



Neural circuitry of masked emotional face processing in youth with bipolar disorder, severe mood dysregulation, and healthy volunteers

Laura A. Thomas^{a,b,*}, Melissa A. Brotman^a, Brian L. Bones^a, Gang Chen^c, Brooke H. Rosen^a, Daniel S. Pine^a, Ellen Leibenluft^a

^a Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, United States

^b Office of the Director, National Institute on Drug Abuse, Bethesda, MD, United States

^c Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, United States

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ABSTRACT

Youth with bipolar disorder (BD) and those with severe, non-episodic irritability (severe mood dysregulation, SMD) show face-emotion labeling deficits. These groups differ from healthy volunteers (HV) in neural responses to emotional faces. It is unknown whether awareness is required to elicit these differences. We compared activation in BD ($N=20$), SMD ($N=18$), and HV ($N=22$) during “Aware” and “Non-aware” priming of shapes by emotional faces. Subjects rated how much they liked the shape. In aware, a face (angry, fearful, happy, neutral, blank oval) appeared (187 ms) before the shape. In non-aware, a face appeared (17 ms), followed by a mask (170 ms), and shape. A Diagnosis-by-Awareness-by-Emotion ANOVA was not significant. There were significant Diagnosis-by-Awareness interactions in occipital regions. BD and SMD showed increased activity for non-aware vs. aware; HV showed the reverse pattern. When subjects viewed angry or neutral faces, there were Emotion-by-Diagnosis interactions in face-emotion processing regions, including the L precentral gyrus, R posterior cingulate, R superior temporal gyrus, R middle occipital gyrus, and L medial frontal gyrus. Regardless of awareness, BD and SMD differ in activation patterns from HV and each other in multiple brain regions, suggesting that BD and SMD are distinct developmental mood disorders.

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1. Introduction

In this study we compared neural activation in youth with bipolar disorder (BD), those with severe, non-episodic irritability (severe mood dysregulation, or SMD), and healthy volunteers (HV) while they completed a paradigm involving processing of faces presented above or below the threshold for awareness. The comparison between SMD and BD is motivated by the recent increase in the prevalence of pediatric BD diagnosed in clinical settings (Blader

Abbreviations: BD, bipolar disorder; SMD, severe mood dysregulation; ADHD, attention deficit hyperactivity disorder; HV, healthy volunteer.

* Corresponding author at: 9000 Rockville Pike MSC 2670, Building 15K, Rm. 204, Bethesda, MD 20892-2670, United States. Tel.: +1 301 402 8468; fax: +1 301 402 6100.

E-mail address: tlaura@mail.nih.gov (L.A. Thomas).

and Carlson, 2007; Moreno et al., 2007). This increase was concurrent with the contention in the child psychiatry literature that BD manifests in youth as severe, non-episodic irritability, rather than with discrete episodes of mania and depression (Biederman et al., 2000). Thus, the SMD phenotype was defined to facilitate research on youth with this controversial phenotype (Leibenluft, 2011). Studies of family history and longitudinal course suggest that BD and SMD are dissociable (Brotman et al., 2006, 2007; Stringaris et al., 2010). However, both SMD and BD youth, but not those with other psychiatric illnesses, show perturbed face-emotion labeling ability (McClure et al., 2003, 2005; Guyer et al., 2007; Schenkel et al., 2007; Rich et al., 2008), although evidence suggests that the neural activity mediating face processing may differ between SMD and BD (Brotman et al., 2010; Thomas et al., 2012, 2013).

Emotional facial expressions can influence responding even in research participants who remain unaware of a face's emotional content (Ohman and Mineka, 2001). Therefore, it is important to test whether neutral activation in response to face emotion differs among SMD, BD, and HV when they are unaware of the emotional face stimulus. Potentially, aberrant automatic (non-aware) processing of emotional stimuli may contribute to symptoms of emotional problems in both BD and SMD. One way to test this hypothesis is through the use of affective priming, which incorporates a technique called backwards masking. In backwards masking, a prime stimulus is presented too quickly to reach awareness, followed by a target stimulus (mask) that is presented long enough to be identified. In affective priming paradigms, the prime consists of an emotional stimulus, typically an emotional face, followed by a mask stimulus that participants are asked to evaluate. Research with affective priming demonstrates that a brief exposure to an emotional-face prime can influence judgments of affectively neutral stimuli that are presented subsequently (Murphy and Zajonc, 1993; Winkielman et al., 1997).

In healthy adults, some evidence suggests that affective priming paradigms can activate a “fast-route” that bypasses conscious perception (LeDoux, 1996) and includes areas such as the amygdala, fusiform gyrus, hippocampus, anterior cingulate, insula, and primary visual cortex (Morris et al., 1998; Whalen et al., 1998; Nomura et al., 2004; Garolera et al., 2007; Kim et al., 2010; Brooks et al., 2012). The subject's inability to identify a prime is thought to result from effects of the target stimulus on the ventral visual stream, which includes the lateral occipital cortex and regions in the lingual and fusiform gyri, regions that mediate object recognition (Ungerleider and Mishkin, 1982; Hasson et al., 2002). Indeed, lateral occipital cortex activation correlates positively with the strength of masking effects in healthy adults (Green et al., 2005).

