

Neural correlates of masked and unmasked face emotion processing in youth with severe mood dysregulation

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Abstract

Reproducibility of results is important in improving the robustness of conclusions drawn from research, particularly in functional magnetic resonance imaging (fMRI). In this study, we aim to replicate a previous study on the neural correlates of face emotion processing above and below awareness level using an independent sample of youth with severe mood dysregulation (SMD) and healthy volunteers (HV). We collected fMRI data in 17 SMD and 20 HV, using an affective priming paradigm with masked (17 ms) and unmasked (187 ms) faces (angry, happy, neutral, blank oval). When processing masked and unmasked angry faces, SMD patients exhibited increased activation in the parahippocampal gyrus (PHG) and superior temporal gyrus relative to HV. When processing masked and unmasked happy faces, SMD patients showed decreased activation in the insula, PHG and thalamus compared with HV. During masked face processing in general across emotions, youth with SMD showed greater ventromedial prefrontal cortex (vmPFC) activation relative to HV. Perturbed activation in emotion processing areas (e.g. insula, PHG, superior temporal gyrus and thalamus) manifests as hyper-sensitivity toward negative emotions and hypo-sensitivity toward positive emotions may be important in the etiology and maintenance of irritability, aggression and depressive symptoms in SMD. vmPFC dysfunction may mediate over-reactivity to face emotions associated with irritability.

Key words: irritability; severe mood dysregulation; functional neuroimaging; backward masking; face emotion processing

Introduction

Severe, chronic irritability is a common and impairing problem, affecting 3–5% of youth (Brotman et al., 2006; Stringaris and Goodman, 2009), and predicts poor outcomes in adulthood, including depressive and anxiety disorders (Brotman et al., 2006; Stringaris et al., 2009), high suicidality (Pickles et al., 2010) and low income and educational attainment (Stringaris et al., 2009). There has been a recent increase in irritability research, partly due to the introduction of disruptive mood dysregulation disorder (DMDD) to

the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Much of the research support for irritability has been derived from studies on severe mood dysregulation (SMD), a phenotype characterized by severe, chronic irritability (Leibenluft et al., 2003; Roy et al., 2014) and upon which DMDD was based.

SMD youth show deficits in face emotion labeling (Guyer et al., 2007; Rich et al., 2008) and aberrant neural responses when processing emotional faces (Brotman et al., 2010; Thomas et al., 2012, 2013, 2014). This work has primarily focused on consciously

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perceived face emotions. Only one study has probed automatic, unconscious face emotion processing in irritable youth using functional magnetic resonance imaging (fMRI) (Thomas et al., 2014). However, there are concerns regarding Type I error in fMRI research (Lieberman and Cunningham, 2009; Poldrack and Mumford, 2009; Vul et al., 2009). Replication studies, particularly in fMRI (Lieberman and Cunningham, 2009; Bennett and Miller, 2010), are critical in validating important results and conclusions drawn from prior research.

Previous literature suggests that emotional processing consists of two distinct but simultaneously activated neural pathways; one mediates explicit, conscious processing, while the other mediates implicit, subliminal processing (LeDoux, 1996; Morris et al., 1998; Whalen et al., 1998). To probe these two processes, researchers typically manipulate the duration of stimuli (e.g. <40 ms for implicit processing and longer for explicit processing; Esteves and Ohman, 1993). A common method to assess implicit emotional processing is backward masking, where a prime stimulus (e.g. emotional face) is presented too briefly to reach awareness, followed by a target stimulus (the 'mask') that is presented long enough to be identified. Using this method, research in healthy adults and those with anxiety and mood disorders has implicated several brain regions in face processing below the awareness level. Some prominent regions include the amygdala, which plays a central role in rapid, automatic, non-conscious processing of affective visual stimuli (Morris et al., 1998; Whalen et al., 1998; Rauch et al., 2000; Sheline et al., 2001; Killgore and Yurgelun-Todd, 2004; Nomura et al., 2004; Armony et al., 2005; Dannlowski et al., 2007a,b; Bryant et al., 2008; Kugel et al., 2008; Carlson et al., 2009; Sabatini et al., 2009; Suslow et al., 2009, 2010a,b; Duan et al., 2010; Victor et al., 2010; Killgore et al., 2014; Lichev et al., 2015), as well as anterior cingulate cortex (Killgore and Yurgelun-Todd, 2004; Duan et al., 2010; Victor et al., 2012) and inferior frontal gyrus (Nomura et al., 2004; Dannlowski et al., 2007b; Duan et al., 2010; Lichev et al., 2015), which have inhibitory control over amygdala responses. Other regions include structures implicated in face perception, such as the fusiform gyrus (Nomura et al., 2004; Suslow et al., 2009; Lichev et al., 2015), middle occipital gyrus (MOG; Suslow et al., 2009, 2010b), superior temporal gyrus (STG; Sabatini et al., 2009; Suslow et al., 2009, 2010b; Victor et al., 2012; Lichev et al., 2015) and insula (Suslow et al., 2009, 2010b; Killgore et al., 2011; Victor et al., 2012). Among these studies, a generally consistent finding that differentiates adult patients with anxiety and/or mood disorders from healthy volunteers (HV) is that the former exhibited heightened amygdala activation during early, automatic stages of emotional processing (Rauch et al., 2000; Sheline et al., 2001; Bryant et al., 2008; Suslow et al., 2010a; Victor et al., 2010).

In contrast to the large body of literature on masked face emotion processing in adults, there are only a few fMRI studies in youth (Pine et al., 2001; Killgore and Yurgelun-Todd, 2007; Monk et al., 2008; Thomas et al., 2014). Masked face paradigm is important to probe the neural correlates of rapid, automatic emotional processing in irritable youth, as the difficulties to regulate emotion may occur without insight or subjective awareness. Prolonged viewing of emotional faces may obscure perturbed neural dysfunction (e.g. in the amygdala) that occurs during early, rapid processing of emotions (Nomura et al., 2004; Monk et al., 2008). Aberrant automatic processing of emotional faces (e.g. angry, happy faces) may contribute to the mood dysregulation and interpersonal difficulties in irritable youth. Thomas et al. (2014) incorporated masked and unmasked faces in one paradigm and found that youth with SMD showed more activation in the MOG when viewing faces that were not

consciously perceived vs consciously perceived, while HV showed the opposite pattern. In addition, youth with SMD exhibited increased activation in the posterior cingulate, STG and MOG when viewing angry faces (regardless of awareness level); youth with SMD also showed increased activation in the STG when viewing happy faces (regardless of awareness level; Thomas et al., 2014). In this study, SMD did not differ from HV in brain activation in response to fearful faces (Thomas et al., 2014).

