whole brain 3D magnetization-prepared rapid acquisition gradient recalled echo sequence (MP-RAGE) with the following sequence parameters: 192 axial slices, 1 mm slice thickness, 256x176 acquisition matrix with a 1 mm² pixel size, 2100 ms repetition time (TR), 1050 ms inversion time (TI), 3.43 ms echo time (TE), 8-degree flip angle (FA), and 1 excitation (total scan time was 4 minutes). For the task, T2*-weighted functional MRI were acquired in the same session using a sequence optimized to reduce blood oxygen-level dependent (BOLD) signal loss in the orbital frontal cortex (Deichmann, Gottfried, Hutton, & Turner, 2003). Specifically, it comprised a whole brain gradient echo echo-planar imaging (EPI) sequence with the following parameters: 38 interleaved axial slices, 3 mm slice thickness, 0.75 mm slice gap, 220 mm x 207 mm acquisition matrix with a 1.7 mm x 1.7 mm pixel size, 2000ms TR, 28ms TE, and an 80-degree FA. Total scan time was 7 minutes 6 seconds (213 continuous volumes). For a handful of participants, EPI coverage did not extend all the way to the inferior-most aspect of the cerebellum, however all of the cerebral cortex was covered for all participants in this study.

MRI data processing

Full analysis code is available online (https://bitbucket.org/lcbd/smd_oddball). MRI data were processed using NiPype (Gorgolewski et al., 2011) leveraging functions from FSL version 5.0 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), FreeSurfer version 6.0 (<http://freesurfer.net/>), the NiPype implementation of Artifact Detection Tools (ART; https://www.nitrc.org/projects/artifact_detect/) as well as custom functions written in Python version 3.4. Structural scans were bias corrected, intensity normalized, skull-stripped, and resampled to 2 mm isotropic voxels (Ségonne et al., 2004). Task fMRI scans were slice-time corrected, realigned to the first volume, and coregistered to the structural scan. Motion parameters from the realignment step as well as the coregistered fMRI scans were used in ART to determine volumes with excessive motion (greater than 1.5 mm) in any direction or outlier intensities (greater than 3 standard deviations from the mean global signal). Participants with motion exceeding this threshold in more than 10% of the task (22

or more volumes out of 213) were removed from the analysis (3 IRR and 3 TD). For the remaining participants, volumes that exceeded these thresholds were corrected for using a modified scrubbing technique. This involved including a vector of zeroes with a 1 at the time of the motion in the design matrix of the GLM (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

Within Subject Oddball fMRI Analysis

First level analyses were conducted in native space. Within each participant, we used a general linear model (GLM) to compute the main effect of each Angry, Happy, and Neutral. This process included convolving a boxcar function of the timing of each condition to the canonical double-gamma function model of the hemodynamic response function (Friston et al., 1997) and including these convolved timeseries in a GLM. The GLM also included both the regressors for the censored motion volumes and all six motion parameters as nuisance variables. Finally, this GLM design matrix also modeled slow drift in signal (autoregression filter of 1) and high-pass (1/128 Hz) filtered the signal before applying the GLM. The resulting parameter estimates for each participant were then spatially normalized to the 2mm isotropic MNI template brain (Evans et al., 1993) and smoothed using a 6mm Full Width Half Maximum Gaussian kernel with FSL's SUSAN function (Smith & Brady, 1997).

Supplementary medication analysis within IRR group

Within the IRR group, we performed independent sample t-tests to test if there were differences in behavioral performance (accuracy and reaction time) during the task between medicated (N=16) and unmedicated (N=8) children. To test if there were differences irritability levels in medicated IRR versus unmedicated IRR children, we used independent sample t-tests for each scale of the MAP-DB. Unmedicated children had higher accuracies for Angry Oddball trials ($t(22)=2.28$, $p=0.032$) and slower reaction times for Angry ($t(22)=2.20$, $p=0.039$) and Neutral Oddball trials ($t(22)=3.29$, $p=0.003$). The two groups did not significantly differ in any other behavioral metric ($t_s < 2.06$, $p_s > 0.05$). Further, the two groups did not significantly differ in any scale of the MAP-DB ($t_s < 0.50$, $p_s > 0.65$), suggesting that medication status was not indicative of disruptive symptom severity.

Supplementary Figure 1: Stacked histogram distribution of the MAP-DB Temper Loss scale. Bin width was automatically generated to produce 20 evenly distributed bins across the range of scores, thus the zero bin includes scores <5.

Supplementary Figure 2: Violin plots for clusters that survived the 52.9 voxel threshold excluding those already visualized in Figure 2.

Group Analysis

Supplementary Table 1: Results of a between condition comparisons clustered at voxel $p < 0.001$, cluster FWE corrected $p < 0.05$, extent > 52.9 . These clusters were extracted controlling for current medication status and age at scan. There were no surviving clusters for the between groups analysis.

Contrast	Region	Peak	Extent	MNI Coordinates		
		<i>t-statistic</i>	<i>voxels</i>	<i>X</i>	<i>Y</i>	<i>Z</i>
Angry > Neutral						
	Left precuneus	5.205	167	-10	-52	36
	Left angular gyrus	4.284	53	-58	-58	26
Happy > Neutral						
	Left supplementary motor area	4.620	60	0	62	8
Angry > Happy						
	<i>None</i>					

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