Compared with healthy subjects, adults with mood and anxiety disorders have increased amygdala activation to masked emotional faces compared with healthy volunteers (Rauch et al., 2000; Sheline et al., 2001; Armony et al., 2005; Dannlowski et al., 2006a,b, 2008; Li et al., 2008; Tsunoda et al., 2008; Suslow et al., 2010). For example,

there is increased amygdala activation to masked emotional faces in adults with unipolar depression compared to their healthy counterparts (Suslow et al., 2010; Victor et al., 2012). In addition, similar studies report that when compared to healthy subjects, patients with schizophrenia have decreased ventrolateral occipital activation when unaware of the mask stimulus (Green et al., 2009).

There have been a few backwards masking paradigms involving youth (Pine et al., 2001; Hall et al., 2007; Killgore and Yurgelun-Todd, 2007; Monk et al., 2008; Viding et al., 2012). However, these studies did not compare awareness states as we do, and to date no fMRI affective priming study includes youth with any mood disorder. Here, we use such a paradigm to compare BOLD activation patterns in pediatric SMD, BD, and HV.

Our experiment used face stimuli presented in unmasked/aware (187 ms) and masked/non-aware (17 ms) conditions. In both conditions the face was followed by an abstract shape, and subjects rated how much they liked the shape. Face emotions were anger, fear, happy, neutral and a blank oval (Suslow et al., 2006). The blank oval was included to disambiguate responses to face emotions from responses to faces per se, and because youth with BD and SMD rate neutral faces more negatively than do HV (Rich et al., 2006; Brotman et al., 2010).

To date, three neuroimaging studies directly compare amygdala activity in BD and SMD during face emotion processing (Brotman et al., 2010; Thomas et al., 2012, 2013). Because these studies used different paradigms, it is difficult to compare their results directly. Brotman et al. (2010) found that SMD, compared to BD and HV youth, exhibited amygdala hypo-activation during explicit processing of neutral faces. However, both Thomas et al. (2012, 2013) found that BD and SMD had similar amygdala dysfunction vs. HV, with Thomas et al. (2012) reporting less modulation of amygdala activity in BD and SMD compared to HV, and Thomas et al. (2013) finding overall hyperactivity in the amygdala to emotional faces in both BD and SMD. Due to these varying results from differing experimental paradigms, we were unable to posit specific hypotheses about how amygdala activity might differ between BD and SMD. However, based on the aforementioned research with adult unipolar depression demonstrating increased amygdala activity to masked emotional faces, as well as previous work with pediatric BD and SMD (Brotman et al., 2010; Thomas et al., 2012), we hypothesized that amygdala activity would be greater for the masked faces in the mood-disordered BD and SMD groups vs. HV.

Additionally, we hypothesized that there would be awareness-modulated group differences in ventrolateral occipital activation based on work in adults with schizophrenia (Green et al., 2009). Possible group differences between BD, SMD, and HV based on awareness would add to data demonstrating that BD and SMD differ clinically, neuropsychologically, and pathophysiologically. These differences suggest that SMD and BD may be manifestations of differing developmental pathologies along a mood disorders spectrum. Comparisons of both groups with healthy age-matched controls will help disentangle possible normative developmental effects vs. the presence of a mood disorder.

2. Methods

2.1. Participants

Usable fMRI data were acquired from 60 subjects, including BD ($N=20$), SMD ($N=18$), and HV ($N=22$). All participants, ages 8–18, were enrolled in an Institutional Review Board-approved study at the NIMH. Parents and youths gave written informed consent/assent. Patients were recruited through advertisements to support groups and presentations at professional meetings. Controls were recruited through advertisements. Subjects 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). Interviewers were masters or doctoral level clinicians with excellent inter-rater reliability ($\kappa > 0.9$ for all diagnoses, including differentiating BD from SMD).

Mood ratings were completed with the BD youths within 48 h of scanning, including the Young Mania Rating Scale (YMRS; Young et al., 1978) and Children's Depression Rating Scale (CDRS; Ponzanski et al., 1979). BD patients were "narrow phenotype," with at least one full-duration (hypo)manic episode characterized by abnormally elevated mood and at least three DSM-IV "B" mania symptoms (Leibenluft et al., 2003). SMD youth had non-episodic irritability, over-reactivity to negative emotional stimuli at least three times/week, and hyperarousal symptoms (see Table 1). Symptoms had to begin before age 12, be present for at least one year with no symptom-free periods exceeding two months, and cause severe impairment in at least one setting (i.e., home, school, peers), and mild impairment in another. Euphoric mood or distinct (hypo)manic episodes lasting more than one day were exclusionary (Leibenluft et al., 2003). HV had no lifetime psychiatric diagnoses and, as ascertained by parent interview, no first-degree relatives with mood disorders.