Here, we modified the task used by Thomas et al. (2014) by removing fearful faces, and thus increasing the number of trials with other faces (e.g. angry, happy faces) and the power of the analyses. We used this modified paradigm to examine masked and unmasked face emotion processing in youth with SMD and HV. Significant contribution of this study to the field includes (i) the examination of automatic, unconscious as well as explicit, conscious face emotion processing in a single paradigm; (ii) an expansion of the scarce literature on automatic, unconscious face emotion processing in irritable youth and (iii) a replication of a previous study with a similar paradigm in an independent sample. As noted above, such replication is rare yet pivotal in neuroimaging and thought leaders in the field have recently expressed concern about the lack of replication among fMRI studies (Lieberman and Cunningham, 2009; Bennett and Miller, 2010; Barch and Yarkoni, 2013; Ioannidis et al., 2014). We hypothesized that there would be awareness-modulated group differences in the MOG (Thomas et al., 2014) and emotion-modulated group differences in the MOG, STG, posterior cingulate, anterior cingulate cortex, posterior insula and inferior parietal lobe (Thomas et al., 2012, 2013, 2014) based on previous research in SMD. Additionally, we hypothesized that youth with SMD, relative to HV, would demonstrate amygdala dysfunction during unmasked (Brotman et al., 2010; Thomas et al., 2012, 2013, 2014) but not masked (Thomas et al., 2014), emotional face processing based on previous research.

Materials and methods

Participants

All participants, aged 8–18 years, were enrolled in an Institutional Review Board-approved study at the National Institute of Mental Health (NIMH). Parents and children gave written informed consent/assent. A total of 47 children (25 SMD and 22 HV) enrolled; 10 subjects were excluded for the following reasons: poor behavioral performance (3 SMD and 2 HV), excessive motion during fMRI acquisition (>3 mm; 2 SMD) and inability to complete the task (3 SMD). The final sample included 17 youth with SMD and 20 HV. Children with SMD were recruited through advertisements to support groups, professional meetings and psychiatrists. HV were drawn from the community through advertisements.

All children were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). The K-SADS-PL, including an additional module for assessing irritability and excessive reactivity to negative stimuli (SMD module), was administered separately to children and parents by masters or doctoral level clinicians with excellent inter-rater reliability ($\kappa \geq 0.9$ for all diagnoses). Patients met criteria for SMD, with severe and impairing irritability, severe outburst and at least three hyperarousal symptoms (e.g. distractibility, racing thoughts or flight of ideas and intrusiveness) beginning before age 12; symptoms were present for at least 1 year (without 2 months symptom-free periods) and caused impairment in at least two of three settings (home, school and with peers).

Hypomanic or manic episodes of 1 day or longer were considered exclusionary, so none of the participants met criteria for bipolar disorder. Comorbid diagnoses are reported in Table 1. For detailed criteria for assessing SMD, please see Leibenluft *et al.* (2003) and Leibenluft (2011). Although DMDD was not proposed at the time of the data collection, all SMD youth also met criteria for DMDD (i.e. irritable mood and temper outbursts, present before age 10), using retrospectively applied criteria.

Other clinician-rated clinical symptoms were assessed in the SMD group using the Children's Depression Rating Scale (Poznanski *et al.*, 1984) and the Pediatric Anxiety Rating Scale (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002) within 48 h of scanning. To evaluate levels of global functioning in children with SMD, clinicians administered the Children's Global Assessment Scale (CGAS; Shaffer *et al.*, 1983).

HV were medication-free and had no lifetime psychiatric diagnoses and no first-degree relatives with mood disorders, as ascertained by parent interview. Exclusion criteria for all participants were IQ < 70, history of head trauma, neurological disorder, pervasive developmental disorder, unstable medical illness or substance abuse/dependence.

Affective priming paradigm

Participants completed a modified affective priming task (Thomas *et al.*, 2014) during fMRI data acquisition. There were four runs in the task: two for the aware condition (with unmasked faces) and two for the non-aware condition (with masked faces). The runs were interleaved, i.e. alternating between aware and non-aware conditions. The order of the runs

was counterbalanced across participants. In both the aware and non-aware conditions, participants indicated on a scale from 1 (did not like) to 5 (liked a lot) how much they liked an abstract shape presented for 3000 ms after the masked or unmasked face (Figure 1). This is to ensure participants were attending to the task by providing a behavioral response and also to test whether responding was influenced by the emotional primes. In the aware condition, a fixation cross (1250–1750 ms, average 1500 ms) followed by a face or blank oval (187 ms) was presented before the shape (3000 ms; Figure 1). In the non-aware condition, subjects saw a fixation cross (1250–1750 ms, average 1500 ms), followed by a face or blank oval (17 ms), a scrambled face mask (170 ms) and finally an abstract shape (3000 ms; Figure 1). Each event was 3187 ms long. The face stimuli were angry, happy, neutral or 'no face' (blank oval); there were 36 trials for each stimulus under each awareness condition. Stimuli were presented randomly. The duration of the task was approximately 28 min. Prior to scanning, outside the scanner on a desktop computer, participants completed a practice run of eight trials for each awareness condition, using faces not presented during scanning.