Exclusion criteria for all subjects were: IQ < 70, history of head trauma, neurological disorder, pervasive developmental disorder, unstable medical illness, or substance abuse/dependence. HV were medication-free. Most BD and SMD youths were medicated; for ethical reasons, only patients failing current psychotropic medication were withdrawn from treatment.

2.2. Behavioral paradigm

In each of two awareness conditions (aware and non-aware), subjects indicated on a scale from 1 (did not like) to 5 (liked a lot) their likeness of an abstract shape presented for 3000 ms (Fig. 1). In the aware condition, a face, fixation point, or blank oval was presented before the shape for 187 ms. In the non-aware condition, a face, fixation point or blank oval ('no-face') was presented for 17 ms, followed by a scrambled face mask for 170 ms, then by the abstract shape. Thus, each event was 3187 ms long. The inter-trial interval was 1250–1750 ms, averaging 1500 ms. The face emotions were anger, fear, happy, and neutral. Stimuli were presented randomly. There were four runs, two for each awareness condition, each with 15 trials of

each stimulus type (anger, happy, fear, neutral, blank oval, fixation).

Prior to scanning, outside the scanner on a desktop computer, subjects completed a practice run of 8 trials each of the awareness conditions, using faces not presented during scanning. Subjects then completed a questionnaire to ensure they were completing the task correctly. If not, the practice was repeated before scanning.

2.3. Image acquisition

Data were acquired on a 3T General Electric scanner. 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).

2.4. Post-scanning assessments

Two out-of-scanner tasks, administered immediately after scanning, assessed whether the awareness manipulation was successful. The post-task order was random. In both, subjects were shown the faces in the non-aware condition and were told about the presence of the face in the "flash" before the shape. In one post-task, subjects were asked to do their best to identify the gender of the face. We combined all subjects' accuracy data and ran one-sample t -tests vs. chance (50%) for each emotion: anger, fear, happy, neutral. In the second post-task, subjects were asked to rate the face emotion (anger, fear, happy, or neutral). To examine if any emotion "leaked" from the mask into awareness, we conducted one-sample t -tests on accuracy for anger, fear, happy, and neutral faces vs. chance (25%). Analyses of variance (ANOVAs) were also run between groups to ascertain performance differences in each post-scanning task.

To ensure that subjects performed the task correctly, they completed a questionnaire after scanning asking, for example, whether they considered their rating of each shape individually or instead pressed random response buttons.

2.5. Behavioral data analysis

Shape ratings and reaction time (RT) were compared in separate Diagnosis(3) \times Emotion(5) \times Awareness(2) ANOVAs. For significant main effects, post hoc LSD t -tests were conducted.

2.6. Imaging analysis

fMRI data were analyzed with Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). The first four volumes in each series were discarded, leaving 704 repetition times per participant. Preprocessing included slice timing correction, motion correction, and the application

Table 1
Diagnostic criteria for severe mood dysregulation.

Inclusion criteria:	Exclusion criteria:
1. Aged 7–17, with the onset of symptoms before age 12	1. The individual exhibits any of these cardinal bipolar symptoms: Elevated or expansive mood. Grandiosity or inflated self-esteem. Episodically decreased need for sleep
2. Abnormal mood (specifically anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable by people in the child's environment (e.g., parents, teachers, peers)	2. The symptoms occur in distinct periods lasting more than 1 day
3. Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness	3. Meets criteria for schizophrenia, schizophreniform disorder, schizoaffective illness, pervasive development disorder, or PTSD
4. Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week	4. Meets criteria for substance use disorder in the past 3 months
5. The symptoms noted in 2–4 above are currently present and have been present for at least 12 months without any symptom-free periods exceeding two months	5. IQ < 70
6. The symptoms are severe in at least one setting (i.e., violent outbursts, assaultiveness at home, school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting	6. The symptoms are due to the direct physiological effects of a drug of abuse, or to a general medical or neurological condition

Adapted from Rich et al. (2007).