Post-task assessments

Immediately after the affective priming task and during structural scanning, two tasks were administered to assess whether the awareness manipulation was successful. The order of the two post-tasks was random. In both, participants were shown the faces in the non-aware condition and informed about the presence of the face in the 'flash' before the shape. In one post-task, participants were asked to identify the gender of the face. We combined all participants' accuracy data and ran one-sample *t*-tests vs chance (50%) for each gender (male, female). In the other post-task, subjects were asked to identify the face emotion (angry, happy or neutral). To examine if any emotion 'leaked' from the mask into awareness, we conducted one-sample *t*-tests on accuracy for angry, happy and neutral faces vs chance (33.3%). These tests were intentionally liberal since the concern here was to identify any evidence of emotion perception in subjects, even at a liberal statistical threshold.

Image acquisition and preprocessing

Data were acquired on a 3T GE scanner with an eight-channel head coil. Structural images used T1-weighted axial acquisition [three-dimensional spoiled-gradient-recall acquisition in the steady state with inversion recovery prep pulse; 256 × 192 matrix, 128 1.2-mm axial slices, 22 cm field of view (FOV)] to allow normalization to standard space (Talairach and Tournoux, 1988). Functional imaging was performed axially using a multi-slice gradient echo-planar sequence (24 cm FOV, 96 × 96 matrix, 38 contiguous 2.6 mm slices, TR = 2300 ms, TE = 25 ms, voxel size = 2.6 × 2.5 × 2.5 mm).

fMRI data were analyzed using Analysis of Functional NeuroImages program (Cox, 1996). The first four volumes in each series were discarded, leaving 704 repetition times per participant. Preprocessing included despiking, slice timing correction, coregistration, spatial smoothing (kernel full width at half maximum = 6), masking, intensity scaling and transformation into Talairach space. Repetitions with motion > 1 mm relative to the preceding repetition were removed from the analysis. Regressors for each emotion in each awareness condition [Emotion (4; angry, happy, neutral, no face) × Awareness (2; aware, non-aware)] were created by convolving stimulus times with a gamma-variate hemodynamic response function.

Table 1. Sample characteristics

Characteristics	SMD (<i>n</i> = 17) Mean ± SD	HV (<i>n</i> = 20) Mean ± SD	<i>t</i> or χ^2	<i>P</i>
Age (years)	14.08 ± 2.79	14.95 ± 2.19	−1.06	0.298
Full-scale IQ ^a	107.19 ± 12.38	115.00 ± 13.18	−1.82	0.078
CDRS	26.65 ± 5.27	—	—	—
PARS ^a	12.13 ± 3.61	—	—	—
CGAS (6 months)	49.41 ± 9.64	—	—	—
Number of medications	1.65 ± 1.54	—	—	—
Number of co-occurring diagnoses	1.71 ± 0.99	—	—	—
	<i>N</i> (%)	<i>N</i> (%)		
Male	13 (76.5)	10 (50)	2.74	0.098
Co-occurring diagnoses				
ADHD	13 (76.5)	—	—	—
Major depression	5 (29.4)	—	—	—
Any anxiety disorder ^b	11 (64.7)	—	—	—
CD	1 (5.9)	—	—	—
Medication at scan				
Unmedicated	6 (35.3)	20 (100)	—	—
Atypical antipsychotic	9 (52.9)	0	—	—
Lithium	1 (5.9)	0	—	—
Antiepileptic	6 (35.3)	0	—	—
Antidepressant	3 (17.6)	0	—	—
Stimulants	3 (17.6)	0	—	—

Note. CDRS, Children's Depression Rating Scale; PARS, Pediatric Anxiety Rating Scale; CD, conduct disorder.

^aMissing data for 1 SMD.

^bIncludes generalized anxiety disorder, separation anxiety disorder, social phobia, panic disorder, post-traumatic stress disorder and obsessive compulsive disorder.

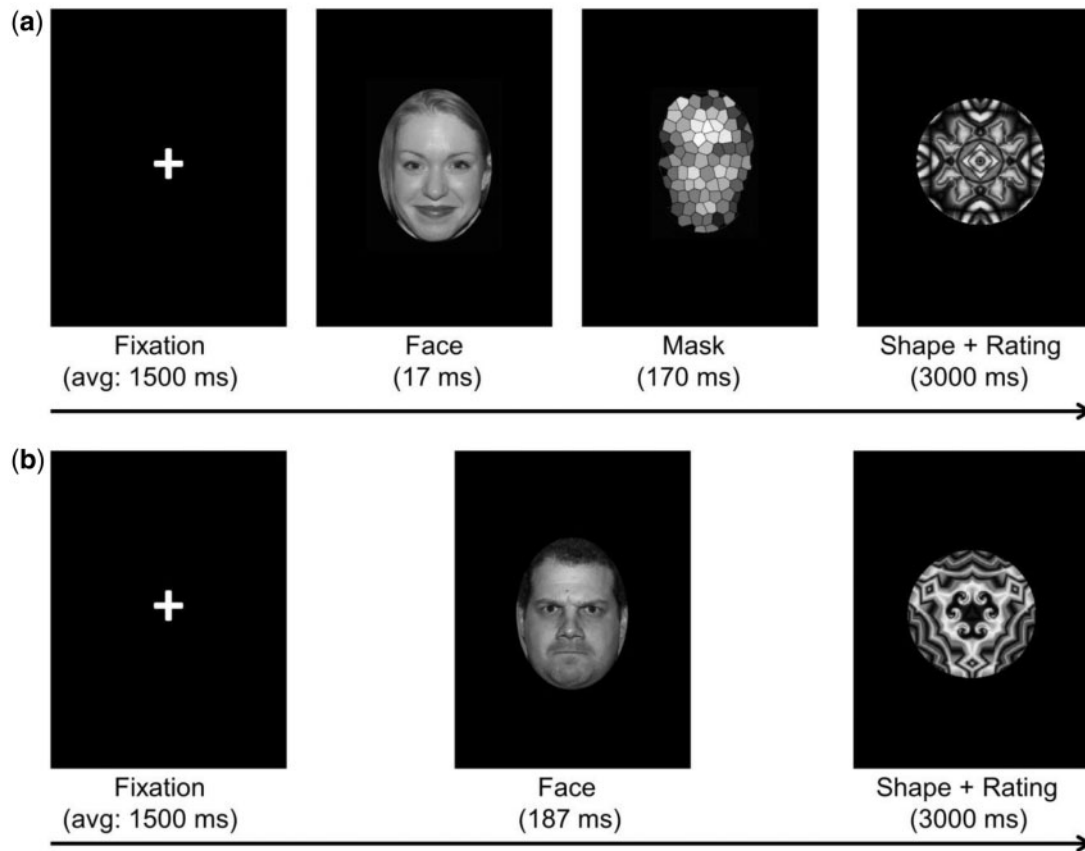


Fig. 1. Affective priming paradigm. (a) Non-aware condition. (b) Aware condition.

Individual-subject linear regression modeling was performed per voxel, with eight task regressors (Emotion \times Awareness) plus one regressor modeling missed trials, a third-order polynomial modeling the baseline drift and six motion parameters. Beta coefficients and *t*-statistics were calculated for each voxel and regressor. Blank-fixation trials provided a baseline.

Data analysis

Behavioral data. Shape ratings and reaction time (RT) on the affective priming task were compared in two separate (one for rating and the other for RT) Diagnosis (2; SMD, HV) \times Emotion (4; angry, happy, neutral, no face) \times Awareness (2; aware, non-aware) repeated-measures analyses of variance (ANOVAs), with Emotion and Awareness as within-subject variables and Diagnosis as a between-subject variable.

fMRI data. At the group level, we conducted a whole-brain Diagnosis (2) \times Emotion (4) \times Awareness (2) ANOVA, using a statistical threshold of $P \leq 0.005$, uncorrected, voxel-wise extent threshold of $k \geq 20$ (Lieberman and Cunningham, 2009). There were no suprathreshold voxels in the three-way ANOVA. Given our primary interest in differences between SMD and HV, analyses then focused on the two-way ANOVAs that included diagnosis, i.e. Diagnosis \times Emotion and Diagnosis \times Awareness. For clusters surpassing this threshold, average signal change values were extracted and post-hoc ANOVAs or *t*-tests were performed in SPSS.

Because masked faces are thought to bypass top-down cortical regulation of the amygdala and elicit amygdala responses

(Whalen et al., 1998; Rauch et al., 2000; Killgore et al., 2014), we also conducted ROI analyses on the left and right amygdala defined by the Talairach-Tournoux Daemon. Mean signal intensity was extracted from each ROI for each stimulus type and was submitted to a Diagnosis (2) \times Emotion (4) \times Awareness (2) ANOVA in SPSS. Post-hoc ANOVAs or *t*-tests were performed in SPSS to understand significant main effects or interactions. In addition, we examined the association between parent- or child-reported irritability (using the Affective Reactivity Index; Stringaris et al., 2012) and the observed brain activation. Given trend-level between-group differences in gender and IQ, additional post-hoc analyses using SPSS were conducted to examine their effects on the fMRI findings. We also conducted post-hoc analyses to test the effects of medication, comorbidities, functional impairment (CGAS), anxiety symptoms and attention-deficit/hyperactivity disorder (ADHD) on the brain activation.

Results

Demographics

Chi-square analysis or *t*-tests were used to compare gender distribution, age and IQ between groups. There were marginally significant between-group differences in gender distribution ($P = 0.098$) and IQ ($P = 0.078$), i.e. SMD youth had a slightly lower IQ and more males compared with HV. Post-hoc analyses were conducted to examine the effect of these factors on our fMRI findings.

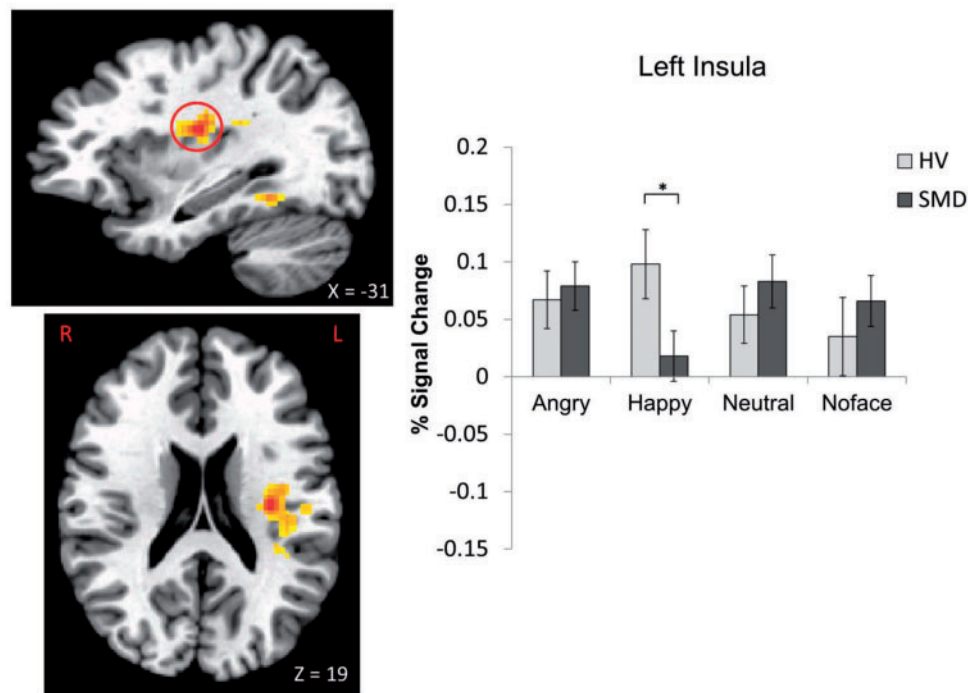


Fig. 2. Diagnosis \times Emotion interaction in the left insula. * $P < 0.05$.

Behavioral data

Rating. There were no significant three-way (i.e. Diagnosis \times Emotion \times Awareness) or two-way (i.e. Diagnosis \times Emotion, Diagnosis \times Awareness or Emotion \times Awareness) interactions or main effect of Diagnosis. Main effects of Emotion ($F_{3,105} = 5.11$, $P = 0.007$) and Awareness ($F_{1,35} = 9.19$, $P = 0.005$) were significant. Somewhat surprisingly, shapes presented after both angry and neutral faces were liked more than those presented after happy and no face ($P \leq 0.04$). Shapes presented in the non-aware condition were liked more than those in the aware condition ($P = 0.005$).