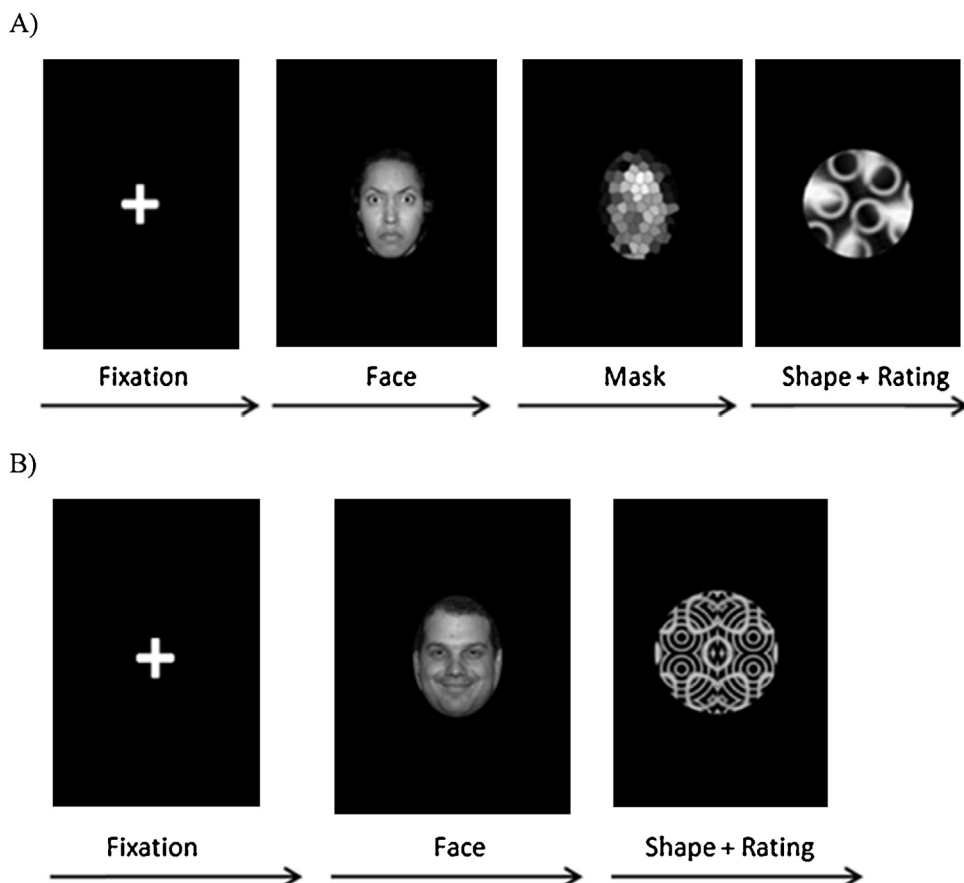


Fig. 1. (A) In the non-aware condition, a face or blank oval was presented for 17 ms, followed by a scrambled face mask for 170 ms and then by the abstract shape. (B) In the aware condition, a face or blank oval was presented before the shape for 187 ms.

of a 6 mm RMS blur. Data were scaled to by the voxel-wise mean so the effect estimates can be interpreted as approximate percent signal changes relative to the baseline condition (fixation). We censored multiple movement spikes greater than 2 mm and excluded participants with more than 10% censored TRs. Three SMD subjects had too much movement for analysis, all other data were usable. For each participant, linear regression modeled baseline drift and residual motion artifacts. Individual beta-coefficient maps were warped into standard space with a high resolution anatomical image that had been normalized manually by identifying the anterior-posterior commissures, midsagittal plane, and outer boundary.

Regressors for each emotion in each awareness condition were created by convolving stimulus times with a gamma-variate hemodynamic-response function. Linear regression modeling was performed per voxel, with ten regressors, one for each stimulus condition (Emotion(5) × Awareness(2)), a third-order polynomial modeling the baseline drift, and 6 motion parameters. Blank-fixation trials provided a baseline. Activation to each stimulus condition is described vs. baseline.

At the whole-brain level, we conducted a group analysis with a Diagnosis(3) × Emotion(5) × Awareness(2) ANOVA. We used a threshold of $p < .005$, $k \geq 20$ at a resolution of $2 \times 2 \times 2$. This joint voxel-wise and cluster-size threshold was used because these parameters are thought to balance Types I and II errors (Lieberman and Cunningham, 2009). Since our main focus was differences in brain activation between diagnostic groups, we also conducted whole-brain Diagnosis × Awareness and Diagnosis × Emotion ANOVAs with the same cluster thresholds. For clusters meeting the threshold, average effect estimates were extracted from each subject, and post hoc ANOVAs were performed in SPSS. Anatomical locations were labeled using the Talairach–Tournoux Daemon (Talairach and Tournoux, 1988).

We performed an ROI analysis using average beta weight estimates in the right and left amygdala, based on the Talairach–Tournoux Daemon (Talairach and Tournoux, 1988). Using commercially available software (PSAW 18.0.1) a repeated-measures Diagnosis × Awareness ANOVA was conducted on the extracted average beta weights. Threshold for significance was $p < .05$, and no correction was needed because there was only one measure per amygdala (i.e., BOLD signal averaged across the structure). Post hoc Tukey HSD-tests were performed when necessary.

In both the whole-brain and amygdala data, we conducted exploratory analyses to examine the impact of comorbid anxiety disorders and current mood state in the regions where the results were significant in the primary analyses.

3. Results

3.1. Demographics

Eighty percent of BD and 94% of SMD patients were euthymic at the time of testing (for BD defined as

YMRS ≤ 12 and CDRS < 40 ; for SMD defined as CDRS < 40). The minority of BD patients were hypomanic (YMRS > 12 and CDRS < 40) or in a mixed state (YMRS > 12 and CDRS ≥ 40), and very few SMD patients were depressed (CDRS ≥ 40) at the time of scanning. CGAS scores demonstrated that, on average, both BD and SMD patients were moderately impaired (41–50). Groups were well matched for age, gender, and intelligence (Table 2).