Reaction time. Similarly, there were no significant three-way and two-way interactions or main effects of Diagnosis and Awareness. Only the main effect of Emotion was significant ($F_{3,105} = 6.56$, $P = 0.002$), i.e. participants responded more slowly to shapes presented after angry or neutral faces than to shapes presented after happy or no face ($P \leq 0.05$).

fMRI data

Whole-brain analysis. There were no significant findings from the Diagnosis \times Emotion \times Awareness interaction. Given our interest in between-group differences, we next examined the two-way interactions of Diagnosis \times Emotion and Diagnosis \times Awareness.

A Diagnosis \times Emotion interaction was found in 10 regions, including the left insula, bilateral culmen and parahippocampal gyrus (PHG), left declive, right thalamus, left cerebellar lingual, right STG and right cingulate gyrus (Table 2, Figures 2–5; see Supplementary Figures S1–S6). These were driven primarily by SMD youth showing hypoactivation during processing of happy faces (Figures 2–4) and hyperactivation during processing of angry faces (Figures 3 and 5) compared with HV. There were also within-group differences across emotion types within SMD patients in the insula, PHG, thalamus and STG ($P \leq 0.02$);

within-group differences in the HV group emerged in the insula and STG ($P \leq 0.03$). In general, SMD youth exhibited the highest activation when viewing angry faces and the lowest activation when viewing happy faces compared with other faces, whereas HV youth exhibited the highest activation when viewing happy faces relative to other faces.

A Diagnosis \times Awareness interaction was found in the left ventromedial prefrontal cortex (vmPFC; $x = -4$, $y = 36$, $z = -9$, $P = 0.005$, $k = 65$; Figure 6). Relative to HV, youth with SMD exhibited hypoactivation during aware condition at a trend level ($t = -1.85$, $P = 0.07$) and hyperactivation during non-aware condition ($t = 3.40$, $P = 0.002$; Figure 6). There was a within-group HV difference, with participants showing less vmPFC activation in the non-aware than aware condition ($t = 5.04$, $P < 0.001$).

ROI analysis. In the left amygdala, there were no three-way or two-way interactions or main effects of Diagnosis and Awareness. However, the main effect of Emotion was significant ($F_{3,105} = 5.29$, $P = 0.003$). Angry, happy and neutral faces activated the left amygdala more than 'no face' stimuli (P values ≤ 0.02). Similarly, in the right amygdala, only the main effect of Emotion was significant ($F_{3,105} = 5.72$, $P = 0.002$). Angry and happy (and neutral at a trend level, $P = 0.075$) faces activated the right amygdala more than 'no face' stimuli ($P \leq 0.001$); angry faces also activated this region more than happy faces ($P = 0.02$) and neutral faces (at a trend, $P = 0.056$).

Post-hoc analyses

Irritability symptoms. We conducted bivariate correlation analyses to assess the associations between parent- or child-reported irritability and brain activation. Results showed that parent- or child-reported irritability was negatively correlated with activation in the right thalamus ($r = -0.37$, $P = 0.035$) during processing of happy faces and positively correlated with activation in the left

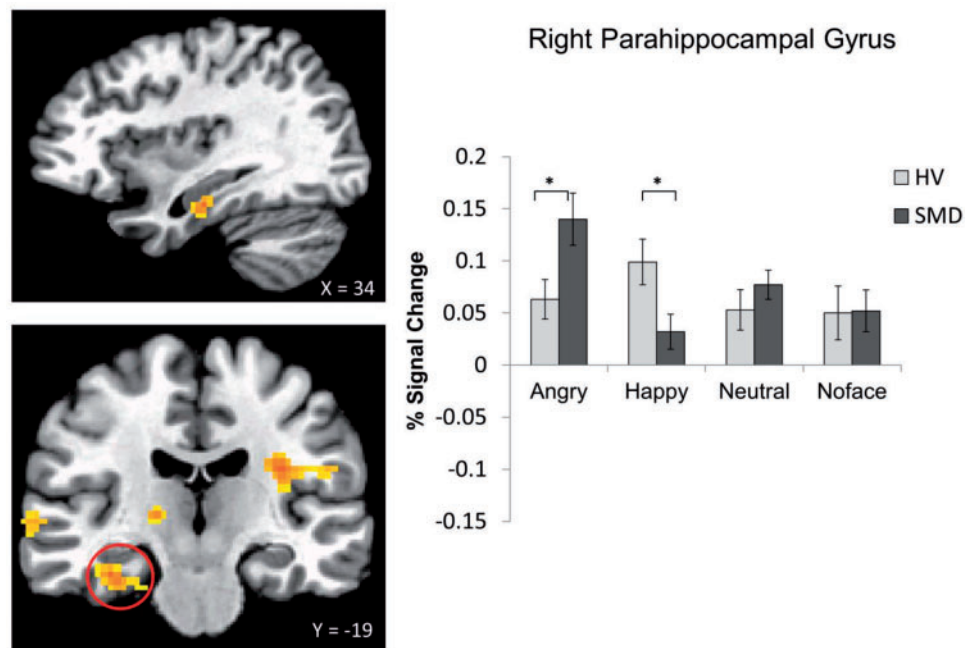


Fig. 3. Diagnosis \times Emotion interaction in the right PHG. * $P < 0.05$.

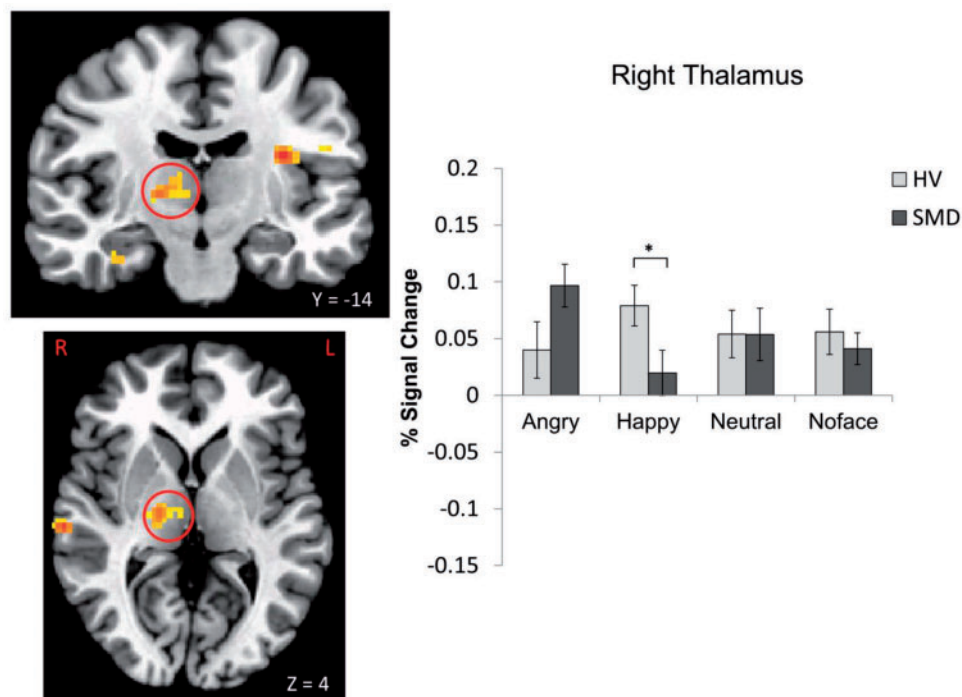


Fig. 4. Diagnosis \times Emotion interaction in the right thalamus. * $P < 0.05$.

vmPFC activation during non-aware condition ($r = 0.46$, $P = 0.007$). These findings are largely consistent with results from the categorical findings indicating SMD hypoactivation to happy faces and SMD hyperactivation during non-aware condition.

Effects of covariates. For the whole-brain analyses, the significant two-way interactions of Diagnosis \times Emotion in the 10 regions and Diagnosis \times Awareness in the left vmPFC all remained significant when covarying IQ and gender (P values ≤ 0.001). For the ROI analyses, the main effect of emotion in the bilateral

amygdala also remained significant when covarying IQ and gender (P values ≤ 0.002). There was no association between observed brain activation (e.g. insula, vmPFC and amygdala) and number of medications, number of comorbidities, functional impairment or anxiety symptoms in SMD patients (P values > 0.05). Because of the small number of SMD without ADHD ($n = 4$), we were not able to compare brain activation between SMD with and without ADHD. Instead, we conducted analyses comparing SMD with ADHD (13 out of 17 SMD) to all HV. All the significant findings in the full sample remained.

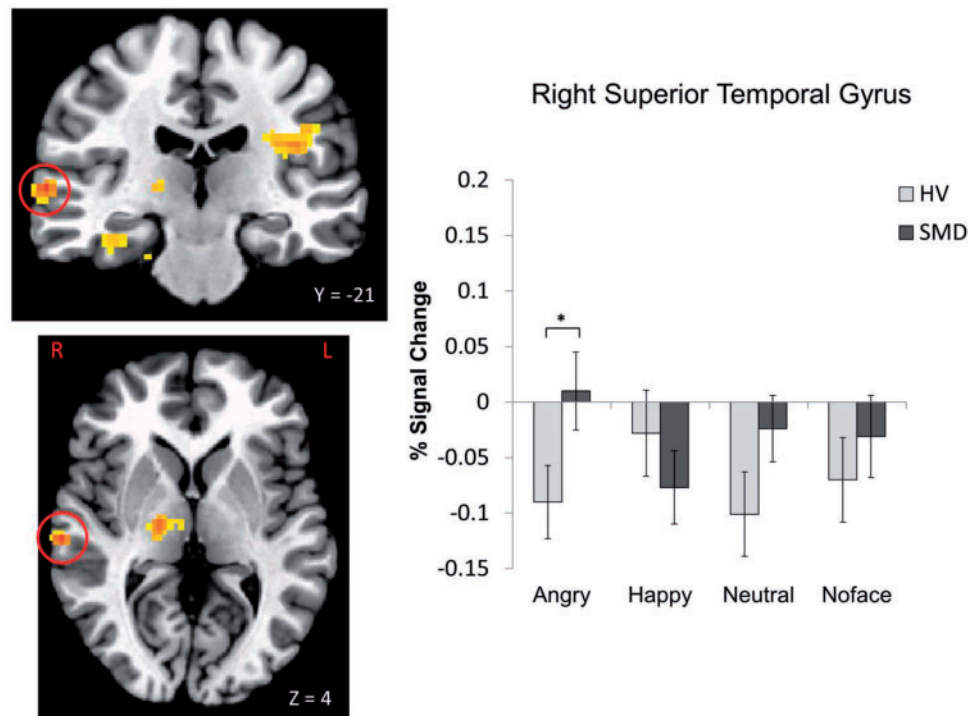


Fig. 5. Diagnosis \times Emotion interaction in the right STG. * $P < 0.05$.

Table 2. Significant Diagnosis \times Emotion interaction

Area of activation	Brodmann area (BA)	Side	Cluster size ^a	Talairach coordinates ^b			Analysis ^c	
				x	y	z	F (3, 33)	P
Insula	BA 13	Left	187	-31	-16	19	8.18	<0.001
Culmen		Left	87	-24	-36	-21	8.47	<0.001
Culmen/PHGs	BA 37	Left	60	-26	-44	-11	7.65	<0.001
PHG		Right	59	34	-19	-19	9.27	<0.001
Declive		Left	52	-19	-76	-19	8.63	<0.001
Thalamus		Right	42	16	-14	4	6.70	0.001
Cerebellar lingual		Left	37	-4	-44	-11	7.26	<0.001
STG	BA 21	Right	34	61	-21	4	7.14	<0.001
Culmen		Right	33	9	-26	-21	7.42	<0.001
Cingulate gyrus	BA 31	Right	26	14	-34	29	7.33	<0.001

^aCluster size was determined using a significance threshold of uncorrected $P \leq 0.005$ and $k \geq 20$.

^bCoordinates refer to the voxel with maximum signal intensity.