3.2. Behavior

There was a main effect of Emotion on ratings ($F(4, 228) = 12.90$, $p < .0001$), with no significant differences across diagnosis (eTable 1). This effect of emotion was contrary to what one might expect based on the emotion of the prime. That is, across groups and awareness conditions, LSD t -tests showed that shapes presented after happy faces were rated more *negatively* than shapes presented after angry ($p < .0001$), fearful ($p < .0001$), or neutral ($p < .0001$) faces. A similar trend was evident for the no-face stimuli, where shapes preceded by no-face stimuli were liked less than those following angry ($p < .001$), fearful ($p < .001$), or neutral ($p < .03$) faces. Finally, shapes following neutral faces were liked less than shapes followed by fear faces ($p < .03$), with a trend for anger faces ($p = .07$). Thus, the emotion on the masked face influenced subjects' ratings of the abstract shape presented subsequently, but this influence was in the opposite direction of the mask, such that priming by negative emotions led to more positive less negative valence ratings.

For RT, there was a main effect of Diagnosis ($F(2, 57) = 4.32$, $p < .02$), with BD responding more quickly than SMD ($p < .04$) and comparisons ($p < .01$).

3.3. Imaging

3.3.1. Whole-brain analysis

We computed a whole-brain Diagnosis × Emotion × Awareness ANOVA. No clusters survived at the cluster threshold of $p < .005$, $k \geq 20$. Given our focus on between-group differences, we next examined the two-way interactions of Awareness × Diagnosis and Emotion × Diagnosis.

Three occipital clusters showed an Awareness × Diagnosis interaction: R middle occipital gyrus (BA18), L middle occipital gyrus (BA 17/18), and L middle occipital gyrus (BA 19) (Table 3a, Fig. 2). Within each cluster, we used within-group paired t -tests to compare activation between the aware and non-aware conditions. Both BD and SMD showed increased activation in the non-aware vs. aware conditions for the first two middle occipital gyrus clusters (R and L); this was also significant for SMD in the third middle occipital gyrus cluster. In contrast, HV showed increased activity for aware vs. non-aware, only in the R middle occipital gyrus cluster.

For the Emotion × Diagnosis interaction, there were five significant clusters: L precentral gyrus (BA 3/4), R posterior cingulate, R superior temporal gyrus (BA 21), R middle occipital gyrus (BA 30), and L medial frontal gyrus (BA10) (Table 3b). Within each cluster, we conducted ANOVAs on

Table 2
Subject characteristics.^a

	BD (N = 20) Mean ± SD	SMD (N = 18) Mean ± SD	HV (N = 22) Mean ± SD	p-Value
Age	15.12 ± 2.77	14.42 ± 1.86	14.75 ± 2.21	NS
WASI Full-Scale IQ	101.00 ± 14.50	104.56 ± 11.23	109.50 ± 12.63	NS
YMRS ^b	8.45 ± 6.00	–	–	–
CDRS ^c	27.47 ± 6.45	25.65 ± 5.24	–	NS
CGAS ^d	48.39 ± 9.29	46.63 ± 14.86	–	NS
Number of medications	3.15 ± 1.73	1.61 ± 1.78	–	0.05
	N (%)	N (%)	N (%)	
Male	8 (40)	12 (67)	9 (41)	NS
Bipolar I	16 (80)	–	–	–
Bipolar II	4 (20)	–	–	–
Mood state ^e				
Euthymic	16 (80)	17 (94)	–	–
Depressed	0 (0)	1 (6)	–	–
Hypomanic	3 (15)	–	–	–
Mixed	1 (5)	–	–	–
Comorbid conditions ^f				
ADHD	12 (60)	14 (82)	–	–
ODD or CD	3 (15)	11 (65)	–	–
Anxiety				
GAD	6 (30)	5 (29)	–	–
SAD	3 (15)	3 (18)	–	–
Social phobia	3 (15)	1 (6)	–	–
Medication				
Unmedicated	2 (10)	8 (44)	22 (100)	–
Atypical antipsychotic	11 (55)	5 (28)	–	–
Lithium	7 (35)	1 (6)	–	–
Antiepileptic	15 (75)	5 (28)	–	–
Antidepressant	6 (30)	4 (22)	–	–
Stimulants	7 (35)	7 (39)	–	–

^a BD, bipolar disorder; SMD, severe mood dysregulation; HV, healthy volunteer.

^b Young Mania Rating Score.

^c Children's Depression Rating Score; missing data from 3 BD & 1 SMD.

^d Children's Global Assessment Scale of the past 6 months; missing data from 2 BD & 2 SMD.

^e Mood state indicated by CDRS (GS N = 17; SMD N = 17), Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders (SIGH-SAD; GS N = 3, SMD N = 1), and YMRS (GS N = 20).

^f Current Comorbid Diagnosis missing for 1 SMD.

Table 3
Whole-brain analysis.