^cStatistics refer to the analysis of the extracted clusters in SPSS.

Post-tasks

Data from the two post-tasks indicate that participants were unaware of the emotional face prime. On both the post-task gender and emotion identification tasks, accuracy was no better than chance level for any emotion (i.e. 50% for gender identification and 33.3% for emotion identification; P values ≥ 0.16).

Discussion

Using an affective priming task, we compared the neural correlates of aware vs non-aware processing of angry and happy faces in youth with SMD and HV. Given the increasing emphasis on reproducibility of imaging results and the concerns regarding Type I error in fMRI research (Lieberman and Cunningham, 2009; Poldrack and Mumford, 2009; Vul et al., 2009), this study

also aimed to replicate a prior study on SMD (Thomas et al., 2014) using a similar paradigm. We found emotion-specific responses in several regions implicated in emotion processing, including the insula, PHG, thalamus and STG. Specifically, in these regions, we found hyperactivation in SMD compared with HV when processing angry faces but hypoactivation when processing happy faces. This is consistent with threat bias and reduced sensitivity to positive affect, linked, respectively, to aggressive and depressive symptoms often observed in irritable youth (Copeland et al., 2013; Leibenluft and Stoddard, 2013). Importantly, STG hyperactivation to angry faces replicated previous findings in an independent sample of youth with SMD (Thomas et al., 2014). In addition, relative to HV, SMD youth exhibited greater vmPFC activation during processing of masked faces, regardless of emotion. Findings with irritability as a

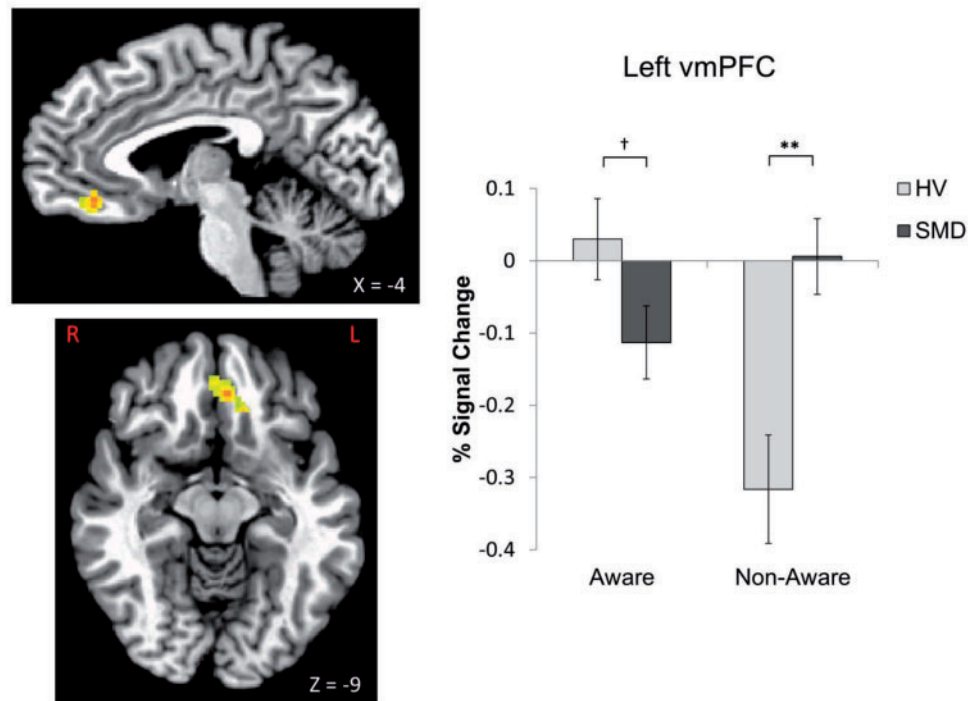


Fig. 6. Diagnosis \times Awareness interaction in the left vmPFC. $F_{1,35} = 18.26$, $P < 0.001$ for Diagnosis \times Awareness interaction. $\dagger P = 0.07$, $**P < 0.01$.

dimensional measure, rather than diagnostic status, are largely consistent with these categorical findings.

Youth with SMD, relative to HV, appeared to be hypersensitive to angry faces (masked or unmasked), manifest as increased activation in the PHG and STG. This is true whether the angry faces were perceived consciously or not. This hypersensitivity to angry faces has potentially important implications for SMD and DMDD, as severely irritable youth often show reactive aggression which may arise from possessing a hostile attribution bias and/or attention bias toward threat (e.g. angry faces). Indeed, previous behavioral research has demonstrated that youth with SMD exhibit an attention bias toward angry faces (Hommer et al., 2014). Similarly, adolescents with conduct disorder show deficits in the recognition of angry faces (Fairchild et al., 2009), and changing the perception of face emotions from anger toward happiness may reduce aggressive behavior (Penton-Voak et al., 2013). However, attention bias toward threat is not specific to irritability or disruptive behavior, as it is one of the most replicated pathophysiological findings in anxiety disorders (Bar-Haim et al., 2007). Heightened activation in the PHG and/or STG in response to angry faces has been reported previously in youth with SMD (Thomas et al., 2014), generalized social phobia (Stein et al., 2002) and pediatric bipolar disorder during euthymia (Pavuluri et al., 2007). Although our post-hoc analyses suggested that the brain activation in these regions was not driven by anxiety symptoms, whether the neural sensitivity to threat, e.g. angry faces, is a shared neural mechanism across these mood and anxiety disorders remains to be empirically tested.