Region	BA	Hemi	k	Coordinates			Post-hoc analysis		
				x	y	z	BD	SMD	HV
<i>(A) Awareness × Diagnosis</i>									
Middle occipital gyrus	18	R	94	26	−83	2	Nonaware > Aware [*]	Nonaware > Aware ^{**}	Aware > Nonaware [*]
Middle occipital gyrus	17/18	L	26	−24	−90	2	Nonaware > Aware ^{**}	Nonaware > Aware ^{**}	ns
Middle occipital gyrus	19	L	22	−35	−67	2	ns	Nonaware > Aware ^{**}	ns
Region	BA	Hemi	k	Coordinates			Post-hoc analysis		
				x	y	z			
<i>(B) Emotion × Diagnosis</i>									
Precentral gyrus	3/4	L	84	−58	−15	29	Happy: BD > HV ^{**}	Neutral: BD > SMD [*]	NoFace: BD > SMD [*]
Posterior cingulate		R	52	16	−33	21	Angry: SMD > HV ^{**}		
Superior temporal gyrus	21	R	31	42	−8	11	Angry: BD > HV [*] , SMD > HV [*]	Happy: SMD > HV [*]	Neutral: BD > SMD [*]
Middle occipital gyrus	30	R	24	34	−52	8	Angry: SMD > BD ^{**} , SMD > HV ^{***}		
Medial frontal gyrus	10	L	23	−10	47	14	Fear: BD > SMD ^{**}	Neutral: BD > SMD ^{**} , BD > HV [*]	

^o $p \leq .06$.

^{*} $p \leq .05$.

^{**} $p \leq .01$.

^{***} $p \leq .0001$.

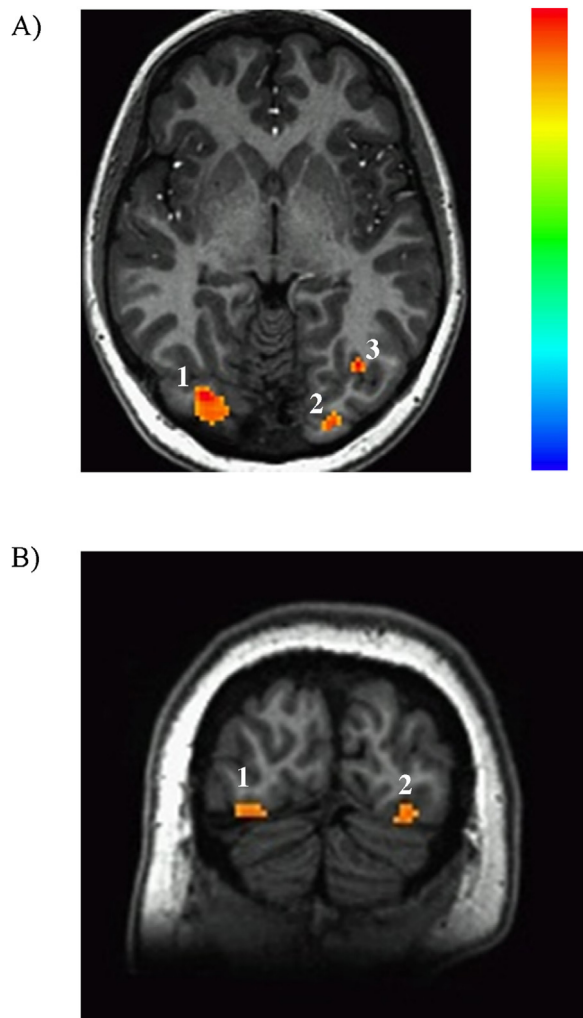


Fig. 2. (A) Axial and (B) Coronal views of the middle occipital clusters significant for the whole-brain analysis of Awareness \times Diagnosis at $p < .005$ and cluster size with the number of voxels $k \geq 20$ (resolution $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$). (1) R middle occipital gyrus BA18; (2) L middle occipital gyrus BA17/18; (3) L middle occipital gyrus BA19. The warmer the color, the higher significance of the cluster. R=L.

each emotion to examine how the groups differed in activation. SMD had more activation than HV during viewing of angry faces in the posterior cingulate, superior temporal gyrus, and middle occipital gyrus. In response to angry faces, SMD also had greater activity than BD in the middle occipital gyrus. BD had greater activation than SMD in the precentral gyrus to neutral and no-face stimuli; in the superior temporal gyrus to neutral faces; and to both fear and neutral faces in the medial frontal gyrus. There was a trend for BD to have greater activity than HV in the superior temporal gyrus in response to angry faces and in the medial frontal gyrus in response to neutral faces (Table 3b).

3.3.2. ROI analysis

Separate Diagnosis \times Emotion \times Awareness ANOVAs were run on the right and left amygdalae. There were no significant interactions, and no main effects of Diagnosis

or Awareness. In the left amygdala there was a main effect of Emotion, with fear eliciting more activity than happy ($p < .05$), neutral ($p < .0001$), or no-face ($p < .01$). Anger elicited more activity than neutral ($p < .01$), and happy more than neutral ($p < .05$). There were no significant findings in the right amygdala.

3.3.2.1. Effect of mood state, medication, and comorbid illnesses. Analyses including only euthymic BD and SMD yielded similar results as those including all subjects. Analyses including only BD without a comorbid anxiety disorder yielded similar results as the primary analysis. However, the results of analyses examining SMD without a comorbid anxiety disorder were equivocal (see Appendix).

3.4. Post-scanning tasks

The data from both post-scanning tasks suggest that subjects were unaware of the emotional face prime. On the post-scanning gender identification task, accuracy was no better than chance for any emotion. Comparing accuracy and RT across diagnoses in an ANOVA, there were no main effects or interactions.

On the post-scanning emotion identification task, after Bonferroni correction, accuracy was no better than chance for any emotion. Comparing accuracy and RT across diagnoses in an ANOVA, there were no main effects or interactions.

4. Discussion

Using an affective priming task, we compared the neural correlates of non-aware vs. aware face-emotion processing in 20 BD, 18 SMD, and 22 HV youth. Previous work has shown deficits in face-emotion labeling tasks, which require subjects to report the emotions that they perceive, in both BD and SMD (McClure et al., 2005; Rich et al., 2006, 2008; Guyer et al., 2007; Brotman et al., 2010). Neuroimaging studies in these patient groups typically utilize tasks where face-emotion displays are presented in a fashion that allows the research participant to label emotion. These studies have found differences in amygdala activity between BD and SMD vs. HV when viewing emotional faces, as well as differences between BD and SMD in other brain regions involved with face processing (Brotman et al., 2010; Thomas et al., 2012, 2013).

The current experiment displayed a face for 17 ms in the non-aware vs. 187 ms in the aware condition, using the expressions anger, fear, happy, neutral, or a blank oval (no-face). Post-task behavioral data showed that the masking procedure was effective, in that participants did not label emotions presented in the non-aware condition more accurately than chance. These procedures differ from those used in prior neuroimaging studies, where face-emotions were prominently displayed (Brotman et al., 2010; Thomas et al., 2012, 2013). Although we were unable to identify any main effects of Awareness or Diagnosis, there were three middle occipital gyrus clusters with significant Awareness \times Diagnosis interactions. HV had greater activation for aware vs. non-aware while both BD and SMD

had greater activation for non-aware vs. aware, suggesting a disruption in ventral visual stream function in these mood disorders. Since the ventral visual stream mediates object identification and recognition (Goodale and Milner, 1992), disruption in these regions amongst BD and SMD in the current experiment suggest broad face-processing deficits.

While displaying face-emotions for brief durations can reduce subject awareness, additional procedures are often needed to ensure lack of awareness in most subjects. The current study used backward masking to further limit subject awareness. The effect of masking in healthy adults is thought to arise from a reentrant pathway in which feedback from visual and other cortical areas affects earlier components of visual processing (Lamme, 2003; Haynes et al., 2005; Dehaene et al., 2006; Carlson et al., 2007; Fahrenfort et al., 2007). In the current study, statistical interactions between diagnosis and the stimulus-awareness conditions were found in regions of this same ventral visual stream pathway. In these regions, awareness had opposing effects in patients and healthy subjects, with the two patient groups showing the same pattern of activation.

Although the experiment was designed to identify regions showing a Diagnosis \times Awareness \times Emotion interaction, the three-way interaction was not significant in any region. In the absence of three-way interactions, we investigated the 2-way interactions involving Diagnosis, since our main goal is to differentiate patients and healthy subjects. However, given the post hoc nature of these analyses, they should be interpreted with caution.

At the whole-brain level there were five regions that showed Emotion \times Diagnosis interactions: L precentral gyrus, R posterior cingulate, R superior temporal gyrus, R middle occipital gyrus, and L medial frontal gyrus (Table 3b). BD had greater activity vs. HV in the precentral gyrus (BA 3/4) in response to happy faces, and vs. SMD in response to neutral and no-face stimuli. The precentral gyrus has been shown to activate in response to viewing (Hooker et al., 2006) or identifying (Morita et al., 2008; Kitada et al., 2010) emotional face expressions. In adult patient populations, such as those with schizophrenia, activity in this region has been shown to be higher vs. healthy controls when viewing emotional faces (Taylor et al., 2012). The current work suggests that this could be true in pediatric bipolar disorder as well. SMD had greater activity vs. HV in the regions important for emotional face processing and social cognition, such as the superior temporal gyrus and posterior cingulate (Hooker et al., 2006; Kitada et al., 2010; Taylor et al., 2012).

Interestingly, BD and SMD also differed from each other in several of these emotion-relevant regions, with BD having higher BOLD activity vs. SMD in the precentral gyrus for neutral and no-face stimuli, superior temporal gyrus for neutral stimuli, and medial frontal gyrus for fear and neutral faces, whereas SMD showed greater activity than BD in the middle occipital gyrus for angry faces. The precentral gyrus is important for executive function, and increased precentral activity for BD vs. controls has been demonstrated in a working memory task (Monks et al.,

2004). Therefore the current data suggest perhaps greater executive function disturbances in BD vs. SMD, since BD had greater BOLD activity in this region vs. both HV and SMD.