In contrast, when viewing happy faces (masked or unmasked), youth with SMD, relative to HV, showed decreased activation in areas such as the insula and thalamus that are highly connected to the amygdala. Insular cortex plays a critical role in mapping visceral states that are associated with emotional experience, giving rise to conscious feelings and

interoceptive awareness (Craig, 2003; Singer et al., 2009). Thalamus, on the other hand, is a key area for relaying sensory information and regulation of arousal (Schiff, 2008; Suslow et al., 2010b). Both areas are important for emotional processing and regulation. Indeed, reduced thalamus activation to happy faces may down-regulate the flow of information to the cortex and make the happy faces less salient, thus suggesting a decreased sensitivity to positive stimuli in SMD youth. Given the large body of literature supporting a diminished sensitivity to positive affect and stimuli in depression (for a review, see Forbes and Dahl, 2005) as well as the longitudinal link between chronic irritability and depressive disorders (Brotman et al., 2006; Stringaris et al., 2009), the extent to which hypoactivation in temporal and limbic regions represents a shared or distinct neural marker in SMD and depressive disorders needs to be determined. This finding in SMD, on the other hand, contrasts with the literature on bipolar disorder during mixed states (euthymic, hypo/manic, depressed or mixed) suggesting increased responsiveness to happy faces (Phillips and Vieta, 2007; Passarotti et al., 2011) and thus provides additional evidence to support that severe, chronic irritability is not a developmental presentation of bipolar disorder (Leibenluft, 2011).

In addition to emotion-specific findings, there were non-emotion-specific group differences in activation in the non-aware condition. SMD youth exhibited greater vmPFC activation compared with HV during the non-aware condition. Further, HV, but not SMD, youth showed differential vmPFC activation between the two awareness conditions. These findings suggest that in youth with SMD, vmPFC failed to go 'offline' even when the stimulus was presented so briefly that it was difficult to perceive. vmPFC plays a key role in generating affective meaning (Roy et al., 2012), regulating limbic activation in response to emotional stimuli (Etkin et al., 2011), and flexibly updating signal value (Viviani, 2014). Thus, vmPFC dysfunction may mediate over-reactivity to face emotions and face-like stimuli. Moreover,

aberrant vmPFC activity may contribute to deficits in 'context-sensitive regulation' (Ochsner, 2008) often observed in SMD. Interestingly, our findings, although without emotion specificity, share similarity to a previous study in which greater activation in the orbitofrontal cortex was found in adults with depression than in controls during masked sad vs neutral faces (Victor et al., 2012). Such similarity is noteworthy given the longitudinal associations between severe, chronic irritability and major depressive disorders (Brotman et al., 2006; Stringaris et al., 2009).

Unlike previous research on unmasked face processing in youth with SMD (Brotman et al., 2010; Thomas et al., 2012, 2013), this study did not find between-group differences in amygdala activation. It should be noted that in a similar paradigm, Thomas et al. (2014) also did not find amygdala dysfunction in SMD. However, there was a significant main effect of emotion in this study, i.e. emotional faces activated the amygdala more than did no face stimuli, suggesting the effectiveness of our masked and unmasked faces in eliciting amygdala responses. Nonetheless, this null finding may be attributable to several reasons, including Type II error and the discrepancy in paradigms across studies. For example, in previous studies where youth with SMD differed from HV in amygdala activation (Brotman et al., 2010; Thomas et al., 2012, 2013), face emotions were consciously processed and displayed for a longer duration (>2500 ms) than in the present study (17 ms for masked faces and 187 ms for unmasked faces). Also, in prior studies, participants were asked to explicitly label emotions or implicitly process emotions rather than indicate how much they liked an abstract shape. Thus, the involvement of amygdala in masked and unmasked face processing in irritable youth remains to be determined pending future work with a larger sample.

Our findings in youth with SMD are relevant and likely to inform future research on DMDD; both SMD and DMDD are characterized by severe irritability and temper outbursts that are developmentally inappropriate and out of proportion to the situation. As described earlier, all our SMD youth in this sample, indeed, met criteria for DMDD. Of note, SMD criteria also require symptoms of hyperarousal (e.g. distractibility, racing thoughts or flight of ideas and intrusiveness), whereas DMDD criteria do not. As a result, our SMD sample is enriched for hyperarousal symptoms, and ADHD may be over-represented compared with studies that recruit youth with DMDD rather than SMD. Nonetheless, given the frequent association between ADHD and irritability (Shaw et al., 2014), we anticipate that many youth with DMDD will also meet criteria for ADHD, even though that is not required for the diagnosis. Thus, while it is unclear whether our finding would generalize to youth with DMDD without hyperarousal symptoms or ADHD, heightened sensitivity toward negative emotions and diminished sensitivity toward positive emotions may be a hallmark pathophysiological feature of irritability.

Several limitations of this study merit comment. First, most SMD youth (>65%) had co-occurring diagnoses (e.g. ADHD and anxiety disorders) and were medicated. Our sample size is not large enough to allow for comparisons of the neural activation between SMD youth with vs without comorbidities or medicated vs unmedicated. However, post-hoc analyses indicate no significant association between brain activation and number of medications, number of comorbidities or anxiety symptoms in SMD youth. Also, fMRI findings remain largely the same when restricting analyses to SMD with ADHD and all HV. Nonetheless, future work with a larger sample is needed to rule out the contribution of medications and comorbidities to our findings and

to examine symptoms dimensionally across groups (Insel et al., 2010). Moreover, we did not find significant three-way interaction of Diagnosis \times Emotion \times Awareness. Whether this is due to a lack of power or true null finding should be clarified in future research, although this negative finding is also reported in a previous study with a similar paradigm (Thomas et al., 2014).

Despite these limitations, our findings partially replicate the study by Thomas et al. (2014) and suggest that youth with SMD may show emotion-specific neural dysfunction in emotion processing areas (e.g. insula, PHG, STG and thalamus) across awareness level. Hyper-sensitivity toward negative emotions (e.g. angry faces) and hypo-sensitivity toward positive emotions (e.g. happy faces) may be important in the etiology and maintenance of irritable, aggressive and depressive symptoms in SMD. In addition, youth with SMD showed vmPFC dysfunction during rapid, automatic processing of face stimuli that were presented below awareness level. If replicated, our findings may have important implications for the treatment of SMD and DMDD. For instance, activation in the emotion processing areas such as insula, PHG, may be used as biomarkers to monitor treatment response. Further, given that irritability is a core feature of SMD and DMDD and a cross-cutting symptom in many pediatric disorders, future research examining the neural correlates of face processing using categorical (i.e. diagnosis) and dimensional (i.e. irritability) approaches would be highly informative.

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Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. None declared.

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