The superior temporal gyrus plays a crucial role in emotional processing and social cognition (Allison et al., 2000; Gallagher and Frith, 2003). Neuroimaging studies with BD adults and youth have demonstrated altered functioning of this region compared to controls (Mitchell et al., 2004; Malhi et al., 2007). The medial frontal gyrus is also implicated in cognitive and emotional deficits in BD, and increased activity in BD youth vs. controls has been demonstrated in an emotional task (Chang et al., 2004). The increased BOLD activity in BD vs. SMD in these regions adds to the mounting data from our lab that BD and SMD process emotional information differently (Brotman et al., 2010; Adleman et al., 2011; Deveney et al., 2012; Thomas et al., 2012, 2013).

Contrary to our hypotheses, we did not see group differences in amygdala activity, although such differences have been observed previously between healthy and clinical populations, such as unipolar depression, post-traumatic stress disorder, and schizophrenia (Rauch et al., 2000, 2010; Sheline et al., 2001; Bryant et al., 2008; Suslow et al., 2010). There may be several reasons to explain this null result. First, while our sample sizes are comparable to others in the clinical literature, they are nonetheless relatively small, leaving open the possibility of a Type II error. Second, the inclusion of the aware condition may have decreased our ability to detect group differences in this region, since other studies have used only non-aware conditions. A future study including a block design of aware and non-aware conditions could help detect differences in the amygdala between BD and SMD. Additionally, the results should be viewed in light of our use of the relatively liberal uncorrected whole-brain threshold of $p < .005$ with a voxel extent of 20 (Lieberman and Cunningham, 2009).

While the study is limited by the inclusion of non-euthymic patients, the results remained largely unchanged when we limited the analysis to only euthymic patients. Most patients were medicated, since ethical issues preclude withdrawing medication for research purposes in these severely ill patients. Furthermore, prior work suggests that psychotropic medications may be more likely to diminish between-group differences than to cause Type I errors (Phillips et al., 2008). Patients with BD had a number of comorbid illnesses, and small numbers precluded post hoc analyses to test the impact of comorbid ADHD on our findings. Nonetheless, the post hoc analysis examining the effect of anxiety disorders generally supported our primary results. To increase power, future studies should include larger sample sizes and a paradigm with fewer emotion conditions and more replicates. For example, since a recent study from our group suggests that BD and SMD differ in the processing of happy faces (Thomas et al., 2012), a future affective priming study might include only positive faces, which would both provide more statistical power and prevent carry-over effects from the processing of negative faces.

SMD youth are characterized by chronic irritability. From a systems neuroscience perspective, irritability may

result from maladaptive responses to frustration, where frustration is conceptualized as the emotional response to blocked goal attainment (Leibenluft, 2011). In this sense, SMD could reflect deficits in regulation of the approach system that mediates responses to desired goals. Indeed, in response to blocked goal attainment, SMD youth report higher levels of frustration than healthy subjects, perhaps due to deficits in their ability to inhibit approach responses when such responses are unsuccessful (Deveney et al., 2013). Future work is needed to test explicitly approach system deficits in this population of highly irritable youth, as well as to understand the pathophysiological correlates of frustration and self-regulation, both in BD and SMD youth.

Additionally, over-reactivity to angry faces could be seen as evidence of dysregulation in the approach system, since anger is generally conceptualized as a negative-valence, approach emotion associated with increased effort toward a goal (Weiner et al., 1982; Lewis et al., 1990). Indeed, in this study, over-reactivity to angry faces was specific to the SMD group in the posterior cingulate, middle occipital gyrus, and superior temporal gyrus. While there was a trend for BD subjects to have over-activity in response in the superior temporal gyrus in response to angry faces, this result did not reach significance.

5. Conclusions

In sum, using an affective priming task, we found that BD and SMD differ from HV in ventral visual stream activation to aware vs. non-aware stimuli, and that the three groups show unique activation patterns to different emotions. BD and SMD have similar deficits in face emotion labeling (Guyer et al., 2007; Rich et al., 2008; Brotman et al., 2010), and we documented previously that these two patient populations differ from each other and from HV in neural activity when processing emotional faces (Brotman et al., 2010; Thomas et al., 2012, 2013). Here, we extend those findings by demonstrating that such between-group differences in neural activity are present even when the faces are processed outside awareness. Data in the current experiment are consistent with previous neuroimaging and clinical studies, which conclude that severe, non-episodic irritability does not appear to be a developmental presentation of BD (Brotman et al., 2006, 2010; Rich et al., 2007; Adleman et al., 2011; Deveney et al., 2012; Thomas et al., 2012, 2013). Further, our data indicate that patients and healthy subjects may differ in their neural responses to emotional stimuli, even when they are not aware of those stimuli. Additional neuroimaging studies are needed to replicate and further specify the nature of aware and non-aware emotion processing dysfunction displayed by BD and SMD.

Conflict of interest statement

The authors have no commercial or financial involvements that might present an appearance of conflict 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.2013.09.007>.

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